

Bipolar remitted patients show emotion-related bias in memories of lifelike events: A study based on the virtual reality paradigm

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Abstract: This study aimed to examine whether patients with bipolar disorder (BD) perceive differences in the encoding and retrieving of autobiographical information related to events with different emotional valence. For this purpose, an experimental task based on the virtual reality paradigm was administered to 14 euthymic BD patients and 23 healthy controls. All participants also had a neuropsychological assessment and completed self-report questionnaires as to mood and psychopathological symptoms. BD patients, when compared to adult controls, recognized more information associated with negative lifelike events and retrieved less information related to positive events. We suggest that changes in processing negative information are caused by the activation of maladaptive emotion-regulation processes, and changes in processing positive information arise from insufficient elaboration of memory traces or from suppression/distortion processes acting during retrieval.

Keywords: Bipolar disorder; autobiographical memory; emotional memory; virtual reality, neuropsychological assessment.

Los pacientes con trastorno bipolar presentan sesgo emocional en memorias de eventos simuladores de la realidad: Estudio basado en el paradigma de realidad virtual

Resumen: Nuestro objetivo era verificar si los pacientes con trastorno bipolar experimentan alteraciones en la codificación y recuperación de la información autobiográfica, referente a eventos con diferentes valencias emocionales. Una tarea experimental basada en el paradigma de realidad virtual fue administrada a 14 pacientes bipolares eutímicos y 23 adultos sanos. Los participantes también fueron objeto de evaluación neuropsicológica y completaron los cuestionarios de autoinforme relativos al estado de ánimo y síntomas psicopatológicos. Los pacientes bipolares, en comparación con los adultos sanos, reconocieron más información asociada a eventos negativos y recuperaron menos información referente a eventos positivos. Se sugiere que las alteraciones en el procesamiento de la información negativa son causadas por la activación de los procesos de regulación emocional desadaptativos, y que las alteraciones en el procesamiento de la información positiva surgen de la elaboración insuficiente de rasgos mnésicos o de procesos de supresión/distorsión que actúan durante la recuperación.

Palabras clave: Trastorno bipolar; memoria autobiográfica; memoria emocional; realidad virtual; evaluación neuropsicológica.

Introduction

Patients with bipolar disorder (BD) in acute depressive and manic phases tend to show mood congruent bias in learning and memory for emotional content (Johnson, 2005; Lex, Hautzinger, & Meyer, 2011). This

bias can be also observable in bipolar remitted patients subjected to high or low mood induction (Nutt & Lam 2011). On the other hand, in the absence of clinically significant symptoms and in the presence of stabilized mood, the retrieval of emotional information seems to be not affected by its valence (Derntl, Seidel, Kryspin-Exner, Hasmann, & Dobmeier, 2009; Lex, Meyer, Marquart, & Thau, 2008). Additionally, in a memory task involving positive and negative stimuli bipolar euthymic patients tend to respond in a way comparable to that of healthy adults (Derntl et al., 2009; Lex et al., 2008). These findings appear to be unexpected, since episodic memory

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impairment is considered as one of the endophenotypic markers of BD (Czepielewski et al., 2015; Malhi et al., 2007; Martínez-Arán et al., 2004). In this context it was suggested that the memory of remitted patients with BD enhances significantly in the presence of emotional content, being these beneficial effects much more pronounced than in healthy adults.

Other authors (Kauer-Sant'Anna et al., 2008) have investigated whether the capacity of recall of BD euthymic patients depends on emotional intensity associated to the processed stimuli. For this purpose neutral and negative stories were presented. Their recall was carried out one week later. BD patients did not benefit from the moderate increase of emotional intensity of the presented stimuli. Their performance also remained unchanged in relation to the stories with high emotional intensity. In respect of healthy adults, the moderate increase of emotional intensity improved their capacity of recall. However, in presence of the highly arousing stories, their performance showed to be significantly worse. BD patients and healthy controls also differed in relation to the subjective perception of the emotional impact of the performed task. Similar effect was observed by Malhi Lagopoulos, Sachdev, Ivanovski and Shnier (2005). In the study developed by these authors, remitted patients with BD revealed to overrate the value of negative stimuli. On the other hand, their evaluation of positive and neutral stimuli was comparable with the evaluation made by healthy subjects.

It has been also shown (Boulanger, Lejeune, & Blairy, 2013; Kim et al., 2014; Mansell & Lam, 2004; Tzemou & Birchwood, 2007) that BD patients process differently the information related with the events from their own life and represented in the event-specific knowledge (ESK; Conway & Pleydell-Pearce, 2000). According to some authors (Boulanger et al., 2013; Kim et al., 2014; Mansell & Lam, 2004), the manifestations of these differences can be observable through the diminished specificity of autobiographical memories (AMs) retrieved on the base of negative cues. Other authors have demonstrated (Bobrowicz-Campos, 2015; Scott, Stanton, Garland, & Ferrier, 2000; Tzemou & Birchwood, 2007) that difficulties in the retrieval of the information represented in the ESK appear in the presence of both, positive and negative cues. Furthermore, Tzemou and Birchwood (2007) have shown that the indices of specificity of AMs retrieved after the presentation of negative cues tend to remain steady over different phases of BD, while retrieval based on positive cues improve significantly on the euthymic phase. These last findings suggest that BD patients process differently the information related to the positive and negative events of

their life. However, given the paucity of data on this topic, future studies specifically focused on it are required.

There is also a need for studies investigating the mechanism underlying reduced specificity of AM in BD. Until now, several hypotheses have been raised, although none of them explain the phenomenon of overgeneral memory in a satisfactory way. For example, according to some authors (Scott et al., 2000), the diminished capacity to retrieve the specific life events constitutes one of the manifestations of cognitive vulnerability to the development of affective symptoms. Other authors (Tzemou & Birchwood, 2007) proposed that overgeneral memory result from the strategic inhibition and functional avoidance of traumatic events. However, this affect regulation hypothesis was not supported by Mowlds et al. (2009), as these authors did not find a significant relation between childhood trauma and AM specificity. For Mansell and Lam (2004), the difficulties in the retrieval of specific AMs arise from the discordant memories of goals-related activities, and for Boulanger et al. (2013) and Kim et al. (2014) these difficulties are related to executive function impairment. The discussion about the mechanism of overgeneral memory became even more interesting after being revealed that the mood state (depressive, manic or euthymic) at the time of event encoding may have a moderating effect on the subsequent retrieval of autobiographical events (King et al., 2013).

