Journal of Affective Disorders

IDENTIFYING NEUROCOGNITIVE HETEROGENEITY IN OLDER ADULTS WITH BIPOLAR DISORDER: A CLUSTER ANALYSIS

--Manuscript Draft--

Manuscript Number:	JAFD-D-21-03671R1
Article Type:	Research Paper
Keywords:	Cognition, Bipolar Disorder, Older Adults with Bipolar Disorder, Heterogeneity, Cluster analysis, Neuropsychology
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Abstract:	Background: Cognitive profiles of BD patients show a demonstrated heterogeneity among young and middle-aged patients, but this issue has not yet deeply explored in Older Adults with bipolar disorder (OABD). The aim of the present study was to analyze cognitive variability in a sample of OABD. Methods: A total of 138 OABD patients and 73 healthy controls were included in this study. A comprehensive neuropsychological assessment was administered. We performed a k-means cluster analysis method based on the neurocognitive performance to detect heterogeneous subgroups. Demographic, clinical, cognitive and functional variables were compared. Finally, univariate logistic regressions were conducted to detect variables associated with the severity of the cognitive impairment. Results: We identified three distinct clusters based on the severity of cognitive impairment: (1) a preserved group (n=58; 42%) with similar cognitive performance to HC, (2) a group showing mild cognitive deficits in all cognitive domains (n=64; 46%) and, finally, (3) a group exhibiting severe cognitive impairment (n=16; 12%). Older age, late onset, higher number of psychiatric admissions and lower psychosocial functioning were associated with the greatest cognitive impairment. Lower age, more years of education and higher estimated IQ were associated with a preserve cognitive functioning. Limitations: The small sample size of the severe group. Conclusions: Cognitive heterogeneity remains at late-life bipolar disorder. Demographic and specific illness factors are related to cognitive dysfunction. Detecting distinct cognitive subgroups may have significant clinical implications for tailoring specific intervention strategies adapted to the level of the impairment and also to prevent cognitive decline.

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Cover Letter

Prof. Eduard Vieta
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October 13, 2021

Dear Editors-in-Chief

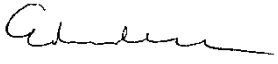
Please find enclosed our manuscript entitled "*Identifying neurocognitive heterogeneity in Older Adults with Bipolar Disorder: a cluster analysis***"** to be considered for publication, as an original article, in *Journal of affective Disorders*, if you find it suitable.

The present original study tries to yield new information about neurocognition in a sample of Older Adults with Bipolar Disorder based on detecting the heterogeneity in the cognitive performance. As far as we know, this is the first attempt to identify cognitive subgroups in a sample of euthymic OABD patients using a cluster analysis method. Overall, the results demonstrated the detection of three well-differentiated groups as well as the demographic and clinical factors associated with the severity of cognitive impairment. These findings may have therapeutic implications and should be considered to design future interventions to treat and prevent cognitive impairment in this understudied population. We believe that these results will help to better understand the neurocognitive heterogeneity in older subjects with bipolar disorder.

This manuscript represents original material and has not previously been published. It is not being considered for publication elsewhere and has been approved by each author. Moreover, all forms of conflict of interest by all authors were clearly identified in the text.

We hope this manuscript will be of interest to you.

Sincerely,



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9th November, 2021

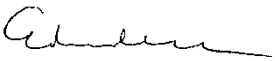
Dear Editor-in-Chief,

Dr. Paolo Brambilla

Thank you for considering our manuscript ID JAFD-D-21-03671 entitled "Identifying neurocognitive heterogeneity in older adults with bipolar disorder: a cluster analysis" for further revision. We are grateful to the reviewers for their effort and comments. We believe that many of the changes they suggested have contributed to improve the quality of the manuscript. We have adjusted the text according to their suggestions as appropriate. We hope that the current version of the paper will be suitable for publication in Journal of Affective Disorders.

We really wish that all the following changes are going to fulfil your expectations and turn the paper into suitable for publication in your journal.

Sincerely,



Eduard Vieta

Reviewer #1: This is a well-written manuscript on the study to identify neurocognitive heterogenity in older adults with bipolar disorder. The paper identified three distinct clusters based on the severity of cognitive impairment and found some demographic and specific illness factors are related to cognitive dysfunction. I recommend this paper for publication after consideration of a minor comment:

In the "RESULTS" section, there were two results showed late onset was a risk factor for cognitive impairment. One is 'Specifically, the SG had a later illness onset than the other two clusters' and another one is 'In regards to clinical outcomes, late onset (OR= 4.76; p= 0.04) and higher number of psychiatric admissions (OR=1.43; p= 0.02) were significantly associated, that is, they were risk factors for cognitive impairment.' Although some studies also show the same result as the current paper, it is suggested to explain why late onset is related to cognitive impairment. Is there any study showing the relationship between early onset and cognitive impairment? Is it possible that the age of onset is skewing due to the very small sample size of SG cluster? Please add some discussions about these questions.

Different clinical factors between early and late onset have been detected across the literature. Apart from the differences found in cognitive performance, the age of onset could be a valid clinical indicator and could help to understand the heterogeneous presentation of the disease (Leboyer et al., 2005). While the onset of early onset patients is more associated with family history of mood disorder, Late Onset is more associated with a cerebrovascular disease. Most of the results in the literature are aimed at an early onset sample as this is the most predominant percentage of this group. Global deficits across several cognitive domains have been detected in OABD with an early onset, such as in attention, memory, executive function among others (Schouws et al., 2007; Tsai et al., 2007).

A little explanation has been added to the discussion section (#page 12): *"Studies have detected a greater presence of medical and neurological burden in late-onset BD patients (Schouws et al., 2010; Vasudev and Thomas, 2010) as well as more signs of cerebrovascular disease compared to HC and early-onset patients (Ramírez-Bermúdez et al., 2021) which may be increasing the magnitude of the cognitive deterioration. Therefore, it is postulated that it may be a disease with a differentiated etiology (Dols and Beekman, 2020; Ljubic et al., 2021). Thus, this result could be reflecting a bias towards a greater cognitive impairment."*

Regarding the issue about the late onset group in our sample, although a little number of patients (n=4) in the SG cluster comprised a late onset, due to the small sample size of the SG cluster, this number represents a higher percentage (36%) within this cluster. Although significant differences were found in ANOVA between all clusters regarding this variable, post-hoc analysis applying Bonferroni correction revealed no differences between groups. Nevertheless, we understand that this may be a limitation and have added it to this section (page #13): *"Third, the late-onset group could be skewing the magnitude of the cognitive impairment, especially in the severely impaired group which was composed of a high percentage of these subjects due to the small sample size of that group".*

Reviewer #2: Manuscript number: JAFD-D-21-03671

This work addresses a topic of major importance which provide a valid addition to the field: exploring the heterogeneity of cognitive impairments in OABD to identify cognitive profiles. The authors find 3 clusters based on severity of cognitive impairment assessed using a wide neurocognitive battery. Despite the promise of the set up for this study, the paper has some weaknesses that need to be addressed.

Introduction

Paragraph 1

- **When the authors report previous evidence on cognitive profile in BD, can they can add if they are referring to BD-I, BD-II or both, and if the people in those studies were euthymic or not. This will help linking the results from previous literature.**

We clarified this point when we introduce the studies which address the heterogeneity issue as follows (Page #1): *"Moreover, substantial evidence points at a further cognitive variability between the young and middle-aged euthymic BD population, including both type I and II, demonstrating the existence of three clusters differentiated by the level of cognitive impairment"*

- **One general comment is the fact that authors are assessing cognitive profile in BD combining a group of people with BD-I and BD-II. Can this have affected the clustering? As authors state in introduction "Several clinical features related to illness severity (i.e. type of BD, number of mood episodes, presence of psychotic symptoms, number of admissions, age of onset) have been proposed as moderators of cognitive function and might potentially explain the variability among patients with BD (Bora, 2018)". Can you please state the rational of combining the groups?**

In order to perform similar analyses in line with many previous reports studying cognitive heterogeneity in BD adults cohorts, we also included both subtypes of bipolar disorder (BD I and BD II) combined. Having similar samples allow us to link the studies with younger populations in which bipolar I and bipolar II patients are also mixed up.

Moreover, the OABD sample includes a lower proportion of BD, dividing the sample by diagnosis subtypes would significantly reduce the total sample, preventing us to perform the analysis with adequate statistical power.

Finally, as it is displayed in table 2, there were no differences regarding the type of diagnosis between clusters (*p-value*=0.454), so that, we believe that no large differences would be found concerning this factor in the present study. However, it is a good consideration to take into account in future studies.

Aims

- **Do you have a specific hypothesis or was this an exploratory study?**

Based on the results of the previous reports performed in adult populations, we also expected to find distinguished groups. We add this point at the end of the introduction section (page #2): "*We expect to find different cognitive subgroups according to the severity of the cognitive impairment."*

- **The aims are quite brief compared to the amount of analysis performed and results provided, perhaps aims can be expanded so they can be more easily related to the following sections?**

We expanded and numbered the aims of the present study as follows (page#2):*"The aims of the present study are: 1) to determine the existence of potential discrete cognitive profiles in a sample of OABD; 2) to detect the clinical and demographic variables associated with each cluster and 3) to identify clinical and demographic variables associated with the severity of cognitive impairment".*

Methods

Participants

- **Information about the clinical sample is somewhat lacking here. Could the authors add the following information:**
  - **How many were recruited?**
  - **How many were included in the final analysis?**

The sample used for the present study belongs to a cohort of people (BD and HC) over the age of 50 who were recruited at the Hospital Clinic of Barcelona specifically for that study or related studies that have the same inclusion and exclusion criteria. As it is a naturalistic research, all participants of the sample were included since they fulfilled all the inclusion and exclusion criteria detailed in the manuscript. This is a well-defined cohort with accurate diagnoses made by professionals with extensive experience in this field.

We explain that point as follows (page #2): *"The sample for the present study belongs to an OABD cohort recruited from the Bipolar and Depressive Disorders Unit of Hospital Clinic of Barcelona".*

- **% of people with BD-I and those with BD-II**

As it is displayed in table 1, a total of 85 (61.6%) BD type I patients were included and 53 (38.4%) BD type II. However, we specified it in the manuscript as follows (page #5): *"A total of 73 HC and 138 OABD (85 type I and 53 type II) over the age of 50 were included in this analysis."*

- **Were participants on medication? If so which medication?**

As it is displayed in table 2 a large proportion of patients were currently in pharmacological treatment. We have extended that information in page #7: "*Relative to pharmacological treatment, a large proportion of patients were currently in treatment with mood stabilizers,*

antipsychotics, antidepressant and anxiolytic, but no significant differences were detected within OABD clusters concerning any kind of treatment. "

o Do participants have other co-occurring psychiatric disorders?

- Regarding medication and co-occurring psychiatric disorders, I wonder if this can affect the results? If so, was this controlled in analyses?

The co-occurring psychiatric diagnoses were:

Co-occurring psychiatric disorder	**N(%)**
Obsessive Compulsive disorder	3 (12,5%)
Anxiety disorder	4 (16,7%)
Eating disorder	1 (4,2%)
Social phobia	1 (4,2%)
Impulse control disorder	2 (8,3%)

As the table shows, a little proportion of OABD patients (11 subjects (7.97%)) had a current comorbid psychiatric diagnosis. For that reason we decided not to control for this variable, as we think had no effect on the final results. However, this issue has been highlighted and added to limitation section, page number #13: *"Finally, the potential confounding variables that could influence cognitive performance, such as pharmacological treatment and comorbid psychiatric disorders, were not controlled in the analysis".*

Demographic, clinical and psychosocial functioning assessment

- Can you please add how questions related to the demographic, clinical and psychological functioning were evaluated in the semi-structured interview? Was it a yes/no answer?

We conducted a semi-structured clinical interview to collect all the data related to the disease. Most of the questions required further clinical exploration, that is, not only yes/no answers, and were registered by a rater specifically trained for this purpose. If any data was unclear, it could be contrasted and completed with the patient's clinical history records. Psychosocial functioning was assessed with the FAST scale, which is a hetero-applied scale through a semi-structured interview conducted by a trained clinician. The level of functioning in each area (autonomy, work, cognitive, finances, interpersonal relationships and leisure) was scored on a Likert scale from 0 to 3, where the higher the score, the worse functioning.

Neuropsychological Assessment.

- Can you please clarify how these assessments were selected?

This is a systematic neuropsychological battery commonly used in our unit for all research projects. This battery was designed following the assessment recommendations of the International Society of Bipolar Disorder Cognition Task Force for bipolar disorders (Yatham et al., 2010), which suggest a compendium of tests that have demonstrated higher reliability and validity in the cognitive assessment for bipolar disorder. Despite in the present study we are assessing older age, since to date a neuropsychological assessment for older age it is not established (Dols et al., 2016), we decided to maintain the same battery used as in younger cohorts.

