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Original Article

Cognitive variability in bipolar II disorder: who is cognitively impaired and who is preserved

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Objectives: Although it is well established that euthymic patients with bipolar disorder can have cognitive impairment, substantial heterogeneity exists and little is known about the extent and severity of impairment within the bipolar II disorder subtype. Therefore, the main aim of this study was to analyze cognitive variability in a sample of patients with bipolar II disorder.

Methods: The neuropsychological performance of 116 subjects, including 64 euthymic patients with bipolar II disorder and 52 healthy control subjects, was examined and compared by means of a comprehensive neurocognitive battery. Neurocognitive data were analyzed using a cluster analysis to examine whether there were specific groups based on neurocognitive patterns. Subsequently, subjects from each cluster were compared on demographic, clinical, and functional variables.

Results: A three-cluster solution was identified with an *intact* neurocognitive group (n = 29, 48.3%), an intermediate or *selectively impaired* group (n = 24, 40.0%), and a *globally impaired* group (n = 7, 11.6%). Among the three clusters, statistically significant differences were observed in premorbid intelligence quotient (p = 0.002), global functional outcome (p = 0.021), and leisure activities (p = 0.001), with patients in the globally impaired cluster showing the lowest attainments. No differences in other clinical characteristics were found among the groups.

Conclusions: These results confirm that neurocognitive variability is also present among patients with bipolar II disorder. Approximately one-half of the patients with bipolar II disorder were cognitively impaired, and among them 12% were severely and globally impaired. The identification of different cognitive profiles may help to develop cognitive remediation programs specifically tailored for each cognitive profile.

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It is nowadays acknowledged that bipolar disorder (BD) is often accompanied by neurocognitive deficits that may be present beyond mood episodes. Despite some inconsistent findings, the latest evidence suggests that there are few differences between the two main BD subtypes, bipolar I disorder (BD-I) and bipolar II disorder (BD-II), in terms of cognition (1, 2). In euthymic patients with BD, cognitive impairments have been mostly identified in attention, memory, and executive functions (3, 4). Research has also shown that cognitive disturbances play an important role in the overall functional outcome of patients with BD (5–9), and it is well established that patients with BD-II present similar psychosocial functioning impairment compared to patients with BD-I (10). All these

data suggest that BD-II is not a milder form of BD (11, 12). Furthermore, some differences have been reported in neural anatomy and function (13–15), supporting the hypothesis of neurobiological differences between the two subtypes. Other differences in psychological factors such as cognitive and coping styles and their relationships with symptoms across BD subtypes have been also described (16). Therefore, there is a substantial body of findings in support of BD-II as a valid category (17).

Although impairments in all the abovementioned neurocognitive domains have been consistently reported in euthymic patients with BD, there is also large neurocognitive heterogeneity among patients and a significant proportion of them do not actually show any neurocognitive impairment (18, 19). Burdick and co-workers (20) suggest that a gradient of severity may be present within BD or, alternatively, qualitatively distinct groups might exist. This heterogeneity in both clinical presentation and neurocognitive performance is an important issue to bear in mind in order to establish more tailored pharmacological and psychosocial interventions.

Cluster analysis, an exploratory data analysis tool, provides an approach to identify groups of patients who share similar neurocognitive patterns. Several studies have used this approach in schizophrenia. However, as far as we know, only one study has been conducted exclusively in patients with BD (20). Burdick and colleagues found a three-cluster solution, with a neurocognitively intact group, a selectively impaired group with moderate deficits and, finally, a globally impaired group with severe deficits across all domains.

Since there is a lack of studies addressing cognitive deficits specifically in BD-II patients, we applied a cluster analysis to a sample of euthymic BD-II patients using a comprehensive neurocognitive battery to assess different neurocognitive functions. We attempted to adjust, to the greatest extent possible, our neurocognitive battery to the International Society for Bipolar Disorders–Battery for Assessment of Neurocognition (ISBD-BANC) proposal, which was designed to be used across a range of multiple neuropsychological research contexts in the field of BD (21). Next, we compared the different clusters on demographic, clinical and functional variables to determine correlates for each group. Following the literature, we hypothesized that different neurocognitive profiles would exist among patients with BD-II, and that distinct clinical and functional variables would be associated with each group of patients.

