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ORIGINAL ARTICLE

The impact of a history of psychotic symptoms on cognitive function in euthymic bipolar patients: a comparison with schizophrenic patients and healthy controls

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DESCRIPTORS:
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Bipolar disorder.

Abstract

Background: About two-thirds of patients with bipolar disorder (BD) have a lifetime history of at least one psychotic symptom. *Objective*: To compare the neurocognitive performance of four groups: BD patients with and without a history of psychotic symptoms (BD HPS+ and BD HPS-, respectively); patients with schizophrenia (SZ); and healthy control (HC) subjects. *Method*: In this cross-sectional study, 35 stabilized patients with SZ, 79 euthymic (44 HPS+ and 35 HPS-) patients with BD, and 50 HC were administered a comprehensive battery of neuropsychological tests. *Results*: There was worse neurocognitive functioning in both BD and SZ patients compared to HC. Overall, data from both groups of BD patients did not differ on sociodemographic, clinical, or neurocognitive variables. However, BD HPS+ patients had significantly more negative symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS), and showed a trend toward worse performance on executive functions compared to BD HPS- patients. Moreover, both BD groups had better performance on all neurocognitive tests compared to SZ group. *Conclusions*: Neurocognitive dysfunction may be more marked in SZ than in BD, yet qualitatively similar. A history of past psychotic symptoms in BD was not associated with more severe cognitive impairment during euthymia. Therefore, BD with psychotic symptoms does not appear to be a distinct neurocognitive phenotype.
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DESCRITORES:
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O impacto da história de sintomas psicóticos na função cognitiva de doentes bipolares eutímicos: comparação com doentes esquizofrênicos e controles saudáveis

Resumo
Introdução: Cerca de dois terços dos pacientes com Transtorno Bipolar (TB) apresentam sintomas psicóticos ao longo da vida. *Objetivo*: Comparar o desempenho neurocognitivo de quatro grupos: pacientes com TB, com e sem histórico de sintomas psicóticos (HPS+ ou HPS-, respectivamente); pacientes esquizofrénicos; e grupo controle (GC) com indivíduos saudáveis. *Métodos*: Estudo transversal no qual 35 pacientes com esquizofrenia (EZ), 79 pacientes com TB na fase eutímica (44 HPS+ e 35 HPS-) e 50 GC foram submetidos a extensa avaliação neuropsicológica. *Resultados*: Observou-se pior funcionamento neurocognitivo em pacientes com TB e com EZ quando comparados ao GC. Os dois grupos de pacientes TB não diferiram em dados demográficos, clínicos ou variáveis neurocognitivas. Entretanto o grupo HPS+ teve mais sintomas negativos mensurados pela Positive and Negative Syndrome Scale (PANSS) e apresentou uma tendência a pior performance nas funções executivas comparativamente aos pacientes HPS-. Além disso ambos os grupos de pacientes TB tiveram melhor desempenho em todos testes neurocognitivos quando comparados aos pacientes com EZ. *Conclusões*: A disfunção neurocognitiva é mais marcada nos pacientes com EZ do que com TB, apesar de ser qualitativamente similar. Um histórico de sintomas psicóticos no TB não associou esta amostra de pacientes eutímicos a um maior prejuízo neurocognitivo. Assim sendo, o TB com sintomas psicóticos parece não possuir um fenótipo neurocognitivo diferenciado.
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Introduction

The traditional Kraepelinian dichotomy of psychoses as completely distinct entities has been challenged by increasing evidence that bipolar disorder (BD) and schizophrenia (SZ) may share several epidemiological, phenomenological, neurobiological, and genetic characteristics.[1-3] Cognitive function is no exception, as bipolar patients exhibit neurocognitive deficits in many of the same domains reported in patients with SZ, although to a lesser extent. Of particular concern are premorbid and current intelligence quotient, and perhaps attention, verbal memory, and executive functions.[2,3]

Cognitive impairments have been reported in nearly all cognitive domains in euthymic BD patients and this is more evident for verbal memory and some executive functions,[4] which seem to remain stable over time.[5] Moreover, first-degree relatives of patients with BD may present with some cognitive deficits, especially in verbal memory and executive functions,[6] suggesting potential trait markers and possibly endophenotypes of BD. Nevertheless, some argue that cognitive deficits during euthymia could be partly explained by residual affective symptoms.[13,14] Other factors such as number and subtype of episodes, duration of illness, age at onset of illness, and number of admissions may also be responsible for the cognitive dysfunction found in BD.[7-9] However, other clinical factors such as rapid cycling, psychotic features, and comorbidity with other axis I disorders, especially anxiety and substance use disorders, remain to be investigated.

About two-thirds of BD patients have a lifetime history of at least one psychotic symptom.[10] The overlap of SZ and BD occurs more commonly in BD patients with psychotic symptoms, which on genetic grounds has been suggested as a specific subtype of BD, probably more similar to SZ.[11] Moreover, the familial aggregation of psychotic features in BD is a consistent finding.[10] Whether psychotic BD represents a distinct biological subtype should be investigated by using neurobiological correlates of psychosis as external validators. The few existing studies have found differences between psychotic and non-psychotic BD with imaging,[12] as well as physiological measures.[13] The extent to which neurophysiological deficits are unique or overlap across BD type I and SZ is unclear, but some deficits (P50 sensory gating, P300, and others) may represent a common physiological mechanism associated with the vulnerability to psychosis in both disorders.[14] However, research on the impact of psychotic symptoms on cognition has yielded conflicting findings. Some authors have found worse cognitive performance in BD patients with psychotic features than in those without,[8,9,11,15-19] while others have found no such association.[20-26] Bora et al. (2010) have recently compared cognition in BD patients with and without a history of psychosis, and their meta-analysis concludes that a history of psychosis is associated with greater severity of cognitive deficits, but that these effects are modest and do not suggest a complete categorical distinction between psychotic and non-psychotic BD.[27] Moreover, out of the 11 studies reviewed, only four examined euthymic patients, and of these, only two examined BD type I patients alone. Moreover, only one study has compared euthymic BD patients with schizophrenia patients and healthy controls.[25]

