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The effects of cognitive reserve and depressive symptoms on cognitive performance in major depression and bipolar disorder

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ABSTRACT

Background: Significant heterogeneity is observed in the cognitive profiles of bipolar disorder (BD) and major depression (MDD), characterized in part by differences in individual and clinical variables such as cognitive reserve (CR) and depression severity. However, no other study evaluated how this variables may interact regarding neurocognitive functioning. The aim of the present exploratory study was to evaluate the interaction between different depressive symptoms severity, CR and diagnosis with neurocognitive functioning.
Method: 202 participants (MDD = 91; BD = 111) classified either as euthymic, with mild depression or moderate to severe depression, and low or high CR completed a neuropsychological evaluation of verbal fluency, working memory (WM), inhibitory control (IC), cognitive flexibility (CF) and attention (Att).
Results: Neuroprotective effects of CR were observed in patients with BD within a major depressive episode in WM, IC, FC and Att. In MDD, CR acted as a neuroprotective factor during euthymia and moderate to severe depression in the same cognitive functions. CR and depression severity differentiated the cognitive profiles of individuals with BD and MDD.
Limitations: Some variables related to neurocognitive performance like medication use, number of mood episodes, illness duration or previous hospitalizations were not controlled.
Conclusion: CR may be protective against cognitive impairment in both BD and MDD, and these effects were observed in euthymia and during depressive episodes of varying severity. These findings highlight the importance of investigating such variables in the neuropsychological evaluation of mood disorders, which may help to understand the cognitive heterogeneity within these populations.

1. Introduction

Bipolar disorder (BD) and major depression (MDD) have a significant impact on cognition and functioning across social, academic and occupational domains. Studies suggest that 30 to 60% of patients with BD and MDD have some form of cognitive impairment during euthymia (Cullen et al., 2016; Iverson et al., 2011; Rock et al., 2014; Salagre et al., 2017; Van Rheenen et al., 2019). Alterations in the executive functions, memory and attention are related to several important clinical variables such as quality of life, academic and occupational performance, as well as medication adherence (Gitlin and Miklowitz, 2017; MacQueen and Memedovich, 2017; Trivedi and Greer, 2014). Though cognitive impairments are observed in most patients with BD and MDD, there is significant variability in the severity of these alterations and in the cognitive functions affected. While some studies report a near-absence of cognitive deficits in patients with these conditions, others find a high prevalence of generalized cognitive impairment (Bora et al., 2013; Burdick et al., 2014; Cotrena et al., 2017; Martino et al., 2018; Miskowiak et al., 2018).

In light of the heterogeneity in cognitive profiles observed in mood disorders, several studies in recent years have looked to clinical, sociodemographic and other individual characteristics as potential causes of cognitive variability in both BD and MDD (Ehrminger et al., 2019; Grützner et al., 2019; Solé et al., 2016; Van Rheenen et al., 2019). One important variable to emerge from these studies was cognitive reserve (CR), which consists of the brain's ability to attenuate cognitive impairments caused by aging or neuropathology (Stern et al., 2018). According to this hypothesis, in the same clinical group individuals with

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lower levels of CR would be more subject to present cognitive impairment when compared to those with higher CR. The presence of varying levels of CR across patients with the same disorder could therefore explain the variation in cognitive impairments displayed by these individuals. CR can be measured based on the intellectual quotient (IQ) and variables which reflect current and previous levels of cognitive stimulation, such as education, occupation and leisure activities such as reading and writing (Cotrena et al., 2019; Grande et al., 2017; Stern et al., 2018).

The concept of CR was initially used exclusively in the context of dementia, but has since garnered increasing attention as a potential influence on symptom expression, functioning and cognitive impairment in psychopathology (Amoretti et al., 2016; Anaya et al., 2016; Barnett et al., 2006). The few studies conducted on CR in populations with mood disorders have produced promising findings. In patients with BD, CR has been found to be associated with better cognitive performance in euthymia, and has proved a significant predictor of functioning and quality of life (Forcada et al., 2014; Grande et al., 2017; Hinrichs et al., 2017; Lin et al., 2020). In MDD, CR has been mostly studied for its influence on symptom expression and risk of psychopathology (Koenen et al., 2009; Schaefer et al., 2017). The few investigations that have examined the influence of CR on cognitive performance in this population observed similar findings, with variables such as higher education or IQ associated with better neurocognitive performance (Venezia et al., 2018; Lee et al., 2018).

