Article

Cognitive Function Across Manic or Hypomanic, Depressed, and Euthymic States in Bipolar Disorder

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Objective: The study aims were to address neuropsychological functioning across different states of bipolar illness and to determine relationships among clinical features, neuropsychological performance, and psychosocial functioning.

Method: Several domains of cognitive function were examined in 30 depressed bipolar patients (DSM-IV criteria for major depression, Hamilton Depression Rating Scale score ≥17), 34 manic or hypomanic bipolar patients (DSM-IV criteria for manic or hypomanic episode, Young Mania Rating Scale score ≥12), and 44 euthymic bipolar patients (6 months of remission, Hamilton depression scale score ≤8, and Young Mania Rating Scale score ≤6). The comparison group consisted of 30 healthy subjects without history of neurological or psychiatric disorders. A neuropsychological battery assessed executive function, attention, and verbal and visual memory.

Results: The three groups showed cognitive dysfunction in verbal memory and frontal executive tasks in relation to the comparison group. Low neuropsychological performance was associated with poor functional outcome. Impairment of verbal memory was related to the duration of illness and the numbers of previous manic episodes, hospitalizations, and suicide attempts.

Conclusions: A poorer performance was observed in all bipolar groups regarding executive function and verbal memory in relation to the healthy comparison subjects. These cognitive difficulties, especially related to verbal memory, may help explain the impairment regarding daily functioning, even during remission. Further studies should focus on testing, whether optimizing prophylactic pharmacological treatment and psychoeducation might reduce cognitive impairment, and whether bipolar patients would benefit from neuropsychological rehabilitation in order to reduce the impact of cognitive impairment in their overall functioning.

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In view of previous research, cognitive function seems to be impaired during the acute phases of bipolar illness. Nevertheless, studies that compare neuropsychological functioning across different clinical states of bipolar disorder are scarce (1). Acutely ill patients have shown dysfunctions in several cognitive areas, such as attention, executive function, learning and memory, and psychomotor speed (2–4). However, it remains unclear whether neuropsychological deficits are stable and exist independently of clinical state. Studies have suggested that cognitive dysfunctions may persist in remission states beyond the episodes of the illness; thus, these deficits may be chronic (5–10). On the other hand, structural and functional neuroimaging techniques have indicated that the subcortical white matter, the basal ganglia, the hippocampus, the amygdala, the frontal lobes, the temporal lobes, and the cerebellum (3, 11, 12) may be involved in bipolar disorder.

To our knowledge, there are no studies comparing manic or hypomanic, depressed, and euthymic bipolar patients and assessing the chronicity of cognitive dysfunctions. Most investigations have compared heterogeneous groups without distinguishing between patients in different states of the illness. The controversy among authors regarding what kind of cognitive functions are impaired during the active periods of the illness and which of these deficits persist in clinical remission may probably be due, in part, to methods limitations.

Moreover, there are some clinical factors that may influence cognitive functioning in bipolar patients, such as the number of episodes (6, 7, 13), especially of the manic type (6, 9, 10, 14–16), as well as chronicity, defined as the duration of the illness (6, 10). Subclinical symptoms, particularly subthreshold depression, may also be involved in neuropsychological performance (2, 7, 17). On the other hand, it has been outlined that bipolar illness is associated with poor functional outcome (18).

Recent reports have emphasized the influence of cognitive dysfunctions in the psychosocial functioning of bipolar patients (16, 18, 19). Illness severity and cognitive impairment are not independent, so it is difficult to assess and discuss their respective influences on functional outcome (16, 18, 20).

The aims of the present study were to ascertain whether bipolar patients showed different patterns of neuropsychological performance, depending on their clinical state. Another aim was to establish whether specific cognitive

deficits could be observed in asymptomatic patients. We hypothesized that acute patients would show an unspecified and generalized neuropsychological pattern of cognitive impairments, whereas the euthymic patients would perform worse than the comparison subjects on tasks regarding verbal memory and executive function. Finally, we hypothesized that there would be a relationship between neuropsychological functioning and several clinical variables, as well as functional outcome. We also expected to find specific cognitive deficits related to poorer social and occupational functioning.

