Journal of Affective Disorders

FACTORS ASSOCIATED WITH THE DISCREPANCY BETWEEN OBJECTIVE AND SUBJECTIVE COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

--Manuscript Draft--

Manuscript Number:	JAFD-D-23-04078R1
Article Type:	Research Paper
Keywords:	bipolar disorder; cognitive impairment; cognitive measures; cobra.
Corresponding Author:	Eduard Vieta University of Barcelona Faculty of Medicine and Health Sciences Barcelona, Catalonia SPAIN
First Author:	Caterina del Mar Bonnín
Order of Authors:	Caterina del Mar Bonnín
	Jose Sánchez-Moreno
	Flavia Moreira Lima
	Xavier Roca
	Xavier Segu
	Laura Montejo
	Brisa Sole
	Diego Hidalgo-Mazzei
	Sara Martin-Parra
	Anabel Martínez-Arán
	Eduard Vieta
	Carla Torrent
	Adriane Rosa
Abstract:	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.
Suggested Reviewers:	K W Miskowiak kamilla.miskowiak@regionh.dk

	Katherine E Burdick kburdick1@bwh.harvard.edu
	Vicent Balanza vicent.balanza@uv.es
	Ivan J Torres Ivan.Torres@ubc.ca
Opposed Reviewers:	
Response to Reviewers:	

Prof. Eduard Vieta
Bipolar Disorder and Depressive Unit
Hospital Clinic of Barcelona,
Clinical Institute of Neuroscience
Villarroel, 170
Barcelona (Spain)

08th August 2023

Prof. P. Brambilla and Prof. J.C. Soares,
Editors-in-Chief
Journal of Affective Disorders

Dear Prof. P. Brambilla and Prof. J.C. Soares,

We hope that this message finds you well. We would like to express our gratitude for the valuable feedback provided by the reviewers on our article entitled *"Factors associated with the discrepancy between objective and subjective cognitive impairment in bipolar disorder",* which was submitted to the Journal of Affective Disorders. Their comments and suggestions have been very helpful in improving the quality of our research. We would like to outline the major changes requested by the reviewers:

- **Data analysis:** we have re-run the analyses for all the models since reviewer #1 asked us to control for confounding variables, and reviewer #2 suggested that age and years of education should be considered. Therefore, the analyses include these variables now. The results and discussion sections have been updated to reflect the impact of these new variables. It is noteworthy that in most cases, the introduction of age and years of education had little effect on the models. However, years of education was found to contribute to one model and estimated premorbid IQ lost significance when introducing these two variables in another model.

- **Discussion enrichment:** Reviewer #2 provided valuable input on other possible reasons that might explain “overreporting” of cognitive subjective complaints in patients with BD. We have expanded our discussion to include this alternative hypothesis, providing a more comprehensive analysis. In particular, we have discussed about the adequacy of traditional neuropsychological tests in capturing subtle changes in cognition and the need to include ecologically valid tests to assess the changes in cognition of patients with BD.
- **Language editing**: since one reviewer considered that the manuscript was not carefully written, we have revised the manuscript. Special attention has been given to improving the clarity and coherence of the introduction and discussion sections.

We believe that these changes have significantly improved the quality of our article, and we hope they address the concerns raised by the reviewers. We are confident that the modifications made aligns the paper more closely with the standards and objectives of the Journal of Affective Disorders. We kindly request that you and the reviewers reassess our article considering these changes. Our answers to all the requests are written below in bold type. The changes performed in the manuscript and tables have been highlighted in yellow. Please find below our detailed responses to each of the reviewers’ comments.

Please do not hesitate to contact with us if you require any further information or have any additional question. We look forward to your response.

Sincerely,

Eduard Vieta & Anabel Martinez-Aran

Dear reviewers,

We appreciate all your comments on the present study, and we value your time and expertise in carefully reviewing the manuscript. We believe that all the comments have been very useful in improving the quality of this report. Our responses to all your queries are provided below in bold type. We have highlighted all the changes made in the manuscript and in the tables in yellow.

Reviewer #1: It is a remarkable paper about the factor associated with the discrepancy between objective and subjective cognitive impairment in bipolar disorder. However, several revisions are required as follows:

1. Most of all, the goodness of fit of linear regression model is considered relatively low. The interpretability for the findings should be thoruthly reviewed.

We understand reviewer's comment. Compared to the original article, Miskowiak and colleagues (2016) reported R-squared that ranged between 0.10 -0.40 and in our study adjusted R-squared range between 0.06 -0.24, which is lower. However, we are not especially concerned about these data since to evaluate the goodness of fit of a given model, indicators other than R-squared shall be considered. For instance, the residuals are also important indicators to look at when evaluating the goodness of fit. in this regard, models with smaller residuals (even though this implies smaller R-squared), might be also good models. Models with less residuals are easier to interpret and to communicate, but on the other hand, they are less accurate and reliable in predictions. When evaluating the goodness of fit of a model we always prefer smaller residuals even though this means lower R-squared.

