Persistent Neuropsychological Deficit in Euthymic Bipolar Patients: Executive Function as a Core Deficit

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Objective: To characterize neuropsychological deficits during the euthymic phase in a sample of bipolar outpatients treated with lithium as the principal mood-stabilizer medication. We sought to determine cognitive functioning of typical bipolar outpatients treated in clinical settings.

Method: Forty-four stable outpatients, fulfilling criteria of bipolar disorder (DSM-IV), were consecutively recruited from a defined catchment area and compared with 46 healthy matched controls in 2003. Patients were remitted for at least 3 months and euthymic (Hamilton Rating Scale for Depression score < 8 and Young Mania Rating Scale score < 6 for at least 3 months). They were receiving lithium as monotherapy (45.5%) or combined with other psychotropic medication (54.5%). Neuropsychological 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: Multivariate analysis of variance showed that euthymic bipolar patients performed significantly worse than controls in measures of executive function ($F = 2.57$, $df = 4,82$; $p = .04$) and inhibition ($F = 3.83$, $df = 2,84$; $p = .03$), after controlling for subclinical symptomatology, years of education, and premorbid intelligence quotient. Processing speed also differed significantly between groups ($F = 3.73$, $df = 2,84$; $p = .03$). The subgroup of patients on lithium monotherapy (45.5%) differed significantly from healthy matched controls on tasks of lack of inhibition ($F = 5.8$, $df = 2,36$; $p = .007$). Executive tasks showed between-subject effects.

Conclusions: These results suggest that impaired executive function and loss of inhibition might be an important feature of bipolar disorder regardless of the severity of the disease or the effects of medication. Also, these executive-type cognitive traits may constitute an endophenotype for further studies on the etiology of bipolar disorder.

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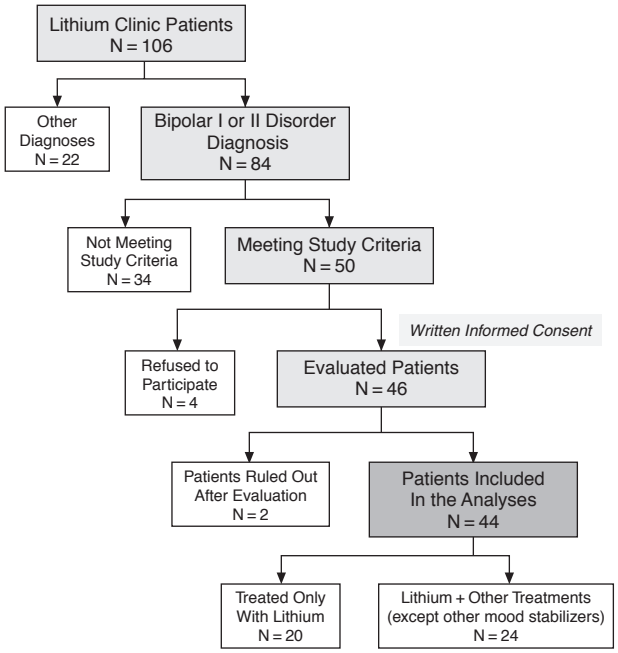
A growing body of evidence suggests that bipolar patients exhibit neuropsychological impairment that persists even during the euthymic state.[1–10] The most common purpose of the studies published so far was to identify the cognitive functions that are more impaired and the clinical factors related to this impairment (i.e., to identify the cognitive functions and the associated clinical factors that have more implications on the psychosocial functioning). A number of recent reviews[11–14] summarize the main results and suggest that euthymic patients seem to show a neuropsychological impairment involving verbal memory, attention, and executive function.

The majority of these studies were conducted in tertiary settings. Thus, previous works may have exhibited a bias toward greater severity when selecting patients and, consequently, toward polypharmacy and other confounding variables (e.g., side effects, interactions).[7,15] In contrast, the study of euthymic outpatients followed during a given period of time in a naturalistic way (for instance, in a lithium clinic) might give the opportunity to assess the cognitive impairment of more representative subjects. These outpatients would presumably be receiving more homogeneous treatments and not selected by their severity. Also, these individuals could show adherence to treatment and be at good disposition of being followed-up.

The use of lithium as a mood stabilizer is still the first-choice treatment for bipolar disorder,[16,17] and its efficacy

Figure 1. Flow Diagram of Patients Selected for the Study



has been proved and accepted.[18] It appears that lithium at therapeutic doses generally does not exert a significant negative effect on cognition,[19] but neither is there evidence of improved cognitive performance when related factors are considered.[20] In any case, it is difficult to control the effect of drugs on cognition. In bipolar disorder, this becomes even more difficult because bipolar patients are usually treated with more than one drug class.[21]

The aim of this study is to determine the neuropsychological performance of euthymic bipolar outpatients from a lithium clinic that covers an entire health area. This approach is of particular relevance because it implies assessing the cognitive functioning of typical bipolar outpatients treated in clinical settings.

