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Neuropsychological Clustering in Bipolar and Major Depressive Disorder

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Abstract

Objectives: Cognitive dysfunction is a key feature of major depressive (MDD) and bipolar (BD) disorders. However, rather than a single cognitive profile corresponding to each diagnostic categories, recent studies have identified significant intra- and cross-diagnostic variability in patterns of cognitive impairment. The goal of this study was to contribute to the literature on cognitive heterogeneity in mood disorders by identifying cognitive subprofiles in a population of patients with MDD, BD type I, BD type II, and healthy adults. **Methods:** Participants completed a neuropsychological battery; scores were converted into *Z*-scores using normative data and submitted to hierarchical cluster analysis. **Results:** Three distinct neuropsychological clusters were identified: (1) a large cluster containing mostly control participants, as well as some patients with BD and MDD, who performed at above-average levels on all neuropsychological domains; (2) a cluster containing some patients from all diagnostic groups, as well as healthy controls, who performed worse than cluster 1 on most tasks, and showed impairments in motor inhibition and verbal fluency; (3) a cluster containing mostly patients with mood disorders with severe impairments in verbal inhibition and cognitive flexibility. **Conclusions:** These findings revealed multiple cognitive profiles within diagnostic categories, as well as significant cross-diagnostic overlap, highlighting the importance of developing more specific treatment approaches which consider patients' demographic and cognitive profiles in addition to their diagnosis. (*JINS*, 2017, *23*, 584–593)

Keywords: Cognition, Mood disorders, Executive function, Cognition disorders, Cluster analysis, Neuropsychology

INTRODUCTION

Cognitive impairment is a key feature of major depressive disorder (MDD) (Pittenger & Duman, 2008) and bipolar disorder (BD) (Torrent et al., 2011) and a major cause of occupational and social disability. One of the most common patterns of cognitive impairment observed in these conditions is executive dysfunction, which is defined as an alteration in cognitive abilities such as inhibitory control, working memory, cognitive flexibility, planning, and problem solving, collectively known as the executive functions (EFs) (Diamond, 2013). Consistent impairments in related functions such as divided attention and verbal fluency have also been identified in both BD (Allin et al., 2010; Păunescu & Micluţia, 2015) and MDD (Backes et al., 2014), with significant implications for psychosocial and occupational functioning (Evans et al., 2013).

Given the impact of these cognitive alterations on functional capacity (Martinez-Aran et al., 2007) and treatment outcomes (Dunkin et al., 2000), several studies have sought to identify the patterns of cognitive impairment associated with specific disorders such as BD and MDD. Unfortunately, few definite conclusions have emerged in this area of research. Although the presence of executive impairments in BD is well-established (Burdick, Goldberg, Harrow, Faull, & Malhotra, 2006), and several studies have investigated their relationship to other clinical features of the disorder, such as disease duration (Bora, Harrison, Yücel, & Pantelis, 2013; Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005; Mora, Portella, Forcada, Vieta, & Mur, 2012), age of onset (Mora et al., 2012), history of psychotic symptoms (Simonsen et al., 2011), and number of mood episodes (Bora et al., 2013), several questions remained unanswered. There is no consensus, for instance, as to the specific cognitive impairments associated with BD (Bourne et al., 2013), their longitudinal course (Samamé, Martino, & Strejilevich, 2014), or their association with dementia (Wu et al., 2013). These data are crucial for interventions and treatment planning.

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Although cognition in MDD has been more extensively studied than in BD, recent studies have shown that even in the former case, there is still much ground to cover. It is still unclear whether illness duration and number of episodes have an impact on cognitive function, as is the extent of the clinical significance of cognitive improvements associated with psychotherapy, neuromodulation and pharmacological treatment (Chakrabarty, Hadjipavlou, & Lam, 2016). Furthermore, the effect size of differences between healthy control participants and subjects with MDD on cognitive functions, such as processing speed and inhibitory control, varies widely across studies and meta-analyses, making it difficult to determine the severity of cognitive impairments associated with the disorder.