Besides this, we would also like to tell the reviewer that we have carefully reviewed the assumptions to perform a linear regression, including collinearity diagnosis, or even performing different models to avoid overfitting, like we have carefully detailed in the method section. We have also reviewed other issues such as outliers, heteroscedasticity and missing data that could impact on the goodness of fit. Finally, one of the explanations that might help to understand the lower R-squared when compared to the original study might be because of smaller sample size of our study, which limits the model's ability to detect significant relationships and also lower R-squared. Nevertheless, the limitation of the sample size has been already pointed out in the discussion section but we have added also some lines explaining that smaller sample size can also influence in the goodness of fit of our models (see page#10):

"(…), 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 and colleagues (2016)."

2. The potential influences of confounding factors on the linear regression model are not adjusted. Further statistical analysis should be required.

We have performed additional analyses, including confounding factors such as age and years of education in each of the linear regressions, since both variables may influence the in reporting cognitive subjective complaints and in the objective cognitive performance. We have decided to include these two variables since reviewer #2 also made a comment related to these potential confounding factors. In general, results have not changed that much, which we believe is quite positive and in favour of the initial models. The most important changes include: a) years of education is significantly contributing to the global sensitivity domain, and increases the R-squared, and b) the premorbid IQ becomes a trend once we introduce age and years of education in the working memory and executive domain. Since we have performed additional analysis for all the linear regressions, in the following pages we present the results and below each analysis we explain the changes added into the manuscript:

GLOBAL SENSITIVITY SCORE:

Model Summary[a]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.599[b]	.359	.265	1.90604

a. Grup Tractament = TAU

b. Predictors: (Constant), Edat, Anys Estudi. Educació, Número Ingressos Basal, Símptomes Psicòtics Lifetime, Número Depressions Basal, Fast Total Puntació Basal

ANOVA[a,b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	83.484	6	13.914	3.830	.004[c]
	Residual	148.952	41	3.633		
	Total	232.436	47			

a. Grup Tractament = TAU

b. Dependent Variable: Global_sensitivity_score_pacientes

c. Predictors: (Constant), Edat, Anys Estudi. Educació, Número Ingressos Basal, Símptomes Psicòtics Lifetime, Número Depressions Basal, Fast Total Puntació Basal

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-5.367	2.361		-2.274	.028		
	Número Depressions Basal	.339	.138	.337	2.459	.018	.833	1.200
	Fast Total Puntació Basal	.048	.023	.290	2.066	.045	.796	1.256
	Anys Estudi. Educació	.226	.088	.343	2.575	.014	.882	1.134
	Número Ingressos Basal	-.303	.152	-.262	-1.987	.050	.896	1.116
	Símptomes Psicòtics Lifetime	.695	.670	.137	1.036	.306	.899	1.113
	Edat	.012	.035	.047	.345	.732	.852	1.174

a. Grup Tractament = TAU

b. Dependent Variable: Global_sensitivity_score_pacientes

Note that all the variables that were statistically significant in the previous model still remain: number of previous episodes (2nd row); FAST (3rd row), number of previous hospitalizations (5th row). However, we have found that years of education (4th row) significantly contribute to the model, increasing also the adjusted R-squared up to 26.5%.

The present results, change some of the previous findings. Hence, we have proceeded to change the manuscript accordingly:

Results section, page#5:

"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 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 significantly contribute to the model".

VERBAL MEMORY SENSITIVITY DOMAIN:

Model Summary[a]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.353[b]	.125	.120	2.58995

a. Grup Tractament = TAU

b. Predictors: (Constant), Edat, Anys Estudi. Educació, Número Depressions Basal, Fast Total Puntació Basal

ANOVA[a,b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	43.890	4	10.972	3.020	.020[c]
	Residual	308.561	46	6.708		
	Total	352.451	50			

a. Grup Tractament = TAU

b. Dependent Variable: verbal_memory_sensitivity_pacientes

c. Predictors: (Constant), Edat, Anys Estudi. Educació, Número Depressions Basal, Fast Total Puntació Basal

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-7.536	2.677		-2.815	.007		
	Anys Estudi. Educació	.066	.108	.089	.613	.543	.911	1.098
	Número Depressions Basal	.373	.181	.308	2.067	.044	.860	1.163
	Fast Total Puntació Basal	.018	.030	.089	.588	.560	.827	1.209
	Edat	.021	.045	.069	.476	.637	.916	1.092

a. Grup Tractament = TAU

Adding age and years of education did not change the model in which depressive episodes remain as the only significant variable contributing to the model. Adjusted R- squared practically remained the same. However, we have proceeded with the changes in the results section (see page#6):

"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."

ATTENTION AND PROCESSING DOMAIN:

Model Summary[a]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.598[b]	.358	.256	2.24026

a. Grup Tractament = TAU

b. Predictors: (Constant), Número Total Episodis Basal, Edat, Puntuació Total Hamilton, Número Ingressos Basal, Anys Estudi. Educació, Fast Total Puntació Basal

ANOVA[a,b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	106.269	6	17.712	3.529	.007[c]
	Residual	190.713	38	5.019		
	Total	296.983	44			

a. Grup Tractament = TAU

b. Dependent Variable: attention_sensitivity_pacientes

c. Predictors: (Constant), Número Total Episodis Basal, Edat, Puntuació Total Hamilton, Número Ingressos Basal, Anys Estudi. Educació, Fast Total Puntació Basal

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-4.238	2.704		-1.567	.125		
	Fast Total Puntació Basal	.072	.034	.378	2.123	.040	.533	1.876
	Edat	.053	.041	.184	1.300	.201	.843	1.186
	Anys Estudi. Educació	.028	.105	.038	.272	.787	.855	1.170
	Puntuació Total Hamilton	.010	.108	.016	.097	.923	.600	1.666
	Número Ingressos Basal	-.457	.185	-.342	-2.472	.018	.881	1.135
	Número Total Episodis Basal	.109	.103	.152	1.064	.294	.826	1.211

a. Grup Tractament = TAU

b. Dependent Variable: attention_sensitivity_pacientes

FAST total score (2nd row) and number of previous hospitalizations (6th row), still remain significant. See page#6:

"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)."