METHOD

Subjects

Patients were enrolled into the study from the Lithium Clinic Program at Hospital Santa Maria, Lleida, Spain. This hospital covers the whole health area, about 140,000 inhabitants. All patients from the Lithium Clinic during 2003 were considered: there were 106 outpatients, 84 of whom had bipolar I or bipolar II disorder diagnoses and 50 of whom met inclusion criteria. Inclusion criteria required that patients fulfilled DSM-IV criteria for bipolar I or II disorder in remission for at least 3 months. Outpatients were described as being in remission if they were clinically stable according to their treating physician for at least 3 months prior to assessment and had been on the same treatment regimen over the same period of time. In addition, following a recent review,[22] patients were characterized as euthymic if they had a total Hamilton Rating Scale for Depression (HAM-D; 17-item[23]) score below 8 and a total Young Mania Rating Scale (YMRS[24]) score below 6 for at least 3 months at the time of assessment. Exclusion criteria were the following: significant physical or neurologic illness, substance abuse or dependence in the last 12 months, electroconvulsive therapy (ECT) in the preceding year, and cotreatment with any mood-stabilizing medication other than lithium.

The final sample included 46 outpatients who agreed to participate and who were evaluated at a full clinical interview by a psychiatrist, the evaluation including demographic, clinical, and treatment characteristics (see Figure 1). Two patients had to be excluded from the sample (one because of a vascular brain illness and the other because his intelligence quotient was below 1 standard deviation [IQ < 80]). Therefore, 44 bipolar outpatients (22 male, 22 female, aged 18–65 years) were included. All patients had blood and urine tests, including thyroid function, serum lithium levels, and urine drug control. The study was approved by the Local Ethics Committee, and written informed consent was obtained from all participants (patients and healthy controls).

Forty-six healthy controls, matched in terms of gender and age, were recruited with 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.[25] They had no first-degree relatives with bipolar or psychosis diagnoses. Control subjects underwent the same exclusion criteria as the patients and were assessed at the same full clinical and demographics interview by a trained psychiatrist.

Demographic and Clinical Data

The demographic and clinical data were systematically obtained and included the following variables: age, gender, years of education, current job status, and family history of mental illness. For bipolar outpatients, the following variables were also obtained: age at onset, duration of illness, age at first psychiatric hospitalization, number of prior manic episodes and hospitalizations, years of stabilization, presence or absence of rapid-cycling pattern, presence or absence of psychotic symptoms, presence or absence of seasonal pattern, presence or absence of suicide attempts, and subtypes of bipolar diagnoses (I or II).

All outpatients were receiving lithium as the only mood-stabilizing medication (dose, 400–1600 mg/day; mean, 1109 mg/day; serum lithium levels, 0.20–1.00 mmol/L; mean, 0.68 mmol/L). The mean duration of treatment with lithium was 5½ years (range, 0.5–18 years). Lithium was given as strictly monotherapy in 20 patients; 13 patients were also receiving standard doses of antidepressants (11 received SSRIs and 2, tricyclic

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antidepressants), and 9 were taking antipsychotics plus lithium (8 received second-generation antipsychotics: olanzapine up to 10 mg/day or risperidone up to 3 mg/day). Finally, 2 patients were taking lithium with antidepressant and antipsychotic drugs. Thus, the present series was not an excessively medicated group.[26]

Assessments

Neuropsychological assessment. Although previous results seem to indicate that tests sensitive to executive functioning should be considered, given the link to psychosocial functioning,[4] we chose neuropsychological tests that were frequently documented in previous literature.[13] Therefore, our battery included neuropsychological tests that tapped into broad cognitive categories in order to provide a more general pattern of cognition. Neuropsychological testing lasted approximately 2 hours and was administered and evaluated by a trained neuropsychologist. The administered tests were the following (detailed references of these tests can be found in Martínez-Arán et al.[8] and Lezak et al.[27]):

- Wisconsin Card Sorting Test (WCST), to assess executive function and perseverative behavior
- Stroop Color and Word Test, to evaluate selective attention and inhibition capacity
- FAS verbal fluency test, to assess executive function
- Digit span subtest from the Wechsler Adult Intelligence Scale (WAIS-III), to evaluate attention (digits forward) and working memory (digits backward)
- Trail Making Test (TMT), to evaluate processing speed (TMT-A) and cognitive flexibility (TMT-B)
- Continuous Performance Test (CPT-II), to evaluate sustained attention, processing speed, and perseverative behavior
- California Verbal Learning Test (CVLT), to evaluate verbal learning, recall, and recognition
- Rey-Osterrieth Complex Figure (ROCF) Test, to evaluate visual memory

The estimated mean intelligence quotient of the subjects was obtained from the weighted scores of Vocabulary and Block Design subtests (WAIS-III[28]). These 2 scores are the most highly correlated with the total IQ.

