ORIGINAL ARTICLE

Cognitive impairment in a Brazilian sample of patients with bipolar disorder

Prejuízo cognitivo em uma amostra brasileira de pacientes com transtorno do humor bipolar

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Abstract

Objective: *Persistent neurocognitive deficits have been described in bipolar mood disorder. As far as we are aware, no study have examined whether the cognitive impairment is presented in the same way in a Brazilian sample.* ***Method:*** *Cognitive function of 66 patients with bipolar disorder (32 with depressive symptoms and 34 euthymic) and 28 healthy subjects was examined using a complete cognitive battery.* ***Results:*** *Patients with bipolar disorder presented a significantly poorer performance in eight of the 12 subtests when compared to healthy subjects. There was no significant difference between the subgroups of patients. These patients showed impairment in both verbal and non-verbal cognitive function.* ***Conclusion:*** *Cognitive impairment was found in both groups of patients with bipolar disorder. The findings described here suggest an overall impairment of cognitive function, independent of mood symptoms. This is in line with data showing that cognitive deficits may be a persistent characteristic of bipolar disorder.*

Descriptors: *Bipolar disorder; Cognition; Neuropsychology; Memory; Attention*

Resumo

Objetivo: *Déficits neurocognitivos persistentes têm sido descritos no transtorno do humor bipolar; entretanto, não há estudos em amostras brasileiras para avaliar se o prejuízo se apresenta da mesma forma.* ***Método:*** *Foi realizada uma avaliação cognitiva em 66 pacientes bipolares (32 com sintomas depressivos e 34 eutímicos) e 28 controles, utilizando-se uma bateria cognitiva completa.* ***Resultados:*** *Em oito dos 12 subtestes avaliados os pacientes apresentaram desempenho significativamente inferior em relação aos controles. Não houve diferença significativa entre os grupos de pacientes. Foram encontrados prejuízos cognitivos tanto na área verbal como na área não verbal da cognição.* ***Conclusão:*** *Foi observada uma performance inferior em ambos os grupos de pacientes com transtorno bipolar. As dificuldades cognitivas encontradas apontam para um prejuízo global no funcionamento cognitivo, independente da presença de sintomas, sugerindo estabilidade ou cronicidade dos déficits cognitivos.*

Descritores: *Transtorno bipolar; Cognição; Neuropsicologia; Memória; Atenção*

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Introduction

Bipolar disorder (BD) is a common disorder which affects approximately 1% of the population, and this prevalence may increase according to the diagnostic criteria used in each study.[1] BD is characterized by episodes of mania, depression and mixed episodes. However, longitudinal studies showed that patients spend most of the time with depressive symptoms, outstripping mania and hypomania by a ratio of 3:1.[2-5] Moreover, BD is associated with chronicity and severity features such as low remission rates,[6] high suicide rates,[7] high prevalence of clinical[8] and psychiatric[9,10] comorbidities. There is also evidence of significant functional impairment in patients with BD. Studies suggest that patients experience difficulties in psychosocial and occupational functioning,[4,6,11,12] and in interpersonal relationships.[13,14] Furthermore, BD is associated with poorer quality of life,[15,16] and cognitive impairment.[17,18]

Researchers have made a great effort to understand the cognitive impairment associated with BD. There is now enough evidence that patients with BD show cognitive impairment during acute phases of illness, which persists during inter-episode periods, even when mood is euthymic. Previous studies have shown that euthymic patients have cognitive deficits, including impairment in learning and verbal memory, executive function and motor coordination.[19-21] In addition, clinical characteristics such as duration of illness, number of previous episodes, suicide attempts and hospitalizations appear to be associated with greater cognitive impairment.[20,22]

Cognitive impairment is a major concern in BD field due to a close association with functional impairment. The understanding of cognitive function in BD could potentially contribute to the development of better strategies to improve overall functioning. Between 30% and 50% of patients with BD experience significant social disability that may be related to persistent cognitive impairment.[23,24] Specifically, memory and learning difficulties, as well as impaired executive function appear to be related to poor psychosocial functioning experienced by the patients even when they are in remission.[25,26]

As far as we know, no studies have examined whether cognitive impairment is present or not on Brazilian samples in a similar way. Thus, the purpose of this study is to examine the cognitive performance of patients with BD, within a depressive episode and with euthymic mood, compared to healthy subjects. We hypothesize, a priori, that bipolar patients with depressive symptoms would perform worse than those with euthymic mood and worse than healthy controls.

