Neurocognitive Impairments and Their Relationship With Psychosocial Functioning in Euthymic Bipolar II Disorder

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Abstract: The aim of this study was to compare neurocognitive functioning between euthymic patients with bipolar I disorder (BDI), bipolar II disorder (BDII), and healthy controls. An additional aim was to estimate the relationship between neurocognitive impairments and psychosocial functioning. Eighty-seven patients with BDI ($n = 48$) or BDII ($n = 39$) and 39 healthy controls were included. All subjects completed an extensive neurocognitive battery. Psychosocial functioning was assessed using the General Assessment of Functioning. Patients with BDII performed more poorly than did the controls in measures of psychomotor speed, verbal memory, and executive functioning. Patient groups did not show differences in any of the cognitive measures assessed. The performance in trail-making test B was the only independent predictor of psychosocial functioning in both patient groups. Patients with BDII have cognitive impairments, and this has a negative influence on their functional outcome. Our results bring additional support to the notion that BDII disorder is not a merely mild type of BDI.

Key Words: Bipolar II disorder, neuropsychology, executive function, verbal memory.

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A growing body of evidence suggests that patients with bipolar disorder (BD) have neurocognitive impairments even during euthymic periods. Independent meta-analyses concluded that the main cognitive domains affected in remitted patients are verbal memory, attention, and executive function (Robinson et al., 2006; Torres et al., 2007). Moreover, negative associations between neurocognitive functioning and different measures of disability have been shown in both cross-sectional (Dickerson et al., 2004; Martinez-Arán et al., 2004; Martino et al., 2008; Zubieta et al., 2001) and longitudinal (Jaeger et al., 2007; Martino et al., 2009) studies. Almost all of these studies were conducted in patients with bipolar I disorder (BDI) or in mixed samples of BDI and bipolar II disorder (BDII). In contrast, few studies were focused on the neurocognitive functioning of patients with BDII.

The common notion that BDII is merely a mild type of BDI has been questioned in recent years. Although BDI has more severe symptoms (Judd et al., 2003; Vieta et al., 1997) and a greater number of hospitalizations (Vieta et al., 1997), BDII often implies a higher episode frequency, comorbidity, suicidal behavior, more time spent ill, and rapid cycling (Vieta et al., 1997, 1999). In this context, it has been stated that there is a need for further research and better descriptions of BDII (Vieta and Suppes, 2008).

Studies focused on the neucognitive functioning of patients with BDII brought evidence about impairments in this population, although some results were inconsistent. There was no uniformity regarding which cognitive domains were affected in BDII; some studies showed impairments in verbal memory (Dittman et al., 2008; Summers et al., 2006; Torrent et al., 2006), and others did not (Hsiao et al., 2009; Simonsen et al., 2008). Regarding the differences between BDI and BDII, two studies reported that cognitive impairments were more severe and pervasive in patients with BDII than in those with BDI (Harkavy-Friedman et al., 2006; Summers et al., 2006), three showed that BDI had a more widespread cognitive dysfunction compared with BDII (Simonsen et al., 2008; Torrent et al., 2006; Hsiao et al., 2009), and another study found similar impairments in BDI and BDII (Dittman et al., 2008). These inconsistent results may be related to methodological factors such as sample strategies, pharmacological exposure, neuropsychological task used, and statistical analysis used, among others. Some differences between BDI and BDII, such as higher psychotic symptoms or hospitalizations in BDI or higher frequency of depressive episodes in BDII, are inherent to these disorders (Vieta and Suppes, 2008; Vieta et al., 1997). It was suggested that matching patient groups in these variables would filter out these inherent differences and thereby provide us with "overselected" groups (Simonsen et al., 2008). However, other clinical and demographical variables that are not inherent to BD subtypes but may influence neurocognitive functioning such as age, years of education, premorbid IQ, length of illness, or subclinical symptoms were not adequately paired in previous studies. For example, several studies clarified the negative influence of clinical and subclinical affective symptoms on neurocognitive functioning in BD (Clark et al., 2002; Martinez-Arán et al., 2004). However, just one of the previous comparative studies mentioned previously (Torrent et al., 2006) included patients with a strict criteria of remission based on low scores in symptoms scales for at least 8 weeks (Tohen et al., 2009). In contrast, one study included BDI and BDII patients in a depressive episode (Harkavy-Friedman et al., 2006), others mixed samples of euthymic and depressive patients (Simonsen et al., 2008; Summers et al., 2006), and others included remitted patients, although some of them had brief previous euthymic periods as inclusion criteria (Dittman et al., 2008; Hsiao et al., 2009). Finally, just one previous study reported that patient groups were paired in terms of psychotropic medications (Summers et al., 2006), whereas, in others, the patients with BDI had higher exposure to antipsychotics, lithium, or combination therapy than did those with BDII (Dittman et al., 2008; Simonsen et al., 2008; Torrent et al., 2006), and, in others, the medications were not well specified (Harkavy-Friedman et al., 2006; Hsiao et al., 2009). Higher exposure to antipsychotics among BDI patients would be expected, taking into account the role of these agents in the prophylaxis of manic relapses (Yatham et al., 2009). However, preliminary evidence suggests that exposure to antipsychotics might have a deleterious effect on verbal memory and executive function performance (Donaldson et al., 2003; Frangou et al., 2005). Although based on high-risk populations (Robinson and Ferrier, 2006) and medication-free patient (Goswami et al., 2006) studies, neurocognitive impairments reported in BD patients cannot be caused by antipsychotic exposure alone; this may contribute to the finding of differences between BDI and BDII. Furthermore, all of these studies have reported antipsychotic exposure in qualitative terms, without information about doses and the time of exposure.

