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Brief Report

Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence

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Objective: To determine if the repeated occurrence of manic episodes in bipolar I disorder (BD-I) patients is associated with reduced cognitive performance, which could in turn imply a worsening in the disorder's evolution.

Method: Cognitive performance in euthymic patients was assessed using attention, memory, and executive function tests on 24 BD-I patients who had experienced only 1 manic episode, on 27 BD-I patients with 2 manic episodes, on 47 BD-I patients with 3 or more manic episodes, and on 66 healthy control subjects.

Results: In BD-I patients, number of manic episodes was positively associated with poorer performance on neurocognitive tests, an association that was not accounted for by depression, disease chronicity, onset, or medication. Significant differences in attention and executive function were found between patients and controls and in those patients who had had just 1 manic episode compared to those who had 3 or more.

Conclusion: The number of manic episodes predicted poor cognitive performance, suggesting that the recurrence of mania may have a long-term neuropsychological impact. Prospective follow-up studies need to be completed to explore this effect further as better treatment adherence may have a protective effect on neurocognitive function.

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Bipolar I disorder (BD-I) patients have been often reported as having alterations in neurocognitive functioning, which appear during both acute stages and euthymic periods (1–3). Such reductions in cognitive function have been found mainly in attention, executive function, and memory (4–9), with significant psychomotor slowing also having been observed (10). However, the affected cognitive domains are not consistent in all studies (11, 12), probably due to methodological differences and the influence of clinical variables that could affect cognitive performance.

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For this reason, our research group has focused on various clinical characteristics and their relation to cognitive function, such as the relationship between the previous course of bipolar disorder and the degree of cognitive impairment when tested in the euthymic state. In this vein, previous research has reported that euthymic subjects drawn from a mixed group of bipolar disorder and unipolar disorder patients with impaired cognitive functioning had more previous hospitalizations than those with normal cognitive performance (13). A further study found that the number and duration of manic episodes throughout patients' lives correlated with poorer performance on executive function tests and that the duration of mania or depression immediately prior to neurocognitive assessment correlated with poorer performance on verbal memory tasks (14).

It has been reported that impairment in cognitive performance may be already present from the onset of the disorder. Patients with bipolar disorder, in contrast to control subjects, have a lower performance in neuropsychological tests from the moment they have their first acute episode (15). Similarly, deficits in attention and executive functioning have been reported in young people who have experienced only a few episodes of bipolar disorder (16). As well as manic episodes, there is a possibility that BD-I related depression has an influence on neuropsychological function. A recent meta-analysis on the effect of depression severity on cognitive performance found reductions in episodic memory, executive function, and processing speed on both timed and untimed tests (17), and prior studies in patients with bipolar disorder have found a negative relationship between number of depressive episodes and cognitive function (e.g., 14, 18), although these studies have typically not tried to distinguish the effects of manic and depressive episodes.

Indeed, the relationship between the recurrence of acute episodes in patients with BD-I and their performance on neurocognitive tests is not fully clear, since many of these studies have been subject to a number of confounding factors, such as the inclusion of noneuthymic patients or patients with residual mood symptoms, the failure to distinguish between BD-I and bipolar II disorder (BD-II) patients, use of too small a sample size, or failure to analyze the effect of medication on neuropsychological assessment results or to establish the effect size (ES) of the differences found.

Assessing cognitive performance of BD-I patients becomes more important when trying to determine if BD-I has a close relationship with functional adaptation. With regard to this issue, it has been found that patients with lower functionality, indicated by low occupational adaptation, show lower cognitive performance, particularly in verbal memory and executive function measurements (19). Low performance in the aforementioned cognitive functions has been reported to correlate with poor psychosocial functioning, higher chronicity, number of hospitalizations, and number of suicide attempts (5).

In order to determine whether or not cognitive impairment is associated with recurrence of manic episodes, this cross-sectional study included healthy controls, grouped patients by the number of experienced manic episodes, and aimed to control for a number of crucial clinical and demographic variables. Importantly, we aimed to include patients that had at least one single manic episode, which is required for BD-I diagnosis. This allowed us to compare the cognitive performance of each group of patients and to identify the differences among patients with a different number of episodes. We hypothesised that the number of manic episodes would be inversely correlated with cognitive function, so poorer neuropsychological test results would be found in patients compared to controls and in patients with higher numbers of manic episodes in comparison to patients with fewer.

Patients and methods

Participants

We assessed 98 BD-I patients and 66 healthy controls. They were all evaluated by a psychiatrist who performed the Diagnostic Interview for Genetic Studies (DIGS), which has been confirmed as a valid and reliable diagnostic measure in a Spanish-speaking population (20). This evaluation was used to confirm that patients fulfilled the DSM-IV criteria for this disorder. All patients reported being euthymic for at least six months, confirmed by clinical record review, and the presence of residual affective symptoms was controlled for, as they needed to score < 8 on the Hamilton Depression Rating Scale (HDRS) (21) and < 6 on the Young Mania Rating Scale (YMRS) (22).

Patients. All BD-I patients who fulfilled the inclusion criteria from a local mood disorders clinic were invited to participate in the study. The recruited patients were divided into three groups, according to the number of acute mixed or manic episodes they had experienced: (i) 24 subjects with only 1 manic episode; (ii) 27 individuals with 2

manic episodes; (iii) 47 individuals with 3 or more manic episodes.

