Journal of Affective Disorders

Sex differences in neurocognitive and psychosocial functioning in bipolar disorder

--Manuscript Draft--

Manuscript Number:	JAFD-D-21-02471R1
Article Type:	Research Paper
Keywords:	Bipolar disorder; Cognition; Psychosocial Functioning; Sex differences
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Abstract:	Background: Sex differences influence the clinical characteristics and course of illness of bipolar disorder (BD). Objective: Therefore, the aim of the present study was to examine the role of sex differences in neurocognitive performance and psychosocial functioning in a large sample of euthymic patients suffering from BD. Methods: The sample included 462 individuals, 347 patients with BD (148 males and 199 females) and 115 healthy controls (HC) (45 males and 70 females). Performance on a comprehensive neuropsychological battery assessing six cognitive domains and psychosocial functioning was compared between groups using linerar mixed models , with sex and group as main effects, group by sex interactions and centre as a random effect Results: Males performed better than females in working memory ($p<0.001$), whereas females outperformed males in the verbal learning ($p=0.03$) and memory recognition ($p=0.04$) tasks. No significant group by sex interactions were detected in cognitive performance There were no overall sex differences or group by sex interactions in psychosocial functioning. Limitations: Lack of assessment of visuo-spatial working memory. Conclusions: There were no overall sex differences in neurocognition and psychosocial functioning. However, small sex differences in some measures of working memory and verbal memory were found. Individual differences of each patient, including sex perspective, should be considered in order to perform a tailored intervention plan adjusted to specific needs in the context of personalized treatment.

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July 8th, 2021

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Dear Professor Paolo Brambilla, Editor-in-Chief

Please find enclosed our manuscript **"Do sex differences really matter in cognitive and psychosocial functioning in bipolar disorder?"** My colleagues and I would be grateful if you would consider the above manuscript for publication as an original article in Journal of Affective Disorders.

Sex differences exist in the clinical characteristics and the illness course of bipolar disorder. Despite sex differences in neurocognition have been previously described in healthy controls, evidence addressing sex differences in neurocognition in bipolar disorder remains unclear given the limited number of studies published reporting conflicting results. Therefore, the aim of the present study is to examine the role of sex differences in neurocognition and psychosocial functioning in a large well-defined sample of euthymic patients with bipolar disorder (148 males and 199 females), compared to a healthy control group (45 males and 70 females). Our findings suggest that women and men are similar on most neurocognitive measures, with only small sex differences in measures related to working memory, verbal memory and attention domains but not in psychosocial functioning. Specifically, females outperformed males in verbal memory and

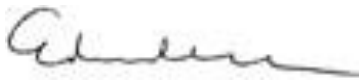
males outperformed females in attention and working memory. This highlights the necessity of personalised treatment depending on individual differences taking sex approach into account when designing an intervention plan.

We believe that these findings will be of interest to the readership of Journal of Affective Disorders as they contribute to the growing evidence of sex differences in cognition and psychosocial functioning in affective disorders.

The present material is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration.

Yours sincerely,

Prof Eduard Vieta, M.D., Ph.D.



Sep 15th 2021
Prof. Eduard Vieta
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Dear Editor-in-Chief
Prof. Paolo Brambilla,

Thank you for considering our manuscript **JAFD-D-21-02471** entitled "**Sex differences in neurocognitive and psychosocial functioning in bipolar disorder"** for further revision in the **Journal of Affective Disorders**. We are grateful to the reviewers for the effort and their comments, we have adjusted the text according to their suggestions and we are convinced that all the changes will contribute to improve our manuscript. The changes appear detailed below in response to the reviewer comment.
Please find our responses in bold face types. We hope that the current version of the paper will be suitable for publication in your journal.

Reviewer #1: The authors performed a cross-sectional study about sex differences and cognitive and psychosocial functioning in bipolar disorder. The cognitive impairment in bipolar disorder patients is a relevant topics in mental health. The study presented by Solé et al. has an appropriate methodological quality. However, I believe the manuscript could perhaps be further improved by the following point:

The authors include BDI and BDII patients in the analyses. However, there is a growing body of evidence in the literature suggesting that BDI patients have a different cognitive profile compared to BDII patients. It would be interesting the authors taking this aspect into account in the analyses, results and discussion section, especially because there is more females with BDII than males in this article.

The authors appreciate the reviewer's point. Indeed, a significant difference in percentages of subtypes was detected between men and women. We agree with the reviewer that we should take this aspect into account. Therefore we have run secondary analyses in order to correct for the effect of those clinical variables that may influence cognition such as bipolar subtype (bipolar I or bipolar II) and lifetime substance misuse. The following clarifications have been added to the manuscript:

Statistical analyses p. 6: ", secondary analyses **patient's** data were carried out in the case of a main effect of sex ~~**(or a p-value lower than 0.1)**~~ in neurocognitive variables. These analyses aimed to ~~**correct**~~ **assess** for the effect of the clinical variables that may influence cognition in males and females."

Results, p. 8: "secondary analyses were run to analyse the effect of those clinical variables, such as diagnosis subtype (bipolar I or bipolar II) and lifetime substance misuse, that may influence cognition. We found a statistically significant effect of diagnosis subtype in working memory index driven (p=0.04) by bipolar type II presenting higher scores than type I. No other significant effects were detected".

Discussion, p: 10: "Therefore, it seems that the possible advantage exhibited by men in verbal working memory capacity might remain in patients with BD, contrary to what happens with the spatial working memory. **Indeed, this better performance in men remained regardless of the bipolar subtype given that, adjusting by diagnosis subtype, the effect of sex remained significantly. Therefore, although there were more females with bipolar type II, the advantage presented by males in working memory still persisted"**

Reviewer #2: This is a timely and important subject particularly because recent publications have pointed out several sources of variability in cognitive performance of patients with mood disorders. Few or none of them have addressed sex as a potential factor of such variations. By contrast, some neuroimaging studies have already reported sex differences in brain structures (as the authors state in their discussion) which may underpin cognitive differences between males and females. However, several factors limit the interpretability of the present findings, and other minor drawbacks should be amended (noted below in order of appearance in the manuscript for the authors convenience).

1.- The title is a bit misleading, as the authors do not finally reply their own question.

The authors thank the reviewer for this request. To avoid potentially misleading the reader, we have now provided a new title: "Sex differences in neurocognitive and psychosocial functioning in bipolar disorder".

2.- Highlights do not provide clear ideas, but a summary of their findings. Please check other examples to go beyond the findings.

We thank the reviewer for raising this relevant point. As suggested, we have now adjusted the Highlights, in order to provide clearer ideas beyond the findings:

Women and men are similar on most neurocognitive measures

Men are only better in working memory and women in verbal learning

No differential sex effects on BD and HC groups are detected

Illness course does not seem influencing on extant sex differences in cognition

No sex differences are detected in psychosocial functioning

3.- Abstract: as the authors may see below, I do not think that the main limitation of the present study is the cross-sectional design, really. Is sex going to change along time? Or may have any influence on other factors that probably change in longitudinal observations?

Thanks to the reviewer for noticing this issue. We wanted to highlight that a cross-sectional design does not allow us to take into account the influence of other factors that probably change in longitudinal observations or provide insight as to whether or not the sex differences change throughout the course of the illness. In order to avoid confusions, we have changed the limitation in the abstract, adding another limitation pointed out in the discussion section:

Abstract: "lack of assessment of visuo-spatial working memory tasks, which may be one sensitive task to detect sex differences".

4.- Why the authors included more females than males in their study?

We thank the reviewer for bringing this to our attention. Our study is based on a non-probability convenience sampling, where the sample is selected from the population only because it is available to the researcher. Therefore, the inclusion of more females than males was random. To clarify this further, we have added the following to the method:

Method, p. 4: "This is a cross-sectional case-control multicentre study of non-probabilistic sampling".

5.- My main concern is the statistical approach of the study for several reasons:
a) please provide the rationale for using generalized linear models to test demographic characteristics and affective symptomatology. What kind of variables were to be adjusted in this first analysis? Why clinical characteristics were then compared with t-tests or chi-square.