These inconclusive data suggest the need for further neurocognitive studies to describe the neurocognitive profile of patients

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with BDII. Likewise, just one study (Torrent et al., 2006) assessed the relationship between neurocognitive impairments and functional outcome in BDII, showing that executive dysfunctions were related to low psychosocial functioning. Therefore, the aim of this study was to compare neurocognitive functioning between euthymic patients with BDI and BDII and healthy controls. Taking into account the methodological limitations of previous studies, we included a large sample of BDI and BDII patients meeting strict euthymia criteria, paired in several clinical and demographical variables of interest, and assessed using a quantitative measure of exposure to psychotropic medications. An additional aim was to estimate the relationship between neurocognitive impairments and psychosocial functioning in patients with BDI and BDII. Based on previous studies, we hypothesize that BDII patients would have cognitive impairments and that this may negatively influence psychosocial functioning.

METHODS

Eighty-seven subjects with BD (48 with BDI and 39 with BDII) were consecutively selected from the outpatient population of the Bipolar Disorder Program of Favaloro University using the following inclusion criteria: age between 18 and 60 years, a diagnosis of BDI or BDII according to DSM-IV using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996), and being euthymic (defined by the following: Hamilton Depression Rating Scale [HDRS], ≤8; Young Mania Rating Scale [YMRS], ≤6) for at least 8 weeks. The exclusion criteria were an antecedent history of substance abuse, a history of mental retardation, neurological disease, or any unstable clinical condition (like hypothyroidism or diabetes) that could affect cognitive performance. In addition, 39 healthy controls matched by age and years of education were included: these controls had no antecedence of neurological disease, they had no history of psychotic or affective disorders among themselves or a first-degree family member, and they were not taking psychotropic medication. The study was approved by the hospital ethics committee in accordance with the Helsinki Declaration of 1975. All subjects gave written informed consent for their participation after receiving a complete description of the study.

Clinical Assessment

In addition to SCID, all subjects were evaluated using the HDRS (Hamilton, 1960) and the YMRS (Young et al., 1978). Additional clinical information was obtained from clinical charts and direct patients interview. Psychosocial functioning was assessed using the General Assessment of Functioning (GAF; DSM-IV). The rater was instructed to use the GAF to measure functioning and not symptoms in the last month because other measures of mood symptoms (HDRS and YMRS) were obtained as a part of the study. Exposure to antidepressants, mood stabilizers, antipsychotics, and benzodiazepines was assessed by the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD; Peralta and Cuesta, 2002). This scale provides a quantitative measure of current exposure to the different groups of psychotropic medications in a 0 to 5 point range (0, no medication; 1, sporadic low dose; 2, continue low dose; 3, middle dose; 4, high dose; and 5, very high dose).