The lack of a consensus on several of these issues is likely to be attributable to the cognitive heterogeneity identified within each diagnostic category (Burdick, Ketter, Goldberg, & Calabrese, 2015). In recent years, studies have made great progress in the study of cognitive heterogeneity within and across psychiatric disorders through cluster analysis and similar methodologies. In 2011, Hermens et al. identified three neurocognitive profiles in a sample of currently depressed patients with several different diagnoses, and similar clinical, demographic and functional characteristics. In 2014, Burdick et al. identified three neuropsychological subgroups in a population of individuals with BD. One of the clusters was found to have predominantly preserved cognition, while another had selective impairments in cognitive ability, and the last displayed global cognitive impairment. Lastly, Lewandowski, Sperry, Cohen, and Öngür (2014) in a study of cross-diagnostic cognitive heterogeneity identified four clusters of neuropsychological performance in a sample composed of participants with schizophrenia, schizoaffective disorder and psychotic bipolar disorder.

These findings have made significant contributions to the comprehension of cognitive functioning in different diagnostic subgroups, and may contribute to the development of treatment planning and intervention strategies aimed at distinct subgroups of patients based on their particular patterns of impairment. Unfortunately, no studies to date have performed a cluster analysis of patients with both MDD and BD, despite the similarity in cognitive profiles displayed by these populations (e.g., Xu et al., 2012).

More recently, in addition to identifying neuropsychological clusters within psychiatric samples, studies have sought to compare each of these groups to healthy control subjects (Solé et al., 2016). This is an important procedure, since it allows for a verification of the extent to which the clusters are clinically meaningful, and actually indicate a departure from normal cognitive functioning. In recent years, increasing attention has been paid to the cognitive variability in healthy adult samples (Rabinowitz & Arnett, 2013), which cannot be reliably captured by central tendency measures such as means and standard deviations. As a result, patients whose scores fall below the normative mean may be erroneously thought to exhibit cognitive impairment, when a closer analysis of the variability in the healthy adult population may reveal scores very close to that obtained by the patient. As a result, rather than comparing the performance of patients with psychiatric disorders to a normative cutoff value, it may be more accurate to actually include healthy adults in the analysis and determine whether the distribution of their cognitive performance does differ from that observed in clinical samples. Recent clustering studies in BD have taken this approach and obtained important evidence of its contribution to the literature.

In the study performed by Solé et al., (2016), for instance, the comparison allowed for the identification of a cognitively intact subgroup of patients with BD type II (BDII), which did not differ from healthy control subjects in any of the cognitive measures used. This finding provides additional support for the idea that some patients with BD have no cognitive impairment and is a far stronger piece of evidence than the mere identification of distinct cognitive profiles with impairments of varying severity within a diagnostic category. A similar conclusion was reached by other clustering studies involving patients with both BD type I (BDI) and BDII (Bora et al., 2016). Unfortunately, these are still the only few clustering studies to involve control subjects and allow for this type of analysis.

Given the contributions of neuropsychological clustering studies to the literature, and the unanswered questions which still abound in the study of cognition in mood disorders, additional clustering studies could help corroborate existing findings and previously identified patterns of cognitive functioning across different populations. Furthermore, the identification of cross-disorder neuropsychological profiles could lend additional support to the cognitive continuum hypothesis (Ancín et al., 2010; Bora, Yucel, & Pantelis, 2009), which suggests that the differences in cognitive impairment between disorders such as schizophrenia and BD are quantitative rather than qualitative. These hypotheses have important implications for diagnostic classification as well as treatment planning, especially in light of the growing interest in cognitive and functional rehabilitation programs (Deckersbach et al., 2010; Torrent et al., 2011), which currently target each disorder as a whole, but could benefit from adjustments for the cognitive subprofiles displayed by each diagnostic category.

In light of these considerations, the aim of the present study was to evaluate the cognitive performance of patients with BDI, BDII, and MDD through hierarchical cluster analysis, with a special focus on executive dysfunction, divided attention, and verbal fluency. The association between each of the cognitive subprofiles identified and participants' clinical and demographic characteristics will also be discussed.

METHOD

Participants

The sample was composed of 153 participants, of whom 66 were adults with no mood disorders, 29 had a diagnosis of BDI, 25 suffered from BDII, and 33 had been diagnosed with MDD.

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Patients were recruited from the mood disorders outpatient unit of a psychiatric hospital, a university teaching clinic, and private practice. Control participants were selected by convenience from work and university settings, as well as the community at large.

All patients were at least 18 years old, and had at least 1 year of formal education. The following exclusion criteria were applied to the sample: uncorrected sensory impairments that would interfere with task performance, neurological conditions, and pregnancy or lactation. Patients with psychotic symptoms at the time of testing or who reported substance abuse within the previous month were also excluded from participation. The control group was selected using the same criteria and was screened for mood disorders according to DSM-5 criteria, cognitive impairment, and intellectual disability.