None of the case groups included individuals who had consumed illicit substances or benzodiazepines during the four weeks prior to the assessment or individuals with background data on other psychiatric or neurological disorders that could relate to neuropsychological alteration, such as epilepsy, mental retardation (IQ < 70), or any treatment with electroconvulsive therapy. Individuals with physical or sensory limitations that could affect their performance during the evaluation were also excluded. All subjects had to be between 18 and 60 years of age and have had 5–16 years of schooling, which restricts the influence of potential illiteracy on neuropsychological performance.

All subjects with BD-I were outpatients at the mood disorders program of the University of Antioquia's School of Medicine, at the University Hospital San Vicente de Paúl in Medellín, Colombia. The research protocol used was approved by the Ethics Committee, and all participants read, understood, and signed an informed consent form before being assessed.

Control subjects. We assessed 66 first-degree relatives, who complied with the same exclusion criteria used for the other participants, with the DIGS to confirm the absence of psychopathology.

Materials and procedures

After the psychiatric interview, all four subject groups were assessed by means of a neuropsychological test battery whose execution took approximately two hours. Every individual chose a day and a time in which he or she felt physically and mentally suitable for such assessment. Standard instructions were used for all subjects, and breaks of 15 minutes were taken in order to prevent biases related to mental fatigue. All tests were carried out in a quiet office, with proper lighting and with as few distractions as possible.

The Wechsler Adult Intelligence Scale (WAIS) (23) was used to determine the participants' intellectual capacity. Furthermore, other tests were used for neurocognitive assessment which measure performance on attention, executive function, memory, and psychomotor speed, which are the cognitive functions that commonly show some kind of alteration in bipolar disorder patients (2, 11).

Attention. Attention was assessed by means of the Continuous Visual Execution Test, also known as A Cancellation Test (24). The Trail Making Test-part B (TMT-B) was used as a measure of executive control (25) together with the Stroop Colour Word Test (26), which also provides information about the capacity to inhibit automatic responses.

Executive function. Executive function was assessed by the short version of the Wisconsin Card Sorting Test (WCST) (27), the Semantic Verbal Fluency Test, and the Phonological Verbal Fluency Tests (28).

Memory. *Verbal memory* was assessed using the test for associative memory with semantic increase (29), which provides information about learning and storing capacity when a verbal stimulus is associated with its visual representation, and short- and long-term recall with keys. *Visual memory* was assessed by the visual reproduction subtest of the Wechsler Memory Scale (WMS) (30) and the immediate recall of the Rey figure for more complex stimuli (31). *Working memory* was assessed by the digits-backward subtest and the digits-forward subtest of the WMS (30), which provided us with information about immediate memory. The *logical memory* subtest of the WMS was also used for both free and cued recall (30).

Psychomotor speed. Different tests were used to determine the processing speed. The main one was the digit-symbol subtest of the WAIS, which also provides information about attentional capacity (23). Other instruments were the Trail Making Test-part A (TMT-A) and TMT-B (25), the Continuous Visual Execution Test (24), and the word-color interference test from the Stroop Test.

Data analysis

To describe the subjects participating in the study, frequency measurements and percentages were used for the qualitative variables (gender and psychiatric medication), and central tendency and dispersion measurements for continuous variables, including age, schooling level, number of total depressive and manic episodes, intellectual coefficient, and the clinical scales to assess manic and depressive symptoms.

The normality assumption was checked with the Kolmogorov-Smirnov test ($n > 50$) or Shapiro Wilk test ($n < 50$), and the homogeneity of variance assumption with Levene's test. Comparison of patient groups versus controls was carried out using Mann-Whitney *U*-tests. Comparison of between-patient groups was conducted using an analysis of covariance (ANCOVA) that allowed

variance from clinical factors to be partialled out in the comparison. Because ANCOVA does not allow standard post-hoc tests used in analysis of variance (ANOVA), post-hoc tests were also completed using Mann-Whitney *U*-tests. To help control for multiple comparisons, a corrected p value < 0.01 was chosen to indicate significance, with a p value < 0.05 indicating a trend to significance. The ES was estimated by considering an ES > 0.70 to be significant (32). All statistical analysis was carried out using SPSS, version 15.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical and demographic characteristics

Table 1 describes the social, demographic, and clinical data of all participants. Patients with multiple episodes had a trend to earlier disease onset ($p = 0.026$) as well as higher chronicity ($p = 0.008$) and a greater number of psychiatric hospitalizations ($p < 0.001$). No significant differences were found between the groups in terms of level of education or in HDRS score. The scores on the YMRS show a trend to significance ($p = 0.020$), but the values fall within the normal range of the general population. Additionally, the scores on these two scales confirm the absence of important residual affective symptoms in both patient groups.

The distribution of substance abuse problems was not significantly different from chance when tested with a Pearson chi-square test when comparing both cases and controls ($\chi^2 = 2.765$, $p = 0.656$) or between cases divided into groups of 1, 2, and 3 or more manic episodes ($\chi^2 = 7.862$, $p = 0.458$), suggesting that the groups were not differentiated by history of prior substance abuse. The distribution of medication types between patient groups did not significantly differ from chance when compared with a chi-square test (lithium: $\chi^2 = 2.982$, $p = 0.225$; carbamazepine: $\chi^2 = 1.034$, $p = 0.596$; valproate: $\chi^2 = 2.891$, $p = 0.236$; antipsychotics: $\chi^2 = 1.156$, $p = 0.561$; antidepressants: $\chi^2 = 1.054$, $p = 0.591$). In the patient sample, a Kruskal–Wallis test found no significant effect of grouping by manic episodes on the number of depressive episodes ($\chi^2 = 8.677$, $p = 0.260$).