In light of the association between better neurocognitive performance and higher levels of CR in psychiatric conditions, it is important to evaluate whether CR can also influence the cognitive repercussions of clinical variables such as depressive symptoms. These symptoms represent the predominant morbidity in both BD and MDD, and are a common cause of cognitive and functional impairment in such conditions (Forte et al., 2015; Gitlin and Miklowitz, 2017; McDermott and Ebmeier, 2009; McIntyre and Calabrese, 2019).

Few studies have investigated the cognitive effects of depressive symptoms on cognition, or considered their potential interaction with variables such as CR (Venezia et al., 2018). As such, the aim of this study was to examine the influence of depressive symptom severity, CR and diagnosis on measures of working memory, inhibition, attention, verbal fluency and cognitive flexibility. It was hypothesized that patients with more severe depressive symptoms would show larger cognitive impairments, and that CR would be associated with better cognitive performance across all cognitive functions and levels of symptom severity.

2. Method

2.1. Participants

The sample consisted of 202 adults (n = 91 with MDD and 111 with BD), aged 18 to 65 years. Patients were recruited from a psychiatric hospital, a university clinic and private practice. The following exclusion criteria were applied: 1) sensory or motor impairments that interfered with the assessment; 2) neurological disorders; 3) psychotic symptoms at the time of testing; 4) substance abuse in the 30 days preceding the study; 5) current pregnancy or lactation.

2.2. Procedures and Instruments

All participants provided written informed consent upon inclusion in the study. This investigation was approved by Research Ethics Committee of the institution where it was conducted (PUCRS CAEE n° 23995513.5.0000.5336; report number 482.688, issued 06/12/2013).

Although most participants had been diagnosed with BD or MDD prior to entering the study, all were administered the *Mini International Neuropsychiatric Interview* (MINI; adapted to Brazilian Portuguese by Amorim, 2000), adjusted to include DSM-5 diagnostic criteria for mood disorders (American Psychiatric Association, 2013). All diagnoses were confirmed by consensus with a psychiatrist and a psychologist with expertise in mood disorders. Mood was evaluated using the Hamilton Depression Rating Scale (HDRS; adapted by Blacker, 2000, published by Gorenstein, Andrade, & Zuardi, 2000) and Young Mania Rating Scale (Vilela et al., 2000). Exclusion criteria and individual characteristics such as age, education, and frequency of reading and writing habits (a measure of daily cognitive stimulation, as described by Pawlowski et al., 2012) were evaluated using a sociodemographic questionnaire. Intelligence was evaluated using the Block Design and Vocabulary subtests of the Wechsler Adult Intelligence Scales (WAIS-III; Nascimento, 2004), which were used to calculated estimated IQ as described by Jeyakumar et al. (2004).

All participants completed a neuropsychological assessment battery which evaluated the following cognitive abilities: attention, verbal fluency, working memory, inhibition and cognitive flexibility. As recommended by Snyder et al. (2015), each cognitive ability was evaluated using at least two instruments in order to provide more accurate results. The assessment battery consisted of the following instruments: i) Trail Making Test (TMT; (Reitan and Wolfson, 1995), adapted and normatized by Zimmermann et al., 2015); ii) Stroop Color Word Test (SCWT; Stroop, 1935, adapted by Zimmermann et al., 2015); iii) Hayling Sentence Completion Test (HSCT; Burgess & Shallice, 1997; adapted and standardized for use in Brazilian Portuguese by Fonseca et al., 2010); iv) Sentence-Word Span subtest, from the Brazilian Brief Neuropsychological Battery NEUPSILIN (Pawlowski et al., 2008); v) Backwards digits span subtest from the Wechsler Memory Scale – Revised (Wechsler, 2002; adapted to Portuguese by Zimmermann et al., 2015); vi) Semantic, ortographic and unconstrained verbal fluency tasks (Montreal Assessment of Comunication Battery-MAC; (Fonseca et al., 2008; Joanette et al., 2004); vii) Modified Wisconsin Card Sorting Test (MWCST; Nelson, 1976, adapted to the Brazilian population by Zimmermann et al., 2015).