It has been clarified in page #4: "*This compendium of test was set following the recommendations of the International Society of Bipolar Disorder for cognitive assessment in bipolar disorder (Yatham et al., 2010)".*

- **Assessment descriptions lack details (e.g. number of items/trials, subtests, which variables were obtained, scoring information etc.). Can you please add more information about the assessments (this can be added to supplementary)**

In the methodology section (page #3) each test is well referenced indicating the complete name, author and version, so that, readers could access to the original source and search more specific information (i.e scoring, administration rules, instructions, description of test, etc). Moreover, the tests and their variables included for the creation of the cognitive composites are also described in detail in the statistical section (page #4) as follows: 1) *attention:* the TMT-A total time score; omission, reaction time and reaction time standard error measures of the CPT-II; 2) *processing speed:* scores of the Digit-Symbol Coding and the Symbol Search subtests of the WAIS-III; 3) *working memory:* scores of Arithmetic, Digits and Letter-Number Sequencing subtests of the WAIS-III; 4) *verbal memory:* the total trials list A (1-5), short free recall, short cued recall, delayed free recall, and delayed cued recall scores of the CVLT-II; 5) *visual memory:* immediate recall of the ROCF; 6) *executive functions:* number of categories and perseverative errors of the WCST; the Interference score of the Stroop Test; TMT-B; the copy score of the ROCF; phonemic (FAS) and semantic (animals) verbal fluency of COWAT.

- **Why only Vocabulary subtest of the WAIS-III was used for estimating IQ?** According to the neuropsychological clinical guidelines (Esther Strauss, Elisabeth M. S. Sherman, 2006; Lezak, 2012) the vocabulary subtest of WAIS-III is a well-recognized test as a measure of the estimated IQ since it achieves a direct and strong correlation with the total IQ.

Statistical analysis

- **I have some concerns here related to the possibility of confounding variables that might be included in the analysis. Did the authors control for age sex and IQ?**

In the first version of the manuscript, we had controlled for age and years of education since there were two variables resulting statistically significant in the ANOVA analysis. However, following the reviewer suggestion we have performed the analysis adjusting by age, years of

education, sex and IQ, resulting in few changes that lie mainly in the differences between the MG and the SG cluster. As a consequence, no significant differences between MG and SG are observed in verbal memory and in working memory. These changes have been added to the result section (page #8): "*However, when MG was compared to SG the cognitive profile displayed no differences in verbal memory (p=0.21) and working memory (p=0.134) while differences were found in the other cognitive domains*".

Moreover, since the z-scores values have changed slightly, they have been modified along the text in the result section. The slight changes resulting from this modification have been included in the results section (page 7 and 8).

We also change the interpretation of these results in the discussion section (page #10): *"Additionally, the group with severe cognitive impairment showed deficits across all cognitive domains but with a moderate to severe impairment compared to the preserved group and the HC. On the contrary, controlling by confounding variables, no differences were found in verbal memory and working memory when comparing to the mild impaired cluster, demonstrating that both clusters cannot be differentiated by the performance in these cognitive domains".*

- **I see in the results section some adjustments are reported, but these are not included here. Perhaps authors can add here that adjustments are done when there is a significant difference between groups for each analysis?**

Following the recommendation previously pointed out by the reviewer we added that information as follows in the statistical section (page #4): **"***An ANCOVA adjusted by age, sex, years of education and estimated IQ was performed to assess the differences between cognitive domains by clusters"* as well as in the results section (page #6): "*Table 3 summarizes the cognitive performance through the cognitive composites between all OABD and HC group expressed in z-scores after adjusting by age, sex, years of education and estimated IQ."*

- **Can you please specify for which analyses did you perform Bonferroni? The authors state significance was set up at was set at p <0.05, but if you used Bonferroni correction this should be much lower and depending on the number of tests in each set of analyses. Can you please report the corrected p-value threshold for each analysis?**

Currently, we specified in both, tables and manuscript, when Bonferroni correction was applied. The tables show the p-values corresponding to the Bonferroni correction. We have better clarified this point as follows (page #4): "*A Bonferroni post-hoc analysis was applied to determine the pairwise differences in all significant demographic, clinical and cognitive variables when comparing HC with OABD cluster as well as within OABD clusters."*

Results

Comparisons between OABD and HC

- **Is it possible to add effect sizes when comparing groups in text or tables?**

As the comparison is made with a control group, effect sizes based on Glass's Delta value have been calculated for the cognitive composites scores when comparing OABD and HC. We added

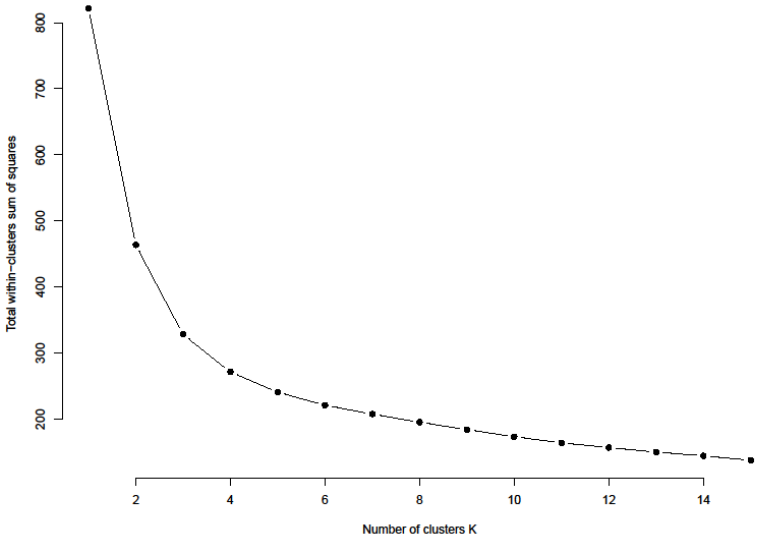
this information in method section (page #4): "*Effect sizes for cognitive scores between HC and OABD were calculated based on Glass's Delta statistic*"

A description of these results is also explained in results section (page #5): *"Moreover, large effect sizes were detected in all cognitive domains (from 6.78 to 11.75)."*

Cluster analysis

- **Could you please comment on how the three cluster classification was defined? Was this an a-priori decision guided from the literature or driven by the data? Please add some clarifications somewhere in the manuscript.**

The classification it is mainly derived from data. The clusters were created using an algorithm based on k-means technic, that is, the groups were driven by the data without any a-priori classification. This method assigns one observation depending on the distance to its centroid. Thus, it classifies an observation to one cluster based on the smallest distance to its centroid and, consequently, it tries the maximization of the distance with the other observations. And for any number of clusters (1,2,3…) we evaluate which number of cluster is the best option for our data sample with the elbow method (a heuristic used in determining the number of clusters in a data set, that consists of plotting the explained variation as a function of the number of clusters and picking the point where the curve visibly bends):



In our sample, the best option is to pick 3 clusters based on 1) the location where the curve visibly bend, 2) the previous literature finding which also detected three clusters and 3) applying the parsimonious model in which the models should have as few parameters as possible and simple explanations should be preferred.

We clarified this issue in the method section (page #4): "*In cluster analysis, the elbow method is used to decide the number of clusters based on the explained variation and choosing the point where the curve visibly bends."*

Discussion

- **The authors state "To the best of our knowledge this is the first attempt, using a cluster analysis approach, to disentangle the heterogeneity of OABD in distinct neurocognitive profiles with prognostic implications". However in the introduction they state "As far as we know, there is only one previous report focused on cognitive heterogeneity in OABD (Martino et al., 2018), which identified three subgroups: 33.3% of patients were cognitively intact, 36.4% showed selective deficits, and 30.3% exhibited global deficits." This seem a contradiction in the manuscript, perhaps the authors can add a clarification on how these results builds on Martino et al., 2018?**

Since different methodologies could lead to different results we added that clarification in the discussion section page number #9: "*Regarding OABD, a cognitive heterogeneity has been previously detected identifying also three cognitive subgroups (Martino et al., 2018) but, instead of applying cluster analysis method they established subgroups based on z-scores".*

- **Can authors add a comment on why late-onset BD is associated with increased cognitive impairment? I would have expected the contrary. Is perhaps late-diagnosis rather than late-onset?**

We provide a little explanation about the late-onset subgroup that also was addressed in response to the reviewer number one. Different clinical factors between early and late onset are detected along the literature data. While the onset of early onset is more associated with family history of mood disorder, late onset is more associated with a cerebrovascular disease. For the present study we considered late-onset a manifestation of a first episode after the age of 50, regardless of whether it was a manic, hypomanic or depressive episode. We also added to the manuscript a clarification to address this surprising concern (page #11): *"Studies have detected a greater presence of medical and neurological burden in late-onset BD patients (Schouws et al., 2010; Vasudev and Thomas, 2010) as well as more signs of cerebrovascular disease compared to HC and early-onset patients (Ramírez-Bermúdez et al., 2021) which may be increasing the magnitude of the cognitive deterioration. Therefore, it is postulated that it may be a disease with a differentiated etiology (Dols and Beekman, 2020; Ljubic et al., 2021). Thus, this result could be reflecting a bias towards a greater cognitive impairment."*

- **Can the authors add a comment on the use of medication in this sample? 32% of their sample was on antipsychotics which have known cognitive side-effects. If confounding by medication cannot be assessed here this should be highlighted as a limitation. The same should be done for co-occurring psychiatric disorders as some have known associated cognitive impairments.**

Cognition can be affected both positively and negatively by medication. While some drugs appear to have a protective effect on cognition, enhancing or maintaining neuropsychological performance, several drugs have negative side effects on cognitive performance, despite reducing affective or psychotic symptomatology. Studies conducted with drug-free bipolar

patients detected a presence of neuropsychological impairment, thus, suggesting that neurocognitive deficits are an integral part of bipolar disorder (Goswami et al., 2009). It would be of great interest to perform long-term studies to clarify this issue. Nevertheless, we added that limitation in page number #12: *"Finally, the potential confounding variables that could be influence cognitive performance such as pharmacological treatment and comorbid psychiatric disorder were not controlled in the analysis".*

Abstract

- **I noticed OABD is not defined in the abstract; please add that this means Older Adults with Bipolar Disorder (OABD) the first time this term appears in the background subsection.**

Thank you for noticing this. We have added the meaning of the acronym has been added in abstract section.

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Highlights

- OABD patients showed deficits across all cognitive domains assessed compared to HC
- Cognitive heterogeneity has been detected in OABD
- Three well-distinguished clusters were demonstrated: 42% of patients showed a preserved cognitive profile, 46% exhibited mild impairment and a 12% of patients showed severe cognitive impairment.
- Outcomes related to cognitive reserve were associated with better cognitive performance while specific illness factors were associated with greater severity of cognitive impairment

ABSTRACT

Background: Cognitive profiles of BD patients show a demonstrated heterogeneity among young and middle-aged patients, but this issue has not yet deeply explored in Older Adults with bipolar disorder (OABD). The aim of the present study was to analyze cognitive variability in a sample of OABD.

Methods: A total of 138 OABD patients and 73 healthy controls were included in this study. A comprehensive neuropsychological assessment was administered. We performed a k-means cluster analysis method based on the neurocognitive performance to detect heterogeneous subgroups. Demographic, clinical, cognitive and functional variables were compared. Finally, univariate logistic regressions were conducted to detect variables associated with the severity of the cognitive impairment.

Results: We identified three distinct clusters based on the severity of cognitive impairment: (1) a preserved group (n=58; 42%) with similar cognitive performance to HC, (2) a group showing mild cognitive deficits in all cognitive domains (n=64; 46%) and, finally, (3) a group exhibiting severe cognitive impairment (n=16; 12%). Older age, late onset, higher number of psychiatric admissions and lower psychosocial functioning were associated with the greatest cognitive impairment. Lower age, more years of education and higher estimated IQ were associated with a preserve cognitive functioning.

Limitations: The small sample size of the severely impaired group.

Conclusions: Cognitive heterogeneity remains at late-life bipolar disorder ~~and~~. ~~d~~Demographic and specific illness factors are related to cognitive dysfunction. Detecting distinct cognitive subgroups may have significant clinical implications for tailoring specific intervention strategies adapted to the level of the impairment and also to prevent cognitive decline.

Keywords: cognition, Bipolar Disorder, Older Adults with Bipolar Disorder, heterogeneity, cluster analysis, neuropsychology.

