VISUAL AND VERBAL MEMORY IN EUTHYMIC BIPOLAR PATIENTS: IMPACTS OF SUBTYPE, PSYCHOTIC SYMPTOMS AND SUICIDE BEHAVIOR

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Abstract

Objective: Recent studies point out to the existence of neuropsychological deficits in patients with bipolar disorder even in euthymic periods. Episodic memory deficits are frequently described in patients with bipolar disorder (BD). This study aims to evaluate the performance of patients with BD compared with health controls on tests of verbal and visual episodic memory. We further considered the bipolar subtype, lifetime history of psychotic symptoms and suicide attempts.

Method: Sixty euthymic BD patients and sixty normal individuals with same age and scolarship were involved in the study. All subjects were submitted to the MINI Neuropsychiatric interview, Raven's Progressive Matrices, Rey Auditory Verbal Learning Test and Rey Complex Figure Test.

Results: Regardless the absence of intelligence differences between BD and Control subjects, the former are impaired in both verbal and visual memory measures. Comparing groups according BD subtype, we found that visual memory presents worse results in Type I patients than in Type II. No differences were found considering history of psychotic symptoms and suicide attempts.

Conclusions: Our results suggests that episodic memory impairments is important in euthymic bipolar patients and not influenced by the subtype and history of psychotic symptoms, and suicide attempts.

Key Words: bipolar disorder, episodic memory, neuropsychology, psychosis, suicide.

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Introduction

Considered the sixth leading cause of disability worldwide, bipolar disorder (BD) is a chronic, clinically severe and common psychiatric disorder that accounts for significant economic, familial and individual burden (Woods 2000). Prevalence rates for BD have been acknowledged to approximate 1 to 2% (Hirschfeld 2001) in the general population. These estimates are probably conservative since when the diagnosis is broadened to include bipolar spectrum disorders, the rate increases to 6 to 7% (Pini et al. 2005, Akiskal 1996).

BD is associated with several psychiatric comorbidities and a range of serious comorbid medical conditions, which leads to a higher mortality rate in untreated BD than in the general population (Oquendo et al. 2000). Furthermore, BD is the psychiatric diagnosis most closely associated with suicidal behavior (Baldessarini et al. 2006). BD patients are also more prone to have forensic problems (about 10% of them), to have very low employment and higher pension or disability benefits. A large proportion never marry and

a vast majority of married patients divorce or experience marital problems (Morgan et al. 2005), reflecting their overall poor social functioning.

Cognitive deficits are associated with poor recovery in these patients since even when euthymic they have altered functions such as memory, attention, executive functions and processing speed (Olley et al. 2005) to such an extent that current employment status is significantly associated with cognitive status (Dikerson et al. 2004). Moreover, cognitive deficits, including those in verbal memory, are a stronger predictor of poor self-reported life quality (Brissos et al. 2008) and overall functional outcome in bipolar patients (Martinez-Aran et al. 2007).

Episodic memory deficit results in BD are rather contradictory since there are positive (Bora et al. 2009, Delaloye et al. 2009, Kieseppä et al. 2005) and negative associations regarding visual episodic memory (Ferrier et al. 1999), performance of BD type II (Hsiao et al. 2009) and bipolar patients not using psychotic medication (Jamrozinski et al. 2009).

An explanation for the disparate findings is the fact that BD is a heterogeneous clinical condition and some subgroups of patients exhibit more severe cognitive impairments than others (Jarmrozinski 2010, Selva et al. 2007). BD subtype (Harkavy-Friedman et al. 2006), lifetime history of psychotic illness (Martinez-Aran et al. 2008) and history of suicide attempt (Malloy-Diniz et al. 2009) are among the clinical features that could affect bipolar patients' performance on cognitive assessments.

The present study aimed to compare the performance of bipolar patients and normal controls on neuropsychological tests of episodic memory for both visual and verbal content. It was hypothesized that clinical variables like subtype, suicide behavior and history of psychotic symptoms could present different patterns of memory functioning.

