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Behavioral flexibility impairment with negative feedback in refractory temporal lobe epileptic patients with unilateral amygdala and hippocampal resection

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Introduction. Patients with amygdala dysfunction generally have behavioral impairment. Temporal lobe surgery might be a model of study of unilateral amygdala resection. The objective of this study was to evaluate behavioral flexibility in epileptic patients who undergo amygdala resection for epilepsy surgery and evaluate its relationship with their neuropsychiatric symptoms.

Material and methods. Ten epileptic patients who underwent amygdala and hippocampal resection (6 left and 4 right) matched by age and educational level with 10 healthy controls were tested with an extensive neuropsychological and neuropsychiatric battery. Psychiatric symptomatology was measured with the positive and negative syndrome scale (PANSS) and the Beck depression inventory. To assess behavioral flexibility the emotion-related visual reversal-learning task (O'Doherty et al., 2001) and the gambling task (Bechara et al., 1994) were used.

Results. Patient's mean scores were: Beck: 8 ± 1.5 ; PANSS positive: 10 ± 1.3 , and negative: 14.4 ± 2.2 ; intellectual quotient (IQ): 101.4 ± 6.3 ; category number in Wisconsin card sorting test: 4.6 ± 2.4 . The emotion-related visual reversal-learning task showed significance differences in the number of reversion: healthy controls: 9.3; epileptic patients: 4.23 ($p < 0.001$); in the number of trials to the first reversion: healthy controls: 5; epileptic patients: 23.42 ($p < 0.05$). There was no correlation between reversion and depression, PANSS and IQ.

Conclusions. Patients with epilepsy who undergo unilateral hippocampal and amygdala resection appear to have alterations in the reversion capacity with an emotional component that would explain the lack of behavior flexibility that they sometimes have and that are not related with either the isolated presence of executive alterations or low intellectual quotient.

Key words:
 Behavioral. Flexibility. Amygdala resection. Epilepsy. Temporal. Surgery. Affective reversal learning.

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Flexibilidad conductual ante un *feedback* negativo en pacientes epilépticos temporales refractarios con resección de amígdala-hipocámpica unilateral

Introducción. Los pacientes con disfunciones amigdalinas suelen presentar alteraciones en su conducta. La cirugía de epilepsia temporal proporciona un modelo de estudio de la resección amigdalina unilateral. El objetivo de este trabajo fue estudiar la flexibilidad conductual ante un *feedback* afectivo negativo en pacientes con resección de amígdala por cirugía de epilepsia y evaluar su relación con los síntomas neuropsiquiátricos.

Material y métodos. Diez pacientes con epilepsia del lóbulo temporal (ELT) con resección de amígdala e hipocampo, 6 derechas y 4 izquierdas, apareados por edad y nivel de educación con 10 sujetos controles normales, fueron evaluados con una extensa batería neuropsicológica y neuropsiquiátrica que incluyó la Escala de síndromes positivos y negativos (PANSS) y la Escala de depresión de Beck. Para estudiar la adaptabilidad conductual se utilizaron el Test de Aprendizaje y reversión afectiva (O'Doherty et al., 2001) y el Test del Casino (Bechara et al., 1994).

Resultados. Los pacientes tenían los siguientes puntajes (en media \pm DE): escala de Beck de $8 \pm 1,5$, PANSS positiva de $10 \pm 1,3$ y negativa de $14,4 \pm 2,2$, un cociente intelectual (CI) de $101,4 \pm 6,3$, las categorías completadas en el Test de las cartas de Wisconsin fueron de $4,6 \pm 2,4$. En el Test de Aprendizaje y reversión afectiva mostraron diferencias significativas en el número de reversiones: controles: 9,3; ELT: 4,23 ($p < 0,001$), y en los ensayos para lograr la primera reversión: controles: 5; ELT: 23,42 ($p < 0,05$). No hubo correlación significativa entre las variables de reversión, depresión, la puntuación de la PANSS o el CI.

