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Research paper

Factors associated with the discrepancy between objective and subjective cognitive impairment in bipolar disorder

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A B S T R A C T

Objective: The aim of this study is to evaluate the discrepancy between objective cognitive measures and cognitive subjective complaints in a sample of euthymic patients with bipolar disorder (BD).
Methods: One hundred and sixteen participants (83 euthymic patients with BD and 33 healthy controls) were enrolled for this study. Patients were assessed with a comprehensive neuropsychological battery and they also reported their subjective cognitive complaints with the Cognitive Complaints in Bipolar Disorder Rating Scale (COBRA). The discrepancy between objective and subjective data was calculated using a novel methodology proposed in a previous study (Miskowiak, 2016). Statistical analyses included Pearson correlations and multiple linear regression.
Results: Higher number of previous depressive episodes was identified as one variable associated with the global sensitivity composite score (Beta = 0.25; $t = 2.1$; $p = 0.04$) and with the verbal learning and memory sensitivity score (Beta = 0.26; $t = 2.16$; $p = 0.03$). That is, patients with more previous depressive episodes tend to over-report cognitive complaints. In contrast, higher number of previous hospitalizations was associated with stoicism in the global total score (Beta = −0.27; $t = -2.24$: $p = 0.029$) and in the domain of attention/processing speed (Beta = −0.34; $t = -2.52$; $p = 0.016$), indicating patients with more hospitalizations tend to report less cognitive complaints.
Discussion: Our study identified some factors that might help to explain the discrepancy between objective and subjective cognitive measures in BD, including number of previous depressive episodes and number of previous hospitalizations. This highlights the need of the combined use of both types of cognitive measures to make an accurate assessment of cognitive dysfunctions and their effective treatment.

1. Introduction

Cognitive dysfunction is a core feature in bipolar disorder (BD) affecting multiple domains including attention, processing speed, verbal memory and executive functions (Bora, 2018; Keramatian et al., 2022). It is well-established that these deficits contribute to functional impairment, often hindering some patients from maintaining employment or educational commitments, engaging in social relationships, or being self-sufficient (Bonnín et al., 2010; Sanchez-Moreno et al., 2009). In line with this, it has been suggested that up to 70 % of patients with

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BD experience some degree of functional impairment related to both subsyndromal symptoms and cognitive deficits (Solé et al., 2018). Furthermore, the existence of cognitive deficits during euthymia has raised some questions regarding patients' awareness of these deficits, resulting in two distinct bodies of literature. Some studies suggest that patients lack of awareness of their cognitive deficits (Burdick et al., 2005; Lima et al., 2018), while other authors argue that subjective and objective measures may be partially correlated (Demant et al., 2015; Rosa et al., 2013). Supporting the first perspective, Burdick et al. (2005) observed that patients with severe symptoms struggled with verbal learning and memory tasks, and the self-assessment of these deficits was not correlated with their actual performance. In the same line, (Van Der Werf-Eldering et al., 2011) also found no association between self-report complaints and objective performance. In support of the second perspective, Demant et al. (2015) identified a link between overall subjective and objective measures of cognitive dysfunction, although not within the individual cognitive domains. Rosa et al. (2013) also described that cognitive complaints were partially correlated with objective measures of memory and executive function. As a result, Miskowiak et al. (2016) suggested that the discrepancies found in the literature could be explained depending on the methodology used. Indeed, using linear correlations to study these discrepancies might not be enough and a more precise method was needed to study this complex relationship. Consequently, to shed some light on this matter, the Danish group proposed a new method for identifying different patients profiles, as follows: one profile consists of *accurate patients*, who are aware of their cognitive abilities and accurately report them; a second group represents a *sensitive group*, these are patients who overreport their cognitive complaints; and the last group, includes *stoic patients*, those who underreport their cognitive difficulties. With this new method, Miskowiak and colleagues found that subsyndromal depressive and manic symptoms, the number of hospitalizations, BD type II and male gender predicted a higher likelihood of being "sensitive", while patients with higher verbal Intelligence Quotient (IQ) tended to be more "stoic". 'Sensitive' patients were also characterized by greater socio-occupational difficulties, higher perceived stress and lower quality of life (Miskowiak et al., 2016).

To the best of our knowledge, only one other study has replicated this method, which included only patients with major depressive disorder (Petersen et al., 2019). However, no single study has replicated these results in a sample with euthymic patients with BD. Therefore, the objective of our report is to apply the method described by the Danish group (2016) in a sample of patients fully remitted (with at least 3 months of euthymia). Moreover, we also assess another key variable that is not examined in the original study: psychosocial functioning.

2. Methods

2.1. Participants

One hundred and sixteen participants (83 outpatients with BD and 33 healthy controls) were enrolled for this study. The patients were recruited between 2009 and 2012 at the Bipolar and Depressive Disorders Unit from the Hospital Clinic of Barcelona. This hospital-based program provides integrated care for difficult-to-treat patients with BD from across Catalonia, as well as care to patients with BD from a specific catchment area in Barcelona (Popovic et al., 2012; Salagre et al., 2018). Inclusion criteria for this study were: a) diagnosis of bipolar disorder type I or II according to DSM-IV-TR criteria; b) age between 18 and 65 years old; c) at least three months of euthymia based on a total score ≤ 8 on the Hamilton Depression Rating Scale (HAM-D) (Cordero Villafáfila and Ramos-Brieva, 1986; Hamilton, 1960) and a total score ≤ 6 on the Young Mania Rating Scale (YMRS) (Young et al., 1978; Colom et al., 2000). Exclusion criteria were: a) current substance abuse; b) significant medical illness or history of head injury that lead to neuropsychological impairment and c) electroconvulsive therapy in the last year. A total of 33 Healthy controls (HC) were screened for personal and family history of any psychiatric condition and for previous or current use of prescribed psychotropic medication. 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 Research Board (HCB/2008/4359). All participants provided written informed consent prior the inclusion in the study after procedures had been fully explained.