Methods and Subjects

Study participants included 60 BD patients recruited from the Núcleo de Transtornos Afetivos from the Psychiatric Service of the Hospital das Clínicas of the Universidade Federal de Minas Gerais. Inclusion criteria consisted of: a) BD diagnosis identified using a structured interview (MINI-PLUS) according to DSM-IV. b) An euthymic state at the time of the neuropsychological assessment as determined by the Brazilian adaptation of the Beck Depression Inventory (BDI) (Gorenstein and Andrade 1998) and the Young Mania Rating Scale (YMRS) (Vilela et al. 2005). Subjects were classified as euthymic if they had both a BDI score lower than 12 points and a YMRS lower than 13. c) At least eight years of formal education. d) Normal intelligence as measured by the Test of Raven's Progressive Matrices (percentile >10) (General Scale, Raven 2002).

Patients were further interviewed by a psychiatrist using a semi-structured interview to collect information regarding socio-demographic and clinical parameters. Episodic memory was evaluated using the Brazilian version of the Rey Auditory Verbal Learning Test (RAVLT) (Malloy-Diniz et al. 2007) and the Rey-Osterreich Complex Figure (ROCF) (Strauss et al. 2006).

The control group consisted of 60 normal subjects recruited from the community. No subject had a history of an axis-1 psychiatric illness according to DSMIV criteria as assessed by the MINI-LUS. The controls had at least eight years of formal education and normal intelligence as measured by the Test of Raven's Progressive Matrices.

Statistical Analysis

Since certain variables exhibited non-normal distributions, groups (bipolar x healthy controls; BD I x BD II; bipolar with psychotic symptoms x no psychotic symptoms) were compared according to polarity of the first episode using the Mann-Whitney test for quantitative variables.

Area under curve measure in Receiver Operator Characteristic Curve (ROC) was used to assess accuracy in comparison between Bipolar and Healthy subjects concerning memory measures. Since our data had nonparametric distribution, we use Cliff's Delta to assess effect size of group's differences (Leech and Onwuegbuzie 2002). We also use Bonferroni's correction for multiple comparison and, therefore results were considered significant when $p < 0.006$. To assess the effects of humor in memory measures in comparisons according to lifetime history of psychotic illness and bipolar subtype, we use Generalized Linear Model considering BDI's and YMRS's results as covariates. Categorical variables were analyzed using chi-square tests.

Results

Sixty bipolar patients were studied (36 BD I; 14 with lifetime history of psychotic symptoms; 14 with lifetime history of suicide attempt). All patients were euthymic at the time of assessment (BD I mean=7.5 and SD=2.5; YMRS mean=4.7 and SD=3.0). Patients and controls did not differ on socio-demographic parameters (age, gender distribution, educational level) or intelligence, but the neuropsychological examination of episodic memory revealed that individuals in the BD group showed less efficient performance in both verbal and visual components. Considering the measures of area under ROC curve we found significant results concerning ROCF retrieval, RAVLT A1, LOT, Proactive interference and Recognition Memory. All results were between 0.7 and 0.9 (Table 1) pointing to a moderate and useful accuracy in discriminate bipolar and comparison control group (Swet 1988). Considering these measures, Cliff's effect size ranging from 0.42 to 0.79 indicated lack of overlap between bipolar and control group. We did not found significant differences for the visuoconstruction score (copy of ROCF), RAVLT's forget speed and retroactive interference (**Table 1**)

Bipolar patients were also analyzed by subtype (BD I or II). Socio-demographic parameters as well intelligence were comparable between the groups. The sole significant difference on the neuropsychological

Table 1. *Comparison between bipolar and healthy controls in sociodemographic and neuropsychological measures*

			Bipolar Disorder				Comparison Control					z our x2	p	Cliff's delta	Area under ROC curve	Standard Error	p
			Mean	Standard Deviation	Count	Column N %	Mean	Standard Deviation	Count	Column N %						
Age			39.78	12.99			38.57	9.07			-.202	.840				
Formal Education	College Level				35	58.3%			37	61.7%						
	Graduated Level				25	41.7%			23	38.3%	0.139	.709				
Gender	Male				19	31.7%			24	40.0%						
	Female				41	68.3%			36	60.0%	0.906	.341				
Raven raw score			45.00	5.58			46.00	2.79			-1.648	.099				
Rey Complex Figure Copy			28.81	7.76			30.93	4.60			-1.095	.273	-0.29	,558	,053	,275
Rey Complex Figure retrieval after 3 minutes			15.68	10.91			26.43	5.96			-5.801	.000	0.79	,807	,042	,000
RAVLT A1 (imediate memory)			5.32	1.28			6.22	1.38			-4.067	.000	0.42	,710	,048	,000
RAVLT Learning over trials			12.87	6.71			18.80	7.21			-4.341	.000	0.46	,729	,046	,000
RAVLT Proactive Interference			0.79	0.27			1.02	0.31			-4.295	.000	0.45	,726	,047	,000
RAVLT Retroactive interference			0.88	0.43			0.95	0.12			-2.567	.010	0.27	,636	,053	,010
RAVLT Forget Speed			0.99	0.29			0.91	0.17			-1.212	.225	-0.17	,437	,053	,232
RAVLT Recognition Memory			11.20	2.33			12.87	1.62			-4.250	.000	0.44	,722	,046	,000

