A study of verbal memory in a sample of euthymic patients with Bipolar Disorder

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Background. Recent studies have confirmed the presence of cognitive impairment in euthymic patients with Bipolar Disorder (BD). A significant relationship between memory difficulties and poor psychosocial adjustment has also been found in these subjects. While some studies suggest that these memory deficits may be secondary to executive functioning instead of being directly related to a primary impairment of the memory systems, others suggest that these memory deficits may be secondary to clinical symptoms. Some authors reject the existence of any relationship between clinical state and neurocognitive impairments and suggest that this relationship may be mediated by other factors. The goal of this research was to replicate the findings of verbal memory impairment in euthymic patients with Bipolar Disorder and relate these impairments with neocortex structures.

Methodology. We carried out a cross-sectional study. The sample was made up of 44 BDI and 9 BDII euthymic patients and 32 healthy subjects, aged 18-65 years. Both groups were evaluated with the California Verbal Learning Test.

Results. Both bipolar patients performed worse than healthy control subjects in most memory measures and showed difficulties in components of memory that are associated with both frontal (semantic organization) and temporal lobe function (recall and recognition).

Conclusions. We have hypothesized that verbal memory could be a trait marker of bipolar disorder.

Keywords: Bipolar Disorder, Cross-sectional study, Euthymic, Neurocognitive impairment, Trait marker, Verbal memory

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Estudio de memoria verbal en una muestra de pacientes con Trastorno Bipolar en fase eutímica

Introducción: Estudios recientes han demostrado la persistencia de disfunciones cognitivas en fases de remisión del trastorno bipolar (TB). Se ha encontrado una relación significativa entre los déficit de memoria y un pobre ajuste psicosocial. Mientras que algunos estudios apuntan a un déficit mnésico secundario a déficit de tipo ejecutivo, más que a una alteración primaria de los procesos de memoria, otros estudios sugieren que los déficit mnésicos podrían ser secundarios a la sintomatología clínica. Otros autores, no encuentran relación entre el estado clínico y los déficit neurocognitivos y sugieren que esta relación debe estar mediada por otros factores. El objetivo de este trabajo fue replicar los hallazgos de déficit en memoria verbal en pacientes con trastorno bipolar en fase eutímica y relacionar dichos déficit con estructuras del neocórtex.

Metodología: Se realizó un estudio transversal. La muestra estuvo compuesta por 44 pacientes eutímicos con TBI, 9 con TBII en fase de eutimia y 32 sujetos sanos, con edades comprendidas entre los 18 y los 65 años. Se utilizó como instrumento de evaluación de la memoria el *California Verbal Learning Test*.

Resultados: Se observaron déficit en los dos subtipos de sujetos con TB, tanto en los componentes de memoria asociados con estructuras frontales (organización semántica) como en los relacionados con estructuras temporales (recuerdo y reconocimiento).

Conclusiones La memoria verbal podrían ser una variable rasgo del TB.

Palabras clave: Déficit neurocognitivo, Estudio transversal, Fase eutímica, Memoria verbal, Trastorno Bipolar, Variable rasgo

INTRODUCTION

Recent studies in the field of Neuropsychological and Neuroimaging studies have demonstrated that patients with

bipolar disorder (BD) not only present cognitive and global functioning impairment during the acute episodes of the disorder but also in its remission periods.[1-10] These findings contradict the initial ideas of Kraepelin and open a new pathway in the study of this mental disorder.

For many years, it was believed that the worse sociolaboral functioning of bipolar patients could be the result of clinical or subclinical affective symptoms, underevaluating the effect of the possible cognitive dysfunctions. Recent findings have affirmed that the clinical state is not so closely related with the general functioning of the patient, although the cognitive impairments are.[10] These data make it necessary to evaluate the cognitive function in these patients both during the active and euthymic periods.

