Quantitative EEG analysis disease during resting and memory task in carriers and non-carriers of PS-1 E280A mutation of familial Alzheimer´s

Análisis del EEG cuantitativo durante tareas de memoria y reposo en portadores y no portadores de la mutación PS-1 E280A de la enfermedad de Alzheimer

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ABSTRACT

Background: *Alzheimer's disease is the most leading cause of dementia in the world; the mutation* PS-1 E280A *alters the gene of the* Presenilin-1 *and causes an early onset familial Alzheimer's disease. This mutation has been found in large kindred of Antioquia, Colombia. The objective of this study was to find differences revealed by electroencephalogram between healthy subjects and asymptomatic carriers that can be used as clinical markers of the disease in this population.*

Methods: EEG *was recorded in 15 asymptomatic E280A carriers and 15 healthy non carriers during resting and a memory task using 64 channels amplifier. Two conditions in the memory*

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task were analyzed: encoding and retrieval, the process of recording and evocating information, respectively. Power spectrum was calculated in delta (0. 5–4. 0 Hz), theta (4. 0–8. 0 Hz), alpha-1 (8. 0–10. 0 Hz), alpha-2 (10. 0–13. 0 Hz), beta (13. 0–25. 0 Hz) and gamma (25. 0–50 Hz) frequency bands for four regions of interest. Changes were evaluated in different conditions by ANOVA analysis.

Results: *In resting condition a significant decrease was found in theta ($p=0.0001$) and an increase in alpha-2 frequencies ($p=0.037$) in carriers compare with controls. During encoding of the memory task theta was significantly lower in carriers compared with controls ($p=0.008$) and comparing resting versus retrieval process for each group, there was more theta synchronization in carriers.*

Conclusion: *Early changes in theta frequencies were observed in the EEG recordings, it could be use as clinical markers in this population. Also it seems carriers activate additional cortical regions in order to conserve successful cognitive functions before clinical impairment.*

KEY WORDS

Alzheimer's Disease
Quantitative EEG
PS-1 E280A mutation
Theta frequency band
Power spectrum
Memory process

RESUMEN

Introducción: la enfermedad de Alzheimer es la principal causa de demencia en el mundo; la mutación PS-1 E280A altera el gen presenilin-1 y causa una variante familiar de la enfermedad que se caracteriza por una aparición temprana. La mutación se ha descubierto en un grupo de familias de Antioquia, Colombia. El objetivo de este estudio fue encontrar diferencias, a partir de registros electroencefalográficos de personas portadores de la mutación en una etapa asintomática y sujetos sanos para evaluar si pueden ser utilizadas como un marcador temprano de la enfermedad en la población portadora de la mutación.

Metodología: se realizaron registros EEG en 15 portadores asintomáticos de la mutación E280A y 15 personas sanas no portadoras durante una tarea de memoria y en reposo utilizando un amplificador de 64 canales. En la tarea de memoria se evaluaron dos condiciones: codificación y evocación; el proceso de memorizar y recuperar la información, respectivamente. La potencia espectral fue calculada en las bandas de frecuencia delta (0,5–4,0 Hz), teta (4,0–8,0 Hz), alfa-1 (8,0–10,0 Hz), alfa-2 (10,0–13,0 Hz), beta (13,0–25,0 Hz) y gamma (25,0–50 Hz) para cuatro regiones de interés. Los cambios del espectro fueron evaluados por análisis de varianza ANOVA.

Resultados: bajo la condición de reposo se encontró una disminución importante en la potencia de la banda teta ($p=0,0001$) y un incremento en la banda alfa-2 ($p=0,037$) en portadores comparados con controles. Durante la tarea de codificación, los portadores mostraron una disminución significativa en la banda teta ($p=0,008$). Al comparar reposo contra memoria de evocación se encontró una mayor sincronización en teta en los portadores de la mutación.