Method

1. Subjects

This is a cross-sectional study, in which the patients were recruited in the Bipolar Disorder Program at Hospital de Clínicas de Porto Alegre. The patients were invited to participate in the study verbally on the day they visited the outpatient clinic, or through a phone call from the researchers based on registration list supplied by the institution. All the patients were diagnosed by trained researchers, using the Structured Clinical Interview of DSM-IV.[27] The presence of symptoms of depression and mania was measured using the Hamilton Depression Rating Scale (HRSD)[28] and the Young Mania Scale (YMRS).[29] A total of 93 patients were assessed initially to participate in the study. However, one was excluded because he had undergone Electroconvulsive Therapy (ECT) less than 6 months previously, six because they had a history of alcohol or drug abuse in the last 6 months, six because of a prior history of neurological disease, eight because they had hypomanic symptoms, and six because they were illiterate. Finally, 32 patients who had depressive symptoms at the time, with scores greater than or equal to 8 on the HDRS,[30] 34 euthymic patients with a score less than 8 on the HDRS and score less than 10 on the YMRS[31] were recruited to participate in this study. Twenty-eight healthy subjects without a history of psychiatric disease, diagnosed using the Structured Clinical Interview of DSM-IV,[27] or a neurological one, were recruited. We ascertained that the healthy individuals did not have a first-degree relative with bipolar mood disorder. The healthy subjects were sampled according to convenience, and the participants were hospital employees, students and people from the community at large indicated by the controls that had been evaluated themselves. The sample size was calculated based on results of a previous study[20] looking for a difference between euthymic bipolar individuals and controls, with a significance level set at 0.05, with 80% power, and the sample was calculated to have a minimum of 31 subjects in each group. This study was approved by the Hospital Ethics Committee (No. 03-186). All the subjects gave their written informed consent to participate in this study after all the procedures had been explained.

2. Cognitive evaluation

After a review of the literature, the Wechsler Adult Intelligence Scale –Third Edition (WAIS III)[32] was chosen as a psychological evaluation instrument. The criterion of choice employed was that the test had already been widely used in neuropsychological evaluation studies on psychiatric patients[17,18,20,22] and that it could evaluate different cognitive skills. The complete cognitive evaluation was performed according to the instructions in the user's handbook, and it was applied by psychologists or psychology students previously trained in a silent environment. The WAIS III[32] subtests used were:

1) Estimated pre-morbid IQ: vocabulary;

2) Verbal area: similarities, arithmetic, digit, information, comprehension, letter-number sequencing;

3) Non-verbal area: picture completion, coding, block design, matrix reasoning, picture arrangement, symbol search.

The Factorial indexes of perceptual organization, operational memory index, processing velocity index, Performance IQ (described below) were calculated. No calculations were performed in the verbal domain, since it was impossible to control statistical analysis for pre-morbid IQ.

1) Factorial Index of Perceptual Organization: picture completion, similarities, information;

2) Factorial Index of Operational Memory: arithmetic, digit, letter-number sequencing;

3) Information Processing Velocity Index: coding, symbol search;

4) Performance IQ: picture completion, coding, block design, matrix reasoning, picture arrangement, symbol search.

3. Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 12.0 was used to perform statistical analysis. The Kolmogorov-Smirnov test was used to test data normality.

The clinical and sociodemographic characteristics of the three groups (with depressive symptoms, euthymic patients and controls) were analyzed using analysis of variance (ANOVA), Chi-square test or Fisher, as appropriate. The three groups were compared regarding cognitive test performance by means of multivariate analysis of variance (MANOVA). Estimated pre-morbid intelligence

and age were the covariates, and three groups were the main factor. Analysis of variance (ANOVA) was used for the factorial indexes and Performance IQ, with the same covariate and main factor employed previously in MANOVA. Tukey's post hoc comparison procedure was used when significant main effects were present. Differences below $p < 0.05$ were considered significant. The effect sizes have been calculated to find the difference between the groups in terms of standard deviation.