Method

Subjects

The patients participating in the present study were enrolled in the Bipolar Disorders Program of the Hospital Clinic of Barcelona. The clinical state of the patients was determined by a psychiatrist responsible for the follow-up of bipolar patients in the Barcelona Bipolar Disorders Program using DSM-IV criteria, the Hamilton Depression Rating Scale (21), and the Spanish version of the Young Mania Rating Scale (22, 23). Subjects with other disorders that could be related to neuropsychological impairment (significant physical or neurological illness, a history of head injury, neurodegenerative disorder, substance abuse or dependence in the last year, mental retardation, ECT in the last year) were excluded. Thirty depressed bipolar patients (DSM-IV criteria for bipolar I or II disorder with major depression; Hamilton depression scale score ≥17), 34 manic or hypomanic bipolar patients (DSM-IV criteria for bipolar I or II disorder with a manic or hypomanic episode; Young Mania Rating Scale score ≥12), and 44 euthymic bipolar patients (DSM-IV criteria for bipolar I or II disorder, at least 6 months of remission, Hamilton depression scale score ≤8, and Young Mania Rating Scale score ≤6) were recruited to participate in this study. Thirty healthy comparison subjects without a psychiatric or neurological history were also recruited from a pool of normal volunteers from the Hospital Clinic of Barcelona and from advertising. The subjects who did not meet the criteria for any axis I psychiatric disorder, as assessed by the Structured Clinical Interview for DSM-IV, were included as normal comparison subjects. We made sure that the comparison subjects had no first-degree relatives with a diagnosis of bipolar disorder. The comparison group included hospital staff with various degrees and also students, workers, and housewives. All subjects gave written informed consent to participate in the study after the procedures had been fully explained. Ethical approval for the study was granted by the hospital ethics committee. The healthy comparison group and patient groups were not significantly different with regard to age, sex, or level of education. The manic group included patients with hypomania and moderate mania because the severity of the episode made the neuropsychological assessment difficult or impossible; thus, patients with current active psychotic symptoms were not included. A total of 168 patients were screened before we arrived at the current group of subjects. The reasons for not entering the study were current substance abuse, presence of psychotic features, history of head injury, neurological illness, mental retardation, and subsyndromal fluctuations. Six patients refused to participate in the study. Several patients met more than one exclusion criteria and were not admitted into the present study. With respect to the comparison group, five subjects could not enter the study (two due to history of head injury and three due to anxiety disorders).

Clinical and Psychosocial Assessment

Clinical variables were collected as part of the protocol of the Bipolar Disorders Program. Psychopathological evaluation was carried out by means of the Spanish version of the Positive and Negative Syndrome Scale (24, 25). Psychosocial functioning was assessed with the General Assessment of Functioning (GAF) (DSM-IV). Occupational functioning was established as "good functioning" when patients were working at a good or acceptable level of functioning or "poor functioning" if they did not work at all or had poor occupational functioning during the last 3 years before the evaluation. The Positive and Negative Syndrome Scale and the GAF were administered by a trained psychiatrist, whereas the neuropsychological evaluation was carried out by a trained neuropsychologist who was blind to the results of the clinical and psychosocial assessments.

Neuropsychological Assessment

An extensive review of previous literature guided the choice of neuropsychological tests used in the present study. In this regard, in order to enhance replication, only tests that were frequently documented by the neuropsychological literature were employed (26, 27). The battery of neuropsychological tests employed were ascribed to broad cognitive categories, despite the need for multiple cognitive abilities for their completion. All neuropsychological tests were administered in a quiet testing room, according to standard instructions for administration. The battery of neuropsychological tests took between 1.5 and 2 hours to complete, basically depending on clinical state, sometimes including a small break halfway through the assessment. The tests administered were the following:

1. Estimated premorbid IQ (26, 27): the WAIS vocabulary subtest (28)
2. Frontal executive function tests: the Wisconsin Card Sorting Test (29), the Stroop Color and Word Test (30), the Controlled Oral Word Association Test FAS, and the animal-naming subtests (31)
3. Tests measuring attention or concentration and mental tracking: the WAIS digit subtest (28) and the Trail Making Test (32)

TABLE 1. Demographic and Clinical Characteristics of Depressed, Manic or Hypomanic, and Euthymic Bipolar Disorder Patients and Healthy Comparison Subjects

