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ORIGINAL ARTICLE

Cognition and functioning in bipolar depression

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Objectives: Depressive symptoms are associated with worse outcomes in patients with bipolar disorder (BD). However, scarce data are available regarding neurocognitive profiles across different areas of functioning among BD patients with moderate and severe depression. Our objective was to assess cognition and global functioning in a group of patients with bipolar depression.
Methods: Data were available for 100 patients with bipolar depression (78% female) and 70 controls (64% female) paired by age and education level. Cognitive function was assessed with a neuropsychological test battery. Functioning was assessed with the Functioning Assessment Short Test.
Results: In patients, severe depression was associated with poorer cognitive performance on measures of executive function. Patients with severe depression showed worse global functioning than those with moderate depression ($z = 2.54$, $p = 0.011$). In patients with severe depression, lower global functioning was associated with lower scores in working memory ($r = -0.200$, $p = 0.010$), and executive function ($r = -0.210$, $p = 0.007$; and $r = 0.293$, $p < 0.001$).
Conclusion: Our findings suggest cognitive impairment and global functioning impairment are associated with the severity of depressive symptoms in bipolar depression. Intensive treatment of depressive symptoms in patients with BD is crucial to improve cognitive functioning and, consequently, functional outcomes.

Keywords: Memory; mood disorders, bipolar; tests/interviews, psychometric; cognitive neuroscience, outcome studies

Introduction

Bipolar disorder (BD) is a chronic, severe, and recurring mood disorder that may also affect cognitive performance and functioning.[1-6] More than 60% of patients with BD have difficulties in performing daily-life routines.[7] Presence of depressive symptoms is associated with worse outcomes.[8] Cognitive impairments in BD are consistently observed during mood episodes.[9-12] However, they can also be identified during euthymia. Cognitive deficits are associated with social impairment and worse course of illness,[13] and contribute significantly to functional disability, impacting global functioning.[14-16]

Deficits in verbal and visual memory and in executive functioning have been demonstrated during depressive episodes,[11] whereas executive dysfunction and attention deficits have been reported in association with manic episodes.[12] A study by Buoli et al.[17] showed that patients with BD assessed during mixed or depressed states performed slightly better than manic patients. However, the data available in the literature are controversial. Other cross-sectional studies have found that depressed patients are the most compromised group in terms of cognition among bipolar patients, especially regarding executive function[18] and motor abilities.[11] Severity of depressive symptoms has been positively correlated with cognitive dysfunction in non-BD samples.[19] However, we were not able to find studies evaluating whether the severity of depressive symptoms can be associated with impaired functioning and cognitive deficits in BD.

The association between depressive episodes and impaired global functioning in dimensions such as work, social life, and family relationships is well documented. In recent studies, neurocognition and emotional regulation were shown to have an important impact on depressive symptoms, which influence psychosocial global functioning.[20] A recent study of patients with type I and II BD (BD-I and BD-II) confirmed verbal memory as a mediator in the relationship between depressive symptoms and functioning. After a 1-year follow-up, subthreshold depressive symptoms predicted worse functional outcome mediated by verbal composite memory scores.[21] However, the study included only euthymic patients with at least a

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moderate level of functional impairment, which may hinder generalization of these results.

Although BD-II is considered a less severe form of BD-I, it is known that the burden of disease does not differ between groups with respect to clinical severity, impairment, patterns of comorbidity, suicide attempts, family history, and treatment. It has also been suggested that patients with BD-II experience the same functional impairments subjects with BD-I may have. During euthymia, both subtypes present similar cognitive deficits with only subtle differences.[22-24] However, during acute depressive episodes, BD-I patients have shown more prominent cognitive impairment compared to unipolar and BD-II patients.[25] This difference may be due to the fact that patients with BD-I report more psychosis than patients with BD-II.[1]

In brief, patients with BD experience impairments in various domains of cognition and global functioning, especially during mood episodes. However, whether severe depression confers additional cognitive and global functioning burdens in this population is unknown. To date, there have been no systematic reports describing neurocognitive profiles in relation to global functioning among BD patients with moderate and severe depression. We set out to study dimensions of cognition and global functioning among BD patients and paired healthy controls, with the hypothesis that cognitive and global functioning impairments would be associated with the severity of depressive symptoms in BD-I and BD-II patients with depression. In addition, we expected that patients with severe bipolar depression would exhibit worse cognitive impairment and global functioning when compared to those with moderate depression.