Methods

Participants

A total of 64 euthymic patients with BD-II were recruited from the Bipolar Disorders Program of Barcelona, at the Hospital Clínic of Barcelona (22). The inclusion criteria were: (i) diagnosis of BD-II according to DSM-IV-TR, (ii) age between 18 and 65 years, (iii) euthymia for at least three months before the study enrollment: Hamilton Depression Rating Scale (HAM-D) score $\leq$8 (23, 24) and Young Mania Rating Scale (YMRS) score $\leq$6 (25, 26). Exclusion criteria were: (i) estimated intelligence quotient (IQ) <85, (ii) any medical or comorbid psychiatric condition affecting neuropsychological performance, and (iii) electroconvulsive therapy within the past year. In order to capture a sample representative of patients seen in clinical practice who are under pharmacological treatment, we set no limits for the use of benzodiazepines. Since these drugs were used mostly at night, all the patients were instructed not to take them within the last 12 hours before the neuropsychological assessment.

A total of 52 healthy controls (HC) without evidence of psychiatric or neurological history were recruited from a pool of volunteers. There were no differences between patients and healthy subjects in terms of age, gender, educational level and estimated premorbid IQ.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and approved by the Hospital Clinic Ethics and Research Board. All participants provided written informed consent prior to inclusion in the study.

Assessment

We gathered all the relevant clinical and sociodemographic data through a clinical interview based on the Structured Clinical Interview for DSM-IV (SCID) (27). The collected data were: age, gender, educational level, number and type of episodes, age at onset, age at first hospitalization, number of hospitalizations, chronicity (years of illness), history of prior suicide attempts, lifetime history of psychotic symptoms, axis II comorbidity, family history of affective disorders and pharmacological treatment. This was a cross-sectional study.

Clinical symptomatology at the time of assessment (severity of depressive and manic symptoms) was evaluated using the YMRS and the HAM-D. The overall functional outcome was assessed by means of the Functioning Assessment Short Test (FAST), an instrument widely used in patients with

BD (28–30), including the BD-II subtype (31). This scale, which was specifically designed to assess functional impairment in psychiatric patients, encompasses 24 items evaluating six functional domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time). The higher the scores, the greater the disability.

Neuropsychological assessment

Based on an extensive review of the literature, all participants completed a comprehensive neuropsychological battery in order to assess different cognitive domains.

- Premorbid IQ was estimated with the Wechsler Adult Intelligence Scale (WAIS-III) vocabulary subtest (32).
- The processing speed domain consisted of two subtests of the WAIS-III: the Digit-symbol Coding and the Symbol Search subtests (32) as well as the Phonemic (F-A-S) and Categorical (Animal naming) components of the Controlled Oral Word Association Test (COWAT) (33) and the Trail Making Test–Part A (TMT-A) (34).
- The working memory (WM) index comprised the Arithmetic, Digits, and Letter-Number sequencing subtests of the WAIS-III (32).
- Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) (35).
- Visual learning and memory were evaluated by means of the Rey Osterrieth Complex Figure (ROCF) (36).
- The executive functions were tested by several tests assessing set shifting, planning, and response inhibition, namely, the computerized version of the Wisconsin Card Sorting Test (WCST) (37), the Stroop Color-Word Interference Test (38), and the Trail Making Test–Part B (TMT-B) (34).
- The attention domain was tested with the Continuous Performance Test–II (CPT-II), version 5 (39).

Statistical analysis

All analyses were performed with the Statistical Package for Social Sciences version 18 (SPSS Inc., Chicago, IL, USA). Initial analyses were conducted to compare sociodemographic and clinical characteristics and cognitive composites between patients with BD-II and HC using *t*-tests for continuous variables and χ^2 tests for categorical variables.

Patients' raw scores on neuropsychological tests were standardized to *z*-scale scores based on the performance of the HC. Furthermore, several *z*-scores of different tests were summed and averaged to create cognitive composites. Following this procedure, cognitive composites were standardized against the composite scores obtained by the HC group. Six cognitive composites were designed to provide a single score in order to cover the main cognitive domains that are presumably affected in BD. The variables included in each cognitive domain were adjusted to cognitive domains proposed by the ISBD-BANC as follows: (i) the processing speed composite was based on the Digit-symbol Coding WAIS-III subtest, the Category fluency (Animal naming), and the TMT-A; (ii) the working memory composite included the Letter-number sequencing and the Digit-span WAIS-III subtests; (iii) the verbal memory index was composed of the total trials 1–5 list A, short free recall, short cued recall, delayed free recall, and delayed cued recall scores of the CVLT; (iv) for visual memory, the delayed recall of the ROCF was included; (v) the executive composite was calculated based on the number of categories and perseverative errors of the WCST, the Stroop Interference Test, and the TMT-B; and (vi) the attention composite score was based on several measures of the CPT-II such as: omission, reaction time and reaction time standard error. *z*-scores obtained from measures of CPT-II, WCST perseverative errors, and TMT-B (with higher scores indicating poorer performance) were reversed before constructing the corresponding composite scores. Examination of performance in the CPT-II revealed extreme scores [more than four standard deviations (SDs) below the mean], and for this reason these scores were truncated to $z = -4.0$. Then, a hierarchical cluster analysis was carried out in order to identify homogeneous subgroups of patients with BD-II based on their cognitive performance in terms of the different composite scores. Similarity between cases was computed with the Euclidian distance and Ward linkage was selected as the agglomeration procedure. Since all variables were standardized (with a mean = 0 and SD = 1) no pre-standardization was needed. Next, the dendogram was visually inspected to establish the appropriate number of clusters to be retained. In addition, a discriminant function analysis (DFA) was also conducted in order to test the validity of the clusters. The cognitive profiles of the patients in the different clusters and the HC were compared using a one-way ANOVA, with group membership (the three clusters and the HC group)