Characteristic	Depressed Patients (N=30)		Manic or Hypomanic Patients (N=34)		Euthymic Patients (N=44)		Healthy Comparison Subjects (N=30)		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df
Age (years)	43.4	10.7	42.4	11.9	39.6	9.5	38.9	12.4	1.28	3, 137
Educational level (years)	11.0	3.0	11.7	3.4	12.9	3.2	12.5	3.2	2.27	3, 136
Premorbid IQ	105.6	10.4	108.2	9.6	107.0	7.2	113.0	9.1	3.94*	3, 137
Age at onset (years)	27.4	9.9	25.7	9.8	24.6	6.9			0.89	2, 104
Duration of illness (years)	16.6	10.2	15.4	11.4	14.9	8.5			0.25	2, 104
Number of episodes										
Total	17.7	22.1	14.4	13.2	13.0	11.3			0.81	2, 100
Manic	3.8	5.9	3.0	4.5	3.1	3.2			0.24	2, 100
Hypomanic	2.6	4.7	3.3	4.5	3.0	5.3			0.14	2, 100
Depressed	10.1	13.3	7.6	10.4	5.3	5.7			2.13	2, 100
Mixed	1.1	2.9	0.5	0.8	1.0	2.1			0.95	2, 100
Number of hospitalizations	1.7	2.3	2.4	3.1	2.6	2.6	—	—	0.83	2, 102
Number of suicide attempts	0.6	1.1	0.7	1.1	0.7	1.6	—	—	0.18	2, 95
Global Assessment of Functioning score	50.5	7.5	49.4	10.3	69.1	13.9	—	—	37.31**	2, 107
Hamilton depression scale score	19.7	3.2	4.9	3.5	3.6	2.6	0.9	1.1	289.46**	3, 137
Young Mania Rating Scale score	1.3	1.5	18.7	5.4	1.4	1.8	0.6	0.9	302.58**	3, 137
Positive and Negative Syndrome Scale score										
Positive	8.5	2.2	17.7	8.3	7.7	1.3	—	—	46.34**	3, 107
Negative	11.2	2.9	8.3	2.0	10.6	4.2	—	—	6.99***	3, 107
General	36.4	6.6	29.7	8.4	23.3	6.6	—	—	29.55**	3, 107
	N	%	N	%	N	%	N	%	χ^2	df
Sex									4.59	3, 138
Male	15	50.0	17	50.0	18	40.9	8	26.7		
Female	15	50.0	17	50.0	26	59.1	22	73.3		
Previous psychotic symptoms	21	75.0	17	53.1	32	72.7			4.26	2, 104
Nonadherence to treatment	10	33.3	13	40.6	15	34.1			0.46	2, 106
Medication										
Lithium	21	70.0	26	81.3	37	84.1			2.26	2, 106
Carbamazepine	8	26.7	10	31.3	11	25.6			0.31	2, 105
Valproate	6	20.0	5	15.6	5	11.6			0.62	2, 105
Antidepressants	17	56.7	5	16.1	6	13.6			19.39**	2, 105
Neuroleptics	9	30.0	26	78.8	25	56.8			15.20**	2, 107

*p=0.01. **p<0.001. ***p=0.001.

4. Tests measuring verbal learning and memory: the California Verbal Learning Test (33) and the Wechsler Memory Scale—Revised (WMS-R) logical memory subtest (34)
5. Tests measuring nonverbal learning and memory: the WMS-R visual reproduction subtest (34)

Statistical Analysis

The four groups (euthymic, manic or hypomanic, depressed, and healthy comparison) were compared regarding clinical and sociodemographic characteristics by using analysis of variance (ANOVA) and the chi-square test, as appropriate. Performance on the neuropsychological tests was compared across the four groups by means of multivariate analysis of variance (MANOVA). Since multiple dependent variables were used, a prior protective MANOVA analysis was performed with estimated premorbid intelligence as the covariate and group as a main factor. Since neuropsychological tests are naturally correlated, this procedure was considered better than Bonferroni inequality correction, which would increase type II error. Group differences between euthymic, manic, depressed, and comparison subjects were tested in a one-way ANOVA, followed by the Tukey post hoc comparison procedure when significant main effects were present. Relationships between test scores that showed statistically significant group differences ($p<0.05$) and clinical variables related to the course and severity of the bipolar patients were tested with Pearson correlations, with a significance level of $p<0.05$. Pearson correlations were also used to analyze relationships between neuropsychological performance and psychosocial functioning. This preliminary analysis was exploratory.