WORKING MEMORY AND EXECUTIVE FUNCTION DOMAIN:

Model Summary[a]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.250[b]	.062	.017	2.14573

a. Grup Tractament = TAU

b. Predictors: (Constant), Vocabulario Estimacion del CI, Edat, Anys Estudi. Educació

ANOVA[a,b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	18.984	3	6.328	1.374	.259[c]
	Residual	285.457	62	4.604		
	Total	304.441	65			

a. Grup Tractament = TAU

b. Dependent Variable: executive_sensitivity_pacientes

c. Predictors: (Constant), Vocabulario Estimacion del CI, Edat, Anys Estudi. Educació

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	-9.170	3.229		-2.840	.006		
	Anys Estudi. Educació	.139	.081	.231	1.723	.090	.839	1.191
	Edat	-.130	.030	-.052	-.400	.688	.925	1.081
	Vocabulario Estimacion del CI	.060	.031	.330	1.970	.055	.817	1.225

a. Grup Tractament = TAU

b. Dependent Variable: executive_sensitivity_pacientes

Adding years and years of education to this model, estimated premorbid IQ is no longer significant. However, neither age nor education significantly contribute to the model. Hence changes in the results section are as follows (see page#6):

"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=0.05."

Even though premorbid IQ is no longer significant, and we did not find any variable that contributed to this domain, we believe that is encouraging that years of education contribute to the global sensitivity model, and the most important thing is that it contributes in the same direction as premorbid IQ (in a positive manner), meaning that the patients with more years of education tended to overreport they deficits. We have added some lines in the discussion explaining this new finding (see page #9):

"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."

We have also added a paragraph in the discussion to explain/hypothesize the lack of variables associated to the working memory and executive domain (see page#8):

"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, changes have also been done on table 3 reporting the new values for the Betas and p values.

3. The reason why the DSM-IV but not DSM-5 has been used as a diagnostic method should be adequately described. The method how the diagnosis of biopolar disorder is confirmed should be additionaly described.

The sample was recruited between 2009 to 2012, as a part of another study. In that period DSM-IV-TR was used as the gold standard for psychiatric diagnosis. The DSM-5 was published in 2013. We have added this information in the method section (see page#2):

"The patients were recruited between 2009 and 2012 at the Bipolar and Depressive Disorders Unit from the Hospital Clinic of Barcelona."

4. The formal standardizations of Spanish versions of all psychometric scales should be additionally described.

We have carefully reviewed all the references provided in the present manuscript and they are all correct. The point is that most of the tests (specially the neuropsychological tests) do not have a Spanish version, but we do have the standardization scores according to the Spanish population. Nevertheless, in the present study raw scores on the objective and subjective measures were standardized against the control group. Since Reviewer #2 also requested us to clarify this, we have added a sentence in the statistical analysis section stating that the standardization of the scores were performed with the control group (see page #4):

"Raw scores, both on the objective and subjective measures, were standardized against the control group."

5. The ethical approval of the institutional review of board should be properly described. (approval number is required.)

We have added the information in the methods section (participants). See page #2:

"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 (register number: 2008/4256)."

Reviewer #2: Thank you for letting me review this study. The article addresses a relevant and interesting topic, but I believe it should be thoroughly revised.

Thank you for your time in reviewing our manuscript. We have addressed each of the questions trying to make our best. We hope that the answers meet with your approval.

-In the abstract and in the methods section the authors state that "One hundred and sixty participants were included". However, there were one hundred and sixteen participants (83 patients and 33 healthy controls).

Thank you for noticing this typo. We have proceeded to correct it (see page#2 and the abstract section):

"One hundred and sixteen participants (83 outpatients with BD and 33 healthy controls) were enrolled for this study".

-Introduction: although cognitive impairment is an important feature of bipolar disorders that warrants consideration, according to the first two sentences it seems that people with bipolar disorder are not capable of doing anything (working, studying or having interpersonal relationships) due to their cognitive impairment.

We want to strike an appropriate balance in our statement, and while we acknowledge that BD is considered the fifth leading cause of disability among psychiatric illnesses (Català-López et al., 2013; Grande et al., 2016), we do not wish to overly dramatize the situation. We aim to highlight the challenges that some patients face in their lives. Nevertheless, we understand the reviewer's concern, and in response, we have included additional sentences in the introduction to clarify that not all patients with BD experience functional impairment (see page#1, introduction section):

"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 BD experience some degree of functional impairment related to both subsyndromal symptoms and cognitive deficits (Solé et al., 2018)."