Psychosocial functioning. Bipolar disorder impacts social functioning, employment, and work productivity. Thus, in this study we considered the working situation: active (which included those subjects with a full-time or partial-time job, students, and housewives), inactive (those unemployed or temporary sick leave), or retirement (permanent sick leave or pensioner). Also, patients were assessed with the Global Assessment of Functioning Scale (GAF[18]) to obtain information about the global activity. This scale is widely used to measure psychosocial functioning.[29]

Statistical Procedures

Data analyses were carried out with the statistical package SPSS 14.0 for Windows (SPSS, Inc.; Chicago, Ill.). Comparisons between groups of sociodemographic characteristics were accomplished with a univariate analysis of variance (ANOVA), by examining a single factor of group (outpatients vs. healthy controls); Student t tests and nonparametric tests were used when needed. Two-tailed tests were used for all of the analyses, and statistical significance was defined as $p < .05$.

Following Lezak et al.,[26] all neuropsychological tasks were sorted out by cognitive domains: executive function, attention, processing speed, verbal memory, and visual memory. Since all cognitive variables met the criteria of normality, parametric tests were applied. Thus, separate multivariate analyses of variance (MANOVAs) were performed for each cognitive domain to protect against inflation of type I error; covariates (those clinical and demographic variables that showed significant differences between groups) were included to control their effects (multivariate analysis of covariance [MANCOVA]): estimated premorbid IQ, years of education, and presence of subclinical manic symptomatology. The 4 following measures were the dependent variables for the executive function MANCOVA: digit span backward, TMT-B, FAS (total score), and number of categories on the WCST. The inhibition domain included the number of perseverative errors on the WCST and inhibition on the Stroop task (the decision to examine inhibition isolated from the executive domain was made for a better pragmatic comprehension of the multivariate results). For the attention domain analysis, dependent variables were digit span forward, detectability index of the CPT, and Stroop task interference. The processing speed domain incorporated the TMT-A and hit reaction time in the CPT. The verbal memory domain took into account first trial of the CVLT, total number of learned words on the CVLT, short- and long-term recall, and recognition. Finally, visual memory was delimited by short- (immediate) and long-term (delayed) recall on the ROCF Test. Significant multivariate F ratios were followed by corresponding univariate comparisons (tests of between-subject effects).

Analyses of executive function, inhibition, attention, processing speed, verbal memory, and visual memory data were also performed in a subset of patients who were receiving only lithium ($N = 20$) compared with 20 healthy matched controls (in terms of age, years of education, and premorbid IQ). Separate multivariate analyses including subclinical manic symptomatology as a covariate (MANCOVAs) were performed for each cognitive domain.

Table 1. Demographic and Clinical Variables for Euthymic Bipolar Patients and Healthy Controls[a]

Variable Tested	Euthymic Bipolar Patients (N = 44)	Healthy Controls (N = 46)	Statistic	p
Age, y	42.59 (13.0)	42.22 (12.4)	t = 0.14	NS
Gender, N			χ^2 = 0.00	NS
Male	22	23		
Female	22	23		
Job situation, N			χ^2 = 9.9	.007
Active	24	39		
Inactive	7	3		
Retirement/disability	13	4		
Family history of mental illness, N			χ^2 = 24.05	< .001
No	8	32		
Yes	36	14		
GAF score	71.59 (9.4)	NA		
Education, y	10.5 (3.2)	12.5 (3.4)	t = –2.86	.005
Estimated premorbid IQ	96.1 (11.3)	107.9 (9.1)	t = –5.47	< .001
Clinical variables				
YMRS score	1.8 (2.3)	0.7 (0.9)	t = 3.01	.003
HAM-D score	1.8 (1.8)	1.4 (1.4)	t = 1.31	NS
Age at onset, y	25.6 (11.5)	NA		
No. of hospitalizations	2.77 (3.34)	NA		
Chronicity, y	16.9 (11.67)	NA		
Total no. of manic episodes	2.45 (2.5)	NA		
Age at first hospitalization, y	29.7 (10.99)	NA		
Years of stabilization[b]	3.4 (3.1)	NA		
Psychotic symptoms, N		NA		
Presence	31			
Absence	13			
Seasonal pattern, N		NA		
Presence	27			
Absence	17			
Rapid-cycling pattern, N		NA		
Presence	1			
Absence	43			
Suicide attempts, N		NA		
Presence	18			
Absence	26			
Lithium				
Years treated with lithium	5.5 (3.9)	NA		
Serum lithium level, mmol/L	0.68 (0.19)	NA		
Lithium dose, mg/d	1104.6 (257)	NA		

[a]Values shown as mean (SD) unless otherwise noted.
[b]Rank of period of stabilization from 3 months to 120 months.
Abbreviations: GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, NA = not applicable, NS = not significant, YMRS = Young Mania Rating Scale.