Although, the studies addressed to AM in BD contribute significantly to the comprehension of functioning of patients with this disorder, it is important to highlight that all of the studies approached the AM processes in a posteriori perspective, without controlling the encoding condition, which weakens the capacity to draw valid conclusions about the underlying mechanism. In order to overcome this methodological fragility a new paradigm based on virtual reality (VR) was proposed (Burgess, Maguire, Spiers, & O'Keefe, 2001). Its implementation allows investigating the lifelike events memory in a controlled condition. Recent research have also shown that VR paradigm can be successfully used in domains of cognitive restructuring and emotional regulation (Belloch, Cabedo, Carrió, Lozano-Quilis, Gil-Gómez, & Gil-Gómez, 2014; Botella, Bretón-López, Serrano García-Palacios, Quero, & Baños, 2014). To the best of our knowledge, there is no study using VR paradigm in BD population with the purpose to examine memory for emotionally charged events.

The aim of this study was to explore whether the remitted patients with BD show alterations in encoding and retrieval of autobiographical information related to events with positive, negative and neutral valence, using an experimental task based on the VR paradigm. Other

aims were to determine relationships among retrieval of lifelike events and neuropsychological performance, and to establish whether, and if so, to what degree the memory for emotionally charged events is affected by mood and psychopathological symptoms.

Method

Participants

The sample was composed by two groups. One group included voluntary individuals with a diagnosis of BD, currently in remission, recruited from the Association for the Support of Depressive and Bipolar Patients (ADEB), Psychiatry Clinic of Coimbra Hospital Centre (CHC) and Rainha Santa Isabel Health House. The enrollment of BD patients was done by institutional psychiatrists and clinical psychologist. They screened for the exclusion criteria all the patients who received health care services in these three institutions from June 2013 to July 2014. The exclusion criteria comprised: criteria for post-traumatic stress disorders as defined in the Diagnostic and statistical manual of mental disorders – IV (DSM-IV; APA 1994); substance abuse or dependence in the last year; learning difficulties or educational level below 4 years; neurodegenerative disorders or cranioencephalic trauma; and electroconvulsive therapy (ECT) in the past 6 months. The reasons for exclusion most frequently met were substance abuse and learning difficulties. There were also several patients who refused their participation in the study. After screening procedures, Structured Clinical Interview for DSM-IV Axis I Disorders was administrated to 17 eligible BD patients with purpose to confirm their diagnosis and obtain other relevant clinical data (SCID-I; First, Spitzer, Gibbon, & Williams, 1997). In addition, the eligible BD patients were rated on the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and Young Mania Rating Scale (YMRS; 1978). The cut-off points for inclusion / exclusion were 8 for HDRS, and 12 for YMRS. At this stage, the authors of the study verified whether the eligible BD patients had already participated in studies with protocols based on the same neuropsychological assessment tools that were administrated in the present one. Three such patients were identified. In order to avoid the potential influence of variables related to previous learning, it was decided to exclude them. The final sample included 14 BD patients.

All patients were medicated during the study. Ten patients were receiving mood stabilizers (1 lithium, 9 sodium valproate) and 3 anticonvulsants. 6 patients were taking antidepressants, predominantly SSRI, being 2 of

them medicated with 2 different types of this medication. Neuroleptics were prescribed to 7 patients, 2 of them were taking more than one type of this medication. 7 patients were receiving benzodiazepines, predominantly diazepam; in 2 of these cases 2 types of benzodiazepines were prescribed. In addition, 2 patients were given anticholinergic drugs.

The comparison group included healthy adult volunteers recruited from general population. To facilitate the recruitment process several sports and cultural associations were contacted, as well as hospital staff, university administrative staff and students from the faculties other than psychology. These subjects were contacted in person by the first author of the study. A total of 25 subjects were screened by study authors with Psychopathological Assessment Questionnaire-II (QAP-II; A.P. Matos, personal communication, March 27th, 2006) to ensure that they or their first-degree relatives do not meet the criteria for any DSM-IV axis I psychiatric disorder or neurodegenerative disorder. This screening procedure resulted on the exclusion of two subjects with history of learning difficulties. Healthy adults were also screened for the previous participation in studies with similar objectives. None such person was identified. Final sample included 23 control subjects.

The study was approved by Ethical Committee of Coimbra Hospital Centre and Support Center for Research in Mental Health of Rainha Santa Isabel Health House. Individually, the participants were given explanations about the purpose and the procedure of this study, and that the confidentiality and their anonymity would be guaranteed. They also signed written consent based on World Medical Association recommendations.

Instruments

Psychopathological Assessment. Clinical data were collected based on SCID-I. In addition, all patients were rated on YMRS and HDRS, and classified on the General Assessment of Functioning Scale (GAF; American Psychiatric Association, 1994). This last scale is one of the indices described in DSM-IV, which purpose is to indicate the level of psychosocial functioning. In addition, Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Portuguese version of Vaz Serra & Abreu, 1973) measuring the severity of depressive symptoms and Cognition Check List for Mania – Revised (CCL-M-R; Beck, Colis, Steer, Madrak, & Goldberg, 2006; translated and adapted for Portuguese population by the authors of present study) assessing the severity of maladaptive beliefs and cognitions associated with mania were administrated. In the present

study BDI obtained internal consistency of .919, and CCL-M-R of .918. The psychopathological assessment was also based on Self-Rating Anxiety Scale (SAS; Zung, 1971; Portuguese version of Vaz Serra, Ponciano, & Relvas, 1982) indicating the severity of anxiety symptoms (with internal consistency obtained in the present study of .859), and Brief Symptom Inventory (BSI; Derogatis, 1993; Portuguese version of Canavarro, 1999) used to identify the psychopathological symptoms and to rate their intensity (with internal consistency obtained in the present study of .978). These measures were completed by both, BD patients and healthy controls.