-It is not clear from reading of the manuscript why a control group was included. I understand that it was because the raw scores on the objective and subjective measures were standardized against the control group. But this should be better clarified in the text and not simple cite the study by Miskowiak et al.

Yes, the reviewer is right: this is the reason why a control group was included. The reviewer's comment made us realize that not clearly stating this in the manuscript may lead to confusion. Hence, we have added a sentence statistical analysis section to clarify it (see page #4):

"Raw scores, both on the objective and subjective measures, were standardized against the control group."

-It would be interesting that the authors include the age range of participants (each group) in the results section: they only state the inclusion criterion that patients had to be aged between 18 and 65 years.

We have added the age range of both groups in table 2. Age range in the patient group is [18-61] and in the control group is [22-60]. We have also added the range in those variables in which patients and healthy controls are compared. Please, see table 2 to see all the changes we have performed.

-The results obtained mainly for objective cognitive performance may be misleading. Despite groups being matched on age and years of education, it is of note that the results of a given person on a given test should be compared with that of a quite homogeneous group of people of the same age range.

We agree with this. Nevertheless, the key point in this article is not to determine the degree of objective impairment compared to a healthy control group, but to evaluate the discrepancy between objective cognitive performance and reported cognitive complaints. In any case, reviewer #1 has also pointed out the importance of considering some confounding variables that we had not included in the original analysis. We have re-run the analyses, taking into account both age and education level. The main results have remained quite robust across all models, with some minor changes that we have already detailed to reviewer #1. To sum up, when introducing these two variables in the different models, years of education become significant in the global sensitivity domain, together with the remaining variables that were found to be significant in the initial analysis. in the working memory and executive domain, when adding these variables, premorbid IQ loses significance and becomes a trend (Beta=0.33; t=1.97; p=0.055). As a result of this, we have proceeded with the changes both in the results and in the discussion sections as we detail:

Results section, page#5:

"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 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 significantly contribute to the model"

Results section, page#6:

"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).”

In the discussion we have added a paragraph with the new results regarding estimated premorbid IQ (see page #8):

“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.”

Also, in the discussion we have added another paragraph as regards to the contribution of the variable “years of education” to the global sensitivity model (see page #9):

“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.”

-I believe that the assumption of "overreporting" cognitive deficits in patients with better objective cognitive functioning in the presence of subjectively reported deficits is wrong. For instance, it has been shown that patients with "preserved cognitive functioning" according to "traditional cognitive tests" have impaired performance in "ecological" tests (Torralva et al 2012). Hence, the discrepancies observed could be explained by the fact that traditional cognitive tests are not capable of capturing some cognitive deficits that patients without a severe cognitive impairment (and preserved metacognitive abilities) can indeed subjectively capture and report. Thus, such patients may not be 'overreporting'.

Yes, this is true, and we agree with the reviewer. Some authors (Spooner & Pachana, 2006; Chaytor & Schmitter-Edgecombe, 2003) already addressed this critical issue about the ecological validity and they pointed out that the tests, initially developed to answer diagnostic questions, are now used to answer questions about real-world functioning with very little empirical evidence to support this practice. Therefore, as the reviewer says, these tests do not necessarily have adequate ecological validity.

We have added some lines in the discussion developing this idea (see page #9):

“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."

-The authors propose that cognitive "deterioration" may be explaining discrepancies between objective and subjective cognitive function: "A 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…". There are a number of reasons -less counterintuitive than this one- that may explain the differences observed between objective and subjective cognitive outcomes such as the one I provide in the paragraph above.

Yes, we also agree with this, and that is why we have added a paragraph in the discussion to emphasize the idea proposed in the previous query. However, if the reviewer does not mind, we would like to retain this explanation, even if it seems counterintuitive.

In our everyday clinical practice, it is quite common for patients with BD to present subjective cognitive complaints or even report a subjective cognitive decline while still performing within the objective "normal" range on standard clinical assessments. This phenomenon might not be unique to psychiatric illnesses; in fact, it was first described in neurodegenerative diseases where some patients reported subjective cognitive decline without clinically significant cognitive impairment (Kielb et al., 2017). There could be several reasons to explain this lack of alignment between the two measures. One of these reasons is the previously mentioned lack of ecological validity of the tests or the insensitivity of standard neuropsychological tests in detecting very subtle changes. However, it has also been described that subjective cognitive complaints may precede objective cognitive impairment in Alzheimer-type dementia (Jessen et al., 2014). We are not suggesting that those patients with BD who "overreport" their cognitive deficits will develop some form of dementia, but we are emphasizing the importance of cognitive subjective complaints since they could predict clinically significant cognitive impairment in the future. Due to the cross-sectional nature of our study, we have not delved deeply into this idea in the discussion, but we hope that this explanation, in addition to the amendments already made in the discussion, will satisfy the reviewer.

-In the results section, note that for the global sensitivity score the authors do not include the R2 for the best adjustment model.

Thank you, please see page #5. Second paragraph in the section of "Global sensitivity composite score":

"The linear regression model was statistically significant (F=3.83, p=0.004; adjusted R^2= 0.265)."

-In the results section, please, replace "Chi test" with "Chi- squared test".