as a fixed factor and the six neurocognitive composites (processing speed, working memory, verbal memory, visual memory, executive function, and attention) as dependant variables. Further, Tukey post hoc comparisons were carried out to identify pair-wise differences between groups. Finally, comparisons (one-way ANOVA and χ^2 applied as appropriate) between the different clusters were carried out to examine possible differences in sociodemographic, clinical, functional, and pharmacological treatment variables. Using an ANOVA model, the three clusters were considered as the fixed factor and the sociodemographic, clinical, and functional variables as the dependant variables. Clusters were also compared regarding frequencies of each type of medication and doses of lithium. Statistical significance was set at $p < 0.05$. Bonferroni corrections were not used due to the exploratory nature of the study.

Results

Regarding clinical and demographic variables, comparisons between patients with BD-II and HC revealed statistically significant differences in global functional outcome (FAST), with better psychosocial functioning for HC ($p < 0.001$) and higher subsyndromal depressive symptom scores (HAM-D) for patients with BD-II ($p < 0.001$). With regard to neurocognition, data analysis revealed that patients with BD-II, as a whole, performed significantly worse than HC on all neurocognitive composites (all $p \leq 0.001$) (Table 1).

BD-II clusters

Four out of 64 patients were excluded from the cluster analysis since some cognitive measures were missing. Visual inspection of the dendogram provided evidence for three clusters for 60 patients with BD-II. The first cluster included 29 subjects (48.3%), the second cluster included 24 patients (40%), and the third cluster included seven patients (11.6%). The DFA also revealed the validity of the three clusters, with the presence of two discriminant functions explaining 92.6% and 7.4% of the variance, respectively (Wilks' $\lambda = 0.159$, $\chi^2 = 100.052$, $p < 0.001$; Wilks'

Table 1. Clinical, sociodemographic, and cognitive variables

	Bipolar II disorder (n = 64)	Healthy controls (n = 52)	Statistical analyses	
Demographic and clinical variables	Mean (SD)	Mean (SD)	*t*	p-value
Age, years	43.92 (9.91)	40.04 (13.42)	−1.736	0.086
Educational level, years	13.94 (3.98)	12.92 (3.81)	−1.373	0.172
Estimated premorbid IQ	107.27 (11.51)	108.27 (8.27)	0.545	0.587
Age at onset, years	25.22 (9.25)	–		
Chronicity	17.63 (11.07)	–		
Total no. of episodes	16.78 (15.56)	–		
Hypomanic episodes	7.02 (7.59)	–		
Depressive episodes	8.75 (8.36)	–		
No. of hospitalizations	0.85 (1.43)	–		
Age at first hospitalization, years	31.88 (10.61)	–		
FAST total score	24.40 (11.68)	4.48 (5.13)	−10.964	**<0.001**
HAM-D score	4.28 (2.61)	1.93 (1.60)	−5.603	**<0.001**
YMRS score	1.74 (1.88)	–		
	n (%)	n (%)	Chi square	p-value
Gender, female	43 (67.2)	34 (65.4)	0.042	0.838
Lifetime psychotic symptoms	17 (26.5)	–		
Psychotic symptoms in first episode	8 (12.5)	–		
Axis II comorbidity	15 (23.4)	–		
Family history of affective disorders	48 (75)	–		
History of suicidal attempt	24 (37.5)	–		
Cognitive composites	Mean (SD)	Mean (SD)	*t*	p-value
Processing speed	−1.09 (1.35)	0.00 (0.76)	5.471	**<0.001**
Working memory	−0.65 (1.14)	0.00 (0.91)	3.344	**0.001**
Verbal memory	−0.79 (1.31)	0.01 (0.92)	3.851	**<0.001**
Visual memory	−0.78 (1.20)	0.00 (1.00)	3.778	**<0.001**
Executive function	−0.60 (1.14)	0.00 (0.72)	3.488	**0.001**
Attention	−1.51 (1.84)	0.00 (0.72)	5.414	**<0.001**

SD = standard deviation; IQ = intelligence quotient; FAST = Functioning Assessment Short Test; HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.
Bold text in the table indicates significant values.