The aims of this study were twofold: 1) to characterize the overall cognitive profile of a well defined sample of euthymic BD patients with a history of psychotic symptoms (BD HPS+) during mood episodes, and of euthymic BD patients without past psychotic symptoms (BD HPS-), as compared

to SZ patients while in remission (severity criteria), and a control group of healthy individuals; 2) to discern whether there is a distinct profile of cognitive impairment in euthymic BD HPS+ patients as compared to euthymic BD HPS- patients.

Based on the literature, we hypothesized that: (1) compared with control subjects, all patient groups would be impaired in most cognitive functions; (2) compared with SZ patients, BD patients would have a qualitatively similar, yet quantitatively different cognitive profile; (3) compared with non-psychotic BD patients, the psychotic BD group would be additionally more impaired on at least some executive and verbal learning tasks.

Method

Subjects

The data reported in the present study are based on the analysis of an ongoing investigation[28] of cognitive functioning in SZ and BD patients. Patients were recruited from *Centro Hospitalar Psiquiátrico de Lisboa*, from Santarém's District Hospital, and from the Portuguese Association of Bipolar and Depressive Patients (ADEB from Portuguese). Thirty-five outpatients with SZ, aged 20-62, were diagnosed according to DSM-IV criteria[29] ascertained by interview with a psychiatrist and medical chart review. Seventy-four outpatients, aged 17-63, with BD type I diagnosed according to DSM-IV criteria,[29] ascertained by psychiatric interview and Mini International Neuropsychiatric Interview (MINI),[30] were also included in the analysis. All patients were evaluated with the Positive and Negative Syndrome Scale (PANSS). Remission in SZ was defined as having a score of mild or less on items 1-3 of the PANSS Positive sub-scale, on items 1, 4, and 6 of the Negative sub-scale, and on items 5 and 9 of the General Psychopathology sub-scale.

Based on patient interview and psychiatric chart review, patients with BD were divided into two groups according to the presence (HPS+) or absence (HPS-) of past psychotic symptoms defined as the occurrence of delusions and/or hallucinations during at least one affective episode, as used previously.[11] Forty-four (60%) patients with BD had a history of psychotic symptoms. Euthymia was defined as a Young Mania Rating Scale (YMRS) score ≤ 6 and a Hamilton Depression Rating Scale (HDRS) score ≤ 8, for at least one month preceding the neurocognitive assessment.

To be included, patients had to be on a stable treatment regimen for at least one month prior to neuropsychological testing. At the time of evaluation, all but one of the BD patients were taking medication. BD patients were predominantly treated with mood stabilizers, either alone (n = 13) or in association with other classes of drug. Four BD patients were treated with antipsychotics alone. On the other hand, all patients with SZ were treated with one (63%) or more antipsychotics; 30 patients with atypical antipsychotics, nine patients with an association of conventional antipsychotics, and three patients with conventional depots alone.

Fifty healthy subjects, age 17-61, recruited by convenience amongst the patients' acquaintances (excluding first-degree relatives) or from hospital personnel, were included as the control group; healthy subjects were screened for psychiatric disorders by means of clinical interview and with the MINI, and excluded if they met the criteria for any psychiatric disorder. No effort was made to match groups on age, sex, and educational level.

Subjects with previous head trauma or neurological illness, substance abuse/dependence or a course of ECT in the preceding six months were excluded. Two BD patients and one healthy control (HC) were left-handed, and one patient with SZ and one HC were ambidextrous, according to the Edinburgh Inventory.[31]

The study was approved by the local Ethics Committee, and all participants provided prior written informed consent.

Neuropsychological assessment

The neurocognitive test battery was directed at the following cognitive domains: *attention and mental control* (Mental Tracking and Digit Span Forward from the Wechsler Memory Scale [WMS], Bells Test); *processing speed* (Symbol Digit Modalities Test, and Trail Making Test part A); *executive functions* (Digit Span backward from the WMS, Stroop Color and Color-Write Tests, Trail Making Test part B, and Towers of Hanoi [ToH], Controlled Oral Word Association [COWA] — Animal Naming, also a test of verbal fluency, Wechsler Intelligence Scale for Adults Revised [WAIS-R] — Comprehension and Similarities sub-tests); and *verbal memory* (WAIS-R — Information sub-test, WMS — Logical Memory). These are well-established tests of which detailed descriptions exist in standard texts.[31] Both psychopathological and neurocognitive assessments were administered on the same day.

Statistical analyses

Comparison of clinical and sociodemographic characteristics between the four groups (HPS+ and BD HPS- patients, SZ patients, and HC) was carried out using ANOVA and x^2 test as appropriate. Because the results on the neurocognitive tests are highly correlated, we used one-way analysis of variance, with sex and group as factors, and age, educational level, and subsyndromal mood symptoms (HDRS, YMRS scores) as covariates (ANCOVA) to compare neurocognitive performances between the four groups. When a significant group effect ($p < 0.05$) was observed, Scheffe Post-Hoc Tests were conducted for significant differences between groups. To indicate the magnitude of differences in neurocognitive performance between the two groups of BD patients and HC, we calculated Cohen's *d* effect sizes (not adjusted for age, educational level, and residual mood symptoms). Performances on neurocognitive tests were also converted to Z-scores (for clarity, negative values express worse performances as compared to control subjects). The two groups of BD patients were also directly compared by Student's t-test and x^2 test. Analyses yielding a p value < 0.05 were considered significant.