In bipolar patients, to identify the variables that would be good predictors of functional outcome as measured by the GAF, we used a hierarchical regression model. The clinical and neuropsychological variables that correlated with the GAF were introduced in the model. In a first block, we introduced scores from the Hamilton depression scale, the Young Mania Rating Scale, and the Positive and Negative Syndrome Scale to control for clinical symptom profiles. In the second block, neuropsychological variables were entered by using a stepwise method. Data

TABLE 2. Performance on Neuropsychological Tests by Depressed, Manic or Hypomanic, and Euthymic Bipolar Disorder Patients and Healthy Comparison Subjects

	Score								MANOVA[a]		
	Depressed Subjects (N=30)		Hypomanic or Manic Subjects (N=34)		Euthymic Subjects (N=44)		Healthy Comparison Subjects (N=30)				
Domain and Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F (df=3, 128)	p	Tukey Post Hoc Test[b]
Frontal executive function											
Wisconsin Card Sorting Test											
Categories	4.6	1.7	4.3	2.0	4.8	1.7	5.4	1.4	1.23	0.30	
Perseverative errors	18.9	10.4	19.8	14.6	16.7	14.6	9.2	7.2	2.96	<0.04	E, M, D < C
Stroop Color and Word Test:											
interference	–2.3	6.6	–0.2	5.5	1.0	6.4	4.9	7.0	5.69	0.001	E, D, M < C
Attention or concentration and mental tracking											
WAIS											
Digit subtest											
Forward	5.3	1.5	5.4	1.1	5.6	1.3	6.3	1.2	1.82	0.15	
Backward	3.8	1.1	4.0	0.9	3.9	1.0	4.8	1.1	3.13	<0.03	E, D, M < C
Trail Making Test											
A	51.2	25.4	41.6	15.0	44.9	18.9	30.1	12.0	4.00	0.009	E, D < C
B	151.2	113.9	131.9	109.7	109.6	64.9	77.7	39.1	2.47	<0.07	D < C
Verbal fluency											
Controlled Oral Word Association Test											
FAS	25.3	12.6	33.8	13.9	33.9	10.5	39.9	11.1	4.99	0.003	D < E, M, C
Animal naming	16.8	5.1	17.7	4.8	17.7	4.1	21.3	4.7	2.87	<0.04	E, D < C
Verbal learning and memory											
California Verbal Learning Test											
List A (total)	43.4	10.1	42.2	12.5	45.1	11.4	54.4	9.6	5.02	0.003	E, M, D < C
Free short recall	7.9	3.3	8.4	3.3	8.8	3.4	11.6	3.2	4.42	0.006	E, M, D < C
Cued short recall	9.9	3.0	9.7	3.4	10.2	2.7	12.8	2.3	5.15	0.002	E, M, D < C
Free delayed recall	8.6	3.1	8.6	3.5	9.5	3.4	12.6	3.0	7.06	<0.001	E, M, D < C
Cued delayed recall	9.5	3.1	9.8	3.3	10.2	2.9	13.2	2.4	6.93	<0.001	E, M, D < C
Recognition hits	13.1	2.1	13.2	2.1	13.7	2.1	14.9	1.3	4.04	0.009	D, M < C
Wechsler Memory Scale—Revised, logical memory											
Immediate recall	49.0	8.9	50.1	9.5	51.3	10.5	59.3	8.1	4.75	0.004	D, M < C
Delayed recall	44.6	7.9	45.4	9.7	47.5	10.9	55.8	7.2	6.32	0.001	D, M < C
Nonverbal learning and memory											
Wechsler Memory Scale—Revised, visual reproduction											
Immediate recall	55.7	10.7	59.0	11.3	59.6	7.8	66.2	7.1	3.49	<0.02	D < C
Delayed recall	51.2	11.3	54.0	12.1	57.3	7.9	65.1	7.5	6.32	0.001	D, M < C

[a] With control for premorbid intelligence, as measured by the WAIS vocabulary test. D=depressed, M=manic or hypomanic, E=euthymic, and C=healthy comparison. Groups on the left-hand side of the equation had worse neuropsychological performance.
[b] The threshold for significance was p<0.05.

analyses were performed by using the SPSS 10.0 statistical package.

Results

Demographic and Clinical Variables

As shown in Table 1, ANOVAs revealed no significant differences in the subjects' demographic variables regarding sex, age, and educational level, except for estimated premorbid intelligence. The patient groups showed no significant differences in clinical variables. The bipolar patients did not differ by treatment with mood stabilizers, whereas by clinical state, we found statistical differences regarding the use of antipsychotics and antidepressants. Most patients were receiving atypical (N=44) instead of conventional (N=16) antipsychotics. No differences were found between groups with regard to benzodiazepine or antipsychotic type.

