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Research report

Toward the identification of neurocognitive subtypes in euthymic patients with bipolar disorder

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ABSTRACT

Background: Cross-sectional and meta-analytic studies showed that patients with bipolar disorder (BD) had neurocognitive impairments even during periods of euthymia. The aim of this study was to estimate the prevalence of BD patients with and without clinically significant cognitive impairments, as well as to analyze clinical and functional variables in these subgroups.
Methods: Hundred patients with BD and 40 healthy controls were assessed with an extensive neurocognitive assessment. Soft (some cognitive domain with a performance below 1.5 SD of the mean) and hard (at least two domains with values below 2 SD of the mean) criteria were utilized to define clinically significant cognitive impairments.
Results: Using both soft and hard criteria, the prevalence of clinically significant cognitive impairments was higher in people with BD than in healthy controls. 70% of patients only showed failures of small effect (d=0.21–0.35) in 2 measures of executive functions. Moreover, 30% of patients were indistinguishable from healthy subjects in terms of both neurocognitive and psychosocial functioning. On the contrary, 30% of the sample showed more severe cognitive deficits than those usually reported in literature and had the worst psychosocial functioning.
Conclusions: The fact that cognitive impairments are very heterogeneous among euthymic patients with BD could contribute to understanding differences in functional outcome. Theoretical and practical implications of these findings are discussed.

1. Introduction

Neurocognitive functioning in euthymic patients with bipolar disorder (BD) has been neglected for decades before the release of a number of recent studies that specifically focused on this topic. Over the last 10–15 years, neuropsychological research has built a robust body of evidence supporting that, compared with healthy controls, euthymic patients with BD have impairments in verbal memory, attention, and executive functions with medium–large effect size (Robinson et al., 2006; Torres et al., 2007; Mann-Wrobel et al., 2011). Cognitive deficits in BD could be extended to different subtypes of the disease (Martino et al., 2011a; Bora et al., 2011) and beyond traditional neurocognitive domains (Martino et al., 2011b; Samamé et al. 2012). Likewise, the association between cognitive deficits and functional outcome reached by the patients with BD has been consistently reported both in cross-sectional (Zubieta et al., 2001; Dickerson et al., 2004; Martinez-Arán et al., 2004) and longitudinal (Jaeger et al., 2007; Tabarés-Seisdedos et al., 2008; Martino et al., 2009) studies.

Therefore, in few years, cognitive impairments changed from being an ignored issue to have an essential role in the pathophysiology and clinical conceptualization of BD. However, the same evidence applies to patients who maintain a high level of social and occupational functioning despite their illness (Coryell et al., 1998; Goldberg and Harrow, 2004). This apparent paradox between patients with high-functioning and cognitive deficits with medium–large effect size could be explained as a consequence of the statistical analysis used in cross-sectional studies and meta-analyses. In fact, the expression of means and effect sizes could be responsible for undetected differences between patient subgroups. An alternative approach is to estimate the

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prevalence of clinically significant cognitive deficits among patients. In a preliminary study from our group, we found that 38% of patients had no clinically significant cognitive deficits, while 40% presented impairments in 1 and 2 cognitive domains, and 22% in 3 or more (Martino et al., 2008). Further studies reported that the prevalence of patients without clinically significant cognitive impairments fluctuates between 43 and 70% (Gualtieri and Morgan, 2008; Reichenberg et al., 2009; Iverson et al., 2011). These findings suggest that studies reporting mean values of neurocognitive functioning in BD might be failing to recognize that a subgroup of patients accounts for most of the impairment. Differences in the prevalence found between studies may depend, at least in part, on the criteria used to define patients with or without clinically significant deficits. Usually, by convention, cognitive impairment is considered when a domain score is more than 2 standard deviations (SD) below the mean. The studies mentioned above used from permissive or 'soft' criteria such as just 1 domain score between 1 and 2 SD below the mean, to more conservative or 'hard' criteria such as 2 domain scores 2 SD below the mean to define patients with clinically significant impairments. A further limitation of these studies was that they employed a sample of convenience in which no formal diagnostic interviewing or symptom rating scales were used.

