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RESEARCH ARTICLE

Alterations of resting-state Gamma frequency characteristics in aging and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is an important brain disease associated with aging. It involves various functional and structural changes which alter the EEG characteristics. Although numerous studies have found changes in delta, theta, alpha, and beta power, fewer studies have looked at the changes in the resting state EEG gamma activity characteristics in AD. This study aimed to investigate the alterations in the frequency and power values of AD patients' resting-state EEG gamma oscillations compared with healthy elderly and young subjects. We performed Fast Fourier Transform (FFT) on the resting state EEG data from 179 participants, including 59 early stage AD patients, 60 healthy elderly, and 60 healthy young subjects. We averaged FFT performed epochs to investigate the power values in the gamma frequency range (28–48 Hz). We then sorted the peaks of power values in the gamma frequency range, and the average of the identified highest three values was named as the gamma dominant peak frequency. The gamma dominant peak frequency of AD patients ($M_{\text{eyes-opened}}$ = 33.4 Hz, $M_{\text{eyes-closed}}$ = 32.7 Hz) was lower than healthy elderly ($M_{\text{eyes-opened}}$ = 35.5 Hz, $M_{\text{eyes-closed}}$ = 35.0 Hz) and healthy young subjects ($M_{\text{eyes-opened}}$ = 37.2 Hz, $M_{\text{eyes-closed}}$ = 37.0 Hz). These results could be related to AD progression and therefore critical for the recent findings regarding the 40 Hz gamma entrainment because it seems they entrain the gamma frequency of AD towards that of healthy young.

Keywords Alzheimer's disease · Electroencephalography (EEG) · Gamma · Gamma Dominant Peak frequency · Aging · Gamma Entrainment

List of abbreviations

AD	Alzheimer's disease.
CDR	clinical dementia rating.
EC	eyes-closed.
EO	eyes-opened.
EOG	electro-oculogram.
EEG	electroencephalogram.
FFT	Fast Fourier Transform.
HE	Healthy elderly.
HY	Healthy young.
MCI	Mild Cognitive Impairment.
MMSE	mini-mental state examination.
MRI	magnetic resonance imaging.
PV cells	parvalbumin positive inhibitory interneurons.
rsEEG	resting-state electroencephalography.

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Introduction

Alzheimer's disease is characterized by hallmark pathological changes, including abnormal accumulation of extracellular amyloid beta aggregates and intracellular neurofibrillary tangles (Bush 2003; Ayton et al. 2013). These molecular changes ultimately lead to progressive loss of the brain's structural and functional integrity (Palop and Mucke 2010a). As a result of these events, neuronal network activity alterations are typically observed in Alzheimer's disease patients (Koenig et al. 2005; Stam et al. 2005; Bokde et al. 2009; Babiloni et al. 2016). As a non-invasive and cost-effective method which offers high temporal resolution; Electroencephalography (EEG) is particularly advantageous for studying changes in neural network activity that occur during both healthy and pathological aging processes (Babiloni et al. 2020). In this exploratory study, we focused on the resting state EEG properties of Alzheimer Disease patients and healthy subjects for investigating the differences in light of the recent gamma entrainment applications' findings which may have a potential therapy effect (Iaccarino et al. 2016; Martorell et al. 2019).

In the resting state EEG studies of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) patients, we can see that the power values of delta and theta oscillations were increased, while the power of alpha and beta oscillations was decreased (Cohen et al. 1983; Jelic et al. 2000; Van der Hiele et al. 2007; Bhattacharya et al. 2011; Lizio et al. 2011; Babiloni 2021). This was commonly referred to as "slowing" of EEG activity (Jeong 2004; Dauwels et al. 2010). On the other hand, the studies that are focused on the gamma activities suggested that hippocampal gamma activities played a contributing role in memory (Mably and Colgin 2018), attention (Fries et al. 2001), and perception (Singer and Gray 1995) related cognitive processes. These cognitive functions deteriorate significantly as Alzheimer's disease progresses (Weintraub et al. 2012; Reid et al. 1996; Amieva et al. 2005; Güntekin et al. 2008; Hsiao et al. 2013; Yener et al. 2008). Hence, the involvement of gamma oscillations in these processes has made them a prominent focus of AD-related research. Furthermore, gamma oscillatory rhythms are thought to reflect inhibitory interneurons that express calcium-binding protein parvalbumin (Bartos et al. 2007). This was supported by studies where restoring the activity of parvalbumin positive inhibitory interneurons (PV cells) via optogenetic stimulation (Verret et al. 2012) or cell transplantation (Martinez-Losa et al. 2018) in AD mice models increased gamma activity, reduced hypersynchronization and improved memory deficits.

There are equivocal results in the literature regarding the changes in gamma oscillations observed in AD. Several studies found decreased synchronization (Stam et al. 2002; Koenig et al. 2005) and power in patients with AD (Herrmann and Demiralp 2005) and multiple AD mice models (Verret et al. 2012; Gillespie et al. 2016; Palop and Mucke 2016; Martinez-Losa et al. 2018), while others found increased power (Van Deursen et al. 2008; Wang et al. 2017) in the gamma frequency band during resting state activity in human participants. Furthermore, increased auditory steady state gamma responses (Osipova et al. 2006; Van Deursen et al. 2011) and increased gamma band power during task performance in Alzheimer's disease patients (Van Deursen et al. 2008) have been observed. In a study (Başar et al. 2016) in which we analyzed sensory and cognitive gamma responses over multiple time and frequency windows, our group found reduced power in sensory gamma responses (0-200ms) in Alzheimer's disease patients. Their cognitive gamma responses (400-600ms), on the other hand, had higher amplitudes and prolonged latencies compared to healthy controls. Several studies which are investigating the alterations in gamma activity during healthy aging processes have reported lower gamma peak center frequencies (Murty et al. 2020) in gamma responses of healthy elderly. Moreover, evoked (Böttger et al. 2002) and induced (Murty et al. 2020) gamma band responses of elderly subjects were found to have lower power values compared to younger subjects. In addition to these findings, aged mice were shown to have reduced hippocampal gamma oscillations (Vreugdenhil and Toescu 2005). Although the precise mechanisms or direction of these observed alterations in gamma band activity are not fully understood, the extent of the empirical data linking altered gamma activity to a variety of cognitive disorders (Herrmann and Demiralp 2005), including Alzheimer's disease (Verret et al. 2012; Palop and Mucke 2016; Başar et al. 2017), points to the significance of gamma oscillations in serving as a potential biomarker for deteriorating cognitive functions (Kitchigina 2018).

In recent years, it was proposed that gamma frequency entrainment may have therapeutic effects on AD (Iaccarino et al. 2016; Adaikkan and Tsai 2020; Chan et al. 2021, preprint). Iaccarino and colleagues found that the amyloid-β levels decrease as a molecular recovery mark after the 40 Hz entrainment with light stimuli in the AD model mice (Iaccarino et al. 2016). There was also a recovery in the memory performances of the AD model mice after the 40 Hz entrainment, and the sound stimulus, together with light stimulus provides better results (Martorell et al. 2019). Together with these, an increase in the activity of the neuroimmune system (Garza et al. 2020) and a decrease in the loss of neurons and synapses (Adaikkan et al. 2019) were observed. In light of these findings, to look at the therapeutic effect of light stimulation on AD patients, the researchers gave 40 Hz light stimulation for 10 days with a 2-hour daily exposure to five AD patients and one Mild Cognitive

Impairment patient (Ismail et al. 2018). However, they did not see a significant decrease in amyloid-β levels. They suggested that future studies could see the recovery effect with more extended treatment. As they suggested, a feasibility study demonstrated that the neural network and the immune system of AD patients were affected by prolonged entrainment application, and the long-term home practice (4–8 weeks) was a safe and tolerable treatment modality for AD patients (He et al. 2021). On the other hand, several studies have examined a range of light stimulation conditions in healthy subjects to identify optimal features for gamma frequency entrainment procedures. For instance, one study found that the 40 Hz entrainment application leads to more widespread entrainment and higher power increases with high intensity (408–435 lumens) than low intensity (208–222 lumens) (Jones et al. 2019). Also, they found that there was the largest response at the 40 Hz entrainment in comparison with 60 and 80 Hz. Furthermore, a study conducted to find the most appropriate entrainment technique in potential treatment studies in the future showed that white light among the red, green and blue lights alternatives, high luminance applications (700 and 400 cd/m2) compared to the low luminance applications (100 and 10 cd/m2), and the applications between 34 and 38 Hz compared to the applications between 40 and 50 Hz was the optimal options (Lee et al. 2021).