Neurocognitive Assessment

Patients and healthy controls completed a neurocognitive battery selected to assess a) attention, using the Forward Digit SPAN (Wechsler, 1955) and the Trail-Making Test part A (TMT-A) (Reitan, 1958); b) psychomotor speed, where simple and complex motor speed were measured using simple tapping, which requires the subject to tap the space bar of the keyboard with the dominant and nondominant index fingers (three trials of 10.5 seconds for each hand) and complex tapping, which requires the subject to tap the left and right sides of the keyboard using the two index fingers in alternating fashion (three trials of 5.5 seconds each); c) verbal memory, using the Memory Battery of Signoret (Signoret and Whiteley, 1979), which evaluates the immediate and delay recall of a short story and the serial learning of a 12-word list of different semantic categories (three trials), free delay recall, and recognition using semantic clues and multiple options of them; and d) executive functions, using the Wisconsin Card Sorting Test (WCST; Heaton, 1981), Phonological Fluency (Benton et al., 1983), and Trail-Making Test part B (TMT-B; Reitan, 1958). Neuropsychological tests were grouped in these domains based on previous literature on BD (Martinez-Arán et al., 2004; Robinson et al., 2006; Torres et al., 2007). In addition, estimated premorbid IQ was calculated using the Wechsler Adult Intelligence Scale vocabulary subtest (Wechsler, 1955). In this task, the examiner asked the meaning of 40 words in their order of difficulty; the results were expressed as T-scores. Vocabulary has been identified as the single best measure of premorbid IQ.

One experienced psychiatrist (S. A. S.) examined clinically all subjects. All neuropsychological tests were administered by another physician (D. J. M.) in a quiet testing room according to a standardized order.

Statistical Analysis

The three groups (BDI, BDII, and healthy controls) were compared on clinical and demographical variables using an analysis of variance (ANOVA), Kruskal-Wallis test, or a chi-squared test, as appropriate. Neurocognitive variables were normally distributed as assessed by the Kolmogorov-Smirnov test. To decrease the risk of type I errors because of the large number of analyses, a one-way multivariate ANOVA was conducted, with all neurocognitive measures as dependent variables and group membership (BDI, BDII, and healthy controls) as factor. It was suggested that, because neuropsychological tests are naturally correlated, this procedure would be better than the Bonferroni inequality correction that would increase type II error (Torrent et al., 2006). The differences between the three groups were analyzed using one-way ANOVA, followed by a Tukey post hoc comparison procedure when significant main effects were present. The effect sizes (Cohen *d*) have been calculated to find the differences between the groups in terms of standard deviation.

Pearson correlation coefficients were calculated to test for the associations between clinical-demographical variables, neurocognitive variables, and psychosocial functioning as measured by the GAF (in nonparametric variables such as the number of previous episodes or admissions, the results were confirmed using the Spearman correlation). The neurocognitive variables with significant correlation with psychosocial functioning (GAF) were considered as possible explanatory variables in a multiple linear regression model (variance expressed as adjusted R^2).

RESULTS

The clinical and demographic features of bipolar patients and healthy controls are shown in Table 1; no differences were found between the groups in terms of age, sex, years of education, premorbid IQ, and scores in the YMRS and HDRS. Patients with BDII had a significantly higher number of previous depressive episodes than did the BDI patients. Patients with BDII had an intermediate level of psychosocial functioning between the BDI and control groups (Table 1). All patients were receiving mood stabilizers at the time of testing; in addition, 38% were receiving antidepressants; 50%, benzodiazepines; and 59%, antipsychotics. Patients with BDI had higher exposure to antipsychotics than those with BDII (72.34% *vs.* 43.58%; $\chi^2 = 7.30$, $df = 1$, $p = 0.007$); no differences were found between patient groups in terms of exposure to other groups of psychotropic medications. Likewise, patients with BDI had a higher dose of antipsychotics assessed using the IFD scale than those with BDII (1.48 [1.08] *vs.* 0.74 [0.96], respectively; $df = 1$; $F = 11.16$; $p = 0.001$). No other differences were found between patients groups

TABLE 1. Clinical and Demographic Characteristics of Bipolar Patients and Healthy Controls