NEUROPSYCHOLOGY OF BD

Although we know that cognitive dysfunctions not only exist during the acute phases but also during the disorder remission periods, there is some debate regarding which cognitive functions are impaired during the active phases and which one of these deficits are maintained during the remission period.[1, 7] Among the most affected domains are attention, learning and memory, psychomotor functioning and frontal executive functions. Some of these deficits persist during the euthymic phases, the most replicated being the executive function, verbal memory and attention.[2, 4, 12-15]

Several authors have studied specific cognitive domains as possible endophenotypes in bipolar disorder. Standing out among them is the role of sustained attention and verbal memory as trait variables of BD due to the persistence of deficit in both in absence of clinical symptoms.[16] This has been one of the findings presenting the greatest consistency among the different works.[14, 15, 17, 18] Deficit has also been observed in verbal memory in unaffected parents and monocygotic twins of patients with BD.[19-22] These data suggest that verbal memory deficit could represent vulnerability markers for BD.[12, 22]

Verbal memory implies different cognitive processes: coding, storing and recall, which in turn are related with different cerebral regions. The temporal regions are involved both in coding and in the recall of verbal information while the strategic and execution of memory aspects depend on prefrontal structures.[23, 24] The relation between executive deficit and verbal memory is still not totally clear. Instead of being two types of independent deficits, it seems that executive deficits prevent the effectiveness of the memory, introducing errors in the coding and/or recall processes.

Thus, the executive type deficits would affect global performance in memory, above all in the tests of list of words that are especially sensitive to executive dysfunctions.[25] The difficulty is found basically in the planning and maintenance of adequate or useful strategies for recovery of material. On the other hand, these memory deficits could also be the result of difficulties in coding information due to attention and concentration disorders.

Finally, the study of the verbal memory deficit has taken on growing interest due to its association with neurophysiological and neuroanatomical abnormalities in frontal and temporal regions, also involved in the physiopathology of bipolar disorder.[26-30]

The aim of our study was to replicate the data of other authors who have found cognitive deficits in patients with bipolar disorder in euthymic phase, specifically focusing on a cognitive domain, which is verbal memory. We also proposed relating said deficits with neocortex structures.

METHODOLOGY

Material and method

A cross-sectional study with a control group was conducted. The experimental group was made up of 53 patients diagnosed of Bipolar Disorder (BD) type I (N=44) or II (N=9), evaluated according to DSM-IV-TR criteria, whose ages ranged from 18-65 years, residents in Madrid and belonging to the Hospital Clínico San Carlos area. The control group (CG) was made up of 32 healthy subjects, residents in Madrid. Inclusion criteria in the patient group were as follows: a) fulfilling the DSM-IV criteria for BD type I or II, b) being in the euthymic phase since at least 3 months prior to participation in it, following the van Gorp criteria (score <6 points on the Hamilton scale and <7 points on the Young mania scale). Exclusion criteria were as follows: a) presence of severe organic disease, b) very low education level or illiteracy, that could make the cognitive study difficult, c) use of anticholinergic medication, d) current consumption of toxic substances (fulfilling the criteria of abuse or dependence, except for tobacco). For inclusion in the control group, the following were ruled out: a) presence of medical and/or psychiatric condition, b) presence of psychiatric background in first degree relatives. Both groups participated in the study voluntarily after having signed the informed consent (**Table 1**).

Evaluation of verbal memory was performed with the California Verbal Learning Test (CVLT).[31]

Procedure

All the participants underwent a semistructured interview in which the following sociodemographic and clinical data were collected: age, gender, medical and

psychiatric background, years of education, age of onset of the disorder (in the patient group), number of episodes (in the patient group), hospitalizations (in the patient group). Furthermore, the following evaluation scales were applied to the patients with bipolar disorder: Hamilton Depression Rating Scale;[32] Young Mania Scale.[33] After, the CVLT (California Verbal Learning Test) was administered to the patients and healthy control subjects.[31] This test has its background in the lists of learning of verbal elements designed to evaluate the use of semantic associations as a word learning strategy. Delis et al.[31] published this test using list A and B of the Rey Auditory Verbal Learning Test. List A is of learning and B of interference. The latter is read to the subject after five trials of list A. Each one of the lists is made up of 16 words belonging to 4 semantic categories. Two of these categories are common to both lists, while the words are not correspondent. List A and B are read only one time in each learning trial. After the fifth trial of list A, list B is read. Immediately after, a free recall test and another recall with cues from list A we call short term is performed. After 20 minutes, another new test of free recall and with cues from list call called long term recall is performed. After, a recognition test is carried out. It is essential to not interrupt the sequential process described.