Methods

Patients with a diagnosis of BD-I or BD-II established by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), between the ages of 20 and 71, were assessed and compared with healthy controls. Eligible patients were required to be experiencing a moderate to severe depressive episode, as determined by a minimum Montgomery-Åsberg Depression Rating Scale (MADRS) score of 12. We further subdivided the patients by severity of major depressive episode into severe and moderate subsets, based on the group median MADRS score. Although this has limitations, we believe it is a reasonable method for achieving a balance between having a high-scoring group and preserving maximum power. The SCID-I and MADRS were administered by experienced psychiatrists. Patients with intellectual disability, defined as an intelligence quotient (IQ) < 70 on the basis of estimates of intellectual functioning measured using the block design and vocabulary subtests of the Wechsler Intelligence Scale for Adults, 3rd edition (WAIS-III), were excluded, as were those with severe clinical illnesses (detected during clinical interviews or during review of medical records).

Controls were selected among blood donors attending a donation center or among chaperones of patients seen at other (non-psychiatric) outpatient units of Hospital de Clínicas de Porto Alegre (HCPA), Brazil; paired by age and sex; and screened using the SCID-I. Subjects with psychiatric symptoms and those who reported having first-degree relatives diagnosed with BD, schizophrenia, or other psychotic disorders were excluded.

The study protocol was approved by the HCPA Ethics Committee, and all participants signed an informed consent form prior to their inclusion in the study.

Assessment

Cognitive functioning was assessed using the WAIS-III digit span subtest[26] (both forward and backward). This test was chosen because it is established in the literature as a means of assessing attention and auditory working memory,[27] skills often impaired in BD. WAIS-III is fully validated in Brazil and has been standardized in our neuropsychiatric battery.[26] We also used the categories completed and perseverative errors parameters of the Wisconsin Card Sorting Test (WCST). This test has been also adapted and standardized to Brazilian Portuguese and can be used with children and adults.[28] WCST and the WAIS-III digit span subtest evaluate executive function (working memory). Impairment in this cognitive domain has been reported as very relevant, and has been indicated by the International Society for Bipolar Disorders (ISBD) as a primary focus of research in patients with BD.[29]

Global functioning was assessed using the Functioning Assessment Short Test (FAST). This instrument was developed to evaluate functional impairment and has been validated in patients with BD, showing excellent test-retest reliability and internal consistency, with a Cronbach's alpha coefficient of 0.95 for the whole scale and excellent test-retest agreement for total FAST scores ($r = 0.90$; $p < 0.001$).[30,31] Previous studies have shown that patients with BD have lower FAST functioning scores compared with healthy controls, and that functional impairment is age-related in patients with BD.[31]

Statistical analysis

Cognitive and global functioning variables were normalized with a Box-Cox data transformation[32] to enable use of parametric analyses. Analysis of variance (ANOVA) was used to compare group differences (BD vs. control and severe vs. moderate depression scores) in means. Chi-square tests were used to compare categorical group differences, and Pearson's coefficient was used for correlations. A normal distribution could not be achieved for functioning scores, which were thus analyzed with nonparametric tests. Comparisons between mean results were adjusted for gender, the only variable significantly different between patients and controls. Effect sizes are described using Hedges' g.[33] Results were considered statistically significant when $p < 0.05$ (two-tailed). As this is an exploratory investigation, an adjustment for multiple comparisons was not undertaken.