Additionally, the distribution of relationship and employment status was not significantly different from chance between cases and controls (relationship: $\chi^2 = 5.209$, $p = 0.391$; employment: $\chi^2 = 3.325$, $p = 0.344$) or between patients divided by manic episodes (relationship: $\chi^2 = 8.677$, $p = 0.370$; employment: $\chi^2 = 4.683$, $p = 0.585$). There was a significant effect of group on IQ when examined using a between-subjects ANOVA [$F_{(3,137)} = 5.239$, $p = 0.002$]. However, the ES was small ($\eta^2 = 0.102$), and all mean scores fell within the normal range (control mean = 99.5, SD = 14.2; 1-episode mean = 96.2, SD = 14.7;

Table 1. Social, demographic, and clinical characteristics

	1 episode (n = 24)	2 episodes (n = 27)	≥ 3 episodes (n = 47)	Controls (n = 66)
Sex, n (%)				
Male	16 (66.6)	16 (59.3)	32 (68.1)	44 (66.6)
Female	8 (33.3)	11 (40.7)	15 (31.9)	22 (33.3)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, years	37.04 (10.19)	39.11 (7.61)	39.26 (8.79)	37.44 (8.57)
Education, years	10.92 (3.79)	9.00 (3.74)	9.13 (3.05)	9.61 (3.28)
Total episodes	2.33 (1.63)	2.59 (0.69)	8.51 (8.31)	
Depressive episodes	1.33 (1.74)	0.54 (0.71)	2.45 (5.50)	
Age of onset, years	25.79 (9.98)	27.37 (7.12)	23.00 (8.37)	
BD-I history, years	12.79 (10.66)	11.70 (7.72)	16.13 (10.98)	
No. of hospitalizations	1.33 (0.87)	2.19 (1.33)	5.04 (3.96)	
HDRS score	1.13 (1.15)	1.48 (1.12)	1.23 (1.09)	1.11 (1.01)
YMRS score	1.21 (1.50)	1.00 (1.39)	0.76 (1.16)	0.55 (1.13)
IQ	96.24 (14.7)	95.76 (15.5)	88.64 (10.89)	99.53 (14.2)
Medications, n (%)				
Lithium	7 (29.17)	7 (25.93)	21 (44.68)	
Carbamazepine	1 (4.17)	0 (0)	1 (2.13)	
Sodium valproate	7 (29.17)	3 (11.1)	7 (14.89)	
Antipsychotic	3 (12.5)	1 (3.7)	4 (8.51)	
Antidepressant	0 (0)	1 (3.7)	2 (4.26)	

BD-I = bipolar I disorder; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

2-episode mean = 95.8, SD = 15.5; 3-episode mean = 88.6, SD = 10.9).

Cognitive performance

Table 2 shows the performance of both patients and normal controls on the various neuropsychological tests. Figure 1 shows the differences between the groups of patients as well as the ES for the differences. Figure 2 shows the differences between the group of patients and the control group as well as the ES for the differences.

Cases versus controls. When comparing each case group with the control group using Mann–Whitney *U*-tests, we found that patients with only 1 manic episode show only a significant difference in working memory as shown by the digits-backward subtest of the Wechsler scale ($p = 0.005$; ES = 0.73). Patients with 2 manic episodes perform even more poorly in comparison to controls, showing deficits on the digits-backward subtest ($p = 0.003$; ES = 0.74), short-term visuo-verbal episodic memory with semantic association ($p < 0.001$; ES = 1.11), delayed recall ($p < 0.001$; ES = 1.13), logical memory recognition ($p < 0.001$; ES = 0.92), and phonological verbal fluency ($p = 0.002$; ES = 0.71). Finally, the group with 3 or more episodes shows a greater range of impairment and large ES, demonstrating deficits in short-term visuo-verbal episodic memory with semantic association ($p < 0.001$; ES = 1.06), long-term recall ($p < 0.001$; ES = 1.12), logical memory recognition ($p < 0.001$; ES = 1.00), and several executive function-related measures, including semantic verbal fluency ($p < 0.001$; ES = 0.86), phonological verbal fluency ($p < 0.001$; ES = 0.87), and Stroop test interference, where differences are found both in execution time ($p = 0.002$; ES = 0.75) and in error rate ($p = 0.007$; ES = 0.70). Additionally, this group also showed psychomotor slowing in tests of executive attention, such as TMT-B ($p < 0.001$; ES = 0.73) and the WAIS digit symbol-coding subtest ($p < 0.001$; ES = 0.96).

Group of patients with 1, 2, and 3 or more manic episodes. As disease onset, chronicity, and score on the YMRS were found to show trends to significance or to be significantly different between patients with 1, 2, or 3 or more manic episodes, these were included as covariates in the ANCOVA analysis. Although number of hospitalisations was found to differ significantly between these groups, as expected, this variable is highly correlated with manic episodes ($r = 0.797$, $p < 0.0001$) and so was not included as a covariate as it largely reflected the same source of variance. Although no significant difference was found between the number of depressive episodes between mania groups, to ensure fully that the results distinguish between the effects of mania and depression, the number of depressive episodes was also included as a covariate.