2.2. Measures

2.2.1. Clinical variables

All relevant demographic and clinical data were gathered through a clinical interview based on the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). The collected data included: age, gender, educational level, occupational status, type of BD, number and type of episodes, age at onset, chronicity (illness duration in years), lifetime history of psychotic symptoms, lifetime history of rapid cycling and family history of affective or psychiatric disorder.

Severity of depressive and manic symptoms at the moment of the assessment was evaluated using the HAM-D and the YMRS, respectively. The overall psychosocial functioning was assessed by means of the Functioning Assessment Short Test (FAST), an interviewer-administered instrument widely used in patients with BD (Bonnín et al., 2018; Rosa et al., 2007). It is a valid and reliable scale that was specifically designed to explore the main functional difficulties presented by patients with psychiatric illnesses and specially BD. The higher the total score indicate greater psychosocial impairment.

2.2.2. Objective cognitive assessment

All participants were assessed using a comprehensive neuropsychological battery. This assessment involved different tests described as follows: estimated IQ was evaluated with the Wechsler Adult Intelligence Scale, vocabulary subtest (WAIS-III, Wechsler, 1997). The attention and processing speed domain consisted of two subtests of the WAIS-III (Wechsler, 1997): the digit-symbol coding and the symbol search and the Trail Making Test –part A (TMT-A) (Reitan, 1958). The working memory domain comprised the arithmetic, digits, and letter-number sequencing of the WAIS-III) (Wechsler, 1997), in order to calculate the Working Memory IQ. Executive functions were tested by several tests assessing set shifting, planning, verbal fluencies, and response inhibition, namely the computerized version of the Wisconsin Card Sorting test (Heaton, 1981) the Stroop Color-Word Interference Test (SCWT) (Golden, 1978), the Trail Making Test –part B (TMT—B) (Reitan, 1958), phonemic fluency (F-A—S) and categorical fluency (animal naming), both components of the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976). Verbal learning and memory was assessed by means of the California Verbal learning Test (CVLT) (Delis et al., 1987). These tests were selected following the guidelines of the International Society for Bipolar Disorders (Yatham et al., 2010), that later on has been improved in subsequent other consensus-based recommendations on how to assess and address cognition in BD (Miskowiak et al., 2017, 2018).

2.2.3. Subjective cognitive assessment

The Cognitive complaints in Bipolar disorder Rating Assessment (COBRA) (Rosa et al., 2013) is a 16-item self-reported instrument that allows to assess cognitive dysfunction including different areas such as executive functions, attention/concentration, processing speed and verbal learning and memory. This scale has been included in several ISBD tasks force as a recommendation tool to assess subjective complaints in this population, since it can be easily applied both in research and clinical settings (Miskowiak et al., 2017, 2018). All items in the COBRA are rated using a 4-point likert-type scale ranging from 0 to 3, described as follows: 0 = never; 1 = sometimes, 2 = often, 3 = always. The total score is obtained when the scores of each item are added up.

Higher scores indicate more subjective cognitive complaints.

2.3. Statistical analyses

First of all, to describe the demographic and clinical characteristics of both samples, *t*-tests were computed to calculate the differences between BD and HC group means for continuous variables including age, years of education, estimated premorbid IQ, HAM-D and YMRS scores. Chi -squared tests were used to compare both groups in gender and occupational status (working or studying vs. not working).

After this, all the analyses to calculate the global sensitivity score and the global sensitivity scores for each domain were applied following the method described in detail by Miskowiak et al. (2016). All the details to calculate the sensitivity scores are fully explained in that paper, but briefly: the sensitivity scores proposed by these authors reflect the degree of discrepancy between patients' subjective difficulties reported on the self-rating questionnaire (COBRA), and the objective performance in the neuropsychological tests. Following this, sensitivity scores are computed as continuous variables ranging from −10 to +10. A score of −10 represents maximum stoicism. In this case, patients report the least subjective difficulties despite performing the worst on objective measures (neuropsychological test). A score of +10 represents maximum sensitivity, with patients reporting the most severe subjective cognitive complaints despite showing the least objective cognitive impairment. Scores around zero indicate concordance between subjective ratings and objective performance. Raw scores, both on the objective and subjective measures, were standardized against the control group. For further details, see Miskowiak et al. (2016).

Like in the original paper, a total four sensitivity scores were calculated: a global sensitivity score, comprising the overall performance scores across all the domains evaluated (see Table 1) and three specific sensitivity domains including: 1) attention and processing speed; 2) verbal learning and memory and 3) executive functions. Table 1 shows the match between the neuropsychological variables and the corresponding self-reported items in the COBRA.

After this, Pearson correlations were conducted between the four sensitivity domains and demographic, clinical and functional variables. These correlations included variables such as the sensitivity scores (a total of four: the global and the three specific domains), age, HAM—D, YMRS, estimated premorbid IQ, years of education, number of total episodes, number of previous depressive episodes, number of previous manic episodes, chronicity (illness duration), number of previous hospitalizations and FAST total score.

