Longitudinal analysis of qEEG in subjects with autosomal dominant Alzheimer's disease due to PSEN1-E280A variant.

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ABSTRACT

Introduction: Alzheimer's disease (AD) is the leading cause of dementia in the world. Synaptic dysfunction is a pathophysiological event that alters neuronal connections at multiple scales: molecular, cellular, brain networks, cerebral cortex, among others. There are different mechanisms that interact to trigger alterations in the homeostasis of synaptic function, among them the most prominent are amyloidosis, tauopathy and inflammation. EEG has been used in recent years as a cost-effective, portable, and noninvasive alternative for the study of biomarkers in Alzheimer's disease.

Methodology: All participants were members of families with PSEN1-E280A genetic variant and healthy controls recruited voluntarily. A longitudinal follow-up was planned, this study collects data from the initial visit and in the first year of follow-up. At each visit, neurological and neuropsychological evaluation and electroencephalogram were performed. We analyzed the resting state EEG spectral power bands and the Alpha/Theta reactivity index.

Results: Alpha1 and Alpha2 frequency bands did not have significant changes in the follow-up year, in the Beta3 frequency band in component 20 and Beta2 in component 22 statistically significant differences were found. However, the distribution of the data in the shift graphs for the Beta frequency band presents some slopes, which indicates a modest effect sizes and low precision.

Conclusion: The Beta frequency band is a potential neurophysiological marker that in preclinical stages of ADAD show statistically significant differences between asymptomatic carriers and non-carriers. This signal is related to components whose origin is estimated in posterior regions, which highlights the importance of previous findings in the precuneus. However, the effect sizes were modest and with low precision. It would recommend larger samples and longer following in future research.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia in the world, it is characterized by the abnormal accumulation of beta-amyloid (Aβ) protein and hyperphosphorylated tau protein (1). About 5-10% of cases with early-onset Alzheimer's disease (EOAD) are of familial origin (FAD) by autosomal dominant inheritance; pathology explained by pathogenic genetic variants of complete penetrance in the amyloid precursor protein (APP) genes (<1%), presenilin 1 (PSEN1) gene (6%) and presenilin 2 (PSEN2) gene (1%). Pathological genetic variants in PSEN1 are the most common cause of FAD (2). The Neurosciences Group of Antioquia has characterized for 30 years an extended family with the genetic variant PSEN1-E280A, with a penetrance of almost 100%, with an amnestic presentation and age of onset of MCI at 44 years and dementia at 49 years. Synaptic dysfunction is a pathophysiological event that alters neuronal connections at multiple scales: molecular, cellular, brain networks, cerebral cortex, among others (1). It is possible that the cognitive alterations in the early stages of the disease are a product of the loss of synapses rather than the loss of neurons. There are different mechanisms that interact to trigger alterations in the homeostasis of synaptic function, among them the most prominent are amyloidosis, tauopathy and inflammation (3). Different biomarkers have been reported in this population in amyloid PET, Tau PET, CSF, and cognitive markers that have allowed to know the different stages of the pathophysiological process in preclinical stages, however, they do not allow to trace phenomena as early as the presence of Aβ oligomers and the process of synaptic dysfunction. EEG has been used in recent years as a cost-effective, portable, and noninvasive alternative for the study of biomarkers in Alzheimer's disease(4,5). EEG has been most widely used in late sporadic AD population at different clinical stages of the disease (6). In the current study we want to perform a longitudinal analysis with resting EEG in asymptomatic population carriers and non-carriers of the PSEN1-E280A genetic variant; also, we want to evaluate some neurophysiological markers proposed in previous EEG studies such as Alpha/Theta reactivity in this population (7).

METHODOLOGY

Subjects

All participants were members of families with PSEN1-E280A genetic variant and healthy controls recruited voluntarily. Asymptomatic subjects between the ages of 20 and 45 years were included: 32 carrier (G1) and 37 non-carrier subjects (G2). Nineteen subjects with MCI and 8 with dementia carriers of this genetic variant were included (SIN), all of them older than 40 years. Finally, 30 community controls recruited voluntarily were included (CTR). Subjects with psychiatric, neurological, or systemic disorders that could affect EEG or cognitive test performance, history of TBI, stroke, use of anticonvulsant drugs or abuse of psychoactive substances were excluded. Participants and evaluators were blinded to genetic status. Groups were matched for age, sex, and schooling as best as possible; however, given the particularities of the population, exact matching is not possible. Participants were evaluated by medical and neuropsychological experts. The inclusion criteria were to perform genotyping for the PSEN1-E280A variant, verify cognitive status according to the protocol of the Neurosciences Group of Antioquia. All subjects signed an informed consent approved by the Ethics Committee Board of the Faculty of Medicine - University of Antioquia.

A longitudinal follow-up was planned with biannual visits for a period of 2 years; this study collects data from the initial visit and in the first year of follow-up. At each visit, neurological and neuropsychological evaluation and electroencephalogram were performed.

At the baseline visit 126 subjects were recruited, for the follow-up visit in the first year there was a loss to follow-up of 11.1%, registering 112 subjects at this visit with the following distribution: 30 asymptomatic carriers (G1), 33 asymptomatic non-carriers (G2), 18 with MCI and 8 with dementia due to AD carrying the PSEN1-E280A variant (SIN), 23 community controls matched for sex and schooling (CTR). Longitudinal analyses were performed with this sample because the participants had neurophysiological recordings at the initial visit and at one-year follow-up. (See table 1).

EEG acquisition

EEG signals were acquired in the resting state for 5 minutes with eyes closed (EC) and with eyes open (EO). EEG data were recorded with a Neuroscan amplifier (Neuroscan Medical System, Neurosoft Inc. Sterling, VA, USA) and a 58 tin-channel cap with electrodes placed according to the international 10-10 system. Signals were recorded at a sampling rate of 1000 Hz, in addition the data were filtered in-line with a band pass filter (0.05 to 200 Hz), and a band reject filter (60 Hz) to remove power supply noise. The reference electrode was located on the right earlobe, and an electrode located at Fz was used as ground. Channel impedance calibration was performed, where the contact impedances of the EEG electrodes were kept below 1 KΩ. The recordings were performed in a Faraday cage, a cabinet isolated from audio and external electromagnetic signals.

EEG data pre-processing and normalization

The EEG data preprocessing was based on the pipeline proposed by Suarez et al (8) and the protocol of the Neuropsychology and Behavior research group (GRUNECO). The processing flow applied to the signals was implemented using Python programming language.

Initially, signal detrending and robust average referencing were performed, where bad channels are excluded and interpolated after referencing, based on the standardized early-stage EEG processing (PREP) pipeline(9). Then, a high-pass FIR filter at 1 Hz with Hamming window, order 3300 and transition bandwidth of 1 Hz was applied, subsequently applied and FastICA algorithm from Scikit-learn library to identify artifactual and neural components (10). Next, epoch segmentation was performed, taking 5-second epochs; to smooth eye blink artifacts, wICA (11) was applied. Afterwards, a low-pass FIR filter of 50 Hz with Hamming window, order of 264 and transition bandwidth of 12.5 Hz was applied, and the remaining noisy epochs were detected and removed, according to the criteria: abnormal linear trends, extreme signal amplitudes, statistically atypical activity, extreme kurtosis values, power spectrum anomaly (12).

Finally, signal normalization was performed according to the methodology proposed by Nima et al. (13), which calculates the record-specific constant by applying a 20 Hz low-pass filter to the recordings and then finding the Huber mean of these, normalization is performed by dividing the data for each channel by the constant found. This approach was considered mainly to reduce channel dispersion, because in EEG there is usually variability in the channels induced by artifacts in the signals (13). The above preprocessing and normalization flow is shown in Figure 1.

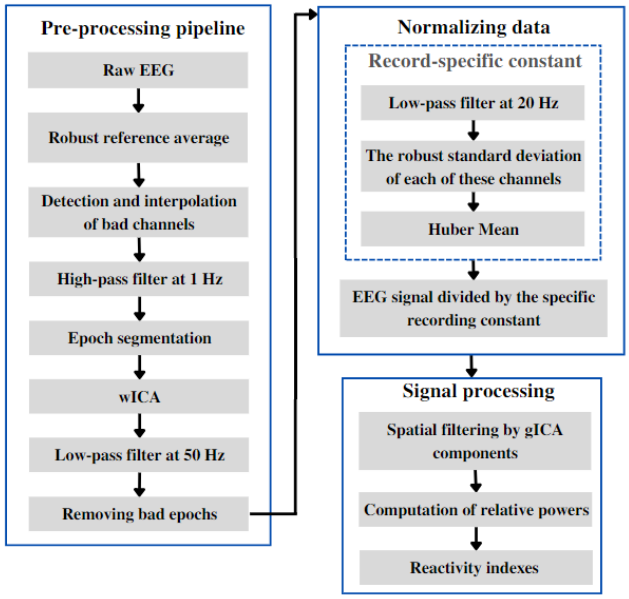


Figure 1. Processing pipeline.

EEG data processing

After normalization of all the signals, the neural independent components (IC) were extracted and calculated using a 58x25 spatial filter based on the study performed by Garcia et al (11). In that study, the group independent component analysis (gICA) was performed, and a classification was made using ICLabel, to find the neural independent components, 8 of the 25 components calculated were selected as neural, and these were the ones that were selected in the present study to be analyzed. Figure 2 shows the topographic head maps corresponding to the neural activity of the selected components.