We analyzed cognitive impairment related to clinical variables, psychosocial functioning, and lithium-related variables in the group of bipolar patients. Given that the low-level mood symptoms may impact cognitive function, partial correlations were carried out for quantitative variables (HAM-D and YMRS scores were controlled for). The association analyses between qualitative variables were performed by using Spearman correlation. In order to allow multiple testing, the significance level for these analyses was established at p = .005 (2-tailed).

RESULTS

Clinical and Psychosocial Assessment

The demographic and clinical characteristics for the euthymic bipolar group and control group are shown in Table 1. The 2 groups did not differ with respect to gender and age, but they did differ in terms of years of education and estimated premorbid IQ. Also, differences between groups were found in YMRS scores but not in HAM-D scores, which suggests the presence of subclinical manic symptomatology in the bipolar group. With regard to other demographic data (work situation), the group of bipolar patients showed worse psychosocial adaptation. None of the patients showed positive results in any of the variables of the blood and urine tests.

For the second set of MANCOVAs, differences between the selected and nonselected patients were analyzed. Remitted bipolar outpatients on lithium monotherapy (N = 20) did not differ from those outpatients receiving lithium plus other medications (N = 24) in almost any of the variables (data not shown), except the patients treated with lithium, who had been stable for a longer time (F = 7.23, df = 1,42; p = .01), were less depressed (F = 4.44, df = 1,42; p = .04), and had better global functioning (F = 7.29, df = 1,42; p = .01). On the

Table 2. Neuropsychological Test Results: Comparison of Euthymic Bipolar Patients and Healthy Controls

Neurocognitive Test	Euthymic Bipolar Patients (N = 44)[a]	Healthy Controls (N = 46)[a]	F (group)[b]	p Value			
				Group	IQ	YE	YMRS
Executive domain							
Digits backward	4.5 (1.6)	6.2 (1.9)	4.44	.04	.001	.01	.04
TMT part B	99.3 (46.6)	61.1 (22.5)	6.13	.01	.02	< .001	.02
FAS	36.0 (11.9)	45.0 (10.5)	2.82	.09	.005	.007	.09
WCST no. of categories	3.9 (1.9)	5.4 (1.2)	2.73	.1	.008	.3	.1
Inhibition domain							
Stroop inhibition	35.8 (9.9)	45.0 (7.6)	7.39	.008	.06	.02	.9
Perseverative errors on WCST	27.4 (19.7)	15.9 (10.9)	1.55	.2	.008	.04	.6
Attention							
Digits forward	7.5 (1.9)	8.9 (1.7)	2.1	.2	.001	.3	.5
Detectability on CPT-II	0.9 (0.5)	0.9 (0.4)	0.02	.9	.6	.6	.8
Stroop interference	–0.8 (6.5)	1.2 (5.4)	0.3	.6	.4	.1	.7
Processing speed							
TMT part A	47.3 (19.9)	30.8 (13.9)	4.84	.03	.02	.02	.9
Hit RT on CPT-II	472.3 (82.7)	426.3 (66.0)	4.05	.05	.4	.03	.3
Verbal memory							
CVLT first trial	6.5 (1.8)	6.8 (1.5)	0.26	.6	.2	.03	.8
CVLT total words	49.9 (10.7)	54.4 (7.6)	0.00	.99	.1	< .001	.9
CVLT immediate recall	10.4 (3.2)	11.6 (2.3)	0.1	.7	.03	< .001	.6
CVLT delayed recall	10.7 (3.3)	12.5 (2.2)	1.2	.3	.2	< .001	.4
CVLT recognition	14.2 (1.6)	14.9 (1.3)	0.9	.3	.3	.004	.9
Visual memory							
ROCF immediate	18.3 (5.9)	23.0 (4.9)	3.72	.06	.04	.001	.6
ROCF delayed	17.4 (5.6)	22.3 (5.3)	4.53	.04	.02	.006	.4

[a]Values shown as mean (SD).
[b]Tests of between-subject effects from the multivariate analyses of variance.
Abbreviations: CPT-II = Continuous Performance Test II, CVLT = California Verbal Learning Test, FAS = verbal fluency test, ROCF = Rey-Osterrieth Complex Figure Test, RT = reaction time, TMT = Trail Making Test, WCST = Wisconsin Card Sorting Test, YE = years of education, YMRS = Young Mania Rating Scale.

other hand, the 20 lithium-treated patients did not differ from the 20 healthy matched controls with respect to gender and age, years of education, or estimated premorbid IQ.

