ARTICLE

The use of the Clock Drawing Test in bipolar disorder with or without dementia of Alzheimer's type

O uso do Teste do Desenho do Relógio em pacientes com transtorno bipolar com e sem demência do tipo Alzheimer

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ABSTRACT

There is limited data regarding the cognitive profile from screening tests of older adults with bipolar disorder (BD) with dementia. **Objective:** To investigate the Clock Drawing Test (CDT) among older adults with BD with and without Alzheimer's disease (AD). **Method:** 209 older adults (79 with BD without dementia and 70 controls; 60 with AD, being 27 with BD) were included to evaluate the performance of three CDT scoring scales, beyond the Mini-Mental State Examination (MMSE) and verbal fluency (VFT). **Results:** Patients with BD without dementia presented with lower scores in MMSE, VF and one CDT scoring scale than controls. Patients with BD and AD presented with lower scores in VF and CDT scoring scales than patients with only AD. All CDT scales presented similar sensitivity and specificity for BD and non-BD groups. **Conclusion:** Elderly subjects with BD showed greater impairment in CDT in both groups of normal cognition and AD.

Keywords: Clock Drawing Test, Alzheimer's disease, bipolar disorder.

RESUMO

Há dados limitados sobre o perfil cognitivo de idosos com transtorno bipolar (TAB) e demência. Previamente, testes de rastreio cognitivo comuns foram pouco estudados. **Objetivo:** Investigar o Teste do Desenho do Relógio (CDT) entre idosos com TAB com e sem doença de Alzheimer (DA). **Método:** Foram incluídos 209 idosos (79 pacientes com TAB sem demência e 70 controles; 60 indivíduos com DA leve, sendo 27 com TAB) para avaliar três escalas de pontuação do TDR, além do *Mini-Mental State Examination* (MMSE) e fluência verbal (FV). **Resultados:** Pacientes com TAB sem demência apresentaram menores escores no MMSE, FV e uma escala de TDR que controles. Pacientes com TAB e DA apresentaram escores mais baixos na FV e em todos os TDR comparados aos apenas com DA. As escalas de CDT apresentaram sensibilidade e especificidade semelhantes para os grupos com e sem TAB. **Conclusão:** Idosos com TAB apresentaram maior comprometimento no TDR em ambos grupos com cognição normal e DA.

Palavras-chave: Teste do Desenho do Relógio, doença de Alzheimer, transtorno bipolar.

Cognitive deficits are a common feature of bipolar disorder (BD), particularly in older adults[1,2]. Meta-analytical data yielded executive and verbal memory impairments as the most common cognitive deficits in BD patients without dementia[3,4]. Cognitive functions such as attention, visual memory, mental speed, language and, to a lesser extent, visuospatial function were also implicated within the spectrum of cognitive dysfunction of these patients[5,6,7]. Cognition seems to be similarly impaired in BD across the life span[8], and geriatric BD patients also show a similar pattern of widespread cognitive dysfunction[9]. However, the severity of cognitive deficits was shown to increase along with the duration of illness and a higher probability of detecting cognitive deficits in BD is seen among patients with early-onset disease or with older age[10].

BD in older adults is associated with increased risk of dementia in the long-term[11,12]. Alzheimer's disease (AD) seems to be the most frequent phenotype among the dementia syndromes developed by BD subjects[2,11,12]. Nevertheless, there is limited data on the cognitive profile of older adults with BD that present with dementia. Few studies compared the cognitive performance of patients with

BD to that of patients with conditions that primarily affect cognition, such as AD[10,13,14]. In this matter, many questions remain along with the proper screening, origin, evolution and impact of cognitive impairment and dementia in BD patients[1,2].

Both neuropsychological and biological markers of cognitive impairment are required for the early or better identification of those BD patients that will present a higher risk for worsening or converting this cognitive dysfunction to dementia[2]. In the absence of these markers, the prompt identification and follow-up knowledge of the neuropsychological deficits presented by these patients are fundamental as long as cognitive impairment negatively affects functional capacity and global prognosis, facilitating the evolution to dementia[15]. In the matter of the most significant cognitive impairments presented by BD patients, the largest effect sizes observed by two meta-analyses indicated that executive function and verbal memory are the most relevant domains[3,4].