Procedures and Instruments

All subjects provided written consent for participation, and the present study was approved by the Research Ethics Committee of the institution where it was conducted. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants took part in at least two assessment sessions lasting approximately one and a half hours each. Inclusion and exclusion criteria were first investigated using a sociocultural and health questionnaire adapted from Fonseca et al. (2012). In addition to collecting demographic data, this instrument also contains a brief inventory used to assess the frequency of reading and writing habits (FRWH). This variable has been previously used as an indirect measure of cognitive reserve and stimulation in BD and MDD (Cotrena, Branco, Shansis, & Fonseca, 2016). The instrument asks participants to rate the weekly frequency with which they read magazines, newspapers, books, and other materials, and write long texts and brief notes. Each item is rated on the following scale: every day (4 points), a few times a week (3 points), once a week (2 points), rarely (1 point), and never (0 points). The scores assigned to each reading and writing activity are added to yield a total FRWH score ranging from 0 to 28.

In addition to these instruments, participants were administered the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; adapted by Chaves & Izquierdo, 1992) with cutoffs adjusted for education by Kochhann, Varela, Lisboa, and Chaves, (2010), to screen for symptoms of dementia. Additionally, the Block Design and Vocabulary Subtests from the Wechsler Adult Intelligence Scales (WAIS-III) (Nascimento, 2004) were used to estimate participant intelligence quotient (IQ) based on the values provided by (Jeyakumar, Warriner, Raval, & Ahmad, 2004).

The neuropsychological battery used in the present study focused on five major cognitive domains, including the three key EFs, as well as verbal fluency and divided attention. Inhibitory control was evaluated using the number of errors on the Stroop Color Word Test (SCWT; Stroop, 1935; Zimmermann, Cardoso, Trentini, Grassi-Oliveira, & Fonseca, 2015), and the time taken to complete parts B of the Hayling Sentence Completion Test (HSCT; Burgess & Shallice, 1997; Fonseca et al., 2010), and the Trail Making Test (TMT; (Reitan & Wolfson, 1995; Zimmermann et al., 2015). The association between the time to completion of parts A and B of the HSCT and TMT were also calculated. These two variables were then used as measures of cognitive flexibility (Arbuthnott & Frank, 2000; Flaudias et al., 2016).

Working memory was evaluated using total scores on the Sentence-Word Span subtest, from the Brazilian Brief Neuropsychological Battery NEUPSILIN (Fonseca, Salles, & Parente, 2009) and the Backwards Digit span subtest from the Wechsler Memory Scale – Revised (Wechsler, 2002; Zimmermann et al., 2015). Verbal fluency was assessed using the total number of words produced in the semantic, phonemic, and unconstrained verbal fluency tasks from the Montreal Communication Assessment Battery (MAC; Fonseca, Parente, Cote, Ska, & Joanette, 2008). Lastly, participants completed a Divided Attention Test (DAT; Sisto, Noronha, Lamounier, Bartholomeu, & Rueda, 2006), a cancellation task that yields a net score of targets cancelled minus omission and commission errors.

Clinical assessments were performed individually, and the presence of mood disorders was examined using DSM-5 criteria (American Psychiatric Association, 2013). All diagnoses were confirmed by consensus with a clinical psychologist with expertise in mood disorders. Participants were administered the Mini International Neuropsychiatric Interview (MINI) (Amorim, 2000), in addition to the Hamilton Depression Rating Scale (HDRS) (Gorenstein, Andrade, & Zuardi, 2000; Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Vilela & Loureiro, 2000; Young, Biggs, Ziegler, & Meyer, 1978), respectively.

Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 21.0. To control for the effects of age and education, participant performance on each of the tasks administered was first converted to *Z*-scores using normative data (*Z*-score = (participant score – normative mean)/standard deviation). To ensure the clustering procedure would not be influenced by extreme values or skewed distributions, the data were submitted to exploratory analysis to identify any outliers. These values were identified using Tukey's boxplot method (1977), which does not make distributional assumptions and is less vulnerable to extreme values (Seo, 2006). Probable outliers, or values beyond the outer fence of the boxplot, were winsorized to three times the interquartile range from the nearest quartile, to minimize any distortions in data analysis while retaining the clinical significance of particularly high or low *Z*-scores.