Title Page (with Author Details)

IDENTIFYING NEUROCOGNITIVE HETEROGENEITY IN OLDER ADULTS WITH BIPOLAR DISORDER: A CLUSTER ANALYSIS.

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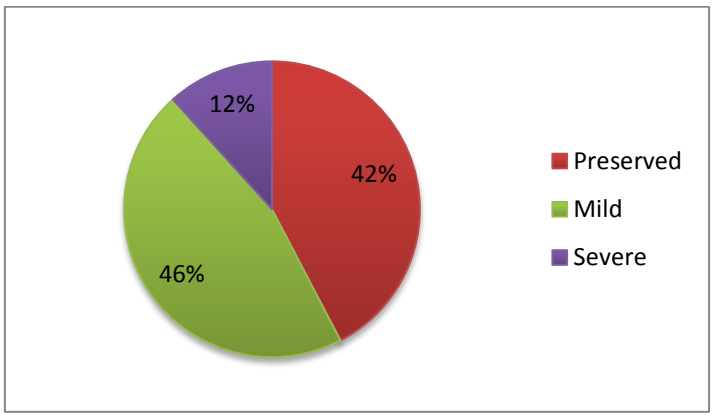
Figure 1. Distribution of cognitive impairment in OABD patients



Figure

Click here to access/download;Figure;Figure 2. Cognitive profile of each cluster.docx

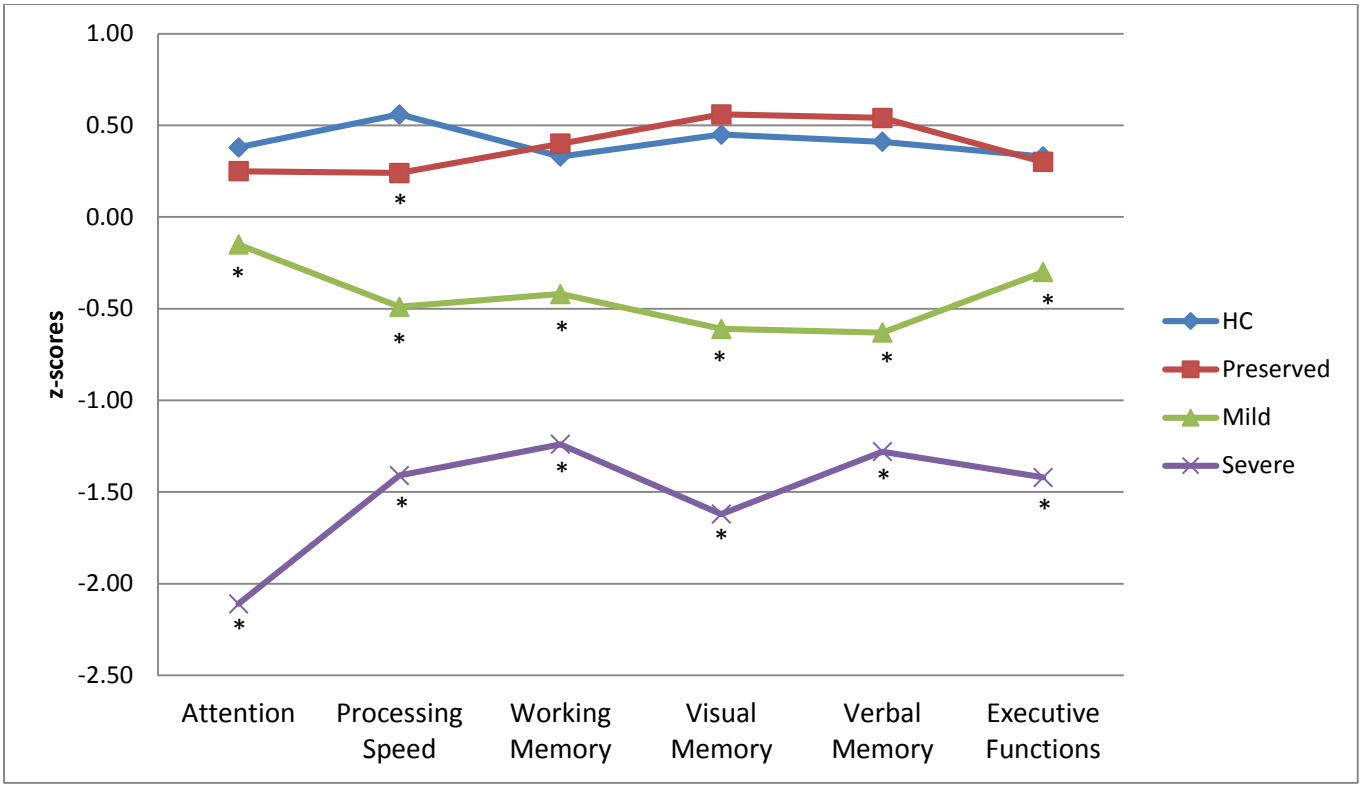


Figure 2. Cognitive profile of OABD clusters and HC

*Significant differences compared to the control group

Table

Table 2. Comparisons in demographic and clinical variables between OABD clusters and HC

	HC (n=73)	Preserved group (PG) (n=58)	Mild group (MG) (n=64)	Severe group (SG) (n=16)	Statistical analysis		Bonferroni post hoc					
		M(SD)	M(SD)	M(SD)	F	p-value	HC vs PG	HC vs MG	HC vs SG	PG vs MG	PG vs SG	MG vs SG
Age	61.73 (6.63)	56.09 (5.27)	60.34 (6.27)	68.38 (8.11)	18.67	<0.001*	<0.001*	1	0.001*	0.001*	<0.001*	<0.001*
Years of education	14.30 (3.81)	14.48 (2.97)	12.92 (3.41)	10.87 (4.73)	5.83	0.001*	1	0.149	0.005*	0.099	0.003*	0.272
Age at illness onset		31.09 (11.39)	31.52 (12.08)	42.67 (20.06)	3.44	0.035*				1	0.035*	0.04*
Years of illness duration		24.76 (11.80)	28.43 (11.54)	25.89 (13.14)	1.351	0.263						
Number of psychiatric admissions		1.49 (2.00)	1.47 (1.63)	5.13 (5.64)	9.554	<0.001*				1	<0.001*	<0.001*
Number of total affective episodes		22.70 (30.74)	14.49 (15.44)	18.75 (23.97)	1.285	0.282						
Number of manic episodes		1.51 (2.33)	2.18 (3.59)	4.25 (8.22)	2.052	0.134						
Number of hypomanic episodes		8.41 (15.23)	3.95 (5.52)	3.63 (2.97)	1.986	0.143						
Number of depressive episodes		11.89 (14.86)	7.91 (10.67)	9.71 (6.92)	1.139	0.324						
Number of suicide attempts		0.75 (1.16)	0.44 (0.8)	1.25 (1.26)	1.372	0.261						
YMRS total score	0.31 (0.82)	1.83 (2.01)	1.65 (2.12)	1 (1.41)	8.76	<0.001*	<0.001*	<0.001*	1	1	1	1
HDRS total score	2.14 (1.92)	4.29 (2.81)	5.72 (4.03)	6.1 (2.81)	16.29	<0.001*	0.001*	<0.001*	0.001*	0.085	0.479	1
FAST total score	3.74 (4.53)	23.76 (11.84)	23.84 (14.36)	42.29 (10.44)	57.93	<0.001*	<0.001*	<0.001*	<0.001*	1	<0.001*	<0.001*
Estimated IQ	113.77 (9.2)	113.33 (9.22)	107.81 (10.54)	103.08 (12.67)	7.93	<0.001*	1	0.003*	0.002*	0.016*	0.005*	0.699
	n (%)	n (%)	n (%)	n (%)	X^2	p-value						
Gender (females)	46(63)	31 (53.4)	31 (48.4)	12 (75)	5.4	0.145						
Diagnostic					1.58	0.454						
BD I		33 (56.9)	43 (67.2)	9 (56.3)								
BD II		25 (43.1)	21 (32.8)	7 (43.8)								
Late onset		4 (7)	6 (10.7)	4 (36.4)	7.96	0.019*				1	0.15	0.27
Psychotic Symptoms (yes)		29 (54.7)	32 (62.7)	6 (66.7)	0.914	0.633						
Catatonic (yes)		1 (2)	3 (6.1)	2 (28.6)	8.28	0.016*				0.871	0.365	0.592
Season pattern (yes)		14 (27.5)	14 (28.6)	2 (28.6)	0.017	0.992						
Rapid Cycling (yes)		5 (9.8)	7 (14.3)	1 (14.3)	0.502	0.778						
Melancholic symptoms (yes)		23 (45.1)	16 (32.7)	2 (28.6)	1.939	0.379						

Atypical symptoms		20 (39.2)	14 (28.6)	2 (28.6)	1.36	0.508	
Medical comorbidities (yes)	38(62.3)	38 (71.7)	39 (75)	9 (100)	6.32	0.097	
Family history of psychiatric disorder		39 (78)	27 (61.4)	5 (62.5)	3.27	0.195	
Suicidal ideation (yes)		33 (63.5)	27 (50.9)	4 (44.4)	2.21	0.331	
Suicidal attempts (yes)		12 (23.5)	8 (15.1)	3 (33.3)	2.16	0.34	
Type of medication		**n (%)**	**n (%)**	**n (%)**	**F**	**p-value**	
Lithium		26 (57.8)	28 (58.3)	6 (60)	0.008	0.992	
Mood stabilizers and anticonvulsants		42 (89.4)	53 (98.1)	12 (100)	2.34	0.101	
Antipsychotics		32 (68.1)	39 (72.2)	11 (91.7)	1.33	0.268	
Antidepressants		25 (53.2)	24 (44.4)	5 (41.7)	0.477	0.622	
Anxiolytic		18 (38.3)	17 (31.5)	4 (33.3)	0.257	0.774	

BD I: Bipolar Disorder type I; BD II: Bipolar Disorder type II; FAST: Functioning Assessment Short Test; HC: Healthy Controls; HDRS: Hamilton Depression Rating Scale; IQ: Intelligence Quotient; M: mean; OABD: Older Adults with Bipolar Disorder; SD: Standard deviation YMRS: Young Mania Rating Scale

Table 4. Univariate Logistic Regressions

	Univariate Logistic Regression comparing PG and MG clusters		Univariate Logistic Regression comparing MG and SG clusters	
	Odds Ratio (Interval Confidence)	***p-value***	**Odds Ratio (Interval Confidence)**	***p-value***
Age	1.14 (1.06-1.22)	<0.001*	1.17 (1.07-1.29)	0.001*
Years of education	0.86 (0.77-0.97)	0.01*	0.86 (0.73 - 1.01)	0.06
Estimated IQ	0.95 (0.91-0.98)	0.005*	0.96 (0.91-1.02)	0.16
FAST	1 (0.97-1.03)	0.98	1.11 (1.03 - 1.21)	0.01*
Number of psychiatric admissions	0.99 (0.80-1.23)	0.96	1.43 (1.06- 1.93)	0.02*
Type of onset (late onset)	1.59 (0.42-5.96)	0.49	4.76 (1.07 - 21.17)	0.04*
Years of illness duration	1.03 (0.99-1.06)	0.10	0.98 (0.92 - 1.04)	0.54
Total number of affective episodes	0.98 (0.96-1.01)	0.14	1.02 (0.97 - 1.06)	0.51
Psychotic symptoms (yes)	1.39 (0.64-3.05)	0.41	0.84 (0.19 - 3.77)	0.82
Number of suicidal attempts	0.73 (0.42-1.26)	0.26	2.24 (0.81 – 6.20)	0.12

FAST: Functioning Assessment Short Test; HC: Healthy Controls; IQ: Intelligence Quotient; MG: Mild group; PG: preserved group; SG: severe group.

