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Cognition and functioning in bipolar depression

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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, worse course of illness,[13] and contribute significantly to functional disability, impacting global functioning.[14-16]

Verbal and visual memory, and executive functioning deficits have been shown in 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 bipolar disorders assessed during mixed or depressed states presented slightly better performance than manic patients. However, the available data 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 in executive function [18] and motor abilities.[11] Severity of depressive symptoms has been positively correlated to 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 to impaired functioning and cognitive deficits in BD patients.

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 showed an important impact on depressive symptoms, which influence psychosocial global functioning.[20] A recent

important study of patients with BD I and II has confirmed verbal memory as a mediator in the relationship between depressive symptoms and functioning. After a 1-year follow-up, subthreshold depressive symptoms predicted a worse functional outcome mediated by verbal composite memory scores.[21] However, the study included only euthymic patients with at least moderate level of functional impairment, which may hinder the generalization of these results.

Although the type II (BPII) Bipolar disorder is considered a less severe form of bipolar I (BPI) disorder, it is known that the burden of disease does not differ between the groups with respect to clinical severity, impairment, patterns of comorbidity, suicide attempts, family history and treatment patterns. It is also suggested that patients with BPII have the same functional impairments subjects BPI may have. Both subtypes, BPI and BPII, during euthymia, present similar cognitive deficits with subtle differences.[22-24] However, during acute depressive episodes, BD I patients showed more prominent cognitive impairment compared to unipolar and bipolar 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]

Summarizing, patients with BD have impairments in various domains of cognition and global functioning, especially during mood episodes. However, it is unknown if severe depression confers additional cognitive and global functioning burden in this population. To date, there are no systematic reports describing neurocognitive profiles in relation to global functioning among BD patients with moderate and severe depression. We set forth to study dimensions of cognition and global functioning among BD patients and paired healthy controls. We hypothesized that cognitive and global functioning impairments are associated with the severity of depressive symptoms in BD I and II patients with depression. In addition, we expected that patients with severe

bipolar depression showed worse cognitive impairment and global functioning when compared with those with moderate depression.

Methods

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

Controls were selected among blood donors attending a hemotherapy center or among people accompanying patients seen at other outpatient units (except for the psychiatric unit) at Hospital de Clínicas de Porto Alegre, paired by age and sex, and were screened also using the SCID-I. Subjects showing 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 Research Ethics Committee of Hospital de Clínicas de Porto Alegre, and all participants signed an informed consent form prior to their inclusion in the study.

Assessment

Cognitive functioning was assessed using the digit span subtest from WAIS-III[26] (both forward and backward). Digit span from WAIS III was chosen because it is an established test in the literature to assess attention and auditory working memory[27], skills often impaired in Bipolar Disorder. WAIS III is fully validated in Brazil and has been standardized in our neuropsychiatric battery[26]. We also used categories completed and perseverative errors from 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 digit span subtest from WAIS-III 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 bipolar disorder, showing excellent test–retest reliability and internal consistency (Cronbach's alpha was 0.95 for the whole scale and Test–retest agreement for total FAST scores was excellent ($r=0.90;P<0.001$).[30,31] Previous studies showed that patients with BD had lower functioning scores in the FAST compared with healthy controls and functional impairment is age-related in patients with BD[31].

Statistical analysis

Cognitive and global functioning variables were normalized with Box-Cox data transformation[32] to enable the use of parametric analyses. ANOVA was used to compare group differences (bipolar disorder versus control and severe versus moderate depression scores) in means, chi-square tests to compare categorical group differences and Pearson's coefficient was used for correlations. A normal distribution could not be achieved for functioning scores, and they were analyzed with non-parametric tests. Comparisons between mean results were adjusted for gender, the only variable with significant differences between patients and controls. Effect sizes are described using Hedges's g[33] . Results were considered statistically significant when (two-tailed) $p<0.05$. Since 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. Median MADRS score in the BD group was 27; this score was used as a cutoff point to distinguish between moderate and severe depression.