Conclusión: se encontraron cambios tempranos de la potencia en la banda teta que pueden ser utilizados como un marcador clínico de la enfermedad en esta población. Una hipótesis adicional basada en los resultados es que los portadores necesitan activar regiones corticales adicionales para conservar las funciones cognitivas antes de empezar un deterioro clínico.

PALABRAS CLAVES

Enfermedad de Alzheimer

EEG cuantitativo

Mutación E280A

Banda de frecuencia teta

Espectro de potencia

Procesamiento de memoria

INTRODUCTION

Alzheimer`s disease (AD) is the most prevalent cause of dementia, a neurodegenerative condition, that generally onset after the age of 65 (1); however there are some mutations that induce the onset of the neurocognitive symptoms under this age (2). Until now, three genes have been related to familial Alzheimer's disease: the Presenilin-1 (PS-1) gene, the amyloid precursor protein (APP), and the Presenilin-2 (PS-2) (3,4)

In Colombia, there is a large family group with a mutation in the PS-1 E280A gene, which codifies Presenilin-1, a co-factor of γ-secretase involved in the production of β-amyloid (5). This mutation has an autosomal dominant inheritance and induces symptoms from the age of 44 years (mild cognitive impairment onset) and dementia at a median age of 46. 8 years (6–9).

Electroencephalography (EEG) might be a powerful and simple tool for the identification of predictive markers of cognitive deterioration, since it can show the rapid and multistage cognitive functions that are affected early in neurodegenerative processes (10).

The main changes in resting EEG recording of sporadic Alzheimer's disease are: slowing of the dominant occipital rhythm (11), early modifications in beta and theta bands and late modifications in alpha and delta bands (12–14). During memory process, one of the earliest and most sensitive EEG changes is the normal synchronization in theta frequencies despite of the increase in its relative power (15). EEG records during memory task in sporadic Alzheimer's disease and mild cognitive impairment patients have demonstrated a lack of theta enhancement in the processing of the cognitive stimulus (16–19), demonstrating affectation of the cholinergic system because theta band has been implicated in optimal working memory and attentional process (20).

Differences in synchronization of alpha and beta bands also have been reported during memory encoding revealed by synchronization likelihood (a measure similar to coherence but sensible to linear and nonlinear interactions) (21). Synchronization likelihood decreased in Alzheimer's disease subjects when they are compared to healthy subjects with subjective memory complains and it is related to semantic memory dysfunction (22).

EEG studies in carriers of mutations have reported important differences when are compared to non-carriers. EEG recordings in resting of ApoE4 carriers, a genetic risk factor for late-onset sporadic AD, have shown decrease in alpha and an increase in delta and theta power (23,24). In an Event Related Potential study (ERP) of semantic processing in asymptomatic subjects with E280A mutation, lower amplitudes and a different topography of N400 potential were observed compared with non-carriers, especially in right inferior-temporal, medial cingulated, left hippocampus and parahippocampus (25).

Another ERP study in the same population showed less positivity in frontal regions and more positivity in occipital regions, during a recognition memory task in asymptomatic carriers compared to controls, which activated frontal areas (26). These differences were more pronounced during the 200-300 msec period.

Finally, a recent quantitative EEG study during resting condition in probable Alzheimer's

disease and asymptomatic E280A carriers found alteration in beta frequency and modifications in front-temporal regions of the spectral parameters before clinical sign of cognitive impairment (3).

In this study we extend the previous research in E280A carriers analyzing the EEG records during resting and a memory task in asymptomatic subjects. The objective was to find differences revealed by EEG between healthy subjects and asymptomatic carriers that can be used as clinical markers in this population.

MATERIALS AND METHODS

The subjects were members of the E280A mutation Colombian kindred. Informed consent for participation was obtained from all subjects according to a general protocol approved by the Human Subjects Committee of *Sede de Investigación Universitaria* of *University of Antioquia*, in Medellin, Colombia. We selected 15 asymptomatic E280A mutation Alzheimer's disease carriers (ACr) and 15 healthy non carriers subjects (control). Table 1 shows the mean values of demographic and clinical characteristic for these groups as well as the results of a *T* test for each of the variables.