Neuropsychological Assessment

Group comparisons: 44 remitted bipolar outpatients vs. 46 healthy controls. After controlling for covariates (subclinical symptoms measured with YMRS scores, years of education, and estimated premorbid IQ), MANCOVA revealed that euthymic bipolar outpatients differed from healthy subjects on tasks of the executive domain ($F = 2.57$, $df = 4,82$; $p = .04$). As shown in Table 2, euthymic bipolar outpatients performed significantly worse on the digit backward and the TMT-B. As revealed by multivariate F ratios, the groups differed in the inhibition domain ($F = 3.83$, $df = 2,84$; $p = .03$). Inspection of univariate comparisons revealed that bipolar outpatients showed lack of inhibition on the Stroop task. Finally, MANCOVA showed that processing speed also differed between groups ($F = 3.73$, $df = 2,84$; $p = .03$). Tests of between-subjects effects indicated that, as compared to healthy controls, remitted bipolar outpatients were slower on TMT-A and CPT-II performance. In contrast, the MANCOVAs carried out to compare group performances on attention, verbal memory, and visual memory failed to reach statistical significance ($p > .12$).

Group comparisons: 20 remitted bipolar outpatients on lithium monotherapy vs. 20 healthy matched controls. MANCOVAs revealed that remitted bipolar outpatients on lithium monotherapy differed significantly from healthy matched controls on those tasks looking at inhibition ($F = 5.8$, $df = 2,36$; $p = .007$). As displayed in Table 3, examination of univariate analyses indicated that bipolar outpatients responded more impulsively on the Stroop task. In contrast, the MANCOVA comparing group performance on executive tasks did not reach statistical significance ($F = 2.15$, $df = 4,34$; $p = .1$), although, as observed in Table 3, digit forward, verbal fluency, and TMT-B scores showed between-subject effects. The MANCOVAs comparing performance on attention, processing speed, verbal memory, or visual memory did not show significant effects.

Association Results (N = 44)

The results of association analyses between neuropsychological variables and psychosocial, clinical, and laboratory variables are shown in Table 4. As suggested by Robinson and Ferrier,[22] the following clinical variables were considered: age at onset, duration of the illness, number of hospitalizations, number of manic episodes, and time of stabilization. We selected the neuropsychological variables in which bipolar patients demonstrated impairment relative to healthy comparison subjects: digit backwards, TMT-A, TMT-B, Stroop inhibition, and CPT-II hit

Table 3. Neuropsychological Test Results: Comparison of Euthymic Bipolar Patients Treated With Lithium Monotherapy and Healthy Controls

Neurocognitive Test	Bipolar Patients With Lithium (N = 20)[a]	Healthy Controls (N = 20)[a]	F (group)[b]	p Value	
				Group	YMRS
Executive domain					
Digits backward	4.5 (1.5)	5.7 (2.1)	5.2	.03	.5
TMT part B	82.7 (28.4)	64 (23.1)	3.9	.05	.8
FAS	36.9 (11.6)	44.5 (9.7)	4.9	.03	.6
WCST no. of categories	3.8 (2.3)	5.4 (1.2)	2.9	.09	.02
Inhibition domain					
Stroop inhibition	35.6 (7.8)	44.9 (6.4)	10.7	.002	.1
Perseverative errors on WCST	23.7 (17.4)	16.7 (10.6)	2.3	.1	.8
Attention					
Digits forward	7.4 (1.8)	8.8 (1.9)	4.6	.04	.8
Detectability on CPT-II	1.07 (0.3)	0.9 (0.3)	0.3	.6	.8
Stroop interference	–1.8 (5.4)	0.5 (4.4)	0.6	.5	.1
Processing speed					
TMT part A	40.5 (15.1)	35.9 (17.6)	1.0	.3	.6
Hit RT on CPT-II	470.4 (72.1)	418.2 (51.7)	3.0	.1	.4
Verbal memory					
CVLT first trial	7.0 (1.7)	6.7 (1.4)	0.4	.5	.9
CVLT total words	52.5 (9.1)	52.4 (7.1)	0.02	.9	.8
CVLT immediate recall	10.9 (2.8)	10.6 (2.1)	0.01	.9	.6
CVLT delayed recall	11.3 (2.6)	12.1 (2.3)	0.9	.4	.8
CVLT recognition	14.7 (1.2)	14.9 (1.4)	0.3	.6	.8
Visual memory					
ROCF immediate	20.0 (5)	22.5 (4.6)	2.6	.1	.7
ROCF delayed	18.9 (4.6)	21.7 (5.5)	3.4	.07	.5

[a]Values shown as mean (SD).
[b]Tests of between-subject effects from the multivariate analyses of variance.
Abbreviations: CPT-II = Continuous Performance Test II, CVLT = California Verbal Learning Test, FAS = verbal fluency test, ROCF = Rey-Osterrieth Complex Figure Test, RT = reaction time, TMT = Trail Making Test, WCST = Wisconsin Card Sorting Test, YE = years of education, YMRS = Young Mania Rating Scale.