This approach was taken into account because gICA allows the sources obtained by the decomposition to be comparable between subjects, due to the fact that concatenation of data from different subjects is used for the decomposition, which implies a common mixture matrix and, subsequently, common comparable sources (14).

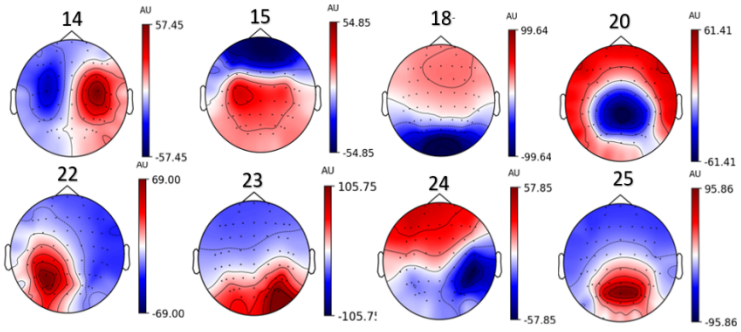


Figure 2. A) Scalp maps projections of the gICA components selected as neural.

The power spectral density was calculated for each neuronal component of the EEG signals, from which the relative power densities were calculated by taking the ratio of the absolute amplitude/power density in a given frequency band to the mean of the amplitude/power density in all frequency bands of the components' spectrum (15). The mean of the following frequency bands was taken: delta (1.5-6 Hz), theta (6-8.5 Hz), alpha 1 (8.5-10.5 Hz), alpha 2 (10.5-12.5 Hz), beta 1 (12.5-18.5 Hz), beta 2 (18.5-21 Hz), beta 3 (21 -30 Hz) and gamma (30-45 Hz) (15).

Having the relative power densities, it was possible to evaluate the alpha theta reactivity in each of the neural components, two formulas were evaluated in this study, where the way to calculate the alpha and theta reactivity indices varies, taking into account the eyes open (EO) and eyes closed (EC) resting state (7). Formula 1 was based on equation 1, with alpha and theta indices according to equations 2 and 3, respectively. Formula 2 was based on equation 1, with alpha and theta indices taken from equations 4 and 5, respectively. For each formula evaluated, 3 results were obtained: alpha 1/theta, alpha 2/theta, and alpha/theta, where alpha corresponded to the average between alpha 1 and 2.

$$I.R\ \alpha/\Theta = \frac{I.R.\alpha}{I.R.\Theta} \quad (1)$$

$$I.R.\alpha = \frac{Power\ \alpha\ (EC - EO)}{Power\ \alpha\ (EC)} \quad (2)$$

$$I.R.\Theta = \frac{Power\ \Theta\ (EC - EO)}{Power\ \Theta\ (EC)} \quad (3)$$

$$I.R.\alpha = \frac{Power\ \alpha\ (EO)}{Power\ \alpha\ (EC)} \quad (4)$$

$$I.R.\Theta = \frac{Power\ \Theta\ (EO)}{Power\ \Theta\ (EC)} \quad (5)$$

Data analysis

Power measurements were evaluated by components and by wave, divided into alpha-1, alpha-2, beta-1, beta-2, beta-3, theta, gamma, delta. The following clinical and sociodemographic variables were included: age, sex, schooling, neuropsychological variables detailed in Table 1. Each participant was included in one of 5 groups according to their initial status, as follows: healthy carriers (G1), healthy non-carriers (G2), MCI and dementia (SIN), healthy controls (CTR).

For the descriptive analysis, qualitative data were presented in tables with absolute and relative frequency measures; and for quantitative data, measures of central tendency and dispersion, mean and standard deviation, or median and range were used, depending on whether the variable has a normal or nonparametric distribution. For the longitudinal analysis, the records of the initial visit and the one-year follow-up visit were taken. Statistical comparison between power by waves and by components was performed using the Kruskal-Wallis test for comparison of multiple variables and the Mann-Whitney test for comparison between pairs of unpaired variables with nonparametric distribution. To compare between quantitative data, the chi-square test or Fisher's test was used when the expected cases in one of the variable values was less than 5. Also, the Mann-Whitney-Wilcoxon test for paired data was used for power comparisons between the two visits.

All these statistical comparisons were run with an alpha of 0.05 in RStudio software (R version 4.1.1).

Alpha theta reactivity indices were analyzed graphically and by means of a statistical test, where the following groups were compared: G1-G2, G1-SIN, CTR-SIN, CTR-G2.

According to G. A. Rousselet (16), to make the most of neuroscience datasets and compare groups, it is important to use graphical methods that allow a more complete visualization of the data for analysis and to better describe how the distributions differ, as well as to implement robust estimators to construct confidence intervals. For this reason, the shift function was implemented to understand and quantify how two distributions differ, and it is both a graphical and an inferential method. Specifically, the shift function describes how one distribution should be rescaled to match another (16). The following were evaluated from these graphs when comparing two groups: differences in deciles, difference in central tendency, slope of the graph, and 95% Brootstrap confidence Interval.

Likewise, the Mann-Whitney U statistical test was performed, a nonparametric test, in which the null hypothesis states that the underlying distribution sample x is the same as the underlying distribution sample y (17), with the aim of finding statistically significant differences between the groups evaluated in a non-graphical way. This test was performed using Python's pingouin library and the significance level considered was 0.05.

RESULTS

- **Sociodemographic and cognitive data**

Table 1 shows sociodemographic and cognitive characteristics of the groups among initial visit (V0) and the first-year follow-up visit (V2). Mean age at V0 was 30.4 years (SD 5.57) in asymptomatic carriers, 31.3 years (SD 6.12) in non-carriers, 46.9 (SD 5.81) in MCI group, 48.9 years (SD 5.44) in the dementia group and 50.1 years (SD 7.72) in controls. Regarding sex, most of the individuals were female except in the MCI (50% male and 50% female) and dementia groups (37.5% female and 62.5% male). Mean years of education in the asymptomatic carriers group was 10.9 years, 13.3 years in non-carriers, 7.33 years in the MCI group, 8.75 years in the dementia group and 8.61 years in healthy controls.

About to cognition, no statistical significance was found in any of the groups between V0 and V2 in MMSE and MoCA scores. Median FAST score was 1.00 (min 1.00, max 2.00) in asymptomatic carriers, non-carriers, and controls, in both V0 and V2. In contrast, the MCI group had a median FAST score of 3.00 (min 3.00, max 5.00) at V0 and 4.00 (min 3.00, max 6.00) at V2; the group of individuals with dementia showed a median score of 4.00 (min 4.00, max 5.00) at V0 and 4.50 (min 4.00, max 9.00) at V2. As with MMSE and MoCA scores, no statistical differences are reported in the FAST scale nor in the rest of the cognitive items.

- **Power spectral density – Transversal Analysis**

We had previously reported findings in spectral power in subjects of the same population with statistically significant differences in Beta and Theta bands, especially in electrodes located in parietal regions to discriminate asymptomatic carriers from non-carriers (11). In this analysis of cross-sectional data from the initial visit (V0), we can evidence findings consistent with the literature regarding the decrease in high frequency bands such as Alpha and Beta and increase in low frequency bands such as delta and theta in subjects with MCI and dementia compared to controls (data no shown). Regarding discrimination between asymptomatic carriers and noncarriers, we observed that the C14 component is the component with a tendency to discriminate in the Alpha1, Alpha2 and Beta3 frequency bands. In the remaining components (C18, C20, C22) highlights the Beta3 frequency band tends to discriminate asymptomatic carriers from noncarriers. However, the slopes the slopes have a poor degree of steepness, and the confidence intervals are wide, in some cases crossing 0, indicating that there are no differences between the two comparison groups. (See figure 3).

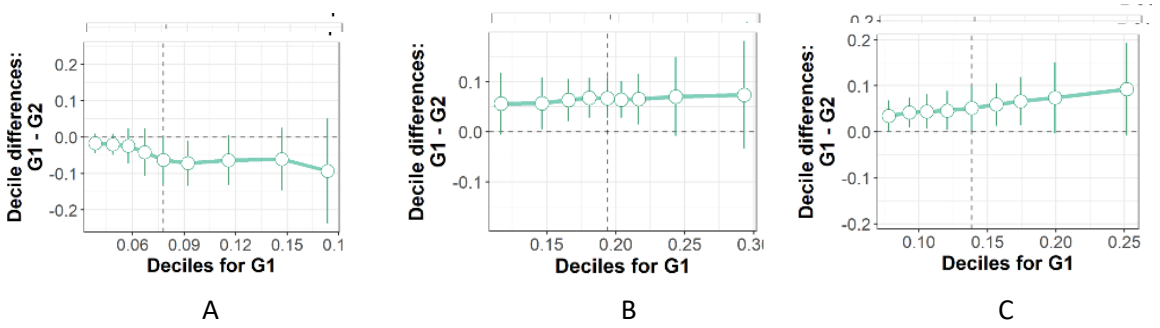


Figure 3. Plots obtained with the shift function, compare groups G1 vs G2: a) C14 component with Alpha2, b) C14 component with Beta3, c) C18 component with Beta3.

Table 1: Sociodemographic and cognitive data.