A thorough review of the literature reveals a lack of research conducted on the frequency changes occurring throughout the course of Alzheimer's disease, particularly when compared to numerous studies on the alterations in power and power density values in patients with Alzheimer's disease. Even though many studies have reported ameliorated pathology and improved cognitive performance after entrainment application at the frequency of gamma oscillations by utilizing various stimulation techniques as previously mentioned, to our knowledge, there have been no reports regarding the alterations in the resting state gamma dominant peak frequency properties of AD patients and healthy subjects. We hypothesized that the gamma dominant peak frequencies of Alzheimer's disease patients are different from those of young and elderly healthy subjects, and we expected that AD patients had lower gamma dominant peak frequencies than healthy subjects. We performed a retrospective analysis of frequency characteristics on resting state EEG recordings from young and elderly healthy subjects and Alzheimer's disease patients in our database to investigate our hypothesis and expectation, identifying their gamma dominant peak frequencies. We were able to detect the natural frequency characteristics of resting state gamma activity in both healthy aging and Alzheimer's disease based on the results of this analysis. Thus, the goal of our study was to fill this gap in the literature concerning resting state EEG gamma dominant peak frequency properties in healthy aging and Alzheimer's disease. We believe that this report will serve as preliminary data for future gamma frequency entrainment studies when determining the optimal gamma frequency for the AD patients and healthy subjects.

Materials and methods

Subjects

To test our hypothesis, resting-state EEG data previously collected by our research group was used. These data were recorded by researchers from Istanbul Medipol University and Dokuz Eylül University between 2016 and 2021. Specifically, the data of 7 healthy elderly participants and 30 Alzheimer's disease patients were taken from Dokuz Eylül University. The rest of the 142 subjects' EEG data were Istanbul Medipol University's data. In total rsEEG data of 179 subjects were included in the study. Ethical approval for this study was obtained from the ethics committee of Istanbul Medipol University (no: E-10840098-772.02-5002). 60 of these subjects were healthy young (31 female, 29 male; mean age: 23.9 ± 3.87, mean education year: 15.9 ± 1.95), 60 subjects were healthy elderly (36 female, 24 male; mean age: 66.7 ± 7.69, mean education year: 10.1 ± 5.14) and 59 subjects were patients with Alzheimer's Disease (38 female, 22 male; mean age: 73.1 ± 6.58, mean education year: 7.63 ± 4.83). Patients with dementia from other causes were excluded based on their MRI scans to ensure the sample's homogeneity. The 59 subjects with Alzheimer's Disease included in this study were diagnosed by neurologists considering the criteria of the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association: NINCDS-ADRDA (McKhann et al. 1984, 2011) and Diagnostic and Statistical Manual of Mental Disorders–4th Edition (American Psychiatric Association 2000). All patients were included during the first year of their diagnosis and had Clinical Dementia Rating (CDR) scores in the range of 1 to 2, which indicates the early stages of the disease trajectory (Khan 2016). As anticipated, there was a statistically significant ($p < .001$) difference between the mean MMSE scores of AD patients ($M = 19.69$, $SD = 4.22$) and healthy elderly ($M = 28.42$, $SD = 1.65$).

Resting-state EEG (rsEEG) Recording

Although resting-state EEG data were collected in different laboratories, the EEG device, instruction, and procedures were the same. EEG signals were amplified with a BrainAmp 32-Channel DC System device (Brain Product GmbH,

Germany). The sampling rate of the recording was 500 Hz, and the band limit was set to 0.01–250 Hz. EEG was recorded using 30 electrodes (Fp1, Fp2, F7 F3, Fz, F4, F8, Ft7, Fc3, Fcz, Fc4, Ft8, Cz, C3, C4, T7, T8, Tp7, Cp3, Cpz, Cp4, Tp8, P3, Pz, P4, P7, P8, O1, Oz, and O2) placed on the elastic cap (Easy-cap) in accordance with the International 10–20 system. 2 additional electrodes (A1 + A2) placed on each earlobe were used as references. Electro-oculograms (EOG) were placed in the medial upper and lateral orbital rim of the left eye to detect eye blinks and movements. Subjects were instructed to remain as still as possible during the recording session. EEG recording of each subject lasted approximately 8 min (4 min for eyes-opened, 4 min for eyes-closed). Impedances of all electrodes were kept below the 15 kΩ. All recordings took place in a dimly lit and shielded room.

Resting-state EEG (rsEEG) data analysis

Preprocessing

Data preprocessing was conducted using the Brain Vision Analyzer 2.2 software. First of all, data were digitally filtered in the range of 0.1–60 Hz using a band-pass filter. An additional Notch filter at 50 Hz was applied to band-pass filtered data. As a next step, Independent Component Analysis (ICA) was performed to remove eye movement and blink artefacts. Maximally two components were extracted from each participant's data. Continuous EEG signals were then segmented into 1000 ms epochs separately for eyes-opened and eyes-closed conditions. Each epoch was visually inspected to detect and reject ones contaminated by muscle and eye artifacts. The numbers of remaining epochs were randomly equalized across the different groups (healthy young, healthy elderly, and Alzheimer's Disease) and conditions (eyes-opened and eyes-closed).

Power spectrum analysis of rsEEG

Power spectrum analysis of rsEEG was performed using Brain Vision Analyzer 2.2 software. Fast Fourier Transform (with 0.977 resolution and Hanning window 10%) was applied to each artifact-free epoch. Then, all FFT-performed epochs were averaged. In this way, power spectral analysis results of rsEEGs that were computed in 2 different conditions (eyes-closed and eyes-opened) on 30 different scalp electrodes were obtained for each subject. In the next step of the analysis, FFT-applied and averaged epochs were filtered in the gamma frequency (28–48 Hz) range. As a final step, frequency (Hz) and power values (μV2) of the three highest peaks in the gamma band were exported for further statistical analysis. Also, we sorted these three highest peaks in terms of their corresponding power values, and called it gamma dominant peak frequency order (Fig. 1).

Statistical analysis

Jamovi (1.6.12 version) was used for statistical analysis. 14 electrodes (F3, F4, C3, C4, T7, T8, TP7, TP8, P3, P4, P7, P8, O1, and O2) were chosen for analysis. These electrodes were selected because they represent the brain's seven distinct locations (frontal, central, temporal, temporoparietal, parietal-1, parietal-2, and occipital) and, according to our previous studies, these electrodes are enough to represent all locations.