The data were processed using the SPSS statistical program for Windows, version 15.0. Performance of the two BD groups and the healthy control group were compared in each one of the neuropsychological variables. For the quantitative variables following a normal distribution, the mean was used as descriptive statistics and the ANOVA test followed by the Bonferroni post hoc test were used as contrast statistics. In the case of quantitative variables that did not adapt to normality, the median was used as descriptive statistics and, as contrast statistics, the non-parametric median test and chi square test. For the frequencies analysis, the chi square test was used. A significance level of $\alpha<0.05$ was adopted.

RESULTS

When the groups of patients and healthy controls were compared, significant differences were found in verbal memory performance, both in learning as well as short and long term recall and as nonsignificant differences in other aspects of the memory: **Tables 2 and 3.**

Table 2 reflects the comparison of means of the variables that followed a normal distribution. We observed a significant principle effect in the ANOVA in most of these variables. However, once the post hoc analysis was carried out, we observed that the differences were due in many cases to the comparison between the BD1 group and the healthy controls. Thus, the subjects with BD1 demonstrated inferior learning to that of the CG group (p=0.001) while those of the BDII only showed a tendency to present the same alteration (p=0.061). In the learning curve of the groups with BD (I and

Table 1 Sociodemographic and clinical characteristics of the sample

	CG (N=32)	BD I (N=44)	BD II (N=9)	p-value	Bonferroni
Gender (% men)	68.2	55.6	50	0.268*	
Age (years)	40.5±15.1	42.95±10.8	46±13.7	0.476	
Years of education	18.9±6.9	14.1±4.6	16.2±4.9	0.003	TBI<CT
Vocabulary (IQ)	44.8±11.6	35.8±12.3	42.4±8.1	0.005	TBI<CT
Age at onset (years)		27.2±11.2	23.1±8.7	0.304	
Years of evolution		15.8±8.3	22.9±13.4	0.159	
Number of admissions		3±3.4	1.2±1.6	0.130	
Number of mania/hypomania episodes		5.7±4.9	4.6±6.4	0.543	
Number of depression episodes		4.2±5.4	7.9±4.6	0.065	

CG: control group; BDI: Bipolar disorder type I; BDII: bipolar disorder type II
* (p-value of X^2)

Table 2 Comparison of means between patients with Bipolar Disorder (BD) I, II and control subjeCGs (CG)

VARIABLES	MEAN ± SD	P- value BDI/BDII/CG	Bonferroni BDI/BDII/CG
Learning (list 1-5)	BDI: 49.36±13.1 BDII: 49.11±15.5 CG: 59.94±9.38	0.001	BDI<CG BDII>CG (tend.) BDI=BDII
Trial 1	BDI: 6.73±2.3 BDII: 7.67±1.6 CG: 8.03±2.08	0.035	BDI<CG BDI=BDII
Trial 2	BDI: 9.16±3 BDII: 8.56±4.2 CG: 11.34±2.26	0.002	BDI=BDII<CG
Trial 3	BDI: 10.48±3.1 BDII: 10.33±3.7 CG: 13.16±2.34	<0.001	BDI=BDII<CG
Trial 4	BDI: 11.39±2.8 BDII: 11.22±3.9 CG: 13.44±2.38	0.005	BDI<CG BDI=BDII
Trial 5	BDI: 11.61±3 BDII: 11.33±4 CG: 13.97±2.1	0.001	BDI=BDII<CG
Short term free recall	BDI: 9.77±3.8 BDII: 10.44±4.6 CG: 12.75±2.79	0.002	BDI<CG BDI=BDII
Long term free recall	BDI: 10.48±3.6 BDII: 10.89±4.8 CG: 12.84±2.76	0.015	BDI<CG BDI=BDII
Recall with short term cues	BDI: 10.34±3.8 BDII: 10.56±3.6 CG: 13.19±2.58	0.002	BDI<CG BDI=BDII
Recall with long term cues	BDI: 11.16± 3.5 BDII: 11.78±4.2 CG: 13.50±2.41	0.009	BDI<CG BDI=BDII
Semantic recall strategies	BDI: 8.14±5.9 BDII: 11.89±7.6 CG: 14.13±7.63	0.001	BDI<CG BDI=BDII
Correct answers of recognition	BDI:14.11±2.2 BDII: 13.89±2.6 CG: 15.06±1.36	0.085	---------