The existence of subgroups in terms of cognitive functioning may have important implications, since typifying homogeneous phenotypes of BD would be useful for genetic, pathophysiological, and therapeutic studies. Therefore, the aim of this study was to expand our prior findings about the prevalence of clinically significant cognitive impairments in a larger sample of BD with strict criteria of euthymia. For this purpose, data were evaluated with two different but complementary analyses. First, patients were separated in those with and without clinically significant deficits using soft and hard criteria. Then, these subgroups were compared for neurocognitive functioning with healthy controls by traditional mean and effect size. An additional aim was to compare these subgroups for clinical variables and functional outcome.

2. Methods

Hundred subjects were consecutively selected from the outpatients population of the Bipolar Disorder Program of the Favaloro University with the following inclusion criteria: age between 18 and 60 years old; diagnosis of BD type I (BDI) or BD type II (BDII) according to DSM-IV using Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996); euthymic (defined by Hamilton Depression Rating Scale ≤ 9 and Young Mania Rating Scale ≤ 8) for at least 8 weeks. Exclusion criteria were: antecedent history of substance abuse, history of mental retardation, neurological disease or any unstable clinical condition (like diabetes or hypothyroidism) that could affect cognitive performance. Additionally, 40 healthy controls matched by age and years of education were included: these had no antecedent of neurological disease, neither history of psychotic or affective disorders in themselves or a first-degree family member, and they were not taking psychotropic medication. The study was approved by the Hospital Ethics Committee and all subjects gave written informed consent for their participation after receiving a complete description of the study.

2.1. Clinical assessment.

In addition to SCID, all subjects were evaluated with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and Young Mania Rating Scale (YMRS) (Young et al., 1978). Additional demographical and clinical information were obtained from clinical charts and direct patients interview (age, gender, years of education, age at illness onset, length of illness, bipolar subtype, previous manic/hypomanic and depressive episodes, and lifetime history of psychosis). When possible, attempts were made to verify these historical data with third-party reports (such as medical records and family interview). Exposure to antidepressants, mood stabilizers, antipsychotics, and benzodiazepines at baseline was assessed by 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 different groups of psychotropic medications in a 0–5 points range (0=no medication, 1=sporadic low dose, 2=continue low dose; 3=middle dose, 4=high dose, and 5=very high dose).

2.2. Neurocognitive assessment

After completion of the baseline clinical assessment, patients performed an extensive neuropsychological battery selected to assess the following cognitive domains: 1) Attention: Forward Digit Span (Wechsler, 1955), and Trail Making Test part A (Reitan, 1958); 2) Verbal memory: Memory Battery of Signoret (Signoret and Whiteley, 1979). This test evaluates the serial learning of a twelve word list of different semantic categories (3 trials), free delay recall, and recognition with semantic clues and multiple options of them; 3) Language: Boston Naming Test (Kaplan et al., 1983); and 4) Executive functions: Wisconsin Card Sorting Test (Heaton, 1981), Trail Making Test part B (Reitan, 1958), Backward Digit Span (Wechsler, 1955), and Phonological Fluency (Benton et al., 1983). Additionally, estimated premorbid IQ was calculated with the WAIS vocabulary subtest (Wechsler, 1955).

One experienced psychiatrist (SAS) examined clinically all subjects at study entry. All neuropsychological tests were administered by other physician (DM) in a quiet testing room according to a standardized order.

2.3. Statistical analysis

Raw-score of neurocognitive performance were transformed to *Z*-scores based on normative data of each test. Soft (at least one cognitive domain with a performance of 1.5 SD below the mean) and hard (at least two domains with values 2 SD below the mean) criteria were utilized to define clinically significant cognitive impairments. Then, three groups were conformed based on soft criteria (S-cognitive-preserved, S-cognitive-impaired, and healthy controls) and 3 based on hard criteria (H-cognitive-preserved, H-cognitive-impaired, and healthy controls).