Insert Table 1 near here

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 according to MADRS median score (cutoff score of 27), the effect sizes of this difference were higher in patients with severe depression (Figure 1). Among patients with bipolar depression, no differences between severity groups were observed in the use of lithium, other mood stabilizers, typical or atypical antipsychotics, benzodiazepines and antidepressants.

Insert figure 1 near here

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

Insert Figure 2 near here

Discussion

The present study investigated the cognition and global functioning in a group of patients with bipolar depression compared with healthy controls. Our main results showed global functioning impairment among BD patients with severe depression and an association between lower global functioning and cognitive impairment in patients with severe depression. Our results 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 on executive function was higher in patients with severe depression when compared with those patients with moderate depression.

The present data also adds 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 the role of depressive symptoms and cognitive impairment on 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 shows that patients presenting "low subthreshold symptomatology" (Hamilton Depression Rating Scale ≤3 and Young Mania Rating Scale ≤2) and "high subthreshold symptomatology" (Hamilton Depression Rating Scale ≥4 and Young Mania Rating Scale ≥3) had low scores in cognitive measures when compared to the healthy control group. The group with higher symptomatology also showed poorer functional outcomes compared to the group with lower symptomatology and healthy controls. We also reported that patients showed impairment in executive

function and working memory compared to healthy controls, and patients with higher scores in MADRS scale showed also impairment in executive function and working memory than those patients with lower scores in MADRS scale. All these studies help to clarify the role of the depressive symptoms in global functioning and cognitive performances, especially in executive function. Our hypothesis is that executive function impairment can cause loss on adaptive plasticity and ineffective responses of perseverance, which, in turn, may impact the 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 an 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 bipolar disorder.

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 the illness. Another important limitation is that "duration of illness" was not assessed in the protocol. That prevented us to investigate whether the cognitive impairment would be associated with the late-stages of illness as previously reported.[35] FAST is a valid instrument to evaluate functioning in patients with BD[30,31]. However, there are some limitations related to the instrument as the limited number of questions, and the fact it is rated by a clinician. Another important

limitation is that patients were in a depressive episode. Then, there is the possibility that the depressive symptoms affected vigilance and engagement during the cognitive assessment, impairing the cognitive performance of these patients. Finally, the cross-sectional design of the study prevents the establishment of a causal relationship between global functioning and cognitive deficits. Cohort studies are warranted so that we can obtain stronger evidence and thus establish such relationships. Nonetheless, this study has certain merits. The results were not impacted by age or years of education in the comparison between patients with BD and controls, or use of psychiatric medication between BD severity subgroups.

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

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Ana Carolina Peuker, Ana Cláudia Loredo, Letícia Czepielewski, Federico Troiano and Gabriel Fries report no financial relationships with commercial interests.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders - DSM-IV-TR. 4ª ed. Porto Alegre: Artmed; 2002.
2. Chaves OC, Lombardo LE, Bearden CE, Woolsey MD, Martinez DM, Barrett JA, et al. Association of clinical symptoms and neurocognitive performance in bipolar disorder: a longitudinal study. Bipolar Disord. 2011;13:118-23.
3. Hellvin T, Sundet K, Simonsen C, Aminoff SR, Lagerberg TV, Andreassen OA, et al. Neurocognitive functioning in patients recently diagnosed with bipolar disorder. Bipolar Disord. 2012;14:227-38.
4. Leboyer M, Kupfer DJ. Bipolar disorder: new perspectives in health care and prevention. J Clin Psychiatry. 2010;71:1689-95.
5. Mann-Wrobel MC, Carreno JT, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. Bipolar Disord. 2011;13:334-42.
6. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand Suppl. 2007; 434:17-26.
7. MacQueen GM,Young LT, Joffe RT. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatr.Scand. 2001; 103:163–170.

8. Strejilevich SA, Martino DJ, Murru A,Teitelbaum J, Fassi G, Marengo E, Igoa A, Colom F..Mood instability and functional recovery in bipolar disorders. Acta Psychiatr. Scand. 2013;128:194–202.

9. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord. 2006; 93:105-15.