Table 4. Associations Between Neuropsychological Variables and Clinical, Psychosocial, and Lithium-Related Variables

Variable	Executive Domain			Processing Speed Domain	
	Digits Backwards	TMT-B	Inhibition Stroop	TMT-A	Hits RT on CPT-II
Clinical[a]					
Age at onset (y)	–0.38*	0.46*	–0.23	0.36	0.10
Duration of the illness (y)	0.08	0.19	–0.30	0.34	0.27
No. of hospitalizations	–0.24	0.05	–0.08	0.23	–0.001
No. of mania episodes	–0.22	0.01	–0.06	0.21	0.01
Time of stability (mo)	–0.11	–0.01	–0.10	0.18	0.10
Psychosocial					
Work situation[b]	–0.13	0.35	–0.35	0.48*	–0.1
GAF[a]	0.03	–0.1	0.06	–0.25	0.09
Lithium-related[a]					
Lithium dose	0.05	0.06	–0.03	0.15	–0.23
Years treated with lithium	–0.20	0.24	–0.30	0.29	0.16
Serum lithium level	–0.44	0.33	–0.31	0.20	–0.09

[a]Partial correlations controlling for affective low-level symptomatology (Hamilton Rating Scale for Depression and Young Mania Rating Scale scores).
[b]Association was calculated by means of the Spearman rho.
*Significant correlation at $p < .005$.
Abbreviations: CPT-II = Continuous Performance Test II, GAF = Global Assessment of Functioning, RT = reaction time, TMT = Trail Making Test.

reaction time. Also, laboratory variables related to lithium were included. For the study of association between lithium-related variables and neuropsychological variables, 8 patients were excluded because the time interval between the neuropsychological assessment and the blood test was longer than 20 days.

As can be observed in Table 4, no clear relations came up from the partial correlations between clinical/laboratory and neuropsychological variables. Additionally, the associations that reached significance ($p < .005$) were not expected: the earlier the onset of the illness, the lesser the impairment. For this reason, we looked for a confounding variable that could explain the lack of association. We found that age correlated with all the neuropsychological tests ($p < .002$) as well as with all the clinical variables (age at onset, $p < .001$; chronicity, $p < .001$;

and time of stability, $p < .004$) and with the years of lithium treatment ($p < .004$), with the exception of the number of manic episodes, number of hospitalizations, serum lithium levels, and lithium doses. Indeed, when age was controlled for, the few associations and tendencies in the initial partial correlations disappeared ($p > .05$). Regarding the psychosocial variables, there was no clear association between GAF scores and cognitive impairment (see Table 4). Only the current job situation significantly correlated with TMT-A performance. Also, there was a tendency between job situation and TMT-B performance and Stroop inhibition.

DISCUSSION

The main finding of the present study is that the sample of lithium-treated euthymic bipolar outpatients displayed cognitive impairment in the executive domain and in processing speed. The cognitive deficits were maintained even after subclinical symptomatology was controlled for. These results suggest that the neuropsychological impairment may be an expression of the disease phenotype and not necessarily bear any relationship with other illness characteristics such as greater severity of the illness or polypharmacy. Indeed, when analyses were repeated for the outpatients treated with lithium monotherapy, the results showed executive dysfunction, as revealed by the performance on the Stroop task, where subjects must inhibit automatic responses. The differences found in processing speed would suggest a more general impairment in euthymic patients. It is possible that processing speed reflected another component of executive dysfunction, as processing slowness has been reported in patients with frontal lobe damage.[30]

A recent review about neuropsychological dysfunction of bipolar disorder[13] suggests that executive-type cognitive traits may constitute a key endophenotype to be considered in future studies of bipolar disorder. Frangou et al.[10] found that in representative treatment samples of remitted bipolar patients, executive dysfunction and lack of inhibitory control seemed to be the core deficit. In this regard, frontal executive dysfunctions, determined by the WCST and the Stroop incongruent condition, have been recently pointed out in euthymic bipolar patients.[31] In a more specific study, Kronhaus et al.[32] have examined the extent of functional abnormalities in neural systems subserving executive function by means of Stroop task performance in a group of remitted bipolar patients. Their results showed decreased ventral prefrontal activity during this task, which may highlight prefrontal cortex as a potential candidate for illness-related dysfunction in bipolar disorder. Therefore, cognitive impairment in patients suffering from bipolar disorder appears to persist throughout remission and may be characterized by impaired performance on tasks involving executive function.

