Deficit of cognitive event-related potentials during a working task in patients with major depression

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Déficit de los potenciales evocados cognitivos durante una tarea de memoria en pacientes con depresión mayor

Summary

Introduction. *To study working memory function in major depression using identification and memory tests with event-related potentials (ERP).*

Methods. *We compared behavioral performance and event-related potentials during the processing of the Sternberg working memory task in 26 patients with major depression and 64 healthy matched control subjects.*

Results. *Depressed patients had more errors and had an increase in reaction time that was superior to the control subjects during the memory test of 5 letters presented. The depressive patients showed increased event-relatd potentials (P300 and N400) between 300-700 milliseconds registered in Pz. The prolonged positive activity in the patients ERPs suggests specific deficit in cortical activity and the large prolonged negativity activity in the patients' ERPs suggests abnormal activation of additional neuronal assemblies than those normally participating in the memory task. These data could reflect either compensatory mechanisms of dysfunction of inhibitory systems.*

Conclusions. *This study provides objective evidence that major depression significantly affects working memory. The ERP changes in depression could be accounted for by cortical activity dysfunction of the central executive control of working memory.*

Key words: *Memory. Depression. P300. P400.*

Resumen

Introducción. *Se estudia la memoria de trabajo en pacientes con depresión mayor mediante pruebas de identificación y memoria verbal con potenciales evocados.*

Métodos. *Comparamos el tiempo de reacción motor, así como los potenciales evocados durante el procesamiento de información visual mediante el paradigma de Sternberg en relación a la memoria verbal en 26 pacientes con depresión mayor y 64 pacientes sanos como grupo control.*

Resultados. *Los pacientes depresivos tuvieron más errores y tuvieron un aumento en el tiempo de reacción superior al de los sujetos del grupo control durante la prueba de memorización de cinco letras presentadas. Los pacientes depresivos mostraron un aumento de la latencia de los potenciales evocados entre los 300-700 mseg registrada en Pz. La latencia prolongada en el componente positivo (P300) de los potenciales evocados sugiere un déficit específico en la actividad cortical, mientras que la latencia prolongada en el componente negativo (N400) sugiere una activación anormal de conjuntos de neuronas cercanas a las que normalmente están implicadas en la tarea de memoria. Estos datos podrían reflejar mecanismos compensatorios o difunciones en los sistemas inhibitorios.*

Conclusiones. *Estos estudios proveen una evidencia objetiva de cómo la depresión mayor puede afectar a los procesos de memoria de trabajo. Los cambios en los potenciales evocados en la depresión podrían venir determinados por la disfunción de la actividad cortical en el control del sistema ejecutivo central de la memoria de trabajo.*

Palabras clave: *Memoria. Depresión. P300. N400.*

INTRODUCTION

Depression has been associated with important alterations and cognitive event-related potentials as well as with memory and attention problems.

Studies with depressive patients in memory tasks make it possible to verify the existence of a serious deterioration of them, a fact that some authors have associa-

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ted with a deficit in frontal cortex functioning[1-5]. Working memory is found among the different types of memory that are most seriously affected in depression. This is a system of temporal storage, of activation and active maintenance of information, processes necessary for any complex cognitive activity. This model includes two large components, one for maintenance and processing of verbal and non-verbal material and another attentional one, called «central executive system, that is responsible for controlling strategy, selection and distribution of data processing[6].

However, in spite of common agreement between many investigators on the existence of memory deficits in depressive patients, neurophysiological mechanisms are still unknown. Some studies consider that these deficits would be associated with an alteration in the central executive system[7], other studies verify cognitive deterioration associated with delay in P300 latency, considering it as an index of cognitive capacity of depressive patients[8]. On the other hand, other authors have verified that greater cognitive deterioration as well as greater seriousness of the depression are associated with greater delay in P300 latency[9,10], while others consider that the deficit is directly related with a decrease in cortical activity and slow down in the perceptive decision processes[11-13].

The apparent contradiction in these results is determined by the different methodologies applied, heterogeneity of the patients, ages, time and seriousness of the disease or type of treatment carried out. Regardless of that stated, we think that serious deterioration exists in the memory of depressive patients that prevents good strategy and also requires greater effort to carry out complex function, a fact that would be reflected by a specific deficit in the executive and attentional function mechanisms, associated with an alteration in prefrontal and cingulate cortex cortical activity[14-16]. These regions have been identified as specific to neuronal activity of attention and memory[17-20]. Recently, different authors have found an important alteration in working memory as well as cognitive event-related potentials in patients with major depression (Pelosi et al., 2000).

The fundamental objective of this present research study is to investigate if the event-related cortical potentials underlying a memory test make it possible to provide neurophysiological support of patients with major depression.

METHODS

Subjects

The control group was made up of 26 subjects without any type of neurological or psychiatric diagnosis. The depression group was made up of 64 patients free of neurological disease, mental retardation or other associated medical diseases; they were diagnosed of major depression according to DSM-IV criteria and the Hamilton scale. The Mini-Mental State Examination (MMSE)[22] was applied to assess cognitive state (table 1). Vision level was normal in all of them.