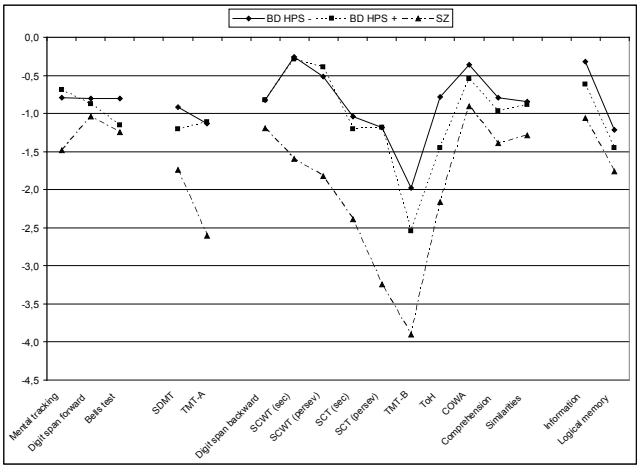
Results

Comparison of clinical groups with HC

The four groups differed significantly in sex, age, educational level, and mood subsyndromal symptoms (Table 1). Significant overall neurocognitive differences between the four groups were found, while there was covariance for the above-mentioned variables (MANCOVA: Pillai´s $F = 2.45$; $p < 0.001$).

Scheffé Post-Hoc Test revealed that the SZ group performed significantly worse than HC on all tests; BD HPS+ patients performed significantly worse than HC on 11 out of 17 tests, whereas BD HPS- patients performed significantly worse than HC on nine tests (Table 2; see also Figures 1). No main effect of either sex or a group by sex interaction was detected in any neuropsychological variable (Table 2). The largest effect sizes (Cohen´s *d*) were found in the SZ group, ranging between 0.75 and 2.06 (mean = 1.25), whereas BD patients showed moderate effect sizes, ranging between 0.19 and 1.35 (mean = 0.71) in BD HPS- patients, and between 0.27 and 1.55 (mean = 0.78) for BD HPS+ patients (Table 2).

Figure 1 Z-scores for 17 neurocognitive test scores achieved by patients with bipolar disorder (with and without history of psychotic symptoms) and patients with schizophrenia, as compared to healthy controls.



BD HPS-: Bipolar disorder patients without history of psychotic symptoms; BD HPS+: Bipolar disorder patients with history of psychotic symptoms; COWA: Controlled Oral Word Association; HPS -: without history psychotic of symptoms; HPS +: with history of psychotic symptoms; ; SCT: Stroop Color Test; SCWT: Stroop Color-Write Test; SDMT: Symbol Digit Modalities Test; SZ: schizophrenia ToH: Hanoi Towers Test; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; WAIS-R: Wechsler Intelligence Scale for Adults – Revised; WMS: Wechsler Memory Scale. For a better understanding of the magnitude of differences between patient groups and healthy controls, all Z-scores are depicted as negative values. Performance of healthy controls on all tests was converted to Z-score of zero.

Comparison of the two groups of BD patients vs. SZ patients

The three patient groups did not differ in age at illness onset or illness duration, but patients with SZ manifested significantly more severe symptoms on all PANSS sub-scales, as compared to both BD groups, and significantly more hospital admissions than the HPS- group (Table 1). Both euthymic BD groups outperformed the SZ group on three timed measures (TMT-A, SCT, and SCWT). Interestingly, a different pattern emerged according to the presence or absence of past psychotic symptoms: the BD HPS+ group performed significantly better than the SZ group on mental tracking and perseverations on the SCWT, whereas the HPS- group did better on SDMT and ToH.

Because medication status differed significantly between the three patient groups regarding lithium, anticonvulsants and antipsychotics (Table 1) we controlled for a potential effect of these medications. All between-groups differences remained, except for Bells test ($F = 1.033$, $p = 0.422$), suggesting that psychotropic medication did not seem to influence neurocognitive differences between the patient groups.

Comparison of the two groups of BD patients

BD patients of both groups (HPS+ and HPS) did not differ significantly regarding number of previous manic or depressive episodes (Table 1), sex, age, educational level, age at illness onset, illness duration, number of hospital admissions, mood symptoms, or type of prescribed medication (data not shown). However, euthymic HPS+ patients with BD had significantly higher scores on the PANSS negative sub-scale ($t = 2.07$, $p = 0.042$).

This variable was used as covariate to better compare overall neurocognitive performance between both BD groups (MANCOVA: Pillai´s $F = 0.97$; $p = 0.52$). ANCOVA revealed that HPS+ patients showed a trend toward a worse performance on one test of executive function, ToH ($F = 2.970$, $p = 0.089$; Cohen's $d = 0.53$).