Once the significant Pearson correlations were identified, four different regression models were performed using each sensitivity score as the dependent variable and the clinical, demographic or functional variables were included as independent variables. All the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0. Statistical significance for all the analyses was set at an alpha level of $p < 0.05$ (two-tailed).

Table 1
Match between the neurocognitive variables and items in the COBRA to calculate sensitivity domains.

Cognitive domain	Neuropsychological tests	COBRA items
Attention and processing speed	WAIS-III Processing Speed IQ index Trail Making Test Part A	5. Do you find it hard to concentrate when reading a book or a newspaper? 8. Does it take you longer than normal to complete your daily tasks? 12. Are you easily distracted? 14. Do you get the impression that you cannot follow a conversation? 16. Do you struggle to keep focused on a particular task for a long time?
Verbal learning and memory	California Verbal Learning Test (five subtests: total recall across trials I-V; short free and cued recall, 30′ delayed free and cued recall).	1. Do you have difficulties to remember peoples' names? 2. Do you have difficulties to find objects of daily use (keys, glasses, wirst watch…? 3. Do you find it difficult to remember situations that were important for you? 4. Is it hard for you to place important events in time? 6. Do you have problems recalling what you have read or have been told recently? 10. When people remind you of a conversation or a comment you heard, do you get the impression that it is the first time you hear it? 15. Have you noticed that you find it difficult to learn new information?
Working memory and executive functions	WAIS-III Working Memory IQ index Wisconsin Card Sorting Test categories Wisconsin Card Sorting Test perseverative errors Trail Making Test Part B Phonemic fluency (F-A—S) Categorical fluency (animal naming)	7. Do you have the feeling that you do not finish what you begin? 9. Have you ever felt disoriented in the street? 11. Is it sometimes difficult for you to find the words to express your ideas? 13. Do you find it hard to do simple mental calculations?

3. Results

3.1. Demographic and clinical characteristics

Patients ($n = 83$) and healthy controls ($n = 33$) did not differ with respect to age, gender, years of education and estimated premorbid IQ. Only significant differences were found in HAM-D scores between groups ($t = 5.2$; $p < 0.001$); psychosocial functioning, measured by means of the FAST scale ($t = 10.\ 6$; $p < 0.01$); cognitive complaints, measured by the means of COBRA ($t = 8.1$; $p < 0.01$) and occupational status (Chi-squared = 14.9; $p < 0.01$). See Table 2 for more details.

3.2. Global sensitivity composite score

Significant correlations were found between the global sensitivity score and previous number of depressive episodes ($r = 0.35$; $p = 0.03$), HAM-D total score ($r = 0.25$; $p = 0.02$), number total episodes ($r = 0.28$; $p = 0.02$), number of previous hospitalizations ($r = -0.25$; $p = 0.03$) and FAST total score ($r = 0.32$; $p = 0.03$).

The linear regression model was statistically significant ($F = 3.83$, $p = 0.004$; adjusted $R^2 = 0.265$). This model included the five variables found to be significant in the correlation analyses and other variables which were not found to correlate with the global sensitivity but that in previous studies have been reported as meaningful variables, such as: bipolar subtype, previous psychotic symptoms, chronicity and gender (Martínez-Arán et al., 2005; Miskowiak et al., 2012, 2016). We also added other variables such as age and years of education since they can play a significant role when explaining the discrepancy between cognitive objective performance and cognitive complaints. The final model with best adjustment included 5 variables, 4 of which were found to be significant: number of previous hospitalizations (Beta = −2.26; $t = -1–98$: $p = 0.05$); number of previous depressive episodes (Beta = 0.33; $t = 2.46$; $p = 0.02$); FAST total score (Beta = 0.29; $t = 2.1$; $p = 0.04$), and

Table 2
Demographical and clinical characteristics of both samples (patients (BD) and healthy controls (HC)).

	BD (n = 83)	HC (n = 33)	
	Mean (SD) [range]	Mean (SD) [range]	t (*p*-value)
Age	43.9 (10.4) [18–61]	40.1 (10.6) [22–60]	1.6 (0.97)
Years of education	14.9 (3.5) [8–21]	13.3 (3.9) [6–21]	1.7 (0.08)
Estimated Premorbid IQ	110.9 (10.6) [85–140]	109.5 (7.7) [90–120]	0.5 (0.32)
HAM-D	5.1 (2.9) [0–8]	1.7 (1.5) [0–4]	5.2 (<0.01)
YMRS	1.6 (2.1) [0–6]	1.7 (1.2) [0–3]	0.6 (0.44)
Chronicity (illness duration in years)	17.2 (8.8)	–	
Number of total episodes	7.5 (4.3)	–	
Number of depressions	4.1 (3.5)	–	
Number of manias	2.1 (2.3)	–	
Number of hospitalizations	1.6 (1.7)	–	
FAST total score	23.4 (13.3) [1–52]	4.1 (4.5) [0–20]	10.6 (<0.01)
COBRA total score	20.6 (9.3) [3–49]	9.0 (5.7) [1–22]	8.1 (<0.01)
	n (%)	**n (%)**	**Chi -squared (p-value)**
Gender (female)	54 (64.3)	18 (54.5)	0.95 (0.40)
Occupation (not working)	45 (53.6)	5 (15.2)	14.9 (<0.01)
Lifetime psychotic symptoms (yes)	49 (60.5)	–	
Diagnosis (Bipolar I subtype)	52 (65)	–	
Lifetime rapid cycling (yes)	8 (10.3)	–	

years of education (Beta = 0.34; $t = 2.57$; $p = 0.01$). Neither lifetime psychotic symptoms (Beta = 0.13; $t = 1.03$; $p = 0.3$) nor age (Beta = 0.04; $t = 0.34$; $p = 0.73$) were not found to contribute to the model.