	Asymptomatic Carriers			Non-Carriers			MCI (Symptomatic carriers)			Dementia (Symptomatic carriers)			Community Control		
	V0	V2		V0	V2		V0	V2		V0	V2		V0	V2	
	(N=30)	(N=30)	p-value	(N=33)	(N=33)	p-value	(N=18)	(N=18)	p-value	(N=8)	(N=8)	p-value	(N=23)	(N=23)	p-value
Age															
Mean (SD)	30.4 (5.57)	31.5 (5.51)	0,515	31.3 (6.12)	32.4 (6.16)	0,489	46.9 (5.81)	48.0 (5.82)	0,794	48.9 (5.44)	50.0 (5.26)	0,752	50.1 (7.72)	51.2 (7.69)	0,272
Median [Min, Max]	29.5 [22.0, 43.0]	31.0 [23.0, 44.0]		30.0 [20.0, 45.0]	31.0 [21.0, 46.0]		46.5 [38.0, 63.0]	47.5 [39.0, 64.0]		49.0 [42.0, 56.0]	50.0 [44.0, 57.0]		49.0 [38.0, 63.0]	50.0 [39.0, 64.0]	
Sex															
Femenino	18 (60.0%)	18 (60.0%)	1,000	21 (63.6%)	21 (63.6%)	1,000	9 (50.0%)	9 (50.0%)	1,000	3 (37.5%)	3 (37.5%)	1,000	12 (52.2%)	12 (52.2%)	1,000
Masculino	12 (40.0%)	12 (40.0%)		12 (36.4%)	12 (36.4%)		9 (50.0%)	9 (50.0%)		5 (62.5%)	5 (62.5%)		11 (47.8%)	11 (47.8%)	
Education															
Mean (SD)	10.9 (3.14)	10.9 (3.14)	0,834	13.3 (2.63)	13.3 (2.63)	0,973	7.33 (5.44)	7.33 (5.44)	0,962	8.75 (3.92)	8.75 (3.92)	1,000	8.61 (4.30)	8.61 (4.30)	0,962
Median [Min, Max]	11.0 [5.00, 18.0]	11.0 [5.00, 18.0]		13.0 [5.00, 17.0]	13.0 [5.00, 17.0]		5.50 [1.00, 18.0]	5.50 [1.00, 18.0]		11.0 [3.00, 13.0]	11.0 [3.00, 13.0]		9.00 [2.00, 16.0]	9.00 [2.00, 16.0]	
MMSE															
Mean (SD)	29.4 (0.932)	29.4 (0.850)	0,772	29.7 (0.816)	29.6 (0.708)	0,540	25.2 (3.79)	23.6 (4.68)	0,200	21.3 (5.82)	15.5 (7.58)	0,233	28.9 (1.20)	28.3 (1.64)	0,201
Median [Min, Max]	30.0 [27.0, 30.0]	30.0 [27.0, 30.0]		30.0 [27.0, 30.0]	30.0 [28.0, 30.0]		25.5 [13.0, 29.0]	24.5 [9.00, 29.0]		23.5 [10.0, 27.0]	19.5 [3.00, 21.0]		29.0 [26.0, 30.0]	29.0 [25.0, 30.0]	
Verbal Fluency															
Mean (SD)	21.7 (3.97)	21.8 (4.01)	0,725	23.0 (3.96)	23.9 (5.13)	0,421	15.5 (4.08)	13.8 (4.95)	0,354	11.8 (4.77)	9.57 (5.50)	0,469	17.0 (3.87)	18.0 (3.24)	0,349
Median [Min, Max]	21.5 [14.0, 29.0]	22.5 [13.0, 28.0]		23.0 [17.0, 32.0]	24.0 [14.0, 32.0]		15.5 [8.00, 22.0]	13.0 [4.00, 22.0]		12.5 [4.00, 19.0]	10.0 [3.00, 20.0]		17.0 [12.0, 26.0]	18.0 [13.0, 24.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (12.5%)		0 (0%)	0 (0%)	
Boston test															
Mean (SD)	12.3 (3.06)	13.3 (1.17)	0,384	13.7 (1.02)	13.8 (0.795)	0,460	12.3 (1.84)	11.4 (2.28)	0,294	11.6 (2.50)	10.6 (3.36)	0,586	12.3 (1.64)	12.6 (2.02)	0,741
Median [Min, Max]	13.0 [0, 15.0]	13.5 [10.0, 15.0]		14.0 [11.0, 15.0]	14.0 [12.0, 15.0]		12.0 [9.00, 15.0]	12.0 [7.00, 15.0]		12.0 [7.00, 14.0]	11.0 [5.00, 14.0]		13.0 [9.00, 15.0]	12.0 [9.00, 15.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (12.5%)		0 (0%)	0 (0%)	
word memory list recall															
Mean (SD)	21.0 (2.86)	21.7 (3.28)	0,466	23.0 (2.55)	23.0 (2.51)	0,905	10.4 (4.27)	9.67 (3.73)	0,736	7.63 (3.89)	6.50 (5.13)	0,624	17.9 (3.18)	19.3 (2.77)	0,130
Median [Min, Max]	21.0 [14.0, 26.0]	21.5 [16.0, 27.0]		23.0 [17.0, 28.0]	23.0 [18.0, 28.0]		10.5 [3.00, 18.0]	10.0 [1.00, 17.0]		7.50 [2.00, 14.0]	6.50 [0, 16.0]		18.0 [11.0, 24.0]	19.0 [14.0, 24.0]	
Intrusions word memory list															
Mean (SD)	0.667 (0.994)	0.600 (1.19)	0,665	0.758 (0.969)	0.818 (1.10)	0,778	6.11 (3.14)	4.83 (3.29)	0,076	4.88 (5.03)	5.67 (4.23)	0,674	1.52 (1.59)	2.43 (2.54)	0,136
Median [Min, Max]	0 [0, 4.00]	0 [0, 6.00]		0 [0, 3.00]	0 [0, 4.00]		6.00 [1.00, 14.0]	4.00 [0, 13.0]		4.50 [0, 15.0]	5.50 [0, 13.0]		1.00 [0, 5.00]	2.00 [0, 9.00]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	2 (25.0%)		0 (0%)	0 (0%)	
Total recognition word memory list															
Mean (SD)	9.80 (0.484)	9.80 (0.484)	1,000	10.0 (0)	9.91 (0.292)	0,149	6.33 (2.33)	5.89 (2.52)	0,739	3.75 (3.11)	2.88 (2.47)	0,445	9.52 (0.790)	9.78 (0.518)	0,212
Median [Min, Max]	10.0 [8.00, 10.0]	10.0 [8.00, 10.0]		10.0 [10.0, 10.0]	10.0 [9.00, 10.0]		7.00 [1.00, 10.0]	6.50 [0, 10.0]		4.00 [0, 9.00]	4.00 [0, 6.00]		10.0 [7.00, 10.0]	10.0 [8.00, 10.0]	
constructional praxis recall															
Mean (SD)	9.03 (1.79)	9.33 (1.95)	0,368	9.67 (1.81)	9.91 (1.16)	0,902	1.89 (2.14)	2.11 (2.27)	0,696	0.750 (1.04)	1.43 (1.13)	0,236	7.52 (3.26)	8.00 (2.50)	0,422
Median [Min, Max]	9.50 [4.00, 11.0]	10.0 [4.00, 11.0]		10.0 [4.00, 11.0]	10.0 [7.00, 11.0]		1.00 [0, 7.00]	2.00 [0, 8.00]		0 [0, 2.00]	2.00 [0, 3.00]		7.00 [1.00, 11.0]	8.00 [2.00, 11.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (12.5%)		0 (0%)	0 (0%)	
MCT free recall															
Mean (SD)	22.8 (5.44)	21.0 (5.39)	0,093	24.1 (3.54)	24.6 (3.98)	0,630	5.12 (4.86)	4.87 (5.67)	0,753	2.80 (2.77)	1.33 (1.37)	0,461	18.5 (4.79)	19.5 (5.11)	0,425
Median [Min, Max]	22.5 [8.00, 32.0]	21.5 [7.00, 30.0]		23.0 [15.0, 30.0]	25.0 [15.0, 30.0]		5.00 [0, 18.0]	4.00 [0, 24.0]		2.00 [0, 7.00]	1.00 [0, 3.00]		19.0 [5.00, 27.0]	19.0 [7.00, 28.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (5.6%)	3 (16.7%)		3 (37.5%)	2 (25.0%)		0 (0%)	0 (0%)	