Thank you. It has been corrected throughout the article and in table 2.

-Please replace the word "determinant" with "predictor" as no causality can be assumed from the findings of this study (being a predictor does not necessarily imply being a "determinant").

This is a very good point. We chose the word “determinant” instead of “predictor” to account for the limitations of a cross-sectional study where “predictor” may not be entirely appropriate. We agree with the reviewer’s suggestion that “determinant” is still not the best choice, and we would like to avoid the word “predictor” as well. Therefore, we have proceeded to replaced it with “factors that might help to explain”. The final sentence in the abstract is as follows:

“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.”

-The article has not been carefully written. Please, revise. Language revision is also needed.

I would like to express my sincere gratitude for your feedback and suggestions on this article. I understand that our English writing may require revision, as it is not our native language. For non-native speakers, it is a daily challenge to engage in scientific writing in English. I appreciate your understanding and patience in this improvement process. Language editing has been applied throughout the article, with particular emphasis on the introduction and the discussion. We hope that these changes have made the article more comprehensible.

Reviewer #3:

The present study aimed to evaluate the discrepancy between objective cognitive measures and cognitive subjective impairments in euthymic patients with bipolar disorder.
The level of awareness of cognitive disorders in these patients is still unclear. According to some studies, patients are not aware of their cognitive deficits (Burdick et al., 2005; Lima et al., 2018), while others suggest that subjective and objective measures might be partially correlated (Demant et al., 2015; Rosa et al., 2013). To explain the discrepancies found in the literature Miskowiak et al., 2016 suggested a new method to identify different profiles of patients with different levels of awareness of cognitive disorders.

The article is generally well written, and the language is appropriate. Some minor revisions are needed.
Limitations of study are very clearly stated. They're lack of causal relationships of discrepancy between the subjective experience and objective dysfunction, a smaller sample size and lack of assessment of the personality variables, cognitive reserve and pharmacological treatment,
Thank you for your comments and for the exhaustive review of the paper, helping us to improve the manuscript. We are also grateful that the reviewer appreciates both the strengths and weaknesses of the present study. If you have any further comments or suggestions in the future, please do not hesitate to ask.

Tables
- Tables as editable text and not as images

Thank you for noticing this. When submitting the paper, we will make sure that the tables appear as editable text and not as images.

- Table 1: As guidelines of journal, avoid using shading in table cells.

Thank you for noticing this. We have proceeded to correct it.

Introduction
- On page 1, line 16: correcting citation. keep only the year in parentheses: "(Rosa et al., 2013)"

We have corrected this and now it is written as follows:

"Rosa et al., (2013) also described that cognitive complaints were partially correlated with objective measures of memory and executive function."

- On page 1, line 17 - 18: not repeat the citation: "As a result of this, in 2016, Miskowiak and colleagues (Miskowiak et al., 2016) suggested..." à "As a result of this, Miskowiak and colleagues (2016) ..."

We have proceeded to correct it:

"As a result of this, Miskowiak and colleagues (2016) suggested that the discrepancies found in the literature could be explained depending on the methodology used;(...)"

Methods

Participants

- On page 2, line 49: replace parentheses by semicolon (Young et al., 1978) (Colom et al., 2000)

Thank you. Now the citations look like follows:

"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)."

- On page 2, line 51: delete text space "year._A total"

Thank you, we have removed the extra space:

"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."

Measures

- On page 2-3: Explain how the assessment instruments were chosen. Please specify why those tools and no others.

We have added some lines at the end of page #3, in the "objective cognitive assessment section" (see page# 3):

"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)."

- On page 3, line 70: delate comma "illnesses, and specially ..."

We have deleted the comma:

"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."

- On page 3, line 79: delate parenthesis "sequencing of the WAIS-III) (Wechsler, 1997)."

"estimated IQ was evaluated with the Wechsler Adult Intelligence Scale vocabulary subtest (WAIS-III, Wechsler, 1997),".

- On page 4, line 104-105: delate parentheses, keep only the year in parentheses. Eliminate text space between parenthesis and dot. "(Miskowiak et al., 2016)_. All …"

We have slightly changed this paragraph to decrease the citation "Miskowiak et al., (2016)":

"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"

- On page 4, line 114: delate parentheses

We have removed the parentheses:

"For further details, see Miskowiak et al., (2016)."

Discussion

- On page 7, line 191: replace semicolon by comma "stoicism; while higher number…"

We have replaced the semicolon by the comma:

"(…) we found that greater number of previous hospitalizations were associated with more stoicism, while higher number of previous depressive episodes and higher scores in the FAST"

- On page 7, line 192: delete comma "Miskowiak et al., (2016), …"

We have deleted the comma:

"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."

- On page 8, line 245: add text space before the parenthesis "a normative group(Lima …"

Thank you for noticing this. We have added a text space:

"(...), which simply rely on the comparison with a normative group (Lima et al., 2018; Miskowiak et al., 2016)."

- On page 8, line 248: remove comma after citation "…Quiroga, 2021), and …"

We have slightly changed the discussion in light of new results. That is how the citation looks like after these changes (see page#9):

"Years of education is another important variable that some authors identify as a key component of the cognitive reserve (Amoretti et al., 2019; Amoretti and Ramos-Quiroga, 2021). In this regard, it could be hypothesized(...)"