This is a very valid point. We specifically chose to use generalized linear models (GLM) to test demographic characteristics and affective symptomatology in order to assess potential interactions about gender (males/females) and group (patients/controls) as well as the effects of main factors (sex and group). Indeed, GLM generalizes the linear model used in ANOVA. Since the first table was a descriptive analysis, no variables were to be adjusted in this analysis. With regards to T-tests or chi-squared analyses, since clinical characteristics refer to patients group, we used these statistical tests for comparing the means (t-test) or percentage (chi- squared) of two groups (i.e. women and men) in

their clinical characteristics. Therefore, in the clinical characteristics were no necessary to assess the potential interactions.

b) I agree to use generalized models for neurocognitive and psychosocial variables as the authors wanted to adjust the findings for several variables. However, linear mixed models would have been a better option because this is a multicentre study and the authors would have been able to include a possible source of variability such as "centre" as a random effect.

We agree on this important point outlined by the reviewer. In accordance with the reviewer's suggestion, we have run linear mixed models to include "centre" as a random effect in cognitive and functioning variables. These new analyses are detailed on the abstract, the statistical analysis, the results, tables 3 and 4 and discussion sections have been amended according to new data.

c) the authors refer to their cognitive outcomes as domains, but the GLM analyses were run for each individual neuropsychological test. I would recommend to explore cognitive domains because the individual performance on a specific task cannot be generalized and therefore, it limits interpretability of the findings. Moreover, many of the comparisons, even when performed with GLM, should be corrected for multiple comparisons, and unfortunately many of the current significant findings would not survive.

We thank the reviewer for this interesting contribution. We have remained the analyses for each individual neuropsychological tests in accordance with previous studies on sex differences in neurocognition in BD (i.e., (Barrett et al., 2008; Bücker et al., 2014; Carrus et al., 2010; Gogos et al., 2010; Popuri, 2012; Tournikioti et al., 2018; Vaskinn et al., 2011) and to facilitate comparability with previous studies. It is important to keep in mind that several meta-analyses on sex differences are focused on neurocognitive tasks (Hyde et al. 2014; Hyde et al. 2016). Moreover, most of them suggest that males and females are much similar in terms of neurocognitive abilities than previously anticipated (Hyde et al. 2016; Miller and Halpern, 2014). Therefore, if we analyze neurocognitive outcomes as domains, as the reviewer suggests, it would be much more difficult to detect any significant difference. In order to avoid confusion and increase consistency between terms used in the present paper and the literature, throughout the manuscript, we have specified that the significant differences we found were related to specific measures assessing the cognitive domains rather the whole domain.

We agree that the statistical analyses would benefit from correcting for multiple comparisons given the risk of type 1 errors. However, Bonferroni method would be highly conservative and might miss real differences, increasing the risk of running type II error. We have included this as a limitation in the discussion section:

Discussion, p. 12: " Importantly, no statistical procedure was used to control for multiple comparisons, which could have introduced type I error".

d) following the previous point, there is no need to perform a secondary analysis to further explore main effects of sex by expanding even more the chance of type I error.

Therefore, I honestly think that the results shoud be repeated so as to test their hypothesis and see the truly interactions of groupXsex using cognitive domains and including "centre" as a random effect.

We appreciate your recommendation. However, and following reviewer 1 recommendation, we think secondary analysis should remain in the manuscript since some clinical variables have been identified in the literature to influence neurocognitive outcome such as diagnosis type and lifetime substance misuse. Nonetheless, we have just applied the secondary analyses in those neurocognitive tests in

which we found a main effect of sex among patients. Significant main effects for sex were observed in CVLT recognition (p=0.03), CVLT total words (p=0.03) and working memory index (p<0.001).

As has been stated in point b), we have repeated all analyses using mixed models to include "centre" as a random effect and made changes accordingly in tables, results, discussion and abstract.

6.- Even so, some comments on the current results follow:
a) it is quite strange to report chi-squared statistics of GLM instead of the Wald or likelihood-ratio statistics. Which one was used for parameter estimates?

Regarding descriptive results and table 1 where we have applied GLM, we agree in this point, in fact we test the statistical significance with Wald test. The point is that this test has an asymptotic $\chi 2$-distribution with one degree of freedom under the null hypothesis, and is what we reported. To clarify this issue, we have changed the statistic in the table 1.

With regard to neurocognitive and psychosocial functioning, as we have changed the statistical approach following the reviewer suggestion, the appropriate statistic has been added in results section and table 3 and 4 (F instead of Wald test).

b) the penultimate sentence of "verbal learning and memory scores" paragraph is a bit confusing ("However, no significant differences between patients and controls..."). Please rewrite it.

We thank the reviewer for pointing this out. We have now removed the sentence as consequence of our new results.

c) In my opinion, if secondary analyses were to be run to test sex differences among patients (which I wouldn't do it), only CVLT recognition shuld be tested because it was the only one to be truly significant (avoid type I error).

Please see point 5 d and Reviewer #1 point 1 below for further information on secondary analyses.

d) apart from what is said above and taking into account that males are often reported to show greater variability than females in a set of human traits and behaviours (Hyde 2014), a previous analysis of cognitive heterogeneity would have been desirable. The authors have published some nice papers on clustering of cognitive performance. Would then sex really matter?

Thank you for this comment. Indeed, different social cognition subgroups in BD differ significantly in sex variable (Varo et al., 2020). However, prior studies on neurocognitive heterogeneity in BD (Burdick et al., 2014; Jensen et al., 2016; Lewandowski et al., 2014; Lima et al., 2019; Solé et al., 2016) do not show this finding. Based on our study, we could not elucidate if sex would influence neurocognitive heterogeneity since this statement is not supported by the data of our study. We believe that these analyses will go beyond the scope of our study. Nevertheless, we take into consideration this comment for future reviews.

7.- The discussion should be tuned down because it is difficult to state that there were significant effects of sex after multiple comparisons correction (these could merely be spurious).

Following the reviewer suggestion, we have checked all statements along the manuscript and we have adjusted them, being more cautious with the expressions and our conclusions regarding effects of sex in neurocognition in bipolar disorder.

Minor points:
- Results: the word "groups" in line 182 should read "group"

We thank the reviewer for this suggestion. We have replaced "groups" in line 182 with "group".

- Discussion: sentence of line 233, does it refer to general population or to patients with BD? One can read the cite but, having it clearly stated will help the readingness.

We have added in sentence of line 233 "in non-clinical population" for clarification purposes.

- Discussion, sentence of line 286, how come "the same sex effect in psychosocial functioning is seen in patients and HC"? It cannot be concluded from the current results.

Thanks for this point. As the reviewer points out, the idea is not well conveyed. This has now been clarified in the manuscript:

Discussion, p.11: "Therefore, there was not sex effect in psychosocial functioning in patients or HC".

- Discussion: Sentences starting in line 301 and 308 go nowhere, because the authors do not discuss the role of hormones or neural changes upon their own results. Therefore, there is no reason to include this here, but acknowledge it as a limitation.

In accordance with the reviewer's comment we have deleted the sentences starting in line 301 and 308. Additionally, we have added a new limitation:

Limitation, p.12: "Lastly, sex hormones and menstrual status in women, which may play a critical role in neural functioning and neuropsychological functioning, were not taken into consideration".

- References: there is a mix between citation within the text (Name and year) and the listing (numbered). Please check.

We have checked again this issue. It seems is a reference manager malfunction. We hope references will appeared correctly in this last version.

- Figure Legends: Caption must be self-explained with all acronyms defined. Does Y-axis refer to raw scores of the test? Please include it.

Thanks for this point. We have included a clarification regarding Y-axis and we have completed the explanation of all acronyms.

- Tables: the same for captions.

Thank you for pointing this out. We have now completed caption with acronyms that were missing.

- Table 1:what were the adjusting variables for quantitative data?

We thank the reviewer for this remark. There were no adjusting variables in table 1 for quantitative data. See point 5a for further information.

- Table 3 and 4: were means adjusted or estimated? if not, why not?

We thank the reviewer for pointing this out. We have added the word "adjusted" before "means" in table 3 and 4.

Additional changes:

Figure 1: since the data has been changed as a result of the new statistical approach following the reviewer's comment, we adapted the figure reporting now the sex significant differences in CVLT recognition, CVLT total words and working memory index.

We really hope that all the above described changes are going to fulfil your expectations and turn the paper into suitable for publication in your very prestigious journal. We thank you for the improvement in the final draft these changes have enhanced.

Yours sincerely,

Eduard Vieta

Highlights

Women and men are similar on most neurocognitive measures

No differential sex effects on BD and HC groups are detected

Illness course does not seem influencing on extant sex differences in cognition

No sex differences were detected in psychosocial functioning

Abstract

Background: Sex differences influence the clinical characteristics and course of illness of bipolar disorder (BD).