Familiar complaints															
Mean (SD)	4.17 (5.27)	3.40 (4.17)	0,557	4.15 (5.75)	1.73 (2.90)	0,069	15.9 (10.8)	23.0 (12.4)	0,084	25.8 (13.2)	23.9 (14.9)	0,461	4.64 (6.08)	6.52 (6.01)	0,176
Median [Min, Max]	1.50 [0, 19.0]	2.00 [0, 15.0]		1.00 [0, 21.0]	0 [0, 10.0]		15.5 [0, 36.0]	25.5 [0, 38.0]		28.5 [0, 45.0]	22.5 [0, 45.0]		0.500 [0, 19.0]	6.00 [0, 22.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (4.3%)	0 (0%)	
Personal complaints															
Mean (SD)	10.6 (6.39)	10.9 (7.04)	0,990	8.58 (5.55)	7.73 (5.57)	0,536	18.9 (7.77)	20.1 (12.1)	0,813	12.6 (12.9)	16.8 (15.5)	0,933	10.8 (5.83)	12.3 (7.19)	0,807
Median [Min, Max]	9.50 [2.00, 28.0]	9.50 [1.00, 32.0]		8.00 [1.00, 21.0]	6.00 [1.00, 20.0]		17.0 [8.00, 34.0]	18.5 [0, 39.0]		11.0 [0, 39.0]	12.0 [0, 41.0]		10.0 [1.00, 22.0]	12.0 [2.00, 28.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (4.3%)	0 (0%)	
INECO															
Mean (SD)	19.9 (3.06)	20.6 (3.24)	0,412	20.7 (3.27)	21.5 (2.73)	0,268	14.0 (3.24)	12.7 (4.83)	0,398	10.7 (4.23)	7.25 (2.82)	0,416	18.5 (3.74)	18.4 (3.44)	1,000
Median [Min, Max]	20.0 [14.0, 28.5]	21.3 [14.0, 26.0]		21.0 [12.5, 26.0]	22.0 [15.0, 26.0]		13.0 [9.00, 20.0]	11.0 [5.00, 21.0]		12.5 [4.00, 15.0]	7.50 [4.00, 10.5]		18.5 [9.50, 26.0]	18.0 [13.5, 23.5]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		2 (11.1%)	3 (16.7%)		2 (25.0%)	2 (25.0%)		0 (0%)	0 (0%)	
FAST															
Mean (SD)	1.13 (0.346)	1.13 (0.346)	1,000	1.06 (0.242)	1.03 (0.174)	0,773	3.39 (0.608)	3.94 (0.998)	0,066	4.13 (0.354)	5.25 (1.83)	0,098	1.09 (0.288)	1.26 (0.449)	0,129
Median [Min, Max]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]		1.00 [1.00, 2.00]	1.00 [1.00, 2.00]		3.00 [3.00, 5.00]	4.00 [3.00, 6.00]		4.00 [4.00, 5.00]	4.50 [4.00, 9.00]		1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	
MoCA															
Mean (SD)	24.2 (2.58)	24.6 (3.09)	0,657	25.9 (2.55)	25.5 (2.50)	0,708	14.4 (4.50)	14.1 (4.02)	0,392	11.5 (5.32)	9.50 (4.09)	0,625	20.6 (4.53)	21.6 (3.96)	0,393
Median [Min, Max]	24.5 [19.0, 28.0]	25.0 [18.0, 30.0]		26.0 [20.0, 29.0]	25.0 [20.0, 30.0]		15.0 [5.00, 20.0]	14.0 [6.00, 19.0]		12.5 [3.00, 18.0]	9.50 [5.00, 15.0]		19.0 [11.0, 29.0]	21.0 [13.0, 29.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (5.6%)	3 (16.7%)		2 (25.0%)	2 (25.0%)		0 (0%)	0 (0%)	
MoCA: adjusted for schooling															
Mean (SD)	24.6 (2.49)	24.5 (5.32)	0,485	25.9 (2.55)	25.8 (2.37)	0,922	15.1 (4.41)	14.9 (3.84)	0,468	12.3 (5.09)	10.3 (3.83)	0,625	21.4 (4.35)	22.3 (3.80)	0,374
Median [Min, Max]	25.0 [19.0, 28.0]	25.0 [1.00, 30.0]		27.0 [20.0, 29.0]	26.0 [20.0, 30.0]		16.0 [6.00, 21.0]	15.0 [7.00, 20.0]		13.5 [4.00, 18.0]	10.5 [6.00, 15.0]		20.0 [12.0, 30.0]	22.0 [14.0, 30.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (5.6%)	3 (16.7%)		2 (25.0%)	2 (25.0%)		0 (0%)	0 (0%)	

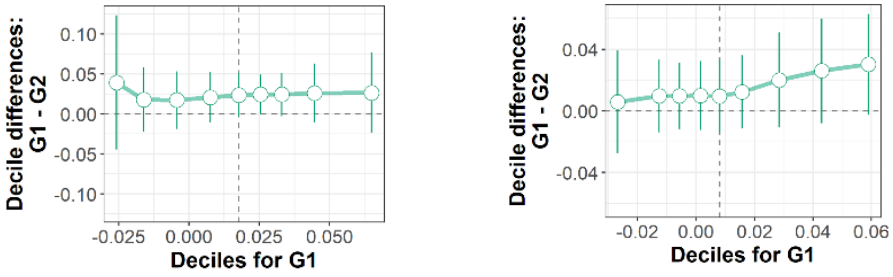
*p-value obtained by McNemar test for qualitative variables and Mann-Whitney-Wilcoxon test for dependent samples for quantitative variables.

- **Power spectral density – Longitudinal Analysis**

To analyzing all groups together comparing the mean of each spectral power band at the initial visit vs. the first-year follow-up visit, we observed statistically significant changes in the Delta, Alpha1, Alpha2, and Beta2 frequency bands. This difference is more prevalent in the components evaluated in the Delta frequency band (Supplementary Table 1). When performing a sub-analysis with the asymptomatic carriers group (G1), we observed statistically significant changes in the Delta and Beta2 frequency bands, being more frequent in Delta frequency band. (See Table 2).

When comparing the changes in the frequency bands in groups G1 (asymptomatic carriers) vs G2 (non-carriers) in a 1-year longitudinal follow-up, we see in shift graphs that in most of neuronal components no differences were found, we observed most of the deciles around zero, with non-linear slopes that showed greater difference towards the deciles located at the extremes (decile 8 and 9), with wide confidence interval. When analyzing the statistically significant findings shown in Table 2, the shift graphs for the Delta band showed nonlinear slopes in the evaluated components; in Beta1 frequency band in C22 component, a slope with a linear tendency with a poor degree of inclination was found, indicating non strong differences between the groups, Finally, frequency band Beta3 in component C20 showed a linear slope especially in the last deciles but with wide intervals that crossed 0, so the differences were not significant in the frequency sense (See Figure 4).

Figure 4. Plots obtained with the shift function: a) C22 component with Beta1. b) C20 component with Beta3.



A B

Table 2: Differences in spectral power bands in components with neuronal origin in asymptomatic carriers. Initial visit (V0) and 1-year follow-up visit (V2).

	DELTA			THETA		
	V0 (N=25)	V2 (N=25)	p-value	V0 (N=25)	V2 (N=25)	p-value
C14						
Mean (SD)	0.120 (0.0603)	0.167 (0.0880)	**0,011**	0.0662 (0.0297)	0.0731 (0.0293)	0,134
Median [Min, Max]	0.115 [0.0284, 0.230]	0.157 [0.0531, 0.422]		0.0589 [0.0220, 0.129]	0.0670 [0.0416, 0.172]	
C15						
Mean (SD)	0.222 (0.108)	0.240 (0.0872)	0,325	0.111 (0.0489)	0.110 (0.0400)	0,979
Median [Min, Max]	0.225 [0.0762, 0.438]	0.249 [0.115, 0.457]		0.112 [0.0389, 0.266]	0.100 [0.0638, 0.202]	
C18						
Mean (SD)	0.168 (0.0761)	0.205 (0.0723)	**0,007**	0.0907 (0.0353)	0.101 (0.0411)	0,230
Median [Min, Max]	0.180 [0.0633, 0.346]	0.213 [0.0800, 0.328]		0.0860 [0.0382, 0.185]	0.0963 [0.0493, 0.257]	
C20						
Mean (SD)	0.141 (0.0688)	0.186 (0.110)	0,075	0.0807 (0.0394)	0.0920 (0.0605)	0,367
Median [Min, Max]	0.129 [0.0293, 0.303]	0.152 [0.0456, 0.441]		0.0794 [0.0274, 0.173]	0.0848 [0.0371, 0.335]	
C22						
Mean (SD)	0.107 (0.0416)	0.161 (0.0893)	**0,002**	0.0757 (0.0356)	0.0869 (0.0427)	0,107
Median [Min, Max]	0.0988 [0.0427, 0.198]	0.144 [0.0546, 0.429]		0.0653 [0.0316, 0.171]	0.0783 [0.0445, 0.222]	
C23						
Mean (SD)	0.129 (0.0655)	0.178 (0.0935)	**0,009**	0.0904 (0.0409)	0.102 (0.0460)	0,101
Median [Min, Max]	0.117 [0.0395, 0.307]	0.162 [0.0590, 0.422]		0.0790 [0.0252, 0.199]	0.0897 [0.0414, 0.204]	
C24						
Mean (SD)	0.0845 (0.0478)	0.159 (0.0866)	**0,000**	0.0775 (0.0528)	0.0916 (0.0471)	**0,037**
Median [Min, Max]	0.0657 [0.0211, 0.216]	0.139 [0.0573, 0.430]		0.0592 [0.0123, 0.242]	0.0902 [0.0317, 0.190]	
C25						
Mean (SD)	0.128 (0.0570)	0.180 (0.0999)	**0,005**	0.0827 (0.0312)	0.0986 (0.0488)	0,241
Median [Min, Max]	0.122 [0.0564, 0.290]	0.161 [0.0611, 0.440]		0.0707 [0.0404, 0.153]	0.0816 [0.0473, 0.189]	
	ALPHA-1			ALPHA-2		
	V0 (N=25)	V2 (N=25)	p-value	V0 (N=25)	V2 (N=25)	p-value
C14						
Mean (SD)	0.0950 (0.0495)	0.0904 (0.0445)	0,895	0.0972 (0.0727)	0.0933 (0.0676)	0,833
Median [Min, Max]	0.0796 [0.0368, 0.203]	0.0745 [0.0488, 0.243]		0.0778 [0.0340, 0.371]	0.0747 [0.0404, 0.374]	
C15						
Mean (SD)	0.0902 (0.0474)	0.0910 (0.0484)	0,672	0.0652 (0.0427)	0.0645 (0.0385)	0,979
Median [Min, Max]	0.0699 [0.0292, 0.213]	0.0769 [0.0451, 0.238]		0.0525 [0.0235, 0.239]	0.0523 [0.0316, 0.215]	
C18						
Mean (SD)	0.150 (0.0801)	0.145 (0.0743)	0,560	0.108 (0.0481)	0.110 (0.0546)	0,833
Median [Min, Max]	0.142 [0.0531, 0.389]	0.118 [0.0669, 0.390]		0.0973 [0.0456, 0.239]	0.0940 [0.0484, 0.290]	
C20						
Mean (SD)	0.141 (0.0693)	0.141 (0.0790)	1,000	0.104 (0.0446)	0.115 (0.0735)	0,791
Median [Min, Max]	0.125 [0.0369, 0.239]	0.111 [0.0417, 0.369]		0.104 [0.0347, 0.215]	0.0875 [0.0390, 0.330]	
C22						
Mean (SD)	0.186 (0.0885)	0.187 (0.0994)	0,958	0.159 (0.0601)	0.151 (0.0769)	0,381
Median [Min, Max]	0.178 [0.0428, 0.329]	0.173 [0.0542, 0.368]		0.153 [0.0444, 0.252]	0.138 [0.0439, 0.294]	
C23						
Mean (SD)	0.248 (0.128)	0.216 (0.120)	0,096	0.139 (0.0506)	0.132 (0.0575)	0,560
Median [Min, Max]	0.246 [0.0621, 0.482]	0.172 [0.0808, 0.505]		0.127 [0.0464, 0.239]	0.124 [0.0348, 0.229]	
C24						
Mean (SD)	0.316 (0.175)	0.266 (0.151)	0,052	0.180 (0.0887)	0.161 (0.0843)	0,252
Median [Min, Max]	0.301 [0.0330, 0.592]	0.246 [0.0690, 0.583]		0.185 [0.0384, 0.449]	0.145 [0.0250, 0.333]	
C25						
Mean (SD)	0.239 (0.136)	0.218 (0.128)	0,200	0.179 (0.0701)	0.172 (0.0930)	0,596
Median [Min, Max]	0.215 [0.0513, 0.482]	0.177 [0.0712, 0.450]		0.188 [0.0676, 0.315]	0.148 [0.0303, 0.373]	