Table 1. Demographic, clinical and cognitive diferences between HC and OABD

	HC (n= 73)	OABD (n= 138)			
	Mean (SD)	**Mean (SD)**	**t-test**	**p-value**	**Glass's Delta**
Age	61.73 (6.63)	59.49 (7.16)	2.22	0.028*	
Years of education	14.30 (3.81)	13.36 (3.57)	1.78	0.077	
Years of illness		26.57 (11.81)			
Age at onset		32.78 (12.76)			
Number of psychiatric admissions		1.74 (2.44)			
Total number of affective episodes		18.64 (23.97)			
Manic episodes		2.03 (3.66)			
Hypomanic episodes		5.97 (11.16)			
Depressive episodes		9.89 (12.66)			
Estimated premorbid IQ	113.77 (9.20)	109.64 (10.71)	2.77	0.006*	
YMRS total score	0.31 (0.82)	1.68 (2.02)	-6.303	<0.001*	
HDRS total score	2.14 (1.92)	5.11 (3.49)	-7.397	<0.001*	
FAST total score	3.74 (4.52)	25.18 (13.80)	-13.961	<0.001*	
	n (%)	**n (%)**	**X^2**	**p-value**	
Gender (female)	46 (63)	74 (53.6)	1.720	0.190	
Type of diagnostic					
BD I		85 (61.6)			
BD II		53 (38.4)			
Late onset		14 (11.3)			
Lifetime psychotic symptoms (yes)		67 (59.3)			
Catatonia		6 (5.6)			
Seasonal pattern		30 (28)			
Rapid Cycling		13 (12.2)			
Melancholic symptoms		41 (38.3)			
Atypical symptoms		36 (33.6)			
Psychotic Depression		25 (22.7)			
Suicide ideation (yes)		64 (56.1)			
Suicide attempts (yes)		23 (20.4)			
Somatic comorbidities (yes)	38 (62.3)	86 (75.4)	3.32	0.068	
Family history of psychiatric disorder (yes)	11 (19.3)	71 (69.6)	37.06	<0.001*	
Family history of affective disorder (yes)	10 (17.5)	62 (62)	28.9	<0.001*	
Family history of suicide attempts (yes)	4 (7)	22 (20.4)	5.01	0.025*	
Cognitive Composites*	**Mean (SD)**	**Mean(SD)**	**X^2**	**p-value**	
Attention	0.44 (0.09)	-0.24 (0.06)	64.35	<0.001*	7.56
Processing Speed	0.61 (0.08)	-0.33 (0.06)	107.97	<0.001*	11.75
Working Memory	0.40 (0.09)	-0.21 (0.07)	46.45	<0.001*	6.78
Visual Memory	0.52 (0.1)	-0.28 (0.08)	50.78	<0.001*	10
Verbal Memory	0.47 (0.10)	-0.25 (0.07)	48.82	<0.001*	7.2
Executive Functions	0.4 (0.07)	-0.21 (0.05)	71.99	<0.001*	8.71

BD I: Bipolar Disorder type I; BD II: Bipolar Disorder type II; FAST: Functioning Assessment Short Test; HC: Healthy Controls; HDRS: Hamilton Depression Rating Scale; IQ: Intelligence Quotient; OABD: Older Adults with Bipolar Disorder; YMRS: Young Mania Rating Scale;

*The differences between both groups in cognitive composites are adjusted by age.

Table

Table 3. Comparisons of neurocognitive performance between OABD clusters and HC

	HC (n=73)	Preserved group (PG) (n=58)	Mild group (MG) (n=63)	Severe group (SG) (n=15)	Statistical analysis		Post Hoc test applying Bonferroni correction					
		M(SD)	M(SD)	M(SD)	X^2	p-value	HC vs PG	HC vs MG	HC vs SG	PG vs MG	PG vs SG	MG vs SG
Attention	0.39 (0.06)	0.27 (0.07)	-0.15 (0.07)	-1.89 (0.16)	182.9	<0.001*	1	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Processing Speed	0.55 (0.06)	0.21 (0.07)	-0.47 (0.07)	-1.16 (0.16)	169.48	<0.001*	0.003*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Working Memory	0.34 (0.06)	0.30 (0.08)	-0.33 (0.07)	-0.74 (0.17)	71.34	<0.001*	1	<0.001*	<0.001*	<0.001*	<0.001*	0.134
Visual Memory	0.45 (0.08)	0.54 (0.10)	-0.56 (0.09)	-1.32 (0.21)	125.77	<0.001*	1	<0.001*	<0.001*	<0.001*	<0.001*	<0.003*
Verbal Memory	0.38 (0.08)	0.53 (0.10)	-0.61 (0.08)	-1.08 (0.21)	110.53	<0.001*	1	<0.001*	<0.001*	<0.001*	<0.001*	0.21
Executive Functions	0.31 (0.04)	0.26 (0.05)	-0.26 (0.05)	-1.21 (0.12)	181.95	<0.001*	1	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

HC: Healthy Controls; M: mean; OABD: Older Adults with Bipolar Disorder; SD: Standard deviation

Results are shown in z-scores adjusted by age, sex, years of education and IQ.

Conflict of interest

EV 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. NA has received CME-related financing from Janssen-Cilag, Lundbeck, Adamed, Pfizer and Boston Scientific, outside the submitted work. MV has received grants from Eli Lilly & Co.; and has served as a speaker for Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag, and Lundbeck.

Author Statement

Contributors

LM conceptualized the study and the design, with substantial contributions from the other authors. Neuropsychological assessment and extraction of data: LM. Interpretation of data, critical revision, intellectual contributions and study supervision: AM, AMA, BS, CMB, EJ, EV and CT. Substantial collaboration to participant's recruitment: AB, AM, AMA, EJ, EV, LM, MV and NA. Statistical analysis: LM and RG. Literature search and wrote de first draft: LM. All authors substantially participated in the final manuscript, which was reviewed, revised and approved by all authors.

Acknowledgments

Authors would like to thank the support of the Spanish Ministry of Science, the CIBER of Mental Health (CIBERSAM); the Comissionat per a Universitats I Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2017 1365), the CERCA Programme/Generalitat de Catalunya, and Instituto de Salud Carlos III for funding through the project PI20/00060 by the Spanish Ministry of Innovation and Science.

Role of the funding source

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

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Supplementary Material

S1.Axis III.docx

INTRODUCTION

Cognitive impairment is well recognized in young and middle-aged euthymic patients with bipolar disorder (BD), who typically may exhibit deficits in executive functions, verbal memory, attention and processing speed (Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007). Likewise, cognitive impairment is also prevalent in Older Adults with Bipolar Disorder (OABD) (Gildengers et al., 2004). Recent meta-analyses focused on OABD populations show large to moderate effect sizes of cognitive deficits in a large spectrum of cognitive domains, such as verbal memory, processing speed, attention, executive functions and working memory when compared to healthy controls (HC) (Samamé et al., 2013; Montejo et al., 2021, *in revision*). However, despite the identification of a concrete cognitive profile, the presence, prevalence and severity of cognitive impairment are notably heterogeneous among patients with BD (Martino et al., 2008). Moreover, substantial evidence points at a further cognitive variability between the young and middle-aged euthymic BD population, including both type I and II, demonstrating the existence of three clusters differentiated by the level of cognitive impairment. In fact, these groups are commonly distributed from preserved cognitive profile, to selective and then to globally impaired where approximately more than a half exhibit some level of cognitive impairment and nearly 1 of 3 patients remains cognitively intact (Burdick and Millett, 2021). When a cluster analysis approach was carried out in adult cohorts, three cognitive subgroups were detected: an intact group (40%) with similar cognitive performance to HC, a selective group (32%) with deficits in processing speed, attention and verbal memory and, a group with global deficits (29%) across many cognitive domains (Burdick et al., 2014). Others authors also found three cluster distribution in which a 30% of patients were cognitively impaired showing deficits in verbal memory, attention, executive function and language when compared with healthy controls (Martino et al., 2014). Similar cognitive variability was also detected when considering only patients with a diagnosis of BD type II (Solé et al., 2016). As far as we know, there is only one previous report focused on cognitive heterogeneity in OABD (Martino et al., 2018), which identified three subgroups: 33.3% of patients were cognitively intact, 36.4% showed selective deficits, and 30.3% exhibited global deficits.

Several clinical features related to illness severity (i.e. type of BD, number of mood episodes, presence of psychotic symptoms, number of admissions, age of onset) have been proposed as moderators of cognitive function and might potentially explain the variability among patients with BD (Bora, 2018). When compared to younger counterparts, OABD present specific features that need to be considered and which my potentially confound or augment cognitive impairment. Among these, greater somatic comorbidities, higher rates of

pharmacological treatment, longer duration of illness, age of onset, and reduced psychosocial functioning have a demonstrated effect on cognitive impairment (Murri et al., 2019; Dols and Beekman, 2020, 2018; Lewandowski et al., 2014; Rise et al., 2016). The study of these characteristics in OABD requires further examination based on empirical evidence in order to improve our understanding of possible unmet needs in this specific population.

The aims of the present study are: 1) to determine the existence of potential discrete cognitive profiles in a sample of OABD; 2) to detect the clinical and demographic variables associated with each cluster and 3) to identify clinical and demographic variables associated with the severity of cognitive impairment. We expect to find different cognitive subgroups according to the severity of the cognitive impairment.

METHODS

Participants

The sample for the present study belongs to an OABD cohort recruited from the Bipolar and Depressive Disorders Unit of Hospital Clinic of Barcelona. This unit belongs to a University Hospital and collaborates in the context of the Spanish Biomedical Research Networking Center on Mental Health (CIBERSAM) (Salagre et al., 2019). The inclusion criteria were: 1) diagnosis of BD type I or II according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR); 2) being euthymic or in partial remission for at least three months prior to inclusion to the study, defined as a score ≤14 in the Hamilton Depression Rating Scale (HDRS) and a score ≤ 10 in the Young Mania Rating Scale; 3) age ≥ 50 years old and 4) obtaining written informed consent. The exclusion criteria were: 1) estimated Intelligence Quotient ≤ 85; 2) presence of any Central Nervous System illnesses, different from psychiatric diagnosis, hampering neuropsychological performance; 3) had been treated with Electroconvulsive Therapy within the past 6 months.

A group of HC over the age of 50 without any psychiatric or neurologic condition was also included from a pool of volunteers. Volunteers were recruited by different non-probability sampling methods (convenience sampling, voluntary sampling and snowball procedure). A clinical interview based on the Structured Clinical Interview for DSM-IV-TR (First et al., 1997) was administered to all participants to determine the presence of any psychiatric diagnosis. The same exclusion criteria for the OABD sample were applied to the HC group.

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

Demographic, clinical and psychosocial functioning assessment

A semi-structured interview was conducted to collect several demographic and clinical factors: age, gender, number of years of education, type of diagnosis, total number of affective episodes, number of each type of episode, specifiers (catatonia, rapid cycling, atypical symptoms, season pattern, etc), age at onset, type of onset (early *vs* late; considering late onset when first episode occurred over 50 years (Depp and Jeste, 2004)), number of psychiatric admissions, years of illness duration, history of suicidal ideation and suicide attempts, lifetime history of psychotic symptoms, somatic comorbidities, family history of affective and psychiatric disorders, family history of suicidal behavior, and, finally, pharmacological treatment. The presence and severity of any depressive and manic symptoms were evaluated using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafafila, 1988) and the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978), respectively. Psychosocial functioning was evaluated by means of the Functioning Assessment Short Test (FAST) (Rosa et al., 2007).

Neuropsychological Assessment

A comprehensive neuropsychological battery was administered examining the following cognitive domains:

- Estimated intelligence quotient (IQ): the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997).
- Attention: Continuous Performance Test–II (CPT-II) version 5 (Conners and Staff, 2000) and the Trail Making Test-part A (TMT-A) (Reitan, 1958).
- Processing speed index: composed by the Digit-Symbol coding and the Symbol Search subtests of WAIS-III (Wechsler, 1997)
- Working memory: including Arithmetic, Digits and Letter-Number Sequencing subtests of the WAIS-III (Wechsler, 1997).
- Verbal learning and verbal memory: California Verbal Learning Test (CVLT) (Delis et al., 1988)
- Visual Memory: Rey-Osterrieth Complex Figure (ROCF) (Rey, 1997)
- Executive functions: Wisconsin Card Sorting Test (WCST) computerized version (Heaton, 1993), Stroop Color-Word Interference Test (SCWT) (Golden, 1978), Trail Making Test-part B (TMT-B) (Reitan, 1958), phonemic verbal fluency (FAS) and semantic verbal fluency (animal naming) components of the Control Oral Word Association test (COWAT) (Benton and Hamsher, 1978).

This compendium of test was set following the recommendations of the International Society of Bipolar Disorder for cognitive assessment in bipolar disorder (Yatham et al., 2010).