Mood Assessment. For mood assessment Questionnaire of Emotions (QE; Pinto-Gouveia & Dias, 1995; as cited by Dias, 2003), elaborated from Multiple Affect Adjective Check List (MAACL; Zuckerman & Lubin, 1965) was used. This measure consists of 24 adjectives of positive and negative valence that refer to the different feelings and that are rated on a Likert scale ranging from 0 (indicator of the absence of emotion at the moment of evaluation) to 6 (indicator of the very intense presence of emotion at the moment of evaluation). Internal consistency of Questionnaire of Emotions in the present study was of .863.

Neuropsychological Assessment. All subjects were administered a neuropsychological battery of tests addressed to assess different cognitive domains. The examined cognitive domains were (i) verbal comprehension using Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) vocabulary subtest (Wechsler, 2008a), with internal consistency obtained in the sample of 2450 adults $> .90$ (Strauss, Sherman, & Spreen, 2006); (ii) phonological fluency using Controlled Oral Word Association Test (COWAT) for P, M, R letters (Benton & Hamsher, 1976), with internal consistency in the present study of .878; (iii) executive function using Wisconsin Card Sorting Test–64 (WCST-6; Kongs, Thompson, Iverson, & Heaton, 2000)¹; (iv) attention and working memory using WAIS-III arithmetic subtest (Wechsler, 2008a), with internal consistency obtained in the sample of 2450 adults $\geq .80$ and $\leq .89$ (Strauss, Sherman, & Spreen, 2006); (v) verbal learning and memory using The Hopkins Verbal Learning Test–Revised (HVLTRV; Brandt & Benedict, 2001; Portuguese version of Fernandes & Pinho, 2010), with internal consistency in the present study of .878; and (vi) non-verbal learning and memory using Wechsler Memory Scale–Third Edition (WMS-III) visual reproduction subtest (Wechsler, 2008b), with internal consistency in the present study of .886.

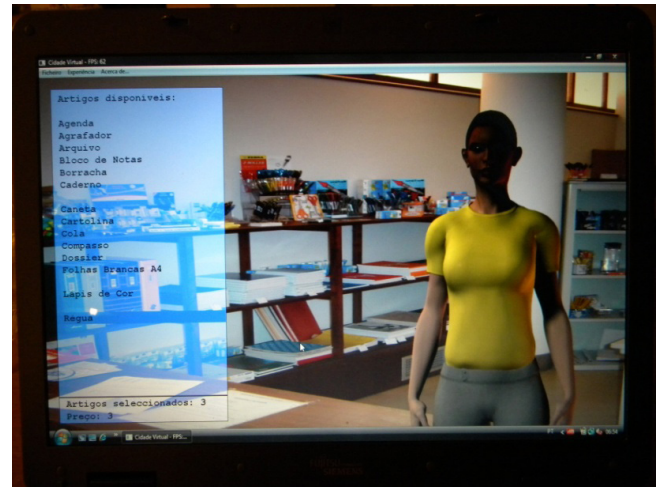
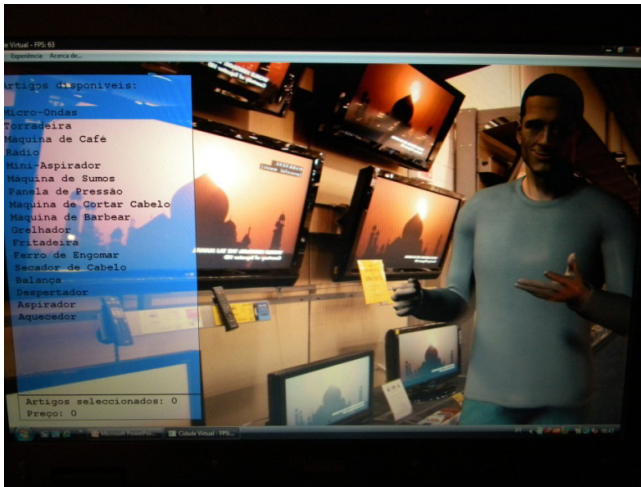
¹ Internal consistency coefficients could not be calculated for WCST-64 as the items of this test are dependent upon one another.

Lifelike Events Memory Assessment. The VR task developed for the purpose of this study was built based on programming language C++ with the API graphics OpenGL. The 3D models and images used for textures definition were downloaded from websites addressed to 3D modeling. In order to guarantee ecological validity, the VR task was contextualized in the scenery of a town that included, among others, the residential buildings, the villas, the church, the stores, the mini market and the factory. The exploration of this town proceeded in a first-person perspective, being the choice of the route dependent on the participant decision.

Initially, participant was asked to move through the town in order to familiarize with the roads, buildings and stores, as well as with the keyboard buttons corresponding to forward, reverse, right and left movements (training task). Once the participant felt confident, he/she was invited to pass to the next stage (information acquisition task), receiving instruction for buying 16 objects in three different stores (mini market, stationery store and appliance store) indicated by the experimenter. The localization of all these stores was identified during the training task. The participant was also informed about the type of stores to be visited. At that point, the participant was instructed to visit the stores in order he/she wishes and to choose any object available in the store (Figure 1a). He/she was also informed that all three stores need to be visited, that it must be purchased at least one object in each store, and that is impossible to go back to a store previously visited. The information about the number of coins available and the number of objects to be bought, as well as the images of objects already acquired were displayed on the monitor during all the task, being possible their consultation in any moment (Figure 1b). During the information acquisition task participant faced three situations: (i) positive valence, consisting of prices reduction; (ii) negative valence, consisting of extra-payment request; and (iii) neutral valence in which the actual and expected product prices did not differ. The sequence of events with emotional valence was the same for all participants. The experimenter did not warn about the existence of these three emotionally charged conditions, being the information about changes or no changes in object prices provided only at the moment of payment. The emotional expressions of sellers were congruent with emotional valence of each condition. The experimenter also did not inform that in a later stage the use of memory strategies will be evaluated.