	BETA-1			BETA-2		
	V0	V2	p-value	V0	V2	p-value
	(N=25)	(N=25)		(N=25)	(N=25)	
C14						
Mean (SD)	0.183 (0.0535)	0.186 (0.0523)	0,751	0.0834 (0.0299)	0.0761 (0.0313)	**0,042**
Median [Min, Max]	0.174 [0.123, 0.325]	0.177 [0.110, 0.335]		0.0819 [0.0475, 0.173]	0.0660 [0.0390, 0.169]	
C15						
Mean (SD)	0.130 (0.0447)	0.140 (0.0495)	0,134	0.0591 (0.0188)	0.0601 (0.0191)	0,615
Median [Min, Max]	0.112 [0.0831, 0.264]	0.131 [0.0824, 0.285]		0.0544 [0.0252, 0.113]	0.0571 [0.0288, 0.0918]	
C18						
Mean (SD)	0.171 (0.0536)	0.168 (0.0492)	0,711	0.0680 (0.0241)	0.0615 (0.0245)	0,096
Median [Min, Max]	0.148 [0.103, 0.296]	0.159 [0.0924, 0.298]		0.0646 [0.0291, 0.124]	0.0639 [0.0225, 0.145]	
C20						
Mean (SD)	0.168 (0.0399)	0.162 (0.0393)	0,542	0.0630 (0.0163)	0.0603 (0.0233)	0,525
Median [Min, Max]	0.162 [0.101, 0.279]	0.157 [0.0724, 0.245]		0.0633 [0.0380, 0.109]	0.0582 [0.0170, 0.116]	
C22						
Mean (SD)	0.203 (0.0651)	0.186 (0.0633)	**0,034**	0.0675 (0.0254)	0.0618 (0.0364)	**0,024**
Median [Min, Max]	0.201 [0.112, 0.361]	0.170 [0.106, 0.303]		0.0651 [0.0352, 0.151]	0.0505 [0.0250, 0.179]	
C23						
Mean (SD)	0.169 (0.0707)	0.158 (0.0709)	0,210	0.0444 (0.0169)	0.0421 (0.0160)	0,411
Median [Min, Max]	0.162 [0.0660, 0.354]	0.151 [0.0558, 0.411]		0.0436 [0.0205, 0.0791]	0.0386 [0.0202, 0.0774]	
C24						
Mean (SD)	0.152 (0.0797)	0.142 (0.0600)	0,252	0.0420 (0.0209)	0.0406 (0.0220)	0,525
Median [Min, Max]	0.146 [0.0369, 0.349]	0.127 [0.0581, 0.255]		0.0373 [0.0132, 0.0909]	0.0320 [0.0147, 0.107]	
C25						
Mean (SD)	0.182 (0.0836)	0.163 (0.0681)	0,059	0.0491 (0.0185)	0.0439 (0.0259)	**0,034**
Median [Min, Max]	0.179 [0.0787, 0.472]	0.161 [0.0800, 0.366]		0.0428 [0.0161, 0.0933]	0.0365 [0.0138, 0.129]	

	BETA-3			GAMMA		
	V0	V2	p-value	V0	V2	p-value
	(N=25)	(N=25)		(N=25)	(N=25)	
C14						
Mean (SD)	0.193 (0.0527)	0.177 (0.0555)	0,101	0.162 (0.112)	0.137 (0.0769)	0,101
Median [Min, Max]	0.197 [0.101, 0.316]	0.156 [0.104, 0.308]		0.132 [0.0321, 0.455]	0.124 [0.0427, 0.315]	
C15						
Mean (SD)	0.172 (0.0616)	0.165 (0.0528)	0,634	0.150 (0.101)	0.129 (0.0606)	0,325
Median [Min, Max]	0.159 [0.0898, 0.299]	0.145 [0.0957, 0.272]		0.122 [0.0404, 0.431]	0.124 [0.0341, 0.261]	
C18						
Mean (SD)	0.143 (0.0562)	0.124 (0.0427)	0,075	0.102 (0.0630)	0.0863 (0.0381)	0,275
Median [Min, Max]	0.138 [0.0525, 0.287]	0.131 [0.0362, 0.203]		0.0769 [0.0233, 0.269]	0.0926 [0.0160, 0.162]	
C20						
Mean (SD)	0.140 (0.0463)	0.120 (0.0434)	**0,032**	0.162 (0.114)	0.124 (0.0891)	0,052
Median [Min, Max]	0.141 [0.0586, 0.239]	0.125 [0.0331, 0.231]		0.157 [0.0244, 0.485]	0.0935 [0.0210, 0.348]	
C22						
Mean (SD)	0.112 (0.0421)	0.0983 (0.0439)	0,101	0.0897 (0.0786)	0.0673 (0.0555)	0,055
Median [Min, Max]	0.0975 [0.0469, 0.212]	0.0832 [0.0397, 0.214]		0.0675 [0.0170, 0.357]	0.0524 [0.0168, 0.299]	
C23						
Mean (SD)	0.0843 (0.0401)	0.0818 (0.0426)	0,711	0.0970 (0.0728)	0.0901 (0.0718)	0,458
Median [Min, Max]	0.0736 [0.0218, 0.193]	0.0670 [0.0299, 0.184]		0.0697 [0.0117, 0.317]	0.0776 [0.0143, 0.311]	
C24						
Mean (SD)	0.0699 (0.0492)	0.0693 (0.0378)	0,895	0.0782 (0.0866)	0.0703 (0.0614)	1,000
Median [Min, Max]	0.0560 [0.0143, 0.221]	0.0609 [0.0187, 0.155]		0.0428 [0.00788, 0.375]	0.0499 [0.0134, 0.234]	
C25						
Mean (SD)	0.0789 (0.0366)	0.0719 (0.0342)	0,164	0.0611 (0.0533)	0.0533 (0.0439)	0,381
Median [Min, Max]	0.0747 [0.0215, 0.163]	0.0736 [0.0185, 0.156]		0.0395 [0.0111, 0.244]	0.0406 [0.00954, 0.177]	

- **Alpha/Theta Reactivity**

When analyzing the shift graphs obtained with formulas 1 and 2, it was observed that in most of the neural components no differences were found between the reactivity indices of the groups compared, presenting differences around 0 in most of the deciles, mainly in the central tendency and in the neighboring deciles; the extreme deciles (decile 1 and decile 9) were the ones that mainly showed greater differences, but also wider confidence intervals. Likewise, when evaluating the slope of the graphs obtained with formula 1, in all cases it was non-linear, and although with formula 2 most of the slopes were non-linear, in some cases slopes with low steepness were shown. The non-linear slopes indicate differences in skewness between distributions of the groups with respect to the reactivity indices, while the slopes indicate differences in the spread between

distributions of the reactivity indices, and slopes with low steepness indicate that the differences are not strong. On the other hand, in both formulas evaluated, most of the confidence intervals of the deciles crossed 0, so that the differences were not significant in the frequentist sense (16).