Results

1. Clinical and demographic variables

The clinical and demographic variables are shown in Table 1. Differences between the groups were identified as age, pre-morbid IQ and sex. No statistically significant difference was seen for full schooling in years between patients and healthy subjects. There was also no difference in duration of illness, presence of psychosis throughout life and medications used among the group of euthymic patients and the depressed. As to the presence of depressive symptoms evaluated by the HDRS, a statistically significant difference was found among the groups of patients. The groups of patients differed as to the presence of manic symptoms evaluated by the YMRS, but the highest score obtained does not characterize a hypomanic episode.

2. Cognitive variables

The cognitive performance in the WAIS III subtests of the groups of patients with depressive symptoms, euthymic patients and controls is shown in Table 2. The results show the presence of cognitive impairment independent of the presence of depressive symptoms, age and pre-morbid IQ. There was no significant difference between the groups of patients (with depressive symptoms and euthymic), in the subtest performance.

In eight out of the 12 subtests evaluated, the patients presented a significantly poorer performance compared to the healthy subjects ($p < 0.005$). Regarding the effect size, there is a moderate difference between euthymic patients and control group in the Matrix Reasoning subtest. A moderate difference was also demonstrated between depressive patients and controls in the following subtests: Similarities, Arithmetic, Comprehension, Letter-Number Sequencing, Coding and Blocks.

The results of Factorial Indexes and Performance IQ are shown in Table 3. Likewise, both groups of patients obtained significantly lower measures ($p < 0.05$) compared to the comparison group, and there was no significant difference between the groups of patients. Regarding effect size, there is a moderate difference in the Perceptual Organization, Operational Memory, Processing Velocity Indexes and Performance IQ between the group of patients with depressive symptoms and the healthy subjects, as well as between the groups of euthymic patients and controls.

Discussion

As far as we are aware, this is the first study that has assessed global cognitive functioning in bipolar patients in South America. In a previous study, Rocca[33] performed a similar analysis. However Rocca[33] conducted an assessment focused on executive functioning.

As expected, both groups of patients (depressive and euthymic patients) presented a poorer cognitive performance in the verbal and non-verbal areas measured by the WAIS III[32] compared to

Table 1 - Clinical and demographic characteristics of the bipolar patients with depressive symptoms, euthymic patients and controls

Characteristics	Patients with depressive symptoms (n = 32)		Euthymic patients (n = 34)		Controls (n = 28)		
	Mean	SD	Mean	SD	Mean	SD	p
Age (years)	45.2	10.5	42.3	13.1	35.1	14.1	0.009*
Educational level (years)	10.5	3.9	10.6	3.4	12.2	3.0	0.120*
Pre-morbid IQ	85.5	9.4	87.4	10.2	98.6	14.6	0.000*
Hamilton Depression Scale score	15.5	5.5	3.9	2.9			0.000*
Young Mania Rating Scale score	4.3	2.2	1.8	2.3			0.000*
Duration of illness	19.84	11.88	15.44	10.67			0.118*
	n	%	n	%	n	%	p
Sex							0.001**
Male	4	12.5	14	41.2	16	57.1	
Female	28	87.5	20	58.8	12	42.9	
THB – type							
THB I	30	93.8	32	94.1			0.100***
THB II	2	6.2	2	5.9			
Presence of psychosis							
Yes	22	68.8	21	61.8			0.736**
No	10	31.2	13	38.2			
Medication							
Mood Stabilizer							
Yes	30	93.8	31	91.2			
No	2	6.2	3	8.8			0.100***
Typical antipsychotic							
Yes	11	34.4	6	17.6			0.204**
No	21	65.6	28	82.4			
Atypical antipsychotic							
Yes	14	43.8	12	35.3			0.652**
No	18	56.2	22	64.7			
Antidepressants							
Yes	5	15.6	7	20.6			0.639**
No	27	84.4	27	79.4			
Benzodiazepines							
Yes	5	15.6	11	32.4			0.194**
No	27	84.4	23	67.6			

** ANOVA ** Chi-Square *** Fisher*

the healthy subjects. We did not find a difference in the cognitive performance between the group of depressed bipolar patients and the euthymic ones. Possibly this is because there was no difference in the clinical and demographic characteristics of the two groups, as to factors involving severity of the disease, such as duration of illness, presence of psychosis throughout life and medications used. Another possible explanation is that the sample size is not large enough to show this difference, considering that the sample was calculated seeking a difference between euthymic patients and healthy subjects. However, our results agree with most studies[19,21,34,35] that indicate real neuropsychological damage.