The assumption of normality and homoscedasticity of each variable was analyzed with the Kolmogorov–Smirnov normality test and Levene test respectively. The three groups were compared for clinical-demographical and neurocognitive variables using analysis of variance (ANOVA), Kruskal–Wallis analysis of variance, or chi squared tests as appropriate. In order to decrease the risk of type I error due to several comparisons a Bonferroni correction was applied. When main effects were presented, post-hoc analysis was performed with Tukey test or Mann–Whitney tests (in the latter instance also with correction for multiple comparisons). The effect sizes (Cohen's D) were calculated to find the differences between the groups in terms of standard deviation.

3. Results

Clinical and demographical features of patients and healthy controls are shown in Table 1. All patients were receiving mood stabilizers at time of testing (IFD mean=3.01, SD=0.88),

Table 1
Clinical and demographical characteristics of bipolar patients and healthy controls (values are expressed as mean, standard deviation is shown in brackets).

	Bipolar patients ($n=100$)	Healthy controls ($n=40$)	Test/p-value
Age[a]	39.55 (10.83)	40.28 (12.03)	$F=0.12$; $p=0.73$
Gender (% female)[b]	64	70	$X^2=0.46$; $p=0.50$
Years of education[a]	14.36 (2.36)	13.88 (2.77)	$F=1.01$; $p=0.30$
Premorbid IQ (Z-score)[a]	0.52 (0.56)	0.48 (0.58)	$F=0.19$; $p=0.56$
YMRS score[c]	0.99 (1.45)	0.73 (0.93)	$Z=-0.36$; $p=0.72$
HDRS score[a]	2.01 (2.00)	1.90 (1.81)	$F=0.091$; $P=0.76$
GAF score[c]	80.18 (9.69)	90.35 (5.58)	$Z=-5.87$; $P<0.001$
Age at onset	27.65 (9.49)		
Length of illness	11.18 (6.67)		
No of previous depressive episodes	3.46 (2.01)		
No of previous hypo/manic episodes	3.18 (2.09)		
Clinical subtype (% type I)	51		
History of psychosis (%)	49		

BD: Bipolar disorder; IQ: Intelligence quotient; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale.
[a] ANOVA (df=1, 139).
[b] Chi-square.
[c] Mann–Whitney.

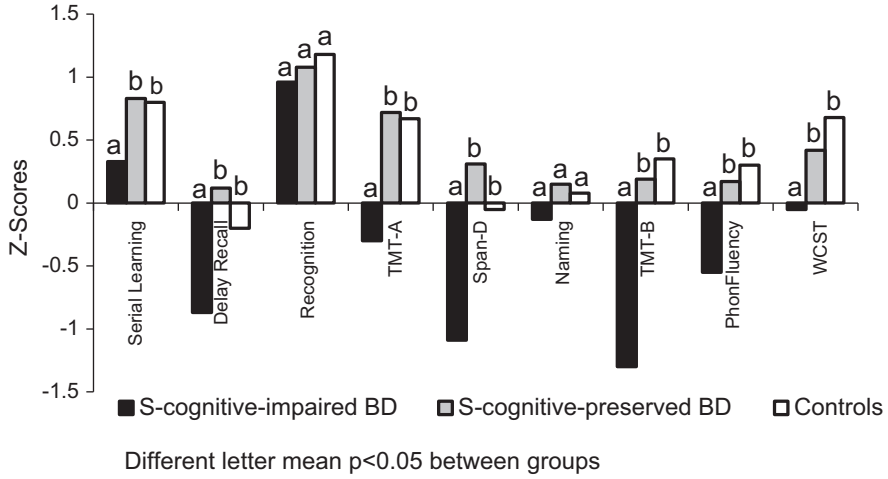

Fig. 1. Comparison of neurocognitive performance between patients with and without clinically significant cognitive impairments defined using 'soft' criteria and healthy controls. BD: Bipolar disorder; TMT-A: Trail Making test part A; Span D: Forward digit Span; TMT-B: Trail Making test part B; PhonFluency: Phonological fluency; WCST: Wisconsin Card Sorting Test.

additionally 38% were receiving antidepressants (IFD mean=2.31, SD=1.07), 55% benzodiazepines (IFD mean=2.00, SD=0.96), and 55% antipsychotics (IFD mean=1.95, SD=0.72).