3.3. Domain-specific sensitivity scores

For the verbal memory sensitivity score, two different clinical variables were found to significantly correlate, which included: number of depressive episodes ($r = 0.32$; $p = 0.01$) and number of total episodes ($r = 0.28$; $p = 0.03$). The FAST total score also showed a positive correlation (r = 0.28; $p = 0.009$).

Since two variables (depressive episodes and total number of episodes) that were included in the model as independent variables showed a strong correlation, two different models were tested including these variables separately. The model with best adjustment included the number of depressive episodes and adding age and years of education as independent variables did not change the final model which explained up to 12 % of the variance (F = 3.02; p = 0.02; adjusted $R^2 = 0.12$), only with the previous number of depressive episodes (Beta = 0.308 $t = 2.06$; $p = 0.04$) as a significant variable.

Regarding the attention and processing speed sensitivity domain, five variables were found to significantly correlate with this domain, which included: age ($r = 0.25$; p = 0.04), HAM-D total score ($r = 0.31$; p = 0.04), number of previous hospitalizations ($r = -0.23$; p = 0.04), number of depressive episodes ($r = 0.37$; $p = 0.002$), number of total episodes ($r = 0.33$; $p = 0.01$) and FAST total score ($r = 0.45$; $p < 0.01$). We also added years of education to take into account the potential influence of this variable. Once again, two different models were tested including separately the variables that highly correlated (depressive episodes and total number of episodes). However, in this case, the model with best adjustment included the total number of episodes, explaining up to 25.6 % of the variance (F = 3.53; adjusted $R^2 = 0.256$; $p = 0.007$). This model comprised a total of six variables (FAST total score, number of previous hospitalizations, HAM-D total score, age, number of previous episodes and years of education), but only two of them were found to be significant: FAST total score (Beta = 0.38; $t = 2.12$; p = 0.04) and number of previous hospitalizations (Beta = −0.34; $t = -2.47$; $p = 0.018$).

Finally, the working memory and executive functions sensitivity domain only correlated with premorbid IQ ($r = 0.27$; p = 0.01). Even though the model was significant, it only explained up to 6 % of the observed variance (F = 6.22; adjusted $r^2 = 0.061$; $p = 0.015$), being the estimated premorbid IQ the only variable in the model (Beta = 0.26; $t = 2.49$; p = 0.015). When adding years and years of education, this variable was no longer significant and became a trend (Beta = 0.33; $t = 1.97$; $p = 0.055$). Table 3 displays the main contributing variables to each of the sensitivity domains assessed.

4. Discussion

To the best of our knowledge, this is the first study to replicate the methodology described by Miskowiak et al. (2016) in assessing the variables associated with the discrepancy between cognitive performance and subjective complaints in a sample of euthymic patients with BD. However, our results differ from those reported in the original study. For example, concerning the global sensitivity score, we found that higher number of previous hospitalizations were associated with more stoicism, whereas a greater number of previous depressive episodes and higher scores in the FAST were associated with more sensitivity. In contrast, Miskowiak et al. (2016) reported that male gender, more mood symptoms (both depressive and hypomanic), bipolar subtype II and more hospitalizations were associated with more sensitivity. Consequently, the number of previous hospitalizations is the only common variable in both studies, but our results are in the opposite direction. It is worth noting that we also observed the same variable to be associated with more stoicism in the attention/processing domain. In this context, patients with a higher number of hospitalizations may have a more

Table 3
Multiple linear regression analyses of predictors of global and domain-specific "sensitivity".

	Dependent variable			
	Global	Verbal learning and Memory	Attention and processing speed	Working memory and executive functions
Independent variables				
Number of depressive episodes	**β = 0.33; p = 0.01**	**β = 0.30; p = 0.04**	–	–
Number of hospitalizations	**β = −0.26;p = 0.05**	–	**β = −0.34; p = 0.018**	–
Number of total episodes	–	–	β = 0.15; p = 0.30	–
HAM-D total score	–	–	β = 0.01; p = 0.92	–
Age	–	–	β = 1.3; p = 0.20	–
FAST total score	**β = 0.29; p = 0.04**	β =0.89; p = 0.56	**β = 0.38; p = 0.04**	–
Psychotic symptoms	β =0.13; p = 0.01	–	–	–
Years of education	**β = 0.34; p = 0.01**			
Premorbid IQ	–	–	–	**β = 0.33; p = 0.055**

Only the results in bold type were found to contribute significantly to the model.

severe form of the illness compared to those with fewer hospitalizations. For instance, the presence of psychotic symptoms has been linked to higher number of hospitalizations (Belteczki et al., 2018). Although, in our model, the variable of lifetime psychotic symptoms did not achieve statistical significance, the number of previous hospitalizations could be viewed as an indirect measure of illness severity. In this regard, it is plausible that stoicism might represent a specific group of BD patients with a more severe illness course and poor insight, akin to people within the schizophrenia spectrum.