10. Iosifescu DV. The relation between mood, cognition and psychosocial functioning in psychiatric disorders. Eur Neuropsychopharmacol. 2012;22 Suppl 3:S499-504.

11. Malhi GS, Ivanovski B, Hadzi-Pavlovic D, Mitchell PB, Vieta E, Sachdev P. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. Bipolar Disord. 2007; 9:114-25.

12. Martinez-Aran A, Vieta E, Colom F, Torrent C, Sanchez-Moreno J, Reinares M, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord. 2004; 6:224-32.

13. Sachs G, Schaffer M, Winklbaur B. Cognitive deficits in bipolar disorder. Neuropsychiatry. 2007; 21:93-101.

14. Fox KH, Davis VG, Kennel C, Walker TM, Burdick KE, Harvey PD. The Brief Assessment of Cognition In Affective Disorders (BAC-A): Performance of patients with bipolar depression and healthy controls. J Affect Disord. 2014; 166:86-92.

15. Depp CA, Mausbach BT, Harmell AL, Savla GN, Bowie CR, Harvey PD, et al. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. Bipolar Disorder. 2012; 14: 217–26.

16. Harvey PD, Wingo AP, Burdick KE, Baldessarini RJ. Cognition and disability in bipolar disorder: lessons from schizophrenia. Bipolar Disorder. 2010; 12: 364–75.

17. Buoli M, Caldiroli A, Caletti E, Zugno E, Altamura AC. The impact of mood episodes and duration of illness on cognition in bipolar disorder. Compr Psychiatry. 2014; doi: 10.1016/j.comppsych.2014.06.001. [Epub ahead of print]

18. Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry. 2004;161:262-70.

19. Lawrence C, Roy A, Harikrishnan V, Yu S, Dabbous O. Association between severity of depression and self-perceived cognitive difficulties among full-time employees. Prim Care Companion CNS Disord. 2013;15(3).

20. Van Rheenen TE, Rossell SL. Objective and subjective psychosocial functioning in bipolar disorder: an investigation of the relative importance of neurocognition, social cognition and emotion regulation. J Affect Disord. 2014;162:134-41.

21. Bonnín Cdel M, González-Pinto A, Solé B, Reinares M, González-Ortega I, Alberich S, et al. CIBERSAM Functional Remediation Group. Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder. J Affect Disord. 2014;160:50-4.

22. Solé B, Bonnin CM, Mayoral M, Amann BL, Torres I, González-Pinto A, et al. the CIBERSAM Functional Remediation Group. Functional remediation for patients with bipolar IIdisorder: Improvement of functioning and subsyndromal symptoms. EurNeuropsychopharmacol. 2014; doi: 10.1016/j.euroneuro.2014.05.010. [Epub ahead of print]

23. Dittmann S, Hennig-Fast K, Gerber S, Seemüller F, Riedel M, Emanuel Severus W, et al. Cognitive functioning in euthymic bipolar I and bipolar II patients. Bipolar Disord. 2008;10:877-87.

24. Pålsson E, Figueras C, Johansson AG, Ekman CJ, Hultman B, Östlind J, et al. Neurocognitive function in bipolar disorder: a comparison between bipolar I and II disorder and matched controls. BMC Psychiatry. 2013;13:165.

25. Xu G, Lin K, Rao D, Dang Y, Ouyang H, Guo Y, et al. Neuropsychological performance in bipolar I, bipolar II and unipolar depression patients: a longitudinal, naturalistic study. J Affect Disord. 2012;136:328-39.

26. Nascimento, E. "Adaptação, validação e normatização do WAIS-III para uma amostra brasileira," in WAIS-III: Manual Para Administração e Avaliação, D. Wechsler, Ed., Casa do Psicólogo, São Paulo, Brazil, 2004.

27. Lera-Miguel S, Andres-Perpina S, Fatjo-Vilas M, Fanana L, Lazaro L. Two-year follow-up of treated adolescents with early-onset bipolar disorder: Changes in neurocognition. J Affect. Disord. 2015; 48-54

28 . Heaton RK, Chelune GJ, Talley JL. Teste Wisconsin de Classificação de Cartas. São Paulo: Casa do Psicólogo; 1981 [Wisconsin Card Sorting Test].