Taking into account "soft" criteria, 70% of patients and 27.5% of healthy controls showed clinically significant cognitive impairments (Chi-square=19.46; $p<0.001$). S-cognitive-impaired patients had lower performance than controls in measures of verbal memory, attention, and executive functions while there were no differences in these variables between S-cognitive-preserved patients and healthy subjects (Fig. 1). Compared with S-cognitive-preserved patients, those with S-cognitive-impaired had a trend to greater number of hospitalizations (mean=0.89, SD=1.54 vs. mean=0.21, SD=0.10; Mann–Whitney $Z=-2.32$; $p=0.020$). There were no other differences between patient groups in terms of demographical and clinical variables (age, gender, years of education, age at illness onset, length of illness, bipolar subtype, previous manic/hypomanic and depressive episodes, and lifetime history of psychosis) as well as in pharmacological exposure (all $p>0,05$). Finally, S-cognitive-impaired patients had worse psychosocial functioning (mean=77.34, SD=9.50) than both S-cognitive-preserved patients (mean=87.03, SD=6.12; Mann–Whitney $Z=-4.67$; $p<0.001$) and healthy controls (mean=90.35, SD=5.58; Mann–Whitney $Z=-6.72$; $p<0.001$), while there was no difference between these last two groups (Mann–Whitney $Z=-2.19$; $p=0.084$).

Considering hard criteria, 30% of patients and 7.5% of controls experienced clinically significant cognitive deficits (Chi-square=6.83; $p=0.009$). Differences between groups in terms of neurocognitive variables are shown in Table 2. H-cognitive-preserved patients had lower performance than controls only in two measures of executive function and with small effect sizes. Contrarily, H-cognitive-impaired patients had poorer neurocognitive functioning in all measures with large effect sizes (Table 2). There were no differences between patient groups for clinical-demographical or pharmacological variables (all $p>0.05$).

Finally, we compared the 30% of patients with best and worst cognitive functioning (S-cognitive-preserved and H-cognitive-impaired respectively) in terms of clinical-demographical variables; results are shown in Table 3. The patients with the best cognitive performance had higher levels of psychosocial functioning than those with the worst cognitive performance.

4. Discussion

Traditional cross-sectional and meta-analytic studies showed consistently that patients with euthymic BD had impairments in

Table 2
Comparison of neurocognitive performance between patients with and without impairments using hard criteria and healthy controls (values are expressed as mean of *Z*-score, standard deviation is shown in brackets).

	H-cognitive-impaired (A) ($n=30$)	H-cognitive-preserved (B) ($n=70$)	Controls (C) ($n=40$)	Test	Groups Comparison; *p*-value (effect size)		
					Av. B	Bv. C	Av. C
Premorbid IQ[a]	0.29 (0.67)	0.62 (0.47)	0.48 (0.57)	$X^2=10.8$	0.06	0.21	0.13
Verbal memory							
Serial learning[b]	−0.35 (1.45)	0.84 (1.11)	0.80 (1.10)	$F=11.3$**	<0.001	0.98	<0.001 (0.96)
Delay recall[a]	−1.57 (1.34)	−0.15 (0.96)	−0.20 (1.26)	$X^2=29.9$**	<0.001	0.90	<0.001 (1.20)
Recognition[a]	0.80 (0.67)	1.08 (0.35)	1.17 (0.35)	$X^2=8.4$			
Attention							
Forward digit span[b]	−1.29 (1.42)	−0.40 (1.27)	−0.05 (1.07)	$F=8.71$**	0.004	0.34	<0.001 (0.98)
Trail making part A[a]	−0.97 (1.84)	0.43 (0.89)	0.67 (0.73)	$X^2=33.8$**	<0.001	0.19	<0.001 (1.45)
Language							
Naming[a]	−0.68 (1.34)	0.23 (0.79)	0.08 (0.98)	$X^2=10.8$*	0.003	0.84	0.04 (0.78)
Executive functions							
Backward Digit span[b]	−0.47 (1.02)	0.41 (0.98)	0.32 (0.90)	$F=9.07$**	<0.001	0.90	0.003 (0.81)
Phonological Fluency[b]	−0.80 (0.80)	−0.14 (0.90)	0.30 (0.74)	$F=14.61$**	0.001	0.21	<0.001 (1.31)
Trail making part B[a]	−2.43 (2.82)	−0.18 (1.05)	0.34 (0.84)	$X^2=38.4$**	<0.001	0.03 (0.31)	<0.001 (1.77)
WCST-perseverative error[a]	−0.35 (1.28)	0.28 (1.17)	0.68 (0.71)	$X^2=18.8$**	0.09	0.03 (0.35)	<0.001 (0.95)