Procedure

A registry of the long latency event-related potentials was carried out during a visual memory task (Sternberg paradigm, 1966)[23] consisting in the presentation of a pseudo-random sequence of 300 visual stimuli of letters lasting 300 msec on a screen, with a 3 sec. ratio. The task consisted in the presentation of 5 letters for 1 minute in the center of the screen that the subject should memorize. After, the patient had to respond to each one of these letters that appeared on the screen among other letters that had not been previously presented. The subjects were trained to extend the middle finger of their right hand as quickly as possible on seeing the letter that had been previously memorized.

The cerebral responses were recorded by electrodes placed on a Medicap helmet following the international system 10/20[24] with reference to the both ear lobes. In order to avoid ocular artifacts, an infraorbital electrode was placed with the same reference. The cortical responses were recorded in the electrode located in Pz and the electromyographic responses were recorded by an active electrode, placed on the common extensor muscle of the fingers of the right hand.

Posterior analysis of the latencies of the different waves was carried out manually and with the cursor on the screen, identifying each one of the waves visually, paying attention to both the negative as well as positive inflections that occur sequentially to the stimulation performed. The analysis window was 1,000 msec from the onset of the visual stimulus.

Statistical analysis

The statistical analysis of the results was performed by using different statistical designs. Depending on the characteristics of the variables, a certain type of statistics was chosen, given that the fundamental mesc of this

TABLE 1. Characteristics of the sample

	Mean	*SD*
Age		
Depression	46.08	14.10
Control	44.08	10.70
Hamilton		
Depression	44.48	9.47
Control	4.19	2.80
MMSE		
Depression	29.41	1.19
Control	30.00	0.00

MMSE: Mini-Mental State Examination.

study is to verify the differences existing between a group of patients with major depression and a group of controls to assess a series of variables.

The neurophysiological variables (latency and amplitude of P3-N4 components in the memory task) were analyzed by MANCOVA (multivariate analysis of covariance), with the factor between diagnostic groups (depression versus control) as dependent variable. Furthermore, reaction times for auditory, visual and memory tasks were analyzed. The variable Age was included as a variable within these analysis. Although the comparison of means test did not show significant differences between the groups, the high variability of the scores (table 1) and the known effect that age has on the factors measured advises us to use the corrected model as reference for the results.

The number of correct answers in the memory task was analyzed with the Student's «t» test.

The neuropsychological variables (logical memory test included in the Wechsler Memory Scale) was analyzed by an ANOVA 2 × 2 (diagnosis × type of logical I-II memory). The significant interaction is analyzed by *a posteriori* comparisons of pairs of means.

All the statistical analysis were performed with the SPSS for Windows, version 8.0.

RESULTS

Figure 1 shows the average of the event-related potentials in response to the visual stimuli to letters. The components of the event-related potentials analyzed are principally characterized by a positive component (P300) having large amplitude that is located around 350 milliseconds followed by another large negative component (N400) located around 450 mseg.

The latencies of the event-related potentials show the significant effect of the Diagnosis variable for the components P3 ($F_{2,87} = 2.504$; $p < 0.05$) and N4 ($F_{2,87} = 3.643$; $p < 0.05$). In all the cases, the effect of the diagnosis shows that the latencies of these components are significantly delayed in the depressive group (table 2).

The amplitudes of these same components do not provide any significant results.

The reaction times provide very similar results, in this case, the diagnosis variable significantly influences the reaction time in the memory task ($F_{2,87} = 5.187$; $p < 0.01$). Again, the depressive group (mean of 357.72 and SD of 100.21) presents much slower responses than the control subject group (mean of 287.42 and standard desviation [SD] of 74.15).

Finally the number of correct answers in the memory task also shows a significant effect of the diagnosis variable ($t = -8.27$; $p < 0.001$). The control subjects present a much higher number of correct answers than the depressive patients.

Analysis of the effect of the diagnostic and memory type (logical I-II) factors provides significant results for all the principal and interaction effects. In the first place,