Previous studies demonstrated that is possible to identify cognitive impairment in BD patients using simple and fast cognitive tests[7,16,17]. However, executive function and verbal memory were not thoroughly explored within these tests, specially comparing BD patients with and without a primary neurodegenerative disease such as Alzheimer's disease[17]. Additionally, recent evidence raised questions over the presence of clinical differences in the performance of older BD patients compared to controls in the Mini-Mental and Clock Drawing[18].

The aim of this study was to better evaluate the performance of the Clock Drawing, a fast and simple test to evaluate general executive and visuospacial skills, in patients with BD in two different states of cognition, i.e. with and without probable dementia of Alzheimer's disease.

METHOD

The present study was conducted at a university-based psychogeriatric clinic (Institute of Psychiatry, University of Sao Paulo, Brazil), addressing a cross-section evaluation of 209 older adults represented by middle-income, community-dwelling individuals from the hospital catchment area. All patients spontaneously sought our service by being a referral center for neuropsychiatric diseases. The study group comprised 79 patients with BD and 70 controls, both without dementia; 60 subjects with mild AD, being 27 with BD and 33 without the mood disorder. The DSM-IV criteria were utilized for the diagnosis of BD and dementia. The diagnosis of probable AD was made according to the NINCDS-ADRDA, and patients with non-AD dementias were excluded from the study. Inclusion criteria for BD patients were: (i) 60 years of age or more; and (ii) euthymic subjects

for at least one month prior to the evaluation, as assessed by clinical impression by a psychiatrist and a maximum score of 7 in the 21-item Hamilton Rating Scale for Depression, and of 4 in the Young Mania Rating Scale. All patients presented stable clinical diseases. Exclusion criteria were illiteracy, mild cognitive impairment, visual and hearing disabilities, evidence of previous traumatic brain injury, and other relevant health conditions that could either affect cognition or limit the administration of neuropsychological tests, including use of medications with cognitive side effects such as benzodiazepines, opioids and anticholinergics. Laboratory tests performed for all participants included blood count and biochemistry, serum levels of glucose, thyroid hormones, folic acid and vitamin B12, lipid profile and immunotests for syphilis. Neuroimaging scans (magnetic resonance) were performed in all subjects. Detailed information about recruitment and inclusion/exclusion criteria pertaining to this cohort can be found in previous publications from our group[11,17,19].

Participants were allocated in two major diagnostic groups according to their cognitive status: mild probable dementia of AD type or without dementia. Diagnosis of dementia was reached at multidisciplinary consensus meetings, taking into account the available clinical, neuropsychological, laboratorial, and neuroimaging data, in addition to information provided by a family member interview. The study protocol comprised patient evaluation with the Brazilian version of the Cambridge Cognitive Test (CAMCOG)[19], which yields scores for the Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT) and Verbal Fluency Test (VFT) (semantic fluency with animal naming). Diagnosis was not based on the CAMCOG score or any results from screening tests. The CDT was additionally scored according to three well-known qualitative and quantitative scales to evaluate executive skills (Shulman, Mendez and Sunderland scoring systems)[20,21,22] BD and non-BD patients were matched for age, education level and cognition (taking into account the CAMCOG total score).

Statistical procedures were undertaken with the Statistical Package for the Social Sciences (SPSS), 18.0 version for Windows, and significance level was defined at 5% (p=0.05). Comparison groups were analyzed for age, education and CAMCOG total score. Categorical variables were analyzed with the Pearson's Chi-squared test. Continuous variables were analyzed with the Mann-Whitney test. Receiver operating characteristic (ROC) curves area analyses were carried out to evaluate the best match between sensitivity and specificity according to the area under the curve obtained for each test, as well as derived cut-off scores, for the cognitive tests to evaluate the cognitive groups between BD and non-BD.

This study was approved by local Ethical Committee and all participants signed an informed consent.

Table 1. Characteristics and cognitive variables of subjects without dementia.

	BD (n=79)	non-BD (n=70)	p*
Age (years)	67.1 (4.0)	68.1 (5.2)	0.142
Female gender (n)	50	60	0.002**
Education (years)	9.1 (4.6)	9.9 (5.0)	0.349
CAMCOG	91.2 (6.5)	92.0 (9.0)	0.146
MMSE	27.1 (2.2)	27.9 (2.3)	0.003
VFT animals	14.9 (4.4)	18.0 (5.5)	0.001
CDT Shulman	3.7 (1.0)	3.8 (0.8)	0.367
CDT Sunderland	8.1 (2.1)	8.7 (1.9)	0.107
CDT Mendez	17.3 (3.9)	18.2 (3.2)	0.037

BD: Bipolar disorder; MMSE: Mini-Mental State Examination; CDT: Clock Drawing Test; VFT: Verbal Fluency Test. *All p values are for Mann-Whitney test, except for (**) with Pearson Chi-square.