BD: Bipolar disorder; IQ: Intelligence quotient; WCST: Wisconsin Card Sorting Test.
[a] Kuskal Wallis test (df=2).
[b] ANOVA (df=2, 138).
* $p<0.05$.
** $p<0.001$ after Bonferroni correction.

Table 3
Clinical and demographical features of patients with better and worse cognitive functioning (values are expressed as mean, standard deviation is shown in brackets).

	H-cognitive-impaired ($n=30$)	S-cognitive-preserved ($n=30$)	Test/*p*-value
Age[a]	41.87 (10.91)	38.00 (11.07)	$F=1.85$, $p=0.18$
Education (years)[a]	14.07 (2.43)	15.00 (2.42)	$F=2.22$, $p=0.14$
Gender (% female)[b]	66.7	63.3	$X^2=0.073$, $p=0.79$
Age at onset[a]	29.50 (9.58)	27.32 (9.39)	$F=0.68$, $p=0.41$
Length of illness[a]	11.86 (7.47)	9.76 (5.61)	$F=1.45$, $p=0.23$
No hypo/manic episodes[a]	3.39 (1.99)	2.50 (1.53)	$F=3.21$, $p=0.079$
No depressive episodes[a]	3.46 (1.91)	3.25 (2.09)	$F=0.15$, $p=0.70$
No hospitalizations[c]	0.64 (1.03)	0.18 (0.48)	$Z=-1.98$, $p=0.048$
Clinical subtype (% type I)[b]	56.7	36.7	$X^2=2.41$, $p=0.12$
History of psychosis (%)[b]	50	36,7	$X^2=1.48$, $p=0.22$
YMRS score[a]	1.13 (1.68)	0.67 (1.29)	$F=146$, $p=0.23$
HDRS score[a]	1.67 (1.99)	2.23 (2.16)	$F=1.12$, $p=0.29$
GAF score[c]	74.20 (9.39)	87.03 (6.12)	$Z=-4.97$, $p<0.001$

BD: Bipolar disorder; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale.
[a] ANOVA (df=1, 59).
[b] Chi-square.
[c] Mann–Witney.

verbal memory, attention, and executive functions with almost all effect sizes between 0.5 and1.0 (Robinson et al., 2006; Torres et al., 2007; Mann-Wrobel et al., 2011). Through an alternative analysis, results of this study partially agree with the above findings, since patients with euthymic BD had higher prevalence of clinically significant cognitive deficits than healthy subjects using both permissive ('soft') and conservative ('hard') criteria. However, this approach provides complementary information regarding that there is a very heterogeneous profile of neurocognitive functioning in BD, corroborating data of some previous studies (Martino et al., 2008; Gualtieri and Morgan, 2008; Reichenberg et al., 2009; Iverson et al., 2011) in a larger sample of patients with strict criteria of euthymia. In fact, we found that 70% of the entire sample (H-cognitive-preserved patients) had relatively preserved cognitive functioning with just two measures of executive functioning below the level of controls with small effect size. These results suggest that the findings of cross-sectional studies and meta-analyses using means and effect sizes might overestimate the true magnitude of cognitive impairments for the majority of patients. Moreover, there was a 30% of the sample (S-cognitive-preserved patients) that was indistinguishable from healthy subjects in terms of both neurocognitive and psychosocial functioning. In contrast, there was a 30% of the sample (H-cognitive-impaired patients) that showed more severe cognitive deficits than those usually reported in the literature; for example, this subgroup of patients had an average effect size of 1.13 and displayed compromised cognitive performance even in domains usually preserved such as naming. Likewise, there was a trend towards greater clinical severity characterized by greater number of hospitalizations among patients with clinically significant cognitive deficits. These findings are related to previous studies reporting a negative association between the number of episodes,