29. Yatham LN, Torres IJ, Malhi GS, Frangou S, Glahn DC, Bearden CE, et al. The International society for bipolar disorders-battery for assessment of neurocognition (ISBD-BANC). Bipolar Disord. 2010;12:351–363.

30. Cacilhas AA, Magalhaes PV, Cereser KM, Walz JC, Weyne F, Rosa AR, et al. Validity of a short functioning test (FAST) in Brazilian outpatients with bipolar disorder. Value Health. 2009;12:624-7.

31. Cacilhas AA, Magalhaes PV, Cereser KM, Walz JC, Weyne F, Rosa AR, et al. Bipolar disorder and age-related functional impairment. Rev Bras Psiquiatr. 2009;31:354-7.

32. Peltier MR, Wilcox CJ, Sharp DC. Technical note: Application of the Box-Cox data transformation to animal science experiments. J Anim Sci. 1998;76:847-9.

33. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. Biol Rev Camb Philos Soc. 2007;82:591-605.

34. Bonnin CM, Sanchez-MorenoJ, Martinez-Aran, A, Sole B, Reinares M, Rosa AR, Goikolea JM, Benabarre A, Ayuso-Mateos JL, Ferrer M, Vieta E, Torrent C. Subthreshold symptoms in bipolar disorder: impact on neurocognition, quality of life and disability. J. Affect. Disord. 2012; 136: 650–9.

35. Rosa AR, Magalhães PV, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, et al. Clinical staging in bipolar disorder: focus on cognition and functioning. J Clin Psychiatry. 2014;75:e450-6.