Results

A total of 100 patients with bipolar depression and 70 healthy controls were included in the sample. Sociodemographic and clinical characteristics of the sample are shown in Table 1. The median MADRS score in the BD

Table 1 Characteristics of the sample

	Bipolar depression (n=100)	Controls (n=70)
Age, mean ± SD	42.3±10.1	41.4±13.1
Female sex, %*	78	64
Years of education, mean (range)	11 (9-14)	12 (8-15)
MADRS, mean ± SD	27.4±7.8	N/A
YMRS, mean (range)	0 (0-2)	N/A
Type I bipolar disorder, %	68	N/A
Current treatment, %		
Lithium	52	
Other mood stabilizers	59	
Atypical antipsychotics	16	
Typical antipsychotics	12	
Antidepressants	20	
Benzodiazepines	43	

MADRS = Montgomery-Åsberg Depression Rating Scale; N/A = not available; SD = standard deviation; YMRS = Young Mania Rating Scale.
*$p < 0.05$.

group was 27; this score was used as a cutoff point to distinguish between moderate and severe depression.

Patients with bipolar depression showed worse working memory scores when compared with controls ($F_1 = 3.93$, $p = 0.049$). Executive functioning was also impaired in patients, who had a higher number of perseverative errors ($F_1 = 10.66$, $p = 0.002$), and a lower number of categories completed ($F_1 = 3.92$, $p = 0.049$) in the WCST compared with healthy controls. When patients were divided by median MADRS score (cutoff score = 27), the effect sizes of this difference were greater in patients with severe depression (Figure 1). Among patients with bipolar depression, no differences between severity groups were observed in use of lithium, other mood stabilizers, typical or atypical antipsychotics, benzodiazepines, or antidepressants.

Global functioning scores were significantly different between patients and controls ($z = 10.11$, $p < 0.001$). Patients with severe depression showed greater impairment of global functioning than did those with moderate depression ($z = 2.54$, $p = 0.011$). Lower global functioning was associated with lower scores on the digit span scale ($r = -0.200$, $p = 0.010$), fewer categories completed ($r = -0.210$, $p = 0.007$), and more frequent perseverative errors ($r = 0.293$, $p < 0.001$). These associations were observed only in patients with severe depression (Figure 2).

Discussion

The present study investigated cognition and global functioning in a group of patients with bipolar depression compared with healthy controls. Our main findings include impairment of global functioning among BD patients with severe depression and an association between lower global functioning and cognitive impairment in patients with severe depression. Our findings also confirmed previous research suggesting impairments in working memory and executive function among BD patients with depression when compared with healthy controls. The effect size of the differences in executive function was greater in patients with severe depression than in patients with moderate depression.