Objective: Therefore, the aim of the present study was to examine the role of sex differences in neurocognitive performance and psychosocial functioning in a large sample of euthymic patients suffering from BD.

Methods: The sample included 462 individuals, 347 patients with BD (148 males and 199 females) and 115 healthy controls (HC) (45 males and 70 females). Performance on a comprehensive neuropsychological battery assessing six cognitive domains and psychosocial functioning was compared between groups using linerar mixed models, with sex and group as main effects, group by sex interactions and centre as a random effect

Results: Males performed better than females in working memory ($p<0.001$), whereas females outperformed males in the verbal learning ($p=0.03$) and memory recognition ($p=0.04$) tasks. No significant group by sex interactions were detected in cognitive performance. There were no overall sex differences or group by sex interactions in psychosocial functioning.

Limitations: Lack of assessment of visuo-spatial working memory.

Conclusions: There were no overall sex differences in neurocognition and psychosocial functioning. However, small sex differences in some measures of working memory and verbal memorywere found. Individual differences of each patient, including sex perspective, should be considered in order to perform a tailored intervention plan adjusted to specific needs in the context of personalized treatment.

TITLE PAGE

Word count: 4,310 (including abstract and text)

Number of figures/tables: 1/4

TITLE: Sex differences in neurocognitive and psychosocial functioning in bipolar disorder

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Figure

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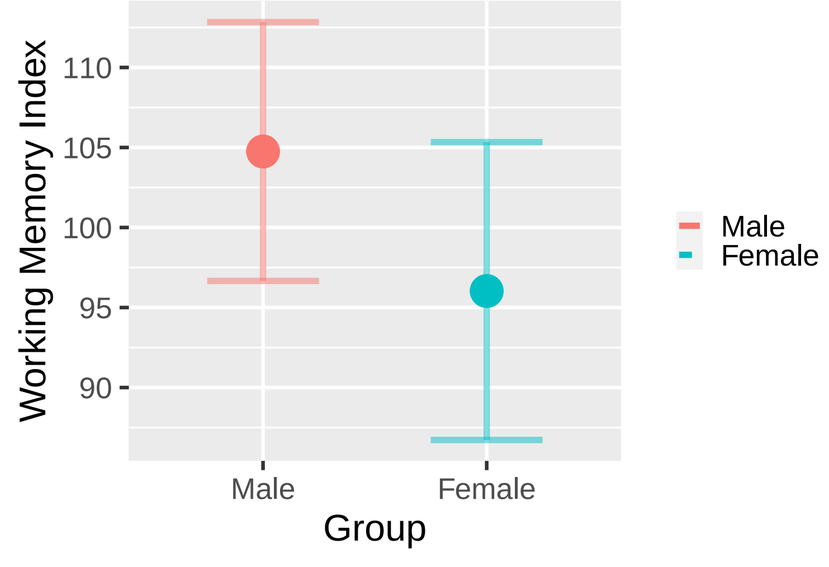

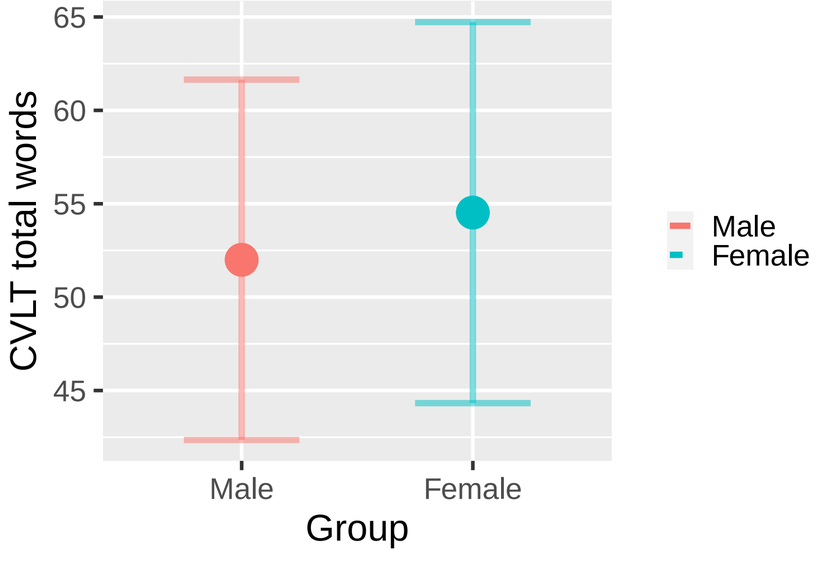

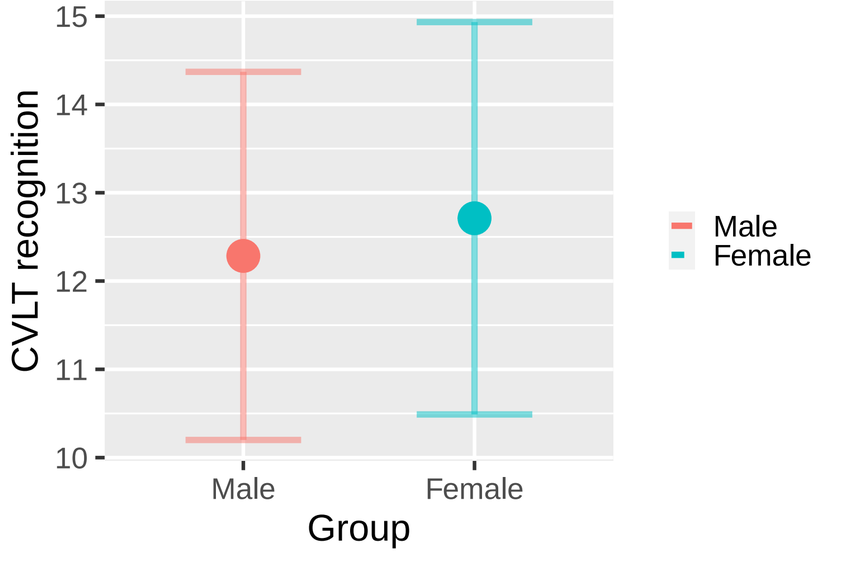

Table

Table 1. Demographic and clinical characteristics of study participants

	BD (n=347)		HC (n=115)		Effect					
	Male (n=148)	**Female (n=199)**	**Male (n=45)**	**Female (n=70)**	**Group**		**Sex**		**GroupXSex**	
Quantitative	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	X^2 (Wald test)	p	X^2 (Wald test)	p	X^2 (Wald test)	p
Age	41.9 (40.3-43.6)	42.4 (40.9-43.8)	39.2 (36.2-42.2)	41.0 (38.6-43.4)	3.26	0.07	0.95	0.33	0.38	0.54
Education level (years)	14.5 (13.9-15.0)	14.2 (13.7-14.7)	14.7 (13.6-15.8)	15.2 (14.4-16.0)	2.29	0.13	0.10	0.74	1.11	0.29
Estimated IQ	109.8 (108.2-111.5)	105.9 (104.6-107.4)	107.7 (104.7-110.6)	108.973 (106.6-111.3)	0.12	0.73	1.31	0.25	5.17	**0.02**
HDRS-17	3.3 (2.9-3.7)	3.8 (3.4-4.1)	2.0 (1.2-2.8)	1.7 (1.1-2.3)	34.6	**<0.001**	0.04	0.83	1.70	0.19
YMRS	1.4 (1.2-1.7)	1.4 (1.2-1.7)	0.8 (0.3-1.3)	0.9 (0.5-1.4)	7.96	**0.01**	0.29	0.59	0.12	0.73
Qualitative	Adjusted prevalence (IC 95%)	Adjusted prevalence (IC 95%)	Adjusted prevalence (IC 95%)	Adjusted prevalence (IC 95%)						
Marital Status (Not married)	64.2 (56.2-71.5)	62.2 (55.3-68.8)	48.4 (31.7-65.5)	42.3 (29.7-56.0)	8.2	**<0.01**	0.42	0.52	0.10	0.75
Occupation (Not working)	45.2 (37.3-53.3)	52.9 (45.8-59.9)	12.5 (4.8-28.9)	17.4 (8.9-31.1)	24.18	**<0.001**	0.99	0.32	0.01	0.91

BD: Bipolar disorder. HC: Healthy control. IC: Lower–Upper values within Wald Confidence Interval of 95%. IQ: Intelligence Quotient. HDRS-17: Hamilton Depression Scale. YMRS: Young Mania Rating Scale. Bold text in the table indicates significant values