2.3. Data Analysis

Data were analyzed using the *Statistical Package for Social Sciences* (SPSS), v. 23.0 for *Windows*. Clinical and demographic variables were compared between groups using One-way ANOVA and chi-square tests. CR scores were calculated using Principal Component Analysis (PCA) of estimated IQ scores, years of education and frequency of reading and writing. A median-split was then used to categorize participant into 'higher' and 'lower' CR groups. Depression severity was categorized according to Zimmerman et al. (2013).

The raw scores of each participant on cognitive assessment instruments were converted into Z-scores using existing normative data. The instruments were classified according to their underlying cognitive functions, and a mean Z-score was calculated for each cognitive skill. The classification was performed based on the theoretical model described by Snyder (2013). Confirmatory factor analysis (CFA) was used to verify the applicability of the model to the data collected in the present study. Model fit was evaluated based on cutoff points recommended in the literature (*root mean square error of approximation* (RMSEA) < 0.06; *comparative fit index* (CFI) AND Tucker-Lewis Index (TLI) > 0.95; *standardized root mean square residual* (SRMR) < 0.09) (Hu and Bentler, 1995). Factor scores were then calculated for each cognitive ability. The effects of diagnosis, depressive symptom severity and CR on cognitive function were evaluated using a Multivariate ANCOVA.

3. Results

3.1. Demographic and clinical characteristics

Participants' clinical and sociodemographic characteristics are shown in Table 1. YMRS scores differed significantly between groups, as

Table 1
Clinical and sociodemographic variables

Variables	MDD (n = 91)	BD (n = 111)	*t*	*p*
Age*	36.79(14.44)	41.87(13.62)	-2.568	.480
Gender (F/M)	65/26	89/22	1.62	.109
Education*[1]	14.68(4.39)	13.52(5.46)		
FRWH*	16.34(5.09)	13.77(5.79)	3.242	< 0.042
IQ*	114.71(12.01)	107.53(12.87)	3.918	.275
HDRS*	9.36(7.16)	13.24(9.3)	-3.1	< 0.047
YMRS*	1.49(1.82)	3.16(3.65)	-3.734	< 0.001
CogRes.*	.2727(.865)	-.2257(1.06)	3.377	.067
HDRS class				
Euthymic	40	29		
Mild	25	40		
Moderate/Severe	12	30		

Note: MDD: major depressive disorder; BD: bipolar disorder; *Data presented as mean followed by standard deviation; [2] Years of formal education; FRWH: Frequency of reading and writing habits; IQ: Estimated intellectual quotient; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; CogRes.: cognitive reserve index

was expected given the nature of BD. Since mean scores on this scale were far below the cutoff point for hypomania, this difference may not be clinically significant. Nevertheless, YMRS scores were statistically controlled in all further analyses.

The principal component analysis revealed that a single component could explain 67% of the common variance shared by the three measures of CR (education, reading and writing, estimated IQ).

3.2. Cognitive Performance

The results of the confirmatory factor analysis are shown in Table 2. The proposed five factor model demonstrated adequate adjustment to the data: RMSEA = 0.045; CFI = 0.96; TLI = 0.95; SRMR = 0.047.

The comparison of factor scores between diagnostic groups, levels of depression severity and CR scores is shown in Table 3. Participants with BD obtained lower scores than those with MDD on all cognitive functions except for verbal fluency. Cognitive performance did not differ between participants with varying levels of depressive symptoms. CR, on the other hand, had a significant effect across all cognitive variables, with the high-CR group consistently outperforming the low-CR group.