	A (n = 48)	B (n = 39)	C (n = 39)	Test	Tukey Post Hoc
Age	37.7 (10.3)	42.8 (10.8)	40.0 (12.9)	$F = 1.89$, $p = 0.15$	
Sex (%Female)	56.3	74.3	69.2	$\chi^2 = 3.66$, $p = 0.16$	
Years of education	13.79 (2.31)	14.75 (2.46)	13.54 (2.86)	$F = 2.55$, $p = 0.082$	
Premorbid IQ (T-score)	55.3 (5.5)	55.2 (5.4)	55.0 (5.6)	$F = 0.13$, $p = 0.87$	
YMRS Score	0.92 (1.25)	1.23 (1.64)	0.65 (.92)	$F = 1.87$, $p = 0.15$	
HDRS Score	2.10 (1.96)	1.95 (2.01)	1.84 (1.79)	$F = 0.20$, $p = 0.81$	
GAF Score	77.42 (9.49)	81.97 (9.50)	89.76 (5.35)	$F = 22.3$, $p < 0.001$	A < B < C
Length of illness, yrs	11.09 (7.57)	11.91 (6.68)	–	$F = 0.24$, $p = 0.62$	
Number of previous depressive episodes	2.89 (1.94)	4.13 (1.67)	–	$\chi^2 = 11.86$, $p = 0.001$	
Number of previous hypomanic/manic episodes	3.21 (2.20)	3.26 (2.24)	–	$\chi^2 = 0.014$, $p = 0.90$	
Number of previous admissions	1.17 (1.72)	0.19 (.52)	–	$\chi^2 = 11.90$, $p = 0.001$	
History of psychosis, n (%)	43 (89)	4 (10)	–	$\chi^2 = 59.4$, $p < 0.001$	

Values are expressed as mean (SD) unless specified otherwise.
A indicates Bipolar I group; B, Bipolar II group; C, control group; IQ, Intelligence Quotient; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; GAF, General Assessment of Functioning.

in term of doses of psychotropic medications (mood stabilizers: 3.06 [0.91] *vs*.2.92 [0.81]; antidepressants: 0.91 [1.26] *vs*. 0.72 [1.19]; and benzodiazepines: 0.93 [1.22] *vs*.1.33 [1.24]).

There was no correlation between neurocognitive measures and the number of previous admissions, depressive episodes, or exposure to antipsychotics (all $p > 0.05$). Consequently, the analysis of group differences in neurocognitive performance was performed without these clinical characteristics as covariates.

A significant overall difference in neurocognitive functioning between the groups was detected using multivariate analysis of variance (Pillai $F = 1.77$; $df = 28,216$; $p = 0.013$). For 8 of 14 comparisons, the differences reached statistical significance ($p < 0.05$); the group mean performance for each neurocognitive measure and the respective analysis of variance are presented in Table 2. Patients with BDI had a significantly poorer performance than healthy controls in all cognitive domains assessed. The higher differences between BDI patients and controls were found in immediate and delay recall (Cohen $d = 0.82$ and 0.89, respectively), followed by phonological fluency ($d = 0.79$), dominant and nondominant simple tapping ($d = 0.67$ and 0.64, respectively), phonological fluency ($d = 0.79$), and forward digit SPAN ($d = 0.64$).

Patients with BDII had a significantly poorer performance than the healthy controls in immediate and delay recall, dominant and nondominant simple tapping, and TMT-B. Likewise, there was a trend to significance in measures of attention (Trail-Making test A, $p = 0.078$). The higher differences between BDII patients and controls were found in immediate and delay recall (Cohen $d = 0.88$ and 0.84, respectively), followed by dominant and nondominant simple tapping ($d = 0.79$ and 0.77, respectively) and TMT-B ($d = 0.62$). Both patient groups did not show differences in any of the cognitive measures assessed. Consequently, analysis of the effect sizes pointed out small differences between the patient groups, with the exception of the forward