Approximately half an hour after concluding the information acquisition task, the participant was requested to complete a questionnaire for evaluating the use of memory strategies. This questionnaire included the re-

a) Choice of objects to purchase



b) Travel around the city

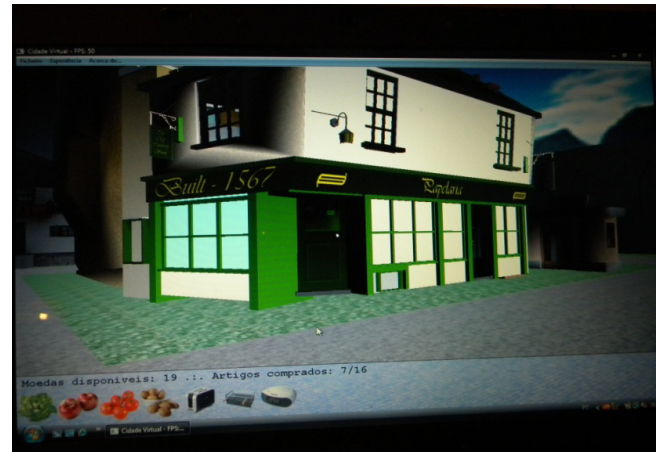
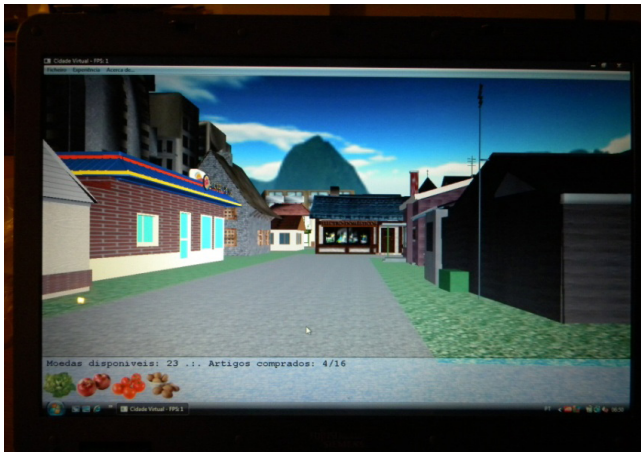


Figure 1. Information acquisition task

call tasks, recognition tasks and visual-spatial orientation tasks. During the recall task subjects were asked to provide two types of information: (i) conceptual, relative to acquired objects, and (ii) contextual, regarding visited stores, number of objects to buy and number of available coins. Processing of conceptual and contextual information was also evaluated through the recognition task. In the conceptual information trials participants were asked to indicate the images of objects previously acquired, and the contextual information trials consisted in the identification of images of visited stores and images of sellers. Regarding the visual-spatial orientation task, it encompassed two localization trials and one orientation trial. In these three trials the participant was given a map of the city. Initially, he/she was asked to localize the visited stores and other important buildings in the city; later, he/she was requested to reproduce the

route that was traveled during the VR simulation. The internal consistency of the VR task obtained in the present study was of .799.

Procedure

The study was conducted individually in two sessions. During the first session informed consent was obtained, and data to examine inclusion/exclusion criteria were collected (SCID-I and QAP-II). BD patients provided additionally information regarding their clinical history (SCID-I). The duration of this session did not exceed 2 hours. At the second session, the neuropsychological battery and the VR task were administered. The order of neuropsychological tasks was counterbalanced to diminish any possible effect of fatigue. After, the participants completed self-questionnaires indicating the presence and

severity of psychopathological symptoms (BDI, CCL-M-R, SAS and BSI) and the questionnaire of emotions. BD patients were further rated on HDRS and YMRS. For BD patients, the second session took around 2.5 hours to complete, including a 15-minutes pauses after each hour of assessment process. Healthy controls needed, approximately, 2 hours for execution of all the tasks.

Data analysis

To compare demographic characteristics of BD patients and healthy controls, *t*-student tests for independent samples and chi-square (χ^2) tests were used, as appropriate. The evaluation of the performance differences on neuropsychological tasks and VR task, and the comparison of psychopathological symptoms severity and mood states were conducted with Mann–Whitney (*U*) test. Differences were considered significant at $p \leq .05$. The effect size was calculated according to the following formula: $r = Z/\sqrt{N}$ (Field, 2004), and the obtained values were interpreted based on indications proposed by Cohen (1988). Thus, *r* of .1 was considered as indicative of small effect size, *r* of .3 as indicative of moderate effect size and *r* of .5 as indicative of large effect size. For analysis of the influence of concomitant variables on dependent variables non-parametric ANCOVA using *F* statistic was performed. To control type I error, significance level $< .05$ was used. The effect size was indicated by coefficient partial eta squared (η_p^2), being its values interpreted based on Cohen (1988) proposal, modified by Marôco (2011). Therefore, η_p^2 values $\geq .5$ pointed to the very large effect size, η_p^2 values ranging from .25 to .5 to the large effect size, η_p^2 values ranging from .05 to .25 to the moderate effect size, and η_p^2 values $\leq .05$ to the small effect size. Finally, Spearman correlations (*rho*) were calculated to determine the magnitudes of the relationships between continuous variables. The obtained *rho* values were interpreted according to Pestana and Gageiro (2014). Very strong correlation was indicated by $\rho \geq (+/-)0.9$ and strong correlation by $\rho > (+/-)0.7$ and $< (+/-)0.89$. The *rho* values ranging from $(+/-)0.4$ to $(+/-)0.69$ were considered as indicative of moderate correlation. Weak correlation was identified through *rho* values $< (+/-)0.4$. Data analyses were performed by using the SPSS Statistics (v. 21, IBM SPSS, New York) program.