The hierarchical clustering procedure used in this study was similar to that described in previous investigations of similar populations (Burdick et al., 2014; Hermens et al., 2011). Patterns of neuropsychological performance were identified using Ward's method of minimum variance (Ward, 1963) with a

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squared Euclidean distance measurement. The optimum number of clusters for the dataset was selected based on a scree plot of agglomeration coefficients and the dendrogram. Once an ideal number of clusters was defined, clinical and demographic variables were compared between groups using one-way analysis of variance (ANOVA), followed by Bonferroni *post hoc* tests, as well as chi-square tests, when applicable. Neuropsychological performance was compared between clusters by one-way analysis of covariance (ANCOVA), to control for the effects of any demographic or clinical variables which differed across clusters.

Lastly, *Z*-scores were classified according to the presence *versus* absence of cognitive impairment (with $Z = -1.5$ as a cutoff point) (Schoenberg et al., 2006). The prevalence of impairment on each measure per cluster was compared using Fisher's exact test. Significance was set at $p < .05$.

RESULTS

A total of 3.86% of values were winsorized to three interquartile ranges from the nearest quartile. There were no significant differences between diagnostic categories in the number of scores submitted to this procedure ($p = .082$).

A three-cluster solution was found to be most appropriate for the dataset based on an analysis of the agglomeration coefficients and the dendrogram produced by the hierarchical clustering procedure. The composition of each cluster in terms of the number of control participants and patients with each of the diagnoses studied is shown in Figure 1.

The demographic and clinical characteristics of each cluster are shown in Table 1. The three clusters differed on several demographic and clinical variables, most notably IQ and HDRS scores. Both are known to have a strong impact on EF and cognition as a whole, and as such, were statistically controlled for all subsequent comparisons of cognitive performance between clusters. The results of these analysis are shown in Table 2.

As can be seen in Table 1, cluster 1 had a significantly higher education level and socioeconomic status (SES) than cluster 3. The omnibus test suggested a significant difference in depression scores between groups. However, pairwise tests were not significant. Nevertheless, the data shown in Table 1 suggests that patients in cluster 2, and especially cluster 3, had higher depression scores than those in cluster 1. Forty-five of the 66 control participants, or 68.2% of healthy adults in the sample, were allocated to this cluster. Approximately half of all patients with MDD ($n = 15$) and BDII ($n = 10$) and one-third of subjects with BDI ($n = 10$) were also assigned to this participant group. These individuals outperformed the remaining clusters on most of the cognitive functions evaluated.

The second cluster only differed from the first with regard to SES and IQ. This cluster included the majority of remaining control participants ($n = 18$), as well as half the remaining patients with MDD ($n = 9$), BDII ($n = 9$), and BDI ($n = 9$). Cluster 2 performed worse than cluster 1 on the TMT, the DAT, and the Backwards Digit Span Task, as well as the verbal fluency tasks. Cluster 2 also obtained higher scores than cluster 3 on the HSCT.

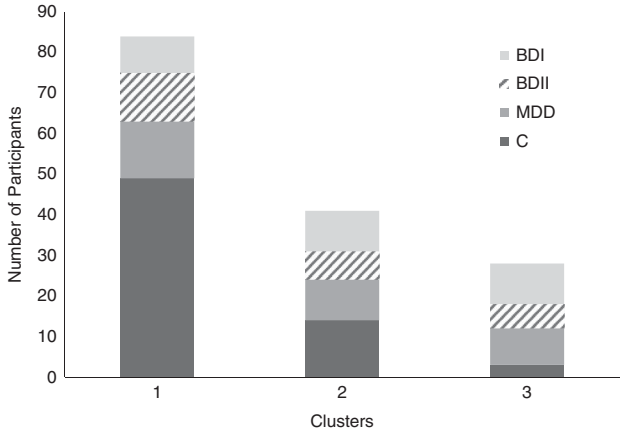

Fig. 1. Composition of neurocognitive clusters. BDI, bipolar disorder type I; BDII, bipolar disorder type II; MDD, major depressive disorder.

Participants in cluster 3 had the lowest levels of cognitive stimulation in the sample, as evidenced by their low frequency of reading and writing. They also had a lower IQ than participants in clusters 1 and 2. Only three control participants were assigned to this group, with the vast majority of participants having a diagnosis of MDD ($n = 9$), BDII ($n = 6$), or BDI ($n = 10$). These individuals obtained the lowest scores in the sample on the HSCT.