Table 2. Characteristics and cognitive variables of subjects with dementia of AD type

	BD (n=27)	non-BD (n=33)	p*
Age (years)	71.3 (6.4)	73.9 (5.5)	0.113
Female gender (n)	23	25	0.364**
Education (years)	4.9 (3.4)	5.6 (4.4)	0.662
CAMCOG	65.2 (14.2)	63.0 (12.3)	0.284
MMSE	20.3 (3.7)	18.7 (4.1)	0.117
VFT animals	7.8 (3.0)	10.8 (4.4)	0.015
CDT Shulman	1.7 (1.4)	2.7 (1.6)	0.016
CDT Sunderland	4.0 (2.6)	5.33 (2.5)	0.032
CDT Mendez	7.4 (7.4)	11.5 (6.8)	0.024

BD: Bipolar disorder; MMSE: Mini-Mental State Examination; CDT: Clock Drawing Test; VFT: Verbal Fluency Test. *All p values are for Mann-Whitney test, except for (**) with Pearson Chi-square.

RESULTS

Characteristics of the sample are presented in Tables 1 and 2, regarding the cognitive condition evaluated (with or without dementia).

Subjects without dementia

BD and non-BD patients did not differ regarding age and schooling; women predominated in the non-BD group. In the cognitive tests, there were not any differences between the groups in the CAMCOG, CDT by Shulman or CDT by Sunderland scores. The two groups differed in the MMSE, VF and the CDT by Mendez scores (Table 1).

Subjects with DAT

BD and non-BD patients did not differ regarding age and schooling and gender. Regarding cognitive tests, there were not any differences between the groups in the CAMCOG, and MMSE scores. The two groups differed in the VF, CDT by Shulman, CDT by Sunderland and CDT by Mendez scores (Table 2).

ROC curve analysis
Subjects without BD

The CAMCOG and the MMSE were the best tests to discriminate subjects with and without dementia. The VF, CDT by Sunderland and CDT by Mendez also showed good sensitivity and specificity in discriminating both groups (Table 3).

Pairwise comparison between ROC curves did not reveal any differences in accuracy between the CAMCOG and the MMSE (p=0.348), the VF and the CDT, regardless of the scoring method (p=0.486 for Shulman, p=0.911 for Sunderland, and p=0.806 for Mendez), and among different scoring methods for CDT (p=0.456 for Mendez vs. Shulman; p=0.466 for Mendez vs. Sunderland; p=0.172 for Shulman vs. Sunderland). The MMSE was more accurate in discriminating the groups than VF (p<0.001), CDT by Mendez (p=0.001), CDT by Shulman (p<0.001), and CDT by Sunderland (p=0.001).

Subjects with BD

The CAMCOG was the best test to discriminate subjects with and without dementia, followed by the MMSE. The VF, CDT by Shulman, CDT by Sunderland and CDT by Mendez also showed good sensitivity and specificity in discriminating both groups (Table 4).

Pairwise comparison between ROC curves did not reveal any differences in accuracy between the CAMCOG and the MMSE (p=0.320), the MMSE and VF (p=0.234), the MMSE and the CDT, regardless of the scoring method (p=0.071 for Shulman, p=0.100 for Sunderland, p=0.112 for Mendez), the VF and the CDT, regardless of the scoring method (p=0.350 for Shulman; p=0.482 for Sunderland, and p=0.444 for Mendez), and among different scoring methods for CDT (p=0.631 for Mendez vs. Shulman; p=0.601 for Mendez vs. Sunderland; p=0.253 for Shulman vs. Sunderland).

Table 3. ROC analysis for cognitive variables of subjects without bipolar disorder.

