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Neurofeedback in Healthy Elderly Human Subjects with Electroencephalographic Risk for Cognitive Disorder

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Abstract. In normal elderly subjects, the best electroencephalogram (EEG)-based predictor of cognitive impairment is theta EEG activity abnormally high for their age. The goal of this work was to explore the effectiveness of a neurofeedback (NFB) protocol in reducing theta EEG activity in normal elderly subjects who present abnormally high theta absolute power (AP). Fourteen subjects were randomly assigned to either the experimental group or the control group; the experimental group received a reward (tone of 1000 Hz) when the theta AP was reduced, and the control group received a placebo treatment, a random administration of the same tone. The results show that the experimental group exhibits greater improvement in EEG and behavioral measures. However, subjects of the control group also show improved EEG values and in memory, which may be attributed to a placebo effect. However, the effect of the NFB treatment was clear in the EG, although a placebo effect may also have been present.

Keywords: Cognitive impairment, electroencephalography (EEG) biofeedback, global deterioration scale, healthy aging, neurofeedback, placebo, quantitative encephalography (QEEG)

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INTRODUCTION

In recent decades, life expectancy has progressively increased, primarily in the most developed countries. There are more than 400 million people over the age of 65, approximately 6% of the world's population, who live in Europe, the United State of America, and Canada. In Mexico, there are 9.4 million people over 60 years old, representing 8.7% of Mexico's population. There are nearly 18 million people with dementia in the world, and 5 million of these individuals are located in Europe [1]. The prevalence of dementia increases with age from 5.0% in those aged 71–79 years to 37.4% in those aged 90 and older in the USA [2]. In the UK, it was estimated that one in 14 people over 65 years of age (7.1%) and one in six people over 80 years of age (16.7%) have a form of dementia [1]. Statistics from the Mexican Social Security Institute reported

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that in subjects over 60 years of age, the prevalence of dementia was 3.5%, and the prevalence of MCI was 30.5% [3].

Over the course of a person's life, both physical and cognitive function naturally decline. Some of the changes that happen are normal, but others are not [4]. Due to the increase in life expectancy, diseases associated with old age are becoming more frequent. Memory has been reported to be the mental process most affected by old age [5–8] but other mental processes such as attention, language, and executive abilities are also altered [9–11]. Normal cognitive decline is different from pathological deterioration in old age. Amnesia and dementia are the two main types of memory disorder found in the clinic. In contrast to amnesia, in which memory-related disorders can be significant and can occur in the absence of significant damage of other cognitive and social areas [12], dementia implies the development of multiple cognitive deficits [13, 14]. Electroencephalography (EEG) changes that may be attributed to the normal aging process include a decrease in frequency [15–17] and amplitude [18] of the occipital alpha rhythm and a topographic reorganization of this rhythm in which it spreads to frontal regions [19]. Another EEG characteristic of normal aging observed during relaxed wakefulness is the appearance of dispersed theta waves associated with a diffuse increase in theta power [6, 16, 20, 21] and the occasional appearance of delta waves, mainly in the temporal leads, predominantly left [6, 20, 21]. Because these changes are normal in aging, the use of a normative database categorized by age takes them into account. Therefore, any deviation from the EEG norms should not be considered to be due to normal aging but rather to other factors, frequently pathological in nature.

Studies of aging in which EEG characteristics are associated with neuropsychological characteristics of normal subjects, subjects with mild cognitive impairment (MCI) and subjects with dementia have shown that individuals with greater cognitive impairment present a greater amount of theta activity than is normal in aging individuals [22–30]. In the later stages of dementia, an excess of delta activity is also observed [22, 27–29, 31, 32]. A chronically slowed occipital alpha rhythm during ongoing wakefulness is a definitive indicator of an underlying pathology, which could be one several neurological and psychiatric disorders [33], including Alzheimer's disease [34].

Several follow-up studies in the elderly [24, 30, 35–37] that included normal subjects, subjects with MCI, and subjects with dementia have been conducted. In all of these studies, the follow-up period was one to two years, except for Prichep et al. [37], in which subjects were followed for 7 years. This study included only normal individuals with subjective memory loss that could not be verified objectively (hence, these subjects were assigned global deterioration scale values of 2). Despite the differences in these studies, they all share the common observation that excessively slow activity in the theta frequency range of an EEG is an excellent predictor of cognitive impairment.