The frequency of impairment on each measure was also compared between clusters. This analysis sought to confirm that the differences in group means did reflect a variation in the pattern of cognitive impairments shown by each group. The results of this analysis are shown in Table 3.

As can be observed in Table 3, the patterns of impairment on all cognitive components, save for divided attention and working memory, differed significantly between groups. In all cases, cluster 1 showed a lower frequency of impairment than expected. In cluster 2, the frequency of impairments on the HSCT was lower than expected, while the opposite was observed for the TMT, the SCWT, and all three verbal fluency tasks. Lastly, cluster 3 showed a higher frequency of impairment than expected across all cognitive tasks.

These findings corroborate and complement those of the ANOVA. Not only do they confirm the superior performance of cluster 1, but they add important information regarding the similarities and differences between clusters 2 and 3. Both clusters showed relatively low impairment rates on divided attention and working memory tasks. However, approximately one-third of participants in both groups showed impairments on the TMT B and the phonemic verbal fluency task, while one-fourth to one-fifth obtained *Z*-scores below −1.5 on the SCWT.

The most prevalent impairment in cluster 2 was observed in the semantic fluency task. Nearly half of participants in this group scored below the cutoff for cognitive impairment.

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Table 1. Demographic and clinical characteristics of each participant cluster

	Cluster 1 (n = 80)	Cluster 2 (n = 45)	Cluster 3 (n = 28)	F or x^2	p-Value	*Post-hoc*
Age[a]	32.54 (13.31)	33.24 (14.18)	39.46 (14.47)	2.72	.069	—
Education[a,b]	15.35 (4.10)	13.66 (4.48)	12.66 (6.17)	4.20	.017	1 > 3
SES[a]	31.21 (7.00)	27.64 (6.00)	26.11 (7.80)	7.41	.001	1 > 2,3
FRWH[a]	17.91 (4.66)	15.96 (5.21)	11.93 (5.14)	15.48	<.001	1,2 > 3
HDRS[a]	6.39 (7.73)	9.84 (10.79)	10.97 (9.89)	3.60	.030	*ns*
YMRS[a]	1.65 (2.28)	1.50 (2.28)	2.55 (4.38)	1.40	.250	—
IQ[a]	119.73 (11.82)	111.02 (12.07)	103.14 (14.29)	20.65	<.001	1 >2 > 3
MMSE[a]	28.79 (1.66)	27.89 (2.29)	27.50 (2.58)	5.21	.007	1 > 3
Gender (F;n)[c]	49 (61.3%)	23 (51.1%)	21 (75.0%)	4.15	0.126	—

[a]Data presented as mean and standard deviation.
[b]Years of formal education.
[c]Absolute and relative frequency of female participants.
SES = socioeconomic status; FRW = frequency of reading and writing habits; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; IQ = intelligence quotient; MMSE = Mini-Mental State Examination.

In cluster 3, however, the worst performance was observed on the HSCT. Both scores obtained from this particular task yielded impairment rates higher than 80%.

To summarize and illustrate our findings, composite scores were calculated for each cognitive domain and plotted in Figure 2. Composite scores were obtained based on the average *Z*-score for each domain, per cluster. The values used to calculate these scores are shown in Table 2.

As can be seen in Figure 2, Cluster 1 performed consistently above the expected average (i.e., $Z = 0$). Cluster 2 obtained near-average scores on the majority of cognitive domains, but had relatively lower scores on verbal fluency measures. Lastly, cluster 3 showed impairments in both inhibitory control and cognitive flexibility, but otherwise behaved similarly to cluster 2.

DISCUSSION

The goal of the present study was to identify cognitive profiles in a mixed population of patients with BDI, BDII, and MDD, and control participants. Three distinct clusters were identified, and significant differences were noted in their demographic and clinical characteristics, as well as the severity and patterns of cognitive impairment. The largest cluster was predominantly composed of control participants with above-average cognitive scores. The second largest participant group performed near the expected average, but showed selective impairments in semantic verbal fluency. The third cluster was mostly composed of patients with mood disorders, and showed significant impairments in both inhibitory control and cognitive flexibility.