Statistical analysis

Initial analysis was conducted to compare demographic, clinical, psychosocial and cognitive variables between OABD and HC using t-test and X^2 test or Fisher's exact test, when appropriate. Neuropsychological variables using composite scores were established as the primary outcome. Patient's raw scores were transformed to *z-scale* score based on the values of the HC group. Composite scores were calculated for each cognitive domain. Thus, z-scores of the different test were summarized and averaged and were then classified in their corresponding cognitive domain. A total of six cognitive domains were calculated. The variables and subtest included in each cognitive domain were: 1) *attention:* the TMT-A total time score; omission, reaction time and reaction time standard error measures of the CPT-II; 2) *processing speed:* scores of the Digit-Symbol Coding and the Symbol Search subtests of the WAIS-III; 3) *working memory:* scores of Arithmetic, Digits and Letter-Number Sequencing subtests of the WAIS-III; 4) *verbal memory:* the total trials list A (1-5), short free recall, short cued recall, delayed free recall, and delayed cued recall scores of the CVLT-II; 5) *visual memory:* immediate recall of the ROCF; 6) *executive functions:* number of categories and perseverative errors of the WCST; the Interference score of the Stroop Test; TMT-B; the copy score of the ROCF; phonemic (FAS) and semantic (animals) verbal fluency of COWAT. The z-scores obtained from all variables of CPT-II, WCST perseverative errors, and TMT-A and TMT-B were reversed before calculating the composite scores since higher score indicates poorer performance. Missing values were imputed using principal component analysis (5.9% imputed). Effect sizes for cognitive scores between HC and OABD were calculated based on Glass's Delta statistic. A cluster analysis was conducted across patients. A K-means clustering algorithm was applied to determine the presence of *k* groups based on *n* observations to define the severity of the cognitive impairment. The number of clusters was determined using the elbow method based on the location of a bend in the plot. In cluster analysis, the elbow method is used to decide the number of clusters based on the explained variation and choosing the point where the curve visibly bends. Then, we added the HC group to set the reference group. Following this, a one-way ANOVA was carried out to explore the differences between clusters in terms of demographic, clinical, psychosocial functioning and cognitive composites. An ANCOVA adjusted by age, sex, years of education and estimated IQ was performed to assess the differences between cognitive domains by clusters. A Bonferroni post-hoc analysis was applied to determine the pairwise differences in all significant

demographic, clinical and cognitive variables when comparing HC with OABD cluster as well as within OABD clusters. Finally, a univariate logistic regression was carried out to explore the demographic and clinical factors associated with cognitive performance. Some variables that were significant in ANOVA analysis as well as those with clinical criteria to affect cognitive performance were analyzed. Statistical difference was set at $p < 0.05$. All analyses were performed using the IBM Statistical Package for Social Sciences version 22 (SPSS) and R 4.0.5 software.

RESULTS

Comparisons between OABD and HC

A total of 73 HC and 138 OABD (85 type I and 53 type II) over the age of 50 were included in this analysis. The characteristics of both groups are displayed in **table 1.** Regarding demographic variables, a significant difference between OABD and HC group was found in age ($p=0.028$), being slightly increased among the HC group. Clinical comparisons between both groups revealed significant differences in overall psychosocial functioning (total FAST score) ($p<0.001$) in which OABD exhibited a poorer functioning when compared to HC. Also, differences between both groups were found in HDRS ($p<0.001$) and YMRS scores ($p<0.001$), where OABD showed higher rates of depressive and hypomanic symptoms. OABD also exhibited more rates of history of suicidal ideation ($p<0.001$), prior suicide attempts ($p<0.001$), family history of psychiatric diagnosis ($p<0.001$), including affective disorder ($p<0.001$). When analyzing somatic comorbidities **(S1),** we detected higher rates of diabetes mellitus type 2 in the OABD group ($p=0.049$). Conversely, the HC group experienced a higher frequency of myocardial infarction ($p=0.006$).

Concerning neurocognition, a significant lower performance was found in the OABD group in all cognitive domains analyzed, that is, in attention ($p<0.001$), processing speed ($p<0.001$), working memory ($p<0.001$), verbal memory ($p<0.001$), visual memory ($p<0.001$) and executive functions ($p<0.001$). Moreover, large effect sizes were detected in all cognitive domains (from 6.78 to 11.75). Additionally, OABD presented lower estimated IQ compared to the HC group ($p=0.006$). No differences were detected concerning the remaining explored variables.

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Cluster Analysis

The elbow method and the visual inspection of the plot suggested the presence of three well distinguished clusters within OABD. Taking into account the severity of the cognitive impairment based on the z-scores compared with the HC group, OABD clusters were classified into three different groups: (1) a cognitively preserved group (PG) (n=58; 42%) characterized by a performance within the average range when compared with HC, (2) a second cluster (n=63; 46.4%) showing mild cognitive deficits (MG) and, finally (3) a group presenting an overall severe cognitive impairment (SG) (n=16; 11.6%) **(Figure 1).**

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Clinical and demographic characteristics by clusters and HC

There were no differences between clusters and HC in terms of gender. Significant differences were found in age across all groups ($p<0.001$) with the exception of the comparison of HC and MG **(table 2).** The SG was found to be the eldest (mean age=68.38; SD=8.11). In addition, differences in terms of years of education were also found between groups. However, post-hoc comparisons revealed that these differences were only significant when comparing the SG with PG ($p=0.003$) and with HC ($p=0.005$) where the SG had less years of education. There were also differences in estimated IQ ($p<0.001$); pairwise comparisons reflected differences between HC and PG with the mild and severe impaired clusters. The SG recorded a lower IQ score (mean 103.8; SD=12.67) while the HC and the preserved group achieved higher levels of IQ.

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Taking into consideration the affective symptoms we found differences between clusters and HC in terms of depressive and hypomanic symptoms in the HDRS ($p<0.001$) and YMRS ($p<0.001$) scales, respectively. In both cases it was the HC group who differed from all OABD clusters while no differences were found across OABD groups (means and standard deviations are displayed in table 2). As expected, OABD clusters exhibited higher depressive and hypomanic sub-threshold symptoms compared to HC. The performance in psychosocial functioning also displayed significant differences in all paired comparisons between groups ($p<0.001$) with the exception of the comparison between PG and MG. Again, the SG exhibited the lowest psychosocial functioning.

When only considering comparisons in clinical variables within the OABD clusters, the SG presented a higher number of psychiatric admissions compared to the MG ($p<0.001$) and the

PG (p<0.001). Moreover, no significant differences were found in total number of affective episodes, in type of BD, in the presence of psychotic symptoms across the lifespan and in disease specifiers (rapid cycling, season pattern, melancholic symptoms and, atypical symptoms). Although a statistical difference was found in catatonic symptoms (p=0.016) pairwise comparisons demonstrated no differences between clusters. Illness duration, measured as number of years of illness since the onset of the first episode until the current age, was not different between groups. However, the age of illness onset was statistically significant (p=0.035) showing differences between SG with PG (p = 0.035) and also with MG (p=0.04). Specifically, the SG had a later illness onset than the other two clusters (age mean: 42.67, SD: 20.06). Consequently, the late onset also displayed significant differences (p=0.019) between all groups, although differences group by group were not maintained in the pairwise comparison. Relative to pharmacological treatment, a large proportion of patients were currently in treatment with mood stabilizers, antipsychotics, antidepressant and anxiolytic, but no significant differences were detected within OABD clusters concerning any kind of treatment. ***Neurocognitive performance by clusters***

Table 3 summarizes the cognitive performance through the cognitive composites between all OABD and HC group expressed in z-scores after adjusting by age, sex, years of education and estimated IQ.

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Our results showed that patients of the preserved cluster (PG) were neurocognitively nearly intact (z-scores ranged from 0.26 to 0.54), showing a similar cognitive profile when compared to the HC group When applying Bonferroni correction, no statistical differences were found between the PG and HC groups in almost every cognitive domains assessed, such as attention, visual memory, verbal memory, executive functions and, working memory. Conversely, the PG exhibited significant lower performance in processing speed (p=0.003) compared to the HC group.

The second cluster, classified as mild cognitive deficits (MG), displayed intermediate cognitive scores with z-scores ranging between 0.15 and 0.61 below the average, therefore showing mild deficits across all cognitive domains. When compared with the HC group a statistically significant poorer performance was found in all cognitive domains (p<0.001). Furthermore, post-hoc pairwise comparison indicated significant differences across all cognitive composites when comparing with PG (p<0.001). However, when MG was compared

to SG the cognitive profile displayed no differences in verbal memory (p=0.21) and working memory (p=0.134) while differences were found in the other cognitive domains.

Finally, the third cluster (SG) was significantly impaired displaying deficits across all cognitive domains. The z-scores means ranged from 0.74 to 1.89 below the mean, thus, showing moderate to severe cognitive impairment. Within this group attention was the most affected cognitive domain (z-score= -1.89; p<0.001) and working memory the least impaired (z-score= -0.74; p<0.001). Likewise, we found neurocognitive differences in all cognitive domains when compared SG with patients of PG as well as with the HC group. **Figure 2** exemplifies the cognitive profile of all groups.

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Univariate logistic regressions between clusters

We also wanted to examine the potential factors that significantly contribute to distinguish between OABD patients from preserved cluster to mildly affected cluster as well as from mildly affected cluster to severely impaired. We introduced several demographic and clinical variables in a univariate logistic regression **(table 4).** We found that the predictors to mild impairment from preserved performance were an increased age (OR=1.14; p<0.001), less years of education (OR=0.86; p=0.01) and lower estimated IQ (OR=0.95; p=0.005). Regarding the outcomes explored to be differentiating the SG from the MG clusters results showed that, in terms of demographic variables, only older age emerged as significant (OR= 1.17; p=0.001) whereas a trend was found concerning years of education (OR=0.86; p= 0.063). In regards to clinical outcomes, late onset (OR= 4.76; p= 0.04) and higher number of psychiatric admissions (OR=1.43; p= 0.02) were significantly associated, that is, they were risk factors for cognitive impairment. Furthermore, low psychosocial functioning was also associated with higher cognitive impairment (OR= 1.11, p= 0.01). No further variables made a significant contribution to differences among clusters.

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DISCUSSION

To the best of our knowledge this is the first attempt, using a cluster analysis approach, to disentangle the heterogeneity of OABD in distinct neurocognitive profiles with prognostic implications. Our results provide substantial evidence regarding the possibility to stratify the

cognitive heterogeneity in OABD into different, neurocognitively defined subgroups. We identified three cognitive groups: a preserved group comparable to HC group in cognitive performance, a group exhibiting mild deficits in all cognitive domains and, finally, a group with moderate to severe cognitive impairment across all cognitive areas. In line with previous studies conducted on middle-aged BD cohorts, we also found three clusters differentiated by the severity of the cognitive impairment (Burdick et al., 2014; Jiménez et al., 2017; Martino et al., 2014, 2008; Solé et al., 2016). Regarding OABD, a cognitive heterogeneity has been previously detected identifying also three cognitive subgroups (Martino et al., 2018) but, instead of applying cluster analysis method they established subgroups based on z-scores.

Notably, comparing with other reports our groups also show a similar percentage distribution across subgroups. We observed that 42% of patients have a similar cognitive performance to HC presenting an almost preserved cognitive profile, except for the lower performance in processing speed compared to HC. It is previously estimated that approximately a half of the patients with BD have an intact cognitive function. Among the few previous study focused on OABD detected that, approximately 30% of OABD patients, did not show significant deficits (Martino et al., 2018). Similarly, Gildengers et al. (2004) reported that roughly 40% of patients remain cognitively preserved. The detection of this preserved group suggests that, despite having a BD diagnosis, there was a significant percentage of patients who demonstrates a similar cognitive performance in comparison to HC. This encouraging finding may have important clinical and research implications to promote the development of a framework focused on preventive intervention strategies also in OABD. Likewise, within the percentage of patients showing cognitive impairment, the literature provides evidence of a distribution in two groups depending on the level of cognitive impairment in terms of number of cognitive domains affected and the severity of the impairment (Burdick and Millett, 2021). We also found that most of the OABD patients were classified in the mildly impaired cluster while a lower percentage presented more severe cognitive impairment.

On the contrary, the main difference comparing our results with the younger cohorts lies in the intermediate group. In contrast to what reported in the aforementioned studies, while we found that the OABD intermediate group displayed deficits across all cognitive domains to a mild level of dysfunction, in other studies the intermediate group showed a selective impairment only in a few cognitive domains (i.e. processing speed, attention, verbal learning and delayed memory) (Burdick et al., 2014; Russo et al., 2017). When comparing the cognitive performance between the preserved cluster and the mild cluster it is worth highlighting the large quantitative difference in the number of cognitive domains altered. Additionally, the group with severe cognitive impairment showed deficits across all cognitive

domains but with a moderate to severe impairment compared to the preserved group and the HC. On the contrary, controlling by confounding variables, no differences were found in verbal memory and working memory when comparing to the mild impaired cluster, demonstrating that both clusters cannot be differentiated by the performance in these cognitive domains. Furthermore, our results indicate that in the mild and in the severe clusters all cognitive domains were affected when compared with the HC group. Analyzing the cognitive profile belonging to each cluster based on the z-scores, we observe that the mild impaired cluster exhibited more pronounced deficits in visual and verbal memory followed by processing speed, while the severe group exhibited remarkable deficits especially in attention, followed by visual memory, executive functions and processing speed domains. Overall, these findings enhances the question about why some patients exhibit cognitive deficits while others remain intact and also reinforce the need to explore both protective and risk factors for cognitive impairment in this specific group of patients.