Table 2. Clinical characteristics of patients with bipolar disorder

	BD (n=347)			
	Male (n=148)	**Female (n=199)**		
	Mean (S.D.)	Mean (S.D.)	t	p
Age at onset	24.95 (8.35)	26.02 (9.05)	-1.12	0.26
Illness duration	16.45 (10.68)	16.06 (9.75)	0.36	0.72
Total number of episodes	12.22 (16.55)	10.86 (11.87)	0.86	0.39
Hypomanic episodes	3.86 (8.55)	3.16 (5.44)	0.91	0.37
Manic episodes	2.70 (3.35)	2.05 (3.04)	1.86	0.07
Depressive episodes	5.37 (8.58)	5.16 (6.55)	0.26	0.80
Mixed episodes	0.45 (1.42)	0.54 (1.54)	-0.50	0.61
Number of hospitalizations	1.79 (1.97)	2.06 (2.41)	1.07	0.28
Age at first hospitalization	30.16 (10.51)	30.84 (9.83)	0.53	0.60
	N (%)	N (%)	X^2	p
Diagnosis (BD-II)	24 (16.2)	55 (28.2)	6.82	**0.01**
Predominant Polarity			5.86	0.05
(Hypo)Manic	36 (25.0)	39 (20.6)		
Depressive	18 (12.5)	43 (22.8)		
Not specified	90 (62.5)	107 (56.6)		
Lifetime psychotic symptoms	101 (68.7)	127 (65.1)	0.48	0.49
Seasonal Pattern	56 (39.4)	75 (39.7)	0.00	0.96
Lifetime rapid cycling	17 (11.7)	23 (11.8)	0.00	0.98
Lifetime atypical symptoms	62 (47.3)	78 (43.6)	0.43	0.51
Psychotic depression	15 (10.7)	38 (20.3)	5.44	**0.02**
Axis I comorbidity	33 (23.2)	36 (19.1)	0.82	0.37
Axis II comorbidity	16 (11.4)	34 (18.1)	2.75	0.10
Axis III comorbidity	44 (30.8)	66 (34.9)	0.63	0.43
Family history of psychiatric disease	100 (68.5)	159 (83.2)	10.13	**<0.001**
Family history of affective disease	95 (65.1)	140 (74.1)	3.19	0.07
Lifetime substance abuse/misuse	63 (44.4)	62 (33.3)	4.16	**0.04**
Suicidal profile			0.57	0.75
Non-suicidal	53 (39.0)	79 (42.0)		
Suicidal ideators	51 (37.5)	63 (33.5)		
Suicidal attempters	32 (23.5)	46 (24.5)		
Current medication				
Lithium	101 (68.7)	124 (63.9)	0.86	0.36
Other anticonvulsants	77 (52.7)	94 (48.5)	0.61	0.43
Antipsychotic	102 (69.4)	130 (67.4)	0.16	0.69
Antidepressants				
MAOIs	0 (0.0)	1 (0.5)	1.00	0.57
Tricyclic	5 (3.4)	9 (4.7)	0.34	0.56
SSRIs	23 (15.6)	36 (18.8)	0.59	0.44
SNRIs	18 (12.2)	21 (10.9)	0.15	0.70
Other antidepressants	5 (3.4)	10 (5.2)	0.63	0.43
Benzodiazepines	45 (30.4)	64 (33.2)	0.29	0.59
Treatment-adherence (no)	52 (38.0)	72 (38.3)	0.00	0.95

Abbreviations: BD: Bipolar disorder. BD-II: Bipolar Disorder type II; MAOIs: Monoamine oxidase inhibitors; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin-noradrenaline reuptake inhibitors. Bold text indicates significant p-values.

Table

Table 3. Main effects and interactions of neurocognitive variables

	BD (n=347)		HC (n=115)		Effect					
	Male (n=148)	Female (n=199)	Male (n=45)	Female (n=70)	Group		Sex		GroupXSex	
	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	F	p	F	p	F	p
Attention										
CPT-II omissions	68.3 (8.4-128.2)	71.5 (10.9-132.1)	62.4 (7.9-116.9)	63.3(6.8-119.8)	2.92	0.08	0.67	0.41	0.32	0.57
CPT-II commissions	49.5 (36.8-62.3)	53.8 (40.7-67.0)	50.5 (39.6-61.3)	50.6 (39.2-62.0)	0.75	0.38	3.19	0.07	2.77	0.09
CPT-II RT	61.2 (54.0-68.4)	60.4 (52.8-68.0)	54.5 (47.8-61.3)	56.6 (50.0-63.1)	9.45	**0.002**	0.12	0.72	0.79	0.37
CPT-II RT(SE)	61.3 (47.0-75.7)	64.5 (49.6-79.4)	54.3 (42.2-66.4)	58.3 (45.6-70.9)	11.77	**0.001**	3.78	0.05	0.04	0.82
CPT-II d’	49.1 (37.9-60.2)	52.3 (40.7-63.9)	50.7 (41.4-59.9)	50.7(41.0-60.5)	0.00	0.99	1.71	0.19	1.58	0.20
CPT-II ß	52.3 (46.6-58.0)	52.3 (45.5-59.2)	51.1 (46.1-56.2)	49.9 (45.3-54.4)	1.22	0.27	0.15	0.70	0.17	0.68
CPT-II block change	52.8 (43.7-61.8)	54.6 (44.5-64.7)	48.2 (41.4-55.0)	50.1 (43.1-56.7)	7.96	**<0.01**	1.41	0.23	0.00	0.98
CPT-II ISI change	53.6 (51.2-56.1)	52.0 (49.9-54.2)	49.4 (44.3-54.5)	54.9 (50.8-59.2)	0.10	0.74	1.13	0.28	3.74	0.05
TMT-A	31.8 (23.4-40.1)	33.8 (24.9-42.8)	25.9 (18.8- 33.0)	28.0 (20.9-35.0)	12.16	**0.001**	1.62	0.20	0.00	0.99
Processing Speed (Index WAIS-III)	101.8 (88.8-114.8)	102.1 (88.6-115.7)	114.2 (103.6-124.8)	114.0 (102.9-125.2)	56.31	**<0.001**	0.00	0.95	0.27	0.87
Working Memory (Index WAIS-III)	102.6 (96.3-108.8)	93.1 (86.3-99.9)	105.6 (99.4-111.8)	99.8 (94.1-105.5)	7.06	**<0.01**	19.28	**<0.001**	1.07	0.30
Verbal learning and memory										
CVLT total words	50.1 (41.5-58.7)	52.3 (43.4-61.2)	53.3 (45.7-60.9)	57.1 (49.3-64.7)	6.95	**<0.01**	4.43	**0.03**	0.30	0.58
CVLT short free recall	10.5 (8.6-12.5)	11.3 (9.3-13.4)	11.8 (10.0-13.6)	11.7 (10.0-13.5)	4.32	**0.03**	0.91	0.34	1.19	0.27
CVLT short cued recall	11.6 (10.1-13.2)	12.3 (10.7-14.1)	12.8 (11.4-14.3)	12.8 (11.4-14.3)	5.91	**0.01**	1.11	0.29	1.27	0.26
CVLT delay free recall	11.2 (9.1-13.3)	11.8 (9.6-13.9)	12.3 (10.5-14.2)	12.4 (10.5-14.3)	4.93	**0.02**	0.79	0.37	0.43	0.50
CVLT delay cued recall	11.7 (9.9-13.6)	12.2 (10.3-14.1)	12.9 (11.2-14.5)	13.1 (11.4-14.7)	7.88	**<0.01**	1.03	0.30	0.21	0.64
CVLT recognition	14.6 (13.8-15.4)	14.8 (14.0-15.7)	14.6 (13.8-15.3)	15.1 (14.4-15.8)	0.34	0.56	4.66	**0.03**	0.76	0.38
Immediate recall logical memory WMS-III	36.9 (26.7-47.03)	36.7 (26.2-47.3)	37.7 (29.1-46.4)	42.9 (33.8-51.9)	6.17	**0.01**	3.48	0.06	3.83	0.05
Delayed recall logical memory WMS-III	22.5 (14.3-30.7)	22.9 (14.4-31.4)	23.6 (16.7-30.6)	26.8 (19.4-34.1)	6.01	**0.01**	3.29	0.07	2.08	0.15
Logical memory retention WMS-III	83.5 (71.6-95.4)	83.2 (70.6-95.7)	80.2 (70.3-90.1)	86.5 (76.1-96.9)	0.00	0.98	3.18	0.07	3.86	0.0
Visual memory (ROFC recall)	19.1 (18.1-20.1)	18.9 (17.9-19.7)	21.4 (19.5-23.4)	22.0 (20.4-23.6)	13.49	**<0.001**	0.05	0.82	0.33	0.56
Executive functions										
ROCF copy	31.4 (30.9-31.9)	31.3 (30.9-31.8)	30.6 (29.6-31.6)	31.4 (30.6-32.2)	0.83	0.36	0.90	0.34	1.35	0.24
TMT-B	84.9 (58.1-111.8)	91.9 (63.6-120.3)	74.3 (50.6-98.0)	69.6 (45.8-93.3)	9.83	**<0.01**	0.05	0.82	1.35	0.24
WCST categories	4.8 (3.8-5.8)	4.8 (3.7-5.8)	4.9 (4.1-5.8)	5.3 (4.4-6.1)	2.39	0.12	0.67	0.41	0.92	0.33
WCST perseverative errors	16.5 (3.8-29.2)	17.8 (4.6-31.0)	17.5 (7.1-28.0)	15.1 (4.0-26.1)	0.25	0.61	0.13	0.71	1.47	0.22
SCWT interference	53.1 (49.2-57.0)	51.9 (47.1-56.7)	53.7 (50.3-57.1)	54.1 (51.1-57.1)	1.71	0.19	0.15	0.69	0.60	0.43
Phonemic fluency	35.2 (30.9-39.5)	34.7 (29..8-39.7)	41.9 (37.7-46.1)	40.7 (37.0-44.4)	22.15	**<0.001**	0.41	0.52	0.08	0.77
Animal naming	19.4 (18.6-20.2)	19.6 (18.9-20.3)	22.8 (21.1-24.6)	22.8 (21.5-24.2)	28.6	**<0.001**	0.02	0.87	0.02	0.87