Table 2. Cognitive profile shown by each cluster

	Cluster 1 (n = 80)	Cluster 2 (n = 45)	Cluster 3 (n = 28)	p-Value	*Post-hoc*
Inhibitory control					
HSCT - TB	0.46 (0.81)	0.24 (1.26)	−2.52 (0.96)	<.001	1,2 > 3
TMT – TB	0.30 (0.67)	−1.03 (1.42)	−0.85 (1.45)	<.001	1 > 2
SCWT Err	0.25 (0.76)	−0.33 (1.35)	−0.10 (1.18)	.041	1 > 2
Cognitive flexibility					
HSCT TB-TA	0.42 (0.86)	0.82 (1.11)	−2.62 (1.03)	<.001	1,2 > 3
TMT B/TMT A	0.09 (0.73)	−0.96 (1.93)	−0.07 (1.17)	<.001	1,3 > 2
Divided attention					
DAT – AoT	0.73 (0.81)	0.11 (0.72)	0.02 (0.73)	.006	1 > 2
Working memory					
DS - Bwd	1.08 (1.26)	0.02 (0.81)	0.18 (1.02)	.001	1 > 2
SWS	0.07 (0.82)	−0.21 (0.95)	−0.40 (0.86)	.565	*ns*
Verbal fluency					
PVF	0.08 (0.93)	−0.88 (0.97)	−0.84 (0.85)	<.001	1 > 2,3
SVF	0.13 (1.01)	−1.29 (1.23)	−1.02 (0.95)	<.001	1 > 2,3
UVF	0.51 (0.88)	−0.39 (0.88)	−0.57 (0.70)	<.001	1 > 2,3

HSCT - TB = Hayling Sentence Completion Test, Part B Time; TMT-TB = Trail Making Test, Part B Time; SCWT Err = Stroop Color-Word Test Errors; HSCT TB-TA = Hayling Sentence Completion Test, Part B-Part A time; TMT B/TMT A = Trail Making Test Part B/Part A ratio; DAT-AoT = Divided Attention Test, Accuracy over Time; DS – Bwd = Digit Span Backward; SWS = Sentence-word Span; PVF = phonemic verbal fluency; SVF = semantic verbal fluency; UVF = unconstrained verbal fluency.

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Table 3. Frequency of impairments per group

	Cluster 1 N_e;N_o (%)[a]	Cluster 2 N_e;N_o (%)	Cluster 3 N_e;N_o (%)	*p*-Value
Inhibitory control				
HSCT - TB	14.6;0 (0%)	8.2;4 (8.9%)	5.1;24 (85.7%)	<.001
TMT – TB	12.5;2 (2.5%)	7.1;14 (31.1%)	4.4;8 (28.6%)	<.001
SCWT Err	10.5;4 (5.0%)	5.9;11 (24.4%)	3.7;5 (17.9%)	.004
Cognitive flexibility				
HSCT TB-TA	13.1;2 (2.5%)	7.4;0 (0%)	4.6;23 (82.1%)	<.001
TMT B/TMT A	7.8;2 (2.5%)	4.4;11 (24.4%)	2.7;2 (7.1%)	.001
Divided attention				
DAT – AoT	.5;1 (1.3%)	.3;0 (0%)	.2;0 (0%)	1.000
Working memory				
DS - Bwd	2.1;0 (0.0%)	1.2;3 (6.7%)	.7;1 (3.6%)	.062
SWS	5.2;3 (3.8%)	2.9;5 (11.1%)	1.8;2 (7.1%)	.253
Verbal fluency				
PVF	12.5;2 (2.5%)	7.1;13 (28.9%)	4.4;9 (32.1%)	<.001
SVF	15.7;2 (2.5%)	8.8;20 (44.4%)	5.5;8 (28.6%)	<.001
UVF	3.3;0 (0%)	1.8;4 (8.9%)	1.1;2 (7.1%)	.011

[a]Expected *n* (observed *n*).
HSCT - TB = Hayling Sentence Completion Test, Part B Time; TMT-TB = Trail Making Test, Part B Time; SCWT Err = Stroop Color-Word Test Errors; HSCT TB-TA = Hayling Sentence Completion Test, Part B-Part A time; TMT B/TMT A = Trail Making Test Part B/Part A ratio; DAT-AoT = Divided Attention Test, Accuracy over Time; DS – Bwd = Digit Span Backward; SWS = Sentence-word Span; PVF = phonemic verbal fluency; SVF = semantic verbal fluency; UVF = unconstrained verbal fluency.