EEG oscillations are strongly related to sensory and cognitive processes [38–41]. Therefore, trying to normalize the EEG by neurofeedback (NFB) is an attempt to improve several cognitive functions. NFB is an operant conditioning procedure through which subjects can learn to modify the electrical activity of their own brain [42]. Different NFB protocols have been used in neurological [43–46] and psychiatric [47–63] patients and have been validated on healthy participants [64, 65], demonstrating the important benefits of NFB on cognitive activity.

In the present research, NFB training that reinforces decreased theta activity was applied with the aim of reducing the probability of posterior cognitive decline by redressing an EEG abnormality present in healthy subjects that could be associated with cognitive decline. Because repetitive high threshold bursting in thalamocortical neurons occurs in the range of 2 to13 Hz, with the precise frequency increasing with increasing depolarization, the same cellular components that underlie thalamic alpha rhythms can also lead to theta rhythms when the thalamocortical neuron population is less depolarized [66]. This fact may be the explanation why using NFB to decrease theta absolute power (AP) could cause not only theta changes, but also alpha changes.

The goal of this work was to explore the effectiveness of a NFB protocol in reducing theta EEG activity in normal elderly subjects who present abnormally high theta AP. The final results will be obtained after 7 years.

MATERIALS AND METHODS

The Ethics Committee of the Neurobiology Institute, National University of Mexico, approved the experimental protocol.

Subjects

Fifty-six subjects ($F = 37$, $M = 19$) between 60 and 84 years of age were studied, and the subjects who met the following criteria were selected: the subjects had to be active, gainfully employed outside the home, should have at least completed elementary school, and have a rating of 2 on the global deterioration scale [67], which means that they are normal elderly subjects with only subjective complaints of memory loss but no objective evidence of memory dysfunction. They have to score more than 80 on the 3rd version of the Wechsler Adult Intelligence Scale (WAIS-III), less than 3 points on the Alcohol Use Disorders Identification Test [68], less than 9 points on the Beck Depression Inventory [69], less than 7 points on the Hamilton Rating Scale for Depression [70], and more than 70% on the Quality of Life Enjoyment and Satisfaction Questionnaire [71]. Psychiatric illnesses were discarded by Mini-Mental State Examination and a psychiatric interview. Individuals who exhibited any of the following conditions were excluded: anemia, hypercholesterolemia, hypothyroidism, uncontrolled insulin-dependent diabetes, or uncontrolled high blood pressure. The subjects did not present with neurological disorders; the audiometric study should be normal or be normalized with the use of hearing aids.

In addition, subjects should have an abnormally high value for the theta AP in at least one lead compared to the normal subjects of the same age. Due to the known intra-individual variability of the EEG, it was necessary to perform two or more EEG recordings to select the lead that reached the most abnormal value in at least two recordings.

The study used the following elimination criteria: head trauma with loss of consciousness, history of alcoholism, absent more than two consecutive days of treatment, and not completing the assessments.

Subjects signed an informed consent form, as stipulated by the Helsinki Declaration (2008) [72].

Fourteen subjects met all criteria. They were pseudorandomly assigned to one of two groups such that, on average, the groups did not differ in age, gender, IQ, per capita income, or the Z value of the theta AP in the lead with the most abnormal value (characteristics of each group are shown in Tables 1 and 2). The experimental group received NFB treatment, and the control group received a sham NFB; both treatments will be described in the section describing the NFB.

Table 1
Characteristics of the samples before treatment.

Variable	Experimental group	Control group
Age*	65.8 ± 2.4	67 ± 4.9
Gender*	$M=2, F=5$	$M=3, F=4$
The most abnormal theta AP Z value*	2.5 ± 0.4	2.8 ± 0.8
Total IQ*	103 ± 7.3	99.2 ± 12.2
Per capita income (Mexican pesos)*	13000 ± 7931	11600 ± 12881

*No significant differences were observed between the two groups.