	AUC	95%CI AUC	Cut-off scores	Sens. / Spec.	p
CAMCOG	0.963	0.906-0.990	81	90.1 / 85.7	<0.001
MMSE	0.972	0.918-0.994	24	93.9 / 91.2	<0.001
VFT animals	0.841	0.752-0.908	14	74.2 / 75.3*	<0.001
CDT Shulman	0.802	0.712-0.874	3	84.8 / 71.4	<0.001
CDT Sunderland	0.848	0.764-0.911	7	78.9 / 74.2	<0.001
CDT Mendez	0.832	0.746-0.898	18	81.8 / 72.8	<0.001

*2 subjects with AD and 5 healthy controls did not perform the VFT; AUC: Area under the curve; Sens.: Sensitivity; Spec.: Specificity; MMSE: Mini-Mental State Examination; CDT: Clock Drawing Test; VFT: Verbal Fluency Test; 95%CI AUC: 95% Confidence interval for AUC; CAMCOG: Cambridge cognitive test; ROC: Receiver operating characteristic.

Table 4. ROC analysis for cognitive variables of subjects with bipolar disorder.

	AUC	95%CI AUC	Cut-off scores	Sens. / Spec.	p
CAMCOG	0.974	0.923-0.995	82	92.6 / 94.9	<0.001
MMSE	0.952	0.892-0.984	23	88.9 / 93.7	<0.001
VFT animals	0.912	0.841-0.958	11	88.9 / 82.3	<0.001
CDT Shulman	0.864	0.784-0.923	3	92.6 / 62.0	<0.001
CDT Sunderland	0.880	0.802-0.935	6	81.5 / 72.2	<0.001
CDT Mendez	0.872	0.793-0.929	15	81.5 / 81.0	<0.001

AUC: Area under the curve; 95%CI AUC: 95% Confidence interval for AUC; CAMCOG: Cambridge cognitive test; ROC: Receiver operating characteristic; MMSE: Mini-Mental State Examination; CDT: Clock Drawing Test; VFT: Verbal Fluency Test.

DISCUSSION

In this study, we evaluated BD versus non-BD subjects with and without probable AD. We explored the performance of the CDT rated with three different scoring scales commonly used for cognitive screening between these groups and we observed clinical differences for BD subjects especially regarding their executive and visuospatial function. We have previously observed with another sample that demented BD patients had a significantly worse performance on the CDT as compared with patients with dementia due to AD[17]. These functions were impaired in both BD with and without dementia, being observed through VF test and CDT. BD subjects without dementia did not performed as mild cognitive impairment at neuropsychological evaluation, but showed lower scores in VF and CDT. This finding is relevant to clinical practice regarding cognitive screening of BD subjects to avoid a false positive result towards a dementia syndrome. It is worth noting that global cognitive measures (CAMCOG and MMSE) remained without significant difference between these two groups. In the group with BD and AD, the observed deficits were naturally even worse especially regarding executive and visuospatial abilities.

In a previous study of our group with a different sample, we evaluated BD subjects without cognitive impairment (controls), with cognitive impairment no dementia (CIND) or mild cognitive impairment (MCI) and dementia in a broader sense (including subjects with possible AD, e.g. vascular dementia)[17]. In that study, we already found a significant clinical difference in executive function among BD subjects compared to healthy controls or those with dementia but without BD. However, subjects with very mild cognitive decline, such as MCI or CIND, were not discriminated through executive tasks, but presented a lower score at the MMSE. In the present study, we used the CDT with three scoring scales to better evaluate both executive and visuospatial tasks in another sample with and without BD in two cognitive states, i.e. dementia of AD type and healthy cognitive controls. We excluded other possible dementia etiologies such as vascular or even mixed vascular and AD.

In the present study, we observed that subjects with BD but without AD showed a lower although not clinically significant MMSE score (27.1 vs. 27.9) and a worse performance in executive and visuospatial tests such as the VF (14.9 vs. 18) and CDT according to Mendez scoring system (17.3 vs. 18.2). These findings are consistent with current evidence since non-demented BD subjects do not usually present a severe cognitive impairment that could be identified by the MMSE, usually ranging between 0.2 to 1.0 standard deviations below the respective norms during neuropsychological evaluation[3,10]. Additionally, previous published studies conducted in samples of non-demented young adults and elderly patients with BD showed very small differences (less than 1 point) in the MMSE score[10,13,23]. Although statistically significant, the clinical meaning of these differences remains uncertain. Furthermore, most relevant cognitive domains affected in BD subjects are verbal memory and executive function. This latter can be better pointed out by brief tests such as the VF and CDT than the MMSE. CDT scales have different scoring protocols and had never been compared between each other among BD subjects. CDT scoring scales have different levels of complexity to evaluate the test through more qualitative (as in Shulman scale) or quantitative (as in Mendez and Sunderland) analysis. Although these scales appear to have similar accuracy according to the literature, more complex and detailed scales such as Mendez are prone to detect more subtle deficits[21].