especially manic ones, and neurocognitive functioning (for reviews see Robinson and Ferrier, 2006). The cross-sectional nature of the present study prevents us from making inferences about the direction of causality of this association as it is not univocal (Martino et al., 2013). Likewise, differences in number of hospitalizations between patient groups were subtle while differences in cognitive performance were pronounced; suggesting that other factors beyond clinical variables could be influencing the development of cognitive deficits in BD.

The heterogeneous picture that emerges from these results regarding neurocognitive functioning might have important theoretical and practical implications. Theoretically, the differences observed in neurocognitive functioning might be explained by the existence of quantitative or qualitative subgroups of patients. Quantitative subgroups would imply the existence of a continuum of severity from patients without impairments to others with very low cognitive functioning. This pattern would be represented graphically as a distribution curve of any cognitive domain for BD patients moved around 0.5 SD below the mean (to the left) of those of healthy controls. Several factors such as genetic polymorphism (Dickerson et al., 2006; Burdick et al., 2007), history of obstetric complications (Martino et al., 2008) and childhood trauma (Savitz et al., 2008), infection with herpes simplex virus type 1 (Dickerson et al., 2006; Gerber et al., 2012), comorbidity with anxiety disorders (Wu et al., 2011) and alcohol abuse/dependence (van Gorp et al., 1998; Levy et al., 2008; Sanchez-Moreno et al., 2009), or exposure to antipsychotics medications (Donaldson et al., 2003; Frangou et al., 2005; Torrent et al., 2011) were related with neurocognitive functioning and might be responsible for these quantitative variations. A non-exclusive alternative to the above one is that the diversity in cognitive status among euthymic patients with BD was due to qualitative subgroups reflecting different underlying pathophysiological processes. This pattern would be better represented graphically as two curves for BD patients; one of these superimposed to that of healthy controls (cognitive preserved patients) while the other moved around 1 SD below the mean (cognitive impaired patients). If this was the case, further studies might focus on differences between these subgroups in pathophysiological aspects such as genetic aspects, biomarkers or structural or functional neuroimaging. Additionally, these subgroups of patients may differ in longitudinal-course or phenomenological features such as premorbid adjustment, counts of recurrences, insight or neurological symptoms which could be also explored in upcoming studies.

Regardless of whether differences in neurocognitive functioning are quantitative or qualitative, the heterogeneity found in this study could have important clinical implications. First, this diversity provides further evidence that justifies the use of neurocognitive assessments as part of the routine examination of patients with BD (Burdick et al., 2005; Martinez-Arán et al., 2005). Furthermore, our results bring additional support to the notion that cognitive status is one of the constraints of the level of functional recovery achieved by patients during euthymic periods (Huxley and Baldessarini, 2007). In fact, in this sample GAF score ranged from a level indistinguishable from healthy controls in S-cognitive-preserved patients to the lower levels in H-cognitive-impaired patients. In other words, neurocognitive functioning could contribute to explain the variability in the level of functional outcome observed in patients with BD during euthymic periods and, therefore, could be thought of as a course modifier of the illness. We think that it is a critical issue since an adequate hypothesis about neurocognitive functioning in euthymic BD must be able to explain why some patients have difficulties in achieving full functional recovery after syndromal remission and also why other patients keep a high level of social and occupational functioning despite their illness. Likewise, cognitive differences might be important in the clinical management and therapeutic. Initially, it should not be assumed that cognitive deficits are a core feature in patients with BD. Then, clinicians always should rule out potentially treatable causes of deficits such as the clinical (i.e. hypothyroidism or metabolic syndrome) or psychiatric (i.e. anxiety disorders or abuse/dependence of alcohol) comorbidity among patients with clinically significant cognitive impairments. Likewise, this subgroup of patients might benefit from using with special caution or avoiding drugs with negative effect on cognition such as benzodiazepines or antipsychotics (Mintzer and Griffiths, 2003; Donaldson et al., 2003; Frangou et al., 2005). On the other hand, even the effectiveness of different psychosocial interventions may be influenced by patients' cognitive status although this has not been formally studied to date. For example, those patients with clinically significant cognitive impairments would have decreased ability to obtain benefit from psychoeducational programs while they might be the primary recipients of cognitive remediation approaches, and vice versa for patients without clinically significant deficits.