The presence of patients with mood disorders in all three clusters suggests that individual characteristics may play a more prominent role in cognitive functioning than diagnostic category. This conclusion supports the findings of previous cluster studies, which identify variable levels of cognitive impairment in samples with BD and MDD (Burdick et al., 2014; Hermens et al., 2011). The distribution of clusters identified in the present study was also similar to that revealed by other similar investigations of psychiatric samples. As noted by Lewandowski et al. (2014), most studies find one neuropsychological intact subgroup, one to three "intermediate" clusters with selective cognitive impairments, and one cluster with significant global neuropsychological deficits. While the present findings corroborate the previous literature in terms of participant distribution across neurocognitive clusters, they also provide additional insight as to the reasons for this distribution and its possible implications.

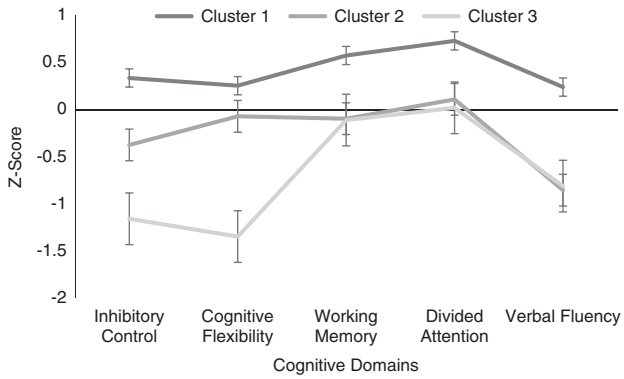

Fig. 2. Cognitive profiles per cluster. Error bars indicate standard error.

The presence of patients with BD and MDD in the largest cluster, which also comprised most control participants, suggests that some patients showed preserved cognitive skills despite the presence of psychopathology. Similar findings have already been reported in the literature, especially in patients receiving pharmacological treatment, such as those in the present study. Xu et al. (2012) found that, after symptom remission, patients with BDI and BDII did not differ from control subjects on measures of EF, attention, and working memory. Similarly, studies of patients with MDD have found that symptom reduction following pharmacological treatment may also attenuate cognitive impairments (Wagner, Doering, Helmreich, Lieb, & Tadić, 2012). The mean HDRS score in cluster 1 was below the cutoff of 8 for mild depression, and YMRS scores were well below any cutoff for mania or hypomania. These results suggest that, in the absence of clinical symptomatology, patients with MDD, BDII, and even BDI may experience marked improvements in cognitive function.

The fact that patients in cluster 1 were relatively young, highly educated, with a high SES and relatively frequent reading and writing habits, all of which have been found to exert a positive effect on cognition in healthy adults, may also have contributed to this outcome (Cotrena et al., 2016; Duncan & Magnuson, 2012; Lenehan, Summers, Saunders, Summers, & Vickers, 2015). Evidence for this hypothesis can be found in a study by Lee, Hermens, Porter, and Redoblado-Hodge (2012), who found that factors such as age and education may attenuate

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the differences in cognitive performance between patients with MDD and control subjects.

Approximately one-third of clinical participants were assigned to cluster 2, which showed predominantly preserved cognitive performance, save for selective cognitive impairments. Although clusters 1 and 2 differed significantly on several cognitive variables according to the ANCOVA, the comparison between these findings and those yielded by the chi-square analysis supports an interesting hypothesis regarding clinical *versus* statistical significance. A statistical difference in *Z*-scores when compared to control subjects, such as that shown by the ANCOVA, is not necessarily indicative of cognitive impairment. For instance, although participants in cluster 2 obtained significantly lower scores than cluster 1 on the DAT and digit span backwards, an analysis of *Z*-scores suggested that very few participants in cluster 2 could be classified as having impairments in either divided attention or working memory.

It is important to note that the reason this discrepancy may have arisen in the present study is the above-average performance of cluster 1, which exceeded the normative range for some neuropsychological tests, and, therefore, set a higher comparative standard than the *Z*-score of 0. Nevertheless, these findings highlight the importance of complementing traditional statistical analysis with a clinical approach, to maximize the generalizability of research findings to clinical practice and treatment, and better comprehend the real-life implications of the findings identified in comparative studies. As such, both ANCOVA and chi-square results should be analyzed in tandem. In cluster 2, a combined evaluation of both sets of results indicates that, while participants showed poorer cognitive performance than that observed in cluster 1, the most marked alterations are limited to the TMT and the semantic verbal fluency task. These alterations are consistent with the literature, which has reported significant impairments on the TMT as well as verbal fluency tasks in both BD and MDD (Bourne et al., 2013; Wagner et al., 2012).