Table 2
Schooling

Experimental group	Control group
College	College
Secondary	High school
College	Primary
Secondary	Secondary
High school	College
College	Secondary
Primary	Secondary

Cognitive instruments

WAIS and NEUROPSI tests were applied, and an EEG was recorded before and after NBF treatment for comparison and to assess the effects of treatment on cognition and brain electrical activity. The second application of WAIS-III was administered six months or more after the first, in accordance with WISC-R recommendations.

NEUROPSI is a neuropsychological test developed by Ostrosky-Solís et al. [73, 74] and normalized on the Mexican population of 6 to 85 year olds. This test includes two subscales: a) Attention and Executive Function and b) Memory. The Total NEUROPSI Score can also be used as an overall assessment of the three domains. These three scores are the only quantitative data that the test provides (for a complete explanation of each test, see Supplementary Data; available online: http://www.j-alz.com/issues/28/vol28-2.html#supplementarydata05).

Electroencephalographic instruments

EEG recording and edition

Subjects were seated in a comfortable chair in a dimly lit room. The EEG was recorded from 19 leads (10–20 International System) using linked ear lobes as a reference. A1A2 reference was used so that the measurements were taken under the same conditions as the normative data. The amplifier bandwidth was set from 0.5 and 30 Hz. The EEG was sampled every 5 milliseconds using a MEDICID IV System and was edited off-line. An expert electroencephalographer, using visual editing, selected twenty-four artifact-free 2.56-second segments for quantitative analysis.

EEG analysis

Analysis was done off-line. The Fast Fourier Transform and the crosspectral matrices were calculated at a frequency of 0.39 Hz, and the following measurements were obtained from each referential lead: the absolute (AP) and relative (RP) powers in each of four frequency bands, delta (1.5–3.5 Hz), theta (3.6–7.5 Hz), alpha (7.6–12.5 Hz), and beta (12.6–19 Hz). The ranges of these bands were selected based on the normative data [75] provided by MEDICID IV.

Z values were calculated using the equation:

$$Z = (x - \mu)/\sigma$$

where μ and σ are the mean and the standard deviation, respectively, of the normative sample at the subject's age.

More than two EEG recordings were collected from each subject to select the lead where the most abnormal Z value of the theta/alpha ratio was observed. NFB was applied based on the EEG activity in this lead. The leads where the reward for theta suppression was administered to the control group were F4, C3, P4, F7, F7, F7, and T5, and in the experimental group they were F4, C3, C3, P3, F7, F8, and T6.The last EEG recording before treatment was used as the "before" in the statistical analysis.

Neurofeedback or sham treatment

NFB treatment

NFB was conducted using an NFB program adapted to the MEDICID IV recording system and software. The EEG recording was obtained from the lead with the most abnormal theta AP, referred to the linked earlobes.

At the beginning of the treatment, the threshold value was set according to two criteria: a) the threshold should be less than the previous Z theta AP value that was obtained, and b) the subject obtained a reward (1,000 Hz tone) between 60% and 80% of the time. Every three minutes, the percentage that the reward was given was quantified; if the percentage was less than 60%, the threshold value was slightly increased, and if the percentage was greater than 80%, the threshold value was slightly decreased.

Throughout the recording, the Z value of the theta AP over 20 milliseconds was computed every 5 milliseconds and compared with the threshold. If this value was lower than the threshold, the reward was given. Subjects were told that it was important to maintain production of the tone for as long as possible, and consequently the tone acquires a positive meaning.

Each individual received 30 training sessions (30 min each) over a period of ten to twelve weeks. At the beginning of each session, the subject was told that if his/her performance was good, he/she would play an attractive game at the end of the session.

Sham treatment

In the sham treatment, all conditions were exactly the same as in the NFB treatment, except that in this case the tone and its duration were random, i.e., not contingent on the EEG activity.

Statistical analysis

Sample sizes were small and a normal distribution was not guaranteed; thus, parametric analyses were inappropriate. To control for Type I error, it was used a non-parametric permutational ANOVA model with two factors: group (CTL versus EXP) and time (before versus after treatment). Using ANOVA [76], the significant effects were tested using the empiric probability distribution of *max F*; interaction group X time was the unique mean effect for determining if the change produced by NFB was equal or different between groups. To assess multiple comparisons, a non-permutational t-test was performed [77]. For each EEG measurement and frequency band, the global null hypothesis tested the equality of means between the times for each group and between the groups for each time, including all leads. Usually the contrasts of ANOVA are only analyzed in the variables where the interaction effect is significant, however, in this study all changes between before and after treatment in each group were of interest, inclusive when the interaction effect was not significant; therefore, it were evaluated the marginal hypotheses as a contrast of ANOVA for each lead. Analyses of the behavioral data were performed in an analogous manner and considered the scores from the WAIS-III and NEUROPSI separately.