In the ANCOVA analyses, main effects for episode number were found for TMT-A [$F_{(6,89)} = 8.591$, $p < 0.0001$], semantic verbal fluency [$F_{(6,89)} = 5.249$, $p < 0.007$], phonological verbal fluency [$F_{(6,89)} = 4.334$, $p < 0.016$], Stroop interference errors [$F_{(6,89)} = 4.563$, $p < 0.013$], time [$F_{(6,89)} = 5.130$, $p < 0.008$], and WAIS digit symbol coding [$F_{(6,89)} = 6.136$, $p < 0.003$]. When comparing the three case groups with one another using post-hoc Mann-Whitney *U*-tests, significant differences in cognitive performance were found between the 1-episode group and the group with patients who have had 3 or more manic episodes in executive function variables, such as verbal semantic fluency ($p = 0.002$; ES = 0.72) and psychomotor speed assessed by TMT-A ($p = 0.005$; ES = 0.73) and by the WAIS digit symbol coding ($p = 0.008$; ES = 0.78). Also, other differences between these two groups were found in other executive function variables, such as phonological verbal fluency ($p = 0.008$; ES = 0.62) and in the variables of the interference component of the Stroop test both in its execution time ($p = 0.036$; ES = 0.57) and in the number of mistakes ($p = 0.037$; ES = 0.51). Differences of a medium ES have also been observed in memory, as shown in visuo-verbal episodic memory with associative semantic in short-term recall ($p = 0.029$; ES = 0.41), long-term recall ($p = 0.028$; ES = 0.45), and WMS logical memory ($p = 0.043$; ES = 0.41).

The differences between patients with 1 manic episode and those with 2 episodes are only significant in the WMS forward and backward digits ($p = 0.046$; ES = 0.65). Likewise, when comparing the group of patients with 2 manic episodes to the group with 3 or more episodes, the only difference is the number of mistakes they made in the conflict component of higher regular intake of lithium on the Stroop test ($p = 0.022$; ES = 0.64).

Discussion

The aim of this study was to determine the relationship between number of manic episodes in BD-I patients and their neurocognitive performance. We found that the higher the number of episodes, the poorer the patients' performance,

Table 2. Neuropsychological results

	1 episode Mean (SD)	2 episodes Mean (SD)	3 episodes Mean (SD)	Controls Mean (SD)	Covariate p-values				Dependent variable p-value
					Depressive episodes	Age onset	Chronicity	YMRS	Manic episodes
TMT-A time	52.50 (18.27)	60.89 (18.08)	74.94 (35.40)	55.89 (19.99)	0.006	0.015	0.043	0.990	0.000
TMT-B time	127.67 (90.48)	154.52 (99.12)	160.15 (91.05)	106.95 (55.88)	0.150	0.789	0.550	0.291	0.266
Semantic Verbal Fluency	17.60 (3.21)	16.52 (3.80)	5.20 (3.08)	18.08 (3.53)	0.033	0.024	0.437	0.725	0.007
Phonological Verbal Fluency	11.23 (2.94)	9.80 (3.32)	9.32 (3.17)	12.31 (3.64)	0.006	0.171	0.375	0.352	0.016
Continuous performance test	31.21 (12.35)	31.15 (8.52)	33.34 (11.19)	27.20 (7.93)	0.013	0.760	0.172	0.851	0.411
Semantic memory with Associative Increment Test									
First recall	8.33 (2.10)	7.96 (3.08)	7.49 (2.28)	9.67 (2.76)	0.072	0.493	0.184	0.615	0.307
Cued short recall	12.83 (2.39)	11.70 (2.69)	11.87 (2.33)	14.06 (1.86)	0.110	0.694	0.104	0.668	0.204
Cued delayed recall	12.75 (2.54)	11.59 (2.72)	11.62 (2.50)	14.03 (1.89)	0.170	0.824	0.048	0.879	0.197
Rey figure–immediate recall	14.79 (5.09)	12.41 (5.35)	13.44 (6.65)	18.33 (10.98)	0.016	0.526	0.976	0.119	0.378
Wisconsin Card Sorting Test (short version)									
Categories	2.67 (1.24)	2.56 (1.12)	2.36 (1.41)	2.79 (1.21)	0.268	0.906	0.113	0.798	0.675
Perseverative responses	19.29 (8.61)	18.26 (8.71)	20.83 (8.65)	16.56 (6.74)	0.402	0.290	0.129	0.806	0.512
Total perseverative errors	26.42 (8.37)	28.26 (9.29)	29.26 (8.37)	25.17 (7.42)	0.394	0.757	0.125	0.695	0.566
Wechsler Memory Scale									
Logical memory	8.92 (2.78)	8.57 (3.07)	7.70 (3.05)	10.05 (3.64)	0.021	0.351	0.836	0.466	0.114
Forward digits	5.42 (0.97)	4.81 (0.88)	5.23 (1.00)	5.39 (1.14)	0.073	0.471	0.600	0.050	0.101
Backward digits	3.08 (1.06)	3.07 (1.07)	3.26 (0.94)	3.83 (1.02)	0.315	0.801	0.594	0.346	0.805
Visual reproduction	7.71 (3.38)	7.30 (2.78)	7.19 (2.82)	8.70 (2.83)	0.032	0.406	0.259	0.787	0.612
Associated pairs	13.69 (4.15)	12.69 (3.38)	12.90 (4.46)	14.86 (3.46)	0.009	0.995	0.399	0.140	0.425
Logical memory–recognition	17.29 (3.13)	16.52 (2.29)	15.83 (3.33)	18.53 (2.14)	0.070	0.433	0.111	0.025	0.078
Stroop Test–conflict mistakes	2.25 (2.95)	1.85 (2.01)	4.45 (4.80)	2.02 (2.00)	0.048	0.604	0.100	0.834	0.013
Stroop Test–conflict time	65.04 (11.91)	67.00 (18.25)	77.94 (26.49)	62.91 (13.78)	0.022	0.939	0.673	0.347	0.008
WAIS–digit symbol	38.63 (12.37)	33.19 (11.8)	30.26 (9.70)	40.92 (12.03)	0.066	0.462	0.308	0.096	0.003