BD: Bipolar disorder. HC: Healthy control.IC: Lower–Upper values within Wald Confidence Interval of 95%. IQ: Intelligence Quotient. CPT-II: Conners’ Continuous Performance Test. CVLT: California Verbal Learning Test.ROCF: Rey-Osterrieth Complex Figure. SCWT: Stroop Colour Word Test. TMT: Trail Making Test. WAIS-III: Wechsler Adult Intelligence Test-III. WCST: Wisconsin Card Sorting Test. WMS: Wechsler Memory Scale. Bold text indicates significant p-values.

Table 4. Main effects and interactions in psychosocial functioning

	BD (n=347)		HC (n=115)		Effect					
	Male (n=148)	Female (n=199)	Male (n=45)	Female (n=70)	Group		Sex		GroupXSex	
	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	Adjusted Mean (IC 95%)	F	p	F	p	F	p
FAST Domains										
Autonomy	2.1 (0.1-5.0)	1.9 (0.0-4.9)	0.4 (0.1-1.5)	0.7 (0.2-1.2)	16.84	**<0.001**	0.37	0.54	0.00	0.94
Occupational	6.9 (6.0-7.8)	7.1 (6.2-7.8)	3.2 (1.2-5.1)	3.0 (1.4-4.5)	28.23	**<0.001**	0.00	0.95	0.05	0.81
Cognitive	4.1 (1.1-7.1)	4.9 (1.8-8.0	2.5 (0.1-4.9)	2.7 (0.1-5.2)	27.07	**<0.001**	2.09	0.14	0.99	0.32
Financial issues	0.8 (0.1-1.9)	0.8 (0.1-1.9)	0.6 (0.0-1.4)	0.5 (0.0-1.4)	3.06	0.08	0.14	0.70	0.09	0.76
Interpersonal relationships	3.2 (0.5-6.0)	3.7 (0.8-6.6)	2.5 (0.4-4.6)	2.1 (0.1-4.4)	11.94	**<0.001**	0.00	0.98	1.73	0.19
Leisure time	1.7 (0.1-3.3)	1.9 (0.2-3.6)	1.6 (0.3-2.9)	1.2 (0.-2.6)	3.36	0.06	0.31	0.57	2.89	0.09
Total FAST	19.1 (6.8-31.2)	20.4 (7.8-33.0)	11.8 (1.8-21.7)	10.6 (0.0-21.2)	46.30	**<0.001**	0.00	0.93	1.12	0.29

BD: Bipolar disorder. HC: Healthy control. IC: Lower–Upper values within Wald Confidence Interval of 95%. Bold text in the table indicates significant values.
FAST: Functioning Assessment Short Test.

Conflict of Interest Statement

Dr. Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (work unrelated to the topic of this manuscript): AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Generalitat de Catalunya (PERIS), the Spanish Ministry of Science and Innovation (CIBERSAM), EU Horizon 2020, and the Stanley Medical Research Institute.

Dr. Martínez-Aran has received funding for research projects and/or honoraria as a consultant or speaker for the following companies and institutions (work unrelated to the topic of this manuscript): Otsuka, Pfizer, AstraZeneca, Bristol-Myers Squibb, Lundbeck, the Spanish Ministry of Economy and Competitiveness and Instituto de Salud Carlos III.

Dr. García-Portilla has been a consultant to and/or has received honoraria/grants from (work unrelated to the topic of this manuscript): Angelini, Alianza Otsuka-Lundbeck, CIBERSAM, Government of the Principality of Asturias, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, and SAGE Therapeutics.

Dr. Sáiz has been a consultant to and/or has received honoraria or grants from (work unrelated to the topic of this manuscript): Adamed, CIBERSAM, European Comission, Government of the Principality of Asturias, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas and Servier.

The other authors have no conflict of interest to declare.

Statements

Contributors

BS, CV and AMA conceived the study, with substantial contributions from the other authors. BS and CV did the literature search and wrote the first draft. All authors substantially participated in the final manuscript, which was reviewed, revised and approved by all authors.

Funding

This research did not received any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

The authors would like to thank the support of the Spanish Ministry of Science and Innovation; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365; 2017 SGR 1355) and the CERCA Programme / Generalitat de Catalunya.

This work has been also supported by the Spanish Ministry of Science, Innovation and Universities integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER) through a 'Miguel Servet' postdoctoral contract (CPI14/00175 to CT), a Miguel Servet II contract (CPII19/00018 to CT), a 'Sara Borrell' contract (CD20/00177 to SA), both co-funded by European Social Fund "Investing in your future", and the FIS grants (PI18/00805, PI18/00789). This work has been also supported by the BITRECS project to NV, which has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754550 and from "La Caixa" Foundation (ID 100010434), under the agreement LCF/PR/GN18/50310006. Thanks the support of the European Union Horizon 2020 research and innovation program (EU.3.1.1. Understanding health, wellbeing and disease: Grant No 754907 and EU.3.1.3. Treating and managing disease: Grant No 945151).

This work has also been supported by the projects SLT006/17/00357 and SLT006/17/00345 in the "Pla estratègic de Recerca i Innovació en Salut 2016–2020" (Health Department). CERCA (Programme/Generalitat de Catalunya) and by the Government of the Principality of Asturias PCTI-2018-2022 IDI/2018/235.

TITLE PAGE

Word count: 4,310 (including abstract and text)

Number of figures/tables: 1/4

TITLE: Sex differences in neurocognitive and psychosocial functioning in bipolar disorder

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Abstract

Background: Sex differences influence the clinical characteristics and course of illness of bipolar disorder (BD).

Objective: Therefore, the aim of the present study was to examine the role of sex differences in neurocognitive performance and psychosocial functioning in a large sample of euthymic patients suffering from BD.

Methods: The sample included 462 individuals, 347 patients with BD (148 males and 199 females) and 115 healthy controls (HC) (45 males and 70 females). Performance on a comprehensive neuropsychological battery assessing six cognitive domains and psychosocial functioning was compared between groups using linerar mixed models, with sex and group as main effects, group by sex interactions and centre as a random effect

Results: Males performed better than females in working memory ($p<0.001$), whereas females outperformed males in the verbal learning ($p=0.03$) and memory recognition ($p=0.04$) tasks. No significant group by sex interactions were detected in cognitive performance There were no overall sex differences or group by sex interactions in psychosocial functioning.

Limitations: Lack of assessment of visuo-spatial working memory.

Conclusions: There were no overall sex differences in neurocognition and psychosocial functioning. However, small sex differences in some measures of working memory and verbal memory were found. Individual differences of each patient, including sex perspective, should be considered in order to perform a tailored intervention plan adjusted to specific needs in the context of personalized treatment.