Table 2
Confirmatory Factor Analysis

	Verbal Fluency	Working Memory	Inhibitory Control	Cognitive Flexibility	Attention
VF Semantic	0.595				
VF Phonemic	0.749				
VF Unconstrained	0.767				
Sentence-Word Span accuracy		0.748			
Digit Span BW		0.587			
HSCT part B errors			0.330		
SCWT word-color errors			0.251		
TMT part B time				0.768	
mWCST pers errors				0.568	
TMT part A time					0.736
HSCT part A time					0.466
SCWT color accuracy					0.562

Note: VF: verbal fluency; TMT: trail making test; BW: backwards; HSCT: Hayling Sentence Completion Test; SCWT: Stroop Color Word Test; mWCST: modified Wisconsin Card Sorting Test; Pers errors: perseverative errors

3.3. Interaction between diagnosis, CR and depressive symptoms

A significant interaction was observed between diagnosis, CR scores and the level of depression severity. This was observed in measures of working memory ($p = 0.004$), inhibition ($p = 0.002$), flexibility ($p = 0.007$) and attention ($p = 0.039$). These results are shown in Figures 1 and 2. Descriptive data are presented in Table Supplementary 1. In BD, euthymic patients with high and low CR did not present distinct neurocognitive functioning in measures of working memory and inhibition. However, significant differences were observed in those with mild and moderate to severe depressive symptoms, with the high-CR group outperforming the low-CR group on all cognitive components. Patients with MDD presented a different pattern: those with high CR and low CR in a mild depressive episode had similar neurocognitive functioning; euthymic and moderate to severe depressed individuals with high CR obtained higher scores than those with low CR.

4. Discussion

This study investigated the effects of diagnosis (MDD vs. BD), depression severity (absent/euthymic vs. mild vs. moderate/severe) and CR (low vs. high) on five different cognitive components: working memory, inhibition, flexibility, verbal fluency and attention. Comparative analyses revealed that patients with MDD outperformed those with BD on all cognitive variables save for verbal fluency. Patients with high CR, regardless of diagnosis, also outperformed those with low CR. No significant differences in cognitive performance were observed between individuals with depressive symptoms of different levels of severity. Interaction effects were also observed between these variables, with the magnitude of the effects of CR varying depending on diagnosis and depression severity.

The superior cognitive performance of patients with higher levels of CR corroborates previous findings in the literature (Anaya et al., 2016; Grande et al., 2017; Lin et al., 2020). Interestingly, CR was the only variable to exert a significant influence on measures of verbal fluency. The present findings support the hypothesis that higher levels of CR can attenuate the neuropathological effects of psychiatric conditions (Grande et al., 2017; Venezia et al., 2018), and lower levels of CR may contribute to the risk of cognitive impairment in patients with these disorders.

In patients with MDD, higher levels of CR were associated with better cognitive performance during euthymia or moderate to severe depression, corroborating previous findings in the literature (Venezia et al., 2018). However, patients with mild depression showed similar patterns of cognitive function regardless of their level of CR. One possible explanation for these findings may be the duration of the depressive episodes experienced by participants. Some studies have found that longer periods of depression are associated with more significant cognitive impairments (Angst et al., 2009; Cysique et al., 2016), and if patients with mild depressive symptoms experienced longer episodes than those with more severe depression, this discrepancy may explain the current findings. Unfortunately, episode length was not controlled in the present study, since our aim was to investigate the association between RC and depression severity rather than duration. Future studies may wish to explore this association in patients with varying levels of CR and depressive episodes of different lengths.

In BD, patients with high CR were more resilient against cognitive impairment, regardless of the severity of depressive symptoms. Regarding euthymic individuals, low to moderate effect sizes in measures of cognitive flexibility and attention between patients with high and low CR corroborates previous findings in the literature (Anaya et al., 2015, Grande et al., 2017). However, CR did not appear to influence performance in measures of working memory. This finding differs from those obtained by Anaya and colleagues (2015), but corroborates the results of Grande et al. (2017). These variations highlight