Lastly, participants in cluster 3 obtained the lowest scores in the sample on the HSCT, and, like cluster 2, displayed a high prevalence of impairments on the phonemic and semantic verbal fluency tasks as well as the TMT. However, unlike cluster 2, whose most prevalent impairment affected less than half of participants, cluster 3 showed impairment rates on the HSCT which surpassed 80%. The presence of impairments on the HSCT corroborates the results of a recent meta-analysis (Wang et al., 2013), which found similar impairments on this measure in patients with BD and schizophrenia. In this study, as well as in the present investigation, patients with BD required a longer span of time than control subjects to inhibit a prepotent verbal response, which suggests an impairment in inhibitory control as well as cognitive flexibility.

The comparison of demographic characteristics between clusters shows that individuals in cluster 3 are less educated and have a lower SES than cluster 1, and have the lowest frequency of reading and writing in the sample. All of these factors may have contributed to the impairments observed. By the same token, they represent targets for lifestyle interventions for cognitive health and stimulation, since some actions, such as the encouragement of reading and writing habits and the pursuit of education, could be within the scope of such treatment programs.

The distribution of diagnostic groups across the three clusters also makes for some interesting conclusions regarding the impact of mood disorders on cognition. The fact that patients with BDI accounted for 35.7% of cluster 3 but only 12.5% of cluster 1 corroborates previous findings regarding the greater severity of cognitive impairment in this disorder relative to BDII and MDD (Xu et al., 2012). This hypothesis is underscored by the fact that only a third of participants with BDI were assigned to cluster 1, as opposed to 40% of patients with BDII and 45.5% of those with MDD. These findings are consistent with previous studies suggesting that MDD may be associated with less severe cognitive impairments than BDII and BDI (Cotrena et al., 2016). Nevertheless, it is important to note that over half the participants in each clinical group were assigned to clusters 2 and 3, suggesting that, although the presence of a mood disorder may not necessarily result in cognitive impairment, it is still likely to do so.

An analysis of the clinical and demographic profiles of patients assigned to different clusters also provides additional insight on the types of variable which may influence cognitive performance in each disorder. Patients with BDI showed a similar profile across all three clusters, suggesting that the clinical and demographic variables assessed in the present study may not be strong contributors to cognitive variability in this population. It is possible that variables such as number of episodes or duration of illness have a greater impact on cognition than education, age, or current symptomatology in BDI. Patients with BDII in cluster 3 showed lower IQ scores and less frequent reading and writing habits than those in the other two clusters, suggesting that cognitive reserve, premorbid IQ, or routine cognitive stimulation may be significant contributors to performance in this disorder. Lastly, in MDD, the only variable to significantly differentiate patients across clusters was the HDRS. This finding suggests that, in MDD, current symptomatology may exert a greater influence on cognitive performance than the other variables measured. Future studies should examine these hypothesis to determine whether they hold true for other samples and cognitive functions.

The present study revealed heterogeneous cognitive profiles within a population of patients with mood disorders. The fact that differences in inhibitory control, cognitive flexibility, divided attention, and working memory survived statistical correction for both depression scores and IQ suggests that intra-diagnostic cognitive subgroups should not be exclusively attributed to factors such as IQ or mood state. Although the present study made some contributions to the literature regarding possible contributors to cognitive preservation, in the form of education and reading and writing, additional studies are still required to determine whether the absence of cognitive stimulation is a cause or a consequence of cognitive impairment, since the presence of attentional,

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memory, or executive alterations may also interfere with the performance of cognitively stimulating tasks.

The presence of subjects with BDI, BDII, and MDD in the most cognitively preserved cluster suggests that the presence of a clinical diagnosis does not necessarily lead to cognitive impairment. The absence of such alterations may be attributable to the neuroprotective effects of cognitive reserve or other demographic variables, such as young age and high educational attainment. These findings highlight the importance of controlling for demographic variables in neuropsychological studies, and of evaluating the association between cognitive performance and individual characteristics in patients with mood disorders. We suggest that future studies verify whether the pattern of clusters identified in the present investigation can be replicated in other samples, so as to contribute to the development of a more reliable, accurate, and detailed model of cognitive functioning in BD and MDD.

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