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ORIGINAL ARTICLE

Cognitive performance and psychosocial functioning in patients with bipolar disorder, unaffected siblings, and healthy controls

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Objective: To assess cognitive performance and psychosocial functioning in patients with bipolar disorder (BD), in unaffected siblings, and in healthy controls.
Methods: Subjects were patients with BD (n=36), unaffected siblings (n=35), and healthy controls (n=44). Psychosocial functioning was accessed using the Functioning Assessment Short Test (FAST). A sub-group of patients with BD (n=21), unaffected siblings (n=14), and healthy controls (n=22) also underwent a battery of neuropsychological tests: California Verbal Learning Test (CVLT), Stroop Color and Word Test, and Wisconsin Card Sorting Test (WCST). Clinical and sociodemographic characteristics were analyzed using one-way analysis of variance or the chi-square test; multivariate analysis of covariance was used to examine differences in neuropsychological variables.
Results: Patients with BD showed higher FAST total scores (23.90±11.35) than healthy controls (5.86±5.47; $p < 0.001$) and siblings (12.60±11.83; p 0.001). Siblings and healthy controls also showed statistically significant differences in FAST total scores (p = 0.008). Patients performed worse than healthy controls on all CVLT sub-tests ($p < 0.030$) and in the number of correctly completed categories on WCST (p = 0.030). Siblings did not differ from healthy controls in cognitive tests.
Conclusion: Unaffected siblings of patients with BD may show poorer functional performance compared to healthy controls. FAST scores may contribute to the development of markers of vulnerability and endophenotypic traits in at-risk populations.

Keywords: Bipolar disorder; siblings; functional impairment; cognition; endophenotype

Introduction

The high heritability of bipolar disorder (BD) has been demonstrated in several twin and adoption studies.[1] The risk of first-degree relatives developing BD is approximately 10-fold higher than that of the general population.[2] Despite the evidence supporting the existence of neurobiological trait abnormalities in individuals at genetic risk for BD, most individuals with a family history of BD will not develop the disorder.[2] Conversely, they may present subtle symptoms or vulnerabilities, which are less studied.

BD is associated with psychosocial functioning decline, and greater impairment is commonly observed at later stages of the illness.[3] Functional disabilities in BD are not limited to symptomatic periods; they may remain present or result in sustained disability.[4] In a follow-up study, after two years, 98% of first-episode manic patients had symptomatic recovery, whereas only 38% had functional recovery.[5] Therefore, the inability of patients with BD to function socially and occupationally and to live independently is not necessarily associated with symptom status.[5]

Neurocognitive deficits have been consistently correlated with functional impairment in BD and have been pointed out as one of the most relevant predictors of functionality in BD.[6-8] Patients with poor functioning have been shown to present poorer cognitive performance, particularly in verbal memory and executive function, even when euthymic.[6,7,9-11] Forcada et al.[8] emphasized that intelligence quotient (IQ), total white matter volume, and course of depressive illness were independently associated with functional outcome in patients (assessed with the Global Assessment of Functioning Scale), but not in relatives (siblings and offspring). Studies with first-episode manic patients have consistently shown deficits in visual, verbal, and working memory when compared to healthy controls.[12,13]

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Some studies have suggested the presence of cognitive dysfunction in unaffected first-degree relatives of patients with BD when compared to healthy controls, particularly in executive function and/or verbal memory.[14-16] Arts et al.,[14] in a meta-analysis, showed a small effect size ($d < 0.500$) for executive function and verbal memory parameters in first-degree relatives.

Moreover, there is evidence supporting the existence of neurobiological trait abnormalities in individuals at genetic risk for BD.[17] A systematic review of neuroimaging studies involving individuals at high genetic risk for BD (twins, siblings, offspring, first-degree, and second-degree relatives of patients) found accumulating structural and functional imaging evidence suggesting abnormalities in this population.[17]

Even though BD has a strong genetic underpinning, little is known about clinical or biological features associated with risk for the illness. In this sense, a better understanding of the familial risk for BD in siblings and of how this familial risk is clinically manifested could help researchers identify heritable sub-phenotypes of the disorder, as this population has high genetic loading for BD because of the shared DNA. It may also shed light on the pathophysiology of the condition, and possibly encourage further research into the genetic architecture of BD.