EEG data were recorded with a Neuroscan unit amplifier (Neuroscan Medical System, Neurosoft Inc. Sterling, VA, USA) (0.1 ± 200Hz band pass) from 64 electrodes positioned according to the international 10-10 system with midline reference (subsequently recomputed to common average) at a sample rate of 1000 Hz. A simultaneous electro-oculogram (0.1 ± 100 Hz band pass) was also recorded. All data were digitized in a continuous recording mode.

Table 1. Demographic and neuropsychological data of ACr and control subjects

	ACr	Control	T test
N	15	15	
Age (years)	28.8 ± 5.1	31.5 ± 5.8	T= -1.04, df= 28 p< 0.3066
Gender (M/F)	5/10	6/9	χ^2= 0.1435, df= 1 p< 0.7048
MMSE	29.6 ± 0.6	29.5 ± 0.9	T= -0.2190, df= 28 p< 0.8283
Education level (ys)	11.9 ± 3.5	11.2 ± 3.4	T= 0.7759, df= 28 p< 0.4443

MMSE: mini-mental state examination; F: female; M: male; df: degree of freedom; χ^2 Chi-squared test

Data were registered during an ERP experiment where participants performed a recognition memory task using color pictures of concrete and namable objects: 50 new stimuli were presented during the study phase, and 100 stimuli (50% old) were presented during the test phase. Each trial began with a 1,000ms fixation character ("+") prior to the presentation of the stimuli. Study stimuli were then presented for 2,000ms followed by the question, "Do you like this item?" Subjects were then prompted to button press to signify their like/dislike judgment and to remember the items for a subsequent memory test. Test stimuli were presented for 1,500ms, followed by the question, "Is this item old or new?" Subjects were then prompted to button press to signify their old/new judgment. Subjects were asked to hold their responses until the question appeared immediately after stimuli presentation to minimize response-related ERP artifact (26).

Other recordings were obtained with subjects resting comfortably with their eyes closed during five minutes. Vigilance was continuously monitored in order to avoid drowsiness. For the analysis of the memory EEG data, three conditions were selected: encoding, hits and correct rejection. Showing the images for the first time was defined as the encoding condition and it is the process where the participant has to record the new information. Hits were defined as the condition where subjects selected an image as repeated correctly and correct rejection was the condition where subjects selected an image as novel correctly. Both conditions hits and correct rejection are part of retrieval memory process and here the participant has to evocate the learned information. Epochs were selected 200ms before the condition event and 1800ms after. The resting data were segmented in epochs of 2s (2000 samples).

The EEG epochs with ocular, muscular and other types of artifact were removed by a computerized automatic procedure based on linear trend, joint probability and kurtosis approach (27). Then, we used independent component analysis (ICA) approach to identify eye blink, muscle and electrical sources visually detected by an expert (C.T.). These sources were removed of the EEG data. Finally, we repeated the automatic procedure in the cleaned EEG ICA-based data to remove the residual epochs with artifacts.

For quantitative analysis, the fast Fourier transform using the Welch approach was computed for 20 artifact-free epochs for each condition (rest, encoding, hits and correct rejection). Relative power was calculated in six EEG bands: delta (0. 5–4. 0 Hz), theta (4. 0–8. 0 Hz), alpha-1 (8. 0–10. 0 Hz), alpha-2 (10. 0–13. 0 Hz), beta (13. 0–25. 0 Hz) and gamma (25. 0–50 Hz). The power measures were normalized by dividing the value in one band with the sum of the power in all bands.