Key words: bipolar disorder, cognition, psychosocial functioning, sex differences

Introduction

It is well-established that a substantial proportion of patients with bipolar disorder (BD) experience neurocognitive impairments, even during periods of remission (Van Rheenen et al., 2020). Previous studies have reported a relationship between a subset of neurocognitive deficits and illness course (i.e number of episodes increased) (Bourne et al., 2013). Beyond clinical variables, other factors, such as sex, may contribute to neurocognitive performance in BD. Sex differences exist in terms of epidemiology, clinical phenomenology, course of illness, and other BD clinical characteristics (Cunningham et al., 2020). Most studies have found a similar prevalence of BD type I among males and females but BD type II disorder is more common in women (Nivoli et al., 2011). Typically, women with BD are at increased risk of presenting with depression (Curtis, 2005; Saunders et al., 2014), rapid cycling, mixed mania and seasonal episodes (Arnold, 2003). Conversely, manic episodes and unipolar mania are more common among men (Diflorio and Jones, 2010). In terms of comorbidities, while comorbid bulimia nervosa, anxiety disorders and post-traumatic stress disorder (Baldassano et al., 2005) are more commonly diagnosed in women, higher rates of comorbid substance use disorders have been observed in the male population (Kessing, 2004).

There is evidence of sexual dimorphism in normal brain structures (Cosgrove et al., 2007), as well as sex differences in neurocognition in healthy controls (HC) with men outperforming women in the visuospatial domain, while women perform better on verbal fluency and verbal learning and memory (Halari et al., 2005). However, evidence addressing sex differences in neurocognition in BD remains unclear given the limited number of studies published reporting conflicting results (Barrett et al., 2008; Bücker et al., 2014; Carrus et al., 2010; Gogos et al., 2010; Popuri, 2012; Tournikioti et al., 2018; Vaskinn et al., 2011). Whereas some studies reported significant sex effects on neuropsychological performance independent of group (e.g. HC vs. patients) (Bücker et al., 2014; Gogos et al., 2010; Popuri, 2012; Vaskinn et al., 2011), others found significant diagnosis group by sex interaction indicating different neurocognitive patterns in BD and HC (Barrett et al., 2008; Carrus et al., 2010; Suwalska and Łojko, 2014; Tournikioti et al., 2018). Thus, the heterogeneity found across studies means that the results on the contribution of sex on neurocognitive differences should be treated with caution. Methodological limitations such as relatively small sample sizes, differences in clinical features of patients, and lack of common cognitive tests between studies could potentially explain the current inconsistencies of study results. Furthermore, none of the aforementioned studies have considered all the main neurocognitive domains that have been reported to be affected in BD, that is, executive function, verbal and visual memory, verbal learning, and attention and processing speed (Bourne et al., 2013). Consequently, a large and homogeneous sample of patients

with BD as well as a comprehensive neuropsychological battery is required to achieve more accurate findings regarding the impact of sex on cognitive performance.

Additionally, neurocognitive impairment has been associated with poor psychosocial functioning in BD (Vieta et al., 2018). Given the demonstrated sex differences in neurocognition, it is possible that sex may also play an important role in psychosocial functioning. However, to our knowledge only two studies have explored this relationship so far, reporting a differential sex profile regarding psychosocial adjustment in BD, with women showing better social (Vaskinn et al., 2011) and occupational (Sanchez-Autet et al., 2018) functioning than men.

Therefore, the specific impact of sex on the pattern and severity of both neurocognitive and psychosocial functioning in BD remains inconclusive. The aim of the current study was to examine sex differences in neurocognition and psychosocial functioning in a large sample of euthymic patients with BD compared to HC. We hypothesized that differential sex effects for the different cognitive domains and psychosocial functioning would exist in BD; however, no directional hypotheses were made in the BD sample given the paucity and inconsistency in the extant literature regarding this topic.

Materials and Methods

Participants

This is a cross-sectional case-control multicentre study of non-probabilistic sampling. A sample of 347 outpatients with BD (148 males and 199 females) was recruited from three centres: the Bipolar and Depressive Disorders Unit at the Hospital Clinic of Barcelona, Benito Menni CASM, and mental health services in Oviedo. All centres are members of the Spanish Network Centre for Biomedical Research in Mental Health (CIBERSAM) (Salagre et al., 2019). The inclusion criteria were: a) received a BD-I or BD-II diagnosis according to DSM-IV-TR criteria, b) aged between 18 and 60 years old, c) being euthymic defined as a score < 8 on the Hamilton Depression Rating Scale [HDRS-17] (Hamilton, 1960; Ramos-Brieva and Cordero-Villafafila, 1988) and < 6 on the Young Mania Rating Scale [YMRS] (Colom et al., 2002; Young et al., 1978) for at least 3 months prior to study enrolment, and d) written informed consent provided. The exclusion criteria were: a) estimated intelligence quotient (IQ) lower than 80, b) presence of any medical or psychiatric comorbidity condition affecting neuropsychological performance, and c) electroconvulsive therapy received within the past year. No exclusion criteria in terms of pharmacological treatment were taken into consideration, including the use of benzodiazepines, in order to capture a representative sample of patients common in the clinical practice.

A total of 115 HC (45 male and 70 female) without evidence of current or past psychiatric or neurological history from a pool of volunteers were recruited. They were subjected to the same exclusion criteria as patients. An additional exclusion criterion was that they should not report having first-degree relatives with a psychiatric disorder.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.," 2013). Approval from each institution's ethics committees was obtained and all participants provided written informed consent prior to their inclusion in the study.

Assessment

Relevant demographic, clinical and pharmacological data were gathered through a clinical interview based on the Structured Clinical Interview for DSM-IV (SCID) and the revision of medical records (First MB, 1997).

In addition, all participants were evaluated with the following scales and instruments:

Depressive and manic symptoms at the time of assessment were assessed by means of the HDRS-17 and the YMRS respectively, with higher scores indicating greater severity.

Level of psychosocial functioning was measured with the Functioning Assessment Short Test (FAST) (Rosa et al., 2007), which consists of a brief interviewer-administered tool specifically designed to assess the main functional difficulties presented by psychiatric patients in 6 functional domains (autonomy, occupational functioning, cognitive functioning, interpersonal relationships, financial issues and leisure time) and is evaluated through a total of 24 items. The FAST scores range from 0 to 72, with higher scores indicating poorer functioning, i.e. greater disability.

A comprehensive neuropsychological battery test was administered to estimate the Intelligence Quotient (IQ) and evaluate the following cognitive domains:

1) The Wechsler Adult Intelligence Scale (WAIS-III) Vocabulary subtest to estimate IQ (Wechsler, 1997).
2) Processing speed, with the processing speed index (PS) of the WAIS-III (Wechsler, 1997) which comprised of two subtests: the Digit Symbol Coding and the Symbol Search.
3) Attention, tested with the Continuous Performance Test–II (CPT-II) version 5 (Conners 2000), and the Trail Making Test-part A (TMT-A) (Reitan, 1958).

4) Working memory, with the working memory (WM) index which includes the Arithmetic, Digits and Letter-number sequencing subtests of the WAIS-III (Wechsler, 1997).
5) Verbal learning and memory, assessed with the California Verbal Learning Test (CVLT) (Delis et al., 1987), and the Logical Memory subtest of the Wechsler Memory Scale-III (Wechsler, 2004).
6) Visual memory, evaluated by means of the Rey-Osterrieth Complex Figure (ROCF) (Rey, 1997).
7) Executive functions, tested by several tasks assessing: set shifting, planning, and response inhibition. The tests used to assess the different tasks were: the computerized version of the Wisconsin Card Sorting Test (WCST) (Heaton, 1993), the Stroop Colour-Word Interference Test (SCWT) (Golden, 1978), the Trail Making Test-part B (TMT-B) (Reitan, 1958). Verbal fluency was evaluated by means of the phonemic (FAS) and semantic (Animal naming) components of the Control Oral Word Association test (COWAT) (Benton and Hamsher, 1978).

Statistical analyses

First, for demographic characteristics and affective symptomatology, Generalized Linear Models (GLM) were carried out with group (control and patients) and sex (male and female) as main factors as well as the interaction between group and sex.

Second, a comparison of clinical characteristics and current pharmacological treatments between males and females with BD was conducted using t-test for the continuous variables and χ^2 tests (or Fisher's exact test) for the categorical ones. Next, performance on the neurocognitive variables and the psychosocial functioning was also compared between groups through linear mixed models with sex and group as main effects, the group by sex interactions and centre as a random effect. All models were adjusted for those clinical variables for which patients and controls differed significantly in the first analysis.