Conclusiones. Los pacientes epilépticos con resección amigdalohipocámpica unilateral tendrían alteraciones en la capacidad de reversión con componente afectivo que explicarían la falta de flexibilidad conductual que a veces presentan los mismos y que no se relacionan

ni con la presencia aislada de alteraciones ejecutivas ni con un bajo cociente intelectual.

Key words:

Aprendizaje. Reversión. Epilepsia. Temporal. Cirugía. Amígdala. Flexibilidad conductual. Conducta.

INTRODUCTION

Patients with temporal lobe epilepsy (TLE) generally have behavioral disorders, whether as ictal or interictal manifestation. Bear and Fedio (1977) developed a personality evaluation scale for epileptic patients in which they described viscosity of speech, hypermoralism, circumstantiality and exaggerated emotional reactivity¹. However, the results were inconsistent and controversial, so that its use was discontinued. However, the patients and family members report some of these disorders, such as viscosity in behavior or speech, that may be interpreted from a neuropsychological point of view as lack of behavioral flexibility, or alterations in behavioral adaptation in the changing circumstances of the social setting. Bechara (2004) calls this «emotional impulsiveness» or inability of the patients to inhibit a previously correct response, but incorrect with the contingencies of the moment². This phenomenon would be similar to that of extinction demonstrated in animals³.

Damasio (1996) proposed his hypothesis of somatic marker describing that the patients with pre-frontal lesions fail in decision making, above all affective ones, in their daily life because they do not use autonomic signals which somehow guide the behavior of normal persons⁴. A stimulus (primary inductor) causes a somatic response, then the presence of another related stimulus (secondary inductor), since a related thought or the presence of the same stimulus, as the presence of drug or possibility of gaining or losing money, generates the same somatic response. It is this somatic response which consciously or unconsciously guides behavior, above all when the options are varied and uncertain⁵.

Bechara et al. (2003) propose that the amygdala participates in associative learning of primary inductors, but once learned, the process becomes independent of the amygdala and it is in the orbitofrontal cortex where the decision making is processed⁶. However, Bar-On et al. (2003) demonstrated poor performance in the Gambling Task in three operated epileptic patients (with resection of amygdala)⁷ and these same authors published a poor performance on the Iowa Test in patients with bilateral lesion of the amygdala⁸.

In 1994, Rolls et al. proposed that the alterations in the behavior of the patients with orbital lesions are due to a failure in the capacity to modify their behavior based on a negative «feedback»⁹. Thus, they used an association/reversion of stimulus/reward paradigm, whose deficit correlated with functional alterations of daily life. These authors propose the magnitudes of awards and punishments (and learning between a visual stimulus and reward or punishment to which

it would be associated would be represented in the orbital cortex and, definitively, an emotion would be precipitated by the punishment or reward to which it would be related)¹⁰. The amygdala and orbital cortex have a key function in this behavioral flexibility. The amygdala sends projections to the posterior orbital cortex via the inferior thalamic peduncle¹¹, the amygdala projects to the dorsomedian nucleus of the thalamus and this in turn to the orbitofrontal cortex¹². There is a neural basal network that intervenes in emotional processing, formed by the orbital cortex, amygdala, dorsomedian nucleus of the thalamus and the ventral striatum, that is clearly anatomically and functionally dissociated with the dorsal via of the prefrontal cortex, dorsal cingulum and the rest of the dorsal neocortex, that intervenes in general cognitive processes^{13,14}. However, the relative contribution of each one of these structures in decision making and in the reversion capacity is a current research subject.

Swainson et al. (2000) found a deficit in the reversion paradigm in patients with amygdala resection due to refractory epilepsy surgery¹⁵. The paradigm consisted in the successive choice between two figures, but the reward to which it was associated was a «correct/incorrect» verbal feedback. Many works state that there would be a dissociation between a verbal feedback, as that used in the Wisconsin card test and in the Swainson et al. work¹⁵ and a feedback associated to an affective consequence, as gaining or losing money¹⁶ or having better or worse food demonstrated in monkeys^{3,17}. Verbal feedback would depend on the dorsolateral prefrontal cortex and affective feedback on the ventrolateral prefrontal cortex¹⁸. Fellows and Farah¹⁶ show reversion alterations in patients with bilateral orbital lesions using an emotional paradigm of two figures, one associated to gaining 50 pesos and another associated to losing 50 pesos. After 8 consecutive trials where the patients and controls learn and chose the figure associated to gaining, there is the reversion. The patients with orbital lesions obtained fewer reversions than the controls.