Patients with past psychotic symptoms ($n = 79$) had significantly fewer years of education ($t = 2.095$; $p = 0.039$), more admissions ($t = -2.324$; $p = 0.022$), worse global functioning measured by GAF ($t = -2.853$; $p = 0.006$), and higher scores on PANSS positive ($t = -3.862$; $p < 0.001$), PANSS negative ($t = -4.988$; $p < 0.001$), PANSS general ($t = -2.636$; $p = 0.01$), and PANSS total ($t = -3.278$; $p = 0.001$), compared with those without psychotic symptoms ($n = 30$). The former group also showed worse performance on three neurocognitive tests: Information ($t = 2.750$; $p = 0.007$), Symbol Digit ($t = 2.599$; $p = 0.011$), and ToH ($t = -3.315$; $p = 0.001$).

Discussion

The results of this cross-sectional study with a well-characterized sample of euthymic patients with BD and remitted patients with SZ, suggest that these diagnoses are associated with cognitive impairment compared to healthy subjects. Although the neurocognitive dysfunction may be quantitatively different in SZ, the changes were qualitatively similar between both diagnostic groups. Nonetheless, we report here similar neurocognitive performance in HPS+ and HPS- patients with BD on all neuropsychological tests, suggesting that past psychotic features in BD do not seem to be associated with a more severe cognitive impairment during euthymia.

As hypothesized, the three patient groups showed overall worse neurocognitive functioning as compared to HC. Patients with SZ presented severe, pervasive cognitive deficits, with many large-effect sizes, whereas patients with BD showed relatively milder and more confined deficits than those of patients with SZ. As previously reported, the performance of both patient groups was similar on several tests, namely those of mental control, language function, visual function, memory function and executive function.[4] Conversely, our

Table 1 Sociodemographic and clinical characteristics of patients with bipolar disorder (with and without history of psychotic symptoms), patients with schizophrenia and healthy controls

Neuropsychological variable	BD HPS- patients (n = 30)		BD HPS+ patients (n = 44)		SZ patients (n = 35)		HC (n = 50)		ANOVA		Scheffe Post Hoc Test [a]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	p	
Age	37.7	10.77	39.4	11.27	40.0	9.79	34.33	10.83	2.794	**0.042**	
Educational level (years)	11.5	3.98	10.36	4.05	9.0	3.46	11.1	4.7	5.547	**0.001**	3 < 4
Age at illness onset (years)	26.4	9.65	24.8	8.90	24.6	7.70	-	-	0.393	0.676	
Illness duration (years)	10.9	8.50	14.3	9.12	15.6	9.41	-	-	2.108	0.127	
Number of admissions	1.4	2.41	2.2	2.04	3.0	2.57	-	-	3.857	**0.024**	1 < 3
Manic episodes	4.7	4.96	5.6	5.14	-	-	-	-	0.376	0.542	
Depressive episodes	6.4	5.45	7.7	7.64	-	-	-	-	0.488	0.488	
HDRS score	2.4	2.67	3.1	2.45	3.2	2.48	0.6	1.08	16.012	**< 0.001**	1 > 4, 2 > 4, 3 > 4
YMRS score	0.8	1.49	1.1	1.75	0.3	0.96	0.1	0.26	7.186	**< 0.001**	1 > 4, 2 > 4, 2 > 3
PANSS positive	7.2	0.46	7.8	2.07	9.3	3.42	-	-	7.493	**0.001**	1 < 3, 2 < 3
PANSS negative	8.4	2.51	9.9	3.91	13.9	3.68	-	-	22.513	**< 0.001**	1 < 3, 2 < 3
PANSS general	18.8	3.35	20.3	4.47	24.7	8.36	-	-	9.554	**< 0.001**	1 < 3, 2 < 3
PANSS total	34.7	5.96	37.9	9.44	48.0	13.17	-	-	16.031	**< 0.001**	1 < 3, 2 < 3
	n	%	n	%	n	%	n	%	χ^2	p	
Gender [b]											
Male	14	46.7	14	31.8	25	71.4	18	36.0	17.172	**< 0.001**	
Female	16	53.3	30	68.2	10	28.6	40	64.0			
Psychiatric medication [b]											
Lithium	15	50.0	12	27.3	2	5.7	-	-	16.885	**< 0.001**	
Anticonvulsants	21	70.0	32	72.7	7	20.0	-	-	25.985	**< 0.001**	
Antipsychotics	16	53.3	29	65.9	35	100.0	-	-	25.014	**< 0.001**	
Antidepressants	13	43.3	14	31.8	8	22.9	-	-	3.062	0.218	
Benzodiazepines	11	36.7	13	29.5	15	42.9	-	-	5.787	**0.015**	

Significance level $p < 0.05$.

[a] 1 = Bipolar patients without history of psychotic symptoms; 2 = Bipolar patients with history of psychotic symptoms; 3 = Schizophrenia patients; 4 = Healthy control subjects

[b] Fisher's exact test

SZ: schizophrenia; BD: bipolar disorder; HC: healthy controls; HPS+: with history of psychotic symptoms; HPS-: without history of psychotic symptoms; PANSS: positive and negative syndrome scale.

findings with the Stroop Test (executive function) suggest that patients with SZ have a disproportionate slowness and significantly more perseverations in incongruent tasks compared to BD patients. This is typically interpreted as an increased susceptibility to interference and a deficit in inhibition, processes that are actively involved in selective attention.[31] Taken together, our findings support the hypothesis that neurocognitive deficits in BD are qualitatively similar to those of SZ, but quantitatively less pronounced, raising the question of the specificity of cognitive deficits in SZ.[2,3] This pattern of cognitive deficit may represent a common pathway within the two disorders.[32]

It is possible that at least some of the variance in cognitive functions in the BD groups, and also in the SZ group, may be due to subsyndromal mood symptoms.[32] However, this possibility was decreased by testing patients while they were in remission and enjoying a period of relative well-being. Since we also controlled for the effects of medication, it seems unlikely that the neurocognitive differences between BD and SZ patients could be explained solely by the levels of subsyndromal symptoms, or treatment regimens.