evaluation was found regarding visual memory (BD I mean=13.3 and SD=11.2; BD II mean=19.2 and SD=9.5; z=2.257; p=0.024). There were no differences on socio-demographic measures (age, education, gender), intelligence and verbal memory between BD I and II patients.

Patients were further analyzed according to lifetime history of psychotic symptoms (n=14) and history of suicide attempt (n = 14). In both analyses, socio-demographic parameters, intelligence levels, visuo construction, verbal and visual memory were comparable.

Considering the effect of humor status on memory measures, we did not found any significant relationship in comparisons according subtype and lifetime history of psychotic illness.

Discussion

The objective of the present study was to evaluate verbal and visual memory in bipolar patients compared to healthy controls as well as to analyze the impact of bipolar type (I or II), history of psychotic symptoms and suicide attempts.

Differences were found between bipolar patients and healthy controls in learning, storage and auditory-verbal recall as well as in visual modality. The results appear to be specific since no differences were found between the groups with regard to general intelligence, visuo construction and socio-demographic data. Some authors argue that poor memory in bipolar patients could be of a motivational nature, particularly in depression since recognition memory is usually preserved in these patients (Ilsley et al. 1995). In the current study, recognition memory was worse in the euthymic bipolar patients compared to controls, and was also worse in BD I and patients with a lifetime history of psychotic symptoms. Therefore, it can be argued that memory difficulties are not related to motivational aspects, persisting even in the stage when memory is assessed on clues given by the examiner.

Regarding the relationship between deficits in verbal and visual episodic memory according BD subtype, a difference was only seen on the retrieval of Rey Complex Figure, which revealed greater visual memory impairment in BD I patients compared to type II. These results are similar to those described in the literature that point to subgroups of BD I patients having impaired cognitive performance compared to BD II (Savitz et al. 2009, Selva et al. 2008). However, the present results differ from those of Hsiao et al (2009), which did not find differences between BD I, II and controls on visual memory. Those authors described worse performance of BD I in verbal memory, perceptual motor skills and executive functions. It is important to note that Rey Complex Figure copy and retrieval are both influenced by executive functions (Watanabe et al. 2009). Therefore, future studies should investigate the relationship between executive function impairment and Rey Complex Figure scores in bipolar patients to elucidate whether visual memory deficits are genuine or are reflections of executive impairment.

As in previous studies, the present one did not find differences between episodic memory in bipolar patients according to lifetime history of psychotic illness (Bora et al. 2007, Kieseppä et al. 2005, Savitz et al. 2005, Savitz et al. 2009) and therefore these results reinforce the hypothesis that memory impairment in BD is independent of this clinical feature. The same conclusion can be extended to the comparison between suicide attempters and non-attempters. As was reported in a previous study performed by the current research group with a sample of BD I outpatients (Malloy-Diniz et al. 2009), the present study did not reveal any differences in verbal and visual memory tests according to lifetime history of suicide attempt.

A methodological strength of the current study was the comparison of bipolar patients and healthy controls of the same age, educational and intelligence levels. Furthermore, the bipolar patients were euthymic during the period of assessment and therefore mood effect in evaluation can be excluded. However, certain limitations must be noted. The sample could be considered small, which reduces statistical power when performing comparisons between subgroups like psychotic symptoms or suicide behavior and a â-error cannot reliably be excluded. Nonetheless, considering the Area under curve ROC, differences between bipolar and control groups had moderate and useful accuracy. Furthermore, Cliff's Delta points to the lack of overlap between bipolar and control groups in those measures that reach statistically significant differences. Second, all subjects were submitted to pharmacological therapy during the study and these treatments may have influenced the results. But, Ancín et al. (2010) suggested that cognitive alterations in bipolar patients cannot be explained by medication because the alterations remained after controlling for medication variables in the statistical analysis of several studies (for example, Fleck et al. 2001) as well as in drug-free euthymic bipolar patients (Goswami et al. 2009). Future studies are needed to clarify the specific effect of medication in episodic memory in bipolar patients.