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

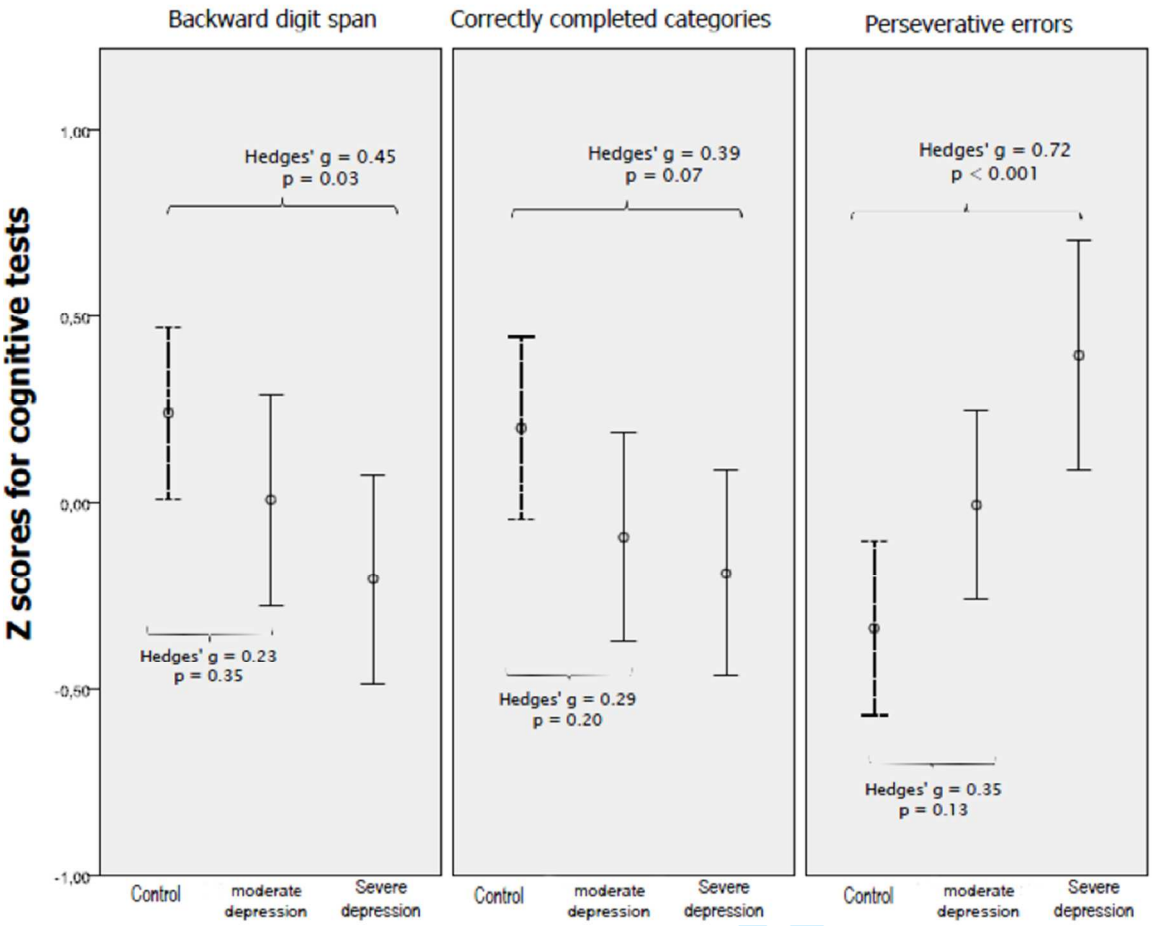

Figure 2. Correlation between domains of cognition and functioning

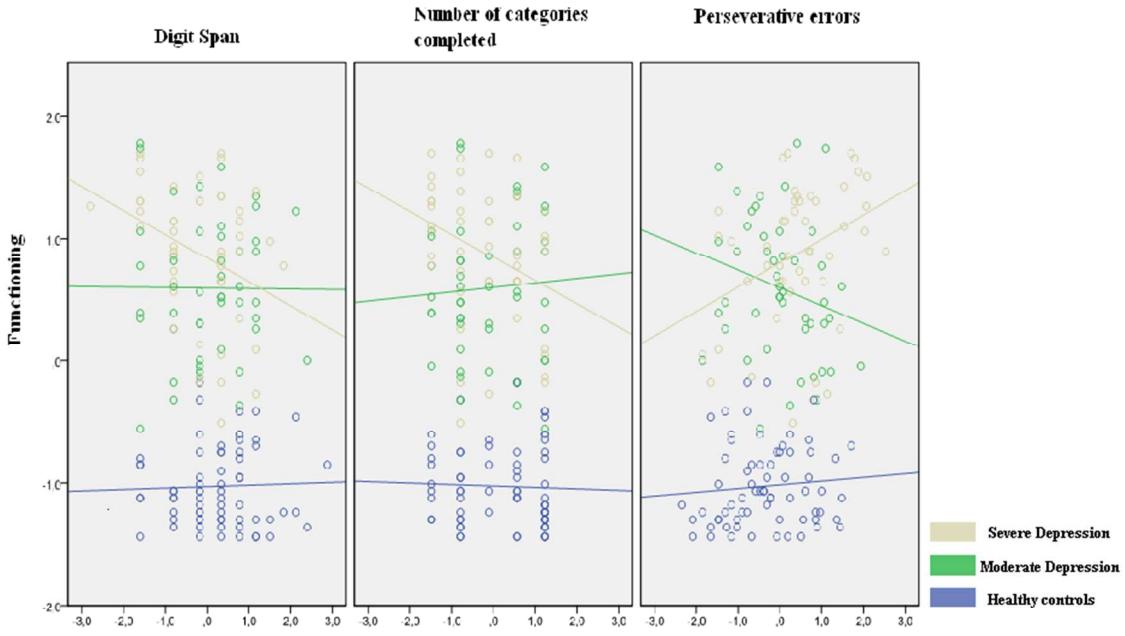

Table 1 Characteristics of the sample

	Bipolar depression (N=100)	Controls (N=70)
Age, mean ± standard deviation	42.3±10.1	41.4±13.1
Female sex (%)*	78	64
Years of education	11 (9-14)	12 (8-15)
MADRS	27.4±7.8	N/A
YMRS	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-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale.

* $p<0.05$