TMT-A = Trail Making Test-part A; TMT-B = Trail Making Test-part B; WAIS = Wechsler Adult Intelligence Scale.

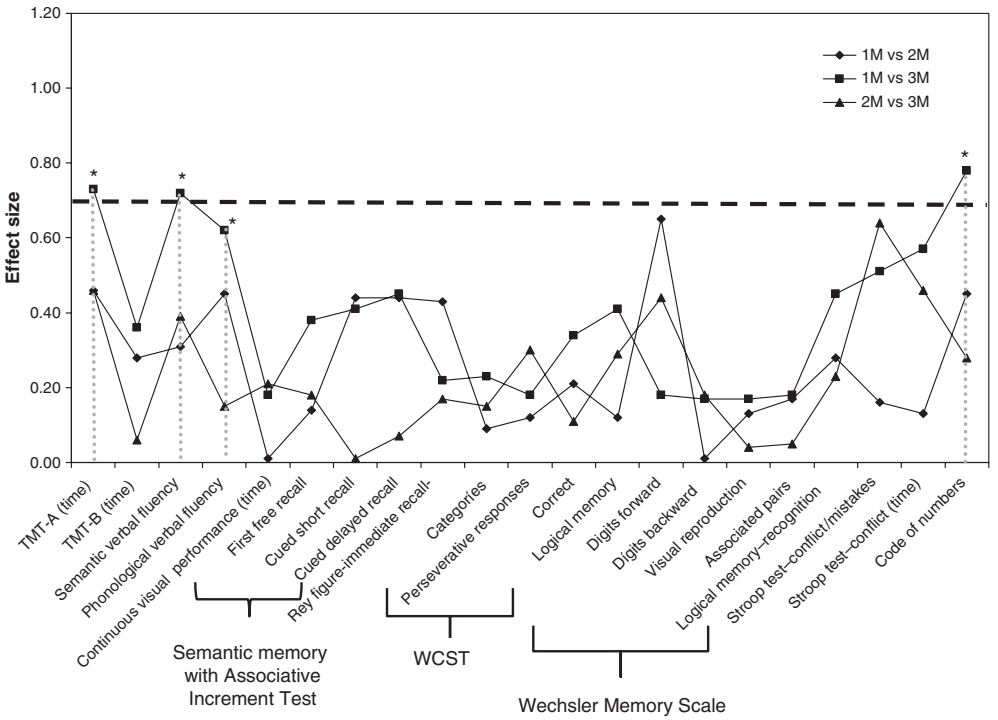

Fig. 1. Differences on neurocognitive performance between groups of patients. ES (effect size) > 0.70. TMT-A = Trail Making Test-part A; TMT-B = Trail Making Test-part B; WCST = Wisconsin Card Sorting Test; 1M vs 2M = 1 manic episode versus 2 manic episodes; 1M vs 3M = 1 manic episode versus 3 manic episodes; 2M vs 3M = 2 manic episodes versus 3 manic episodes. *p < 0.01.