In addition to these results on cognitive heterogeneity, we tried to explore the demographic and clinical outcomes associated with the severity of the cognitive impairment within OABD clusters as well as the protective factors associated with the preserved group. The univariate regression logistic analysis carried out to distinguish between the mild cluster and the severe cluster indicated that an older age, late onset, number of psychiatric admissions and, psychosocial functioning was the factors associated with higher cognitive impairment. On the contrary, the univariate logistic regression performed between the preserved and the mild impaired clusters showed that older age, fewer years of education and lower estimated IQ were correlates of mild cognitive impairment. That is, considering these last findings, it seems that the greater cognitive severity is explained by indicators of disease severity (such as number of admissions and an onset after the age of 50), while what is protecting the intact group to a mild impairment would be some factors related to cognitive reserve (such as educational level and IQ). These findings may reflect that at an early cognitive stage some components of cognitive reserve may be playing an important role in protecting against mild cognitive impairment. However, when cognitive impairment is more pronounced, the clinical indicators of disease severity have the greatest impact on hampering cognitive performance. Psychosocial functioning was significantly impaired across all clusters and it was also associated with higher cognitive impairment in the logistic regression analysis. The group exhibiting the poorest cognitive performance had also the lowest psychosocial functioning. This finding is in line with the link between neurocognition and functioning that has been widely documented across literature (Bonnín et al., 2010; Bonnín et al., 2019; Martinez-Aran et al., 2007; Sanchez-Moreno et al., 2018; Solé et al., 2018) indicating greater difficulties in

psychosocial functioning as cognitive impairment increases. Moreover, since we detected a distribution of the cognitive deficits across all cognitive domains, and even with mild impairment, it is expected that the impact on psychosocial functioning will be greater than when only a few domains are affected. Likewise, the cognitive heterogeneity could be considered as a predictor of psychosocial functioning in BD patients (Burdick & Millett, 2021). However, the direction of the relationship between neurocognition and functioning could be also reciprocal and interrelated; thus, to modify the performance in psychosocial functioning could promote changes in neurocognition. Thus, it is important to pay special attention to patient's functioning in their daily activities even in OABD not only to estimate the cognitive performance but also for the assessment of relevance or need for implementing interventions in order to improve it. It is also necessary to apply functional remediation program (Torrent et al., 2013) extending the age range and including OABD, but adapting the program in order to personalize sessions to late stages (Salagre et al., 2018). This finding based on the cognitive clusters, which are very informative of heterogeneity, opens an opportunity for the design of personalized treatments adapted to the cognitive profile.

There is evidence supporting that cognitive dysfunction in BD seems to be negatively associated with specific illness factors such as number of episodes, subtype of diagnosis, number of hospitalizations, illness duration, history of psychotic symptoms, among others (Bora, 2018; Bora et al., 2010; Cardoso et al., 2015; Mann-Wrobel et al., 2011; Switalska, 2013). Specifically in OABD, a recent study (Beunders et al., 2021) identified that having five or more hospitalizations, a higher number of depressive episodes and later illness onset were factors associated with a worse cognitive performance. Similarly, Murri et al., (2019) explored several clinical risk factors for cognitive dysfunction in late-life BD and identified older age, fewer years of education, late onset and older age at onset as contributing variables. Furthermore, in our study, we observed that the number of years of education decreased as the severity of cognitive impairment increased, as shown in the differences between the higher cognitively impaired group with the preserved group and with the HC. In this sense, it should be pointed out that educational level is considered as a main contributing component to cognitive reserve as well as the IQ (Amoretti and Ramos-Quiroga, 2021; Stern, 2009). The cognitive reserve plays an important role as a protective factor against cognitive decline (Stern, 2009). Although it has only been studied in middle-aged samples, the cognitive reserve has been proposed as a moderator of cognitive performance in BD (Grande et al., 2017). Specifically, it has been hypothesized that having a diagnosis of BD may hinder the performance of activities that are considered to increase cognitive reserve (leisure activities, educational level, etc.) and this could explain partially the cognitive variability (Tsapekos et al.,

2020). Hence, our finding highlights the important role that cognitive reserve plays on cognitive function in OABD and research is warranted to explore this further. Concerning demographic variables we found that age was a critical factor associated with neurocognitive impairment. In line with this finding, Lewandowski et al., 2014 described the influence of older age on cognitive performance in a sample of BD I; specifically, they found a poor performance on processing speed in the geriatric population in comparison to their healthy peers. Furthermore, it has been suggested that BD illness produces accelerated aging (Rizzo et al., 2014).

Equally, the univariate logistic regression analysis also highlighted an association of late onset with the severity of cognitive impairment. The severally impaired group was the group with later illness onset revealing that this group was partially composed of a late-onset percentage of subjects. The literature supports that late-onset BD patients present higher cognitive impairment than those whose illness emerged earlier (Martino et al., 2013; Schouws et al., 2009),. Studies have detected a greater presence of medical and neurological burden in late-onset BD patients (Schouws et al., 2010; Vasudev and Thomas, 2010) as well as more signs of cerebrovascular disease than HC and early-onset patients (Ramírez-Bermúdez et al., 2021) which may be increasing the magnitude of the cognitive deterioration. Therefore, it is postulated that it may be a disease with a differentiated etiology (Dols and Beekman, 2020; Ljubic et al., 2021). Thus, this result could be reflecting a bias towards a greater cognitive impairment.

As previously mentioned, the number of psychiatric admissions was also associated with the severity of cognitive dysfunction. The relationship between the number of hospitalizations and cognitive impairment was expected since the number of hospitalizations is a marker of the severity of the illness and, in turn, is related to cognitive dysfunction. Furthermore, the higher number of hospitalizations could indicate a greater severity of episodes (both depressive and manic), possibly a greater recurrence of episodes, longer episode duration and, consequently, a reduction in the inter-episodes recovery. Certainly, all these illness-related events may impact on the preservation of the cognitive status. Previous reports (Cardoso et al., 2015; Kessing & Andersen, 2004) supported that a larger number of episodes was related to higher cognitive impairment in terms of neurocognitive decline. On the contrary, another study did not find evidence supporting the association between increased number of episodes and an increased risk of cognitive decline (Martino et al., 2013). Our results partially comport with previous studies focused on OABD by identifying almost the same clinical factors associated with cognitive function such as number of episodes, number of admissions, later age at illness onset in OABD (Beunders et al., 2021; Martino et al., 2018) and

also cognitive reserve as a protective factor. In summary, our results reinforce that the heterogeneity can be classified into well-defined groups, which has important prognostic implications as it helps to define the characteristics of each group and also to design appropriate intervention strategies. Therapeutic approaches focused in clinical and demographic modifiable factors should be considered as a preventive treatment against both cognitive and functioning impairment. In that sense, interventions to enhance some modifiable factors of cognitive reserve have been designed (de la Serna et al., 2021) and could be useful to apply in order to anticipate the appearance of a cognitive decline.

This study has a number of limitations which must be mentioned. First, the small sample size of the SG cluster suggests that results must be interpreted with caution. A larger sample size would have allowed us to make more generalized and solid conclusions. As a result of the small sample for each variable of interest, especially in the SG cluster, we could not carry out multiple logistic regressions; hence, the results of the univariate regressions analysis are limited. Secondly, despite fulfilling older age criteria, the mean age of our patients was relatively young, thus limiting the generalizability of our results to eldest population. Third, the late-onset group could be skewing the magnitude of the cognitive impairment, especially in the severely impaired group which was composed of a high percentage of these subjects due to the small sample size of that group. Finally, the potential confounding variables that could be influence cognitive performance such as pharmacological treatment and comorbid psychiatric disorder were not controlled in the analysis.

To conclude, this is the first study to detect heterogeneous subgroups in a euthymic OABD sample using a cluster method analysis as well as to identify specific factors associated with higher cognitive impairment. Our results, in line to what observed in younger cohorts, indicate that cognitive variability is still present in OABD patients. These findings highlight that cognitive heterogeneity in OABD could be organized in distinguishable clusters, thus, having outstanding clinical and functional implications. The potential value of this analysis is that it illustrates the specific demographic and clinical characteristics of each group. Understanding the cognitive heterogeneity in late ages of BD may have important clinical implications. It could be useful not only to identify underlying mechanisms of cognitive impairment but also to develop treatment strategies adjusted to patient's level impairment and, importantly, to apply preventive strategies against cognitive decline. Further studies are needed to explore the relationship between the specific clinical factors and cognitive dysfunction in OABD.

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INTRODUCTION

Cognitive impairment is well recognized in young and middle-aged euthymic patients with bipolar disorder (BD), who typically may exhibit deficits in executive functions, verbal memory, attention and processing speed (Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007). Likewise, cognitive impairment is also prevalent in Older Adults with Bipolar Disorder (OABD) (Gildengers et al., 2004). Recent meta-analyses focused on OABD populations show large to moderate effect sizes of cognitive deficits in a large spectrum of cognitive domains, such as verbal memory, processing speed, attention, executive functions and working memory when compared to healthy controls (HC) (Samamé et al., 2013; Montejo et al., 2021, *in revision*). However, despite the identification of a concrete cognitive profile, the presence, prevalence and severity of cognitive impairment are notably heterogeneous among patients with BD (Martino et al., 2008). Moreover, substantial evidence points at a further cognitive variability between the young and middle-aged euthymic BD population, including both type I and II, demonstrating the existence of three clusters differentiated by the level of cognitive impairment. In fact, these groups are commonly distributed from preserved cognitive profile, to selective and then to globally impaired where approximately more than a half exhibit some level of cognitive impairment and nearly 1 of 3 patients remains cognitively intact (Burdick and Millett, 2021). When a cluster analysis approach was carried out in adult cohorts, three cognitive subgroups were detected: an intact group (40%) with similar cognitive performance to HC, a selective group (32%) with deficits in processing speed, attention and verbal memory and, a group with global deficits (29%) across many cognitive domains (Burdick et al., 2014). Others authors also found three cluster distribution in which a 30% of patients were cognitively impaired showing deficits in verbal memory, attention, executive function and language when compared with healthy controls (Martino et al., 2014). Similar cognitive variability was also detected when considering only patients with a diagnosis of BD type II (Solé et al., 2016). As far as we know, there is only one previous report focused on cognitive heterogeneity in OABD (Martino et al., 2018), which identified three subgroups: 33.3% of patients were cognitively intact, 36.4% showed selective deficits, and 30.3% exhibited global deficits.

Several clinical features related to illness severity (i.e. type of BD, number of mood episodes, presence of psychotic symptoms, number of admissions, age of onset) have been proposed as moderators of cognitive function and might potentially explain the variability among patients with BD (Bora, 2018). When compared to younger counterparts, OABD present specific features that need to be considered and which my potentially confound or augment cognitive impairment. Among these, greater somatic comorbidities, higher rates of

pharmacological treatment, longer duration of illness, age of onset, and reduced psychosocial functioning have a demonstrated effect on cognitive impairment (Murri et al., 2019; Dols and Beekman, 2020, 2018; Lewandowski et al., 2014; Rise et al., 2016). The study of these characteristics in OABD requires further examination based on empirical evidence in order to improve our understanding of possible unmet needs in this specific population.

The aims of the present study ~~is~~ are: 1) to determine the existence of potential discrete cognitive profiles in a sample of OABD~~; , as well as~~ 2) to detect ~~those~~ the clinical and demographic variables associated with each ~~of them~~cluster and 3) to identify clinical and demographic variables associated with the severity of cognitive impairment. We expect to find different cognitive subgroups according to the severity of the cognitive impairment.

METHODS

Participants

The sample for the present study belongs to an OABD cohort ~~Patients were~~ recruited from the Bipolar and Depressive Disorders Unit of Hospital Clinic of Barcelona. This unit belongs to a University Hospital and collaborates in the context of the Spanish Biomedical Research Networking Center on Mental Health (CIBERSAM) (Salagre et al., 2019). The inclusion criteria were: 1) diagnosis of BD type I or II according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR); 2) being euthymic or in partial remission for at least three months prior to inclusion to the study, defined as a score ≤14 in the Hamilton Depression Rating Scale (HDRS) and a score ≤ 10 in the Young Mania Rating Scale; 3) age ≥ 50 years old and 4) obtaining written informed consent. The exclusion criteria were: 1) estimated Intelligence Quotient ≤ 85; 2) presence of any Central Nervous System illnesses, different from psychiatric diagnosis, hampering neuropsychological performance; 3) had been treated with Electroconvulsive Therapy within the past 6 months.