Table 3
Cognitive functioning by diagnosis, depression severity and CR

Cognitive Functions	MDD (n = 91)	TB(n = 111)			Eut	Mild	MoD/S	F	p	Low CR	High CR	F	p
			F	p									
VF*	0.09(0.10)	-0.75(0.91)	1.35	0.247	0.08(0.17)	0.03(0.18)	-0.1(0.15)	0.52	0.594	-0.19(0.09)	0.21(.1)	8.16	< 0.005
WM*	0.16(0.09)	-0.11(0.08)	4.86	< 0.029	0.01(0.09)	0.07(0.09)	0.005(0.13)	0.12	0.881	-0.26(0.08)	0.32(0.09)	21.42	< 0.001
IC*	0.23(0.12)	-0.12(0.10)	4.73	< 0.031	0.1(0.12)	0.01(0.12)	0.04(0.17)	0.12	0.885	-0.29(.1)	0.4(0.12)	17.11	< 0.001
CF*	0.19(0.09)	-0.08(0.07)	5.25	< 0.023	0.14(0.09)	0.12(0.09)	-0.1(0.13)	1.33	0.266	-0.29(0.8)	0.41(0.09)	33.04	< 0.001
Att.*	0.18(0.09)	-0.08(0.07)	4.71	< 0.031	0.15(0.09)	0.1(0.09)	-0.09(.013)	1.2	.301	-0.25(0.8)	0.36(0.94)	25.12	< 0.001

Note: MDD: major depressive disorder; BD: bipolar disorder;Eut: euthymia; Mild: mild depression; MoD/S: moderate to severe depression; Low CR: low cognitive reserve; High CR: high cognitive reserve *Data presented as mean followed by standard deviation; VF: Verbal Fluency; WM: Working Memory; IC: Inhibitory Control; CF: Cognitive Flexibility; Att.: Attention.

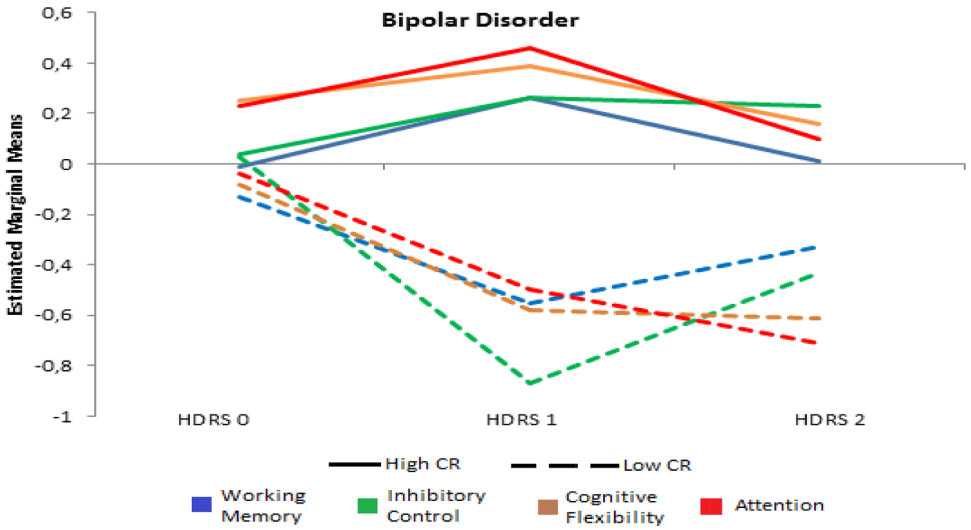

Figure 1. Note: HDRS: Hamilton depressive rating scale; 0: euthymic; 1: mild depression; 2: moderate/severe depression; High CR: high cognitive reserve; Low CR: low cognitive reserve.