In formula 1, group differences were observed between G1 and G2 in components C23 (in alpha/theta), C20 and C23 (in alpha1/theta), as well as differences between CTR and G2 in components C18 (in alpha/theta, alpha1/theta and alpha2/theta) and C25 (in alpha/theta). In these results, all group differences in reactivity indices were positive, with higher reactivity indices in G1 compared to G2, as well as higher values of CTR indices compared to G2; likewise, the slopes generated between the deciles were non-linear. The graphs that show in a representative way what has been described above for differences and non-differences between groups with formula 1 are shown in Figure 5. It is important to note that there are group differences in Figure 5c, but the differences in the deciles appear to be very close to zero due to the wide confidence intervals; the differences in the different deciles are around 2.5.

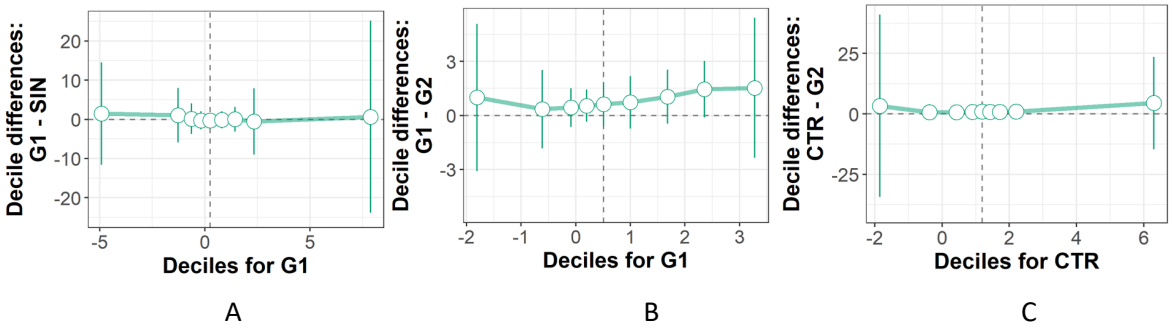


Figure 5. Plots obtained with the shift function: a) C24 component with alpha/theta, no group differences between G1 and SIN, b) C23 component with alpha/theta, group differences between G1 and G2, c) C18 component with alpha1/theta, group differences between CTR and G2.

In formula 2, group differences were observed between G1 and G2 in component C24 in alpha/theta, between G1 and SIN in component C18 in alpha/theta and C24 in alpha1/theta. Also, between CTR and SIN with alpha/theta in components C18, C20, C22, C24 and C25, in alpha1/theta in components C14, C15, C18, C22, C23 and C25. Finally, between CTR and G2, with alpha/theta in components C20, C23, C24 and C25, with alpha1/theta in components C14, C18, C20, C22, C23 and C25, and with alpha2/theta in component C25. As could be seen from the graphs obtained with this formula, negative differences, non-linear behavior of the deciles and slopes with low gradients between the different deciles predominated. In general, there were higher values of G2 indices with respect to G1, higher values of G2 with respect to CTR and SIN with respect to CTR; likewise, G1 and SIN show differences in the distribution due to the positive slope with low inclination. Figure 6 shows some graphs that are representative of the behavior described above for differences and non-differences between groups with formula 2.

All the results that showed differences when performing the Mann-Whitney U test also showed differences in the graphs when using the shift function, however, not all the results that showed differences graphically gave group differences in the statistical test, this is due to the assumptions made by the statistical tests that can affect the final result of the test, while the implemented graphical method allowed observing the differences along the distribution in a better way, as it is a more robust method for analyzing group differences (16).

Considering these results, formula 2, both graphical and statistical, resulted in a greater number of results showing group differences.

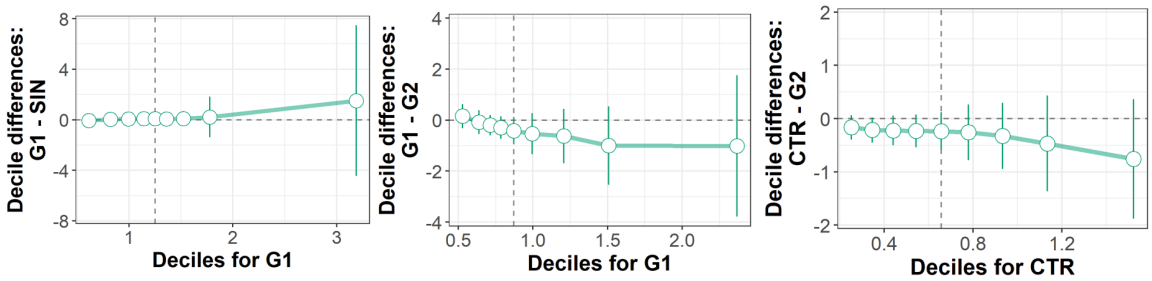


Figure 6. Plots obtained with the shift function: a) C23 component with alpha2/theta, no group differences between G1 and SIN, b) C24 component with alpha/theta, group differences between G1 and G2, c) C25 component with alpha1/theta, group differences between CTR and G2.

Tables 3 and 4 show the results that showed statistically significant differences with the Mann-Whitney U test, using formulas 1 and 2. These tables show the reactivity index, the component, the groups evaluated (A and B), and the U and p values of the test.

Table 3. Mann-Whitney U test results showing differences using formula 1.

Test				MWU	
Reactivity index	**Component**	**A**	**B**	**U-val**	**p-val**
alpha-theta	**C18**	**CTR**	**G2**	834.00	0.02
alpha1-theta	**C18**	**CTR**	**G2**	859.00	0.01
alpha2-theta	**C18**	**CTR**	**G2**	879.00	0.00

Table 4. Mann-Whitney U test results showing differences using formula 2.

Test				MWU	
Reactivity index	**Component**	**A**	**B**	**U-val**	**p-val**
alpha-theta	**C18**	**CTR**	**SIN**	193.00	0.01
		G1	**SIN**	177.00	0.03
	C20	**CTR**	**G2**	434.00	0.02
	C22	**CTR**	**SIN**	235.00	0.05
	C23	**CTR**	**G2**	424.00	0.02
	C24	**CTR**	**G2**	455.00	0.04
		G1	**G2**	357.00	0.05
	C25	**CTR**	**G2**	445.00	0.03
alpha1-theta	**C14**	**CTR**	**G2**	453.00	0.04
			SIN	215.00	0.02
	C18	**CTR**	**G2**	438.00	0.03
			SIN	170.00	0.00
	C20	**CTR**	**G2**	404.00	0.01
	C22	**CTR**	**G2**	439.00	0.03
			SIN	178.00	0.00
	C23	**CTR**	**G2**	420.00	0.02

			SIN	234.00	0.04
	C24	**G1**	**SIN**	184.00	0.05
	C25	**CTR**	**G2**	427.00	0.02
			SIN	212.00	0.02

- **Neuropsychological data**

A boxplot of the MMSE results of each of the evaluated groups is presented (G1 and G2 are presented as healthy "SAN") (See Figure 7). Subsequently, a correlation was made between the MMSE result and the spectral power data of each of the frequency bands in the components with neuronal origin. A negative correlation coefficient with statistical significance ($p<0.05$) was found for the Beta3 frequency band in components C18, C20, C22, C23, C24 and C25. In these same components, a positive correlation coefficient with statistical significance was found for the Alpha1 and Alpha2 frequency bands. No statistically significant findings were found for the other frequency bands (See figure 8).

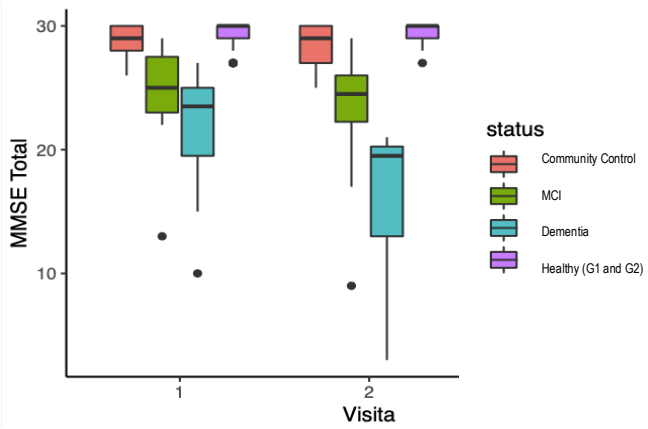


Figure 7: boxplot MMSE in all groups: Community control, MCI (Mild cognitive impairment), Dementia, Healthy (G1 and G2 groups).