Therefore, the objective of this study was to investigate the presence of neurocognitive and functioning impairment in patients with BD, in unaffected siblings, and in healthy controls, comparing siblings to the two other groups, in an attempt to characterize neuropsychological performance and psychosocial functioning in a Brazilian population at genetic risk of developing BD. Considering that cognitive deficits are one of the most relevant predictors of functioning in BD, we thought it would be interesting to asses cognitive performance and functioning in unaffected siblings. We hypothesized that patients with BD and unaffected siblings would show impaired performance on cognitive and psychosocial functioning tests when compared with healthy controls.

Methods

Participants

This is a cross-sectional study reporting data obtained at the Bipolar Disorder Program, at Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul, southern Brazil. Participants included outpatients receiving a diagnosis of BD type I at the program, one or more unaffected siblings of each patient included, and healthy controls. Thirty-six patients with BD, 39 unaffected siblings, and 44 healthy subjects were included. All patients were tested for mood symptoms and psychosocial functioning; a subgroup of 21 patients, 14 siblings, and 22 healthy controls underwent a battery of neuropsychological tests. Inclusion criteria for patients were: having a diagnosis of BD type I according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), being on current pharmacological treatment, being euthymic for at least 45 days, presenting scores $\leqslant 7$ on the Hamilton Depression Rating Scale (HDRS). and the Young Mania Rating Scale (YMRS), not having neurological diseases or severe clinical illnesses, having siblings without a diagnosis of BD, and agreeing to participate in the study.

Siblings were included if they did not have a psychiatric diagnosis according to DSM-IV, if they scored $\leqslant 7$ on HDRS and YMRS, did not have neurological diseases or severe clinical illnesses, and if they agreed to participate in the study.

Finally, controls were volunteer blood donors invited and recruited at the Blood Bank of the HCPA. Inclusion criteria for the control group were: not having a psychiatric diagnosis according to DSM-IV, scoring $\leqslant 7$ on HDRS and YMRS, not having neurological diseases or severe clinical illnesses, having a negative psychiatric history, having a negative family history of psychiatric disorders (considering all first degree-relatives), and agreeing to participate in the study. Individuals with unstable inflammatory diseases were excluded. All controls underwent a comprehensive clinical interview conducted by a well-trained psychiatrist, using a short version of the SCID-I.

All the procedures described in this study were approved by the local Research Ethics Committees. Written informed consent was obtained from all the participants prior to any study procedures.

Assessment

Depressive and manic symptoms were assessed using HDRS and YMRS, respectively. Cognitive performance was assessed with a focus on executive function and verbal memory, areas that have been demonstrated to be relevant in BD.[18] Executive function was evaluated using the Stroop Color and Word Test[19] and the standard score of the Wisconsin Card Sorting Test (WCST).[20] Verbal memory was measured using the California Verbal Learning Test (CVLT).[21]

Psychosocial functioning was assessed using the Functioning Assessment Short Test (FAST), a four-point Likert-type scale containing 24 items whose scores may range from 0 to 72; higher scores indicate poorer functional status.[22] The scale covers six specific areas of psychosocial functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. The FAST has been validated for use both in the Brazilian population[23] and in patients with BD,[22] and has been reported to be sensitive to change.[24,25]

Statistics

Statistical analyses were performed using the SPSS version 19.0. The three groups (patients, siblings, and healthy controls) were compared with regard to clinical and sociodemographic characteristics using either analysis of variance or the chi-square test, as appropriate. Multivariate analysis of covariance (MANCOVA) was performed to examine differences in neuropsychological variables between groups. Cognitive variables were used as dependent variables, mood symptoms (HDRS and YMRS results) as covariates, and the group was the main factor. Comparisons showing significant effects were further analyzed using MANCOVA followed by Tukey's honestly significant difference post-hoc tests.

Pearson's correlation was used to evaluate the relationship between functioning, cognitive variables, and clinical variables in the group of patients with BD. A linear regression model was used to identify the best predictors of psychosocial functioning; all clinical variables showing correlation with FAST scores were tested. All analyses were two-tailed. Significance was set at $p < 0.050$.

Results

Thirty-six patients with BD, 39 unaffected siblings, and 44 healthy subjects were included in the study. Sociodemographic variables and mood rating scale scores are shown in Table 1. Variables, including gender, age, and years of education were not significantly different between patients, siblings, and control groups.

Patients, siblings, and healthy controls all showed very low sub-threshold symptoms, as indicated by mood rating scale scores. However, there were statistical differences in depressive and manic symptom scores between patients and healthy controls ($p < 0.010$) and between siblings and healthy controls ($p < 0.010$). As expected, patients with BD showed higher FAST total scores (23.91 ± 11.35) when compared to both healthy controls (5.86 ± 5.48; $p < 0.001$) and siblings (12.60 ± 11.83; $p < 0.001$). Siblings and healthy controls also showed statistical differences in FAST total scores ($p = 0.008$).