$\lambda = 0.766$, $\chi^2 = 14.503$, $p = 0.013$, respectively). A total of 90% of subjects were correctly classified in the DFA. Verbal memory and attention composites showed the highest standardized coefficients (−0.67 and 0.49, respectively) and therefore these composites had a contribution than the other composites to the assigning of patients with BD-II to the clusters.

Patients in the first group were neurocognitively preserved when compared with the HC group (*intact group*), with scores between 0.5 SD above the mean and 1.0 SD below the mean (Fig. 1). The second cluster had an intermediate neurocognitive profile (*selective group*) with a statistically significantly poorer performance in all cognitive domains when compared to the HC. However, they did not differ from the intact group in working memory ($p = 0.088$) and executive function ($p = 0.087$) domains. The scores obtained by this group of patients ranged between 0.5 and 1.7 SDs below the mean, therefore showing mild deficits. It is worth mentioning that scoring ≤1.5 SD below the HC group mean captures participants performing below the normative seventh percentile level, for instance, in processing speed, verbal memory and attention. Finally, patients in the third cluster were significantly impaired in all cognitive domains (*globally impaired group*). All neurocognitive composites showed significant differences compared with patients in the intact group. However, when compared with the selective group, the globally impaired group showed a statistically significantly poorer performance in processing speed ($p = 0.003$), working memory ($p = 0.002$), executive functions ($p < 0.001$), and attention domains ($p < 0.001$), whereas there were no significant differences in verbal ($p = 0.993$) and visual memory ($p = 0.077$). All scores obtained by the globally impaired group ranged between 1.5 and 4.5 SDs below the mean, and hence impairment ranged from moderate to severe, with the exception of verbal memory, where only a mild deficit (<1.5 SD) was detected (Table 2).

Comparisons between BD-II clusters on sociodemographic and clinical variables

There were no differences among the three clusters in age ($p = 0.057$), gender ($p = 1.000$), and educational level ($p = 0.057$). There were, however, differences on estimated premorbid IQ ($p = 0.002$), with pair-wise comparisons indicating statistically significant differences between patients belonging to the globally impaired group and the other two groups (Table 3), but not between the selective and the intact groups.

When clinical variables were considered, no significant differences were found for age at illness onset ($p = 0.348$), chronicity ($p = 0.074$), total number of episodes ($p = 0.540$), number of hypomanic episodes ($p = 0.350$), number of depressive episodes ($p = 0.692$), number of hospitalizations ($p = 0.870$), manic/depressive symptomatology at the time of assessment ($p = 0.783$ and $p = 0.138$, respectively), lifetime psychotic symptoms ($p = 0.558$), or family history of affective disorders ($p = 0.118$).

Concerning functional outcome, significant differences emerged among groups ($p = 0.021$). Specifically, the globally impaired group showed poorer global functioning compared to the other two groups. When the different domains of the FAST were analyzed, a significant effect of group was also found for leisure performance ($p = 0.001$). In this sense, the globally impaired group presented greater difficulties than both the intact and the selective groups. When the influence of pharmacological treatment was evaluated, no differences were observed among the three clusters on type of medication [lithium ($p = 1.000$), other mood stabilizers ($p = 0.394$),

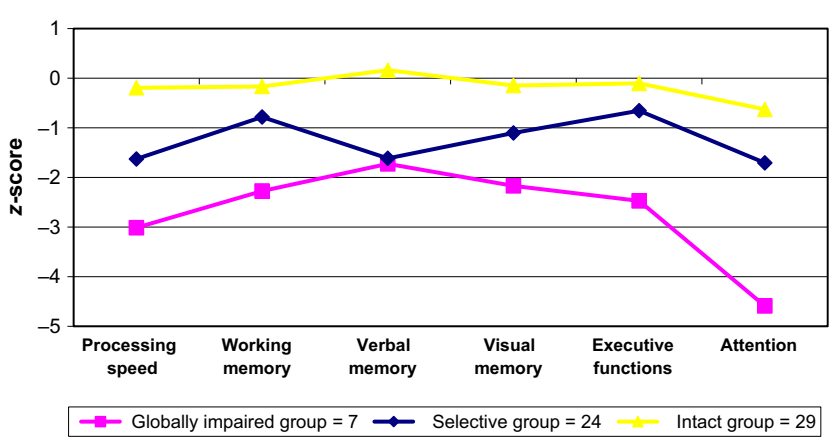

Fig. 1. Neurocognitive profiles of three bipolar II disorder (BD-II) clusters.