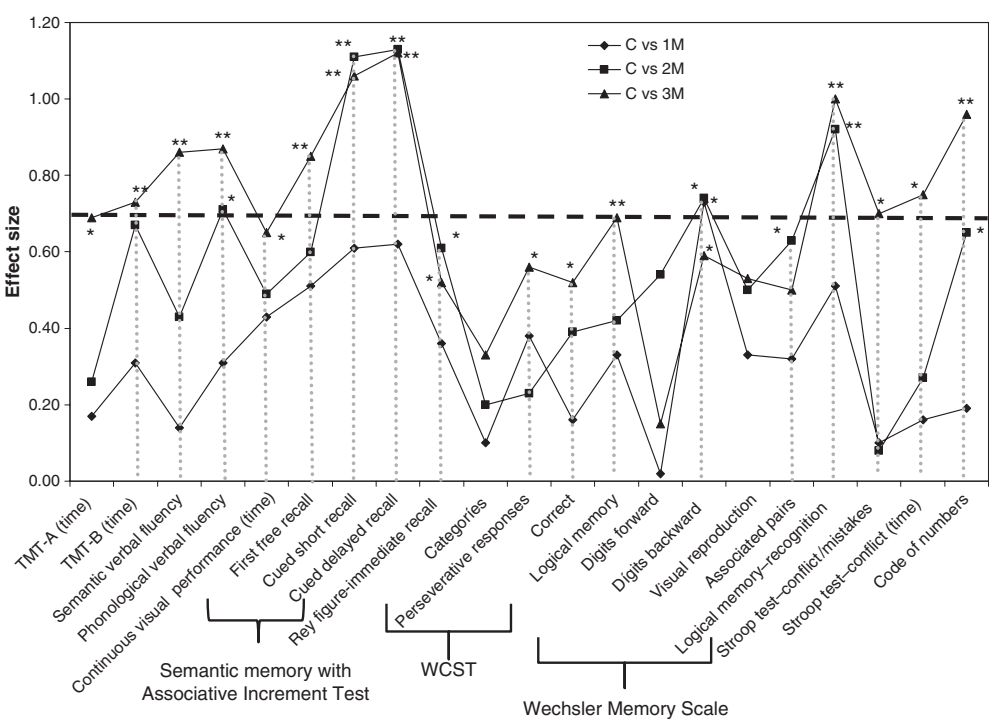

Fig. 2. Differences on neurocognitive performance between groups of patients and control group. ES (effect size) > 0.70. TMT-A = Trail Making Test-part A; TMT-B = Trail Making Test-part B; WCST = Wisconsin Card Sorting Test; C vs 1M = controls versus 1 manic episode; C vs 2M = controls versus 2 manic episodes; C vs 3M = controls versus 3 manic episodes. *p < 0.01; **p < 0.001.

both when the patient groups were compared with one another with relevant clinical factors included as covariates and when they were compared with the control group. This suggests that recurrence of manic episodes is specifically associated with cognitive impairment, mainly evidenced by deficits in executive function, episodic memory, and reduced psychomotor slowing.

To date, we have found no studies whose aim was specifically to determine the effect that recurrence of manic episodes has on neurocognitive performance. However, some studies have analyzed the relationship between neurocognition and total number of episodes, as well as the relationship between neurocognitive performance and other variables which indicate a worsening of the disorder. It has been reported that duration of episodes of mania or depression correlates negatively with performance on verbal memory and on several executive function measurements (14). Likewise, it was also found that a more severe course (greater number of episodes, longer duration of the disease, more hospitalizations) is related to poorer performance on memory, attention, and abstraction tasks (33).

The findings of a more recent study (34), which compared the performance of 16 BD-I patients with one acute episode, 30 BD-I patients with multiple acute episodes, and 20 healthy controls, provides more limited support for the hypothesis that number of episodes is related to cognitive impairment. The single-episode group tended to perform significantly worse than the multiepisode group, although the latter did show an impairment in the number of perseverative answers on the WCST when compared to single-episode patients. However, the small sample size or the influence of uncontrolled variables, such as pharmacological treatment, may explain the discrepancy with this study that did control for these possible confounding factors. In contrast, similar studies have provided more support for the idea that number of episodes and cognitive dysfunction are linked in BD-I. Studies by Thompson et al. (10) and Zubieta et al. (18) found that executive function deficits were frequent and that higher numbers of manic and depressive episodes in BD-I patients correlated with lower performance on executive function tests.

In addition to executive function deficits detected by the WCST, this present study reported a decrease in semantic verbal fluency (phonological verbal fluency showed a trend to significance) with a large ES in the comparison between controls and patients with 2 and 3 or more manic episodes, and between patients with 1 and patients with 3 or more manic episodes. This test is known to rely on both verbal and executive abilities, in contrast to the nonverbal WCST, making it a good indicator of the presence of additional executive difficulties. Furthermore, manic episodes were related to an increase in time needed to complete both the TMT-A and the Stroop conflict condition. Along with the significantly reduced digit-symbol coding performance, this suggests that processing speed—particularly related to executive tasks—is also impaired, indicating a general pattern of reduced executive/attentional control. Owing to the reliance of verbal and visual recall on executive function, it is not clear to what extent the significant differences in verbal free recall and Rey figure tests between controls and patient groups are due to primary executive impairments or reductions in the function of more fundamental memory mechanisms.

These findings can be tentatively interpreted in light of studies on neuroanatomical differences in BD-I patients. Indeed, it has been suggested that acute episodes may lead to neuropathology (35). A structural magnetic resonance imaging (MRI) study by Strakowski et al. (36) examined this hypothesis in 17 patients with multiple episodes and 32 healthy controls, finding that patients with a higher number of manic episodes had larger lateral ventricles, which did not seem to be secondary to the fact that periventricular structures were smaller, with the additional finding that first-episode patients had a larger than average striatum and putamen. These findings are in line with previous studies in which patients with first episode or adolescent patients had larger ventricles than healthy patients (37, 38). Differences in lateral ventricle structure seem to be common among BD-I patients: the left lateral ventricle was found to be larger in BD-I patients than in BD-II patients. Indeed, in BD-I patients, left lateral ventricle sizes were found to be twice as large as in any other group (39). Although the relationship between lateral ventricle differences and cognitive function has not been directly tested in BD-I, studies on healthy elderly participants (40), vascular dementia patients (41), and patients with schizophrenia (42) have all found associations between lateral ventricle differences and reduction in attentional/executive performance.

Although this study suggests the possibility that the recurrence of manic episodes may be involved in the reduction of cognitive function, it is not possible to make a strong causal link on the basis of a cross-sectional study. Indeed, it could be that patients who go on to have higher numbers of manic episodes have a poorer cognitive baseline, as

suggested by recent studies finding that nonaffected relatives of patients with bipolar disorder show differences in memory and executive function when compared to nonrelative controls (43, 44). Additionally, there may be an interaction with aging itself, in that younger patients with fewer manic episodes might be more likely to have other episodes as time goes on. There is some evidence against this in our data, in that the results remained significant when age of onset and disease chronicity were entered as covariates, but only a prospective follow-up study can provide strong evidence to suggest that recurrence of manic episodes leads to increasing cognitive impairment. Furthermore, although we demonstrated that the diagnosis of substance dependence and the distribution of medication types were not significantly different between groups, figures for total intake over the lifetime or clinical history were not available, leaving open the possibility that there may have been some contribution from these sources to differences in cognitive performance. Additionally, we did not include data concerning self-harm or suicide attempts, which may also have contributed to changes in cognitive function. However, because, as far as we know, this is first study to look specifically at the link between manic episodes and cognition by controlling for depressive episodes and clinical symptoms, we feel the data provide important preliminary evidence on which further studies should be based.