In total, 4 mixed design repeated measures analysis of variance (ANOVA) analyses were designed. Two different $7 \times 3 \times 2 \times 3$ mixed design repeated measures ANOVAs were performed to analyze the differences in power values of the peaks between the groups. Within-group factors were as follows: location (seven levels: frontal [F3-F4], central [C3-C4], temporal [T7-T8], temporo-parietal [TP7-TP8], parietal-1 [P3-P4], parietal-2 [P7-P8], and occipital [O1-O2]), gamma dominant peak frequency order (three levels: first peak, second peak, and third peak), and hemisphere (two levels: left, right). Group (three levels: healthy young, healthy elderly, Alzheimer's Disease) was the between-group factor. The same design was used for both eyes-opened and eyes-closed conditions. Similar to the analyses of the power values, the frequency values of peaks were also analyzed with mixed design repeated measures ANOVA. Location (seven levels: frontal [F3-F4], central [C3-C4], temporal [T7-T8], temporo-parietal [TP7-TP8], parietal-1 [P3-P4], parietal-2 [P7-P8], and occipital [O1-O2]), the gamma dominant peak frequency order (three levels: first peak, second peak, and third peak), and hemisphere (two levels: left, right) were within-subject factors and the group as between-subject factor (three levels: healthy young, healthy elderly, Alzheimer's Disease). This design was applied to both eyes-opened and eyes-closed conditions.

Jamovi (1.6.12 version) (2021) was also used for post-hoc analyses. Bonferroni correction was used for multiple comparisons. The significance level was determined as $p < .05$. Greenhouse-Geisser corrected p values are reported.

Results

Frequency peak analysis of eyes-opened condition

A 7 (location: F3-F4, C3-C4, T7-T8, TP7-TP8, P3-P4, P7-P8, O1-O2) x 3 (gamma dominant peak frequency order: 1st, 2nd, 3rd) x 2 (hemispheres: right, left) x 3 (groups: Alzheimer Disease, healthy elderly, healthy young)

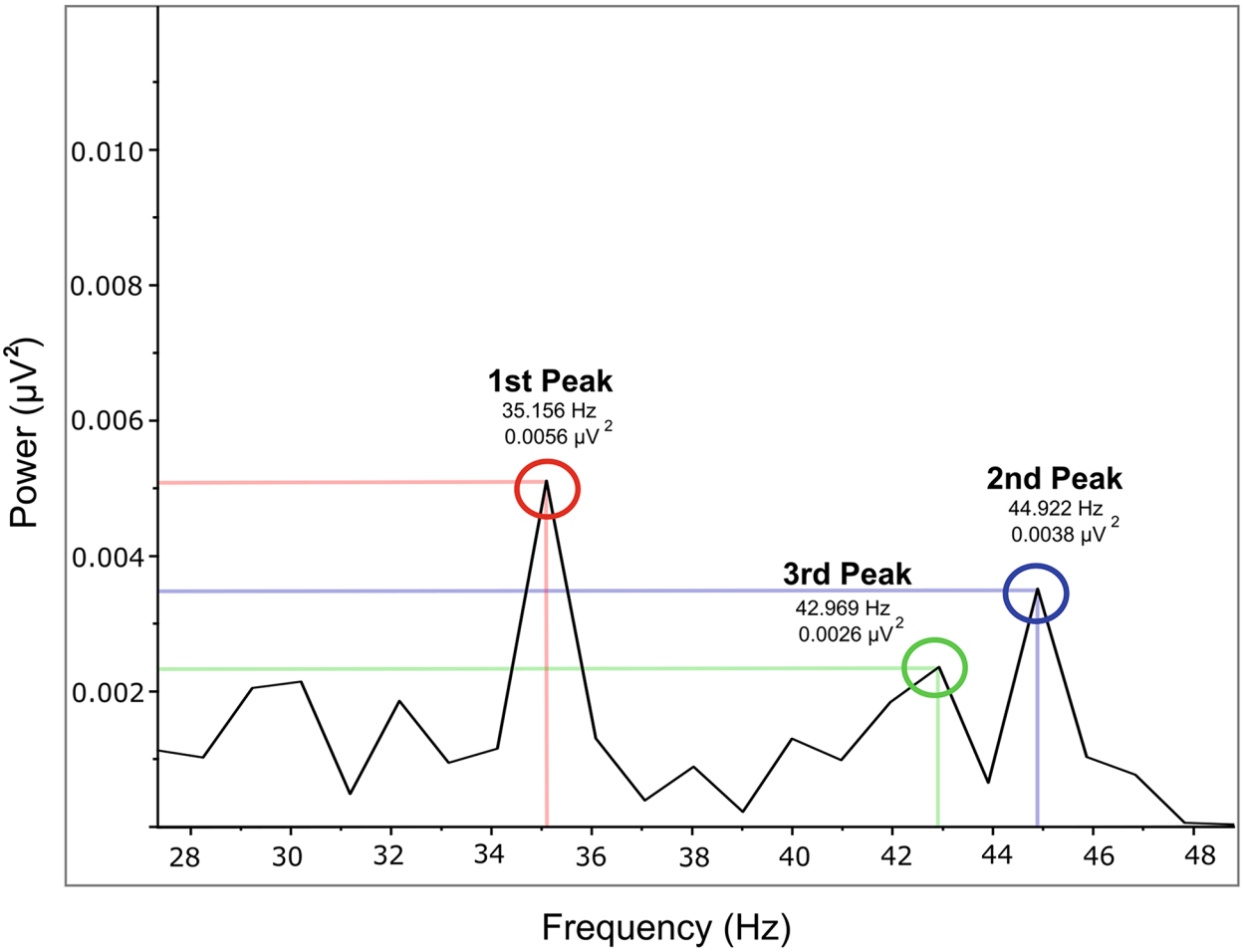

Fig. 1 Determination of the three highest gamma peaks for calculating the gamma dominant peak frequency method. The gamma dominant peak frequency is the average frequency value of the three highest gamma peaks

Greenhouse-Geisser corrected mixed design repeated measures ANOVA, in which the groups variable were between-subjects and all other variables were within-subjects variables, indicated that there was a main effect of groups in terms of gamma dominant peak frequency values, $F(2, 176) = 40.7$, $MSe = 221$, $p < .001$, $\eta 2 = 0.14$. A bonferroni corrected post-hoc analysis indicated that participants with Alzheimer Disease (AD) ($M = 33.4$, $SD = 3.22$) had lower gamma dominant peak frequency values than healthy elderly participants (HE) ($M = 35.5$, $SD = 2.00$) and healthy young participants (HY) ($M = 37.2$, $SD = 1.25$), $ps < 0.001$ (Fig. 2). Also, HE participants had lower gamma dominant peak frequency values than HY participants, $p < .001$. Moreover, there was a main effect of location on gamma dominant peak frequency values, $F(5.26, 926.47) = 46.36$, $MSe = 37.34$, $p < .001$, $\eta 2 = 0.07$. There was also an interaction between location and groups in terms of gamma dominant peak frequency values, $F(10.53, 926.47) = 13.41$, $MSe = 37.34$, $p < .001$, $\eta 2 = 0.04$. The post-hoc analyses indicated that the gamma dominant peak frequency values of AD participants were different from HE participants at the F3-F4 ($M_{AD} = 32.70$, $SD_{AD} = 3.92$; $M_{HE} = 35.13$, $SD_{HE} = 3.11$), P3-P4 ($M_{AD} = 31.66$, $SD_{AD} = 3.51$; $M_{HE} = 34.25$, $SD_{HE} = 3.00$), and O1-O2 ($M_{AD} = 31.83$, $SD_{AD} = 3.04$; $M_{HE} = 34.66$, $SD_{HE} = 2.96$) locations. Also, the gamma dominant peak frequency values of AD participants were different from HY participants at the C3-C4 ($M_{AD} = 32.38$, $SD_{AD} = 3.91$; $M_{HY} = 36.48$, $SD_{HY} = 2.48$), TP7-TP8 ($M_{AD} = 36.55$, $SD_{AD} = 4.01$; $M_{HY} = 37.89$, $SD_{HY} = 2.36$), P3-P4 ($M_{AD} = 31.66$, $SD_{AD} = 3.51$; $M_{HY} = 37.48$, $SD_{HY} = 2.60$), P7-P8 ($M_{AD} = 33.34$, $SD_{AD} = 3.91$; $M_{HY} = 37.72$, $SD_{HY} = 2.63$), and O1-O2 ($M_{AD} = 31.83$, $SD_{AD} = 3.04$; $M_{HY} = 38.49$, $SD_{HY} = 2.73$) locations. For HE participants, the gamma dominant peak frequency values were different from HY participants at the P3-P4 ($M_{HE} = 34.25$, $SD_{HE} = 3.00$; $M_{HY} = 37.48$, $SD_{HY} = 2.60$), P7-P8 ($M_{HE} = 35.40$, $SD_{HE} = 2.63$; $M_{HY} = 37.72$, $SD_{HY} = 2.63$), and O1-O2 ($M_{HE} = 34.66$, $SD_{HE} = 2.96$; $M_{HY} = 38.49$, $SD_{HY} = 2.73$) locations, $ps < 0.05$ (Fig. 3). Additionally, there