- In the future studies, it would be interesting to include a longer-term follow-up. Should we expect a change in subjective perception? Could it evolve over time and how?

We believe that in a follow-up study subjective cognitive complaints would predict cognitive impairment, since this relationship has already been found in neurodegenerative diseases like Alzheimer-type dementia (Jessen et al., 2014; Kielb et al., 2017); however, this is a hypothesis based on our clinical experience and it might be too speculative to develop it in the discussion. As suggested, we have completed the sentence with this hypothesis when talking about the future studies (see page #10):

"Further longitudinal studies should evaluate 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."

References

Add dot after journal "…in mental disorders. Eur Neuropsychopharmacol. 49, 113…"

Thank you, we have corrected the citation

Reviewer #4:

The current study of the relationship between objective cognitive performance and subjective cognitive impairment in patients with bipolar disorder and healthy controls, is a replication study of a previous report by another group. Replication studies are often somewhat undervalued but are essential for the progress of research. Cognitive impairment in bipolar disorder, although less prominet than manic or depressive episodes, is a major concern of patients as well as clinicians. In their study, although using similar methods, these authors report to some extend different findings than the original study. These differences are adequately addressed in the discussion section. Limitations of the study, e.q. not including teh impact of pharmacotherapy, als also adequately mentioned. I have no further comments. This report is an improtant contribution to the study of cognitive fuinctioning in severe psychiatric illness.

We are grateful for your constructive feedback and your recognition of the importance of replication studies in advancing research, especially in the context of severe psychiatric illnesses. We value your time and expertise in reviewing our manuscript, and we are grateful for your support. If you have any further comments or suggestions in the future, please do not hesitate to ask.

References:

Catala-Lopez F, Genova-Maleras R, Vieta E, Tabares-Seisdedos R. The increasing burden of mental and neurological disorders. Eur Neuropsychopharmacol 2013;23:1337– 1339. 5.

Chaytor, N., Schmitter-Edgecombe, M. The Ecological Validity of Neuropsychological Tests: A Review of the Literature on Everyday Cognitive Skills. Neuropsychol Rev 13, 181–197 (2003). https://doi.org/10.1023/B:NERV.0000009483.91468.fb
Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet 2016;387(10027):1561–1572.

Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G,Dubois B, Dufouil C, Ellis KA, van der Flier WM, Glodzik L, van Harten AC, de Leon MJ, McHugh P, Mielke MM, Molinuevo JL, Mosconi L, Osorio RS, Perrotin A, Petersen RC, Rabin LA, Rami L, Reisberg B, Rentz DM, Sachdev PS, de la Sayette V, Saykin AJ, Scheltens P, Shulman MB, Slavin MJ, Sperling RA, Stewart R, Uspenskaya O, Vellas B, Visser PJ, Wagner M; Subjective Cognitive Decline Initiative (SCD-I) Working Group. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014 Nov;10(6):844-52. doi: 10.1016/j.jalz.2014.01.001. Epub 2014 May 3 PMID: 24798886; PMCID: PMC4317324.

Kielb S, Rogalski E, Weintraub S, Rademaker A. Objective features of subjective cognitive decline in a United States national database. Alzheimers Dement. 2017 Dec;13(12):1337-1344. doi: 10.1016/j.jalz.2017.04.008. Epub 2017 Jun 3. PMID: 28586648; PMCID: PMC5712483.

Spooner DM, Pachana NA. Ecological validity in neuropsychological assessment: a case for greater consideration in research with neurologically intact populations. Arch Clin Neuropsychol. 2006 May;21(4):327-37. doi: 10.1016/j.acn.2006.04.004. Epub 2006 Jun 12. PMID: 16769198.

Highlights

- Understanding the factors contributing to the discrepancy between objective and subjective cognitive impairment can serve to guide clinical assessment and to treat the cognitive dysfunction.
- Number of previous depressive episodes may represent a key variable that helps to explain the discrepancy between objective and subjective cognition in euthymic patients with BD since it was associated with greater sensitivity in the global model and also in the memory domain.
- The combined use of both subjective and objective cognitive measures is needed to make an accurate assessment of cognitive dysfunctions and their effective treatment.

Abstract

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.

FACTORS ASSOCIATED WITH THE DISCREPANCY BETWEEN OBJECTIVE AND SUBJECTIVE COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

Bonnín CM[1,5,6 Ψ], Sánchez-Moreno J[1,3,4,5 Ψ], Lima F[7], Roca X[8,9], Segú X[1], Montejo L[1,3,4,5], Solé B[1,3,4,5], Hidalgo-Mazzei D[1,3,4,5], Martin-Parra S[1,3,4,] , Martínez-Arán A[1,2,3,4,5 *], Vieta E[1,2,3,4,5 *], Torrent C[1,3,4,5 ω], Rosa AR[7,10 ω]

[1]Bipolar and Depressive Disorders Unit, Hospìtal Clinic de Barcelona. c. Villarroel, 170, 08036 Barcelona, Spain.

[2]Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), c. Casanova, 143, 08036 Barcelona, Spain.

[3]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), c. Villarroel, 170, 08036 Barcelona, Spain.