As to the verbal area of cognition, both the depressed patients and euthymic group had statistically lower scores than controls in three out of the six subtests applied. The main findings were in the measures sensitive to attention impairment and operational memory (digits, letter-number sequencing, and arithmetic). Attention impairment has already been described in other studies.[31,36] Martinez-Arán et al.,[25] in a study with euthymic type I and II bipolar patients, found attention impairment evaluated by the digits subtest of the WAIS and the Trail Making Test. Thompson et al.,[18] using different evaluation instruments, including the digits backward, found that the patients recalled a smaller number of digits than the controls. One of the important criteria for the diagnosis of depression according to DSM-IV is impaired attention, and this is therefore a bias in our study. Furthermore, it is known that attention is the base of all cognitive processes. When altered it contributes to changes in other functions such as psychomotor skill, learning, memory and executive function.[37] Possibly, therefore, the involvement shown in the other subtests is a consequence of lack of attention, which is a secondary involvement, not a primary one, proper.

Several findings indicate work memory impairment in bipolar patients.[38,39] Thompson et al.[18] in a study with euthymic bipolar patients and controls using the digit as a measure of work memory, found a poorer performance in patients compared to the controls, even after post-hoc analysis to control for residual symptoms that might be confounding the finding. Furthermore, it seems that memory deficits affect the patients' functioning. In a recent study it was demonstrated that euthymic patients with a low level of functioning (GAF < 60) experienced more memory impairment than those with a high level of functioning. This suggests that difficulties in holding and remembering information may be a problem in the occupational and interpersonal functioning of these individuals.[25]

In the non-verbal area of cognition, where visual attention, information processing speed, spatial perception, logical reasoning and orientation are evaluated, the patients had a poorer performance compared to the healthy subjects. This performance may have been influenced by the fact that four out of the six subtests that make up this area are timed. Thus, it is possible that patients with depressive symptoms who are using psychotropic drugs and who may present psychomotor slowness achieve a poorer performance compared to the healthy subjects, but since the patients participating in our study used different medications, sometimes even more than one, it was impossible to isolate any interference by this confounding factor. In a recent study[40] comparing a sample of lithium-treated euthymic bipolar outpatients and controls, it was found that the patients presented cognitive impairment in the executive domain and in the processing speed even after the subclinical symptoms were controlled. According to these authors, the results suggest that neuropsychological impairment may be an expression of the disease phenotype and not necessarily be related to other characteristics such as more severe illness or polypharmacy. In another study comparing euthymic bipolar patients on monotherapy with lithium or valproate, both groups performed worse compared to the controls, especially in the memory tests, which suggests that the two medications have a similar effect on immediate verbal memory, or also that the cognitive deficit is intrinsic to the BD.[41]

Although we have not been able to evaluate the effect of clinical factors on cognition, a series of prior studies has looked at this topic. Data suggest that the size of the deficit is related to the severity of symptoms during the active phases of the disease or

Table 2 - Cognitive performance in the WAIS III subtests of bipolar patients with depressive symptoms, euthymic patients and controls

Subtest	Patients with depressive symptoms (n = 32)		Euthymic patients (n = 34)		Controls (n = 28)		MANOVA[a]			Conhen's d		
	Mean	SD	Mean	SD	Mean	SD	F (df = 2;93)	p	Tukey's Post hoc test[b]	Av.B	Bv.C	Av.C
Verbal area (WAIS III)												
Similarities	7.7	3.5	7.9	3.3	12.4	4.5	2.36	0.1		0.03	0.49	0.50
Arithmetic	5.72	2.1	6.9	2.2	9.5	3.4	5.64	0.01*	A, B < C	0.27	0.41	0.56
Digits	5.6	2.2	6.1	1.6	9.0	3.6	4.36	0.02*	A, B < C	0.08	0.46	0.47
Information	6.6	2.6	6.9	2.9	9.9	4.3	0.58	0.56		0.05	0.38	0.42
Comprehension	6.9	2.8	7.3	3.0	11.0	3.7	2.87	0.06		0.07	0.48	0.52
Sequence of numbers-letters	6.0	2.5	6.4	2.3	9.8	3.7	4.07	0.02*	A, B < C	0.08	0.48	0.52
Executive area (WAIS IIII)												
Complete figures	5.4	2.1	5.8	2.2	8.9	3.9	3.77	0.03*	A, B < C	0.09	0.44	0.49
Coding	4.8	1.7	5.8	2.2	8.6	2.9	9.11	0.00*	A, B < C	0.25	0.48	0.62
Cubes	6.2	2.4	7.3	2.3	9.3	2.3	3.46	0.04*	A, B < C	0.23	0.40	0.55
Matrix reasoning	7.9	2.5	7.6	2.2	11.1	3.1	5.35	0.01*	A, B < C	0.06	0.55	0.45
Picture arrangement	6.6	2.2	6.5	1.9	9.0	3.8	1.39	0.25		0.02	0.38	0.36
Symbol search	6.4	2.3	6.6	2.6	9.0	2.5	4.04	0.02*	A, B < C	0.04	0.43	0.48