In case of significant interactions between sex and group in demographic characteristics, affective symptomatology, neurocognitive variables and the psychosocial functioning, post-hoc Bonferroni pairwise comparisons were applied.

Finally, secondary analyses patient's data were carried out in the case of a main effect of sex in neurocognitive variables. These analyses aimed to assess the effect of the clinical variables that may influence cognition in males and females. Estimated Marginal Means or adjusted prevalence and 95% confidence interval (CI) were reported for each variable of interest. Data were analysed with the IBM Statistical Package for Social Sciences version 23. All analyses were two-tailed with alpha set at $p < 0.05$.

Results

Demographic and clinical variables

As shown in Table 1, there were main effects of group for HDRS-17 (χ^2=34.6; p<0.001) and YMRS (χ^2 =7.96; p=0.01), marital status (χ^2=8.20; p<0.01) and occupational status (χ^2=24.18; p<0.001). The clinical group reflected more subsyndromal depression and mania symptoms than HC, as well as higher rates of not-working and not being married patients when compared to the HC sample. While no main effects of sex were found, there was a significant group by sex interaction for estimated IQ (χ^2 =5.17; p=0.02). Post-hoc Bonferroni revealed no differences in IQ in both female and male clinical patients when compared to their HC counterparts. Nevertheless, male patients in the clinical group showed higher IQ compared to their female counterparts (being both within the normative mean) (see details in Table 1).

Among patients, main effects of sex for diagnosis of BD type II (χ^2 =6.82; p=0.01), rates of psychotic depression (χ^2=5.44, p=0.02), family history of psychiatric disease (χ^2=10.13, p<0.001), and lifetime abuse/misuse (χ^2=4.16, p=004) were found. While female patients presented a higher percentage of diagnosis of BD type II, as well as higher rates of psychotic depression and family history of psychiatric disease than men, male patients reported a higher percentage of lifetime substance misuse than females. No differences regarding remaining variables were observed (see details in Table 2).

Neurocognitive variables

When analysing *attention* scores, there were significant main effects for group for CPT-II reaction time (RT) (F=9.45, p<0.01), CPT-II RT standard error (SE) (F=11.77, p=0.001), CPT-II block change (F=7.96, p<0.01) and TMT-A (Fχ^2=12.16, p=0.001) driven by BD reporting higher scores compared to HC. There were no significant main effects of sex nor group by sex interactions in any other variable related to attention domain (all details concerning neurocognitive results are shown in Table 3).

Also, main effect of group for *working memory* index (F=7.07, p<0.01) was found, driven by patients presenting lower scores than HC. Significant main effect for sex was also observed in working memory index (F=19.28, p<0.001) with males displaying a better performance than females (see Figure 1). There were no significant group by sex interactions.

When comparing *verbal learning and memory* scores for BD and HC, results showed main effects of group for CVLT total words (F=6.95, p<0.01), CVLT short free recall (F=4.32, p=0.03), CVLT short cued recall (F=5.91, p=0.01), CVLT delay free recall (F=4.93, p=0.02), CVLT delay cued recall (F=8.57, p<0.01), logical memory I WMS-III (F=8.40, p<0.001), and logical memory II WMS-III (F=7.88, p<0.01).

These were driven by patients displaying lower performance in all of the above measures compared to HC. There were significant main effects for sex in CVLT total words (F=4.43, p=0.03) and recognition (F=4.66, p=0.03), with males underperforming in comparison to females (see Figure 1). There were no significant group by sex interactions

Similarly, main effects of group for *processing speed* index (F=56.31, p<0.001), *visual memory* (F=13.49, p<0.001) and some variables related to *executive functions:* cognitive flexibility, (TMT-B (F=9.83, p<0.01)), verbal fluency (phonemic fluency (F=22.15, p<0.001) and animal naming (F=28.65, p<0.001)) were also observed. In all of the aforementioned tasks HC outperformed patients. There were no main effects of sex or group by sex interactions.

Of note is that all of the main effects and interactions remained significant after controlling for residual depressive and manic symptoms.

Furthermore, secondary analyses were run to analyse the effect of those clinical variables, such as diagnosis subtype (bipolar I or bipolar II) and lifetime substance misuse, that may influence cognition. We found a statistically significant effect of diagnosis subtype in working memory index (p=0.04) driven by bipolar type II presenting higher scores than type I. No other significant effects were detected.

Psychosocial Functioning

Main effects of group, even after controlling for subsyndromal depressive and manic symptoms, were observed in the total FAST score (F=46.30, p<0.001), and for four out of six psychosocial functioning domains (autonomy (F=16.84, p<0.001), occupational (F=28.23, p<0.001), cognitive (F=27.07, p<0.001), and interpersonal relationship (F=11.94, p=0.001)). The patients sample presented a poorer functional outcome compared to HCs. No other main effects or interactions were found (see details in Table 4).

Discussion/Conclusion

The main findings emerging from our analysis is the presence of significant sex effects on specific neurocognitive measures related to working memory and verbal memory domains. Specifically, the analysis was conducted in a large sample of euthymic patients with BD using a comprehensive neuropsychological battery covering 6 neurocognitive domains. Males performed better than females in working memory tasks, whereas women outperformed men in the verbal learning and memory recognition tasks, regardless of being patients or HC. As expected, compared to the control group, patients with BD presented overall cognitive deficit, which was further reflected the majority of subtests, except for specific executive functions such as inhibitory control and set-shifting and

planning. Lastly, we examined the global psychosocial functioning and their specific domains but no sex differences were detected. Currently, the relatively few studies addressing the impact of sex on cognitive measures in BD present inconsistent findings (Tournikioti et al., 2018). Sex differences in cognitive performance have been broadly described in the general population, although recent meta-analyses have suggested that women and men are more similar on most neurocognitive variables than was previously assumed (Hyde, 2016). Traditionally, it has been assumed in non-clinical population that females tend to outperform males in verbal abilities, with the opposite observed in visuospatial tasks, for example, in visuospatial working memory (Halari et al., 2006). This advantage in spatial working memory in males remained in early stages of the BD (Bücker et al., 2014) but not in patients presenting a multi-episode course of illness (Barrett et al., 2008; Suwalska and Łojko, 2014). Independently of diagnosis group (BD vs HC), we found that male participants showed a better performance in *working memory* (Digits, Letter-number sequencing and Arithmetic subtests) than females. We examined a different component within the working memory, the verbal component, which is different from the visuo-spatial component. In line with our results, some studies carried out in the general population showed that men perform better on mental arithmetic, when compared to females (Kaufman et al., 1991; Lynn and Irwing, 2008; Whitley et al., 2016), and, to a lesser extent, in the digit span (Lynn and Irwing, 2008). Therefore, it seems that the possible advantage exhibited by men in verbal working memory capacity might remain in patients with BD, contrary to what happens with the spatial working memory. Indeed, this better performance in men remained regardless of the bipolar subtype given that adjusting by diagnosis subtype the effect of sex remained significantly. Therefore, although there were more females with bipolar type II, the advantage presented by males in working memory still persisted.When we analyzed the *verbal learning and memory* domain, we found a significant sex effect in the CVLT learning and recognition tasks with females performing better than males. These findings suggest that sex may modulate, to some extent, verbal memory function, which is linked to a greater benefit in females compared to males in the learning task as well as in recognition when retrieval of information may be compromised. The latter might also suggest that females are better at learning and encoding processes since they can better recognize learned information, regardless of the efficiency of spontaneous retrieval. Additionally, trends in interaction between group and sex were detected in immediate verbal memory as well as percentage of retention of WMS-III stories which might indicate a differential effect of sex on logical memory between the BD and HC group. Specifically, it might suggest an advantage in logical memory for women in the control group but not among female patients. Female patients presented a higher percentage of diagnosis of BD type II, higher rates of psychotic depression and family history of psychiatric disease and a trend to depressive predominant polarity. Thus, one may argue that the

burden of disease might have repressed the advantage in the immediate verbal memory presented in HC females. However, further studies are needed to clarify the potential effects of clinical variables between men and women in cognition. Carrus et al. (Carrus et al., 2010) found group by sex interactions in immediate memory WMS-III, although with different patterns. Specifically, they did not find a difference between HC males and HC females, however, female patients and HC performed better in immediate memory than male patients. Female patients also performed better in auditory delayed memory than male patients. In contrast, Gogos et al. (Gogos et al., 2010) and Vaskinn et al. (Vaskinn et al., 2011)found better overall performance by females, including patients and HC in delayed verbal memory, but not for the stories.