[4]Institute of Neurosciences (UBNeuro)

[5]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

[6]Psychiatry Department, Institut d'Investigació Biomèdica-Sant Pau (IIBSANT PAU), Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Catalonia, Spain.

[7]Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

[8]Unitat de Conductes Addictives, Servei de Psiquiatria, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[9]Institut d'Investigació Biomèdica- Sant Pau (IIB SANT PAU), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[10]Department of Pharmacology, Health Basic Science Institute, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil; Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

Ψ The authors should both be considered joint first authors

ω The authors should both be considered joint senior authors

***Corresponding author: Eduard Vieta & Anabel Martinez-Aran**

Bipolar Disorder and Depressive Unit at the Hospital Clinic i Provincial. Clinical Institute of Neuroscience. Hospital Clinic of Barcelona, Villarroel, 170. 08036 Barcelona, Spain.

Tel.: +34 93 227 54 01; fax: +34 93 227 5795. E-mail address at: evieta@clinic.cat; amartiar@clinic.cat

Conflict of interests

EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, Medincell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work;

DHM has received CME-related honoraria and served as consultant for Abbott, Angelini, Ethypharm Digital Therapy and Janssen-Cilag, with no financial or other relationship relevant to the subject of this article.

All authors report no financial or other relationship relevant to the subject of this article.

Role of the funding source This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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.

Data Availability

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

Author Statement Contributors

CMB, JSM, CT and ARR designed the study. CMB and ARR analyzed and interpreted the data. CMB and JSM wrote the first draft of the manuscript. FM, XR, XS, LM, BS, DHM, SMP, AMA, EV, CT and ARR provided significant intellectual contribution to the manuscript. All authors had read and approved the final version of this manuscript for submission.

Acknowledgments

The authors would like to thank the support of the Instituto de Salud Carlos III, the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2021-SGR-01358) and the CERCA Programme/Generalitat de Catalunya. Carla Torrent would like to thank Instituto de Salud Carlos III (ISCIII), PI17/01066, PI20/00344, co-funded by the European Union. Adriane R Rosa thanks to the productivity grant from the CNPq-Brazil, process number 302382/2019-4. Adriane R Rosa would like to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-Brazil) e Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil-(CAPES). We thank the University of Barcelona for the Open access of this paper.

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 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 and colleagues (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 and colleagues (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.

Methods

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 – 65 years old; c) at least three months of euthymia based on a total score $\leq$ 8 on the Hamilton Depression Rating Scale (HAM-D) (Cordero-Villafáfila and Ramos-Brieva, 1986; Hamilton, 1960) and a total score $\leq$ 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.

Measures

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.

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 a., 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).

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.

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.

<<Insert table 1 about here>>

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).

Results

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.

<<insert table 2 about here>>

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 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.

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.

<<Insert table 3 about here>>

Discussion

To the best of our knowledge, this is the first study to replicate the methodology described by Miskowiak and colleagues (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 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.

~~The present results could also be interpreted in light of the cognitive reserve; in this regard, premorbid IQ has been identified as one of the key components of the cognitive reserve (Amoretti et al., 2019; Amoretti and Ramos-Quiroga, 2021) and some studies have also~~

~~identified a close relationship between cognitive reserve and executive functions (Cotrena et al., 2021, 2020), hence it could be hypothesized that patients with higher premorbid IQ (and higher cognitive reserve) might be more sensitive and aware to the loss of faculties in this specific domain.~~

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 and colleagues (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.

References

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

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

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. Iowa City, IA: University of Iowa.

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

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

Colom, F., Vieta, E., Martinez-Aran, A., Reinares, M., Benabarre, A., Gasto, C., 2000. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. Journal of Clinical 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.

~~Cotrena, C., Branco, L.D., Ponsoni, A., Shansis, F.M., Fonseca, R.P., 2021. Cognitive reserve may outperform age, mood and psychiatric comorbidities as a predictor of executive functioning in bipolar disorder and healthy adults. J Clin Exp Neuropsychol 43, 611–622. https://doi.org/10.1080/13803395.2021.1981251~~

~~Cotrena, C., Damiani Branco, L., Milman Shansis, F., Paz Fonseca, R., 2020. "Influence of modifiable and non-modifiable variables on functioning in bipolar disorder: a path analytical study." Int J Psychiatry Clin Pract 24, 398–406. https://doi.org/10.1080/13651501.2020.1779307~~

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

Delis DC, Kramer JH, Kaplan E, O.B., 1987. California verbal learning test. New York, NY: Psychological Corporation.

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 MB; R Spitzer; M Gibbon, 1997. Structured clinical interview for DSM-IV Axis I Disorders. American Psychiatric Press Inc, Biometric Research Department ed. Whashington DC.

Golden, C., 1978. Stroop Color and word test. Chicago, IL: Stoelting.

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. Odessa, FL: Psychological Asessment Resources.