[a] *With control for premorbid intelligence, as measured by the WAIS vocabulary test and control for age.*
[b] *The threshold for significance was p < 0.05. A = Patients with depressive symptoms; B = Euthymic patients; C = Controls*

Table 3 - Factorial Indexes and Execution IQs of the bipolar patients with depressive symptoms, euthymic patients and controls

Measure	Patients with depressive symptoms (n = 32)		Euthymic patients (n = 34)		Controls (n = 28)		MANOVA[a]			Conhen's d		
	Mean	SD	Mean	SD	Mean	SD	F (df = 2;93)	p	Tukey's Post hoc Test[b]	Av.B	Bv.C	Av.C
Perceptual organization index	79.2	11.1	80.5	10.6	98.1	15.4	6.57	0.0002*	A, B < C	0.06	0.55	0.58
Operational memory index	74.0	9.6	77.5	10.3	95.5	19.1	7.41	0.0001*	A, B < C	0.17	0.51	0.58
Processing velocity index	77.1	8.5	79.5	10.1	93.4	12.8	8.38	< 0.0001*	A, B < C	0.13	0.52	0.60
Execution IQ	76.3	10.1	77.8	9.8	95.6	16.2	7.87	0.0001*	A, B < C	0.08	0.55	0.58

[a] With control for premorbid intelligence, as measured by the WAIS vocabulary test and control for age
[b] The threshold for significance was p < 0.05
A = Patients with depressive symptoms; B = Euthymic patients; C = Controls

to the cumulative effect of the repeated episodes of mania and depression, especially the presence of psychosis.[19] Martinez-Arán et al.[20] found that the duration of illness, number of manic episodes, hospitalizations and attempted suicide were associated with poorer cognitive performance. On the other hand, Selva et al.,[34] comparing bipolar patients with and without a prior history of psychosis did not find a difference in the cognitive performed. We believe that there must be an association between the worse prognosis factors and cognitive performance, although it is not clear how this occurs, and which are the main factors that can influence the decline of cognition. Further research is required.

Clearly, these data present some limitations. All the patients were using medication and most of them more than one. Future studies on drug-free patients are needed. Another fact that should not be ignored is that our sample was collected at a center of reference in our country, where there is probably a high concentration of severe cases.

Conclusion

In conclusion, lower performance was observed both in the verbal area and in the non-verbal area of cognitive functioning, in the groups of bipolar depressed and euthymic patients compared to the healthy subjects, suggesting stability or chronicity of cognitive deficits. This study confirmed that the results of this South American sample provide similar results to those of data found in other regions. Thus, based on these initial findings, more specific studies can be performed, such as correlations with clinical factors, functionality, neurobiological markers and neuroimaging. Ultimately, further research is needed to find out whether cognitive impairment becomes worse or remains the same over the years, and longitudinal research will be required. Moreover, it is important to evaluate whether the .bipolar patients would benefit from rehabilitation, an approach already developed for other disorders.

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Júlia J. Schneider	UFRGS	CAPES* CNPq* FIPE-HCPA*	—	—	—	—	—
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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UFRGS = Universidade Federal do Rio Grande do Sul; HCPA = Hospital de Clínicas de Porto Alegre; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; RS = Rio grande do Sul; FIPE = Fundo de Incentivo à Pesquisa e Ensino.
For more information, see Instructions for authors.

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