RESULTS

During the NFB session, the reward percentage was rarely observed to be lower than 60% in all subjects of the experimental group. Therefore, suppression of theta activity was the main aspect of reinforcement.

Behavioral and cognitive results

The Verbal Comprehension Index ($p = 0.02$) and Verbal IQ ($p = 0.05$) from WAIS-III and the Total Score on the NEUROPSI test ($p = 0.01$) significantly increased in the experimental group. In both groups, a significant increase ($p = 0.01$ for both) in the Memory

Score of the NEUROPSI battery was observed. In the control group, there was a significant decrease ($p = 0.05$) in the WAIS Performance IQ. These results are shown in Fig. 1 (for details, see Supplementary Table 1 and Supplementary Table 2).

The results from the non-parametric permutational ANOVA model showed that the interaction effect was significant only for the WAIS-III variables: Full Scale IQ (Fmax = 5.0417, Threshold = 0.9552, $p < 0.0001$), Performance IQ (Fmax = 3.9329, Threshold = 0.8969, $p < 0.0001$), Verbal Comprehension Index (Fmax = 3.4093, Threshold = 0.6795, $p < 0.0001$), Working Memory Index (Fmax = 0.6463, Threshold = 0.5870, $p = 0.0420$), and Perceptual Organization Index (Fmax = 3.7878, Threshold = 0.8944, $p < 0.0001$). In the Working Memory Index and the Perceptual Organization Index, no significant changes were observed when before versus after treatment was independently compared in each group. In the Full Scale IQ and Verbal Comprehension Index, the significance of the interaction effects may be explained by the significant increase in the experimental group, while in the control group there were no significant differences. The significant interaction effect in the performance IQ was due to the significant decrease observed in the control group; however, no significant differences were observed in the experimental group. The significant interaction effects observed for the Working Memory Index and Perceptual Organization Index may be explained by the different directions of the changes between the groups, although the changes were not significantly different in any group, and the mean values showed that the change was in a negative direction for both indices in the control group. In the experimental group, the Working Memory Index increased, and the Perceptual Organization Index was similar.

EEG results

In all subjects of the experimental group the most abnormal Z theta AP value selected for NFB decreased, reached normality ($Z < 1.465$) in four out of the seven subjects (Z values before and after treatment for each subject are shown in the Supplementary Table 3). The leads selected for NFB were different for each subject (except C3 that was selected in 2 subjects), and this could be the reason why theta AP at these leads did not show significant differences when before versus after treatment were compared.