Ilzarbe, L., Vieta, E., 2023. The elephant in the room: Medication as confounder. European Neuropsychopharmacology 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., 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

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

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., 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., 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., 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

Miskowiak, K.W., Petersen, J.Z., Ott, C. V., Knorr, U., Kessing, L. V., Gallagher, P., Robinson, L., 2016a. 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

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. European Neuropsychopharmacology 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., Mercadé, C., Sánchez-Moreno, J., Solé, B., Mar Bonnin, C. Del, 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

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

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

Solé B, Bonnin CM, Jiménez E, Torrent C, Torres I, Varo C, Valls E, Montejo L, Gómez-Ocaña C, Tomioka Y, Vieta E, Martinez-Aran A, Reinares M. Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. Acta Psychiatr Scand. 2018 Jun;137(6):516-527. doi: 10.1111/acps.12871. Epub 2018 Mar 5. PMID: 29508379.

Torralva T, Strejilevich S, Gleichgerrcht E, Roca M, Martino D, Cetkovich M,Manes F. Deficits in tasks of executive functioning that mimic real-life scenarios in bipolar disorder. Bipolar Disord. 2012 Feb;14(1):118-25. doi: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 LN, Torres IJ, Malhi GS, Frangou S, Glahn DC, Bearden CE, Burdick K, Martínez-Arán A, Dittmann S, Goldberg JF, Ozerdem A, Aydemir O, Chengappa KN. The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). Bipolar Disord. 2010 Jun;12(4):351-63. doi: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.

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 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 and colleagues (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 and colleagues (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.

Methods

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 – 65 years old; c) at least three months of euthymia based on a total score $\leq$ 8 on the Hamilton Depression Rating Scale (HAM-D) (Cordero-Villafáfila and Ramos-Brieva, 1986; Hamilton, 1960) and a total score $\leq$ 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.

Measures

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.

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 a., 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).

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.

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.

<<Insert table 1 about here>>

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).

Results

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.

<<insert table 2 about here>>

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 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.

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.

<<Insert table 3 about here>>

Discussion

To the best of our knowledge, this is the first study to replicate the methodology described by Miskowiak and colleagues (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 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.

~~The present results could also be interpreted in light of the cognitive reserve; in this regard, premorbid IQ has been identified as one of the key components of the cognitive reserve (Amoretti et al., 2019; Amoretti and Ramos-Quiroga, 2021) and some studies have also~~

~~identified a close relationship between cognitive reserve and executive functions (Cotrena et al., 2021, 2020), hence it could be hypothesized that patients with higher premorbid IQ (and higher cognitive reserve) might be more sensitive and aware to the loss of faculties in this specific domain.~~

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 and colleagues (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.

References

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

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

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. Iowa City, IA: University of Iowa.

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

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

Colom, F., Vieta, E., Martinez-Aran, A., Reinares, M., Benabarre, A., Gasto, C., 2000. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. Journal of Clinical 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.

~~Cotrena, C., Branco, L.D., Ponsoni, A., Shansis, F.M., Fonseca, R.P., 2021. Cognitive reserve may outperform age, mood and psychiatric comorbidities as a predictor of executive functioning in bipolar disorder and healthy adults. J Clin Exp Neuropsychol 43, 611–622. https://doi.org/10.1080/13803395.2021.1981251~~

~~Cotrena, C., Damiani Branco, L., Milman Shansis, F., Paz Fonseca, R., 2020. "Influence of modifiable and non-modifiable variables on functioning in bipolar disorder: a path analytical study." Int J Psychiatry Clin Pract 24, 398–406. https://doi.org/10.1080/13651501.2020.1779307~~

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

Delis DC, Kramer JH, Kaplan E, O.B., 1987. California verbal learning test. New York, NY: Psychological Corporation.

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 MB; R Spitzer; M Gibbon, 1997. Structured clinical interview for DSM-IV Axis I Disorders. American Psychiatric Press Inc, Biometric Research Department ed. Whashington DC.

Golden, C., 1978. Stroop Color and word test. Chicago, IL: Stoelting.

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. Odessa, FL: Psychological Asessment Resources.

Ilzarbe, L., Vieta, E., 2023. The elephant in the room: Medication as confounder. European Neuropsychopharmacology 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., 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

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

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., 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., 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., 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

Miskowiak, K.W., Petersen, J.Z., Ott, C. V., Knorr, U., Kessing, L. V., Gallagher, P., Robinson, L., 2016a. 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

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. European Neuropsychopharmacology 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., Mercadé, C., Sánchez-Moreno, J., Solé, B., Mar Bonnin, C. Del, 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

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

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

Solé B, Bonnin CM, Jiménez E, Torrent C, Torres I, Varo C, Valls E, Montejo L, Gómez-Ocaña C, Tomioka Y, Vieta E, Martinez-Aran A, Reinares M. Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. Acta Psychiatr Scand. 2018 Jun;137(6):516-527. doi: 10.1111/acps.12871. Epub 2018 Mar 5. PMID: 29508379.

Torralva T, Strejilevich S, Gleichgerrcht E, Roca M, Martino D, Cetkovich M,Manes F. Deficits in tasks of executive functioning that mimic real-life scenarios in bipolar disorder. Bipolar Disord. 2012 Feb;14(1):118-25. doi: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 LN, Torres IJ, Malhi GS, Frangou S, Glahn DC, Bearden CE, Burdick K, Martínez-Arán A, Dittmann S, Goldberg JF, Ozerdem A, Aydemir O, Chengappa KN. The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). Bipolar Disord. 2010 Jun;12(4):351-63. doi: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.

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?

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)	-	

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.