Results

Demographic and clinical variables

As it was shown in Table 1, groups did not differ in age ($p = .609$) and education ($p = .235$). Also, the distri-

bution of gender was not significantly different between both groups ($p = .445$). In relation to clinical variables, 10 subjects from BD group had diagnosis of bipolar I disorder, and the remaining 4 of bipolar II disorder. The mean age of onset of BD was approximately 33 years, and the mean duration of illness 12 years. Patients had, on average, 8 previous symptomatic episodes. Approximately, 10% of these episodes were characterized by the presence of psychotic symptoms, being their occurrence reported by 7 subjects. Five BD patients had comorbid diagnosis of anxiety disorders, 4 of generalized anxiety disorder and 1 of social anxiety disorder. Four patients had history of abusive consumption of alcohol and substance; however, in none of these cases, the pattern of abusive consumption had manifested within the year prior to assessment. None of the patients had sleep or eating disorders. The clinical characteristics of BD patients are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the sample

	BD group		Control group		χ^2
	N = 14		N = 23		
Female / male	10/4		19/4		.642
	Range	M (SD)	Range	M (SD)	<i>t</i>
Age	32-65	45.07 (8.65)	28-62	46.74 (10.00)	.517
Education	4-18	12.00 (4.79)	6-19	13.61 (3.31)	1.209
	M(SD)				
Age of onset	32.64 (8.11)		—		—
Duration of illness	12.43 (7.41)		—		—
Previous symptomatic episodes	7.57 (5.96)		—		—
- depressive	3.79 (3.47)		—		—
- manic	2.29 (2.70)		—		—
- hypomanic	1.50 (2.88)		—		—
GAF	70.71 (9.58)		—		—
HDRS	5.43 (2.24)		—		—
YMRS	2.79 (2.01)		—		—

Note: BD: bipolar disorder patients; GAF: General Assessment of Functioning Scale; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale. * $p < .05$; ** $p < .01$.

Psychopathological and mood assessment

As can be seen in Table 2, BD patients, when compared to healthy controls, obtained significantly higher

score on BDI ($r = .27, p = .049$) and CCL-M-R ($r = .38, p = .010$). Differences registered in relation to BSI were marginally significant ($p = .077$). Both groups did not differ on SAS ($p = .174$) and QE ($p = .155$).

Table 2. Psychopathological and mood assessment

	BD group		Control group		Mann-Whitney (<i>U</i>)
	Mean	SD	Mean	SD	
BDI	15.86	13.23	8.43	4.13	108.00*
CCL-M-R	33.93	17.89	21.09	10.55	87.00**
SAS	40.29	10.44	37.04	9.08	130.50
BSI	70.71	45.76	49.22	38.27	115.00
QE	56.43	17.71	50.09	20.59	128.00

Note: BD: bipolar disorder patients; BDI: Beck Depression Inventory; BSI: Brief Symptom Inventory; CCL-M-R: Cognition Checklist for Mania - Revised; QE: Questionnaire of Emotions; SAS: Self-Rating Anxiety Scale. * $p < .05$; ** $p < .01$.

Neuropsychological assessment

Neuropsychological test results are displayed in Table 3. Although both groups were equivalent in terms of educational level, they significantly differed in performance on vocabulary subtest, being BD patients those who had worse results ($p = .010, r = .42$). Significant differences were also observed in relation to phonological fluency: BD patients obtained lower score for total responses ($p = .027, r = .32$) and for words beginning with letter P ($p = .033, r = .30$) and R ($p = .005, r = .42$). The differences on number of generated words beginning with letter M were marginally significant ($p = .071$). The number of errors was equivalent in both groups ($p = .258$). BD patients also showed diminished performance on arithmetic subtest ($p = .007, r = .40$).

Furthermore, BD patients obtained lower score on WCST-64. Significant differences were observed in relation to the number of correct responses ($p = .028, r = .31$) and conceptual level of responses ($p = .017, r = .35$), and marginally significant differences in relation to the number of perseverative responses ($p = .076$) and number of perseverative errors ($p = .054$). There were no differences on number of non-perseverative errors ($p = .478$).

Regarding HVLTV, BD patients recalled fewer words than control subjects on the immediate recall task ($p < .001, r = .54$) and delayed recall task ($p = .019, r = .34$). They also showed poorer performance on the recognition task ($p = .001, r = .51$). Learning capacity revealed to be preserved ($p = .361$), as well as retention ($p = .273$). The groups differed additionally on visual re-

production subtest. BD patients obtained significantly lower score on the immediate recall task ($p = .005, r = .42$), delayed recall task ($p = .003, r = .45$), and recognition task ($p = .016, r = .35$). Impairment was also observed at the level of retention ($p = .011, r = .38$).

Table 3. Neuropsychological assessment

	BD group		Control group		Mann-Whitney (<i>U</i>)
	Mean	SD	Mean	SD	
Vocabulary	31.93	16.77	45.35	9.91	80.00*
Phonological Fluency Total	25.50	16.50	35.13	8.45	99.50*
Item P	9.36	6.55	12.91	3.01	102.50*
Item M	8.64	5.94	10.91	4.32	114.00
Item R	7.50	4.77	11.30	3.38	80.50**
Errors	3.64	2.34	3.35	2.79	140.00
Arithmetic	8.50	4.22	12.00	3.03	84.50**
WCST - 64					
correct responses	42.21	12.25	49.35	6.03	100.00*
perseverative errors	12.36	13.91	5.57	2.64	110.00
non-perseverative errors	8.93	6.09	9.09	5.66	159.00
perseverative responses	16.36	19.21	7.30	3.32	115.00
conceptual level of responses	35.14	16.67	46.04	9.04	93.50*
HVLTV					
immediate recall	21.07	7.64	29.09	3.54	55.50***
learning capacity	2.86	2.21	3.09	1.28	149.50
delayed recall	7.21	3.96	9.96	1.43	96.00*
retention	.78	.35	.89	.11	141.50
recognition	8.87	4.04	11.61	1.12	76.50*
Visual Reproduction					
immediate recall	59.21	23.85	79.30	10.52	79.50**
delayed recall	43.57	28.37	70.43	17.96	73.50**
retention	.68	.25	.88	.16	88.00*
recognition	40.57	5.72	44.43	3.22	93.50*

Note: BD: bipolar disorder patients; HVLTV: Hopkins Verbal Learning Test - Revised; WCST - 64: Wisconsin Card Sorting Test - 64. * $p < .05$; ** $p < .01$; *** $p < .001$.