A group of HC over the age of 50 without any psychiatric or neurologic condition was also included from a pool of volunteers. Volunteers were recruited by different non-probability sampling methods (convenience sampling, voluntary sampling and snowball procedure). A clinical interview based on the Structured Clinical Interview for DSM-IV-TR (First et al., 1997) was administered to all participants to determine the presence of any psychiatric diagnosis. The same exclusion criteria for the OABD sample were applied to the HC group.

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

Demographic, clinical and psychosocial functioning assessment

A semi-structured interview was conducted to collect several demographic and clinical factors: age, gender, number of years of education, type of diagnosis, total number of affective episodes, number of each type of episode, specifiers (catatonia, rapid cycling, atypical symptoms, season pattern, etc), age at onset, type of onset (early *vs* late; considering late onset when first episode occurred over 50 years (Depp and Jeste, 2004)), number of psychiatric admissions, years of illness duration, history of suicidal ideation and suicide attempts, lifetime history of psychotic symptoms, somatic comorbidities, family history of affective and psychiatric disorders, family history of suicidal behavior, and, finally, pharmacological treatment. The presence and severity of any depressive and manic symptoms were evaluated using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafafila, 1988) and the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978), respectively. Psychosocial functioning was evaluated by means of the Functioning Assessment Short Test (FAST) (Rosa et al., 2007).

Neuropsychological Assessment

A comprehensive neuropsychological battery was administered examining the following cognitive domains:

- Estimated intelligence quotient (IQ): the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997).
- Attention: Continuous Performance Test–II (CPT-II) version 5 (Conners and Staff, 2000) and the Trail Making Test-part A (TMT-A) (Reitan, 1958).
- Processing speed index: composed by the Digit-Symbol coding and the Symbol Search subtests of WAIS-III (Wechsler, 1997)
- Working memory: including Arithmetic, Digits and Letter-Number Sequencing subtests of the WAIS-III (Wechsler, 1997).
- Verbal learning and verbal memory: California Verbal Learning Test (CVLT) (Delis et al., 1988)
- Visual Memory: Rey-Osterrieth Complex Figure (ROCF) (Rey, 1997)
- Executive functions: Wisconsin Card Sorting Test (WCST) computerized version (Heaton, 1993), Stroop Color-Word Interference Test (SCWT) (Golden, 1978), Trail Making Test-part B (TMT-B) (Reitan, 1958), phonemic verbal fluency (FAS) and semantic verbal fluency (animal naming) components of the Control Oral Word Association test (COWAT) (Benton and Hamsher, 1978).

This compendium of test was set following the recommendations of the International Society of Bipolar Disorder for cognitive assessment in bipolar disorder (Yatham et al., 2010).

Statistical analysis

Initial analysis was conducted to compare demographic, clinical, psychosocial and cognitive variables between OABD and HC using t-test and X^2 test or Fisher's exact test, when appropriate. Neuropsychological variables using composite scores were established as the primary outcome. Patient's raw scores were transformed to *z-scale* score based on the values of the HC group. Composite scores were calculated for each cognitive domain. Thus, z-scores of the different test were summarized and averaged and were then classified in their corresponding cognitive domain. A total of six cognitive domains were calculated. The variables and subtest included in each cognitive domain were: 1) *attention:* the TMT-A total time score; omission, reaction time and reaction time standard error measures of the CPT-II; 2) *processing speed:* scores of the Digit-Symbol Coding and the Symbol Search subtests of the WAIS-III; 3) *working memory:* scores of Arithmetic, Digits and Letter-Number Sequencing subtests of the WAIS-III; 4) *verbal memory:* the total trials list A (1-5), short free recall, short cued recall, delayed free recall, and delayed cued recall scores of the CVLT-II; 5) *visual memory:* immediate recall of the ROCF; 6) *executive functions:* number of categories and perseverative errors of the WCST; the Interference score of the Stroop Test; TMT-B; the copy score of the ROCF; phonemic (FAS) and semantic (animals) verbal fluency of COWAT. The z-scores obtained from all variables of CPT-II, WCST perseverative errors, and TMT-A and TMT-B were reversed before calculating the composite scores since higher score indicates poorer performance. Missing values were imputed using principal component analysis (5.9% imputed). Effect sizes for cognitive scores between HC and OABD were calculated based on Glass's Delta statistic. A cluster analysis was conducted across patients. A K-means clustering algorithm was applied to determine the presence of *k* groups based on *n* observations to define the severity of the cognitive impairment. The number of clusters was determined using the elbow method based on the location of a bend in the plot. In cluster analysis, the elbow method is used to decide the number of clusters based on the explained variation and choosing the point where the curve visibly bends. Then, we added the HC group to set the reference group. Following this, a one-way ANOVA was carried out to explore the differences between clusters in terms of demographic, clinical, psychosocial functioning and cognitive composites. An ANCOVA adjusted by age, sex, years of education and estimated IQ was performed to assess the differences between cognitive domains by clusters. A Bonferroni post-hoc analysis was applied to determine the pairwise differences in all significant

demographic, clinical and cognitive variables when comparing HC with OABD cluster as well as within OABD clusters. Finally, a univariate logistic regression was carried out to explore the demographic and clinical factors associated with cognitive performance. Some variables that were significant in ANOVA analysis as well as those with clinical criteria to affect cognitive performance were analyzed. Statistical difference was set at $p < 0.05$. All analyses were performed using the IBM Statistical Package for Social Sciences version 22 (SPSS) and R 4.0.5 software.

RESULTS

Comparisons between OABD and HC

A total of 73 HC and 138 OABD (85 type I and 53 type II) over the age of 50 were included in this analysis. The characteristics of both groups are displayed in **table 1.** Regarding demographic variables, a significant difference between OABD and HC group was found in age ($p=0.028$), being slightly increased among the HC group. Clinical comparisons between both groups revealed significant differences in overall psychosocial functioning (total FAST score) ($p<0.001$) in which OABD exhibited a poorer functioning when compared to HC. Also, differences between both groups were found in HDRS ($p<0.001$) and YMRS scores ($p<0.001$), where OABD showed higher rates of depressive and hypomanic symptoms. OABD also exhibited more rates of history of suicidal ideation ($p<0.001$), prior suicide attempts ($p<0.001$), family history of psychiatric diagnosis ($p<0.001$), including affective disorder ($p<0.001$). When analyzing somatic comorbidities **(S1),** we detected higher rates of diabetes mellitus type 2 in the OABD group ($p=0.049$). Conversely, the HC group experienced a higher frequency of myocardial infarction ($p=0.006$).

Concerning neurocognition, a significant lower performance was found in the OABD group in all cognitive domains analyzed, that is, in attention ($p<0.001$), processing speed ($p<0.001$), working memory ($p<0.001$), verbal memory ($p<0.001$), visual memory ($p<0.001$) and executive functions ($p<0.001$). Moreover, large effect sizes were detected in all cognitive domains (from 6.78 to 11.75). Additionally, OABD presented lower estimated IQ compared to the HC group ($p=0.006$). No differences were detected concerning the remaining explored variables.

----------INSERT TAB. 1 ABOUT HERE----------

Cluster Analysis

The elbow method and the visual inspection of the plot suggested the presence of three well distinguished clusters within OABD. Taking into account the severity of the cognitive impairment based on the z-scores compared with the HC group, OABD clusters were classified into three different groups: (1) a cognitively preserved group (PG) (n=58; 42%) characterized by a performance within the average range when compared with HC, (2) a second cluster (n=63; 46.4%) showing mild cognitive deficits (MG) and, finally (3) a group presenting an overall severe cognitive impairment (SG) (n=16; 11.6%) **(Figure 1).**

----------INSERT FIG.1 ABOUT HERE ----------

Clinical and demographic characteristics by clusters and HC

There were no differences between clusters and HC in terms of gender. Significant differences were found in age across all groups ($p<0.001$) with the exception of the comparison of HC and MG **(table 2).** The SG was found to be the eldest (mean age=68.38; SD=8.11). In addition, differences in terms of years of education were also found between groups. However, post-hoc comparisons revealed that these differences were only significant when comparing the SG with PG ($p=0.003$) and with HC ($p=0.005$) where the SG had less years of education. There were also differences in estimated IQ ($p<0.001$); pairwise comparisons reflected differences between HC and PG with the mild and severe impaired clusters. The SG recorded a lower IQ score (mean 103.8; SD=12.67) while the HC and the preserved group achieved higher levels of IQ.

----------INSERT TAB. 2 ABOUT HERE----------

Taking into consideration the affective symptoms we found differences between clusters and HC in terms of depressive and hypomanic symptoms in the HDRS ($p<0.001$) and YMRS ($p<0.001$) scales, respectively. In both cases it was the HC group who differed from all OABD clusters while no differences were found across OABD groups (means and standard deviations are displayed in table 2). As expected, OABD clusters exhibited higher depressive and hypomanic sub-threshold symptoms compared to HC. The performance in psychosocial functioning also displayed significant differences in all paired comparisons between groups ($p<0.001$) with the exception of the comparison between PG and MG. Again, the SG exhibited the lowest psychosocial functioning.

When only considering comparisons in clinical variables within the OABD clusters, the SG presented a higher number of psychiatric admissions compared to the MG ($p<0.001$) and

the PG (p<0.001). Moreover, no significant differences were found in total number of affective episodes, in type of BD, in the presence of psychotic symptoms across the lifespan and in disease specifiers (rapid cycling, season pattern, melancholic symptoms and, atypical symptoms). Although a statistical difference was found in catatonic symptoms (p=0.016) pairwise comparisons demonstrated no differences between clusters. Illness duration, measured as number of years of illness since the onset of the first episode until the current age, was not different between groups. However, the age of illness onset was statistically significant (p=0.035) showing differences between SG with PG (p = 0.035) and also with MG (p=0.04). Specifically, the SG had a later illness onset than the other two clusters (age mean: 42.67, SD: 20.06). Consequently, the late onset also displayed significant differences (p=0.019) between all groups, although differences group by group were not maintained in the pairwise comparison. Relative to pharmacological treatment, a large proportion of patients were currently in treatment with mood stabilizers, antipsychotics, antidepressant and anxiolytic, but no significant differences were detected within OABD clusters concerning any kind of treatment.

Neurocognitive performance by clusters

~~Since age, sex and educational level were found to be significant between groups, an ANCOVA analysis adjusted by age and years of education was carried out.~~ **Table 3** summarizes the cognitive performance through the cognitive composites between all OABD and HC group expressed in z-scores after adjusting by age, sex, years of education and estimated IQ.

----------INSERT TAB. 3 ABOUT HERE ----------

Our results showed that patients of the preserved cluster (PG) were neurocognitively nearly intact (z-scores ranged from 0.26 to 0.54), showing a similar cognitive profile when compared to the HC group ~~(z-scores ranged from 0.24 to 0.56).~~ When applying Bonferroni correction, no statistical differences were found between the PG and HC groups in almost every cognitive domains assessed, such as attention, visual memory, verbal memory, executive functions and, working memory. Conversely, the PG exhibited significant lower performance in processing speed (p=0.00~~5~~3) compared to the HC group.

The second cluster, classified as mild cognitive deficits (MG), displayed intermediate cognitive scores with z-scores ranging between 0.15 and 0.6~~3~~1 below the average, therefore showing mild deficits across all cognitive domains. When compared with the HC group a statistically significant poorer performance was found in all cognitive domains (p<0.001).

Furthermore, post-hoc pairwise comparison indicated significant differences across all cognitive composites when comparing with PG ~~and SG groups~~ (p<0.001). However, when MG was compared to SG the cognitive profile displayed no differences in ~~-~~verbal memory (p=0.21) and working memory (p=0.134) while differences were found in the other cognitive domains.

Finally, the third cluster (SG) was significantly impaired displaying deficits across all cognitive domains. The z-scores means ranged from ~~1.24~~0.74 to ~~2.11~~1.89 below the mean, thus, showing moderate to severe cognitive impairment. Within this group attention was the most affected cognitive domain (z-score= ~~-2.11~~1.89; p<0.001) and working memory the least impaired (z-score= -0.74~~1.24~~; p<0.001). Likewise, we found neurocognitive differences in all cognitive domains when compared SG with patients of PG ~~and MG groups~~ as well as with the HC group. **Figure 2** exemplifies the cognitive profile of all groups.