Neuropsychological Variables

Neuropsychological performance across manic or hypomanic, depressive, and euthymic bipolar patients and their relation to the healthy comparison subjects is presented in the Table 2. MANOVA yielded Pillai's F=1.66, df= 45, 321, p=0.007 for the main effect, indicating that there were overall differences in neuropsychological performance between the groups. The results revealed the presence of specific cognitive dysfunctions among bipolar patients, regardless of clinical state, after control for estimated premorbid IQ. These results did not substantially change after the introduction of other possible confounding variables, such as age and years of education, so we only introduced as a covariate the estimated premorbid IQ.

For 16 of 19 comparisons, the differences reached statistical significance (p<0.05). Acute and remitted bipolar patients displayed poor performance in the verbal memory

TABLE 3. Relationship of Clinical Features and Functional Outcome to Neuropsychological Performance of Depressed, Manic or Hypomanic, and Euthymic Bipolar Disorder Patients and Healthy Comparison Subjects

	Pearson's Correlation (r)									
Measure	Global Assessment of Functioning	Duration of Illness	Age at Onset	Hospitalizations	Total Episodes	Manic Episodes	Hypomanic Episodes	Depressive Episodes	Mixed Episodes	Suicide Attempts
Wisconsin Card Sorting Test perseverative errors	–0.21*	0.32**	0.01	0.23*	0.10	0.16	0.02	0.07	–0.02	0.08
Trail Making Test A	–0.15	0.28**	0.15	0.05	0.09	0.14	0.02	0.04	0.08	0.25*
Controlled Oral Word Association										
FAS	0.31**	–0.15	–0.21*	–0.01	–0.05	–0.06	0.02	–0.04	–0.08	–0.16
Animal naming	0.12	–0.12	–0.14	–0.14	–0.04	–0.04	–0.01	0.01	–0.13	–0.11
WAIS digit subtest backward	0.23*	–0.16	–0.16	0.01	–0.02	–0.02	0.02	–0.06	0.17	0.06
Wechsler Memory Scale—Revised										
Logical memory										
Immediate recall	0.27*	0.24*	–0.01	–0.19	0.22	–0.12	0.33**	0.28*	–0.03	–0.01
Delayed recall	0.35**	0.13	0.03	–0.12	0.09	–0.13	0.21	0.12	–0.06	–0.08
Visual reproduction										
Immediate recall	0.19	0.12	0.08	–0.08	0.25*	0.09	0.17	0.27*	0.10	0.25*
Delayed recall	0.32**	0.00	–0.04	–0.02	0.15	–0.04	0.19	0.14	0.08	0.11
Stroop interference	0.21*	–0.07	0.01	0.06	–0.05	–0.03	–0.02	–0.05	–0.04	0.07
California Verbal Learning Test										
List A	0.34**	–0.23*	–0.05	–0.22*	–0.05	–0.21*	0.14	–0.04	–0.01	–0.22*
Free short recall	0.33**	–0.29**	–0.02	–0.26**	–0.09	–0.22*	0.13	–0.07	–0.12	–0.21*
Cued short recall	0.25*	–0.26**	0.01	–0.22*	–0.05	–0.24*	0.14	0.00	–0.10	–0.26**
Free delayed recall	0.36**	–0.29**	–0.03	–0.24*	–0.09	–0.26**	0.18	–0.09	–0.07	–0.27**
Cued delayed recall	0.33**	–0.24*	–0.04	–0.24*	–0.07	–0.27**	0.16	–0.03	–0.09	–0.33**
Recognition hits	0.29**	–0.05	–0.02	–0.04	–0.01	–0.06	0.04	0.03	–0.11	–0.15

*p<0.05. **p<0.01.

domain. All patient groups scored lower than the comparison subjects on the California Verbal Learning Test learning task. Short and long delay recall, in both free and cued forms, were significantly poorer in all bipolar groups than in the comparison subjects. The comparison subjects recalled significantly more words than did the patients, regardless of their clinical state. Only the acutely ill patients had significantly poorer performance on the California Verbal Learning Test recognition task in verbal immediate and delayed recall (WMS-R logical memory subtest) and in visual delayed recall (WMS-R visual reproduction subtest) than the comparison subjects. The depressed patients were also impaired in visual immediate recall in relation to the comparison subjects.