As a result, we had a matrix of 64x6x20 with values of power for each subject, where 64 was the number of channels, 6 the number of bands and 20 the number of epochs selected. Then, four regions of interest (ROI´s) were computed: *frontal -F-*: (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8); *temporal -T-*: (FT7, FC5, FC6, FT8, T7, C5, C6, T8, TP7, CP5, CP6, TP8); *central -C-*: (FC3, FC1, FCZ, FC2, FC4, C3, C1, CZ, C2, C4, CP3, CP1, CPZ, CP2, CP4) and *parieto-occipital -PO-*: (P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, P03, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, CB2) (figure 1). The original 64x6x20 matrix was reduced to 4x6x20 as the power mean between the channels of the ROI´s for each band. Finally, we averaged the power in the 20 epochs.
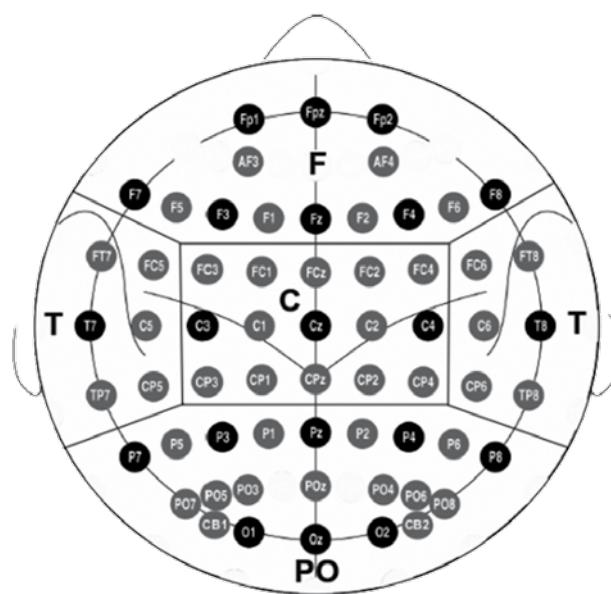
Figure 1. Schematic picture of the 64 electrodes system and the ROI´s generated. F: frontal; T: temporal; C: central; PO: parieto-occipital

The power values were compared by means of ANOVA analysis. The main working hypothesis of the present study was that the power spectrum in ACr is abnormal compared with control. To test this hypothesis the ANOVA had the factors subjects (ACr and control), ROI´s (F, C, T, and PO) and the power spectrum for a band in one condition as independent variable. Also, we compare conditions for each group by means of

ANOVA with the factors condition (resting, encoding, hits and correct rejection), ROI´s (F, C, T, and PO) and the power spectrum for a band in one group as independent variable. The statistical analysis was carried out in Matlab ®. Statistical significance was defined as the *p* values lower than 0.05.

RESULTS

Neither demographic information (age, gender and education level) nor neuropsychological examination differences were found (Table 1). No differences were found in the score of the memory task between ACr and control groups as were expected because the asymptomatic condition of the population.