The proportion of BD patients with lifetime psychotic features in this study (60%) is very similar to that reported for larger samples.[27] The two BD groups presented very similar neurocognitive performances, as reflected by trivial to small effect sizes in the majority of tests. This suggests that a prior history of psychotic symptoms may not be associated with a more severe cognitive impairment in BD, which is in line with previous reports.[19-25] However, a recent meta-analysis concluded that while there is a greater severity of cognitive deficits in BD HPS+, these were modest, and therefore no categorical separation could be drawn between BD HPS+ and HPS- patients.[27] Discrepant results are probably due to methodological differences, such as the use of small,

Table 2 Neuropsychological variables of patients with bipolar disorder (with and without history of psychotic symptoms), patients with schizophrenia and healthy controls

Neuropsychological variable	BD HPS- patients (n = 30)		BD HPS+ patients (n = 44)		SZ patients (n = 35)		HC (n = 50)		ANCOVA [a]		Scheffe Post Hoc Test [b]	Effect sizes Cohen's *d*		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	p		1 vs 4	2 vs 4	3 vs 4
Attention and mental control														
Mental tracking	5.8	2.51	6.0	2.26	4.5	2.19	7.3	1.89	12.372	**< 0.001**	1 < 4, 2 < 3.4, 3 < 4	0.70	0.63	1.39
Digit span (WMS)	8.5	1.61	8.3	1.96	7.9	1.90	10.5	2.25	16.155	**< 0.001**	1 < 4, 2.3 < 4	0.98	1.04	1.23
Bells Test (omissions)	2.7	3.47	3.4	4.16	3.6	4.61	1.1	2.00	3.166	**0.002**	2.3 < 4	0.97	1.19	1.89
Processing speed														
SDMT	42.7	12.80	38.6	15.10	30.6	11.71	56.4	14.82	39.532	**< 0.001**	1 < 3.4, 2.3 < 4	0.68	0.81	1.16
TMT-A (sec)	55.3	36.47	55.0	25.95	78.0	50.76	38.0	15.34	10.556	**< 0.001**	1.2 < 3, 3 < 4	0.19	0.27	1.06
Executive functions														
SCWT (sec)	62.0	23.86	62.5	16.18	80.4	27.87	58.5	13.69	7.893	**< 0.001**	1.2 < 3, 3 < 4	0.34	0.30	0.98
SCWT (perseverations)	0.7	1.64	0.6	1.23	1.7	2.04	0.3	0.77	5.786	**< 0.001**	2 < 3, 3 < 4	0.90	0.85	1.30
SCT (sec)	156.6	44.84	161.9	57.91	201.3	86.17	122.4	32.99	12.652	**< 0.001**	1.2 < 3, 2.3 < 4	0.52	0.73	0.87
SCT (perseverations)	5.6	9.38	5.6	5.67	11.2	15.39	2.4	2.72	7.196	**< 0.001**	3 < 4	0.85	1.02	1.60
TMT-B (sec)	155.4	128.83	175.7	124.32	224.5	129.92	84.6	35.83	17.215	**< 0.001**	1 < 4, 2.3 < 4	0.75	1.22	1.82
ToH (moves)	18.1	7.92	22.9	9.85	28.0	10.11	12.5	7.17	15.338	**< 0.001**	1 < 3.4, 2.3 < 4	0.36	0.64	1.03
COWA	16.5	6.66	15.6	4.36	13.9	4.15	18.2	4.70	9.401	**< 0.001**	3 < 4	0.78	0.99	1.33
Comprehension (WAIS-R)	14.2	6.78	13.0	6.24	10.2	7.30	19.4	6.60	26.029	**< 0.001**	1 < 4, 2.3 < 4	0.91	0.93	1.45
Similarities (WAIS-R)	9.6	5.39	9.2	6.39	6.4	4.93	15.5	7.04	52.128	**< 0.001**	1 < 4, 2.3 < 4	0.61	0.72	0.75
Verbal memory function														
Information (WAIS-R)	19.0	3.59	17.4	6.41	15.0	6.39	20.7	5.36	17.385	< 0.001	1 < 4, 2.3 < 4	0.36	0.56	0.98
Logical memory (WMS) [c]	5.8	1.90	5.2	2.25	4.4	1.51	9.0	2.62	30.916	< 0.001	1 < 4, 2.3 < 4	1.35	1.55	2.06

[a] Analyses of variance (ANCOVA) with sex, age, educational level, HDRS, and YMRS as covariates.

[b] 1 = Bipolar patients without history of psychotic symptoms; 2 = Bipolar patients with history of psychotic symptoms; 3 = Schizophrenia patients; 4 = Healthy control subjects;

[c] BD HPS- n = 21, BD HPS+ n = 30, SZ n = 21, HC n = 47

BD: bipolar disorder; COWA: Controlled Oral Word Association; HC: healthy controls; HPS -: without history of psychotic symptoms; HPS +: with history of psychotic symptoms; SCT: Stroop Color Test; SCWT: Stroop Color-Write Test; SDMT: Symbol Digit Modalities Test; SZ: schizophrenia ToH: Hanoi Towers Test; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; WAIS-R: Wechsler Intelligence Scale for Adults – Revised; WMS: Wechsler Memory Scale. The sign (>) indicates better performance, and not actual scores on the tests.

heterogeneous samples. It is noteworthy that most previous research assessed non-euthymic patients, with acute symptoms possibly confounding the results.