All patient groups showed neuropsychological impairment on the Stroop Color and Word Test interference score, as well as in other frontal executive tasks, such as the Wisconsin Card Sorting Test perseverative errors and digit subtest backward subtests, in relation to the healthy comparison subjects. Furthermore, regarding verbal fluency, also related to frontal executive function, the depressed patients had lower scores for phonemic fluency (the FAS subtest) than the other three groups. Moreover, the euthymic and depressed patients scored lower on category fluency (the animal-naming subtest). Finally, the depressed and euthymic bipolar patients scored lower on some attentional tasks (Trail Making Test A) than the comparison subjects.

Correlations Between Variables

Pearson correlations (Table 3) indicated that psychosocial functioning in bipolar patients was associated with neuropsychological measures rather than with clinical variables. No relationship was found between psychosocial functioning and chronicity (duration of illness), total episodes, types of episodes, or numbers of hospitalizations or suicide attempts, whereas social and occupational functioning was related to some measures of frontal executive function (the Stroop Color and Word Test, the Wisconsin Card Sorting Test, the FAS subtest, and the digit subtest backward) as well as to learning and memory tasks (WMS-R subtests and the California Verbal Learning Test). Clinical variables were also associated with neuropsychological measures. Therefore, the patients with a longer duration of illness showed more memory dysfunctions, more slowness or diminished attention (the Trail Making Test A), and committed more perseverative errors (the Wisconsin Card Sorting Test). The numbers of hospitalizations and suicide attempts also were related to memory measures. When we separated different types of episodes, we observed that patients who had suffered more manic episodes showed more cognitive dysfunction in verbal learning and memory.

ANOVAs showed that bipolar patients with previous psychotic symptoms scored lower on the performance of verbal memory measures: logical memory subtest immediate recall ($F=6.97$, $df=1, 97$, $p=0.01$) and delayed recall

(F=8.82, df=1, 97, p=0.004), California Verbal Learning Test learning task (F=15.01, df=1, 102, p<0.001), free short recall (F=22.15, df=1, 102, p<0.001), cued short recall (F=17.87, df=1, 102, p<0.001), free delayed recall (F=15.05, df=1, 102, p<0.001), and cued delayed recall (F=17.37, df=1, 102, p<0.001). The results did not differ when we included only the euthymic patients. The bipolar I patients scored lower than the bipolar II patients in the verbal memory domain, significantly so on the California Verbal Learning Test learning task (F=4.09, df=1, 103, p<0.05) and in free (F=5.02, df=1, 103, p<0.03) and cued (F=5.28, df=1, 103, p<0.03) short recall. No differences regarding neuropsychological measures were found between groups regarding lithium treatment, which was the most used mood stabilizer among the patients.

Occupational functioning was analyzed among the patient groups, and no significant differences were found (χ^2=2.51, df=2, p=0.29). Hence, neuropsychological performance between patients showing "good" and "poor" occupational functioning was analyzed by using ANOVA. Significant differences were found between groups, so the patients with better occupational functioning performed better on the FAS (F=5.93, df=1, 102, p<0.02) and on all measures of verbal memory (California Verbal Learning Test): list A (F=13.73, df=1, 105, p<0.001), free short recall (F=12.99, df=1, 105, p<0.001), cued short recall (F=10.95, df=1, 105, p=0.001), free delayed recall (F=14.84, df=1, 105, p<0.001), cued delayed recall (F=13.49, df=1, 105, p<0.001), and recognition hits (F=8.36, df=1, 105, p=0.005).

Linear regression analysis with hierarchical methods showed that psychosocial functioning was associated with affective symptoms (the Hamilton depression scale and the Young Mania Rating Scale) (t=–5.63, df=95, p<0.001). In the subsequent block, neuropsychological variables were introduced stepwise. Only the California Verbal Learning Test learning task appeared in the equation (t=2.95, df=95, p=0.004); overall, the model reached significance (F=20.58, df=3, 95, p<0.001).

Discussion

Cognitive Impairment in Bipolar Disorder

The three groups of bipolar patients displayed worse performance than the comparison group, mainly on measures of verbal memory and executive functioning.