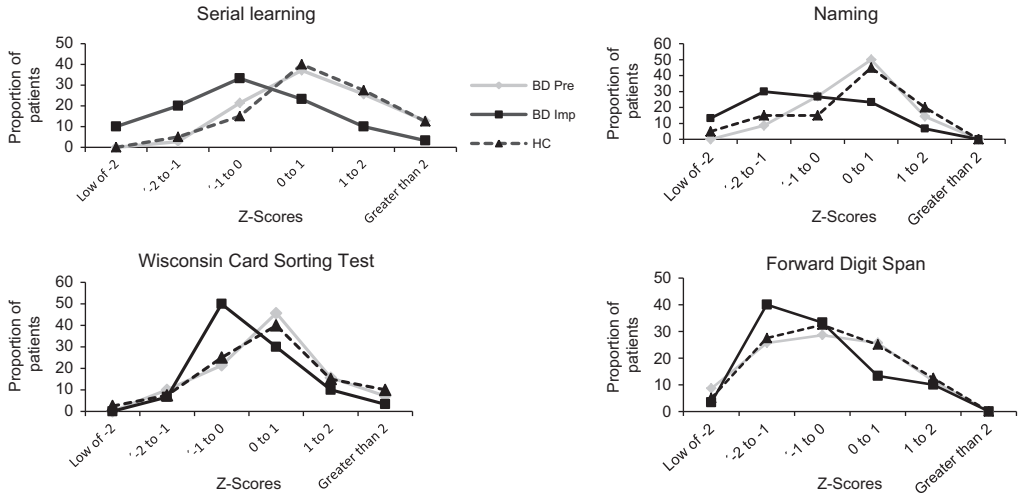

Fig. 2. Distribution of performance in patients with and without impairments using hard criteria and healthy controls. BD Pre: H-cognitive-preserved bipolar disorder patients; BD Imp: H-cognitive-impaired bipolar disorder patients; HC: controls.

Some limitations of our study should be considered. First, our sample size, despite being larger than those of previous studies, is relatively small to evaluate the distribution of cognitive deficits in subgroups of patients. However, it is interesting to note that when H-cognitive-impaired patients are excluded, the distribution of the 70% remaining patients closely reproduces that of healthy controls in most cognitive domains (Fig. 2). Additionally, all patients included in the study were taking psychotropic medication and we cannot discount the influence of drugs on cognitive functioning. Likewise, we classified patients as with or without clinically significant cognitive impairment, although it might be possible that subgroups of patients could be identified better using another measure (i.e. with and without clinically significant executive function or verbal memory impairments). Finally, we did not include any measure of inhibitory control which could be particularly affected in BD and, therefore, we may have underestimated the prevalence of cognitive deficits in our sample.

Notwithstanding these limitations, our study provides useful information complementary to that of earlier studies of neurocognitive functioning in BD. In summary, our results show that cognitive impairments are very heterogeneous in euthymic patients with BD which could contribute to understand differences in functional outcome. Further studies are needed to improve our understanding about the nature of this heterogeneity and its clinical and therapeutic implications.

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Conflict of interest

No conflict declared.

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