In all these works, the alterations in the decision making tests and in those of reversion were not due to alterations in working memory, since dissociations were found: poor performance on «Gambling Task» with good performance in spatial visual working memory¹⁹, as the failures in reversion tests, with indemnity of the working memory²⁰, although a good working memory is necessary to obtain good performance in the «Gambling Task»¹⁹.

No works that evaluate the reversion capacity with an affective «feedback» in patients with unilateral lesion of amygdala or its correlation with the «Gambling Task», executive functions and neuropsychiatric symptoms have been published up-to-date.

The objective of the present work was to study the behavioral flexibility to a negative affective «feedback» in patients with unilateral amygdala resection due to epilepsy surgery and correlate these results with the psychiatric symptoms present in these patients.

MATERIALS AND METHODS

Ten patients who underwent amygdala and hippocampus resection, 6 right and 4 left, as surgical treatment of temporal lobe epilepsy refractory to drug treatment were evaluated in our Memory Research Laboratory (GCBA). These were referred from the Epilepsy Site of the Hospital Francés of Buenos Aires, matched by age and education with 10 normal control subjects. All the participants in the study signed an informed consent. The clinical protocol was subjected to the ICH Rules of the Good Clinical Practices, to the last revision of the Declarations of Helsinki²¹ and to the internal regulations of the health authorities of the Government of the city of Buenos Aires.

To rule out an underlying intellectual deficit that would interfere with the evaluation, those patients with a score equal to or greater than 28 on the Mini-Mental State Examination (MMSE)²² and a Global Intelligence Quotient (IQ) equal to or greater than 90 on the Wechsler adult intelligence scale²³ were selected. Patients with criteria for major depressive episode, dysthymia or any of the Axis I psychotic disorders of DSM IV²⁴ were hospitalized.

A semistructured neuropsychiatric interview that included the Beck depression scale²⁵ and the Positive and Negative Psychotic Symptoms Scale (PANSS)²⁶ was performed.

As part of the neuropsychological evaluation, the Wisconsin card sorting test²⁷ was used to evaluate executive functions and a computerized version of the «Gambling Task»²⁸ was used to evaluate decision making.

An adaptation of the associative and reversal learning task was used to study reversion capacity with a negative emotional feedback²⁹. The latter was done by successively presenting a print with a triangle and with a square to the subjects. The patient should choose a figure that will allow him/her to gain a certain amount of money, however, a certain amount of money will also be lost every once in a while with the two figures. The subject can choose the same figure as many times as he/she believes to be convenient or change his/her choice as desired. The objective is for the subject to realize which one of the figures will make him/her gain more and lose less. Initially the «good» figure is the triangle, where 7 out of every 10 moves will be a gain and 3 gain and loss, but with positive balance (for example, gain 110 and lose 30). The «bad» figure is the square, where 6 out of every 10 moves leads to gaining and losing but with negative balance (for example gaining 60 and losing 75) and 4 lead to gaining, but with a lower value than the triangle. After five consecutive trials where the subject chooses the triangle, reversion occurs and the good one becomes the square. There are at least 55 trials, that make it possible to have a maximum of eleven reversions. A count is also made of how many trials were needed to learn which was the figure linked to greater reward and less punishment. The difference with

the original version of the test consists in that the difference between the values associated to the two figures is very subtle (the good figure in the original lead to gains of, for example, 300 and losses of 20 and the bad figure to gains of 40 and losses of 600) besides evaluating at least 55 trials and evaluating learning capacity. The difference with the Fellows and Farah work¹⁶ consisted in the capacity to evaluate the relative valence of the stimuli (both make the subject gain and lose money) and where the consequence is not linked to a single outcome since the subject gains and loses with both, the same as that of Bechara et al.³⁰. The difference with the «Gambling Task» consists in the fact that it does not require indemnity of the working memory since there are only two stimuli that the patient has during all the test, and furthermore, it measures reversion capacity.