Regarding the *attention domain*, our findings indicate no significant sex effects, only a trend in response speed consistency was found as indicator of inattention. Indeed, males seems to perform better than females independently of diagnostic group. These results are near with those found by Popuri et al. (Popuri, 2012), who reported that males outperformed females on measures of sustained attention. Regarding *executive function,* our results are in line with most previous studies (Barrett et al., 2008; Bücker et al., 2014; Carrus et al., 2010; Gogos et al., 2010; Suwalska and Łojko, 2014), where no group by sex interactions were found, indicating that sex had a similar impact in this domain in both BD and HC. However, our findings disagree somewhat with the results of Vaskinn et al. (Vaskinn et al., 2011) and Tournikioti et al. (Tournikioti et al., 2018), who found significant sex differences in *processing speed* (Vaskinn et al., 2011) as well as in *visual learning and spatial recognition memory* (Tournikioti et al., 2018). Vaskinn et al. (Vaskinn et al., 2011) detected that females performed better than males in Digit symbol test, while we did not detect differences between sexes. Nonetheless, in our study, processing speed was assessed through two tasks instead of one. While Tournikioti et al. (Tournikioti et al., 2018) found that males outperformed females in visual learning and spatial recognition memory, among HC but not in patients, we observed that patients showed a significant poor visual memory execution regardless of sex.

Lastly, regardless of sex, patients with BD displayed higher psychosocial functioning impairment than their healthy counterparts. Therefore, there was not sex effect in psychosocial functioning in patients or HC. This finding contrasts with those studies that showed a better psychosocial outcome for women with BD (Sanchez-Autet et al., 2018; Vaskinn et al., 2011). This inconsistency may be due to the fact that the Vaskinn et al. (Vaskinn et al., 2011) study included a clinical-rated self-report measure, which is not comparable with the FAST scale, used in our study (Vaskinn et al., 2011). Similar to the current study, Sanchez-Autet et al. (Sanchez-Autet et al., 2018) used the FAST, however recruited patients were in different phases of the illness. Our findings suggest that the lack of sex

differences in psychosocial functioning may be explained by the fact that the sex differences observed in cognitive performance are minor to generate sex differences between groups.

Affective symptoms and several clinical factors have been associated with poor cognition in BD (Bonnín et al., 2010; Bourne et al., 2013). In our case, we found differences in some clinical variables among the patients, which may influence cognitive sex differences such as bipolar subtype. A statistically significant difference was not detected in treatment-related variables, such as type of medication received. Therefore, it is unlikely that our findings would be explained by differences between male and female BD patients regarding illness severity, type of medication or clinical symptomatology.

Sexual dimorphism appears to influence sex differences in cognition (Andreano and Cahill, 2009). Sexual dimorphism of brain structures are the basis of sex differences in cognition in healthy populations. Recent studies suggest that sexual dimorphism may explain why sex impacts the bipolar illness in a different manner (Bücker et al., 2014). For instance, Shi et al. (Shi et al., 2018) found that, among patients with BD, right hippocampal volume loss was more evident in females than males. However, this finding was not observed in control subjects. It is well known that the hippocampus is essential for the different processes of learning and memory (representing spatial information, autobiographical memories) (Eichenbaum, 2000), but also closely involved in emotion processing and regulation (Fanselow and Dong, 2010; Frey et al., 2007), which is one of the core disturbance in BD. Genotype-by-sex interactions may be also influencing cognition and brain structures, therefore, it will be important to analyse these potential interactions in BD (Blokland et al., 2019).

Nevertheless, the findings of the present study should be interpreted in light of the following limitations. One limitation of the study was the cross-sectional design, which provides no insight as to whether or not these sex differences change throughout the course of the illness. Although there were no differences in patients regarding type of medication, we cannot rule out the potential effect on neurocognitive performance of the medication regimes and dosage, which were not controlled in our study. Another limitation is related to the neurocognitive battery of tests. Our battery of tests did not include visuo-spatial working memory tasks, which may be one sensitive task to detect sex differences. Importantly, no statistical procedure was used to control for multiple comparisons, which could have introduced type I error. Lastly, sex hormones and menstrual status in women, which may play a critical role in neural functioning and neuropsychological functioning, were not taken into consideration. Despite these limitations, the strengths of our study include a large well-defined sample of euthymic patients with BD, a comprehensive cognitive battery assessing all the

neurocognitive domains compromised in BD as well as a psychosocial functioning measure (i.e. FAST).

Overall, it is difficult to conclude to what extent neurocognitive impairment in BD is influenced by sex. This is due to the paucity of studies aimed to examine sex differences in neurocognition in BD as well as several main methodological issues related to sample sizes, diagnostic comparison groups, demographic and clinical characteristics of samples and variability in neurocognitive tasks used. Thus, further studies investigating the sex issue in cognition, also including the subjective cognition (Navarra Ventura et al., 2019), are needed. Another useful approach would be neuroimaging as well as longitudinal studies. They can be useful to elucidate sexual dimorphism and they might explain the nature and developmental trajectory of different neurocognitive deficits between women and men in BD. Finally, studies should also consider menstrual status in women in cognitive functioning as well as other cultural or environmental factors that could be influencing both the cognition and psychosocial functioning, such as academic background or gender stereotyping which have become a focus of interest in this research area (Jäncke, 2018).

To sum up, our findings suggest that women and men are similar on most neurocognitive measures, with only small sex differences in cognitive performance found in measures related to working memory and verbal memory domains but not in psychosocial functioning. Specifically, females outperformed males in verbal learning and males outperformed females in working memory. Our findings highlight the importance of looking into sex differences when designing cognitive remediation interventions.

Statements

Contributors

BS, CV and AMA conceived the study, with substantial contributions from the other authors. BS and CV did the literature search and wrote the first draft. All authors substantially participated in the final manuscript, which was reviewed, revised and approved by all authors.

Funding

This research did not received any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

The authors would like to thank the support of the Spanish Ministry of Science and Innovation; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365; 2017 SGR 1355) and the CERCA Programme / Generalitat de Catalunya.

This work has been also supported by the Spanish Ministry of Science, Innovation and Universities integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER) through a 'Miguel Servet' postdoctoral contract (CPI14/00175 to CT), a Miguel Servet II contract (CPII19/00018 to CT), a 'Sara Borrell' contract (CD20/00177 to SA), both co-funded by European Social Fund "Investing in your future", and the FIS grants (PI18/00805, PI18/00789). This work has been also supported by the BITRECS project to NV, which has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754550 and from "La Caixa" Foundation (ID 100010434), under the agreement LCF/PR/GN18/50310006. Thanks the support of the European Union Horizon 2020 research and innovation program (EU.3.1.1. Understanding health, wellbeing and disease: Grant No 754907 and EU.3.1.3. Treating and managing disease: Grant No 945151).

This work has also been supported by the projects SLT006/17/00357 and SLT006/17/00345 in the "Pla estratègic de Recerca i Innovació en Salut 2016–2020" (Health Department). CERCA (Programme/Generalitat de Catalunya) and by the Government of the Principality of Asturias PCTI-2018-2022 IDI/2018/235.

Conflict of Interest Statement

Dr. Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (work unrelated to the topic of this manuscript): AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Generalitat de Catalunya (PERIS), the Spanish Ministry of Science and Innovation (CIBERSAM), EU Horizon 2020, and the Stanley Medical Research Institute.

Dr. Martínez-Aran has received funding for research projects and/or honoraria as a consultant or speaker for the following companies and institutions (work unrelated to the topic of this manuscript): Otsuka, Pfizer, AstraZeneca, Bristol-Myers Squibb, Lundbeck, the Spanish Ministry of Economy and Competitiveness and Instituto de Salud Carlos III.

Dr. García-Portilla has been a consultant to and/or has received honoraria/grants from (work unrelated to the topic of this manuscript): Angelini, Alianza Otsuka-Lundbeck, CIBERSAM, Government of the Principality of Asturias, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, and SAGE Therapeutics.

Dr. Sáiz has been a consultant to and/or has received honoraria or grants from (work unrelated to the topic of this manuscript): Adamed, CIBERSAM, European Comission, Government of the Principality of Asturias, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas and Servier.

The other authors have no conflict of interest to declare.

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Figure Legends

"Fig. 1." Sex effect on Working Memory Index, CVLT total words and CVLT recognition

Y-axis: raw scores

Abbreviations: CVLT= California Verbal learning Test