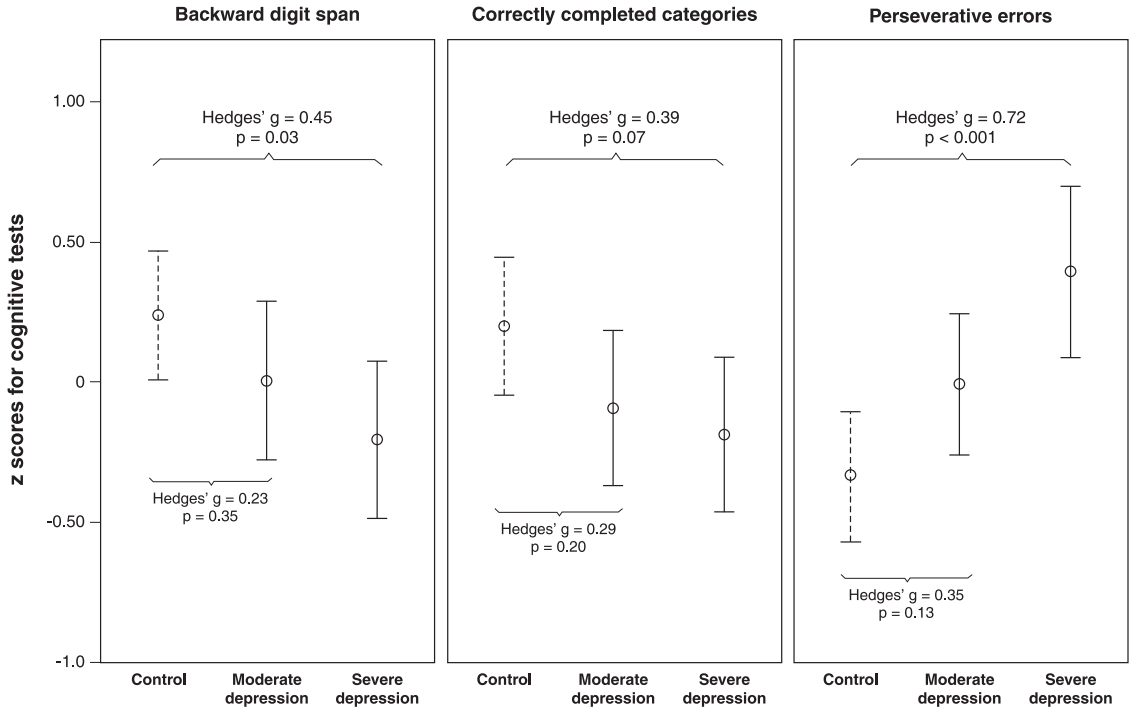


Figure 1 Comparison between healthy controls, patients with moderate depression, and patients with severe depression in domains of cognition.