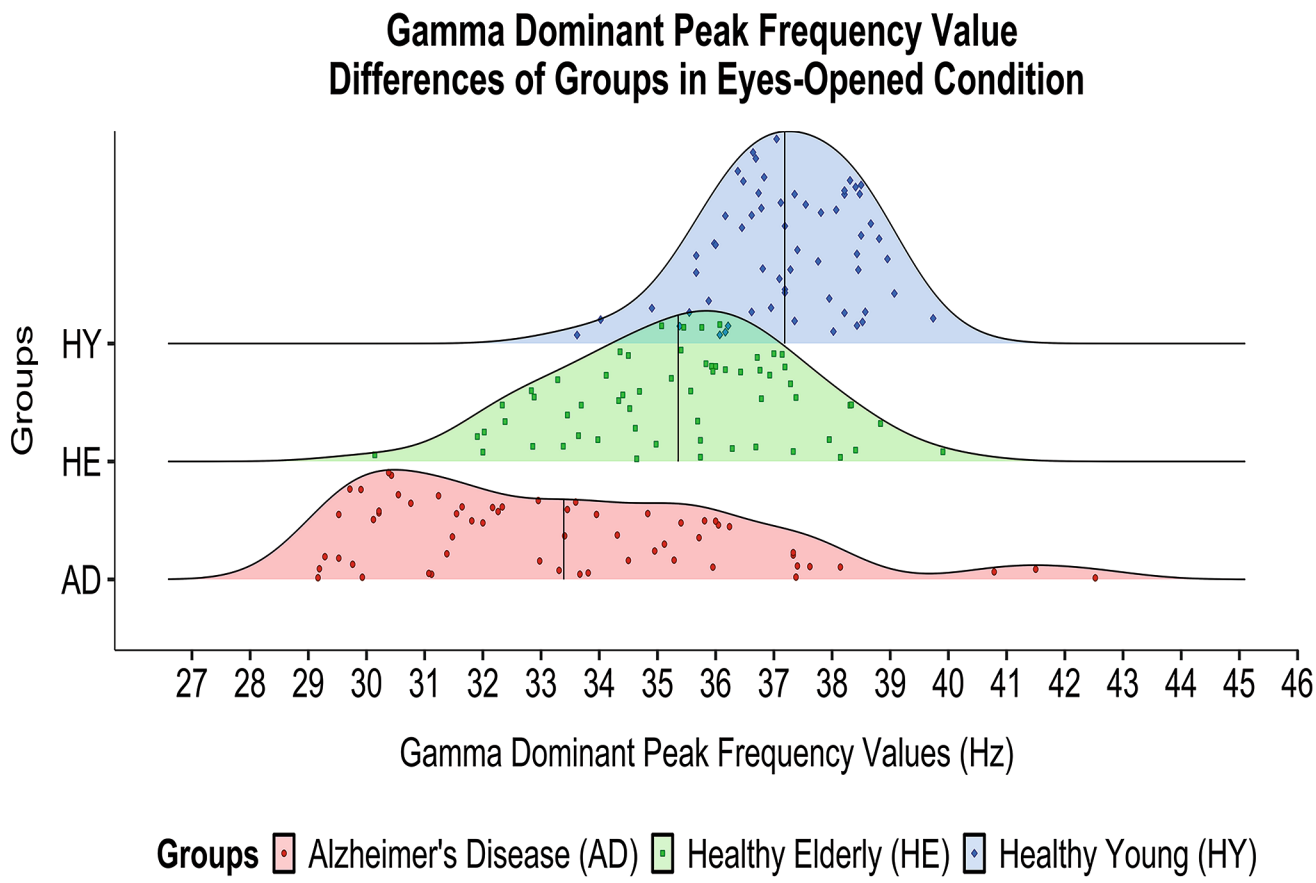

Fig. 2 Individual gamma dominant peak frequency values were calculated as the average of the highest three peaks detected in the gamma frequency band (28–48 Hz) and displayed as dots of various colors for each subject group for eyes-opened conditions. The black lines in the middle of the distributions indicate the mean value of each subject group and each dot indicates one subject in each subject group. Also, the distribution density of each group was depicted as colored areas on the y axis and the gamma dominant peak frequency values were depicted on the x axis. As shown in the figure, AD subjects had lower gamma dominant peak frequency values than HE and HY groups. Furthermore, the HE group had lower gamma dominant peak frequency values than the HY group, $ps < 0.001$

was a main effect of gamma dominant peak frequency order, $F(1.93,\ 339.66) = 31.55$, $MSe = 30.85$, $p < .001$, $\eta 2 = 0.01$. However, there was no interaction between gamma dominant peak frequency order and groups, $p > .10$. Bonferroni post-hoc analysis indicated that the first peak of AD participants ($M = 32.9$, $SD = 3.71$) was lower than the first peak of HE participants ($M = 34.6$, $SD = 2.60$) and HY participants ($M = 36.5, SD = 1.74$), $ps < 0.01$. Also, the second peak of AD participants ($M = 33.2, SD = 3.15$) was lower than the second peak of HE participants ($M = 35.6$, $SD = 2.33$) and HY participants ($M = 37.2, SD = 1.67$), $ps < 0.001$. The third peak of AD participants ($M = 34.1$, $SD = 3.16$) was also lower than the second peak of HE participants ($M = 35.8$, $SD = 2.09$) and HY participants ($M = 37.9, SD = 2.10$), $ps < 0.001$. Moreover, HE participants had lower values than HY participants for all three peaks, $ps < 0.05$ (Fig. 4). In addition to these, hemisphere had no main effect on gamma dominant peak frequency values and no interaction with groups, $ps > 0.10$.

Frequency peak analysis of eyes-closed condition

A 7 (location: F3-F4, C3-C4, T7-T8, TP7-TP8, P3-P4, P7-P8, O1-O2) x 3 (gamma dominant peak frequency order: 1st, 2nd, 3rd) x 2 (hemispheres: right, left) x 3 (groups: Alzheimer Disease, healthy elderly, healthy young) Greenhouse-Geisser corrected mixed design repeated measures ANOVA, in which the groups variable were between-subjects and all other variables were within-subjects variables, demonstrated that participants groups had a main effect on gamma dominant peak frequency values in eyes-closed condition, $F(2, 176) = 56.1$, $MSe = 206$, $p < .001$, $\eta 2 = 0.17$. It means that AD participants ($M = 32.7$, $SD = 3.15$) had lower gamma dominant peak frequency than HE participants ($M = 35.0$, $SD = 1.79$) and HY participants ($M = 37.0$, $SD = 1.27$), $ps < 0.001$. Also, HE participants had lower gamma dominant peak frequency than HY participants in terms of bonferroni post-hoc analysis, $p < .001$ (Fig. 5).