This is clearly an important issue, as, if the hypothesis suggested by the current study is verified (namely, that manic relapse may cause cognitive decline), the importance of early intervention and good treatment adherence becomes not only a matter of symptom control but a potentially important intervention to protect against functional decline. Indeed, this is in line with evidence suggesting that early treatment may have neuroprotective effects, as has been reported with regard to the use of mood stabilizers preventing loss of brain volume in BD-I patients (45). This hypothesis might also indicate that quick and constant adherence to treatment could be key in bipolar disorder patients, as recurrence of acute episodes normally correlates with periods of treatment abandonment and entails disturbances to leading a functional life and performing everyday activities (46–49), as well as the cognitive difficulties discussed above.

Furthermore, the link between neurocognitive performance and the number of manic episodes may help construct etiological or staging models of the disorder, which could be useful to predict the course of the disorder on the basis of a cognitive profile. Such treatment models have been elaborated for schizophrenia and, when applied, have been to shown to decrease the rate of first-episode presentation (50, 51). An exploration of this area may additionally help elucidate whether there are different endophenotypes underlying bipolar disorder, and future mediation analyses may help distinguish these on the basis of cognitive and symptom profiles.[1]

An initial staging model of bipolar disorder is already in development (52), and we suggest that the initial asymptomatic or at-risk stage could include a reduced capacity for memory and executive function, potentially helping to make a differential diagnosis between an initial depressive episode that will later lead to a diagnosis of major depression and one that could later lead to a diagnosis of bipolar disorder with future manic or hypomanic episodes. A monotherapy treatment with antidepressants, which has been associated with mania onset and with an increase in frequency cycles (53) and mixed episodes (54) in which there is evidence for higher suicide risk (55), could thus be prevented.

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References

1. Savitz J, Solms M, Ramesar R. Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. Bipolar Disord 2005; 7: 216–235.
2. Quraishi S, Frangou S. Neuropsychology of bipolar disorder: a review. J Affect Disord 2002; 72: 209–226.
3. Bearden CE, Hoffman KM, Cannon TD. The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. Bipolar Disord 2001; 3: 106–150.
4. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand Suppl 2007; 434: 17–26.
5. Martínez-Arán A, Vieta E, Reinares M et al. Cognitive function across manic or hypomanic, depressed and euthymic states in bipolar disorder. Am J Psychiatry 2004; 161: 262–270.
6. Clark L, Iversen SD, Goodwin GM. Sustained attention deficit in bipolar disorder. Br J Psychiatry 2002; 180: 313–319.
7. Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. Psychol Med 2000; 30: 1025–1036.
8. Ferrier IN, Stanton BR, Kelly TP, Scott J. Neuropsychological function in euthymic patients with bipolar disorder. Br J Psychiatry 1999; 175: 246–251.
9. Van Gorp WG, Altshuler L, Theberge DC, Mintz J. Declarative and procedural memory in bipolar disorder. Biol Psychiatry 1999; 46: 525–531.