Patients also showed higher functional impairment than healthy controls when FAST domains were analyzed separately (all $p < 0.004$). When compared with siblings, patients showed higher functional impairment in the autonomy ($p \leqslant 0.001$), occupational ($p \leqslant 0.001$), cognition ($p = 0.004$), financial ($p = 0.030$), and interpersonal relationships ($p = 0.010$) domains. There were also statistical differences between siblings and healthy controls, with siblings showing higher impairment in cognition ($p = 0.010$), interpersonal relationships ($p = 0.003$), and leisure time ($p = 0.040$). FAST scores obtained for all three groups are shown in Table 2.

Because the groups differed in terms of HDRS scores, MANCOVA was used to control for potential confounders, using the group as the main factor. The analysis revealed significant differences in functioning between the groups, even when HDRS was used as a covariate (Pillai's $F = 3.620$, degrees of freedom [df] = 2, $p \leqslant 0.001$).

Neuropsychological results are shown in Table 3. MANCOVA (Pillai's $F = 1.481$, $df = 2$, $p < 0.001$) was performed for the main effect and revealed significant differences in cognitive performance between the groups. Patients performed worse than both healthy controls and siblings on all CVLT sub-tests (all $p < 0.010$). Executive function showed significant differences between patients and healthy controls in the number of correctly completed categories on WCST ($p = 0.030$). The same pattern was found when HDRS and YMRS scores were used as covariates in MANCOVA. Medications currently in use by the patients who performed neuropsychological tests are shown in Table 1.

Correlations were found between CVLT long delayed free recall and HDRS ($r = -0.44$, $p = 0.020$), and between CVLT total recall and HDRS ($r = -0.51$, $p \leqslant 0.010$). There were also significant positive correlations between FAST total scores and HDRS ($r = 0.65$, $p < 0.001$), number of previous depressive episodes ($r = 0.55$, $p = 0.002$), number of previous manic episodes ($r = 0.63$, $p < 0.001$), and number of previous hospitalizations ($r = 0.38$, $p = 0.03$).

Finally, in the linear regression model, HDRS scores, number of depressive episodes, number of psychiatric hospitalizations, and number of manic episodes were entered simultaneously as predictors into a regression equation using FAST total scores as the dependent measure. Only HDRS scores remained a significant predictor of FAST total scores ($B = 1.81$, standard error = 0.57, $p = 0.004$).

Table 1 Demographic and clinical characteristics of patients with BD, unaffected siblings, and healthy controls

Characteristics	Patients (n=36)	Siblings (n=39)	Controls (n=44)	p-value
Age (years)*	47.25 (10.16)	49.76 (15.02)	45.84 (12.15)	0.359
HDRS score*	4.11 (2.94)	3.59 (3.50)	0.70 (1.15)	> 0.001
YMRS score*	0.94 (1.53)	0.10 (1.53)	0.09 (0.36)	0.001
Sex†				0.134
Male	9 (25.00)	12 (30.76)	20 (45.45)	
Female	27 (75.00)	27 (69.23)	24 (54.54)	
Illness duration‡	19.78 (11.54)			
Current medications§				
Lithium	14 (58.33)			
Valproic acid	12 (50.00)			
Typical antipsychotics	2 (8.34)			
Atypical antipsychotics	12 (50.01)			
Antidepressants	2 (8.34)			
Benzodiazepines	3 (12.51)			

Data presented as mean (standard deviation) or n (%).
BD = bipolar disorder; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.
* p-value by ANOVA.
† p-value by chi-square test.
‡ Illness duration calculated considering age at diagnosis of BD.
§ Medications currently in use by patients who completed the neuropsychological battery (n=21).