Table 2. Comparisons between the three neurocognitive bipolar disorder clusters and the healthy controls

	Globally impaired[a] (G) (n = 7)	Selectively impaired (S) (n = 24)	Cognitively intact (I)[b] (n = 29)	Healthy controls (HC) (n = 52)	Statistical analyses		Post hoc tests					
					F	p-value	G vs S	G vs I	G vs HC	S vs I	S vs HC	I vs HC
Processing speed	−3.01 (1.18)	−1.62 (0.96)	−0.19 (0.99)	0.00 (0.76)	37.087	**<0.001**	**0.003**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.792
Working memory	−2.27 (0.82)	−0.78 (0.96)	−0.16 (0.98)	0.00 (0.91)	14.279	**<0.001**	**0.002**	**<0.001**	**<0.001**	0.088	**0.006**	0.870
Verbal memory	−1.72 (0.82)	−1.61 (1.13)	0.16 (0.80)	0.01 (0.92)	24.884	**<0.001**	0.993	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.902
Visual memory	−2.16 (1.14)	−1.10 (1.11)	−0.14 (0.93)	0.00 (1.00)	14.077	**<0.001**	0.077	**<0.001**	**<0.001**	**0.005**	**<0.001**	0.926
Executive function	−2.47 (0.94)	−0.65 (1.16)	−0.10 (0.68)	0.00 (0.72)	19.880	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.087	**0.010**	0.944
Attention	−4.58 (1.16)	−1.70 (1.72)	−0.62 (1.14)	0.00 (0.72)	27.056	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.014**	**<0.001**	0.287

Bold text in the table indicates significant values.
Values are presented as mean (standard deviation).
[a]11.6%.
[b]40%.
[c]48%.

antipsychotics (p = 0.275), antidepressants (p = 1.000), or anxiolytics (p = 0.270)]. Possible associations between doses of lithium or benzodiazepines and neurocognitive composites were also explored, but no statistically significant correlations were observed. Consequently, analyses of group differences in cognitive performance were performed with no need to control for treatment characteristics. Concerning lithium doses, which ranged from 200 to 1,600 with a mean dosage of 939.13 (±310.04 SD) mg/day, there were no significant differences among the three clusters (p = 0.684).

Discussion

As far as we know, this is the first hierarchical cluster analysis aiming to examine cognitive profiles in a sample exclusively composed of euthymic patients with BD-II. Similar to recent literature on BD (20), the analysis provides a three-cluster solution: a neuropsychological intact group of patients, a globally and significantly cognitively impaired group and an intermediate neuropsychological group.

First, verbal and visual memory domains may play an important role in the differentiation between the preserved group and the impaired groups, since the impaired groups showed mild to moderate deficits in these areas, and did not differ significantly from one another. Second, it seems that significant processing speed and attentional impairments might lead to more difficulties in other cognitive areas, since patients in the globally impaired group showed severe impairments in these areas. Likewise, these deficits may seriously compromise functional outcome, since the globally impaired group was the most functionally affected. Third, working memory and executive functions might also discriminate between the selective and the globally impaired groups. The former had a similar performance to the intact group, although it was statistically different from that of the HC. However, this lower performance was non-clinically meaningful since *z*-scores did not exceed −1 SD. In contrast, the globally impaired group showed higher deficits (moderate) in both cognitive areas.

It is interesting to remark that approximately 48% of patients with BD-II presented a preserved neuropsychological performance. This prevalence of cognitive normality does not seem surprising given previous findings of similar levels of performance in patients with BD-I and psychotic patients with BD (18, 19). Even so, a large number of different criteria have been used to establish the prevalence of neurocognitive impairment. For instance,

Table 3. Comparisons of clinical and sociodemographic characteristics between the three clusters