TABLE 2. Neurocognitive Evaluation of Bipolar Patients and Healthy Controls

						Cohen d		
	A (n = 48)	B (n = 39)	C (n = 39)	ANOVA (df = 2)	Tukey Post Hoc	A *vs.* B	B *vs.* C	A *vs.* C
Psychomotor speed								
Dominant simple tapping	30.38 (3.79)	29.88 (5.85)	33.05 (3.98)	$F = 5.04$, $p = 0.008$	A = B < C	0.13	0.79	0.67
Nondominant simple tapping	27.09 (5.14)	26.54 (4.81)	29.71 (4.08)	$F = 4.70$, $p = 0.011$	A = B < C	0.10	0.77	0.64
Complex tapping	38.67 (11.91)	36.45 (9.56)	41.74 (8.57)	$F = 2.47$, $p = 0.089$	A = B = C	0.18	0.61	0.35
Verbal memory								
Immediate recall	7.33 (1.91)	7.25 (2.11)	8.37 (1.26)	$F = 4.35$, $p = 0.015$	A = B < C	0.04	0.88	0.82
Delay recall	6.82 (2.04)	6.90 (2.23)	8.18 (1.52)	$F = 5.64$, $p = 0.005$	A = B < C	0.03	0.84	0.89
Serial learning	10.12 (1.39)	10.30 (1.40)	10.23 (1.48)	$F = 0.17$, $p = 0.84$	A = B = C	0.12	0.05	0.07
Free delay recall	8.46 (2.02)	8.82 (2.04)	8.54 (2.08)	$F = 0.27$, $p = 0.69$	A = B = C	0.17	0.13	0.03
Recognition	11.79 (0.50)	11.83 (0.38)	11.86 (0.36)	$F = 0.34$, $p = 0.78$	A = B = C	0.10	0.07	0.19
Attention								
Forward digit SPAN	5.58 (1.27)	6.07 (1.29)	6.20 (.96)	$F = 3.19$, $p = 0.048$	A = B = C	0.37	0.13	0.64
Trail making part A	40.00 (18.51)	41.20 (16.70)	32.09 (10.84)	$F = 3.11$, $p = 0.045$	A = B = C	0.07	0.49	0.42
Executive functions								
Phonological fluency	15.25 (5.28)	16.45 (4.29)	18.14 (3.62)	$F = 4.10$, $p = 0.019$	A < C; B = A, C	0.32	0.46	0.79
Trail making part B	98.0 (45.6)	99.5 (44.9)	71.3 (17.2)	$F = 4.77$, $p = .010$	A = B < C	0.03	0.62	0.58
WCST-total errors	20.96 (13.44)	23.10 (17.95)	17.29 (12.15)	$F = 1.47$, $p = 0.23$	A = B = C	0.11	0.47	0.27
WCST-perseverative errors	10.56 (7.53)	12.40 (9.90)	8.60 (5.15)	$F = 2.19$, $p = 0.11$	A = B = C	0.18	0.38	0.26

Values are expressed as mean (SD) unless specified otherwise.
A indicates Bipolar I group; B, Bipolar II group; C, control group; WCST, Wisconsin Card Sorting Test.

digit SPAN (d = 0.37) and phonological fluency (d = 0.32). On the forward digit SPAN, the ANOVA revealed significant differences between the groups. Post hoc comparisons showed that the BDI group had a trend to perform more poorly than the healthy control group (p = 0.057), whereas the BDII patients did not perform significantly different from BDI (p = 0.14) and control groups (p = 0.89). Similarly, on the phonological fluency, the ANOVA revealed significant differences between the groups. Post hoc comparisons showed that the BDI group performed significantly below than the control group (p = 0.014), whereas the BDII group did not differ from BDI (p = 0.43) and control groups (p = 0.24).

In BDII patients, there was a relationship between hypomanic subclinical symptoms (YMRS score) and performance in measures of attention (TMT-A: R = 0.032; p = 0.047) and executive function (TMT-B: R = 0.034; p = 0.034) and between the number of previous hypomanic episodes and the measures of attention (TMT-A: R = 0.038; p = 0.036; SPAN-D: R = −0.040; p = 0.026) and number of previous admissions and psychomotor speed (Dominant Tapping: R = −0.033; p = 0.048). Likewise, in the BDII group, exposure to benzodiazepines was related with the performance in measures of psychomotor speed (Dominant Tapping: R = −0.040; p = 0.010), attention (TMT-A: R = 0.041; p = 0.010), and executive function (TMT-B: R = 0.040; p = 0.012; WCST-Perseverative Errors: R = 0.034; p = 0.033 and WCST Total Errors: R = 0.038; p = 0.015), whereas no relationship was found among exposure to mood stabilizers, exposure to antipsychotics, and exposure to antidepressants with neurocognitive functioning. In BDI patients, there was a correlation between the number of previous manic episodes and the measures of attention (TMT-A: R = 0.035; p = 0.016) and executive function (TMT-B: R = 0.041; p = 0.004). Similarly to BDII, the BDI group had a negative correlation between exposure with benzodiazepines and a measure of executive function (TMT-B: R = 0.034; p = 0.018) and a trend toward significance with psychomotor speed (Dominant Tapping: R = −0.027; p = 0.060), attention (TMT-A: R = 0.027; p = 0.060), whereas no relationship was found between exposure to mood stabilizers, exposure to antipsychotics, and exposure to antidepressants with neurocognitive functioning.