BDI: bipolar disorder type I; BDII: bipolar disorder type II; CG: control group

II) and the controls during the five trials, it was observed that, as the global significance shows, subjects with BD had greater difficulties for acquisition and coding of information, showing a significantly lower performance regarding the CG during the five learning trials ($0.001<p<0.035$). In trials 2, 3 and 5, the post hoc analysis showed that the two subgroups of patients performed the task worse than the healthy controls, there being no significant differences between the two clinical subtypes; while in trials 1 and 4, the differences were only significant between BD1 and the CG ($p=0.034$ and $p=0.007$, respectively). However, progression in learning during the successive trials was observed: patients with BD remembered more words as they passed from trial 1 to trial 5, above all in trials 2 and 3, although the results continue to be significantly lower than in the CG. The free recall results, both short-term and long-term, were significantly worse for the BD1 group compared to that of the CG ($p=0.012$ and $p=0.013$, respectively). Subjects with BD1 also showed a significantly lower performance than the CG group in recall with cues, both short-term and long-term $p=0.002$

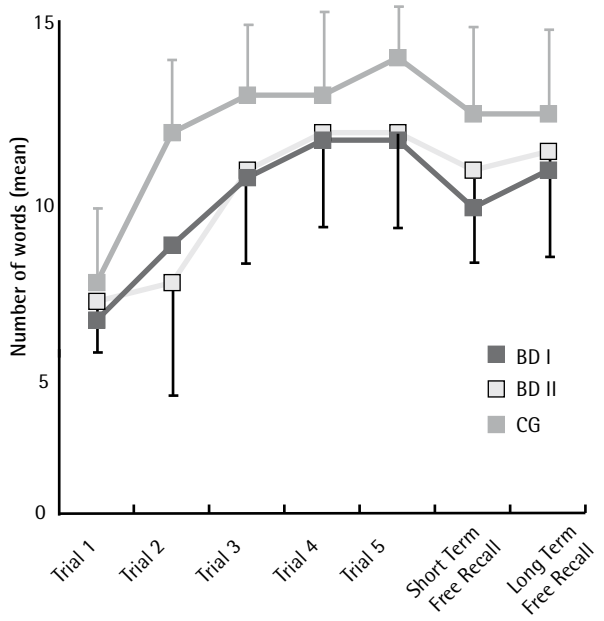

Figure 1 — *Learning curves of patients with between patients with Bipolar Disorder (BD) I, II and control subject group (CG)*

and p=0.007, respectively). Significant difficulties were also observed in the BD1 group in the use of semantic strategies of recall, which facilitate subsequent recovery of the information (p=0.001). Results in recognition were inferior in the BD group compared to the CG group, although we only observe the tendency (p=0.085). We did not find significant differences between the two groups of patients in any of the normal variables studied.

Table 3 shows the comparison of medians of the variables that did not follow a normal distribution. We only found significant differences with an effect of the diagnosis on the total perseverations (p=0.045), the two types of patients committing a higher number of them. However, when we performed a post hoc analysis, the statistical significance was not maintained for any of the comparisons. The rest of the non-parametric variables did not show any significant association even though the median values showed worse performance of the subjects with BD.

Finally, we did not find statistically significant associations between the cognitive variables and the pharmacological data collected in these patients: lithium, lithium values, antipsychotics, antidepressants and benzodiazepines (data not shown).