The number of previous depressive episodes may also be a key variable in explaining the discrepancy between objective and subjective cognition in euthymic patients with BD, as it was associated with increased sensitivity in both the global model and the verbal memory domain. This suggests that patients with higher number of previous depressive episodes are more likely to overreport cognitive dysfunction in general and may also they might report more difficulties in retrieving and encoding information. These findings align with a recent publication that indicated that previous number of depressive episodes, along with other clinical variables, was associated with increased cognitive complaints (Grover et al., 2023). In accordance with this, our present results suggest that patients with more depressive episodes tend to exhibit a more pessimistic outlook with an increased self-criticism, which may influence their perceptions of cognitive abilities and ultimately contribute to the discrepancy between objective performance and subjective complaints. Furthermore, previous literature also suggests that patients' insight into their own cognitive abilities depends on several factors, including metacognitive capacity and severity of mood symptoms. Therefore, it could reflect a negative bias in patients' perception of their cognitive abilities (Miskowiak et al., 2016).

Functional outcome also appears to be a relevant variable that contributes to explaining the discrepancy between the subjective experience and objective cognitive dysfunction, both in the global sensitivity and in the attention and processing speed domain. In both models, this variable displayed a positive correlation, indicating that patients with poorer functioning were more sensitive. However, it is likely that those patients experiencing greater difficulties in interpersonal relationships, occupational functioning and autonomy (areas assessed in the FAST scale) also reported more cognitive complaints or even attributed their challenges in performing activities of daily living are a result of memory deficits, attention lapses, or difficulties in planning and organizing. In this regard, some studies have already highlighted that patients with more subjective complaints also exhibit poorer psychosocial functioning (Grover et al., 2023; Martínez-Arán et al., 2005). Nevertheless, the cross-sectional nature of the present study does not allow us to draw any causal relationships. We cannot determine whether “sensitive” patients are more aware of their difficulties in daily life and, as a result, report more subjective complaints, or if it is the other way around.

Estimated premorbid IQ appeared to be a relevant variable in the working memory and executive domain. However, after adding other variables such as age and years of education, this variable became a trend. In fact, among all the models presented in this study, this one is the weakest. We wonder If this might be related to the “artificial” grouping of the objective neuropsychological tests and the corresponding self-reported items in the COBRA (Table 1). Although we used the same classification as in the original article (Miskowiak et al., 2016), it is a theoretical proposal based on clinical expertise that is not without limitations. Other studies may use different approaches based on empirical data (e.g., Principal Component Analysis) that could potentially enhance the clustering and pairing between objective neuropsychological tests and self-reported items in the COBRA.

Finally, years of education significantly contributed to the global sensitivity domain, indicating that patients with more years of education tended to overreport subjective cognitive deficits in general. Years of education is another important variable identified by some authors as a key component of cognitive reserve (Amoretti et al., 2019; Amoretti and Ramos-Quiroga, 2021). Therefore, it could be hypothesized that patients with more years of education (and higher cognitive reserve) are more sensitive and aware of cognitive skill decline. These findings are congruent with previous studies showing that euthymic BD patients, even with intact cognitive function, can still experience daily cognitive and psychosocial difficulties (Lima et al., 2019). In this sense, it is suggested that a person might experience cognitive complaints such as concentration problems and memory lapses during work, even when the neuropsychological performance is adequate. One potential explanation for the subjective–objective discrepancy is that subjective measures may better capture patients' decline in cognitive capacity from supra-normal premorbid levels than objective tests, which rely on comparisons with normative groups (Lima et al., 2018; Miskowiak et al., 2016). Another explanation that might help to understand overreporting of cognitive subjective deficits could be related to the insensitivity of traditional neuropsychological tests in detecting subtle changes in cognition. In fact, it has been observed that some patients with BD do not exhibit cognitive impairment when assessed with traditional tests, but they do when they are evaluated with more ecologically valid tests that closely resemble everyday life activities (Torralva et al., 2012). If this were the case, patients may not be overreporting their deficits; they might be noticing a subjective cognitive decline that neuropsychological tests with lower ecological validity are unable to detect.

At this point, it is important to analyze why the present results differ significantly compared to the report by Miskowiak and colleagues, even though we used the same method. Firstly, the sample we analyzed consisted of euthymic patients, whereas Miskowiak and colleagues' sample included more heterogeneous patients with a greater presence subsyndromal symptoms. In line with this, Miskowiak and colleagues found a significant effect of the subsyndromal depressive symptoms (HAM-D) in the global sensitivity. In our sample, HAM-D correlated with global sensitivity but it did not reach significance when included in the regression model. This could be partially explained by the low mean in the HAM-D scores ($=5.2 \pm 2.9$) in our sample. Secondly, we introduced not only the assessment of demographic and clinical variables but also a measure of functioning, broadening the study of factors that could potentially explain the discrepancy between objective performance and subjective complaints. Our results indicate that functioning, along with certain clinical variables, may partially explain the discrepancy found in the global sensitivity score and in the attention and processing speed domain. Our sample also differed in several variables that should be noted: we included fewer patients with BD type II, patients were older, more chronic (with more years of illness), and our sample size was smaller. This latter limitation might restrict the ability to identify relationships that could have been detected with a larger sample, and it might have contributed to the fact that our models demonstrated reduced goodness of fit when compared to those presented in the original study by Miskowiak et al. (2016). All these differences in sample characteristics and the assessment of variables, in addition to the inherent the heterogeneity in BD (Burdick and Millett, 2021), may partly account for the different results.