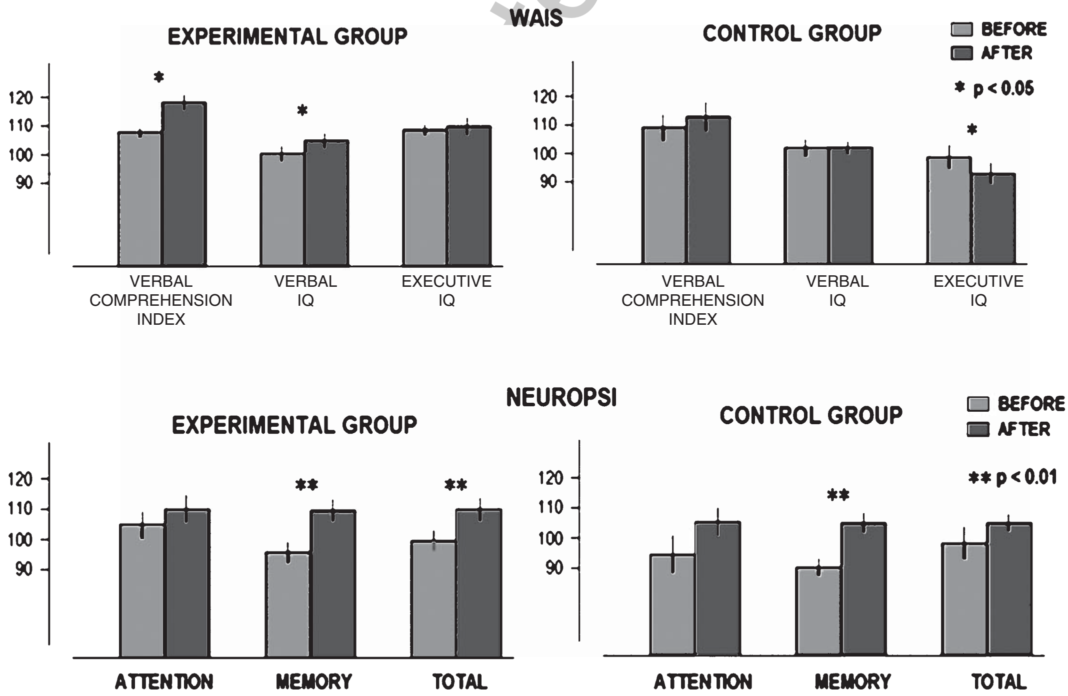

Fig. 1. Significant differences between the before and after results of WAIS-III and NEUROPSI tests. In WAIS-III, the experimental group exhibited improvements in Verbal Comprehension Index and Verbal IQ, whereas the Executive IQ of the control group deteriorated. The NEUROPSI Memory Score increased in both groups, although improvement in the total score was only observed in the experimental group.

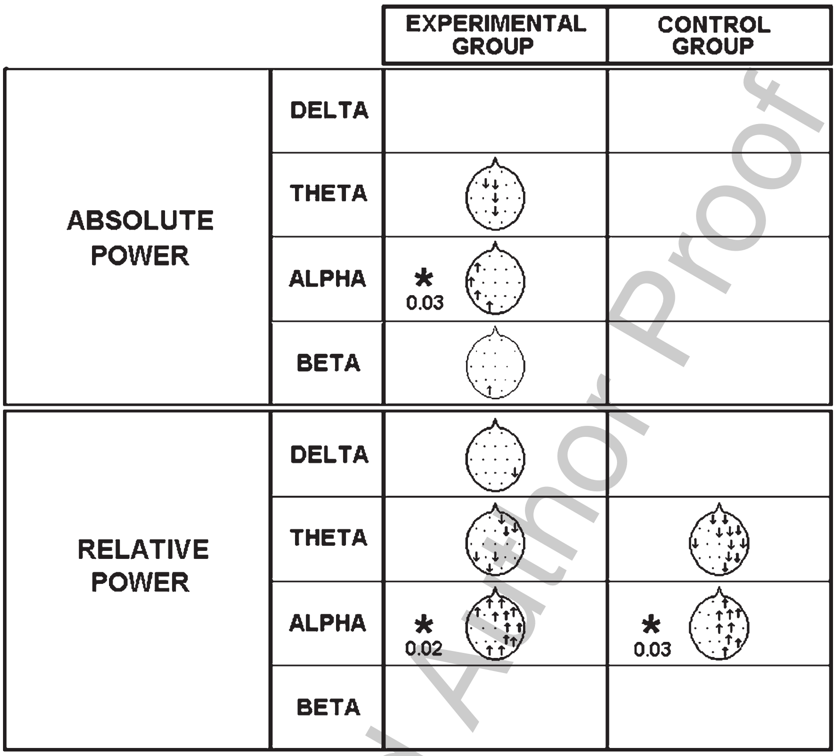

Fig. 2. Significant differences in the absolute and relative powers were observed between the before and after samples. An asterisk (*) indicates a significant deviation from the global hypotheses involving all leads; the probability value appears below the asterisk. In the drawings of the heads, significant differences deviating from the marginal hypotheses (independent leads) are shown; upward arrows indicate that power increased, while downward arrows indicate that power decreased. Absolute power changes before and after NFB were only found in the experimental group.