In resting condition the power showed a decrease in the theta and alpha-1 bands frequencies for ACr versus control in all ROI´s. This decrease was significant for theta ($F_{1,112}=16.52$, $MSe=0.07131$; $P=0.0001$) but not for alpha-1. Also we found a power increase in ACr versus Control for delta and alpha-2 in all ROI´s but just the last band was significant ($F_{1,112}=4.44$, $MSe=0.0165$; $P=0.0373$) (figure 2). In beta and gamma were not difference found.
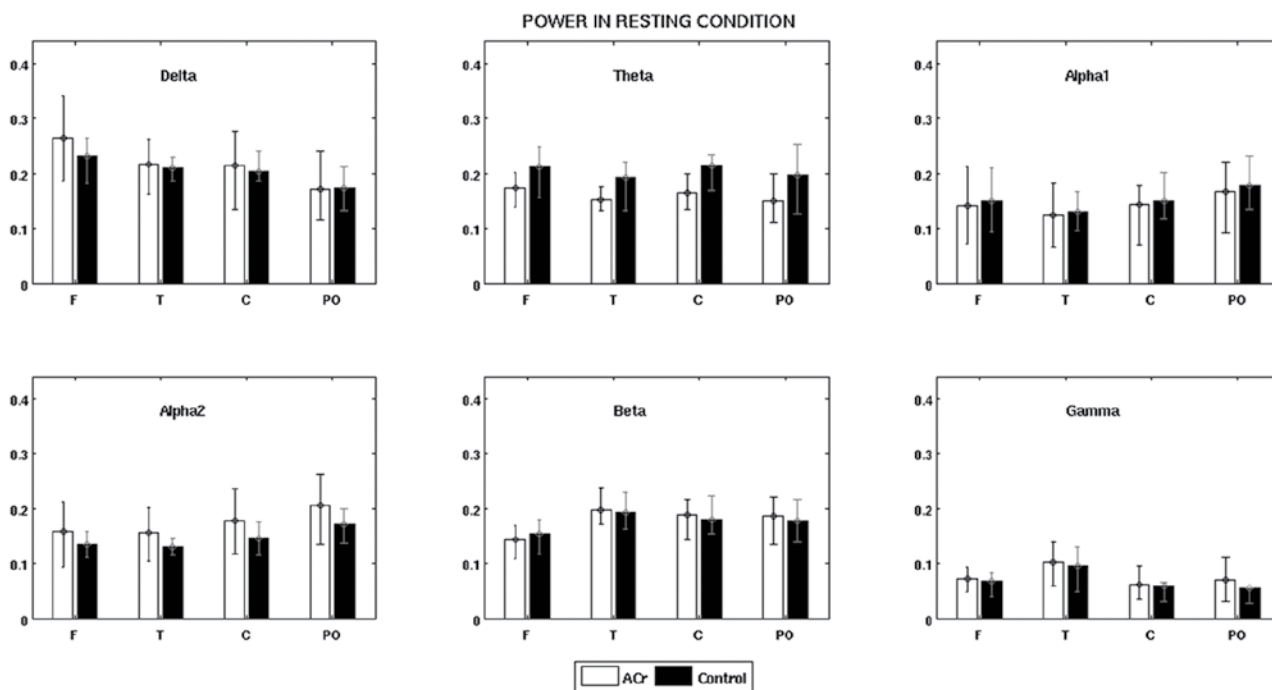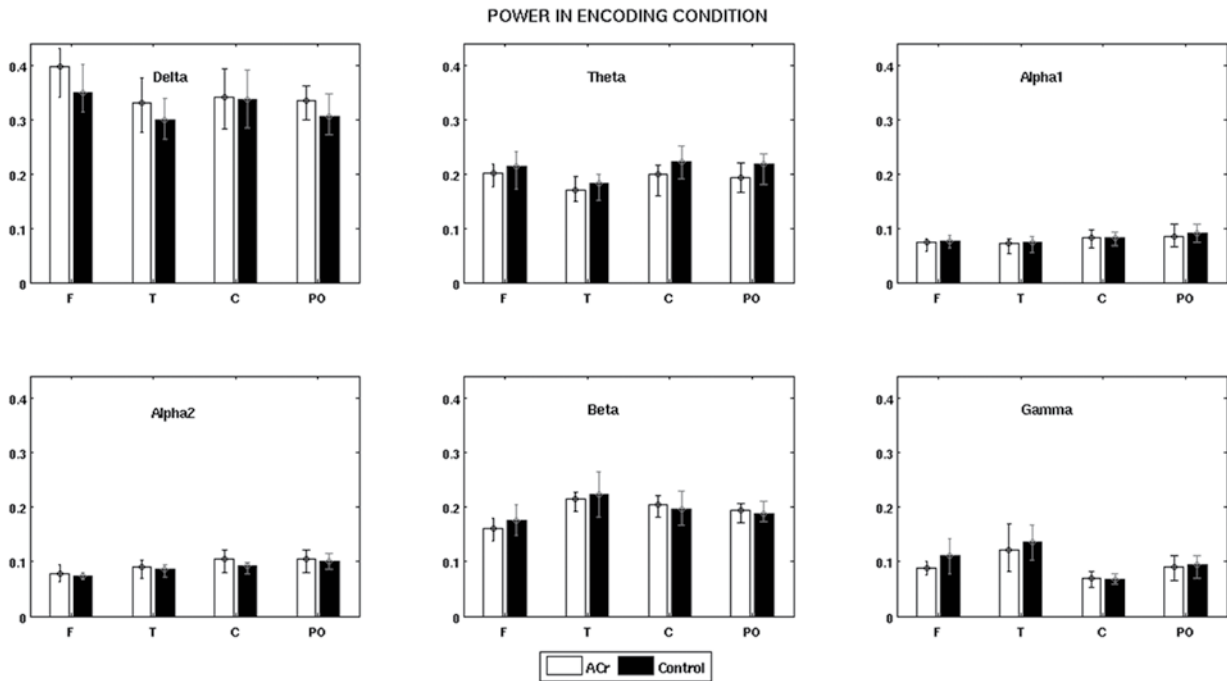