Among patients with BDII, psychosocial functioning was related with performance in dominant (R = 0.44, p = 0.006) and nondominant (R = 0.46, p = 0.004) simple tapping, forward digit SPAN (R = 0.39, p = 0.013), TMT-A (R = −0.61, p < 0.001), and TMT-B (R = −0.62, p < 0.001). The regression model reached significance (F = 5.06, df = 6, p = 0.002) explaining nearly 35% of variance (R^2 = 0.442, adjusted R^2 = 0.355) in psychosocial functioning. Performance in TMT-B was the only independent predictor of psychosocial functioning (β = −0.52; t = −3.18; p = 0.003). In the BDI group, psychosocial functioning correlated with performance in forward digit SPAN (R = 0.34, p = 0.019), TMT-A (R = −0.45, p = 0.001), phonological fluency (R = 0.38, p = 0.007), and TMT-B (R = −0.51, p < 0.001). We ran a regression model including these measures as possible explanatory variables and GAF score as dependent variable. Overall, the model reached significance (F = 6.20, df = 4, p = 0.001) explaining nearly 25% of variance (R^2 = 0.297, adjusted R^2 = 0.249). Performance in TMT-B was the only independent predictor of psychosocial functioning (β = −0.41; t = −2.82; p = 0.006).

DISCUSSION

The first finding of this study was that patients with euthymic BDII had poorer neurocognitive functioning than did the healthy controls. This result agrees with previous studies focused on fully euthymic BDII patients (Dittman et al., 2008; Hsiao et al., 2009; Torrent et al., 2006). In our study, BDII patients had impairments in measures of psychomotor speed, verbal memory, and executive functions compared with healthy controls. Likewise, there was a trend to significance in measures of attention (p = 0.078 in TMT-A). The impairments in attention-psychomotor speed agreed with all three previous studies (Dittman et al., 2008; Hsiao et al., 2009; Torrent et al., 2006), whereas deficits in executive functions were reported in two previous studies (Dittman et al., 2008; Torrent et al., 2006) but not in the other (Hsiao et al., 2009). On the contrary, just one of these three previous studies reported impairments in verbal memory in BDII patients (Torrent et al., 2006) as in our study, but in the other two studies, the patients had a performance similar to that of healthy controls (Dittman et al., 2008; Hsiao et al., 2009). These inconsistencies regarding verbal memory performance may lie in different tests used in all studies and other methodological factors mentioned below. Another two studies that included a mixed sample of euthymic and depressed BDII patients also found impairments in attention and executive function compared with healthy controls, although impairments in verbal memory were reported in one study (Summers et al., 2006) but not in the other (Simonsen et al., 2008). Taken together, these findings suggest that impairments in attention-psychomotor speed and executive functions persist in BDII patients even during euthymic periods, whereas performance in verbal memory requests further research. On the other hand, we did not find differences in neurocognitive functioning between BDI and BDII patients. Our results are consistent with those of a previous study in euthymic patients (Dittman et al., 2008) but not with others (Hsiao et al., 2009; Torrent et al., 2006). In the study of Torrent et al. (2006), the patients with BDI had a lower performance score than those with BDII in all measures of verbal learning and memory, in one of the four measures of executive function, and in any measure of attention, with small effect sizes for all positive findings. Likewise, in the study by Hsiao et al. (2009), BDII patients performed equally with BDI patients in measures of working memory but performed better in measures of psychomotor speed, verbal memory, and executive function.

Another finding of this study was that cognitive impairments might contribute to explain the reduced ability to regain premorbid levels of social and vocational functioning after episodes of remission in BDII patients. We found a positive correlation between performance in psychomotor speed, attention, and executive function with psychosocial functioning assessed using the GAF. When we included these measures in a regression analysis, the model reached significance, explaining nearly 35% of variance in psychosocial functioning, and a measure of executive dysfunction (TMT-B) was the only independent predictor. Our result closely reproduces the one of the only previous study that explored the relationship between neurocognitive impairments and functional outcome in euthymic BDII (Torrent et al., 2006). In that study, impairments in TMT-B were the only neurocognitive predictor of psychosocial functioning among patients with BDII, explaining around 18% of variance. These results suggest that the correlations between cognitive impairments and functional recovery in euthymic patients are independent of the subtype of bipolar disorder.