Table 2 Psychosocial functioning as assessed by specific FAST domains in patients with BP, unaffected siblings, and healthy controls

FAST	Patients* (n=33)	Siblings† (n=35)	Controls (n=43)	F/p-value‡
Total score	23.91 (11.35)	12.60 (11.83)	5.86 (5.48)	32.01/< 0.001
Autonomy	3.41 (2.85)	1.26 (2.47)	0.63 (1.04)	15.80/< 0.001
Occupational	5.38 (4.79)	1.69 (2.55)	0.86 (1.39)	21.20/< 0.001
Cognitive	6.47 (3.49)	4.11 (3.11)	2.14 (2.29)	19.83/< 0.001
Financial	1.94 (2.09)	0.97 (1.58)	0.53 (0.85)	7.81/0.001
Interpersonal relationships	4.69 (3.05)	2.86 (3.37)	0.79 (1.47)	19.72/< 0.001
Leisure time	2.03 (1.59)	1.71 (1.84)	0.91 (0.97)	5.89/0.004

Data presented as mean (standard deviation).
BD = bipolar disorder; FAST = Functioning Assessment Short Test.
* Patients showed higher functional impairment than healthy controls (all $p < 0.004$), higher impairment than unaffected siblings in autonomy ($p = 0.001$), occupational functioning ($p < 0.001$), cognition ($p = 0.004$), financial ($p = 0.03$), and interpersonal relationships ($p = 0.01$).
† Unaffected siblings showed higher impairment than healthy controls in cognition ($p = 0.01$), interpersonal relationships ($p = 0.003$), and leisure time ($p = 0.04$).
‡ p-value by ANOVA.

Discussion

To the authors' knowledge, this is the first study to compare cognitive performance and psychosocial functioning between patients with BD, unaffected siblings, and healthy controls. The findings of this research can be summarized as follows: 1) there were significant differences in memory tasks and executive function between patients and healthy controls, but not between siblings and controls; 2) patients showed higher functional impairment according to FAST scores compared to both healthy controls (all domains) and unaffected siblings (some domains); 3) there were statistical differences between siblings and healthy controls in FAST total scores and in specific domains of the scale, namely, cognition, interpersonal relationships, and leisure time.

With regard to patients and healthy controls, our findings are consistent with previous studies that have shown higher cognitive impairment, in particular in executive function and verbal memory, in remitted patients with BD compared to controls,[7,10,11] as well as greater functioning impairment in patients vs. healthy controls.[3]

However, our study also showed poorer psychosocial functioning in unaffected siblings of patients with BD compared to healthy controls, as measured by the FAST. To our knowledge, this is the first study to evaluate psychosocial functioning in siblings using this instrument. Linnen et al.,[26] Ellenbogen et al.,[27] and Ostiguy et al.[28] investigated psychosocial functioning in the offspring of patients with BD, but those authors evaluated specifically interpersonal relationships; all three studies found some degree of impairment in the domain assessed. Bella et al.[29] evaluated other areas in addition to interpersonal relationships in children of patients with BD, and also found impairment. However, we could not find other studies assessing psychosocial functioning in unaffected siblings of patients with BD.

The FAST scores obtained in the present study placed siblings in an intermediate position between patients with BD and healthy controls, suggesting that psychosocial functioning could be either an endophenotypic trait or a sign of vulnerability and/or resilience in this population. Rosa et al.[3] found higher FAST scores in late-stage BD patients than in early-stage patients, and suggested that FAST scores could have the potential to distinguish between patients in early vs. late stages of BD. We could speculate that the results obtained with siblings in the present study are consistent with the staging model of BD - siblings might have a so-called latent-stage BD,[30] as a

Table 3 Cognitive performance of patients with BD, unaffected siblings, and healthy controls

	Patients (n=21)	Siblings (n=14)	Controls (n=22)	ANOVA F/p-value	Post-hoc
CVLT total recall	42.61 (10.57)	50.56 (8.07)	51.65 (10.75)	5.45/0.007	P < HC, S*
CVLT short delayed free recall 1	8.22 (2.96)	10.89 (2.11)	11.39 (2.65)	9.40/< 0.001	P < HC, S†
CVLT long delayed free recall 2	8.78 (2.84)	11.11 (2.65)	10.11 (2.97)	5.63/0.006	P < HC, S‡
CVLT short delayed cued recall 1	9.43 (2.46)	11.50 (1.65)	11.65 (2.55)	6.45/0.003	P < HC, S§
CVLT long delayed cued recall 2	9.22 (2.71)	11.78 (2.13)	11.70 (2.40)	7.77/0.001	P < HC, S‖
Stroop Color and Word Test	107.93 (69.13)	82.77 (19.05)	79.60 (56.81)	1.80/0.173	P = HC = S
WCST perseverative errors	83.61 (13.93)	80.06 (15.14)	88.13 (16.30)	1.46/0.240	P = S = HC
WCST number of correctly completed categories	2.70 (1.29)	2.89 (1.53)	3.74 (1.35)	3.62/0.033	P < HC¶