The manic or hypomanic, depressed, and euthymic patients performed poorer on new learning as well as on recall than the comparison subjects, even when semantic cues were provided to enhance the recovery of information. These results suggest that verbal learning and memory seem to be impaired in bipolar disorder, independently of clinical state, so that problems in encoding and also probably in the retrieval of verbal information are involved. Furthermore, the acutely ill patients showed statistical differences from the comparison group regarding recognition memory. These results suggest that complex memory processes seem to be impaired in remitted patients. Furthermore, acutely ill patients score lower on the performance of simpler memory tasks. The impairment of verbal memory has been also found in other studies of acute (35, 36) and remitted states (6, 8, 9). Deficits in verbal memory, especially in retrieval, suggest the implication of frontal structures, whereas encoding impairment is interpreted as dysfunction of the medial temporal lobe (36, 37). On the other hand, significant diminished performance on the Stroop interference task was found in all bipolar groups, which reflects deficits of selective attention and executive function, in relation to the healthy comparison subjects. Trichard et al. (38) previously reported that Stroop test performance did not totally improve with recovery from depression, whereas other authors have suggested that performance is preserved in euthymic bipolar patients (6). Furthermore, bipolar patients had lower scores in other measures of frontal executive function, such as the digit subtest backward and perseverative errors task (Wisconsin Card Sorting Test), as has been previously reported (6, 13). In verbal fluency, the depressed group showed more impairment in letter fluency than the other groups (38, 39). Tukey post hoc comparisons failed to distinguish acutely ill and remitted bipolar patients in several neuropsychological measures, which supports the hypothesis of enduring cognitive impairment during euthymic periods. Nevertheless, some distinctions on the pattern of neuropsychological performance between the bipolar groups have been detected, as noted previously.

Clinical Features, Psychosocial Functioning, and Cognitive Function

Performance on verbal learning and memory tasks significantly correlated with psychosocial functioning, chronicity, and the numbers of hospitalizations and suicide attempts, as well as with the number of manic episodes. Several authors have found a negative correlation between the number of previous manic episodes and verbal learning (9, 10). In this regard, the bipolar I patients showed more verbal memory impairment than the bipolar II patients. Our data suggest the relevance of preventing manic episodes, since they probably have a greater impact on cognitive functioning (6, 9, 14–16). On the other hand, the patients with previous psychotic symptoms had poorer performance in verbal memory tasks, regardless of their current clinical state. Psychotic features have been described to have an effect on cognitive function (40) and have been related to a more severe and chronic course of the illness (18). The number of hospitalizations has been associated with poor cognitive functioning by other authors (41, 42).

Likewise, after control for low levels of symptoms, the patients with difficulties retaining information had a poorer functional outcome. Furthermore, when occupational functioning was analyzed, the patients with poorer functioning had more deficits in verbal memory, and in

verbal fluency, which is consistent with findings regarding use of the GAF.

Disturbances in verbal learning and memory may limit the response to pharmacological treatment, most likely by means of poor compliance (43). Moreover, difficulties in storing and retrieving new information may limit the benefits from psychological interventions. Temporal limbic structures regulate mood and memory processes, so theories such as the sensitization/kindling model (44) could explain the deficits of learning and memory as well as more relapses in bipolar patients, as have been previously reported (5). The existence of frontal executive dysfunctions in bipolar disorder cannot be roundly confirmed in our study because impairment was found on several (Stroop Color and Word Test interference, digit subtest backward, and verbal fluency tasks) but not all measures (Trail Making Test B), probably in part because of data dispersion. The frontal lobes, especially the prefrontal cortex, are probably involved in neuropsychological performance in at least a subset of bipolar patients.