Furthermore, it is important to consider some limitations of our study when interpreting the present results. Firstly, the cross-sectional nature of the study does not allow us to establish causal relationships; in fact, it cannot be ruled out that all the variables labeled as independent in our models may have bidirectional relationships with the dependent variables (sensitivity scores). Secondly, our models did not include other variables that could help to explain the discrepancy, such as personality variables (particularly those related to clusters including self-expectation, self-criticism and perfectionism), cognitive reserve, type and dosage of pharmacological treatment (Ilzarbe and Vieta, 2023). Emotional cognition was not measured either (de Siqueira Rotenberg et al., 2023; Kjærstad et al., 2023; Varo et al., 2021). Further longitudinal studies should assess changes between objective and subjective cognitive measures and variables associated with such changes over time and ultimately, determine whether the presence of subjective cognitive complaints precedes objective cognitive impairment in the

future.

Comprehending the factors contributing to the discrepancy between objective and subjective cognitive impairment can guide clinical assessment and the treatment of cognitive dysfunction. It also raises the possibility that cognitive complaints might be considered as an additional variable for assessing complete recovery in patients with BD. To establish it as a cornerstone of recovery, a better understanding of the variables associated with subjective complaints is needed. Nevertheless, self-reported cognitive tools cannot replace objective neuropsychological tests (Miskowiak et al., 2017), since many patients with BD face challenges in accurately reporting their deficits (Martínez-Arán et al., 2005; Miskowiak et al., 2016; Rosa et al., 2013; Träger et al., 2017; Van Der Werf-Eldering et al., 2011). It remains unclear which variables might explain this inaccuracy, and the results so far are inconclusive. Future studies should consider the assessing of additional variables, such as the above-mentioned cognitive reserve, personality tratis, insight and lifestyle variables (Van Rheenen and O'Neil, 2022). Additionally, investigating the stability of this discrepancy across lifespan in patients with BD could yield valuable insights. A separate study of the three different profiles (accurate, sensitive and stoic), might help in better understanding and characterizing the specific variables associated with each group.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

CRediT authorship contribution statement

C.M. Bonnín: Conceptualization, Supervision, Writing – original draft, Writing – review & editing, Data curation, Investigation. **J. Sánchez-Moreno:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing, Data curation, Investigation. **F. Lima:** Visualization, Writing – review & editing. **X. Roca:** Visualization, Writing – review & editing. **X. Segú:** Visualization, Writing – review & editing. **L. Montejo:** Visualization, Writing – review & editing. **B. Solé:** Visualization, Writing – review & editing. **D. Hidalgo-Mazzei:** Visualization, Writing – review & editing. **S. Martin-Parra:** Visualization, Writing – review & editing. **A. Martínez-Arán:** Supervision, Visualization, Writing – review & editing. **E. Vieta:** Supervision, Visualization, Writing – review & editing. **C. Torrent:** Conceptualization, Formal analysis, Supervision, Writing – review & editing. **A.R. Rosa:** Conceptualization, Formal analysis, Supervision, Writing – review & editing.

Declaration of competing interest

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Data availability

The data supporting the findings of this study are available upon request from the corresponding author.

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References

Amoretti, S., Ramos-Quiroga, J.A., 2021. Cognitive reserve in mental disorders. Eur. Neuropsychopharmacol. 49, 113–115. https://doi.org/10.1016/J.EURONEURO.2021.04.011.

Amoretti, S., Cabrera, B., Torrent, C., Bonnín, C.D.M., Mezquida, G., Garriga, M., Jiménez, E., Martínez-Arán, A., Solé, B., Reinares, M., Varo, C., Penadés, R., Grande, I., Salagre, E., Parellada, E., Bioque, M., Garcia-Rizo, C., Meseguer, A., Anmella, G., Rosa, A.R., Contreras, F., Safont, G., Vieta, E., Bernardo, M., 2019. Cognitive reserve assessment scale in health (CRASH): its validity and reliability. J. Clin. Med. 8 https://doi.org/10.3390/JCM8050586.

Belteczki, Z., Rihmer, Z., Ujvari, J., Lamis, D.A., Dome, P., 2018. Differences in clinical characteristics between bipolar patients with current psychotic symptoms and those who have never been psychotic. Psychiatr. Danub. 30, 183–188. https://doi.org/10.24869/PSYD.2018.183.

Benton, A., Hamsher, K., 1976. Multilingual Aphasia Examination. University of Iowa, Iowa City, IA.

Bonnín, C.M., Martínez-Arán, A., Torrent, C., Pacchiarotti, I., Rosa, A.R., Franco, C., Murru, A., Sanchez-Moreno, J., Vieta, E., 2010. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. J. Affect. Disord. 121, 156–160. https://doi.org/10.1016/j.jad.2009.05.014.

Bonnín, C.M., Martínez-Arán, A., Reinares, M., Valentí, M., Solé, B., Jiménez, E., Montejo, L., Vieta, E., Rosa, A.R., 2018. Thresholds for severity, remission and recovery using the functioning assessment short test (FAST) in bipolar disorder. J. Affect. Disord. 240, 57–62. https://doi.org/10.1016/j.jad.2018.07.045.

Bora, E., 2018. Neurocognitive features in clinical subgroups of bipolar disorder: a meta-analysis. J. Affect. Disord. 229, 125–134. https://doi.org/10.1016/J.JAD.2017.12.057.

Burdick, K.E., Millett, C.E., 2021. Cognitive heterogeneity is a key predictor of differential functional outcome in patients with bipolar disorder. Eur. Neuropsychopharmacol. 53, 4–6. https://doi.org/10.1016/j.euroneuro.2021.06.008.

Burdick, K.E., Endick, C.J., Goldberg, J.F., 2005. Assessing cognitive deficits in bipolar disorder: are self-reports valid? Psychiatry Res. 43–50. https://doi.org/10.1016/j.psychres.2004.12.009.