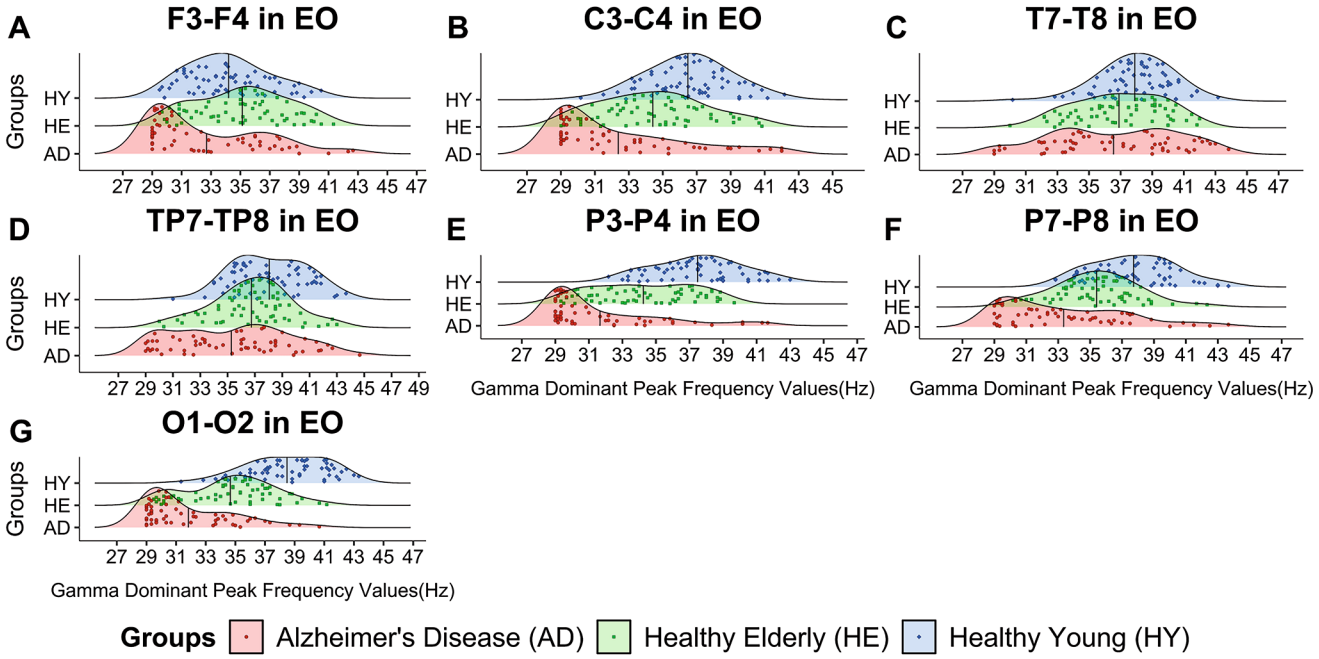

Fig. 3 Gamma dominant peak frequency differences of the groups in eyes-opened condition (EO) for all electrode pairs. The individual gamma dominant peak frequency values were calculated as the average of the highest three peaks detected in the gamma frequency band (28–48 Hz) and displayed as dots of various colors for each subject group for eyes-opened conditions. The black lines in the middle of the distributions indicate the mean value of each subject group, and each dot indicates one subject in each subject group. Also, the distribution density of each group was depicted as colored areas on the y axis and the gamma dominant peak frequency values were depicted on the x axis. (A) F3-F4*, (B) C3-C4*, (C) T7-T8, (D) TP7-TP8*, (E) P3-P4*, (F) P7-P8*, and (G) O1-O2* electrode pairs distributions in eyes-opened condition. As seen in the figure, AD patients had lower gamma dominant peak frequency values than HE subjects at P3-P4*, P7-P8*, and O1-O2*. Also, AD patients had lower gamma dominant peak frequency values than HY subjects at C3-C4*, T7-T8*, TP7-TP8*, P3-P4*, P7-P8*, and O1-O2*. Furthermore, HE subjects had lower gamma dominant peak frequency values than HY subjects at TP7-TP8*, P3-P4*, P7-P8*, and O1-O2*, (*: $p < .05$)

Additionally, there was a main effect of location on gamma dominant peak frequency values, $F(5.10, 897.18) = 39.38$, $MSe = 36.83$, $p < .001$, $\eta 2 = 0.05$. Also, there was an interaction between location and groups, $F(10.20, 897.18) = 12.96$, $MSe = 36.83$, $p < .001$, $\eta 2 = 0.04$. The post-hoc analyses indicated that the gamma dominant peak frequency values of AD participants were different from HE participants at the P3-P4 ($M_{AD} = 31.17$, $SD_{AD} = 3.04$; $M_{HE} = 34.25$, $SD_{HE} = 2.83$), P7-P8 ($M_{AD} = 32.24$, $SD_{AD} = 3.54$; $M_{HE} = 35.18$, $SD_{HE} = 2.62$), and O1-O2 ($M_{AD} = 31.33$, $SD_{AD} = 3.04$; $M_{HE} = 34.81$, $SD_{HE} = 2.82$) locations. In addition, the gamma dominant peak frequency values of AD participants were different from HY participants at the C3-C4 ($M_{AD} = 32.61$, $SD_{AD} = 2.29$; $M_{HY} = 36.04$, $SD_{HY} = 2.59$), T7-T8 ($M_{AD} = 35.00$, $SD_{AD} = 4.11$; $M_{HY} = 38.12$, $SD_{HY} = 2.05$), TP7-TP8 ($M_{AD} = 34.07$, $SD_{AD} = 4.34$; $M_{HY} = 38.20$, $SD_{HY} = 2.63$), P3-P4 ($M_{AD} = 31.17$, $SD_{AD} = 3.04$; $M_{HY} = 37.32$, $SD_{HY} = 2.83$), P7-P8 ($M_{AD} = 32.24$, $SD_{AD} = 3.54$; $M_{HY} = 38.50$, $SD_{HY} = 2.11$) and O1-O2 ($M_{AD} = 31.33$, $SD_{AD} = 3.04$; $M_{HY} = 37.43$, $SD_{HY} = 2.80$) locations. The gamma dominant peak frequency values of HE participants were different from HY participants at the TP7-TP8 ($M_{HE} = 35.70$, $SD_{HE} = 2.56$; $M_{HY} = 38.20$, $SD_{HY} = 2.63$), P3-P4 ($M_{HE} = 34.25$, $SD_{HE} = 2.83$; $M_{HY} = 37.32$, $SD_{HY} = 2.83$), P7-P8 ($M_{HE} = 35.18$, $SD_{HE} = 2.62$; $M_{HY} = 38.50$, $SD_{HY} = 2.11$) and O1-O2 ($M_{HE} = 34.81$, $SD_{HE} = 2.82$; $M_{HY} = 37.43$, $SD_{HY} = 2.80$) locations, $ps < 0.05$ (Fig. 6). Similar to eyes-opened condition, gamma dominant peak frequency order had a main effect on gamma dominant peak frequency values, $F(1.90, 334.16) = 22.21$, $MSe = 33.17$, $p < .001$, $\eta 2 = 0.01$. Also there was no interaction, $p > .10$. Bonferroni post-hoc analysis indicated that the first peak of AD participants ($M = 32.3$, $SD = 3.62$) was lower than the first peak of HE participants ($M = 34.2$, $SD = 2.58$) and HY participants ($M = 36.5$, $SD = 2.25$), $ps < 0.01$. Also, the second peak of AD participants ($M = 32.6$, $SD = 3.22$) was lower than the second peak of HE participants ($M = 35.1$, $SD = 2.30$) and HY participants ($M = 37.2$, $SD = 1.39$), $ps < 0.001$. The third peak of AD participants ($M = 33.2$, $SD = 2.92$) was also lower than the third peak of HE participants ($M = 35.6$, $SD = 1.82$) and HY participants ($M = 37.3$, $SD = 1.88$), $ps < 0.001$. Moreover, HE participants had lower values than HY participants for all three peaks, $ps < 0.02$ (Fig. 7). Hemisphere had also no main effect and interaction with groups, $p > .10$.