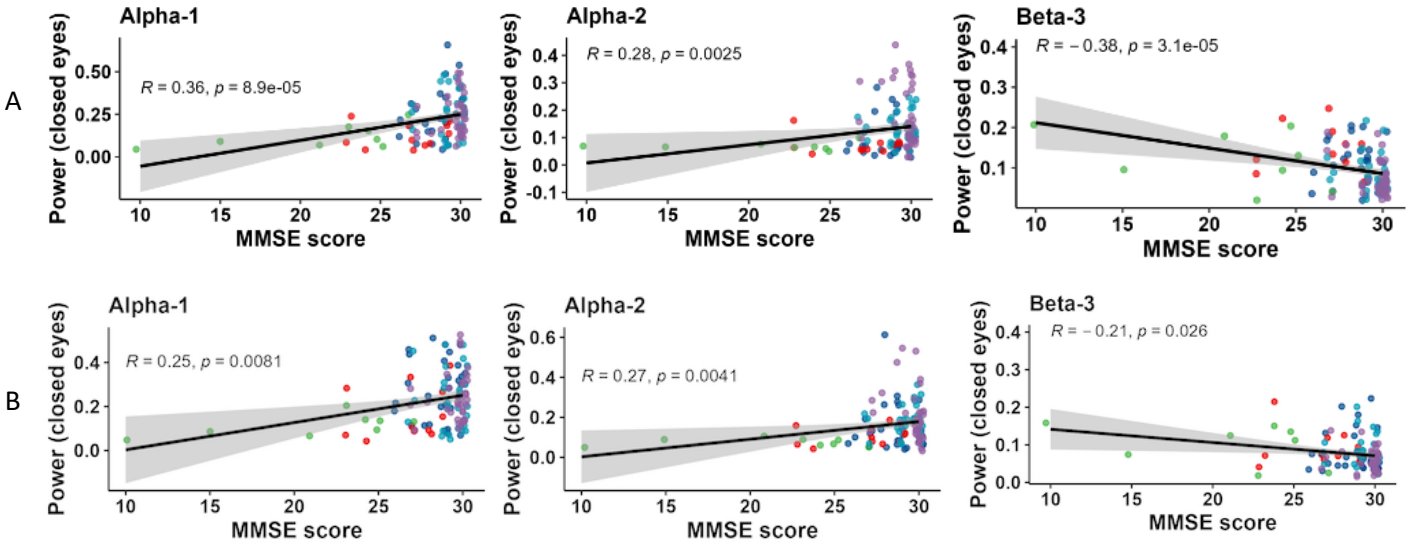


Figure 8: Pearson's correlation of total MMSE vs spectral frequency bands Alpha1, Alpha2 and Beta3 in components C23 (A) and C25 (B).

Discussion

Currently, the diagnosis of AD in the research context is based on the use of biomarkers that track pathophysiological phenomena such as amyloidosis, tauopathy and neurodegeneration in pre-clinical stages and clinical stages of the disease (18). Most of the instruments used to identify these biomarkers require high-tech equipment, are expensive and their availability is limited in middle-to low-income countries as is the case in Colombia (19). It is necessary to advance in the search for low-cost and accessible biomarkers that can be used in the clinical context with the objective of identifying population that may be susceptible to intervention. EEG is a noninvasive, cost-effective, available, and reproducible technique that could be postulated as an alternative in the search for early biomarkers in AD (18). This study is the first longitudinal study in an asymptomatic population carrying the PSEN1-E280A genetic variant by means of resting EEG and its objective was to evaluate possible neurophysiological markers that can track disease progression.

Previously, differences have been described in people with AD (symptomatic and pre-symptomatic) and controls by means of resting state EEG recording. In clinical stages, an increase in slow frequency bands (Delta and Theta) and an increase in fast frequency bands (Alpha, Beta and Gamma) have been described (4). On the contrary, in pre-clinical stages of the disease, an opposite phenomenon has been described, decrease of spectral density in slow frequency bands and increase in fast frequency bands (20). This relationship between the spectral power of slow and fast bands explains the need to use ratios in the search for biomarkers that amplify the differences between control groups and patients.

In our analysis of spectral power in the resting state, taking as reference the components with a neural origin, in a cross-sectional study we found a tendency to differentiate the groups of asymptomatic carriers vs. non-carriers with the Alpha1, Alpha2 and Beta3 frequency bands; finding a lower power in asymptomatic carriers vs. non-carriers in the Alpha frequency bands and a higher power in the Beta frequency bands. When performing the same analysis in the longitudinal follow-up, the Alpha1 and Alpha2 frequency bands did not have significant changes in the follow-up year, but the Beta3 frequency band in component 20 and Beta2 in component 22 statistically significant differences were found, but with low accuracy. Finally, the Delta frequency band presented statistically significant differences in several components between the initial visit and the follow-up visit, however, the distribution of the data in the shift graphs for the Beta frequency band presents slopes with poor slope, which indicates a poor strength in the difference between both groups with wide confidence intervals; and in the case of the Delta frequency band, it presents nonlinear slopes.

In other longitudinal studies with population with subjective cognitive impairment and positive amyloid, they found a higher theta power in those subjects who progressed (mean 0.13 [SD 0.05]) vs subjects who did not progress (mean 0.10 [SD 0.03]; $p < 0.01$) (21); another study with adults under 65 years of age with positive amyloid, found a higher relative theta power that was related to the clinical progression of these individuals (22). When analyzing the ranges used for the frequency bands in these two studies (delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10. 5-13 Hz), beta 1 (13-20 Hz), beta 2 (20-30 Hz), and gamma (30-40 Hz)), we found differences with the recommendations given by the International Federation of Clinical Neurophysiology (IFCN) - EEG research workgroup in 2020 (15), where they give recommendations on frequency and topography for resting EEG analysis and record the following ranges in frequency bands: delta (1. 5-6 Hz), theta (6-8.5 Hz), alpha 1 (8.5-10.5 Hz), alpha 2 (10.5-12.5 Hz), beta 1 (12.5-18.5 Hz), beta 2 (18.5-21 Hz), beta 3 (21 -30 Hz) and gamma (30-45 Hz) (15). In this sense, incipient findings such as the significant changes reported in the Delta frequency band in the group of asymptomatic carriers take relevance and would be congruent with those reported in the literature.

Using EEG, several cross-sectional studies have reported differences in carriers of the PSEN1-E280A genetic variant when compared with non-carriers in clinical and pre-clinical stages (20,23,24). In these studies, a decrease in the Theta frequency band and an increase in Alpha2 were found in carriers of this genetic variant (25). Other studies in relation to the precuneus region have been performed finding less deactivation in PSEN1-E280A carriers in memory tasks using fMRI (26,27), hypometabolism using FDG PET, decreased cortical thickness measured by MRI (28) and increased connectivity in visual processing tasks using EEG (29). In conclusion, hindbrain

regions have been proposed as one of the areas that are pathologically and functionally affected in preclinical stages of AD (30). These data are congruent with the results obtained in this study in components such as C22 and C25, related to the precuneus region and superior parietal lobe.

In a previous study with the same population as this study, Garcia et al, were able to classify with up to 83% accuracy preclinical AD in asymptomatic carriers (G1) compared to non-carriers (G2), using spectral features on gICA components, suggesting the importance of Beta banding over regions such as the Precuneus, Superior Parietal Lobe and Medial Frontal Gyrus in the development of early familial AD (11). These findings are congruent with longitudinal analyses, where the Beta frequency band presents statistically significant differences over time and retains discrimination ability between both comparison groups (G1 vs G2).

In summary, Beta frequency band is a potential neurophysiological marker that in preclinical stages of ADAD show statistically significant differences between asymptomatic carriers and non-carriers. Additionally, this signal is related to components whose origin is estimated in posterior regions, which highlights the importance of previous findings in the precuneus. Future research is required with a larger sample and with longer follow-ups to evaluate changes in the progression of the disease and compare results with available screening instruments for dementia. This study has some limitations. One of them is that our results should be taken cautiously because they would apply to this sample of asymptomatic individuals with the PSEN1 E280A variant for ADAD. Also, 11% of the individuals were unable to continue with the follow-up because of the pandemic, thus accuracy got affected by reduced sample size.

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Supplementary Table 1: Differences in spectral power bands in components with neuronal origin in all subjetcs. Initial visit (V0) and 1-year follow-up visit (V2).