Statistical method

The results of the patients and control subjects are expressed in mean (M) and standard deviation (SD). The Student's t test for parametric variables was used to compare the demographic data of age, schooling and Mini-Mental State Exam (MMSE) between patients and controls. Analysis of variance (ANOVA) was done for the reversion test and learning curve of the Gambling Task (the differences between moves 1 to 20, and 81 to 100 were compared). The Spearman test was used as correlation test due to the non-linear characteristics of the variables to be correlated and the values were expressed in rho (correlation index). A $p = 0.05$ was considered significant. SPSS software for Windows³¹ was used for all the statistical analysis.

RESULTS

The demographic data of the study population can be seen in table 1. It can be seen that there are no significant differences in age, schooling and global cognitive performance (according the Mini-Mental State, MMSE) (table 1).

In regards to the executive functions study with the Wisconsin card sorting test²⁷, the patients with temporal lobe epilepsy (TLE) completed $4,6 \pm 2,4$ categories and had $17,2 \pm 17$ perseverative errors and $12,5 \pm 11,7$ non-perseverative errors.

In the learning and reversion test under study²⁹, the patients had significant differences in reversion number and trials necessary to achieve the first reversion (table 2).

In the «Gambling Task»²⁸ (fig. 1) we observe the curves achieved by the patients and controls. The differences between moves 1 to 20 and 81 to 100 were compared with an analysis of variance (ANOVA) in order to evaluate the results of the learning curve of the strategy that makes them choose the most beneficial groups while they are doing the task. In the control subjects, there were significant differen-

Table 1	Demographic data		
	Patients TLE	Subjects controls	p
Age (years)	42.2 ± 3.1	41.0 ± 2.6	ns
Schooling (years)	14.1 ± 1.1	13.8 ± 1.0	ns
MMSE	28.7 ± 0.5	29.3 ± 0.1	ns
Age of onset of episode	11.2 ± 7.2		
Depression scale	8.0 ± 1.5		
Positive PANSS	10.0 ± 1.3		
Negative PANSS	14.4 ± 2.2		
Total IQ	101.4 ± 6.3		

MMSE: Mini-Mental State Examination²²; Beck Depression Scale²⁵; positive and negative PANSS syndrome Scale²⁶; Total IQ: global intelligence quotient²³. The values are expressed in mean ± standard deviation. ns: not statistically significant.

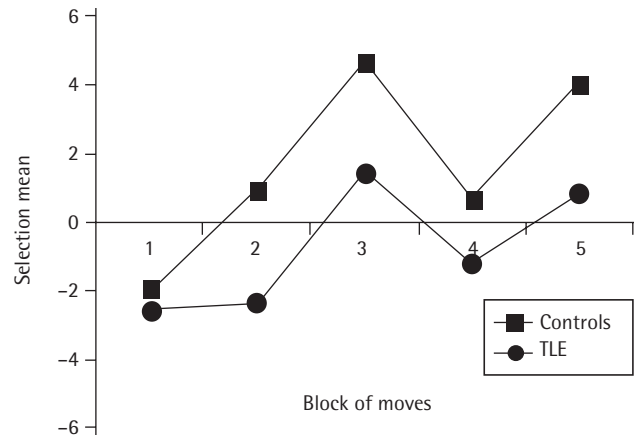


Figure 1 Curves of «Gambling Task». The results correspond to the «selection means» of the patients (TLE) and of the control subjects during each one of the five blocks of 20 moves each one. The result (selection mean) represents the selections of the beneficial groups (C + D) minus the selection of the non-beneficial groups (A + B).

ces (critical F: 4.493; F: 5.890; p < 0.02), representing a change in strategy as the test progressed between the last moves (81 to 100) and the first ones (1 to 20). No significant differences (critical F: 4.5; F: 1.02; p = ns) were obtained in the epileptic patients, that is, these patients do not have a strategy learning curve that makes them choose the most beneficial groups as they are doing the tasks (fig. 1).

