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Neurocognitive heterogeneity in older adults with bipolar disorders

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ABSTRACT

The aim of this study was to estimate the prevalence of clinically significant cognitive deficits in a sample of euthymic older age bipolar disorder (OABD) patients, and its relationship with functional outcome. Sixty-six outpatients and 30 controls completed a neuropsychological battery and a measure of psychosocial functioning. There were 33.3% (CI95% 22–44%) of patients without clinically significant cognitive deficits, 36.4% (CI95% 24–48%) with selective deficits, and 30.3% (CI95% 19–41%) with global deficits. Patients without cognitive deficits were indistinguishable of healthy controls in terms of psychosocial functioning, while patients with cognitive impairments had lower functional outcome. Neurocognitive and psychosocial functioning might be heterogeneous among patients with OABD.

1. Introduction

Patients with bipolar disorder (BD) exhibit persistent cognitive dysfunctions during periods of euthymia, with medium-to-large effect sizes of impairment noted for verbal memory, attention, and executive functions (Mann-Wrobel et al., 2011). Notwithstanding this general profile, it was suggested that deficits could be heterogeneous. A recent study reported that 30% of euthymic BD patients were indistinguishable from healthy controls regarding neurocognitive and psychosocial functioning, while another reported that 30% had cognitive impairment of greater magnitude than reported in the literature (Martino et al., 2014). Another research using multivariate analysis identified 3 neurocognitive subgroups of patients: 1) an intact group with a similar performance to healthy controls (31.6%), 2) a selective impairment group (28.7%), and 3) a global impairment group with a performance comparable to patients with schizophrenia (39.7%) (Burdick et al., 2014). Consistently, another study reported 40% of BD patients with normal neurocognitive performance and 19% with global deficits, while the remaining patients showed some selective deficits (Lewandowski et al., 2014).

In the last decade, a growing body of evidence has revealed that older adults with BD (OABD) have cognitive deficits of similar magnitude to those reported in younger adults (Samamé et al., 2013). However, the proportion of patients with clinically significant cognitive deficits in this population has not been evaluated to date. Therefore, the aim of this study was to estimate the prevalence of clinically significant cognitive deficits in a sample of euthymic OABD patients. An additional aim was to assess the relationship between clinically significant cognitive deficits with clinical variables and functional outcome.

2. Methods

Sixty-six outpatients with BD were consecutively selected with the following inclusion criteria: age older than 50 years (based on Sajatovic et al., 2015), diagnosis of BDI or BDII using Structured Clinical Interview for DSM-IV, and euthymic (Hamilton Depression Rating Scale ≤ 8 and Young Mania Rating Scale ≤ 6) for at least 8-weeks. Exclusion criteria were: history of substance abuse, neurological disease, or any other unstable clinical condition that could affect cognitive performance. Additionally, 30 healthy controls without history of psychotic or affective disorders among themselves or first-degree family members were included.

All subjects completed neuropsychological tests described in detail in previous studies of our group (Martino et al., 2014). Briefly, it included the following tests selected to assess 4 cognitive domains: 1) Attention: Forward Digit Span, and Trail Making Test part A; 2) Verbal memory: Memory Battery of Signoret; 3) Language: Boston Naming Test; 4) Executive functions: Wisconsin Card Sorting Test; Trail Making Test part B; and Phonological Fluency. Additionally, estimated premorbid intelligence quotient (IQ) was calculated by using the WAIS vocabulary subtest. Raw-score of neurocognitive performance were transformed to Z-scores based on normative data of each test. A

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Table 1
Clinical-demographical features and neurocognitive performance of bipolar patients and healthy controls (values are expressed as mean, standard deviation is shown in brackets).

	Bipolar patients (n = 66)	Healthy controls (n = 30)	Test/p-value
Age	63.65 (8.03)	65.13 (10.14)	t = 0.76; df = 46.3; p = 0.44
Gender (% female)	68.18	80	X^2 = 1.42; df = 1; p = 0.23
Years of education	12.27 (3.51)	11.97 (3.02)	t = -0.41; df = 94; p = 0.68
Premorbid IQ (Z-score)	0.17 (0.67)	0.25 (0.45)	t = 0.19; df = 80.3; p = 0.56
YMRS score	1.06 (1.68)	0.57 (0.82)	t = -1.94; df = 93.5; p = 0.056
HDRS score	1.64 (2.52)	2.17 (2.05)	t = 1.01; df = 94; p = 0.32
GAF score	77.75 (10.76)	86.83 (4.50)	t = 5.63; df = 92.1; p < 0.001
Length of illness	24.16 (14.28)		
Clinical subtype (% type I)	30.3		
History of psychosis (%)	25.76		
History of hospitalization (%)	24.24		
Mood stabilizers (%)	100.00		
Benzodiazepines (%)	56.10		
Antidepressants (%)	47.00		
Antipsychotics (%)	53.00		
Neurocognitive assessment (Z-score)			
Immediate logical memory	-2.10 (2.05)	-0.92 (1.39)	t = 2.85; df = 94; p = 0.004*
Delayed logical memory	-2.03 (1.81)	-0.81 (1.28)	t = 3.30; df = 94; p = 0.001*
Serial learning	0.61 (1.74)	1.50 (1.90)	t = 2.26; df = 94; p = 0.026
Free delay recall	-0.80 (1.86)	-0.15 (1.71)	t = 1.62; df = 94; p = 0.11
Recognition	1.27 (0.93)	1.64 (0.51)	t = 2.06; df = 94; p = 0.042
Forward digit span	-0.87 (1.32)	-0.14 (0.99)	t = 3.00; df = 94; p = 0.004*
Boston naming test	-0.55 (1.39)	-0.09 (0.91)	t = 1.91; df = 94; p = 0.059
Phonological fluency	-0.48 (1.09)	0.26 (0.80)	t = 3.32; df = 94; p = 0.001*
Backward digit span	0.14 (1.13)	0.84 (1.24)	t = 2.67; df = 94; p = 0.009
WCST-perseverative errors	-0.04 (1.06)	1.00 (0.99)	t = 4.55; df = 94; p < 0.001*