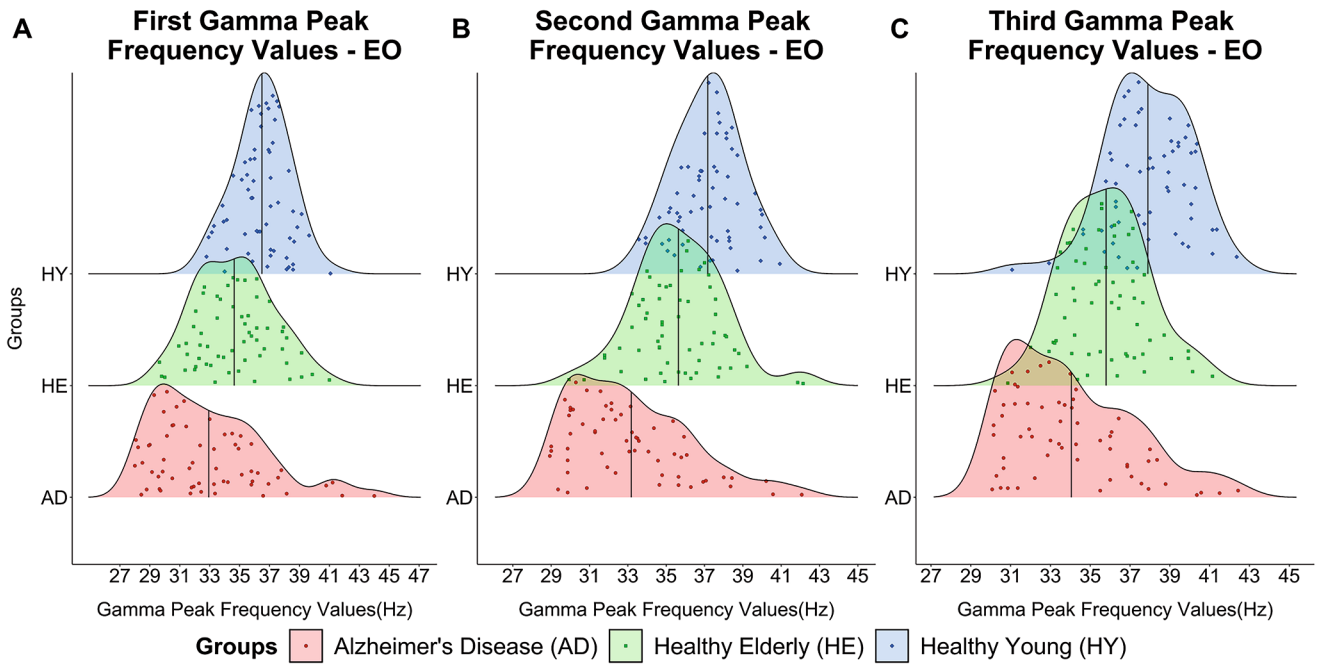

Fig. 4 Three highest gamma peak frequency differences of the groups in eyes-opened condition (EO) for all electrode pairs. The individual gamma peak frequency values were demonstrated as dots of various colors for each subject group. The black lines in the middle of the distributions indicate the mean value of each subject group, and each dot indicates one subject in each subject group. Also, the distribution density of each group was depicted as colored areas on the y axis and the gamma dominant peak frequency values were depicted on the x axis. (A) First gamma peaks**, (B) Second gamma peaks***, (C) Third gamma peaks***, (**: $p < .01$, ***: $p < .001$). As seen in the figure, AD patients had lower gamma peak frequency values than HE and HY subjects for all three peaks, ($ps < 0.01$). Furthermore, HE subjects had lower gamma peak frequency values than HY subjects for all three peaks, ($ps < 0.05$)

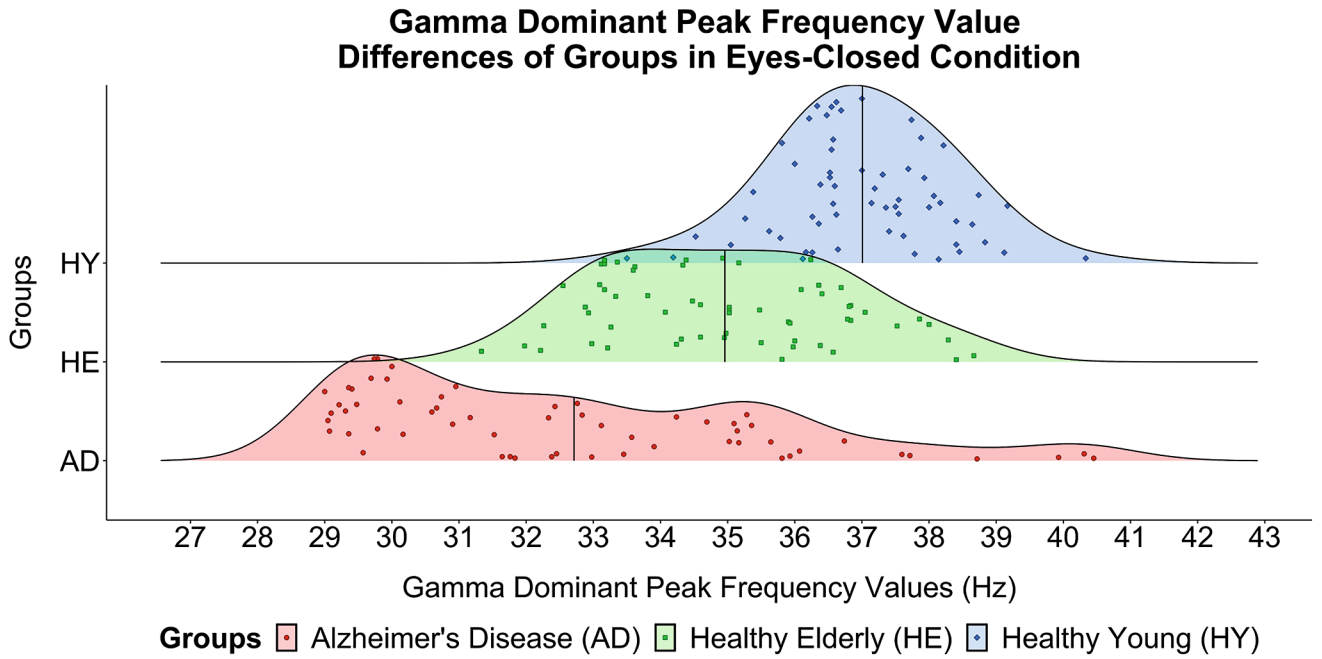

Fig. 5 Individual gamma dominant peak frequency values were calculated as the average of the highest three peaks detected in the gamma frequency band (28–48 Hz) and displayed as dots of various colors for each subject group for eyes-closed conditions. The black lines in the middle of the distributions indicate the mean value of each subject group, and each dot indicates one subject in each subject group. Also, the distribution density of each group was depicted as colored areas on the y axis and the gamma dominant peak frequency values were depicted on the x axis. As shown in the figure, AD subjects had lower gamma dominant peak frequency values than HE and HY groups. Furthermore, the HE group had lower gamma dominant peak frequency values than the HY group, $ps < 0.001$