	Globally impaired (G) (n = 7) Mean (SD)	Selectively impaired (S) (n = 24) Mean (SD)	Cognitively intact (I) (n = 29) Mean (SD)	Statistical analyses		Post hoc tests		
				F	p-value	G vs S	G vs I	S vs I
Age, years	45.43 (9.91)	46.96 (9.20)	40.48 (10.21)	3.005	0.057			
Educational level, years	10.33 (2.65)	14.04 (3.98)	14.66 (4.06)	3.021	0.057			
Estimated premorbid IQ	93.57 (12.15)	106.88 (9.53)	110.17 (11.29)	6.762	**0.002**	**0.015**	**0.001**	0.509
Age at onset, years	29.00 (10.84)	23.54 (8.96)	25.17 (7.98)	1.076	0.348			
Chronicity	15.14 (10.14)	21.65 (12.71)	14.83 (9.31)	2.725	0.074			
Total no. of episodes	11.40 (7.23)	18.74 (19.97)	15.07 (11.74)	0.623	0.540			
No. of hypomanic episodes	4.40 (5.07)	8.48 (10.13)	5.82 (4.77)	1.070	0.350			
No. of depressive episodes	7.00 (2.45)	9.48 (10.43)	7.68 (6.73)	0.371	0.692			
No. of hospitalizations	1.17 (1.16)	0.83 (1.75)	0.83 (1.31)	0.140	0.870			
Age at first hospitalization, years	34.33 (10.11)	35.79 (14.61)	27.67 (5.69)	1.688	0.209			
FAST Total Score	36.50 (14.96)	23.82 (9.64)	22.00 (11.46)	4.153	**0.021**	**0.044**	**0.016**	0.841
FAST Autonomy	4.40 (3.91)	2.24 (2.92)	2.39 (2.69)	1.137	0.330			
FAST Occupational	11.60 (6.54)	9.47 (5.22)	8.00 (6.20)	0.874	0.425			
FAST Cognitive	9.40 (4.82)	6.15 (2.81)	5.43 (3.23)	3.019	0.060			
FAST Financial	0.80 (1.30)	1.12 (1.21)	0.78 (1.16)	0.405	0.669			
FAST Relationships	6.40 (2.96)	4.65 (3.63)	3.96 (3.09)	1.156	0.325			
FAST Leisure	4.20 (1.30)	1.53 (1.23)	1.48 (1.62)	7.670	**0.001**	**0.002**	**0.001**	0.993
HAM-D score	6.17 (2.31)	4.45 (2.95)	3.81 (2.32)	2.059	0.138			
YMRS score	2.00 (2.09)	1.50 (1.65)	1.81 (2.04)	0.246	0.783			
	n (%)	**n (%)**	**n (%)**	χ^2	**p-value**			
Gender, female	5 (71.4)	16 (66.7)	19 (65.5)	0.089	1.000			
Lifetime psychotic symptoms	1 (16.7)	8 (33.3)	6 (20.7)	1.377	0.558			
Family history of affective disorders	5 (83.3)	15 (62.5)	25 (86.2)	4.262	0.118			
Type of medications								
Lithium	3 (42.9)	11 (47.8)	13 (46.4)	0.054	1.000			
Other anticonvulsants	4 (57.1)	11 (47.8)	19 (67.9)	2.096	0.394			
Antipsychotic	5 (71.4)	11 (47.8)	10 (37.0)	2.726	0.275			
Antidepressant	4 (57.1)	12 (52.2)	14 (51.9)	0.066	1.000			
Anxiolytic	4 (57.1)	9 (40.9)	8 (27.6)	2.472	0.270			
Lithium doses, mean (SD)	900 (141.42)	880 (193.21)	1,000 (409.87)	0.387	0.684			

SD = standard deviation; IQ = intelligence quotient; FAST = Functioning Assessment Short Test; HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.
Bold text in the table indicates significant values.

if we had used the so-called soft criteria (at least one cognitive domain with a performance of 1.5 SDs below the mean) and hard criteria (at least two domains with values of 2 SDs below the mean) proposed by Martino and colleagues (40), rates of neurocognitive impairment would have varied considerably in the same sample of patients with BD-II: 44 patients (68.7%) would have been considered as neurocognitively impaired with the soft criteria (31.3% unimpaired), whereas 19 patients (29.6%) would have been classified as impaired with the hard criteria (70.3% unimpaired). Therefore, different results would have been obtained depending on the criteria employed to define patients with or without clinically significant deficits. For that reason, there is a need to reach a consensus concerning the cut-off values with which to establish neurocognitive impairment in BD. We should take into account that the main objective of the cluster analysis is not to establish levels of impairment but to gather together a set of subjects in such a way that subjects in the same cluster are more similar (e.g., in their neuropsychological pattern) than those individuals belonging to other groups. Cluster analysis provides another way to understand the nature of the neurocognitive heterogeneity in BD.