Colom, F., Vieta, E., Martinez-Aran, A., Reinares, M., Benabarre, A., Gasto, C., 2000. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. J. Clin. Psychiatry 61, 549–555. https://doi.org/10.4088/JCP.v61n0802.

Cordero Villafáfila, A., Ramos-Brieva, J.A., 1986. Factor structure of the Castillian version of the Hamilton rating scale for depression. Actas Luso Esp. Neurol. Psiquiatr. Cienc. Afines 14, 339–342.

Delis, D.C., Kramer, J.H., Kaplan, E., O.B., 1987. California Verbal Learning Test. Psychological Corporation, New York, NY.

Demant, K.M., Vinberg, M., Kessing, L.V., Miskowiak, K.W., 2015. Effects of short-term cognitive remediation on cognitive dysfunction in partially or fully remitted individuals with bipolar disorder: results of a randomised controlled trial. PloS One 10, e0127955. https://doi.org/10.1371/journal.pone.0127955.

First, M.B., Spitzer, R., Gibbon, M., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders. American Psychiatric Press Inc, Biometric Research Department, Washington DC.

Golden, C., 1978. Stroop Color and Word Test. Stoelting, Chicago, IL.

Grover, S., Avasthi, A., Chakravarty, R., Dan, A., Chakraborty, K., Neogi, R., Desouza, A., Nayak, O., Praharaj, S., Menon, V., Deep, R., Bathla, M., Subramanyam, A.A., Nebhinani, N., Ghosh, P., Lakdawala, B., Bhattacharya, R., 2023. Subjective cognitive deficits and its correlates among patients with bipolar disorder: findings from the bipolar disorder course and outcome study from India (BiD-CoIN study).