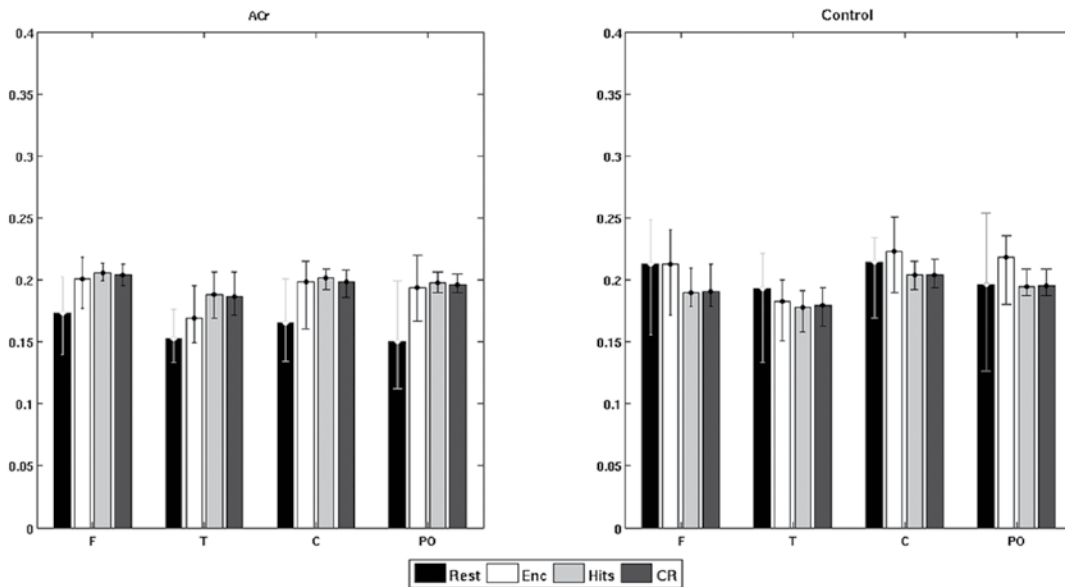**Figure 2.** Power spectrum in resting condition for ACr and control group.
The power measures were normalized. The vertical line in the bars represents the 25th percentile, mean and 75th percentile. F: frontal; T: temporal; C: central; PO: parieto-occipital

During encoding, theta frequencies were significantly lower in ACr compared with controls ($F_{1,112}=7.23$, $MSe=0,01915$; $P=0,0083$) for all ROIs (figure 3). No differences were found in other bands, neither for hits and correct rejection.

POWER IN ENCODING CONDITION

Figure 3. Power spectrum in encoding condition for ACr and Control group.
The power measures were normalized. The vertical line in the bars represents the 25th percentile,
mean and 75th percentile. F: frontal; T: temporal; C: central; PO: parieto-occipital

Figure 4. Power spectrum for theta band in resting and memory conditions for ACr and control
group. The power measures were normalized. The vertical line in the bars represents the 25th
percentile, mean and 75th percentile. F: frontal; T: temporal; C: central; PO: parieto-occipital

Comparing resting and memory conditions, differences in theta band were found in ACr group for resting versus encoding ($F_{1,112}=21.73$, $MSe=0.0407$; $P=6.36\times10^{-6}$), resting versus hits ($F_{1,112}=52.13$, $MSe=0.0654$; $P=1.98\times10^{-11}$) and resting versus correct rejection ($F_{1,112}=46.38$, $MSe=0.0589$; $P=1.86\times10^{-10}$) for all ROI´s. In control group no significant differences were found for resting versus memory. Figure 4 show the magnitude of these powers in both groups.