CONCLUSION AND DISCUSSION

In our study, patients with bipolar disorder in the euthymic phase presented significant deficit in verbal memory processes versus the healthy control group. When the patient sample was separated into bipolar I and bipolar II, we did not find significant differences between both groups. The memory deficit remains with statistically significant values in the BDI regarding the control group while the patients with BDII, although they maintain their deficits in the memory processes, only reach significant tendency in some variables. These data suggest that the lack of statistical significance between both groups is probably due to the sample size of the BDII. If this is confirmed by

Table 3 — **Comparison of medians between patients with Bipolar Disorder (BD) I, II and control subjeCG group (CG)**

VARIABLES	MEDIAN (IQR P25-P75)	P- value BDI/BDII/CG	Two by two Comparisons BDI/ BDII/CG
Semantic learning strategies	BDI: 13.5 (8 - 20.75) BDII: 11 (10.5 - 26.5) CG: 23.5 (11 - 35.5)	0.117	BDII<CG (tend.)
Total perseverations	BDI: 5 (3 - 10.75) BDII: 7 (1 - 9) CG: 2 (0-6.75)	0.045	--------
Intrusions (learning 1-5 and free recall)	BDI: 4 (1 - 7.75) BDII: 3 (1 - 7) CG: 2 (0 - 5)	0.473	--------
False positive recognition	BDI: 1 (0 - 2) BDII: 1 (0 - 3) CG: 0 (0 - 1)	0.171	--------

BDI: bipolar disorder type I; BDII: bipolar disorder type II; CG: control group; IRQ: interquartile range

increasing the number of patients with BDII, our study would support the authors who propose the existence of cognitive deficits common to both subtypes.[34-36]

The deficit in the verbal memory processes among the BDI/BDII/CG groups was manifested during the learning, free recall and short and long-term cue recall tests, semantic strategies of recall and perseveration. These patients showed difficulties to organize information during learning and when we analyze these curves, we verified a significant pattern between both groups of BD, with significant incorporation of new words until trial 3. During the recovery process, they presented difficulties to organize the search based on semantic strategies. During the recall test with cues, their performance did not achieve normalization, a marked deterioration in relationship to the CG persisting. They presented a significantly higher number of perseverations, a greater number of intrusions, and a lower number of correct answers in recognition of words than the control subjects, although the last two parameters did not achieve statistical significance.

Our results coincide with those of other studies that have demonstrated that the presence of cognitive deficits in patients with BD is not only and exclusively limited to the acute phases of the disorder but rather that, although in different grade, these persist during the remission periods,[4, 5, 10, 15, 17, 18, 24, 26, 37] without the existence of discrepant data. Studies that have evaluated the learning of lists of words with other tests such as the Rey Auditory Verbal Learning Test, RAVLT[38] or the Wechsler memory scale-revised WMS-R[39] also coincide in detecting the presence of these deficits.[4] The finding of cognitive impairments in patients with BD both in the acute phase and in remission has lead to the statement that the cognitive deficit in BD is a stable characteristic of the disorder. Given that this deficit has also been observed in unaffected relatives of patients with BD[19] the verbal memory deficit could represent a marker of vulnerability for BD. Some studies have found evidence that the executive function and verbal memory could be candidates of neurocognitive endophenotypes in BD.[40]

Verbal memory depends on the adequate capacity to codify, store and recover verbal information.[27] Learning a list of words may be facilitated if the items are grouped into semantic categories (e.g. tools, clothes, fruits, etc.).[29] Subjects who spontaneously group the items in this way during the coding process recall more words afterwards compared to those who do not do so. The use of semantic strategies during coding is a complex skill that depends on different cognitive processes and that implies a wide variety of cerebral regions and neuronal circuits. On the one hand, it implies the need to inhibit other emergent cognitive activities in favor of the use of the semantic grouping. Furthermore, it implies a semantic processing of the information and an update and reorganization of the verbal information in the working memory, grouping the words into their respective categories.

In our study, the subjects with BD had significant difficulties to organize the information and use semantic grouping strategies that would facilitate learning and subsequent recall of the list of words.

Deckersbach T, et al.[18] obtained identical results and concluded that the verbal memory problems during the euthymic phases of BD could at least partially be secondary to difficulties in the use of semantic strategies during learning. These same authors as well as us observed that the subjects with BD not only had difficulties in the spontaneous use of semantic strategies (learning phases and free recall), but also in the use of semantic strategies when these were provided to them (recall phase with cues).