Lifelike events memory assessment

As can be seen in Table 4, BD patients recalled less information than control subjects, being the differences observed in relation to contextual information statistically significant ($r = .58, p < .001$), and in relation to con-

ceptual information marginally significant ($p = .087$). Furthermore, an analysis based on emotionally charged conditions (positive, negative and neutral) was done. It encompassed uniquely conceptual information. Results from Mann–Whitney test revealed that recall of objects acquired in positive condition was significantly poorer in BD group, as compared to control group ($r = .35$, $p = .030$). Both groups did not differ in recall of objects acquired in negative ($p = .245$) and neutral conditions ($p = .868$). In order to collect more data about the responses' pattern of each group intrusion errors were counted. The total number of wrong responses given by BD patients was equivalent to that of controls ($p = .945$). The absence of significant differences was also confirmed for intrusion errors committed in relation to positive ($p = .780$), negative ($p = .950$) and neutral conditions ($p = .930$).

In relation to recognition of conceptual and contextual information, in both cases, the performance of BD patients and control subjects revealed to be equivalent

(conceptual information: $p = .222$; contextual information: $p = .907$). Equivalence between BD and control groups was also attested for recognition of objects acquired in positive ($p = .320$) and neutral conditions ($p = .931$). Regarding the negative condition, BD patients recognized significantly more objects than control subjects ($p = .020$, $r = .38$). The performance in recognition of acquired objects was additionally screened for the presence of false positives. Total number of errors did not differ between groups ($p = .668$). The absence of significant differences was also observed in relation to positive ($p = .398$), negative ($p = .591$) and neutral conditions ($p = .251$).

Regarding the visual-spatial orientation task, the Mann – Whitney comparison indicated that in none of the three trials BD patients differed significantly from controls [stores' localization (localization task I): $p = .881$; other buildings' localization (localization task II): $p = .563$; orientation: $p = .994$].

Table 4. Lifelike events assessment

	BD group		Control group		Mann-Whitney (<i>U</i>)
	Mean	SD	Mean	SD	
(%) Recalled objects – total	48.21	19.98	60.60	19.62	106.50
- positive condition	49.29	26.75	69.98	24.78	92.50*
- negative condition	47.08	30.87	57.00	23.74	123.50
- neutral condition	61.92	37.31	62.74	33.23	155.50
(%) Recalled contextual information	66.67	34.59	96.38	8.64	63.00***
Errors in recall – total number	1.86	1.92	1.78	1.59	158.50
- positive condition	.57	.76	.48	.67	152.00
- negative condition	.50	.52	.61	.89	157.50
- neutral condition	.79	1.31	.70	.97	157.50
(%) Recognized objects – total	83.04	10.52	76.90	15.01	122.00
- positive condition	81.61	11.93	84.23	19.44	129.50
- negative condition	93.19	10.62	78.70	19.21	90.00*
- neutral condition	63.61	41.82	70.47	30.91	158.00
(%) Recognized contextual information	61.91	10.19	62.32	7.81	157.00
False positive on recognition – total number	5.21	1.60	4.00	3.81	147.00
- positive condition	1.57	3.87	1.35	1.80	135.00
- negative condition	1.93	4.45	1.13	1.55	144.50
- neutral condition	1.71	9.35	1.52	1.81	125.50
Localization task – I (%)	30.95	38.04	26.09	30.08	155.00
Localization task – II (%)	19.05	18.19	15.94	17.99	142.50
Orientation task (%)	46.70	26.21	44.82	16.99	160.50

Note: BD: bipolar disorder patients; * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 5. Correlations between psychopathological symptoms and mood, and VR task

	BD group								Control group							
	VR task-recall				VR task-recognition				VR task-recall				VR task-recognition			
	Total	+	-	+/-	Total	+	-	+/-	Total	+	-	+/-	Total	+	-	+/-
BDI	-.131	-.278	-.175	-.475	.424	.117	.126	.215	-.065	-.029	-.080	-.269	-.096	.102	-.003	-.263
CCLM-R	-.266	-.466	-.205	-.526	-.375	-.395	-.156	-.330	-.268	-.359	-.266	-.190	-.252	-.421	.051	-.460
SAS	.097	-.068	-.015	-.384	.466	.148	.038	.291	-.384	-.394	-.206	-.428	-.206	.002	.026	-.445
BSI	.105	-.042	.027	-.406	.408	.217	.169	.258	-.189	-.192	-.226	-.233	-.039	.095	.092	-.168
QE – DM	.275	.320	.053	.118	.559	.292	.033	.435	.112	-.036	-.011	-.036	.092	.159	-.018	.084
QE - SA	.261	.137	.229	.192	.069	-.303	-.144	.110	.031	-.068	.064	-.098	.053	.177	.042	.063

Note: QE-DM: Questionnaire of emotions – Dysphoric Mood; QE-SA: Questionnaire of emotions – State of Agitation; Total: indicator of recall /recognition of conceptual information acquired in all conditions; + indicator of recall /recognition of conceptual information acquired in positive condition; – indicator of recall /recognition of conceptual information acquired in negative condition; +/- indicator of recall /recognition of conceptual information acquired in neutral condition. Values presented in bold indicate correlations statistically significant.

Lifelike events memory and verbal comprehension

Taking into account that BD patients differed significantly from controls subjects on verbal comprehension (vocabulary subtest of WAIS-III), an additional analysis, testing the influence of this variable on recall and recognition of conceptual and contextual information, was conducted. This analysis was based on non-parametric ANCOVA employing verbal comprehension as the covariate. The results revealed that the differences on conceptual information recall observed between the BD and the control groups cannot be explained based on differences in verbal comprehension ($F(1, 37) = .505, p = .482, \eta_p^2 = .014$). From the other side, it was demonstrated that differences in verbal comprehension influenced performance on contextual information recall ($F(1, 37) = 8.966, p = .005$), contributing for 20% of observed variance ($\eta_p^2 = .204$). Regarding the recognition task, both conceptual information and contextual information were not affected by verbal comprehension [conceptual information: $F(1, 37) = 1.895, p = .177, \eta_p^2 = .051$; contextual information: $F(1, 37) = .113, p = .739, \eta_p^2 = .003$].