Studying a sample of true euthymic BD patients may reduce the additional effect of past psychotic symptoms in neurocognitive test performance. Four studies have compared the neurocognitive function of psychotic and non-psychotic euthymic BD patients to those of HC[11,16,19,25] and of healthy relatives.[26] Of these, three studies did find some selective differences in neurocognitive performance, which their authors attributed to the presence of past psychotic features. It has been suggested that psychotic BD might represent a distinct subgroup of BD with impairments in three working memory/executive tasks.[11] Moreover, differences were found in the number of categories of the Wisconsin Card Sorting Test (WCST), suggesting that deficits in cognitive flexibility could be a trait marker of psychotic features in BD.[16] More recently, Martinez-Arán et al. (2008) found greater impairment on verbal memory assessed with a list-learning task in BD HPS+ patients as compared to both HC and BD HPS- patients.[19]

Although our findings are in contrast to previous studies, a closer inspection of data reveals that the proportion of impaired neuropsychological variables were 1/17,[16] 5/16 (all from the same list-learning test),[32] and 1/19 (after controlling for treatment and mood symptoms).[11] Furthermore, we did not use any of the tests in which differences were reported in the above-mentioned studies. Taken together, the literature suggests that cognitive function may be more similar than different during euthymia, independently of lifetime psychotic symptoms.

Conversely, only one of four studies, which similarly compared psychotic and non-psychotic patients with BD to those with SZ, reached a negative finding. Szoke et al. (2008) compared the cognitive performances of subjects with SZ, BD HPS+, BD HPS-, schizoaffective disorder, and HC using WCST and TMT.[25] Psychotic and non-psychotic BD patients showed similar results and both BD groups outperformed the SZ group on the WCST. Although all subjects were euthymic, they were assessed just before discharge and clinical symptoms were not controlled. Thus, as the authors acknowledge, the influence of symptoms could not be completely ruled out. The

use of only two executive tasks instead of a comprehensive neuropsychological battery further limited this comparison. Therefore, ours is the first study with a large sample of well-defined euthymic BD patients reporting a similar performance on a broad range of cognitive tests, regardless of a history of psychosis over their lifetime, and results suggest that if there is an effect of psychosis on neurocognitive performance, it is not very strong.

Our two BD groups were similar in demographic and clinical terms, as well as in medication usage. This latter issue is important because cognitive dysfunction in BD has also been associated with antipsychotic medication rather than with psychotic symptoms by some investigators,[20,22] but not others.[11,19] In our study, psychotropic medication did not seem to influence neurocognitive differences between patients' groups. Lithium and most anticonvulsants may impair associative fluency, verbal memory, short- and long-term memory, and processing speed, although apparently in a reversible way,[33] and the more beneficial cognitive effects seen with atypical antipsychotics in SZ patients have not been sufficiently proven in BD patients.[33] Therefore, the possibility that some treatments may negatively impact cognitive function cannot be excluded, especially with high doses or with combination therapy.[33] Interestingly, BD HPS+ patients presented significantly more negative symptoms than their non-psychotic counterparts, and cognitive similarities remained after covariation for that difference. The relationship between negative symptoms and cognition during euthymia has not been well studied, although negative symptoms have been associated with poorer cognitive functioning in remitted BD patients.[34] Moreover, significant associations have been found in euthymic patients with variables more related to SZ, such as family history of SZ and a history of mood-incongruent psychotic features, and factors which are correlated with negative symptoms in SZ, such as a history of obstetric complications, the level of premorbid functioning, and younger age at illness onset.[35] Finally, SZ patients with predominantly negative symptoms may have more extensive neurocognitive involvement and worse neuropsychological performance than euthymic BD patients.[36]

It should be pointed out that the neuropsychological tests frequently used in studies in subjects with psychiatric disorders were designed to evaluate patients with focal brain damage, and may not be sensitive enough to detect the subtle putative neurocognitive differences between psychotic and non-psychotic BD patients. With this in mind, to better evaluate psychiatric disorders such as BD, the use of experimental tasks in which single cognitive constructs are manipulated has been proposed.[11] This may also explain the trend to poorer performance that our BD HPS+ patients showed on the ToH. Moreover, performance on this task was significantly correlated with past psychotic symptoms among the BD sample. The ToH is generally regarded as a measure of executive functioning, requiring processing mediated by the frontal cortex, and may be more sensitive in detecting subtle lesions that psychotic symptoms might produce in prefrontal circuits. This suggests that psychotic symptoms may have underlying neural correlates that are, at least partially, independent of those associated with non-psychotic BD.

History of psychotic symptoms over patients' lifetime would be less relevant than the BD phenotype and most, if not all, cognitive dysfunctions might stem from the disease process itself. It is possible that certain clinical factors, such as the number and duration of mood episodes, illness duration, number of hospitalizations, and co-morbid conditions, would negatively influence cognition.[7] In this sense, cognitive impairment could be the result of the non-linear action of factors, such as inherited vulnerability, allostatic load, sensitization/kindling and coping.[37] Psychotic symptoms in BD have been associated with longer recovery periods from mood episodes and more manic episodes.[19,38] In our sample, the number of admissions was associated with more psychotic features, which corroborates the previous data.[16] Number of hospitalizations is probably a proxy measure of illness severity, and as such, may suggest a direct relationship between illness severity and neurocognitive functioning. Nevertheless, it remains unclear whether psychotic BD conveys a more severe prognosis.[39]