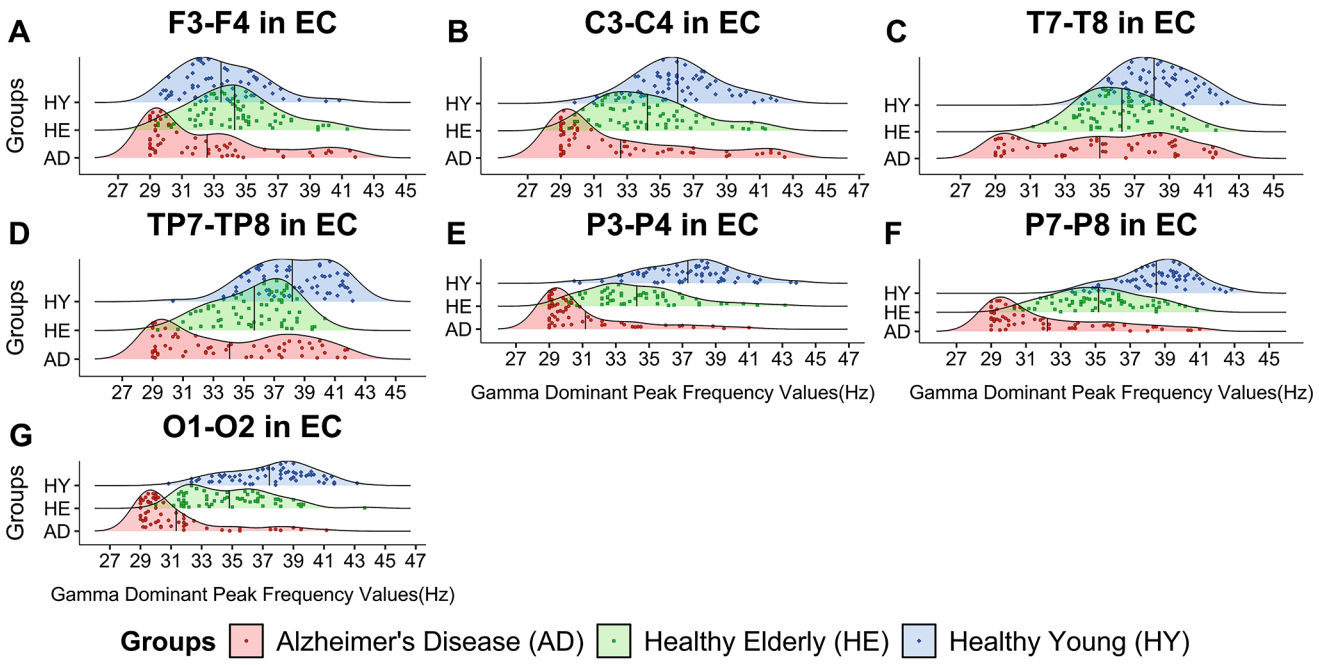

Fig. 6 Gamma dominant peak frequency differences of the groups in eyes-closed condition (EC) for all electrode pairs. The individual gamma dominant peak frequency values were calculated as the average of the highest three peaks detected in the gamma frequency band (28–48 Hz) and displayed as dots of various colors for each subject group. The black lines in the middle of the distributions indicate the mean value of each subject group and each dot indicates one subject in each subject group. Also, the distribution density of each group was depicted as colored areas on the y axis and the gamma dominant peak frequency values were depicted on the x axis. (A) F3-F4, (B) C3-C4*, (C) T7-T8*, (D) TP7-TP8*, (E) P3-P4*, (F) P7-P8*, and (G) O1-O2* electrode pairs distributions in eyes-closed condition (*: $p < .05$). As seen in the figure, AD patients had lower gamma dominant peak frequency values than HE subjects at F3-F4*, P3-P4*, and O1-O2*. Also, AD patients had lower gamma dominant peak frequency values than HY subjects at C3-C4*, TP7-TP8*, P3-P4*, P7-P8*, and O1-O2*. Furthermore, HE subjects had lower gamma dominant peak frequency values than HY subjects at P3-P4*, P7-P8*, and O1-O2*, (*: $p < .05$)

Power analysis of eyes-opened condition

A mixed design repeated measures ANOVA was performed for investigating the power value of the first three peak frequencies of the participant groups. This 7 (location: F3-F4, C3-C4, T7-T8, TP7-TP8, P3-P4, P7-P8, O1-O2) x 3 (gamma dominant peak frequency order: 1st, 2nd, 3rd) x 2 (hemisphere: right, left) x 3 (groups: Alzheimer Disease, healthy elderly, healthy young) Greenhouse-Geisser corrected mixed model ANOVA indicated that there was a main effect of participant groups, $F(2, 176) = 29.5, MSe = 2.36, p < .001, \eta 2 = 0.15$. The effect is related to AD participants group because the bonferroni post hoc analysis showed that AD participants ($M = 0.33$, $SD = 0.41$) had higher power value than HE participants ($M = 0.04$, $SD = 0.03$) and HY participants ($M = 0.04$, $SD = 0.03$), $ps < 0.001$. However, there was no difference between HE participants and HY participants, $p = 1$ (Fig. 8). Together with this, there was a main effect of location, $F(2.50, 439) = 18.18, MSe = 0.59, p < .001, \eta 2 = 0.03$. Also, there was an interaction between location and participant groups, $F(5.00, 439) = 9.60$, $MSe = 0.59$, $p < .001$, $\eta 2 = 0.03$. The P3-P4 electrode pair ($M = 0.07$, $SD = 0.14$) had the lowest power value, and the T7-T8 electrode pair ($M = 0.24$, $SD = 0.55$) had the highest power value. Additionally, gamma dominant peak frequency order had a main effect on power value, $F(1.07, 188) = 61.26$, $MSe = 0.01, p < .001, \eta 2 = 0.0008$. There was also an interaction between gamma dominant peak frequency order and participant groups, $F(2.14, 188) = 8.62, MSe = 0.01, p < .001$, $\eta 2 = 0.0002$. Bonferroni post-hoc analysis demonstrated that all three power values were not different for HE participants and HY participants, $ps = 1$. However, the power value of first peak of AD participants ($M = 0.35$, $SD = 0.44$) was higher than the first peaks of HE participants ($M = 0.05$, $SD = 0.04$) and HY participants ($M = 0.04$, $SD = 0.04$), $ps < 0.001$. Also, the power value of the second peak of AD participants ($M = 0.32$, $SD = 0.41$) was higher than the second peaks of HE participants ($M = 0.04$, $SD = 0.04$) and HY participants ($M = 0.04, SD = 0.03), ps < 0.001$. The third peak of AD participants ($M = 0.31, SD = 0.38$) was higher than the third peaks of HE participants ($M = 0.04$, $SD = 0.03$) and HY participants ($M = 0.03$, $SD = 0.03$), $ps < 0.001$.