DISCUSSION

In the present study we analyzed the pattern of the EEG during resting condition and memory process revealed by power spectrum. As we expected, comparing the changes of power from resting to encoding there were a decrease of high frequencies (alpha-1, alpha-2, beta and gamma) and an increase in low frequencies (delta and theta) for both groups ACr and control. EEG in healthy people during memory process has changes in theta and alpha activity; theta synchronizes with an increased in task demands (theta power increases), whereas alpha desynchronizes (alpha power decreases) (28,29).

The activity of theta has been reported in episodic long-term and working memory; its oscillations seem to be responsible for the integration of top-down and bottom-up information during the encoding phase, while alpha desynchronization correlates with semantic memory performance (30,31)

This has been found specially in working memory studies, but theta is also associated with attentional processing, spatial navigation and long-term memory processes (18). During memory process, we also found a decrease in synchronization for alpha frequencies in both, ACr and control, as it has been reported in literature (30,32).

Despite of power in theta frequencies was lower in ACr than control for resting and encoding, if

we compare resting versus memory conditions (encoding, hits and correct rejection) for each group, there was more synchronization for all ROI´s in ACr. It seems as though ACr subjects create different connectivity pathways in order to get a good cognitive function (compensation hypothesis). This hypothesis has been made through several Alzheimer's disease studies specially in subjects at risk of developing the disease because of mutations and this could be observed in early stages of the disease and in preclinical stages (10,26,33,34) like in this study.

There is evidence of neuro-pathologycal changes in carriers of E280A years before onset of symptoms. Functional imaging during memory task in ACr subjects from 18-26 years old showed greater activation in hippocampal and para-hippocampal regions and less activation in precuneus and posterior cingulate regions (35). And later at age 28,3 years, there is evidence of accumulation of amyloid-beta (Aβ) in a florbetapir binding PET study in posterior cingulate, precuneus, parietotemporal, frontal, and basal ganglia regions (36). This early changes could cause a different pattern in the connectivity process and therefore in the electrical pattern registered in EEG.

Interestingly, we observed a decreased in theta power frequency during resting condition and memory process at preclinical stages of the disease. A similar study in the same population with older asymptomatic carriers (at the age of 39. 9 years) and in probable Alzheimer disease (carriers with mild symptoms) showed a significant increase of theta during resting condition in probable Alzheimer's disease compared with controls (3). A similar finding had been reported in sporadic Alzheimer's disease (12).

It seems at very early state of the disease (at age of 28. 8 years) there is a decrease in theta band and then it starts to increase at the onset of the disease. It could be explained by the Aβ accumulation pattern that begins at age of 28. 3 years. As we said before, there are changes

in the activation of brain areas during memory processing in carriers previous to the accumulation of Aβ and these could be reflected in the decrease of power in theta frequencies revealed by EEG.

As in previous studies in asymptomatic carriers of E280A mutation, we found differences compared with controls; there is a decrease in EEG activity in a basal state and affectation of power during memory process mainly in theta frequencies. It seems as though carriers need more neural activation in order to have a good neurocognitive function as it was revealed by neuropsychological tests.

CONCLUSION

The EEG recordings revealed early changes mainly in theta frequencies in E280A carriers that can be used as a clinical marker in this population. Also, it seems these subjects activate additional cortical regions in order to conserve successful cognitive functions before clinical impairment; however, more studies are needed in this population in order to clarify the structural and functional difference that these subjects have and that were reveled in the EEG recording but not in the clinical evaluation.

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Conflict of interest

There is not conflict of interest in this study.

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