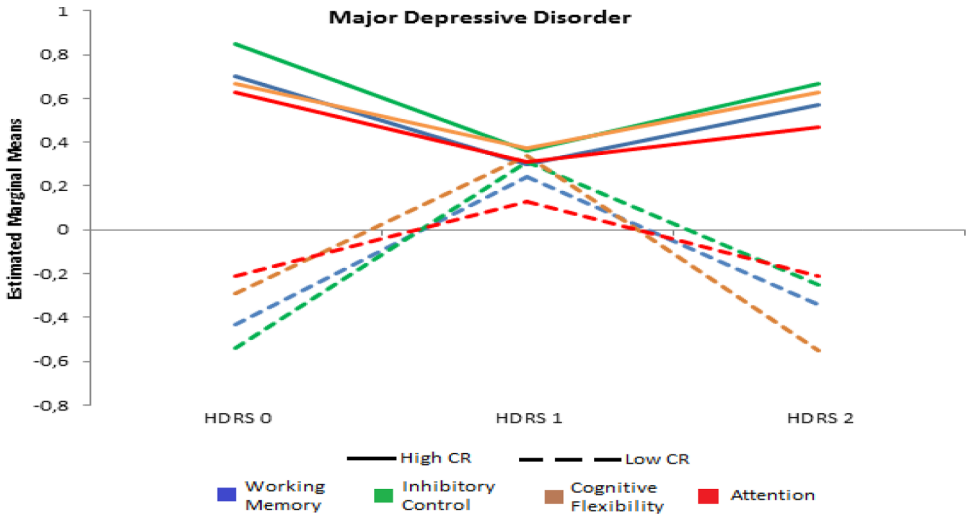

Figure 2. Note: HDRS: Hamilton depressive rating scale; 0: euthymic; 1: mild depression; 2: moderate/severe depression;High CR: high cognitive reserve; Low CR: low cognitive reserve.

the need for additional studies of the effects of CR on different cognitive functions in patients with BD.

Interestingly, the present findings also showed a significant difference between the cognitive performance of patients with BD and MDD after controlling for mood symptoms and CR. Among euthymic patients with low CR, those with MDD performed worse than those with BD on the majority of cognitive functions, with low to moderate effect sizes. The opposite occurred in the high CR group. There is also variability with regards to the differences in cognitive performance between BD and MDD as a whole (Liu et al., 2019; Samamé et al., 2017; Terachi et al., 2017). The present findings suggest that the variability in previous studies could be caused by individual differences in CR. It is possible that within each diagnostic category, some individuals may be particularly vulnerable to cognitive impairment as a result of low CR. This variable may also interact with current mood and affect patients with BD and MDD in different ways. As such, it is important that CR and

its association with other clinical variables be investigated in future studies of cognition in mood disorders.

Differences in the neuroprotective effects of CR on the clinical groups evaluated may indicate specific neurocognitive mechanisms for BD and MDD. One implication of such findings lies in the potential of CR as a possible target for intervention, considering that CR is measured by lifetime events that are modifiable (e.g., education, occupation and daily cognitive stimulation) (Stern et al., 2018). As observed, in the absence of compensatory processes such as CR it is possible that individuals with BD in a major depressive episode may present more significant changes in neurocognitive functioning compared to MDD. Therefore, this subgroup of individuals with BD may benefit from interventions aimed at CR.

The present findings should be interpreted in light of some limitations. We did not control for the effects of medication, which may have affected cognitive performance in some of participants studied. The same is true for clinical variables such as the number of mood episodes, illness duration or previous hospitalizations. The reason these variables were not included in the present study is that patients could only provide this information via self-report, and we had no objective means of confirming the data (e.g. through medical records). Self-report of clinical symptoms is notoriously unreliable in patients with mood disorders, especially given the impairments in autobiographical memory experienced by these individuals (Bozikas et al., 2019; Tremain et al., 2019). As such, rather than risking the inclusion of potentially biased or mistaken data in our study, we opted to exclude these variables altogether.

Despite these limitations, the present study makes an important contribution to the literature by suggesting that CR may be protective against cognitive impairment in both BD and MDD. These effects were observed in euthymia, as well as during depressive episodes of varying severity. These findings highlight the importance of investigating and controlling for CR and depressive symptom severity when evaluation cognition in mood disorders. The identification of variables which can influence cognitive function in mood disorders may shed light on the reasons for the cognitive heterogeneity within these populations, and help inform treatment interventions. Future studies may wish to investigate these variables in larger samples, with different patterns of episode duration, and adopting a longitudinal design, in order to make more definitive claims regarding the direction of the relationship between RC, depressive symptoms and cognitive performance.

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Author contributions

André Ponsoni was involved in study design, data collection and manuscript drafting. Laura Damiani Branco contributed to data collection, data analysis and manuscript drafting. Charles Cotrena was involved in data collection and manuscript drafting. Flávio Shansis contributed to data collection and manuscript drafting. Rochele Paz Fonseca was involved in manuscript drafting. All authors read and approved the final version of this manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.143.

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