With respect to the sample of euthymic outpatients assessed in this study, there are some characteristics that need to be discussed. The criteria for euthymia are not identical across studies published in the literature. A complete absence of symptoms is not a realistic target for all patients with bipolar disorder, but establishing a consensus definition of euthymia that can readily be applied would increase comparability for future studies. Such a definition might be implemented by considering measures of clinical scales and, when necessary, by including subclinical symptomatology as covariates. In the present study, the criteria for euthymia were established following some of the previous works.[2,4,8] Among the outpatients, only 2 became euthymic just 3 months before assessment, and more than half of the sample had been euthymic for more than 36 months. The fact that most of the outpatients had been euthymic for a long time might increase the reliability of the results. Another characteristic that we would like to discuss is that this sample might be representative of patients who attend a lithium clinic in any given area, i.e., patients who show some clinical features such as unified treatment, which makes the sample more homogeneous. However, these patients also represent a self-selected population in which at least patients at high risk of poor outcome are underrepresented.[33] Nevertheless, there seems to be an executive dysfunction in euthymic bipolar outpatients that is independent of severity and of polypharmacy.

In contrast to expectations, our verbal memory results differed from those of previous findings, which suggested persistent verbal memory dysfunctions during euthymic states as a potential cognitive endophenotype.[8,22,34] The present results show that bipolar patients treated for a long time with lithium, as monotherapy or combined treatment, had a performance on measures of verbal memory similar to that of healthy controls. The lack of verbal memory impairment has been reported in studies that point to the neuroprotective properties of lithium.[35] When pharmacologic therapy is more complex (i.e., more than 2 drugs), this probably additionally affects cognition, and particularly verbal memory. In this regard, some authors have reported that verbal memory was more impaired in euthymic patients treated with more medications, which suggests that prophylactic treatment should be simplified when possible to reduce cognitive impairment in bipolar patients.[36]

Regarding the association analyses, no clear relationships were found between performance on neuropsychological tests and other variables. It has to be remarked that low-level mood symptoms were controlled for, thus blurring relations found in previous studies. The fact that no associations were found could be explained in terms of age at the time of assessment. Younger patients of this sample were those with earlier age at onset, shorter duration of illness, and less time of stability. Thus, current

age affects many of the clinical variables and performance on all of the neuropsychological tests (the younger they are, the better they perform). Nevertheless, an association was found between the current job situation and cognitive functioning: active outpatients displayed better performance than those who were inactive or retired. This result would be in agreement with the idea that the exhibited neuropsychological impairment may be a contributory factor to a poor psychosocial outcome.[15,37] Indeed, it has been described that between 30% and 50% of patients with bipolar disorder experience significant psychosocial disability that may be linked to persistent cognitive impairment.[38]

No association between neuropsychological performance and lithium-related variables was found. Therefore, with the present results we are not able to determine whether the lithium serum levels, the lithium doses, or the duration of the treatment affect cognition. Lithium has been well studied in terms of its effects on cognition (for a review, see Pachet and Wisniewski[19]), and evidence of mild impairment in psychomotor speed, verbal memory, and subjective cognitive complaints has been found with lithium treatment. As discussed in Pachet and Wisniewski,[19] lithium also appears not to have a negative effect on visuospatial constructional skills and attention/concentration and does not have a negative cumulative effect on cognition. To our knowledge, there has been only 1 study performed with functional magnetic resonance imaging, tapping into the cognitive impairment of euthymic bipolar patients treated with lithium as the unique mood stabilizer.[39] That study focused on working memory and suggested that the neuropsychological deficit might be related to the failure in engaging fronto-executive areas of the brain.

In summary, there exists an executive dysfunction in euthymic bipolar outpatients undergoing treatment with lithium. This cognitive impairment may be a potential endophenotype of bipolar disorder regardless of the severity of the disease or the effects of the medication. Studies on severity-based and polymedicated populations might have overestimated impairments in domains such as memory or learning and their impact on psychosocial outcome. Thus, psychotherapeutic approaches should address the persistent executive difficulties in order to improve the quality of life of bipolar patients. In addition, it would be desirable to develop cognitive rehabilitation programs, known to partly remediate the neuropsychological and psychosocial impairments in schizophrenia, to bipolar disorder. These programs should explore benefits across other clinical and therapeutic aspects, such as insight, compliance, or response to psychological interventions.