BD: Bipolar disorder; IQ: Intelligence quotient; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; WCST: Wisconsin Card Sorting Test
* Significant after Bonferroni correction.

cognitive domain was considered affected when performance in at least one test of that domain was 1.5 SD below the mean. Psychosocial functioning was assessed with the General Assessment of Functioning (GAF).

The Hospital Ethics Committee approved the study and all subjects gave written informed consent.

3. Results

Clinical-demographical features and neurocognitive performance of patients and healthy controls are shown in Table 1.

There were 33.3% (CI95% 22–44%) of patients without clinically significant cognitive deficits, which was significant lower than the 63.33% observed among healthy controls (X^2 = 7.59, df = 1, p = 0.006). Among the remaining patients, 36.4% (CI95% 24–48%) had selective cognitive deficits (1 cognitive domain affected), and 30.3% (CI95% 19–41%) had global deficits (2 or more cognitive domains affected). There were no differences between patients with cognitive indemnity, selective deficits, and global deficits in terms of clinical subtype (X^2 = 1.50, df = 2, p = 0.47), history of psychosis (X^2 = 2.44, df = 2, p = 0.29) and hospitalizations (X^2 = 2.06, df = 2, p = 0.36). Similarly, there were no differences in these subgroups of patients regarding the length of illness (Kruskal-Wallis $\times^2$ = 3.09, df = 2, p = 0.21) and exposure to benzodiazepines, antidepressants, and antipsychotics (all p > 0.05). In contrast, there was a trend towards different ages at illness onset (Kruskal-Wallis $\times^2$ = 4.70, df = 2, p = 0.095), which were statistically significant among the cognitive indemnity (median = 36.50, range = 20–50) and global deficit (median = 46.00, range = 18–70) subgroups (Mann-Whitney Z = 2.17, p = 0.030). Consistently, there was a positive correlation between the number of cognitive domains affected and age at illness onset (Spearman R = 0.33, p = 0.010). On the other hand, patients with cognitive indemnity had a better level of psychosocial functioning (median = 85.00, range = 70–95) than patients with selective (median = 76.50, range = 51–94) or global deficits (median = 79.00, range = 45–90) (Kruskal-Wallis $\times^2$ = 11.67, df = 2, p = 0.003). Finally, there were no differences in psychosocial functioning among patients with cognitive Indemnity and healthy controls (median = 87.50, range = 80–95) (Mann-Whitney Z = −1.34, p = 0.18).

4. Discussion

We identified a 33.3% of patients without clinically significant cognitive deficits, while there was a 36.4% with selective cognitive deficits and 30.3% with global deficits. These subgroups of patients differed regarding psychosocial functioning, which closely reproduce results in younger patients (Burdick et al., 2014; Lewandowski et al., 2014; Martino et al., 2014). Overall, the findings suggest the existence of a subgroup of about one-third of patients seen throughout the different age ranges, which would show cognitive indemnity and psychosocial functioning comparable to that of healthy controls.

At present it is not clear what is the reason for the cognitive heterogeneity among patients with BD, and it was suggested that this could respond to quantitative or qualitative variations (Martino et al., 2014). In this study we found no relationship between the neurocognitive subtype and measures of clinical severity as a history of psychosis or hospitalizations. Likewise, we found no relationship between the number of cognitive domains affected and a measure of chronicity such as length of illness. However, this result should be interpreted with caution since it could be because we included patients regardless of the age of onset of the disease. In fact, OABD actually constitute a heterogeneous population composed of both early-onset patients (EO-BD) who develop their illness during early adulthood and late-onset patients (LO-BD) who experienced their first mood episode at an older age. Previous studies suggested that LO-BD patients had more extensive and severe cognitive impairments than patients with EO-BD suggesting pathophysiological differences such as cardiometabolic risk factors and white matter disease among the former (Martino et al., 2013). Consistently, we found that patients with global deficits had a higher age at illness onset than patients with cognitive indemnity and a positive correlation between the number of cognitive domains affected and age at onset. Therefore, further studies could assess the role of chronicity in

cognitive functioning using only a sample of patients aged with EO-BD.

Regardless of the cause, the heterogeneity in cognitive functioning among OABD patients might have clinical and therapeutic implications. First, this reinforces the need to include neurocognitive assessments as a tool in the routine clinical examination of these patients. Second, clinicians should always assess potential treatable causes of cognitive deficits, such as subclinical symptoms, hypothyroidism, psychotropic medications, or psychiatric comorbidity (such as anxiety disorders or substance abuse), before attributing impairment to BD (Martino et al., 2014). Finally, OABD patients with clinically significant cognitive deficits might benefit from using with special caution or avoiding drugs with negative effect on cognition and are included in cognitive or functional remediation programs (Bonin et al., 2016).

In summary, our study provides useful information complementary to that of cross-sectional studies and meta-analysis, identifying that cognitive functioning is highly heterogeneous among OABD patients. Future studies are needed to identify the causes of heterogeneity in cognitive functioning in BD.

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