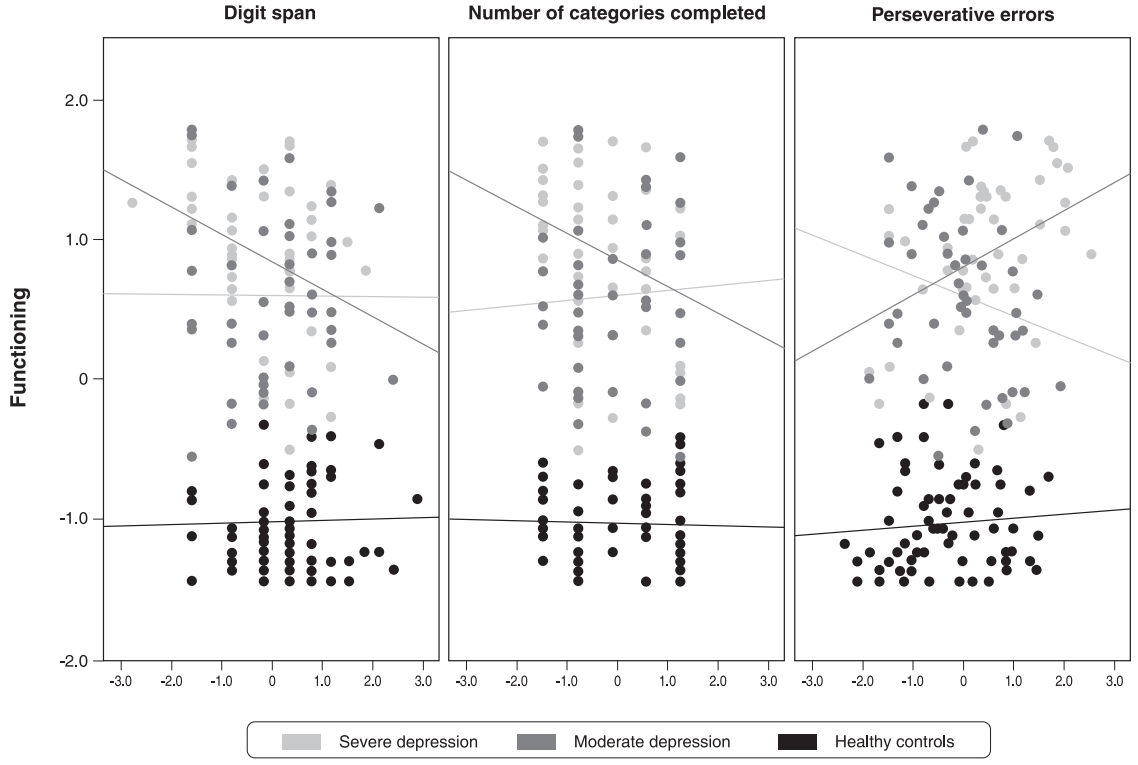


Figure 2 Correlations between domains of cognition and functioning. The y axis represents functioning as measured by the Functioning Assessment Short Test (FAST; the higher the score, the poorer the functioning); the x axis represents standardized scores.

The present data also add to the notion that cognitive performance among bipolar patients varies as a function of the severity of depression, especially because only patients with severe depression showed impairment in executive function and working memory compared to healthy controls. The results of this study confirm previous findings that showed a role of depressive symptoms and cognitive impairment in global functioning in BD patients, and highlight the fact that depressive symptoms also affect cognitive performance.[21] Our results are also partially consistent with a study by Bonnin et al.,[34] which showed that patients exhibiting low levels of subthreshold symptomatology (Hamilton Depression Rating Scale [HDRS] $\leqslant$ 3 and Young Mania Rating Scale [YMRS] $\leqslant$ 2), defined as asymptomatic, and those with higher levels of subthreshold symptomatology (HDRS $\geqslant$ 4 and YMRS $\geqslant$ 3), defined as subsyndromic, both scored low on cognitive measures when compared to healthy controls. The subsyndromic group also had poorer functional outcomes than the asymptomatic group and healthy controls. In our sample, patients showed impairment in executive function and working memory compared to healthy controls, and patients with higher MADRS scores also exhibited impairment in executive function and working memory as compared to those patients with lower MADRS scores. These findings and those of the aforementioned studies help clarify the role of depressive symptoms in global functioning and cognitive performance, and especially in executive function. Our hypothesis is that executive function impairment can cause loss of adaptive plasticity and ineffective responses of perseverance, which, in turn, may impact global functionality and intensify depressive symptoms.[20]

These findings also can be interpreted in light of the potential impact of impaired attention, concentration, and flexibility as observed in these patients - abilities that are necessary to successfully engage in social and work interactions and to achieve adequate functional performance.[11] Furthermore, functional impairments are considered potential indicators of the chronicity and deterioration observed in BD.[35] However, in the present study, functional impairment was associated with deficits in working memory and executive function only in patients with severe depression. This finding may point to a possible heterogeneity of the mechanisms underlying functional impairment in BD.

A limitation of the present study is the fact that only patients experiencing a depressive episode were assessed. Future studies are warranted to investigate alterations specifically related with different phases of illness. Another important limitation is that duration of illness was not assessed in the protocol, which precluded investigation of whether cognitive impairment would be associated with the late stages of BD, as previously reported.[35] FAST is a valid instrument for evaluation of functioning in patients with BD.[30,31] However, it poses some limitations, such as the limited number of questions and the fact it is rated by a clinician. Another major limitation is that, as all patients were experiencing a depressive episode, their depressive symptoms may have affected vigilance and engagement during the cognitive assessment, thus impairing cognitive performance. Finally, the cross-sectional design of the study

prevents the establishment of a causal relationship between global functioning and cognitive deficits. Cohort studies are needed to provide stronger evidence and establish whether such relationships exist. Strengths of the present study include the fact that results were not impacted by age or educational attainment in the comparisons between BD patients and controls, or by use of psychiatric medication between BD severity subgroups.

In summary, the present study demonstrated an association between severity of depressive symptoms and variation in global functioning and cognition, especially in working memory and executive function, among patients with bipolar depression. Within this context, an assessment of the pattern of cognitive performance and of its impact on global functioning may help improve treatment planning for patients with bipolar depression.

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Disclosure

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