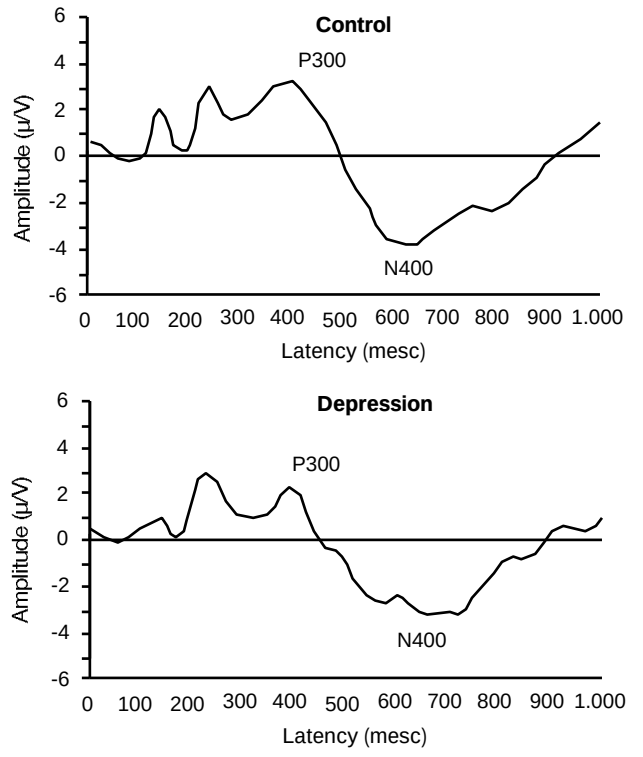

Figura 1. *Graphic representation of the event-related potentials (waves P3 and N4) during the memory task of letters in the electrode Pz.*

the principal effect of diagnosis ($F_{1,88} = 74.970$; $p < 0.001$) is significant. This indicates that, independently of condition I or II, the controls remember much more information than the depressive group. In turn, the principal effect of type of memory ($F_{1,88} = 29.645$; $p < 0.01$) is significant, showing, as was to be expected, that short term memory (logical I memory), is greater than delayed recall (logical II memory). However this effect is modulated by the group to which the subject belongs, as is demonstrated by the interaction of diagnosis × type of memory ($F_{1,88} = 8.024$; $p < 0.01$); while the degree of forgetting is minimum in the control group, this effect is much greater in the depressive group. That is, it is not only the level of global recall that distinguishes the patients and controls but also the rate of forgetting ($t = 6.973$; $p < 0.001$) (table 3).

TABLE 2. Latency of the P3 and N4 waves during the letters memory task

	Diagnosis	*Mean*	*SD*	*N*
LP3M	Depression	435.44	89.92	64
	Control	392.81	56.04	26
	Total	423.12	83.57	90
LN4M	Depression	506.94	102.11	64
	Control	448.35	64.24	26
	Total	490.01	96.19	90

TABLE 3. Diagnostic effect and type of memory

Diagnosis	*Memory T*	*Mean*	*SD*
Depression	I	13.687	0.546
	II	11.859	0.570
Control	I	21.846	0.857
	II	21.269	0.894

CONCLUSIONS

Our first analysis of the results allows us to state that our patients do not differ from the control subjects in regards to cognitive level since there are not only no significant differences in the MMSE but also the scores are practically the same. These results verify that depression does not directly affect the global cognitive processes or general intelligence but specifically affects the attentional and memory processes, as is deduced from the differences found in both the short term as well as long term verbal memory processes. This indicates that the controls remember much more information than the depressive subjects, while short term memory (logical I memory) is greater than delayed recall (logical II memory). On the other hand, we have also verified that the degree of forgetting is minimum in the control group, a fact that does not occur in the depressive patient group, which means that the depressive patients not only manifest a decrease in the level of recall but also in the rate of forgetting[25,26].

The latency increase of P300 is directly related with an important deterioration in the information processing in this type of patients. In this sense, other authors have found a direct relationship between the increase of P300 latency, the cognitive deterioration process and the duration of the disease[10,27]. From this point of view, in fact, the P300 is considered as a categorization and evaluation index of the cognitive processes in regards to capacity of immediate memory that we need to perform any task. Truly, the P300 wave could be considered as the subproduct of the neural processes necessary to adapt the present scheme of the subject to the new environmental demands[28]. During this process, the participation of working memory is necessary as time storage that allows for the maintenance of the scheme and its comparison with the new information[29].

On the other hand, the results obtained with the N400 wave seem to reflect important alterations of the patients with depression in the memory processes, given that the increase of the needs of memory to be able to memorize and remember 5 letters suggests an important increase in the memory processes, a fact that could be directly related with this late negative component of the event-related potentials[30,31]. In this sense, different authors assume that the increase of latency of this negative component would be more related with the effort needed to be able to process complex stimuli more than to perform automated processes[32].

Although the psychophysiological bases underlying cognitive functions of the P300 and N400 components are still little explained, the differences found in the depressive group compared to the control one could be related with specific deficits in different components of the neuronal network of the central control system of working memory, probably in the dorsolateral area of the prefrontal lobe, as has been verified in different research studies[3,19,20]. A result that we feel has great importance is the very high number of errors made by the depressive patients compared to the controls. This result could, on the one hand, identify the alteration of the attentional processes when the task becomes complicated and demands greater attentional capacity, a fact that would justify the deficits founds in the event-related potentials, principally in the P300 wave in depressive patients.

Finally, such a lengthened reaction time as that found in the depressive group compared to the normal subject group, that has been found by other authors[21], justifies the difficulties of the depressive patients in information processing (stimulus recognition, decision making, preparation for response and, finally, performance), processes directly related with attentional and working memory.

In conclusion, we could state that the results seem to verify an important alteration in the neuronal networks responsible for attention and working memory in patients with major depression.

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