Indian J. Psychiatry. 65, 345. https://doi.org/10.4103/INDIANJPSYCHIATRY.INDIANJPSYCHIATRY_367_22.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Heaton, R.K., 1981. Wisconsin Card Sorting Test Manual. Psychological Asessment Resources, Odessa, FL.
Ilzarbe, L., Vieta, E., 2023. The elephant in the room: medication as confounder. Eur. Neuropsychopharmacol. 71, 6–8. https://doi.org/10.1016/j.euroneuro.2023.03.001.
Keramatian, K., Torres, I.J., Yatham, L.N., 2022. Neurocognitive functioning in bipolar disorder: what we know and what we don't. Dialogues Clin. Neurosci. 23, 29–38. https://doi.org/10.1080/19585969.2022.2042164.
Kjærstad, H.L., Søhol, K., Vinberg, M., Kessing, L.V., Miskowiak, K.W., 2023. The trajectory of emotional and non-emotional cognitive function in newly diagnosed patients with bipolar disorder and their unaffected relatives: a 16-month follow-up study. Eur. Neuropsychopharmacol. 67, 4–21. https://doi.org/10.1016/J.EURONEURO.2022.11.004.
Lima, F.M., Cardoso, T.A., Serafim, S.D., Martins, D.S., Solé, B., Martínez-Arán, A., Vieta, E., Rosa, A.R., 2018. Validity and reliability of the cognitive complaints in bipolar disorder rating assessment (COBRA) in Brazilian bipolar patients. Trends Psychiatry Psychother. 40, 170–178. https://doi.org/10.1590/2237-6089-2017-0121.
Lima, F., Rabelo-da-Ponte, F.D., Bücker, J., Czepielewski, L., Hasse-Sousa, M., Telesca, R., Sole, B., Reinares, M., Vieta, E., Rosa, A.R., 2019. Identifying cognitive subgroups in bipolar disorder: a cluster analysis. J. Affect. Disord. 246, 252–261. https://doi.org/10.1016/J.JAD.2018.12.044.
Martínez-Arán, A., Vieta, E., Colom, F., Torrent, C., Reinares, M., Goikolea, J.M., Benabarre, A., Comes, M., Sánchez-Moreno, J., 2005. Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? Psychother. Psychosom. 74, 295–302. https://doi.org/10.1159/000086320.
Miskowiak, K., Vinberg, M., Christensen, E.M., Kessing, L.V., 2012. Is there a difference in subjective experience of cognitive function in patients with unipolar disorder versus bipolar disorder? Nord. J. Psychiatry 66, 389–395. https://doi.org/10.3109/08039488.2012.658862.
Miskowiak, K.W., Petersen, J.Z., Ott, C.V., Knorr, U., Kessing, L.V., Gallagher, P., Robinson, L., 2016. Predictors of the discrepancy between objective and subjective cognition in bipolar disorder: a novel methodology. Acta Psychiatr. Scand. 134, 511–521. https://doi.org/10.1111/acps.12649.
Miskowiak, K., Burdick, K., Martinez-Aran, A., Bonnin, C., Bowie, C., Carvalho, A., Gallagher, P., Lafer, B., López-Jaramillo, C., Sumiyoshi, T., McIntyre, R., Schaffer, A., Porter, R., Torres, I., Yatham, L., Young, A., Kessing, L., Vieta, E., 2017. Methodological recommendations for cognition trials in bipolar disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force. Bipolar Disord. 19, 614–626. https://doi.org/10.1111/bdi.12534.
Miskowiak, K.W., Burdick, K.E., Martinez-Aran, A., Bonnin, C.M., Bowie, C.R., Carvalho, A.F., Gallagher, P., Lafer, B., López-Jaramillo, C., Sumiyoshi, T., McIntyre, R.S., Schaffer, A., Porter, R.J., Purdon, S., Torres, I.J., Yatham, L.N., Young, A.H., Kessing, L.V., Vieta, E., 2018. Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. Bipolar Disord. 20, 184–194. https://doi.org/10.1111/BDI.12595.
Petersen, J.Z., Porter, R.J., Miskowiak, K.W., 2019. Clinical characteristics associated with the discrepancy between subjective and objective cognitive impairment in depression. J. Affect. Disord. 246, 763–774. https://doi.org/10.1016/j.jad.2018.12.105.
Popovic, D., Reinares, M., Goikolea, J.M., Bonnin, C.M., Gonzalez-Pinto, A., Vieta, E., 2012. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur. Neuropsychopharmacol. 22, 339–346. https://doi.org/10.1016/j.euroneuro.2011.09.008.
Reitan, R.M., 1958. Validity of the railmaking test as a indication of organic brain damage. Percept. Mot. Skills 8, 271–276.
Rosa, A.R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the functioning assessment short test (FAST) in bipolar disorder. Clin. Pract. Epidemiol. Ment. Health 3, 5. https://doi.org/10.1186/1745-0179-3-5.
Rosa, A.R., Mercadé, C., Sánchez-Moreno, J., Solé, B., Del Mar Bonnin, C., Torrent, C., Grande, I., Sugranyes, G., Popovic, D., Salamero, M., Kapczinski, F., Vieta, E., Martinez-Aran, A., 2013. Validity and reliability of a rating scale on subjective cognitive deficits in bipolar disorder (COBRA). J. Affect. Disord. 150, 29–36. https://doi.org/10.1016/j.jad.2013.02.022.
Salagre, E., Dodd, S., Aedo, A., Rosa, A., Amoretti, S., Pinzon, J., Reinares, M., Berk, M., Kapczinski, F.P., Vieta, E., Grande, I., 2018. Toward precision psychiatry in bipolar disorder: staging 2.0. Front. Psychiatry 9, 641. https://doi.org/10.3389/fpsyt.2018.00641.
Sanchez-Moreno, J., Martinez-Aran, A., Tabarés-Seisdedos, R., Torrent, C., Vieta, E., Ayuso-Mateos, J.L., 2009. Functioning and disability in bipolar disorder: an extensive review. Psychother. Psychosom. 78, 285–297. https://doi.org/10.1159/000228249.
de Siqueira Rotenberg, L., Kjærstad, H.L., Varo, C., Vinberg, M., Kessing, L.V., Lafer, B., Miskowiak, K.W., 2023. The longitudinal trajectory of emotional cognition in subgroups of recently diagnosed patients with bipolar disorder. Eur. Neuropsychopharmacol. 71, 9–24. https://doi.org/10.1016/J.EURONEURO.2023.03.005.
Solé, B., Bonnin, C.M., Jiménez, E., Torrent, C., Torres, I., Varo, C., Valls, E., Montejo, L., Gómez-Ocaña, C., Tomioka, Y., Vieta, E., Martinez-Aran, A., Reinares, M., 2018 Jun. Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. Acta Psychiatr. Scand. 137 (6), 516–527. https://doi.org/10.1111/acps.12871 (Epub 2018 Mar 5. PMID: 29508379).
Torralva, T., Strejilevich, S., Gleichgerrcht, E., Roca, M., Martino, D., Cetkovich, M., Manes, F., 2012 Feb. Deficits in tasks of executive functioning that mimic real-life scenarios in bipolar disorder. Bipolar Disord. 14 (1), 118–125. https://doi.org/10.1111/j.1399-5618.2012.00987.x.
Träger, C., Decker, L., Wæhrens, E.E., Knorr, U., Miskowiak, K., Vinberg, M., 2017. Influences of patient informed cognitive complaints on activities of daily living in patients with bipolar disorder. An exploratory cross-sectional study. Psychiatry Res. 249, 268–274. https://doi.org/10.1016/j.psychres.2016.12.058.
Van Der Werf-Eldering, M.J., Burger, H., Jabben, N., Holthausen, E.A.E., Aleman, A., Nolen, W.A., 2011. Is the lack of association between cognitive complaints and objective cognitive functioning in patients with bipolar disorder moderated by depressive symptoms? J. Affect. Disord. 130, 306–311. https://doi.org/10.1016/j.jad.2010.10.005.
Van Rheenen, T.E., O'Neil, A., 2022. What can lifestyle factors tell us about cognitive dysfunction in bipolar disorder? Eur. Neuropsychopharmacol. 64, 1–3. https://doi.org/10.1016/J.EURONEURO.2022.07.574.
Varo, C., Kjærstad, H.L., Poulsen, E., Meluken, I., Vieta, E., Kessing, L.V., Vinberg, M., Miskowiak, K.W., 2021. Emotional cognition subgroups in mood disorders: associations with familial risk. Eur. Neuropsychopharmacol. 51, 71–83. https://doi.org/10.1016/J.EURONEURO.2021.05.003.
Wechsler, D., 1997. The Wechsler Adult Intelligence Scale-III (WAIS-III).
Yatham, L.N., Torres, I.J., Malhi, G.S., Frangou, S., Glahn, D.C., Bearden, C.E., Burdick, K., Martínez-Arán, A., Dittmann, S., Goldberg, J.F., Ozerdem, A., Aydemir, O., Chengappa, K.N., 2010 Jun. The International Society for Bipolar Disorders-Battery for assessment of Neurocognition (ISBD-BANC). Bipolar Disord. 12 (4), 351–363. https://doi.org/10.1111/j.1399-5618.2010.00830.x (PMID: 20636632).
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.