Data presented as mean (standard deviation).
BD = bipolar disorder; CVLT = California Verbal Learning Test; HC = healthy controls; P = patients; S = siblings; WCST = Wisconsin Card Sorting Test.
* $p \leqslant 0.01$ between patients and healthy controls, $p = 0.01$ between patients and unaffected siblings.
† $p \leqslant 0.01$ between patients and unaffected siblings, $p < 0.01$ between patients and healthy controls.
‡ $p \leqslant 0.01$ between patients and healthy controls, $p \leqslant 0.01$ between patients and unaffected siblings.
§ $p \leqslant 0.01$ between patients and unaffected siblings, $p \leqslant 0.01$ between patients and healthy controls.
‖ $p \leqslant 0.01$ between patients and unaffected siblings, $p < 0$ .01 between patients and healthy controls.
¶ $p = 0.03$ between patients and healthy controls.

result of the biological underpinnings of BD that they share. Conversely, it is also possible that the siblings selected for the present study had a high level of resilience, as they remained without psychiatric diagnosis despite the genetic and environmental factors shared with the patients. Of note, the mean age of siblings in our sample was 45.6 years, which is beyond the first peak age of BD onset (BD type I has two peaks of onset age, the first at 15-24 years and the second at 45-54 years).[31]

Neurocognitive deficits in patients with BD, an established part of the disorder, have been strongly correlated with poor functioning[6-8] and with other clinical factors, such as disease severity, chronicity, and residual symptoms.[9,32] Another study has shown that patients with multiple-episode BD have poorer functioning, especially in the FAST autonomy, occupational, interpersonal relationships, and leisure time domains, compared to first-episode patients.[33] Finally, Forcada et al.[8] showed that IQ, total white matter volume, and a predominantly depressive illness course were independently associated with functional outcomes in patients with BD, but not in their relatives.

In line with the findings described above, the present study found poor cognition and functioning in patients with BD. CVLT parameters in patients were different from those obtained for controls and also for siblings, reinforcing the effect of the disease on cognitive outcomes. This finding highlights the damage caused by number of episodes and number of hospitalizations, as suggested by Strakowski et al.,[34] who have shown abnormalities in neural circuits involved in mood regulation and cognition in multiple-episode patients. In the present study, CVLT, Stroop Color and Word Test, and WCST results were similar in siblings and controls.

There are studies reporting significant impairment of verbal working memory in siblings of patients with BD compared to healthy controls.[35,36] Similar results have been found in comparisons between first-degree relatives (siblings, parents) and healthy controls.[37,38] Conversely, other authors have reported negative results for verbal learning, with no differences between first-degree relatives of patients with BD and healthy control groups.[39,40] However, comparison across those studies is limited, as samples are not homogenous with regard to the type and age of first-degree relatives included (siblings, offspring, and parents).

Kulkarni et al.[35] assessed sample similar to ours, i.e., middle-aged siblings and controls. In that study, unaffected siblings performed poorly on the Tower of London Test (a planning test) and on Rey's Auditory Verbal Learning Test , but there were no significant differences between siblings and healthy controls on the Stroop Color and Word Test, the WCST, and the Iowa Gambling Task (IGT). Nehra et al.[36] also reported poor performance of middle-aged unaffected siblings of patients with BD in verbal learning tests, assessed using the Hopkins Verbal Learning Test-Revised. Again, these controversial findings reported for unaffected relatives may be explained by heterogeneous samples (type and age of relative assessed) and by methodological differences, e.g., in the cognitive tests employed. Moreover, in our study, only a sub-group of participants (smaller sample size) underwent the neurocognitive test battery, reducing the power to detect subtler impairments - which we would expect to be the case with siblings, considering their intermediate position between patients and controls in terms of functional scores. Further studies are warranted to assess cognitive reserve in siblings of patients with BD, given the apparently relevant role played by this variable in cognitive impairment in BD.[32]

Our findings need to be considered in light of two major limitations: first, our small sample size; second, the cross-sectional design of our study. It would be interesting to see the effects of a larger sample and of a longitudinal design on the results here reported.

In conclusion, the present study suggests that unaffected siblings of patients with BD may have poorer functional performance when compared to healthy controls, probably as a result of the genetic background that they share with the patients. The use of FAST scores may contribute to the development of markers in at-risk populations, and may be considered as an endophenotypic trait. It remains to be known whether the impairment of psychosocial functioning found in unaffected siblings has any effect on their quality of life. Further prospective studies are needed to improve our knowledge in this area and help identify endophenotypes.

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Disclosure

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