When we performed a correlation analysis with the Spearman non-parametric variables test (table 3), we found r = 0.698 (p < 0.05) among the trials to complete the first category in the Reversion Test and initial trials (1 to 20) of the «Gambling Task». The other variables did not correlate with the neuropsychiatric symptoms of the PANSS scale or Beck depression inventory (Table 3).

DISCUSSION

Epileptic patients had fewer reversions in comparison with the controls and had greater difficulty in associative learning

Table 2	Results of the associative learning Test and Reversion to a negative «feedback»			
	Patients TLE	Subjects controls	Anova (crit. F 4.38)	p
Number of reversions	4.4	9.3	(F = 28.4)	p < 0.001
Trials for 1 st reversion	23.4	4.9	(F = 4.9)	p < 0.05

The values are expressed in mean ± standard deviation.

and stimulus reversion with emotional component. This fault was also observed in the «Gambling Task» where the patients did not have an appropriate learning curve between the last twenty moves and the first twenty ones. This shows difficulties in the strategy change when the contingencies of the setting are changed. We also found a positive correlation between the number of trials to achieve the first reversion

Table 3	Correlation analysis between the study variables in patients with TLE	
	Associative learning test and reversion	
	Number of reversions	Trials for 1 st reversion
Gambling Task		
Initial trials (1 to 20)	0.285 (ns)	0.698 (p < 0.05)
Final trials (80 to 100)	0.396 (ns)	0.356 (ns)
Beck depression scale	-0.362 (ns)	0.457 (ns)
Positive PANSS	0.172 (ns)	0.245 (ns)
Negative PANSS	-0.486 (ns)	0.428 (ns)
MMSE	0.214 (ns)	0.254 (ns)
Total IQ	0.385 (ns)	0.133 (ns)
Verbal IQ	0.294 (ns)	0.367 (ns)
Executive IQ	0.238 (ns)	0.348 (ns)

MMSE: Mini-Mental State Examination²²; Beck Depression Scale²⁵; positive and negative PANSS syndrome Scale²⁶; Total IQ: global intelligence quotient²³. The values are expressed in mean ± standard deviation. ns: not statistically significant.

and moves 1 to 20 of the «Gambling Task». The first half of the «Gambling Task» that correlates with the associative learning in the reversion test is sensitive to dopaminergic manipulation, with worse performance with dopaminergic blockers such as haloperidol and better performance with dextroamphetamines in healthy volunteers^{15,30,32}. Patients with Parkinson's disease and working memory impairments improve with L-dopa as the meso-cortical pathway that involves the dorsal striatum and dorsolateral prefrontal cortex on the one hand and the ventral striatum and orbitofront cortex on the other. However, they worsen in decision making tests, or a «lack of sensitivity to reward» is observed as there is a hyperdopaminergia in the mesolimbic pathway that affects the ventral striatum³³. There should be a balance between the dorsal striatum and dorsolateral prefrontal cortex on the one hand and the ventral striatum and orbitofront cortex on the other, since a hyperdopaminergia in the ventral pathway would cause impulsive and perseverative responses, with deficit in behavioral flexibility, although performance in tests such as Wisconsin card sorting improves³⁴. No significant correlation was found between the negative or positive PANSS scales and the reversion test (trials to achieve the first reversion or total number of reversions) or with the performance of the «Gambling Task» in any of the five blocks. However, the patients had a mildly increased negative PANSS scale (mean \pm SD: 14.4 \pm 2.2), due to the presence of apathy symptoms. The literature widely shows the correlation between apathy and hypodopaminergia in the mesolimbocortical pathway (ventral striatum and cingulate cortex) that could explain the lack of flexibility or insensitivity to emotional feedback in the present sample.

Our patients were not depressed and we also found no significant correlation between the Beck depression scale and all the other variables of the «Gambling Task» or Reversion Test. The Bechara et al. works³⁰ show that the facilitation of serotonergic transmission through fluvoxamine improves the second part of the «Gambling Task», where performance is more conscious. This coincides with our result, where the patients apparently will not have any alterations in serotonergic neurotransmission.