The results of the AP and RP comparisons between before and after treatment in each group are shown in Fig. 2. The global null hypothesis was rejected only in the alpha band when the value before treatment was compared with the value after treatment. In the experimental group, the alpha AP ($p = 0.03$) and RP ($p = 0.02$) both showed significant increases; the alpha RP also increased significantly ($p = 0.03$) in the control group. The leads implicated by the marginal changes in the experimental group were: P3, O1, F7, and T3 in alpha AP and Fp1, Fp2, F4, C4, P4, O1, O2, F7, F8, T4, T6, and Fz in alpha RP. In the control group, the leads that exhibited increases in the alpha RP were located in the right hemisphere (Fp2, F4, C4, P4, O2, F8, T6) or at the midline (Fz, Cz). The results of the AP and RP comparisons are shown in Fig. 2.

In the EEG theta band, only marginally significant ($p < 0.05$) differences were observed between before and after treatment. In the experimental group, the theta AP decreased significantly in the F3 and midline leads, and the theta RP decreased in the right frontal (Fp2, F4, F8) and left posterior areas (O1, T5, Pz). In the control group, only the theta RP was reduced, and this reduction was observed in many leads (Fp1, Fp2, F4, C4, P4, O2, F8, T3, T4, T6, and Fz).

Also in the experimental group, the beta AP increased in O1, and the delta RP increased in T6. However, it is necessary to keep in mind that these isolated results could be spurious (for details, see Supplementary Figure 1).

The results from the non-parametric permutational ANOVA model showed significant interaction effects in the alpha (Fmax = 11.6340, Threshold = 1.4327, $p < 0.0001$) and beta (Fmax = 7.0512, Threshold = 3.3920, $p = 0.0020$) bands for the AP measurements, and the results for the RP measurements only exhibited a significant interaction effect in the beta band (Fmax = 5.1265, Threshold = 2.8474, $p = 0.0087$). The interaction effects of the alpha AP may be explained by the fact that there was a significant increase after NFB treatment in the experimental group and no significant changes were observed in the control group.

The significant effect observed for the beta AP and RP may be explained by the different patterns of change in the groups. Although no significant differences were observed between the before versus after treatments in any group, the mean values indicate that the beta AP in the control group showed an increase in all leads, while in the experimental group the beta AP decreased in the frontal leads, showed no difference in the central lead, and increased in the remaining leads. In relation to the beta RP, the control group increased in all of the leads that were observed, and the experimental group increased in the fronto-central and midline leads and decreased in the temporo-occipito-parietal areas.

DISCUSSION

Many investigations have focused on the cognitive and electroencephalographic characteristics of the elderly. Two conclusions have been drawn from these studies. First, as people age normally, the EEG slows, and cognitive processes decline. Second, when the degree of cognitive impairment is more severe, the EEG frequently shows deviations from the normative data. Other research has shown that these two characteristics are related. Furthermore, some studies have shown that EEG activity can predict the development of MCI or dementia. The main predictor is an excess of theta activity during relaxed wakefulness, which could be considered to be an electroencephalographic indicator of risk for cognitive disorder.

In the present study, the effectiveness of an NFB treatment that reinforces theta reduction is assessed in elderly participants with abnormally high theta AP values. Results support the hypotheses that were established for the experimental group in this investigation as positive changes were observed both in behavior/cognition and in the EEG. However, the predictions regarding the control group were not fulfilled.

The experimental group showed improved verbal processing, reflected in an increase in the Verbal Comprehension Index and Verbal IQ. This improvement was not observed in the control group, suggesting that the development of verbal skills is related to the NFB treatment. The experimental group also exhibited improvements in total score (including attention, executive functions, and memory) and the memory score of the NEUROPSI battery. However, improvement in the latter subtest was also observed in the control group. It can be concluded that the development of attention and executive functions is probably related to the NFB treatment, but contrary to the hypotheses, the improvement in memory processes observed in both groups treated with the sham NFB may be a placebo effect.

The authors have no explanation for the decline in the WAIS Performance IQ observed in the Control Group; Botwinick [78] suggests that executive functions suffer deterioration with aging, but it is noteworthy that this group exhibited a decline in such a short time (approximately 7 months).

When changes in all EEGs were analyzed, reduced theta AP and increased alpha AP were only observed in the experimental group. Changes observed in the RP are influenced by changes at all frequencies, while the changes observed in the AP are more precise in the bands to which they refer. The mechanism described by Hughes et al. [66], showing that alpha or theta production depends on the depolarization of the same thalamic neurons, can explain why alpha increases when only theta is under treatment.