Therapeutic Interventions

Psychotherapeutic approaches should integrate these difficulties in order to improve the quality of life of bipolar patients. Neuropsychological dysfunctions should be taken into account in their pharmacological treatment in order to use medications with fewer cognitive side effects. With respect to lithium, differences between patients were not found in those taking and not taking lithium. A longitudinal study (45) showed stable cognitive performance over a 6-year follow-up period. Regarding anticonvulsants, research has found little evidence of cognitive impairment (46), although concentration problems have been described with the use of valproate or carbamazepine (47). With respect to antipsychotics, the use of conventional neuroleptics may have a detrimental effect on motor functioning with short-term administration and sometimes may have a beneficial effect on vigilance and visual processing with long-term administration. Most authors indicate that antipsychotics probably do not improve cognitive functioning but do not worsen it either. Furthermore, deficits are usually more related to anticholinergic medication than to antipsychotics, and only three of our patients were taking anticholinergics. Most of them were taking atypical antipsychotics. Probably, newer antipsychotic drugs would improve cognitive deficits more than typical antipsychotics (48, 49), especially as maintenance treatment in patients with predominantly manic episodes. Thus, olanzapine have been demonstrated to decrease rates of relapse into manic episodes better than lithium (50). With regard to antidepressants, research also indicates that they are not related to cognitive dysfunction (51). More mood stabilizers that ameliorate depression are needed (52), either alone or combined with other agents, to treat subsyndromal features, that may involve worse cognitive and functional outcome. Early diagnoses and accurate treatments, either pharmacological or psychological, should be established to prevent manic episodes and psychotic features that can result in long-term cognitive function impairment. The main goal of the therapy should be to satisfy the need for lifelong effective treatment and the achievement of full remission (20).

Limitations

Among the limitations of the present study is that the group sizes should have been larger in order to demonstrate significant differences more clearly. There are some baseline differences in premorbid IQ between the groups. The battery of neuropsychological tests should have assessed more widely attentional processes that are superficially examined, taking into account that evidence of implications of sustained attention impairment in bipolar disorder have been recently reported in euthymic patients (10). It is likely that attentional abilities also may be impaired in remitted bipolar patients. Impairment on the Trail Making Test A and the Stroop Color and Word Test was found in acute and remitted patients, but this was not enough to confirm attentional deficits. On the other hand, the lack of reaction time measures in the present study represented a limitation, especially in trying to establish differences between acutely ill and remitted patients. Interpretation of the results is sometimes difficult from the neuropsychological point of view because of overlap between the cognitive functions assessed by each test. All patients were taking medication. Although there were no baseline differences among the groups concerning mood stabilizers, one cannot exclude the influence of drugs on the results, particularly as far as differences between the patients and comparison subjects were concerned. Moreover, differences regarding antipsychotics and antidepressants were found among groups in relation to clinical state. The lack of significant association between lithium and cognitive disturbances may be related to the number of patients in our sample which was too small to provide statistical power. The best way to establish whether cognitive impairment is related to illness and not to medication would be the inclusion of drug-free or drug-naive bipolar patients, but drug-free euthymic patients are rarely found. On the other hand, most patients receive combined treatments and enrolled in studies of varying dosages. Our study was cross-sectional, so further longitudinal designs may help to ascertain whether cognitive impairment constitutes a trait rather than a state in bipolar disorder and to determine neuropsychological profiles.

Clinical Implications

The clinical implications of the persistence of cognitive dysfunctions are chronicity, treatment noncompliance, and poor social outcome (20). Disability and poor outcome, as well as cognitive dysfunctions, have been associated with schizophrenia rather than with bipolar disorder, but there are progressively more signals of cognitive and

psychosocial impairment in bipolar disorder (8, 13, 19, 53). Our study indicates that poor functional outcome is related to cognitive dysfunction and that these dysfunctions are also observable in remitted patients.

Future Directions

More research on first-episode patients and high-risk populations and long-term follow-up studies are required to answer several questions: Are cognitive dysfunctions present before illness onset? Is cognitive impairment stable or progressive? Which is the real impact of medication on the cognitive functioning of these patients? Rehabilitation programs should be adapted to cognitive impairment profiles in bipolar disorder. These programs should explore benefits over other clinical and therapeutic aspects, such as insight, compliance, or response to psychological interventions.

Conclusions

In conclusion, a poorer performance was observed in all bipolar groups with regard to verbal memory and executive function in relation to healthy comparison subjects, suggesting stability or chronicity of cognitive deficits. Specific cognitive functions are impaired in bipolar patients and seem to resemble those of schizophrenia patients, although cognitive disturbances probably are more marked in schizophrenia (19). Patients with a history of psychotic symptoms, bipolar I type, a longer duration of illness, and a large number of manic episodes are more likely to show neuropsychological disturbances. These cognitive difficulties in bipolar patients, especially related to verbal memory, may help explain the impairment in daily functioning, even during remission. Prevention of relapse through a suitable prophylactic treatment and psychoeducation (54) might help reduce or prevent cognitive impairment in bipolar patients. These patients may benefit from neuropsychological rehabilitation to minimize the effect of cognitive dysfunction on their overall functioning.

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