When AD subjects with BD were compared to those without BD but with this type of dementia, cognitive deficits observed among the group without AD were more pronounced. Subjects with BD and AD presented a significant decline in VF (7.8 vs. 10.8) and in all three CDT scoring scales. It is worth noting that global cognitive measures (CAMCOG and MMSE) remained without significant difference between these two groups. Global cognitive measures do not appear to present a significant different between euthymic BD and non-BD control groups according to a recently published metanalysis with late-life BD patients[18]. Previous studies evaluating verbal fluency in adults with BD produced inconsistent results. Four of these studies reported some degree of impairment in euthymic BD subjects[6,8,24,25], whereas four other studies did not report any clinically significant difference between BD subjects and healthy controls[26,27,28,29,30].

On the other hand, studies exploring the performance of the CDT among BD subjects are sparse. In one study with a small sample of early and late-onset BD patients, CDT was scored according to Shulman scale[16]. CDT was abnormal in 42.3% of the total sample, in which 36.5% were from the early-onset group and 50% from subjects with onset between 40 and 50 years old. However, this study lacked a comparison group. Another study evaluated the CDT between BD subjects and healthy matched controls according to the scale of Rouleau et al.[29]. The authors did not find a significant difference between these groups. Our previous study evaluated the CDT according only to Shulman scale between BD and non-BD patients with normal cognition, CIND/MCI and dementia (possible and probable AD)[17]. We found a significant difference only between BD and non-BD subjects with dementia, in which the CDT was more impaired among BD group. In a broader sense, CDT may detect a more pronounced executive dysfunction among BD subjects, only clinically detected in more cognitively compromised patients.

In a qualitative analysis (data not shown) of the CDT from BD compared to non-BD subjects without dementia, observed errors in clock drawings involved time indication, especially positioning the right minute hand. The discrimination between these two groups required a more complex and quantitative scale (Mendez). When patients with dementia were evaluated, both conceptual (e.g. inaccurate time setting, missing numbers, number substitutions) and visuospatial errors (e.g. numbers distribution, distance between the numbers) on the CDT were observed. All three scales could discriminate between the two groups (BD vs. non-BD). However, there were not typical errors within the BD group, but instead, a global impairment especially regarding visuospatial organization, that was more severe than that observed from the non-BD group.

Global cognitive measures such as the MMSE and the CAMCOG presented a higher sensitivity and specificity in subjects without BD. In the group of BD subjects, VF test showed a clinically relevant increase in sensitivity (from 74.3 to 88.9%) and specificity (from 75.3 to 82.3%), which is in agreement with the expected more common executive dysfunction among these subjects[3,10,18]. However, CDT did not present a higher accuracy as expected among BD subjects. All three CDT scoring systems remained with a similar accuracy between the two groups, although two of the scoring systems (Shulman and Sunderland) showed a higher sensitivity among BD subjects.

Potential limitations of our study must be addressed. The study had a transversal design and the samples with and without dementia cannot be directly compared. Our study was not controlled for the potentially deleterious effects of the short and long-term use of psychotropic drugs on cognition. This is a frequent and special concern among BD patients although few studies reported a correlation between medication use and cognitive performance. Previously, a study observed a negative influence over verbal memory by mood stabilizers and impairments in psychomotor speed, attention, and executive function with the use of benzodiazepines[5]. However, another study did not find any correlation with a particular class of medication[7]. In a previous study of our group, we observed that valproate was the only drug associated with a negative effect on verbal fluency among patients with dementia[17].

Cognitive impairment is a common clinical problem associated with BD patients, even in euthymic periods. In spite of a presumed stability of the cognitive impairment among the majority of patients through their life span, these deficits seems clinically important interfering negatively in functional capacity and exerting a negative effect on the global prognosis of these patients[15]. Additionally, the characterization and follow-up of these cognitive deficits are relevant since the risk to develop dementia among BD patients is almost three times higher especially among older patients, when compared to non-BD age-matched population[11,12,30]. In this matter, the identification of cognitive impairments cannot only rely on neuropsychological evaluation because of cost and time consuming, and the utilization of brief and common tests such as the CDT are of utmost interest.

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