Correlations between lifelike events memory and psychopathological symptoms

Furthermore, the results of conceptual information recall and recognition were correlated with psychopathological symptoms. For this analysis the Spearman test was used. The indices of lifelike events memory included the total score and scores obtained in positive, negative and neutral conditions. In case of psychopathological symptoms, analysis of correlations comprised

total score of BDI, CCL-M-R, SAS and BSI. Spearman coefficients for these variables are displayed on table 5.

In BD group, none significant correlation was found. In control group, recall of objects acquired in neutral condition correlated negatively with SAS ($p = .042$). In addition, recognition of objects acquired in positive and neutral condition correlated negatively with CCL-M-R (positive condition x CCL-M-R: $p = .046$; neutral condition x CCL-M-R: $p = .027$); and recognition of objects acquired in neutral condition correlated negatively with SAS ($p = .034$).

Correlations between lifelike events memory and mood

Also an analysis of correlation between recall and recognition of conceptual information and mood was conducted. The variables relative to lifelike events memory included total score and scores obtained in positive, negative and neutral conditions; mood variables included QE subscales of dysphoric mood and state of agitation. As can be seen in Table 5, Spearman test indicated one significant correlation in BD group, between total score of conceptual information recognition and dysphoric mood ($p = .038$). There were no significant correlations in control group.

Correlations between lifelike events memory and cognitive functions

The results from lifelike events memory task were additionally correlated with some measures of cognitive functioning. The first included the total scores of recall and recognition of conceptual and contextual information. Measures of cognitive functioning were: (i) results

of immediate and delayed recall, retention and recognition, obtained in HVLT-RV and visual reproduction subtest; (ii) total score and number of errors committed in phonological fluency task; (iii) number of correct, perseverative and conceptual level responses from WCST-64; and (iv) total score of the arithmetic subtest. The results of correlational analysis between lifelike events memory and cognitive functions are displayed in Table 6.

In BD group, the recall of conceptual information correlated significantly with HVLT-RV immediate and delayed recall (immediate recall: $p = .027$; delayed recall: $p = .032$), visual reproduction immediate and delayed recall (immediate recall: $p = .035$; delayed recall: $p = .003$), visual reproduction retention ($p = .003$), phonological fluency total score ($p = .006$), and WCST-64 perseverative response ($p = .007$). Regarding BD patients' recall of contextual information, it correlated significantly with HVLT-RV immediate and delayed recall (immediate recall: $p = .003$; delayed recall: $p = .002$) and HVLT-RV retention ($p = .021$), visual reproduction immediate and delayed recall (immediate recall: $p = .001$; delayed recall: $p = .006$), and visual reproduction recognition ($p = .005$), phonological fluency total score ($p = .006$), arithmetic total score ($p < .001$), and all of three measures of WCST-64 (correct responses: $p = .006$; perseverative responses: $p = .005$; conceptual level responses: $p = .022$).

In control group, recall of conceptual information correlated significantly with HVLT-RV recognition ($p = .033$), visual reproduction immediate recall ($p = .022$) and recognition ($p = .013$), phonological fluency total score ($p = .039$) and WCST-64 perseverative response ($p = .031$). There were no significant correlations between cognitive functioning and recall of contextual information achieved by controls subjects.

In relation to recognition of conceptual information, BD patients results correlated significantly with HVLT-RV delayed recall ($p = .049$) and retention ($p = .043$), and visual reproduction delayed recall ($p = .002$) and retention ($p = .008$). There were no significant correlations between recognition of contextual information and performance in neuropsychological tasks achieved by BD patients.

Also in control group recognition of conceptual information correlated significantly with some measures of cognitive functioning (visual reproduction' immediate recall: $p = .040$; WCST-64 perseverative responses: $p = .037$). Regarding correlations between recognition of contextual information and neuropsychological results, none significant association were found.

Discussion

The principal aim of this study was to verify whether the BD patients in remission show alterations in encod-

Table 6. Correlations between cognitive functions and VR task

		BD group				Control group			
		VR recall		VR recognition		VR recall		VR recognition	
		CI	CTI	CI	CTI	CI	CTI	CI	CTI
Immediate recall	HVLT-RV	.589	.725	.475	.002	.111	.192	.179	-.298
	Visual Reproduction	.565	.806	.522	.101	.474	-.004	.431	-.133
Delayed recall	HVLT-RV	.574	.760	.535	.008	.004	.027	.069	-.173
	Visual Reproduction	.737	.689	.755	.205	.384	.167	.295	-.103
Retention	HVLT-RV	.530	.608	.546	.123	-.115	.194	-.071	-.042
	Visual Reproduction	.733	.514	.672	.264	.245	.311	.199	.022
Recognition	HVLT-RV	.181	.084	.180	.059	.446	.247	.306	-.024
	Visual Reproduction	.372	.699	.247	-.088	.509	.031	.305	.005
FF- Total		.694	.695	.516	.098	.432	-.305	.254	.197
FF- Errors		.074	-.295	.157	.114	.018	-.079	.098	-.025
WCST-64 - Correct Responses		.418	.693	.114	.048	.276	-.156	-.195	.030
WCST-64 - Perseverative Responses		-.680	-.699	-.266	-.289	-.450	-.142	-.438	.072
WCST-64 - Conceptual Level of Responses		.404	.603	.168	.034	.199	-.248	-.220	.067
Arithmetic		.530	.854	.412	-.036	.092	.140	.245	.044

Note: CI: Conceptual Information; CTI: Contextual information; Values presented in bold indicate correlations statistically significant.

ing and retrieval of autobiographical information related to events with positive, negative and neutral valence. For this purpose an experimental task based on the VR paradigm was used. BD patients, as compared to healthy controls, obtained worse results in the recall of information that was acquired in positively charged condition, and better results in the recognition of information that was acquired in negatively charged condition. On the other hand, the recognition of information associated to the condition with positive valence and the recall of information related to the condition with negative valence were equivalent in both groups. These findings point to the existence in the BD euthymic phase of alterations in the memory processes for the emotionally charged information, suggesting additionally that the mechanism underlying these alterations depends on the valence (positive or negative) of processed information. They are also consistent with the findings obtained by Scott et al. (2000) and Tzemou and Birchwood (2007) indicating that BD patients use cognitive styles that are dysfunctional and that makes them more vulnerable to develop depressive symptoms.