	DELTA			THETA		
	V0 (N=93)	V2 (N=93)	p-value	V0 (N=93)	V2 (N=93)	p-value
C14						
Mean (SD)	0.122 (0.0692)	0.142 (0.0848)	**0,018**	0.0736 (0.0457)	0.0728 (0.0391)	0,368
Median [Min, Max]	0.106 [0.00266, 0.370]	0.134 [0.00300, 0.428]		0.0652 [0.00721, 0.234]	0.0670 [0.00282, 0.202]	
C15						
Mean (SD)	0.218 (0.109)	0.225 (0.120)	0,500	0.106 (0.0551)	0.101 (0.0489)	0,157
Median [Min, Max]	0.206 [0.0155, 0.529]	0.208 [0.00643, 0.671]		0.104 [0.0173, 0.317]	0.0919 [0.00391, 0.265]	
C18						
Mean (SD)	0.166 (0.0788)	0.195 (0.104)	**0,005**	0.108 (0.0659)	0.105 (0.0574)	0,893
Median [Min, Max]	0.151 [0.0497, 0.365]	0.176 [0.0117, 0.707]		0.0887 [0.0198, 0.338]	0.0963 [0.00541, 0.314]	
C20						
Mean (SD)	0.137 (0.0743)	0.156 (0.106)	0,278	0.102 (0.0768)	0.0920 (0.0676)	0,189
Median [Min, Max]	0.127 [0.00307, 0.347]	0.146 [0.00243, 0.469]		0.0826 [0.00531, 0.387]	0.0825 [0.00347, 0.335]	
C22						
Mean (SD)	0.123 (0.0589)	0.157 (0.0884)	**0,001**	0.0999 (0.0700)	0.105 (0.0690)	0,135
Median [Min, Max]	0.111 [0.0427, 0.281]	0.144 [0.0247, 0.429]		0.0770 [0.0228, 0.370]	0.0878 [0.0122, 0.376]	
C23						
Mean (SD)	0.144 (0.0782)	0.195 (0.109)	**0,000**	0.108 (0.0726)	0.114 (0.0636)	0,126
Median [Min, Max]	0.121 [0.0395, 0.337]	0.184 [0.0448, 0.554]		0.0916 [0.0223, 0.382]	0.102 [0.0163, 0.296]	
C24						
Mean (SD)	0.118 (0.0776)	0.162 (0.0971)	**0,000**	0.108 (0.0874)	0.113 (0.0826)	0,171
Median [Min, Max]	0.0960 [0.0164, 0.468]	0.142 [0.0217, 0.430]		0.0797 [0.0123, 0.458]	0.0906 [0.0169, 0.382]	
C25						
Mean (SD)	0.159 (0.0873)	0.190 (0.101)	**0,003**	0.107 (0.0654)	0.116 (0.0698)	0,092
Median [Min, Max]	0.146 [0.0352, 0.470]	0.186 [0.0399, 0.507]		0.0941 [0.0202, 0.345]	0.0997 [0.0198, 0.350]	
	ALPHA-1			ALPHA-2		
	V0 (N=93)	V2 (N=93)	p-value	V0 (N=93)	V2 (N=93)	p-value
C14						
Mean (SD)	0.117 (0.0795)	0.105 (0.0667)	0,079	0.110 (0.0822)	0.0973 (0.0676)	0,054
Median [Min, Max]	0.0920 [0.00768, 0.498]	0.0881 [0.00992, 0.320]		0.0801 [0.00991, 0.448]	0.0819 [0.0139, 0.397]	
C15						
Mean (SD)	0.105 (0.0737)	0.0983 (0.0594)	0,637	0.0743 (0.0520)	0.0696 (0.0418)	0,437
Median [Min, Max]	0.0840 [0.0143, 0.443]	0.0828 [0.0105, 0.300]		0.0620 [0.0130, 0.349]	0.0600 [0.0174, 0.238]	
C18						
Mean (SD)	0.172 (0.0973)	0.157 (0.105)	**0,020**	0.114 (0.0736)	0.0997 (0.0606)	**0,025**
Median [Min, Max]	0.151 [0.0183, 0.464]	0.124 [0.0119, 0.536]		0.0933 [0.0152, 0.461]	0.0893 [0.0151, 0.428]	
C20						
Mean (SD)	0.159 (0.0986)	0.138 (0.0943)	**0,002**	0.0985 (0.0615)	0.0930 (0.0647)	0,069
Median [Min, Max]	0.151 [0.00711, 0.549]	0.112 [0.00635, 0.478]		0.0907 [0.0103, 0.345]	0.0797 [0.0116, 0.330]	
C22						
Mean (SD)	0.208 (0.127)	0.192 (0.121)	**0,025**	0.144 (0.0818)	0.133 (0.0837)	**0,019**
Median [Min, Max]	0.181 [0.0246, 0.618]	0.165 [0.0179, 0.546]		0.125 [0.0212, 0.406]	0.116 [0.0225, 0.397]	
C23						
Mean (SD)	0.225 (0.128)	0.196 (0.121)	**0,001**	0.126 (0.0852)	0.109 (0.0755)	**0,010**
Median [Min, Max]	0.210 [0.0394, 0.657]	0.167 [0.0173, 0.554]		0.0988 [0.0276, 0.438]	0.0840 [0.0193, 0.387]	
C24						
Mean (SD)	0.282 (0.162)	0.250 (0.160)	**0,002**	0.153 (0.110)	0.133 (0.0994)	**0,013**
Median [Min, Max]	0.264 [0.0330, 0.715]	0.206 [0.0247, 0.759]		0.124 [0.0305, 0.558]	0.106 [0.0193, 0.488]	
C25						
Mean (SD)	0.233 (0.132)	0.210 (0.128)	**0,011**	0.161 (0.102)	0.146 (0.102)	**0,016**
Median [Min, Max]	0.211 [0.0430, 0.527]	0.170 [0.0187, 0.561]		0.138 [0.0321, 0.546]	0.118 [0.0209, 0.488]	

	BETA-1			BETA-2		
	V0	V2	p-value	V0	V2	p-value
	(N=93)	(N=93)		(N=93)	(N=93)	
C14						
Mean (SD)	0.176 (0.0518)	0.181 (0.0526)	0,314	0.0724 (0.0270)	0.0690 (0.0246)	0,055
Median [Min, Max]	0.169 [0.0738, 0.325]	0.171 [0.0922, 0.335]		0.0639 [0.0215, 0.173]	0.0654 [0.0300, 0.169]	
C15						
Mean (SD)	0.136 (0.0485)	0.141 (0.0472)	0,120	0.0577 (0.0213)	0.0568 (0.0199)	0,863
Median [Min, Max]	0.120 [0.0659, 0.308]	0.132 [0.0562, 0.294]		0.0549 [0.0112, 0.126]	0.0541 [0.0189, 0.106]	
C18						
Mean (SD)	0.153 (0.0494)	0.156 (0.0514)	0,685	0.0583 (0.0237)	0.0551 (0.0215)	0,083
Median [Min, Max]	0.142 [0.0445, 0.296]	0.156 [0.0530, 0.298]		0.0529 [0.00566, 0.124]	0.0525 [0.0130, 0.145]	
C20						
Mean (SD)	0.156 (0.0451)	0.153 (0.0443)	0,525	0.0552 (0.0192)	0.0539 (0.0202)	0,498
Median [Min, Max]	0.149 [0.0501, 0.342]	0.154 [0.0551, 0.308]		0.0549 [0.0110, 0.109]	0.0509 [0.0158, 0.116]	
C22						
Mean (SD)	0.171 (0.0610)	0.167 (0.0588)	0,317	0.0583 (0.0249)	0.0525 (0.0250)	**0,000**
Median [Min, Max]	0.162 [0.0398, 0.361]	0.164 [0.0522, 0.373]		0.0541 [0.00584, 0.151]	0.0489 [0.0108, 0.179]	
C23						
Mean (SD)	0.132 (0.0529)	0.128 (0.0505)	0,205	0.0445 (0.0195)	0.0405 (0.0156)	**0,021**
Median [Min, Max]	0.127 [0.0443, 0.354]	0.121 [0.0443, 0.411]		0.0436 [0.0112, 0.124]	0.0380 [0.00619, 0.0805]	
C24						
Mean (SD)	0.126 (0.0609)	0.126 (0.0504)	0,765	0.0396 (0.0195)	0.0382 (0.0195)	0,277
Median [Min, Max]	0.120 [0.0356, 0.349]	0.122 [0.0307, 0.255]		0.0352 [0.00929, 0.104]	0.0347 [0.0111, 0.107]	
C25						
Mean (SD)	0.149 (0.0645)	0.143 (0.0547)	0,108	0.0433 (0.0202)	0.0393 (0.0189)	**0,004**
Median [Min, Max]	0.141 [0.0434, 0.472]	0.132 [0.0392, 0.366]		0.0399 [0.0101, 0.126]	0.0353 [0.00804, 0.129]	

	BETA-3			GAMMA		
	V0	V2	p-value	V0	V2	p-value
	(N=93)	(N=93)		(N=93)	(N=93)	
C14						
Mean (SD)	0.169 (0.0652)	0.169 (0.0640)	0,759	0.160 (0.131)	0.164 (0.135)	0,875
Median [Min, Max]	0.170 [0.0349, 0.341]	0.161 [0.0506, 0.379]		0.121 [0.0157, 0.567]	0.117 [0.0282, 0.562]	
C15						
Mean (SD)	0.156 (0.0663)	0.158 (0.0665)	0,966	0.147 (0.117)	0.151 (0.122)	0,646
Median [Min, Max]	0.148 [0.0161, 0.356]	0.144 [0.0310, 0.348]		0.115 [0.00864, 0.539]	0.112 [0.0190, 0.561]	
C18						
Mean (SD)	0.123 (0.0628)	0.121 (0.0561)	0,665	0.105 (0.0982)	0.111 (0.106)	0,635
Median [Min, Max]	0.111 [0.00792, 0.335]	0.112 [0.0348, 0.265]		0.0730 [0.00436, 0.498]	0.0737 [0.0137, 0.558]	
C20						
Mean (SD)	0.126 (0.0548)	0.130 (0.0578)	0,483	0.167 (0.143)	0.184 (0.157)	0,247
Median [Min, Max]	0.122 [0.0241, 0.275]	0.126 [0.0266, 0.303]		0.114 [0.0157, 0.583]	0.128 [0.0180, 0.586]	
C22						
Mean (SD)	0.102 (0.0543)	0.0989 (0.0540)	0,702	0.0936 (0.0891)	0.0957 (0.104)	0,893
Median [Min, Max]	0.0974 [0.00734, 0.294]	0.0822 [0.0246, 0.253]		0.0608 [0.00375, 0.433]	0.0573 [0.00835, 0.486]	
C23						
Mean (SD)	0.0954 (0.0555)	0.0939 (0.0516)	0,600	0.126 (0.112)	0.125 (0.106)	0,827
Median [Min, Max]	0.0784 [0.0197, 0.247]	0.0811 [0.00952, 0.237]		0.0809 [0.0102, 0.431]	0.0836 [0.00791, 0.464]	
C24						
Mean (SD)	0.0754 (0.0534)	0.0764 (0.0516)	0,884	0.0983 (0.111)	0.101 (0.113)	0,515
Median [Min, Max]	0.0560 [0.0117, 0.227]	0.0609 [0.0135, 0.239]		0.0536 [0.00429, 0.448]	0.0559 [0.00760, 0.493]	
C25						
Mean (SD)	0.0754 (0.0439)	0.0759 (0.0463)	0,722	0.0717 (0.0802)	0.0796 (0.0941)	0,768
Median [Min, Max]	0.0665 [0.0151, 0.223]	0.0601 [0.0108, 0.231]		0.0405 [0.00547, 0.449]	0.0461 [0.00714, 0.425]	