Drug names: lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Kessing LV. Cognitive impairment in the euthymic phase of affective disorder. Psychol Med 1998;28:1027–1038
2. van Gorp WG, Altshuler L, Theberge DC, et al. Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence: a preliminary study. Arch Gen Psychiatry 1998;55:41–46
3. Ferrier IN, Stanton BR, Kelly TP, et al. Neuropsychological function in euthymic patients with bipolar disorder. Br J Psychiatry 1999; 175:246–251
4. Clark L, Iversen S, Goodwin GM. Sustained attention deficit in bipolar disorder. Br J Psychiatry 2002;180:313–319
5. Cavanagh JTO, Van Beck M, Muir W, et al. Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. Br J Psychiatry 2002;180:320–326
6. Raymont V, Bettany D, Frangou S. The Maudsley Bipolar Disorder Project: clinical characteristics of bipolar disorder I in a Catchment area treatment sample. Eur Psychiatry 2003;18:13–17
7. Donaldson S, Goldstein LH, Landau S, et al. The Maudsley Bipolar Disorder Project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. J Clin Psychiatry 2003;64:86–93
8. Martínez-Arán A, Vieta E, Colom F, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry 2004;161:262–270
9. Thompson JM, Gallagher P, Hughes JH, et al. Neurocognitive impairment in euthymic patients with bipolar affective disorder. Br J Psychiatry 2005;186:32–40
10. Frangou S, Donaldson S, Adjulis M, et al. The Maudsley Bipolar Disorder Project: executive dysfunction in bipolar disorder I and its clinical correlates. Biol Psychiatry 2005;58:859–864
11. Martinez-Aran A, Vieta E, Colom F, et al. Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. Psychother Psychosom 2000;69:2–18
12. Quraishi S, Frangou S. Neuropsychology of bipolar disorder: a review. J Affect Disord 2002;72:209–226
13. Savitz J, Solms M, Ramesar RS. Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. Bipolar Disord 2005;7: 216–235
14. Krabbendam L, Arts B, van Os J, et al. Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. Schizophr Res 2005;80:137–149
15. Martínez-Arán A, Penadés R, Vieta E, et al. Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. Psychother Psychosom 2002; 71:39–46
16. Bowden CL. New concepts in mood stabilization: evidence for the effectiveness of valproate and lamotrigine. Neuropsychopharmacology 1998;19:194–199
17. Bauer MS, Mitchner L. What is a "mood stabilizer"? an evidence-based response. Am J Psychiatry 2004;161:3–18
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
19. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. Psychopharmacology (Berl) 2003;170:225–234
20. MacQueen GM, Marriott M, Begin H, et al. Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. Bipolar Disord 2003;5:349–355
21. Schou M. The combat of non-compliance during prophylactic lithium treatment. Acta Psychiatr Scand 1997;95:361–363
22. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord 2006;8:103–116
23. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
24. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
25. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version, User's Guide. Barcelona, Spain: Masson; 1999
26. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the

NIMH life chart method. J Clin Psychiatry 2003;64:680–690
27. Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th ed. New York, NY: Oxford University Press; 2004
28. Wechsler D. Wechsler Adult Intelligence Scale-III. Technical Manual (Spanish Version). Madrid, Spain: TEA Ediciones; 2001
29. Dean BB, Gerner D, Gerner RH. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in bipolar disorder. Curr Med Res Opin 2004; 20:139–154
30. Baird A, Dewar BK, Critchlev H, et al. Cognitive functioning after medial frontal lobe damage including the anterior cingulate cortex: a preliminary investigation. Brain Cogn 2006;60:166–175
31. Frangou S, Dakhil N, Landau S, et al. Fronto-temporal function may distinguish bipolar disorder from schizophrenia. Bipolar Disord 2006; 8:47–55
32. Kronhaus DM, Lawrence NS, Williams AM, et al. Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. Bipolar Disord 2006;8:28–39
33. Maj M, Pirozzi R, Magliano L, et al. Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998;155:30–35
34. Glahn DC, Bearden CE, Niendam TA, et al. The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. Bipolar Disord 2004;6:171–182
35. Manji HK, Duman RS. Impairments on neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacol Bull 2001;35:5–49
36. Martinez-Aran A, Vieta E, Colom F, et al. Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? Psychother Psychosom 2005;74:295–302
37. Martinez-Aran A, Vieta E, Torrent C, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. Bipolar Disord 2007; 9:103–113
38. Zarate CA Jr, Tohen M, Land M, et al. Functional impairment and cognition in bipolar disorder. Psychiatr Q 2000;71:309–329
39. Monks PJ, Thompson JM, Bullmore ET, et al. A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. Bipolar Disord 2004;6:550–564