According to Bearden et al. (2006), the performance on recognition tasks allows to infer about the encoding processes. Thus, it seems unlikely that the limitations observed on the recall of the contents with positive valence have their origin in the encoding processes, being more plausible the hypothesis indicating as the basis of these limitations the alterations on the retention and retrieval processes. Conway and Pleydell-Pearce (2000) have suggested that the integration of episodic contents in the autobiographical knowledge is influenced by the hierarchy of the present goals and by the model of psychological present, both dependent on the memory of the previous experiences and on the personal knowledge about the world. In this perspective, further elaboration of memory traces requires identification of processed contents as relevant and attribution to them of the personal meaning. In the case in which these two processes (identification and attribution of personal meaning) are not satisfactorily completed, the experience is deprived of the proper contextualization, and the accessibility of the detailed information regarding this experience becomes significantly diminished. Alternatively, the processed contents are preserved; however in the recall moment, the experience details that show to be discrepant with the hierarchy of the present goals and/or with the model of psychological present become suppressed or distorted (Conway & Pleydell-Pearce, 2000). In our opinion, the positive lifelike event might constitute the experience highly incongruent with the expectations of BD patients, affecting the elaboration of the respective

memory traces or requiring the adaptive response in the moment of retrieval. The diminished accessibility to the discordant memories of goals-related activities in BD was also suggested by Mansell and Lam (2004).

Regarding the contents with negative valence, the obtained data suggest that in BD euthymic phase their encoding is significantly enhanced. The impact of negative stimuli on memory formation in BD was also observed by Kauer-Sant'Anna et al. (2008). However, these authors demonstrated additionally that the performance of BD patients may depend on the emotional intensity of the processed stimuli, being substantially improved on the presence of the stimuli extremely negative, but not moderately negative. This hypothesis is particularly interesting as it indicates the possible reasons of non-existence of the differences between BD patients and healthy controls in the emotional memory tasks conducted by other authors (Derntl et al., 2009; Lex et al., 2008). It is also important to highlight that, according to Kauer-Sant'Anna et al. (2008) and Malhi et al. (2005), BD euthymic patients perceive the stimuli with negative valence in an altered way, rating them as more negative than healthy controls. It is probable that the results of this evaluation are reflected on the personal meaning attributed to the processed information, contributing to the alterations on the memory processes.

Despite BD patients, as compared to healthy controls, recognized more information related to the negatively charged condition, the results of recall of this type of information were equivalent in both groups. This pattern of responses suggests that the accessibility of the contents with negative valence might be modulated by additional factors, such as emotional regulation processes (Philippot, Schaefer, & Herbet, 2003). The possible influence of this variable on the retrieval of emotional memories, more specifically of AMs associated to cues with positive and negative valences, has been already indicated by Tzemou and Birchwood (2007). However, not all authors obtained results consistent with this hypothesis (Mowlds et al., 2009). The activation of strategic inhibition to avoid harmful memories in the VR context seems quite unlikely. Although, given that spending sprees is one of the common symptoms of mania, it is possible that the negative lifelike event leading to the unexpected spending of money worked as a trigger and activated emotional regulation processes.

It is also important to highlight that the results of BD patients in the recall and recognition of lifelike events with neutral valence were comparable to those obtained by healthy adults. As was previously written, the episodic memory impairment has been indicated as one of the trace markers of BD (Czepielewski et al., 2015; Malhi et

al., 2007). Our results are in agreement with these findings, showing that the performance of BD euthymic patients in the immediate and delayed recall and in the recognition of visual and verbal stimuli is considerably diminished. Significant changes were also observed in relation to the contextual information recall in lifelike events memory task. In this perspective, the absence of differences in the recall and recognition of lifelike events with neutral valence can be interpreted as indicative of significant enhancement of BD patient memory in the presence of clear references to his own person. In our opinion these findings are consonant with the conception according to which BD patients manifest cognitive vulnerability to develop affective symptoms (Scott et al., 2000; Tzemou & Birchwood, 2007), as they reveal the tendency of BD patients to focus excessively on him/herself.

The absence of significant correlations between lifelike events memory and psychopathological symptoms suggests that the mechanisms underlying the processing of information emotionally (positively and negatively) charged do not depend on the clinical symptomatology present at the moment. On the other hand, the dysphoric mood was positively associated to recognition (but not to recall) of information related to the lifelike events. Interestingly, this association was revealed only in relation to the totality of responses. Future studies are needed for better comprehension of this relation between dysphoric mood and memory for lifelike events.

The study of correlations between lifelike events memory and neuropsychological performance showed that the recall of conceptual and contextual information may be modulated by deficits on episodic memory and executive functions. In future studies this relation should be clarified.

Limitations

This study has few limitations. The most important is related with the small sample size, as it reduces significantly the generalizability of obtained findings. In addition, the groups were not equivalent at the level of verbal comprehension. This difference showed to be irrelevant for the performance on the recall and recognition of conceptual information and the recognition of contextual information. But, on the other hand, it contributed to the observed variance on the recall of contextual information. Thus, in future studies the variable of cognitive comprehension should be controlled in order to facilitate the inference about retrieval strategies. Moreover, the BD patients were subjected to the different pharmacological treatments, which make impossible the analysis

of the influence of variables related to the types and quantity of taken drugs on cognitive performance.

Regarding VR task, in future studies the level of complexity should be reduced, principally in the respect to actions that need to be carried out simultaneously. Also, the recall and recognition tasks should be more equivalent, being based on both verbal and non-verbal material, and the recall tasks should include additionally the free-recall trial. Furthermore, the order of exposure of stimuli emotionally charged was deliberately maintained (positive, negative, neutral), which eventually could influence the participants performance. Thus, our recommendation for future studies is to counterbalance the order of stimuli exposure and examine whether it contributes to the variance on the obtained results.

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