Finally, our results do not support the idea that psychotic BD is closer to the SZ spectrum disorders, at least on the basis of neurocognitive findings. However, much more research is needed and the search for valid endophenotypes of psychotic BD is thought to have relevant implications for diagnosis, prognosis, and treatment.[10]

Our findings should be considered cautiously due to several limitations. First, our sample comprised a larger proportion of male in the SZ group and sex differences in neurocognitive function have been demonstrated.[40] However, sex was used as a covariate in all comparisons and there was no significant interaction between sex and diagnostic group. Second, psychotic symptoms were narrowly defined, capturing only hallucinations and/or delusions, and were not assessed by means of structured instruments.[24] Because disorganized thought or behaviour was not considered, some BD patients may have been misclassified as non-psychotic. Nevertheless, our definition is consistent with that in the previous literature.[11,19] Third, low premorbid intellectual functioning has been found in patients with SZ but not in non-psychotic BD patients:[41] although we did not control for this factor in our study, we controlled for the educational level, which correlates highly with premorbid IQ. Finally, the study was cross-sectional, and all patients except one were medicated, compared to none of the HC.

Conversely, the strengths of this study include the relatively large sample of BD patients, inclusion of homogeneous groups, with assessment of a broad range of psychopathological symptoms and clearly defined criteria for euthymia, and use of an extensive neurocognitive test battery administered to all participants by the same investigator.

Conclusions

To our knowledge, this is the first study to compare directly HPS+ and HPS- euthymic BD type I patients and SZ patients with severity remission criteria to HC with a comprehensive neuropsychological assessment. Our findings suggest that the patterns of neurocognitive dysfunction may be quantitatively more marked in SZ than in euthymic BD patients, but seem qualitatively similar in both disorders. Our results also suggest that past psychotic features in BD are not associated with a more severe cognitive impairment during euthymia, and cast

doubt on whether psychotic BD is a distinct phenotype, from a neurocognitive perspective. The neurocognitive performance of psychotic BD patients does not seem to be closer to that of SZ patients, questioning the role of psychotic symptoms in favour of a continuum between mood disorders and the schizophrenic spectrum. The performances in cognitive functioning of BD HPS+ patients occupying a position more or less intermediate between those of BD HPS- patients and SZ patients may be attributed to other clinical variables, possibly to the presence of negative symptoms which deserve further investigation.

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References

1. Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. Schizophr Res. 2004;71(2-3):405-16.
2. Daban C, Martinez-Arán A, Torrent C, Tabarés-Seisdedos R, Balanzá-Martínez V, Salazar-Fraile J, Selva-Vera G, Vieta E. Specificity of cognitive deficits in bipolar disorder versus schizophrenia: A systematic review. Psychother Psychosom. 2006;75(2):72-84.
3. Krabbendam L, Arts BM, van Os J, Aleman A. Cognitive functioning in patients with schizophrenia and bipolar disorder: A quantitative review. Schizophr Res. 2005;80(2-3):137-49.
4. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand Suppl. 2007;(434):17-26.
5. Balanzá-Martínez V, Tabares-Seisdedos R, Selva-Vera G, Martínez-Arán A, Torrent C, Salazar-Fraile J, Leal-Cercós C, Vieta E, Gómez-Beneyto M. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: A 3-year follow-up study. Psychother Psychosom. 2005;74(2):113-9.
6. Balanzá-Martínez V, Rubio C, Selva-Vera G, Martinez-Aran A, Sánchez-Moreno J, Salazar-Fraile J, Vieta E, Tabarés-Seisdedos R. Neurocognitive endophenotypes (Endophenocognitypes) from studies of relatives of bipolar disorder subjects: A systematic review. Neurosci Biobehav Rev. 2008;32(8):1426-38.
7. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disorder. 2006;8(2):103-16.
8. Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, Benabarre A, Goikolea JM, Brugué E, Daban C, Salamero M. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord. 2004;6(3):224-32.
9. Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry. 2004;161(2):262-70.
10. Goes FS, Sanders LL, Potash JB. The genetics of psychotic bipolar disorder. Curr Psychiatry Rep. 2008;10(2):178-89.
11. Glahn DC, Bearden CE, Barguil M, Barrett J, Reichenberg A, Bowden CL, Soares JC, Velligan DI. The neurocognitive signature of psychotic bipolar disorder. Biol Psychiatry. 2007;62(8):910-16.
12. Reite M, Teale P, Rojas DC, Arciniegas D, Sheeder J. Bipolar disorder: anomalous brain asymmetry associated with psychosis. Am J Psychiatry. 1999;156(8):1159-63.
13. Sánchez-Morla EM, García-Jiménez MA, Barabash A, Martínez-Vizcaíno V, Mena J, Cabranes-Díaz JA, Baca-Baldomero E, Santos JL. P50 sensory gating deficit is a common marker of vulnerability to bipolar disorder and schizophrenia. Acta Psychiatr Scand. 2008;117(4):313-8.
14. Martin LF, Hall MH, Ross RG, Zerbe G, Freedman R, Olincy A. Physiology of schizophrenia, bipolar disorder, and schizoaffective disorder. Am J Psychiatry. 2007;164(12):1900-6.
15. Albus M, Hubmann W, Wahlheim C, Sobizack N, Franz U, Mohr F. Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. Acta Psychiatr Scand. 1996;94(2):87-93.
16. Bora E, Vahip S, Akdeniz F, Gonul AS, Eryavuz A, Ogut M, Alkan M. The effect of previous psychotic mood episodes on cognitive impairment in euthymic bipolar patients. Bipolar Disord. 2007;9(5):468-77.
17. Glahn DC, Bearden CE, Cakir S, Barrett JA, Najt P, Serap Monkul E, Maples N, Velligan DI, Soares JC. Differential working memory impairment in bipolar disorder and schizophrenia: Effects of lifetime history of psychosis. Bipolar Disord. 2006;8(2):117-23.
18. Zubieta JK, Huguelet P, O'Neil RL, Giordani BJ. Cognitive function in euthymic bipolar I disorder. Psychiatry Res. 2001;102(1):9-20.
19. Martinez-Arán A, Torrent C, Tabares-Seisdedos R, Salamero M, Daban C, Balanza-Martinez V, Sanchez-Moreno J, Manuel Goikolea J, Benabarre A, Colom F, Vieta E. Neurocognitive impairment in bipolar patients with and without history of psychosis. J Clin Psychiatry. 2008;69(2):233-9.
20. Donaldson S, Goldstein LH, Landau S, Raymont V, Frangou S. The Maudsley Bipolar Disorder Project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. J Clin Psychiatry. 2003;64(1):86-93.