----------INSERT FIG.2 ABOUT HERE ----------

Univariate logistic regressions between clusters

We also wanted to examine the potential factors that significantly contribute to distinguish between OABD patients from preserved cluster to mildly affected cluster as well as from mildly affected cluster to severely impaired. We introduced several demographic and clinical variables in a univariate logistic regression **(table 4).** We found that the predictors to mild impairment from preserved performance were an increased age (OR=1.14; p<0.001), less years of education (OR=0.86; p=0.01) and lower estimated IQ (OR=0.95; p=0.005). Regarding the outcomes explored to be differentiating the SG from the MG clusters results showed that, in terms of demographic variables, only older age emerged as significant (OR= 1.17; p=0.001) whereas a trend was found concerning years of education (OR=0.86; p= 0.063). In regards to clinical outcomes, late onset (OR= 4.76; p= 0.04) and higher number of psychiatric admissions (OR=1.43; p= 0.02) were significantly associated, that is, they were risk factors for cognitive impairment. Furthermore, low psychosocial functioning was also associated with higher cognitive impairment (OR= 1.11, p= 0.01). No further variables made a significant contribution to differences among clusters.

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DISCUSSION

To the best of our knowledge this is the first attempt, using a cluster analysis approach, to disentangle the heterogeneity of OABD in distinct neurocognitive profiles with prognostic implications. Our results provide substantial evidence regarding the possibility to stratify the cognitive heterogeneity in OABD into different, neurocognitively defined subgroups. We identified three cognitive groups: a preserved group comparable to HC group in cognitive performance, a group exhibiting mild deficits in all cognitive domains and, finally, a group with moderate to severe cognitive impairment across all cognitive areas. In line with previous studies conducted on middle-aged BD cohorts, we also found three clusters differentiated by the severity of the cognitive impairment (Burdick et al., 2014; Jiménez et al., 2017; Martino et al., 2014, 2008; Solé et al., 2016). Regarding OABD, a cognitive heterogeneity has been previously detected identifying also three cognitive subgroups (Martino et al., 2018) but, instead of applying cluster analysis method they established subgroups based on z-scores.

Notably, comparing with other reports our groups also show a similar percentage distribution across subgroups. We observed that 42% of patients have a similar cognitive performance to HC presenting an almost preserved cognitive profile, except for the lower performance in processing speed compared to HC. It is previously estimated that approximately a half of the patients with BD have an intact cognitive function. Among the few previous study focused on OABD detected that, approximately 30% of OABD patients, did not show significant deficits (Martino et al., 2018). Similarly, Gildengers et al. (2004) reported that roughly 40% of patients remain cognitively preserved. The detection of this preserved group suggests that, despite having a BD diagnosis, there was a significant percentage of patients who demonstrates a similar cognitive performance in comparison to HC. This encouraging finding may have important clinical and research implications to promote the development of a framework focused on preventive intervention strategies also in OABD. Likewise, within the percentage of patients showing cognitive impairment, the literature provides evidence of a distribution in two groups depending on the level of cognitive impairment in terms of number of cognitive domains affected and the severity of the impairment (Burdick and Millett, 2021). We also found that most of the OABD patients were classified in the mildly impaired cluster while a lower percentage presented more severe cognitive impairment.

On the contrary, the main difference comparing our results with the younger cohorts lies in the intermediate group. In contrast to what reported in the aforementioned studies, while we found that the OABD intermediate group displayed deficits across all cognitive domains to a mild level of dysfunction, in other studies the intermediate group showed a selective impairment only in a few cognitive domains (i.e. processing speed, attention, verbal learning and delayed memory) (Burdick et al., 2014; Russo et al., 2017). When comparing the

cognitive performance between the preserved cluster and the mild cluster it is worth highlighting the large quantitative difference in the number of cognitive domains altered. Additionally, the group with severe cognitive impairment showed deficits across all cognitive domains but with a moderate to severe impairment compared to the ~~other clusters~~preserved group -and the HC. On the contrary, controlling by confounding variables, no differences were found in verbal memory and working memory when comparing to the mild impaired cluster, demonstrating that both clusters cannot be differentiated by the performance in these cognitive domains. Furthermore, our results indicate that in the mild and in the severe clusters all cognitive domains were affected when compared with the HC group. Analyzing the cognitive profile belonging to each cluster based on the z-scores, we observe that the mild impaired cluster exhibited more pronounced deficits in visual and verbal memory followed by processing speed, while the severe group exhibited remarkable deficits especially in attention, followed by visual memory, executive functions and processing speed domains. Overall, these findings enhances the question about why some patients exhibit cognitive deficits while others remain intact and also reinforce the need to explore both protective and risk factors for cognitive impairment in this specific group of patients.

In addition to these results on cognitive heterogeneity, we tried to explore the demographic and clinical outcomes associated with the severity of the cognitive impairment within OABD clusters as well as the protective factors associated with the preserved group. The univariate regression logistic analysis carried out to distinguish between the mild cluster and the severe cluster indicated that an older age, late onset, number of psychiatric admissions and, psychosocial functioning was the factors associated with higher cognitive impairment. On the contrary, the univariate logistic regression performed between the preserved and the mild impaired clusters showed that older age, fewer years of education and lower estimated IQ were correlates of mild cognitive impairment. That is, considering these last findings, it seems that the greater cognitive severity is explained by indicators of disease severity (such as number of admissions and an onset after the age of 50), while what is protecting the intact group to a mild impairment would be some factors related to cognitive reserve (such as educational level and IQ). These findings may reflect that at an early cognitive stage some components of cognitive reserve may be playing an important role in protecting against mild cognitive impairment. However, when cognitive impairment is more pronounced, the clinical indicators of disease severity have the greatest impact on hampering cognitive performance. Psychosocial functioning was significantly impaired across all clusters and it was also associated with higher cognitive impairment in the logistic regression analysis. The group exhibiting the poorest cognitive performance had also the lowest psychosocial functioning.

This finding is in line with the link between neurocognition and functioning that has been widely documented across literature (Bonnín et al., 2010; Bonnín et al., 2019; Martinez-Aran et al., 2007; Sanchez-Moreno et al., 2018; Solé et al., 2018) indicating greater difficulties in psychosocial functioning as cognitive impairment increases. Moreover, since we detected a distribution of the cognitive deficits across all cognitive domains, and even with mild impairment, it is expected that the impact on psychosocial functioning will be greater than when only a few domains are affected. Likewise, the cognitive heterogeneity could be considered as a predictor of psychosocial functioning in BD patients (Burdick & Millett, 2021). However, the direction of the relationship between neurocognition and functioning could be also reciprocal and interrelated; thus, to modify the performance in psychosocial functioning could promote changes in neurocognition. Thus, it is important to pay special attention to patient's functioning in their daily activities even in OABD not only to estimate the cognitive performance but also for the assessment of relevance or need for implementing interventions in order to improve it. It is also necessary to apply functional remediation program (Torrent et al., 2013) extending the age range and including OABD, but adapting the program in order to personalize sessions to late stages (Salagre et al., 2018). This finding based on the cognitive clusters, which are very informative of heterogeneity, opens an opportunity for the design of personalized treatments adapted to the cognitive profile.

There is evidence supporting that cognitive dysfunction in BD seems to be negatively associated with specific illness factors such as number of episodes, subtype of diagnosis, number of hospitalizations, illness duration, history of psychotic symptoms, among others (Bora, 2018; Bora et al., 2010; Cardoso et al., 2015; Mann-Wrobel et al., 2011; Switalska, 2013). Specifically in OABD, a recent study (Beunders et al., 2021) identified that having five or more hospitalizations, a higher number of depressive episodes and later illness onset were factors associated with a worse cognitive performance. Similarly, Murri et al., (2019) explored several clinical risk factors for cognitive dysfunction in late-life BD and identified older age, fewer years of education, late onset and older age at onset as contributing variables. Furthermore, in our study, we observed that the number of years of education decreased as the severity of cognitive impairment increased, as shown in the differences between the higher cognitively impaired group with the preserved group and with the HC. In this sense, it should be pointed out that educational level is considered as a main contributing component to cognitive reserve as well as the IQ (Amoretti and Ramos-Quiroga, 2021; Stern, 2009). The cognitive reserve plays an important role as a protective factor against cognitive decline (Stern, 2009). Although it has only been studied in middle-aged samples, the cognitive reserve has been proposed as a moderator of cognitive performance in BD (Grande et al., 2017).

Specifically, it has been hypothesized that having a diagnosis of BD may hinder the performance of activities that are considered to increase cognitive reserve (leisure activities, educational level, etc.) and this could explain partially the cognitive variability (Tsapekos et al., 2020). Hence, our finding highlights the important role that cognitive reserve plays on cognitive function in OABD and research is warranted to explore this further. Concerning demographic variables we found that age was a critical factor associated with neurocognitive impairment. In line with this finding, Lewandowski et al., 2014 described the influence of older age on cognitive performance in a sample of BD I; specifically, they found a poor performance on processing speed in the geriatric population in comparison to their healthy peers. Furthermore, it has been suggested that BD illness produces accelerated aging (Rizzo et al., 2014).

Equally, the univariate logistic regression analysis also highlighted an association of late onset with the severity of cognitive impairment. The severally impaired group was the group with later illness onset revealing that this group was partially composed of a late-onset percentage of subjects. The literature supports that late-onset BD patients present higher cognitive impairment than those whose illness emerged earlier (Martino et al., 2013; Schouws et al., 2009), ~~thus, this result could be reflecting a bias towards a greater cognitive impairment~~. Studies have detected a greater presence of medical and neurological burden in late-onset BD patients (Schouws et al., 2010; Vasudev and Thomas, 2010) as well as more signs of cerebrovascular disease than HC and early-onset patients (Ramírez-Bermúdez et al., 2021) which may be increasing the magnitude of the cognitive deterioration. Therefore, it is postulated that it may be a disease with a differentiated etiology (Dols and Beekman, 2020; Ljubic et al., 2021). Thus, this result could be reflecting a bias towards a greater cognitive impairment.

As previously mentioned, the number of psychiatric admissions was also associated with the severity of cognitive dysfunction. The relationship between the number of hospitalizations and cognitive impairment was expected since the number of hospitalizations is a marker of the severity of the illness and, in turn, is related to cognitive dysfunction. Furthermore, the higher number of hospitalizations could indicate a greater severity of episodes (both depressive and manic), possibly a greater recurrence of episodes, longer episode duration and, consequently, a reduction in the inter-episodes recovery. Certainly, all these illness-related events may impact on the preservation of the cognitive status. Previous reports (Cardoso et al., 2015; Kessing & Andersen, 2004) supported that a larger number of episodes was related to higher cognitive impairment in terms of neurocognitive decline. On the contrary, another study did not find evidence supporting the association between

increased number of episodes and an increased risk of cognitive decline (Martino et al., 2013). Our results partially comport with previous studies focused on OABD by identifying almost the same clinical factors associated with cognitive function such as number of episodes, number of admissions, later age at illness onset in OABD (Beunders et al., 2021; Martino et al., 2018) and also cognitive reserve as a protective factor. In summary, our results reinforce that the heterogeneity can be classified into well-defined groups, which has important prognostic implications as it helps to define the characteristics of each group and also to design appropriate intervention strategies. Therapeutic approaches focused in clinical and demographic modifiable factors should be considered as a preventive treatment against both cognitive and functioning impairment. In that sense, interventions to enhance some modifiable factors of cognitive reserve have been designed (de la Serna et al., 2021) and could be useful to apply in order to anticipate the appearance of a cognitive decline.

This study has a number of limitations which must be mentioned. First, the small sample size of the SG cluster suggests that results must be interpreted with caution. A larger sample size would have allowed us to make more generalized and solid conclusions. As a result of the small sample for each variable of interest, especially in the SG cluster, we could not carry out multiple logistic regressions; hence, the results of the univariate regressions analysis are limited. Secondly, despite fulfilling older age criteria, the mean age of our patients was relatively young, thus limiting the generalizability of our results to eldest population. Third, the late-onset group could be skewing the magnitude of the cognitive impairment, especially in the severely impaired group which was composed of a high percentage of these subjects due to the small sample size of that group. Finally, the potential confounding variables that could be influence cognitive performance such as pharmacological treatment and comorbid psychiatric disorder were not controlled in the analysis.

To conclude, this is the first study to detect heterogeneous subgroups in a euthymic OABD sample using a cluster method analysis as well as to identify specific factors associated with higher cognitive impairment. Our results, in line to what observed in younger cohorts, indicate that cognitive variability is still present in OABD patients. These findings highlight that cognitive heterogeneity in OABD could be organized in distinguishable clusters, thus, having outstanding clinical and functional implications. The potential value of this analysis is that it illustrates the specific demographic and clinical characteristics of each group. Understanding the cognitive heterogeneity in late ages of BD may have important clinical implications. It could be useful not only to identify underlying mechanisms of cognitive impairment but also to develop treatment strategies adjusted to patient's level impairment and, importantly, to apply

preventive strategies against cognitive decline. Further studies are needed to explore the relationship between the specific clinical factors and cognitive dysfunction in OABD.

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