The nature of memory impairment in BD and its probable role as a possible endophenotype should be investigated further and consider neuropsychological variables and genetic polymorphisms in affected bipolar patients and their unaffected relatives. Furthermore, variables such as age of first hospitalization, number of manic and depressive episodes, comorbidites and other clinical variables should be included in the research agenda. Findings from these studies would lead to better understanding BD and improved clinical practices with this population.

References

Akiskal HS (1996). The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. *Journal of Clinical Psychopharmacology* 16, 2, 4S-14S.

Ancín I, Santos JL, Teijeira C, Sánchez-Morla EM, Bescós MJ, Argudo I, Torrijos S, Vázquez-Álvarez B, De La Vega I, López-Ibor JJ, Barabash A, Cabranes-Díaz JA. (2010) Sustained attention as a potential endophenotype for bipolar disorder. *Acta Psychiatrica Scaninavica* 25.

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J (2006). Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disorders* 8, 1, 625-639.

Bora E, Vahip S, Akdeniz F, Gonul AS, Eryavuz A. Ogut M (2007) The effect of previous psychotic mood episodes on cognitive impairment in euthymic bipolar patients. *Bipolar Disorders* 9, 468-77.

Bora E, Yucel M, Pantelis C (2009). Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of Affective Disorders* 113, 1-20.

Brissos S, Dias VV, Kapczinski F (2008). Cognitive Performance and Quality of Life in Bipolar Disorder. *Canadian Journal of Psychiatry* 53, 517-524.

Delaloye C, Moy G, Baudois S, de Bilbao F, Remund CD, Hofer F (2009). Cognitive features in euthymic bipolar patients in old age. *Bipolar Disorders* 11, 7, 735-43.

Dickerson FB, Boronow JJ, Stallings CR, Origoni AE, Cole S, Yolken RH (2004). Association between cognitive functioning and employment status of persons with bipolar disorder. *Psychiatric Services* 55, 1, 54-8.

Ferrier IN, Chowdhury R, Thompson JM, Watson S, Young AH (2004). Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. *Bipolar Disorders* 6, 4, 319-322.

Fleck DE, Sax KW, Strakowski SM (2001). Reaction time measures of sustained attention differentiate bipolar disorder from schizophrenia. *Schizophrenia Research* 52, 3, 251-259.

Gorenstein, C, Andrade L (1998). Inventário de depressão de Beck: propriedades psicométricas da versão em português. *Revista Psiquiatria Clínica* 25, 5, 245-250.

Goswami U, Sharma A, Varma A (2009). The neurocognitive performance of drug-free and medicated euthymic bipolar patients do not differ. *Acta Psychiatrica Scandinavica* 120, 6, 456-463.

Harkavy-Friedman JM, Keilp JG, Grunebaum MF, Sher L, Printz D, Burke AK (2006). Are BPI and BPII suicide attempters distinct neuropsychologically? *Journal of Affective Disorders* 94, 1, 255-259.

Ilsley JE, Moffoot APR, O'Carroll RE (1995). An analysis of memory dysfunction in major depression. *Journal of Affective Disorders* 35, 1-2, 1-9.

Jamrozinski K, Gruber O, Kemmer C, Falkai P, Scherk H (2009). Neurocognitive functions in euthymic bipolar patients. *Acta Psychiatrica Scandinavica* 119, 365-374.

Jamrozinski K (2010). Do euthymic bipolar patients have normal cognitive functioning? *Current Opinion in Psychiatry* 23, 3, 255-260

Hirschfeld RM (2001). Bipolar spectrum disorder: improving its recognition and diagnosis. *The Journal of Clinical Psychiatry* 62, 5-9.

Hsiao YL, Wu YS, Wu JY, Hsu MH, Chen HC, Lee SY, et al. (2009). Neuropsychological functions in patients with bipolar I and bipolar II disorder. *Bipolar Disorder* 11, 5, 547 - 54.