21. Goldberg TE, Gold JM, Greenberg R, Griffin S, Schulz SC, Pickar D, Kleinman JE, Weinberger DR. Contrasts between patients with affective disorders and patients with schizophrenia on a neuropsychological test battery. Am J Psychiatry. 1993;150(9):1355-62.
22. Frangou S, Donaldson S, Hadjulis M, Landau S, Goldstein LH. The Maudsley Bipolar Disorder Project: executive dysfunction in bipolar disorder I and its clinical correlates. Biol Psychiatry. 2005;58(11):859-64.
23. Reichenberg A, Harvey PD, Bowie CR, Mojtabai R, Rabinowitz J, Heaton RK, Bromet E. Neuropsychological Function and Dysfunction in Schizophrenia and Psychotic Affective Disorders. Schizophr Bull. 2009;35(5):1022-9.
24. Selva G, Salazar J, Balanzá-Martínez V, Martínez-Arán A, Rubio C, Daban C, Sánchez-Moreno J, Vieta E, Tabarés-Seisdedos R. Bipolar I patients with and without a history of psychotic symptoms: Do they differ in their cognitive functioning? J Psychiatr Res. 2007;41(3-4):265-72.
25. Szoke A, Meary A, Trandafir A, Bellivier F, Roy I, Schurhoff F, Leboyer M. Executive deficits in psychotic and bipolar disorders - implications for our understanding of schizoaffective disorder. Eur Psychiatry. 2008;23(1):20-25.
26. Savitz J, van der Merwe L, Stein DJ, Solms M, Ramesar R. Neuropsychological status of bipolar I disorder: impact of psychosis. Br J Psychiatry. 2009;194(3):243-251.
27. Bora E, Yücel M, Pantelis C. Neurocognitive markers of psychosis in bipolar disorder: A meta-analytic study. J Affect Disord. 2010;127(1-3):1-9.
28. Brissos S, Dias V, Carita, Martinez-Arán A. Quality of Life in Bipolar Type I Disorder and Schizophrenia in Remission: Clinical and neurocognitive correlates. Psychiatry Res. 2008;160(1):55-62.
29. American Psychiatric Association - APA. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington; 1994.
30. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(1):22-33.
31. Lezak M, Howienson D, Loring D. Neuropsychological assessment. Oxford University Press: Oxford; 2004.
32. Martinez-Arán A, Penades R, Vieta E, Colom F, Reinares M, Benabarre A, Salamero M, Gastó C. Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. Psychother Psychosom. 2002;71(1):39-46.
33. Goldberg JF. Adverse cognitive effects of psychotropic medications. In: Cognitive dysfunction in bipolar disorder: a guide for clinicians. Washington, DC: American Psychiatric Publishing; 2008. p.137-58.
34. Atre-Vaidya N, Taylor MA, Seidenberg M, Reed R, Perrine A, Glick-Oberwise F. Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. Neuropsychiatry Neuropsychol Behav Neurol. 1998;11(3):120-26.
35. Ameen S, Ram D. Negative symptoms in the remission phase of bipolar disorder. German J Psychiatry. 2007;10(1):1-7.
36. Buchanan RW, Strauss ME, Kirkpatrick B, Holstein C, Breier A, Carpenter WT Jr Neuropsychological impairments in deficit vs nondefict forms of schizophrenia. Arch Gen Psychiatry. 1994;51(10):804-11.
37. Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, Kauer-Sant'anna M, Grassi-Oliveira R, Post RM. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev. 2008;32(4):675-92.
38. Brockington IF, Hillier VF, Francis AF, Helzer JE, Wainwright S. Definitions of mania: concordance and prediction of outcome. Am J Psychiatry. 1983;140(4):435-39.
39. Keck PE Jr, McElroy SL, Havens JR, Altshuler LL, Nolen WA, Frye MA, Suppes T, Denicoff KD, Kupka R, Leverich GS, Rush AJ, Post RM. Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. Compr Psychiatry. 2003;44(4):263-69.
40. Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S, Tsuang MT. Are there sex differences in neuropsychological functions among patients with schizophrenia? Am J Psychiatry. 1998;155(10):1358-64.
41. Reichenberg A, Weiser M, Rabinowitz J, Caspi A, Schmeidler J, Mark M, Kaplan Z, Davidson M. A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and non-psychotic bipolar disorder. Am J Psychiatry. 2002;159(12):2027-35.