There is an important debate about the origin of the verbal memory impairments in these patients. The medial temporal regions of the cortex are responsible both for the coding and verbal information recall while the prefrontal cortex intervenes in the strategic and executive aspects of the memory, to improve recovery. If we observe the learning and free recall curves in the subjects studied, we verify that there is less learning and less recovery in both free recall and with clues in the patients with BDI and II versus the GC. The lower significance of these data found in the BDII group is very likely due to the small size of this sample, since there are no differences in the variables studied between the bipolar I and bipolar II subjects. Therefore, we see that the patients studied in this work showed difficulties both in the memory components associated with frontal structures (semantic organization) and in those related with temporal structures (recall and recognition). These data suggest that verbal memory impairment in euthymic bipolar patients affects both the coding processes and those of information recovery, although the improvement in the learning curve that the patients are capable of obtaining suggests that the coding is better conserved and supports the fact that the dysfunction is greater in the prefrontal cortex neurons.

Several studies have found neuroanatomical and neurophysiological abnormalities in temporal and frontal regions in subjects with BD. Thus, it seems that these structures could be involved in the physiopathology of the bipolar disorder[28] and also in the verbal memory deficits. Neuroimaging studies suggest that the semantic grouping processes depend both on the integrity of the prefrontal regions of the cerebral cortex and their interactions with medial temporal lobe structures,[30, 41, 42] as well as the integrity of the orbitofrontal cortex.[43] The spontaneous use of semantic strategies could be related with the ventral prefrontal cortex while the use of semantic strategies when they are facilitated would be related with the dorsolateral prefrontal cortex.[30] The orbitofrontal cortex would have a central role in the inhibition of automatic actions in favor

the initiation of conscious strategic behaviors aimed at a goal, such as semantic grouping.[43] The dorsolateral prefrontal cortex, on the other hand, seems to be involved in the updating, manipulation and reorganization of the working memory.[44] Neuroimaging studies with healthy volunteers have observed increases in the activation of said zones associated to semantic grouping during coding.[41] Recent studies suggest the involvement of the dorsolateral prefrontal cortex in BD,[42] although there are some discrepancies in the literature. While a reduced volume has been detected in some studies in subregions of the prefrontal lobe,[45, 46] others have not found this.[47] Some studies have demonstrated a reduced density in neuronal and glial cells in the dorsolateral prefrontal cortex,[48] and a decrease in the number and size of the neuron soma of the anterior cingulate cortex.[49]

On the other hand, damage in the medial temporal lobe (hippocampus and adjacent structures) hinder the ability to learn and retain new information.[50] Studies with neuroimaging in healthy volunteers show that the activity of the hippocampus increases during information coding and recall.[51] In the case of BD, the findings regarding the temporal lobe are inconsistent: while some studies have found increases or decreases in the temporal lobe volume,[52] others have not found alterations.[53]

In our study, we have observed poor performance in subjects with BD in recognition memory. Recognition memory, measured through the number of correct answers, was significantly lower in patients with BD. These findings support the hypothesis of a possible involvement of frontal and temporal structures in these subjects. In the literature, there are discrepancies regarding the deficit of this cognitive function in BD. Some authors[10, 19] have described a recognition memory deficit, however, it was not possible to establish this alteration in other works.[11] We think that it is possible that said discrepancies in most of the cases are due to methodological differences. In some other cases, the lack of significant findings may be explained by the use of a sample with a reduced size.

One of the limitations of our study could be that we did not control for the possible confounding effects of the medication on the cognitive performance of the patients. This is largely because the subjects were receiving several drugs simultaneous, this hindering the isolation of each one of the effects. However, and after analyzing the possible influence of each one of the drugs (separately) on the results of the verbal memory, our results would support those described by other authors who suggest that the deficits present in these patients cannot be totally explained by the medication.[54-56]

The findings of structural and functional abnormalities in BD present some discrepancies and the capacity to relate the neuropsyhcological findings with specific cerebral regions is still no more than an attempt. Most of the works coincide in stating that there is a verbal memory deficit in these subjects. Our study shares many of the limitations found in these studies, but point to the relation between the alteration of certain cerebral structures and the cognitive deficits found in these patients. We consider that the new lines of research should focus on the study of the processes more than on the global results, and on establishing clear relations between said process and the alterations found, both on the structural as well as functional level, in the brain of the subjects with BD.

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