Although parts of our findings are consistent with previous works, there are some differences that should be mentioned. The sample of unimpaired patients in the study conducted by Burdick and colleagues (20) was smaller than the intact group in our study; hence, their severely impaired cluster (near 40%) was larger than ours (11.6%). This difference might be explained by the fact that our sample was exclusively composed of patients with BD-II, a subtype of patients who may be less neurocognitively affected to a lesser degree in

quantitative terms (41–43). Despite this, Burdick et al. did not find any differences regarding the diagnostic subtype distributions by neurocognitive cluster. Other possible explanations for the differences between studies may be related to differences in sample sizes or to the cluster analysis procedure by itself, since it is more sensitive to group by similarity in pattern of performance than by level of impairment. However, other factors may also be related to discrepancies between the two studies: for instance, the fact that patients with BD-II had a higher premorbid IQ and lower subsyndromal depressive symptom scores in comparison with the patients from the study by Burdick and colleagues.

It is also remarkable that deficits in the globally impaired group of patients were sited more than 2 SDs below the mean of the HC, ranging from moderate to severe impairment in all neurocognitive domains, with the exception of a mild deficit in verbal memory. In the light of previous evidence concerning BD-II, we did not expect to detect a global cognitive impairment but rather mild or moderate deficits in specific cognitive areas (42, 43). Nevertheless, this neurocognitive subgroup consisted of only seven patients (12%) and it is therefore not possible to draw any strong inferences regarding the nature of the cognitive deficits in this group. No clinical variables related to severity of the illness, such as the total number or type of episodes, explained this global neurocognitive impairment. These data contrast with the findings of Burdick et al. (20) and with several other previous studies (3, 44), whereas they are similar to those of another study that did not find any relationship between neurocognitive performance and illness duration in patients with BD-II (42). Moreover, our study failed to detect any differences among clusters in terms of psychotic and subsyndromal symptomatology. Nevertheless, it should be kept in mind that psychotic symptoms are not as common in BD-II as they are in patients with BD-I, and that in patients with BD-II they only occur in the context of depressive episodes. Furthermore, studies reporting an association between number of episodes and cognitive impairment have suggested that most of the harm was specifically associated with the number of manic episodes, which are absent in BD-II (45, 46). In this regard, meta-analytic findings have suggested that patients with BD-II would be less impaired than those with BD-I, which could be related to neurotoxic effects of severe manic episodes on medial temporal structures (1). Nevertheless, it is important to mention that, although several cross-sectional studies have suggested an association between a higher number of episodes and cognitive dysfunction, there is no conclusive evidence of this, with current longitudinal research findings not supporting the notion of a progressive cognitive decline over time in BD (47, 48). On the other hand, regarding the absence of differences in subsyndromal depressive symptoms, this may be influenced by a lack of statistical power due to the small size of each cluster (mainly the globally impaired), and thus results should be interpreted in the light of this caveat.

Beyond cognitive variables, regarding the functional outcome, the globally impaired group showed a poorer global functional performance and more difficulties to engage in leisure activities, whereas the other two groups did not differ from each other. In this sense, our data are congruent with those of previous studies indicating that cognitive disturbances play an important role in the overall functional outcome of patients with BD. Likewise, numerous studies have established a predictive value of cognition for the functional outcome of BD (8, 49, 50). However, it is worth mentioning that the association between cognition and functional outcome is not yet completely understood. Through the use of latent class analysis to classify patients on the basis of their functional outcome, Reinares et al. (51) reported that the variability in functional outcome derived from true heterogeneity within the patient population, which could be captured by at least two dimensions representing clinical severity and cognitive dysfunction. Another issue to take into account is that subjective cognitive complaints do not always correspond to objective cognitive impairment, as some patients may be unable to correctly evaluate their own cognitive function (52, 53). Interestingly, subjects with BD-II have been found to experience more cognitive complaints than those with BD-I (52, 54). Other studies have found a strong association between subjective cognitive function and self-rated psychosocial function, highlighting the potential role of subjective cognitive measures as clinically relevant tools to elucidate the functional level of patients with BD (53). In addition, another reason for the conflicting evidence regarding this association could be related to the inability of neuropsychological tests to reflect a cognitive decline from premorbid levels, whereas observer-based measures such as the FAST may better capture patients' loss of functional capacity.

Finally, clusters differed in premorbid IQ. Specifically, patients in the globally impaired group were characterized by a significantly lower premorbid IQ, as in the study conducted by Burdick and colleagues (20). In our study, premorbid IQ was estimated with the vocabulary subtest, a

measure that is highly correlated with education and which may also be a good indicator of premorbid functioning. Concerning educational level, our study was not able to detect significant differences between groups, although a trend was found in this regard. Patients belonging to the globally impaired group showed lower attainments. However, as Lewandowski et al. (55) pointed out, the direction of the relationship between educational level and neurocognitive performance is still not clear. Similarly, due to the fact that all patients in the globally impaired group showed an estimated lower premorbid IQ, we cannot rule out the possibility that the marked functional impairment could reflect a lower IQ or, alternatively, that the global cognitive deficits could merely reflect a lower IQ. Nonetheless, we should take into consideration that IQ was within the normal range without clinical significance.