Although the reward was given selecting the EEG change in the lead with the most abnormal Z value of theta AP that was found in the EEG recordings previous to the NFB treatment, and these leads varied according to the subject, the results of the EEG changes after the treatment in the experimental group did not coincide with those that were rewarded. The topography of the significant changes observed in the theta AP was in F3 and Fz, Cz and Pz. In no case the site selected for the reward was in these midline leads.

Also, both groups exhibited reduced theta RP and increased alpha RP. Likewise, the reduction in the Z value of theta AP in the lead selected for the treatment was observed in both groups but was more significant, on average, in the group that received NFB treatment. Therefore, it is possible that in addition to the changes attributable to NFB, there were changes due to other causes. There are not many reports on the placebo effect and the EEG; however, some changes in EEG after placebo administration have been described [79]. It is important to remember that cognitive changes must also involve changes in the neural networks and that the EEG is not a byproduct of neural activity but is the activity that underlies mental processes [80] as it represents a feedback mechanism that modulates and guides neuronal circuit activity [81]. Subjects in both groups introduced many changes into their lives; for example, all increased their level of social activity, talking with a therapist and other subjects while waiting for the NFB session; all talked about events, recalling his/her own story; and some of them drove a car over the considerable distance between the city in which they all lived and the Institute. These uncontrolled variables, present in both groups, could be responsible for cognitive and electroencephalographic changes not attributable to NFB treatment.

In the experimental group, the reduction in theta AP was significant in the midline and left frontal leads. This reduction could have induced the improvement in attention that was reflected in the total score of the NEUROPSI test. It has been reported that the midline theta was generated in the cingulate cortex [82, 83] and this structure was activated during attention tasks [84]. Therefore, a tendency to normalize the midline theta activity in aging subjects may explain this behavioral result. This group also showed an increase in alpha AP, primarily in the left hemisphere; this change was probably related to the improvement in verbal processes that was measured by the Verbal IQ and Verbal Comprehension Index from WAIS.

The NEUROPSI Total Score, which improved in this group, also evaluates executive functions. The improvement may be correlated with the observed electroencephalographic improvement in the frontal lobes, predominantly in the left hemisphere (theta AP reduction at F3 and Fz and alpha AP increase at F7). Executive or directive capacities of human behavior, i.e., the ability to have a specific goal and to be able to organize the means to achieve it, have been attributed to the frontal lobes [85]. Gómez- Beldarrain [86] has observed a relationship between the cognitive aspects of executive function and the dorsolateral frontal region. It is important to note, however, the commitment of the entire prefrontal cortex to executive functions [85].

The NFB has proven to be useful in treating many neurological and psychiatric diseases. To the authors' knowledge, only one investigation that applies NFB to the elderly with the aim of improving cognitive activity has been carried out. Angelakis et al. [87] reinforced increases in the alpha peak, which correlates positively with cognitive performance. Their results suggest that this NFB protocol improves cognitive processing speed and executive function but has no clear effect on memory. Similar results were seen in this study of a protocol NFB reinforcing theta reduction. As shown by Hughes et al. [66], alpha and theta originate in the same thalamic cells; therefore, decreasing theta will augment alpha, and vice versa. Those results, the results of Angelakis et al. [87], and the results in this paper may advocate similar processes. However, the present manuscript is a pioneering work because, to our knowledge, there are no precedents exploring NFB treatment based on the electroencephalographic alterations of a population without any neurological or psychiatric disease and subsequent comparison with results from a control sham group.

One caveat of the present work was the way in which NFB was administered because the maintenance of a constant reward percentage range did not ensure a consistent suppression of the theta AP. However, as mentioned above, values lower than 60% were rarely observed; therefore, most of the time theta suppression was reinforced. An important feature of the present procedure was that the reinforcement was not contingent upon every response (reduction of Theta AP); rather, reinforcement was administered intermittently (only between 60% and 80% of the time). It is well established that intermittent reinforcement produces greater resistance to extinction than does continuous reinforcement [88], and this may have been an important factor in maintaining the positive behavioral and cognitive changes associated with NFB. However, further research is needed to validate this proposition.

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