In our sample, BDII patients with a higher number of previous hypomanic episodes and admissions had poorer performance in psychomotor speed and attention. A previous study found a relationship between the number of previous episodes and performance in psychomotor speed and executive functions in euthymic patients with BDII (Dittman et al., 2008). These results suggest that, among patients with BDII, a higher severity of illness characterized by a higher number of episodes and admissions might be associated with poorer cognitive functioning, which resembles findings reported in BDI. In fact, a review showed a negative association between the number of episodes, especially manic ones, and the number of admissions with cognitive functioning (Robinson and Ferrier, 2006). However, the direction of causality is unclear; these results might mean both that the experience of successive episodes is associated with a progressive cognitive decline and that more severe and static cognitive impairments are the cause of a poorer illness course. Further longitudinal

studies are needed to elucidate the static or progressive nature of cognitive impairments in both subtypes of BD.

The results of this study have clinical and theoretical importance. First, our findings support that patients with BDII have cognitive impairments even during remission. From this perspective, cognitive deficits may be considered as another clinical manifestation of this disorder, and it would be useful to assess neurocognitive functioning as a routine in clinical practice. Furthermore, the relationship between cognitive impairments and psychosocial functioning suggests that these deficits would be a rational target of treatment. The development of pharmacological or psychosocial strategies to improve cognitive impairments may lead to more comprehensive treatments of this kind of symptoms and contribute to the enhancement of the functional outcome of BDII patients. Finally, our results that show similar neurocognitive performance between patients with BDI and BDII bring support to the hypothesis that BDII is not merely a mild BDI. Alternatively, BDII would be conceptualized as a different phenotypic dimension of the illness characterized by higher episode frequency, comorbidity, suicidal behavior, more time spent ill, and rapid cycling (Vieta et al., 1997, 1999) than that observed in BDI, with a similar magnitude of cognitive impairments in both subtypes.

Some limitations of our work have to be acknowledged. First, a larger sample size could potentially have demonstrated much clearer differences between patient groups and controls in performance in attention and executive function. Likewise, a larger sample size could allow us to construct more complex regression models including other variables of interest (*e.g.*, length of illness or number of previous episodes) to predict psychosocial functioning. Although we reported adjusted R^2 statistics, which account for the number of variables entered in the models, they could have been too many for our sample size and may have artificially inflated the fit of our overall models. In addition, all patients included in the study were taking psychotropic medications, and we cannot discount the influence of drugs in cognitive functioning. Different with almost all studies, we used a quantitative measure (IFD) to pair the subgroups in terms of exposure to medication and to control statistically its effects when it was necessary. We did not find any relationship between antipsychotic exposure and neurocognitive performance, probably reflecting the low dose used in our sample (IFD: 1.48 [1.08] in BDI, and 0.74 [0.96] in BDII). It would be desirable for further studies to use, in addition to a qualitative description of percentage of patients exposed to antipsychotics, a quantitative measure of this exposure (*i.e.*, a scale as used in our study or chlorpromazine equivalents) to explore the relationship with neurocognitive functioning and to use it as a covariate when necessary. Preferably, this approach would be used to obtain a measure of exposure to other psychotropic drugs (*i.e.*, benzodiazepines) that might influence neurocognitive functioning, as we found in our study. An additional limitation is that psychosocial functioning was assessed using GAF scores. Although the rating was independent of psychiatric symptom severity, this is a single-item score and does not cover multiple domains of functioning. Therefore, future research in BDII should use more multidimensional measures of functioning. Finally, the cross-sectional design did not allow the exploring of the static or progressive nature of cognitive impairments in patients with BDI and BDII.

CONCLUSIONS

In summary, patients with euthymic BDII show impairments in psychomotor speed, verbal memory, and executive functions, reproducing closely the profile and magnitude of cognitive deficits of patients with BDI. The association between neurocognitive impairments and psychosocial functioning in BDII might be as strong as that consistently found in BDI patients. This points out the importance of developing strategies to improve cognitive impairments which may lead to the enhancement of the functional outcome in patients with BDII.

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