Interestingly, leisure activities, premorbid IQ and educational level have been considered as proxy measures of cognitive reserve (56–58). Cognitive reserve appears to be protective against cognitive and functional decline (58, 59). In fact, some authors have suggested that the implementation of programs based on functional remediation (60) and aiming to enhance cognitive reserve in early stages of the illness may help to prevent the potential decline of cognitive and psychosocial functioning (58, 61). Therefore, early detection of patients with BD-II with lower scores in these proxy variables may be useful for the implementation of programs designed to prevent a putative cognitive decline.

Likewise, the identification of different neurocognitive profiles may help to design tailored cognitive and functional remediation programs. In this sense, the efficacy of functional remediation has also been demonstrated when applied to neurocognitively impaired patients (BD-I and BD-II), improving not only functional outcome but also some cognitive functions such as verbal memory (62). Moreover, another point to bear in mind is that neurocognitive impairment might help to explain, at least to some extent, the success or failure of other psychological interventions.

Our data may not be totally comparable to those of Burdick and colleagues (20) because of the use of different neurocognitive batteries. As Lewandowski and colleagues (55) have already pointed out, differences in cluster profiles may reflect, at least in part, the different tests used to obtain the clusters. Actually, one of the strengths of our study is the use of a very comprehensive neuropsychological battery, which was specifically designed for the assessment of patients with BD. Additionally, this battery also prioritizes the accurate assessment of some cognitive domains which have been traditionally reported to be impaired in this group of patients, for instance, the executive functions. The inclusion of more difficult measures or a larger number of tests tapping each cognitive domain would lead to increased test sensitivity (63). In this regard, the ISBD-BANC proposal incorporates some more complex cognitive measures with the goal to be sensitive in identifying patients with lesser cognitive impairment. Our battery is not identical but is equivalent to the ISBD-BANC proposal, since we used most of the recommended tests or nearly identical versions (21). Despite the fact that social cognition was not assessed in the current study, a large amount of evidence indicates that patients with BD might actually have quite preserved social cognition, with only impairment in a few social cognition components (64–67). However, it is important to highlight that, in the study conducted by Burdick and colleagues, patients in the cognitively intact group were superior to the HC in the social cognition task. Hence, social cognition should be assessed in future cluster analysis research in order to replicate these results in BD-II samples.

This study has some limitations. First, a larger samples of patients with BD-II will be required to replicate our results to support the reproducibility of the neurocognitive subtypes, since the unequal size of clusters may have differentially influenced the power of the study. In addition, larger group sizes could result in more significant differences in clinical and demographic variables being obtained. In this sense, one methodological caveat to take into account is that our study was an exploratory analysis with a descriptive purpose, and therefore Bonferroni correction was not used to control for multiple comparisons, which may have increased the false positive rate in the study. A second limitation has to do with the tertiary nature of the Barcelona Bipolar Disorder Program. Our sample may represent a more severely affected subgroup of patients which may limit the generalizability of our results and might not be representative of all patients with BD. Third, a cross-sectional design does not make it possible to assess the stability of these neurocognitive profiles. Finally, the effects of psychopharmacological treatments were not analyzed. Definitive data are lacking concerning the influence of drugs on cognition in BD (68, 69).

Conclusions

Despite the abovementioned limitations, our study adds to the canon of knowledge about cognitive heterogeneity among patients with BD and,

specifically, within the BD-II subtype. This cognitive variability highlights the need to design tailored programs aimed at improving cognition and psychosocial functioning. Proxies related to cognitive reserve may have a significant impact on both cognitive and psychosocial functioning and should be considered in future studies. According to our results, nearly 50% of patients with BD-II were cognitively preserved, while severe global deficits affected almost 12% of patients. Cognitive deficits are associated with poor psychosocial functioning but this relationship appears not to be linear; some patients who show cognitive impairment may have good functioning, whereas other patients who are cognitively preserved may be functionally impaired. These findings have implications for the concept of staging (70), which may help to guide specific and tailored pharmacological and psychosocial interventions to distinct patient subgroups (71, 72). In addition, the inclusion of other clinical variables such as affective temperaments as well as comorbidities that might have a substantial impact on neuropsychological performance in patients with BD-II (72–75) could be of interest to provide additional information concerning the possible influence of these factors in the different cognitive profiles. Meanwhile, according to our findings, the assessment of neuropsychological performance appears to be as relevant in BD-II as in BD-I, and should probably be part of the standard baseline evaluation in all patients with BD.

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