Kieseppä T, Tuulio-Henriksson A, Haukka J, Van Erp T, Glahn D, Cannon TD, Partonen T et al. (2005). Memory and verbal learning functions in twins with bipolar-I disorder, and the role of information-processing speed. *Psychological Medicine* 35, 2, 205-215.

Leech NL, and Onwuegbuzie AJ (2002). *A Call for Greater Use of Nonparametric Statistics*. Papper presented at the Annual Meeting of the Mid-South Educational Research Association, Chattanooga.

Malloy-Diniz LF, Lasmar VA, Gazinelli LDE S, Fuentes D, Salgado JV (2007). The Rey Auditory-Verbal Learning Test: applicability for the Brazilian elderly population. *Revista Brasileira De Psiquiatria* 29, 4, 324-9.

Malloy-Diniz LF, Neves FS, Abrantes SS, Fuentes D, Corrêa H. (2009). Suicide behaviour and neuropsychological assessment of type I bypolar patients. *Journal of Affective Disorders* 112, 1-3, 231-236.

Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, Malhi GS, Gonzalez-Pinto A, Daban C, Alvarez-Grandi S, Fountoulakis K, Kaprinis G, Tabares-Seisdedos R, Ayuso-Mateos JL (2007). Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord* 9, 103-113.

Martinez-Aran 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 (2008). Neurocognitive impairment in bipolar patients with and without history of psychosis. *The Journal of Clinical Psychiatry* 69, 233-9.

Morgan VA, Mitchell PB, Jablensky AV (2005). The epidemiology of bipolar disorder: sociodemographic, disability and service utilization data from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Bipolar Disorders* 7, 326-37.

Olley A, Malhi GS, Mitchell PB, Batchelor J, Lagopoulos J, Austin MP. (2005). When euthymia is just not good enough: the neuropsychology of bipolar disorder. *The Journal of Nervous and Mental Disease* 193, 323-30.

Oquendo MA, Waternaux C, Brodsky B, Parsons B, Haas GL, Malone KM, Mann JJ (2000). Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. *Journal of Affective Disorders* 59, 107-117.

Pini S, de Queiroz V, Pagnin D, Pezawas L, Angst J, Cassano GB, Wittchen HU. (2005). Prevalence and burden of bipolar disorders in European countries. *European Neuropsychopharmacology. The Journal of the European College of Neuropsychopharmacology* 15, 425-34.

Raven JC (2002). *Matrizes Progressivas*: *Escala geral.* Casa do Psicólogo, São Paulo.

Savitz J, Lucki I, Drevets WC (2009). 5-HT1A receptor function in major depressive disorder. *Progress in Neurobiology* 88, 1, 17-31.

Savitz J, Solms M, Ramesar R (2005). Neurocognitive function as an endophenotype for genetic studies of bipolar affective disorder. *NeuroMolecular Medicine* 7, 275 - 286.

Savitz JB, Van Der Merwe L, Stein DJ, Solms M, Ramesar RS (2008). Neuropsychological task performance in bipolar spectrum illness: genetics, alcohol abuse, medication and childhood trauma. *Bipolar Disorders* 10, 479-94.

Selva G, Salazar J, Balanzá-Martínez V, Martínez-Arán A, Rubio C, Daban C, Sánchez-Moreno J, et al. (2007). Bipolar I patients with and without a history of psychotic symptoms: Do they differ in their cognitive functioning? *Journal of Psychiatric Research* 41, 3-4, 265-272.

Strauss E, Sherman EMS, Spreen O (2006). *A compendium of neuropsychological tests: administration, norms, and commentary*. Oxford, Oxford University Press.

Swet JA (1988). Measuring the accuracy of diagnostic systems. *Science* 240, 1285 - 93.

Vilela J, Crippa J, Del-Ben C, Loureiro S (2005). Reliability and validity of a Portuguese version of the Young Mania Rating Scale. *Brazilian Journal of Medical and Biological Research* 38, 9.

Watanabe K, Ogino T, Nakano K, Hattori J, Kado Y, Sanada S, Ohtsuka Y (2005). The Rey-Osterrieth Complex Figure as a measure of executive function in childhood. *Brain and Development - International edition* 27, 564-569.

Woods SW (2000). The economic burden of bipolar disease. *The Journal of Clinical Psychiatry* 61, Suppl 13, 38-41.