In the present sample, we found no correlations between the total or executive IQ, number of WCST categories and number of reversions, trials necessary to achieve the first reversion, or any of the five blocks of the «Gambling Task». This has already been demonstrated in previous works, where the alterations in the social life of patients with lesions and poor performance in the «Gambling Task» are dissociated from good performance in the Wisconsin card sorting test, with maintenance of intelligence quotient^{5,35}.

The neurofunctional studies (by functional magnetic resonance or positron emission tomography) in healthy volunteers report that the association of a stimulus and behavior that it generates. For example, choosing between two stimuli that consist in two abstract figures, one linked to gaining a certain amount of money and the other to loss,

and the reversion between the two stimuli and the association of gain or loss (that which led to gaining makes one lose and vice versa, similar to the paradigm used as Reversion Test in the present work) generates a response in a neural network formed mainly by the orbital amygdala-cortex, anterior cingulate, and ventral striatum. Reversion or extinction of the stimuli or the stimulus devaluation studies³⁶ generate a differential response in each one of these areas, showing great neuroanatomic specificity. The amygdala, ventral striatum and medial orbital cortex would intervene in associative learning, the lateral orbital cortex would be activated on inhibiting a response when it is no longer appropriate because the contingencies changed (reversion), it being in charge of generating a behavior based on the changing circumstances of the setting^{29,35,37,38}. The amygdala also is involved in the capacity of generating a behavior when the circumstances of the setting change, since it was demonstrated that it is activated proportionally to the extinction capacity of a response³⁹. The authors determined that the amygdala is involved in a re-learning of the stimulus-reward association. Thus, instead of inhibiting a previous behavior, it is involved in a rapid re-association that permits a different behavior, as was demonstrated by Fellows and Farah¹⁶ for the ventromedial prefrontal cortex. The anterior cingulum is activated after the behavior generated, it monitors and up-dates the association between behavior and the result or response of the setting³⁶.

In the orbital cortex, the abstract representation of reward would be codified. It would have a relative valence, since a stimulus linked to a certain magnitude of reward, on confronting another with less representation of magnitude, would act as positive reinforcement. However, when it confronts another that represents a greater magnitude of reward, it would behave as a devaluated stimulus or one with negative reinforcement^{10,36,40}. Furthermore, these studies were conducted with different stimuli or primary inductors represented in the reward system, regardless of whether they were abstract, such as gaining or losing money, or stimuli associated to drug consumption, or specific ones, such as food. All suggest a general mechanism of associating learning and reversion of an emotional stimulus and its reward.

In our reversion paradigm, the patients with amygdala resection had a defect in stimulus/reward associative learning. As has been demonstrated in functional neuroimages and healthy volunteers, the amygdala is involved in the expectation of gaining (once the stimulus is chosen, expect to gain)⁴¹. Our patients may have a defect in the Reversion Test both due to the alteration in the initial associative learning, such as «on-line» maintenance of the stimulus/reward association, or in the defect in the relative valence measurement between both stimuli, as has been demonstrated in functional studies in healthy volunteers with orbital cortex⁴⁰, or due to defect in the evaluation of the stimulus intensity, as has been also demonstrated in healthy volunteers and activation studies^{42,43} or due to defects in the «somatic

marker» where our patients may have an alteration in the reversion test due to a decrease of the amygdala activation and consequently of the skin conductance or of all visceral manifestations that represent the «somatic marker»⁴.

In summary, the unilateral lesion of the amygdala causes alterations in the associative learning of the stimulus and its reward. This is demonstrated in the present work by the greater amount of trials that the patients needed to achieve the first reversion, alterations in the capacity to change the strategy when the contingencies of the setting change, demonstrated as the lower number of reversions achieved and lack of learning in the «Gambling Task». This may be explained by alterations in the orbital prefrontal cortex (by phenomena of amygdala disconnection) or by a direct amygdala alteration in the rapid associative relearning of the reward stimulus when the contingencies of the setting change^{28,36,39}.

These neuropsychological alterations in the «Gambling Task» and Reversion Test would explain the lack of behavioral flexibility which is sometimes expressed and that are not explained by the presence of psychiatric disorders or by deficit in the intelligence quotient or of the executive functions.

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