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10. Thompson JM, Gallagher P, Hughes JH et al. Neurocognitive impairment in euthymic patients with bipolar affective disorder. Br J Psychiatry 2005; 186: 32–40.
11. Robinson LJ, Thompson JM, Gallagher P et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord 2006; 93: 105–115.
12. Martínez-Arán A, Vieta E, Colom F et al. Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. Psychother Psychosom 2000; 69: 2–18.
13. Tham A, Engelbrektson K, Mathé AA, Johnson L, Olsso E, Aberg-Wistedt A. Impaired neuropsychological performance in euthymic patients with recurring mood disorders. J Clin Psychiatry 1997; 58: 26–29.
14. Van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W. Cognitive impairment in euthymic bipolar tfmisc @|Frame Misc.patients with and without prior alcohol dependence: a preliminary study. Arch Gen Psychiatry 1998; 55: 41–46.
15. Albus M, Hubmann W, Wahlheim C, Sobizack M, Franz U, Mohr F. Contrasts in neuropsychological test profile between patients with first episode schizophrenia and first-episode affective disorders. Acta Psychiatr Scand 1996; 94: 87–93.
16. Kolur US, Reddy YC, John JP, Kandavel T, Jain S. Sustained attention and executive functions in euthymic young people with bipolar disorder. Br J Psychiatry 2006; 189: 453–458.
17. McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. J Affect Disord 2009; 119: 1–8.
18. Zubieta J, Huguelet P, O'Neil RL, Giordani BJ. Cognitive function in euthymic bipolar I disorder. Psychiatry Res 2001; 102: 9–20.
19. Martínez-Arán 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.
20. Roca M, Martin-Santos R, Saiz J et al. Diagnostic Interview for Genetic Studies (DIGS): inter-rater and test-retest reliability and validity in a Spanish population. Eur Psychiatry 2007; 22: 44–48.
21. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 12: 56–62.
22. Young RC, Biggs JT, Siegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978; 133: 429–435.
23. Wechsler D. Wechsler Adult Intelligence Scale: Manual. New York: Psychological Corporation, 1955.
24. Ardila AE, Rosselli ME, Puente AE. Neuropsychological evaluation of the Spanish-speaker: a reply to Artiola i Fortuny. Clin Neuropsychol 1996; 13: 537–542.
25. Reitan RM, Wolfson D. The category test and the Trail Making Test as measures of frontal lobe functions. Clin Neuropsychol 1995; 9: 50–56.
26. Spreen O, Strauss E. A Compendium of Neuropsychological Tests. Administration, Norms and Commentary. New York: Oxford University Press, 1991.
27. Nelson H. A modified card sorting test sensitive to frontal lobe defects. Cortex 1976; 12: 313–324.
28. Rosselli M, Ardila A, Rosas P. Neuropsychological assessment in illiterates: II. Language and praxic abilities. Brain Cogn 1990; 12: 281–296.
29. Pineda D, Galeano L, Giraldo Y. Test de Memoria Semántica con Incremento Asociativo. Neuropsicología, Evaluación Clínica y Psicometría. Monografías de Actualización en Neurociencias 7. Colombia: Editores Bustamante E y Betancur S, 1991.
30. Wechsler D. Wechsler Memory Scale–Revised. New York: Psychological Corp/Harcourt Brace Jovanovich, 1987.
31. Osterrieth P. Le test de copie d'une figure complexe. Archives de Psychologie 1944; 30: 205–220.
32. Cohen J. Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Hillsdale: Lawrence Earlbaum Associates, 1988.
33. Denicoff KD, Ali SO, Mirsky AF et al. Relationship between prior course of illness and neuropsychological functioning in patients with bipolar disorder. J Affect Disord 1999; 56: 67–73.
34. Nehra R, Chakrabarti S, Pradhan B, Khehra N. Comparison of cognitive functions between first- and multi-episode bipolar affective disorders. J Affect Disord 2006; 93: 185–192.
35. Altshuler LL. Bipolar disorder: are repeated episodes associated with neuroanatomic and cognitive changes? Biol Psychiatry 1993; 33: 563–565.
36. Strakowski SM, DelBello MP, Zimmerman ME et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am J Psychiatry 2002; 159: 1841–1847.
37. Botteron KN, Vannier MW, Geller B, Todd RD, Lee BCP. Preliminary study of magnetic resonance imaging characteristics in 8 to 16-year-olds with mania. J Am Acad Child Adol Psychiatry 1995; 34: 742–749.
38. Strakowski SM, Wilson DR, Tohen M, Woods BT, Doublass AW, Stoll AL. Structural brain abnormalities in first-episode mania. Biol Psychiatry 1993; 33: 602–609.
39. Hauser P, Matochik J, Altshuler LL et al. MRI-based measurements of temporal lobe and ventricular structures in patients with bipolar I and bipolar II disorders. J Affect Disord 2000; 60: 25–32.
40. Breteler MM, van Amerongen NM, van Swieten JC et al. Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging. The Rotterdam Study. Stroke 1994; 25: 1109–1115.
41. O'Sullivan M, Morris RG, Huckstep B, Jones DK, Williams SC, Markus HS. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. J Neurol Neurosurg Psychiatry 2004; 75: 441–447.
42. Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. Am J Psychiatry 1999; 156: 1336–1341.
43. Quraishi S, Walshe M, McDonald C et al. Memory functioning in familial bipolar I disorder patients and their relatives. Bipolar Disord 2009; 11: 209–214.
44. Bora E, Vahip S, Akdeniz F, Ilerisoy H, Aldemir E, Alkan M. Executive and verbal working memory dysfunction in first-degree relatives of patients with bipolar disorder. Psychiatry Res 2008; 161: 318–324.
45. Chang K, Barnea-Goraly N, Karchemskiy A et al. Cortical magnetic resonance imaging in familial pediatric bipolar disorder. Biol Psychiatry 2005; 58: 197–203.
46. Colom F, Vieta E, Martínez-Arán A et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003; 60: 402–407.
47. Colom F, Vieta E, Sánchez-Moreno J et al. Stabilizing the stabilizer: group psychoeducation enhances the stability of serum lithium levels. Bipolar Disord 2005; 7 (Suppl. 5): 32–36.

48. Colom F, Vieta E, Sánchez-Moreno J et al. Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial. Br J Psychiatry 2009; 194: 260–265.
49. Vieta E, Rosa AR. Evolving trends in the long-term treatment of bipolar disorder. World J Biol Psychiatry 2007; 8: 4–11.
50. Kapczinski F, Dias VV, Kauer-Sant'Anna M et al. Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother 2009; 9: 957–966.
51. McGorry PD, Yung AR, Phillips LJ et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry 2002; 59: 921–928.
52. Berk M, Conus P, Lucas N et al. Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord 2007; 9: 671–678.
53. Post RM, Altshuler LL, Frye MA et al. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. Bipolar Disord 2001; 3: 259–265.
54. Berk M, Dodd S. Are treatment emergent suicidality and decreased response to antidepressants in younger patients due to bipolar disorder being misdiagnosed as unipolar depression? Med Hypotheses 2005; 65: 39–43.
55. Berk M, Hallam K, Lucas N et al. Early intervention in bipolar disorders: opportunities and pitfalls. Med J Aust 2007; 187: S11–S14.