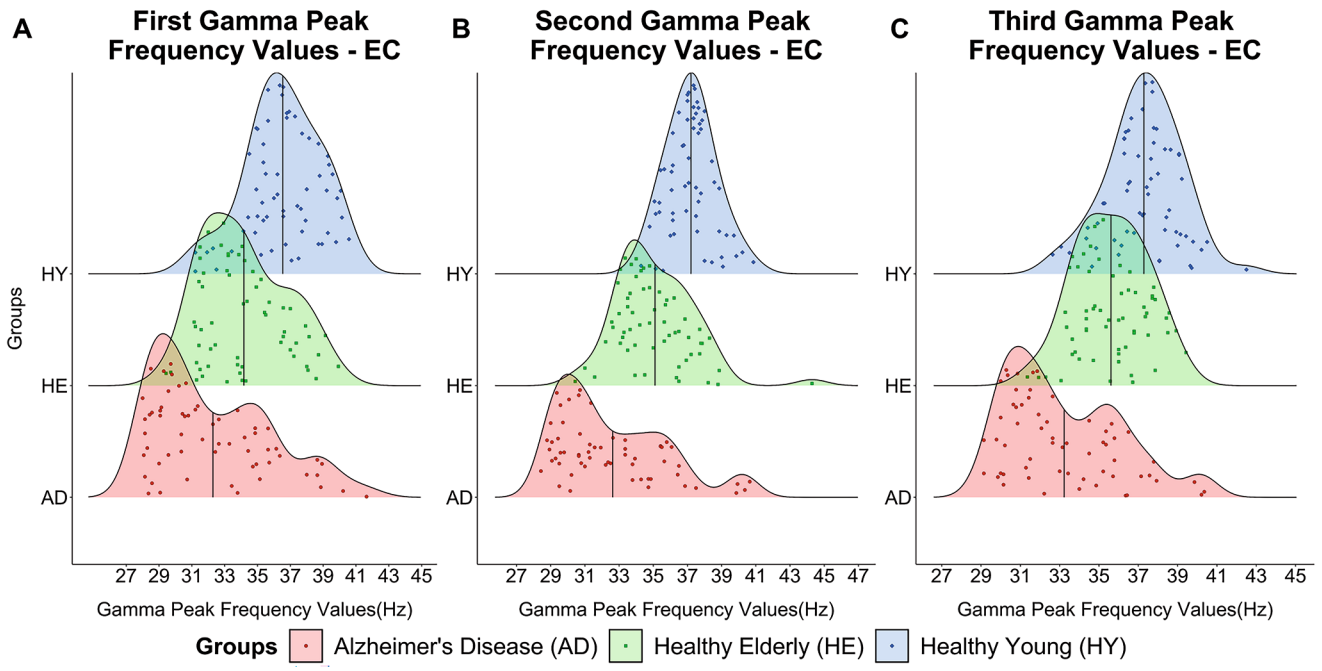

Fig. 7 Three highest gamma peak frequency differences of the groups in eyes-closed condition (EC) for all electrode pairs. The individual gamma peak frequency values were demonstrated as dots in different colors for each subject group. The black lines in the middle of the distributions indicate the mean value of each subject group, and each dot indicates one subject in each subject group. Also, the distribution density of each group was depicted as colored areas on the y axis and the gamma dominant peak frequency values were depicted on the x axis. (A) First gamma peaks**, (B) Second gamma peaks***, (C) Third gamma peaks***, (**: $p < .01$, ***: $p < .001$). As seen in the figure, AD patients had lower gamma peak frequency values than HE and HY subjects for all three peaks, ($ps < 0.001$). Furthermore, HE subjects had lower gamma peak frequency values than HY subjects for all three peaks, ($ps < 0.02$)

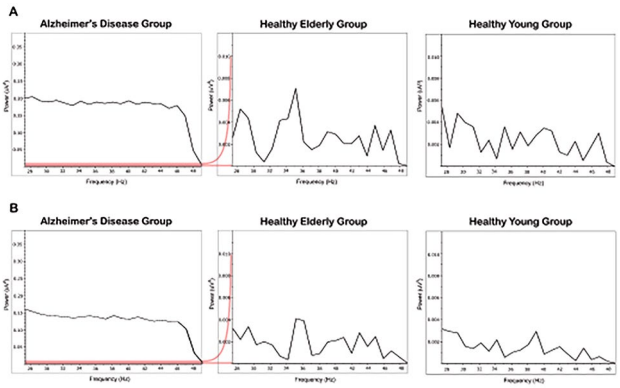

Fig. 8 Power value differences of the groups in P7-P8 electrode pair. (A) The power value differences of groups at the P7-P8 electrode pair in eyes-opened condition. (B) The power value differences of groups at the P7-P8 electrode pair in eyes-closed condition. To emphasize the scale differences of the y-axis among the groups, we used red lines as a reference for the distribution ranges of the HY and HE subject groups in the AD patient group distribution

Power analysis of eyes-closed condition

For the power analysis of the eyes-closed condition, a mixed design repeated measures ANOVA was performed as well as the eyes-opened condition. This 7 (location: F3-F4, C3-C4, T7-T8, TP7-TP8, P3-P4, P7-P8, O1-O2) x 3 (gamma dominant peak frequency order: 1st, 2nd, 3rd) x 2 (hemispheres: right, left) x 3 (groups: Alzheimer Disease, healthy elderly, healthy young) Greenhouse-Geisser corrected mixed model ANOVA demonstrated that the participant groups had a main effect on the power values, $F(2, 176) = 24.60$, $MSe = 0.01$, $p < .001$, $\eta 2 = 0.15$. As reported by the bonferroni post-hoc analysis, AD participants ($M = 0.25$, $SD = 0.35$) had higher power value than HE participants ($M = 0.03$, $SD = 0.03$) and HY participants ($M = 0.03$, $SD = 0.02$), $ps < 0.001$. There was no difference between HE participants and HY participants, $p = 1$ (Fig. 8). Furthermore, there was a main effect of location, $F(2.53, 445) = 12.90$, $MSe = 0.27$, $p < .001$, $\eta 2 = 0.02$; and interaction between location and participant groups, $F(5.07, 445) = 7.18$, $MSe = 0.27$, $p < .001$, $\eta 2 = 0.02$. The lowest power value was at the P3-P4 electrode pair ($M = 0.068$, $SD = 0.14$), and the highest was at the F3-F4 electrode pair ($M = 0.15$, $SD = 0.36$). Also, there was a main effect of gamma dominant peak frequency order, $F(1.15, 201) = 54.78$, $MSe = 0.009$, $p < .001$, $\eta 2 = 0.001$. There was an interaction between gamma dominant peak frequency order and participant groups, $F(2.29, 201) = 9.84$, $MSe = 0.009$, $p < .001$, $\eta 2 = 0.0003$. Bonferroni post-hoc analysis indicated that the first peak's power value of AD participants ($M = 0.27$, $SD = 0.37$) is higher than the first peaks' power

value of HE participants ($M = 0.04$, $SD = 0.04$) and HY participants ($M = 0.03$, $SD = 0.02$), $ps < 0.001$. Similarly, the second peak's power value of AD participants ($M = 0.25$, $SD = 0.35$) is higher than the second peaks' power value of HE participants ($M = 0.03$, $SD = 0.03$) and HY participants ($M = 0.02$, $SD = 0.02$), $ps < 0.001$. For the third peaks, AD participants ($M = 0.24$, $SD = 0.33$) had higher power value than HE participants ($M = 0.02$, $SD = 0.02$) and HY participants ($M = 0.02$, $SD = 0.01$), $ps < 0.001$.

Discussion

This paper investigated the gamma dominant peak frequencies of Alzheimer's disease patients, healthy elderly, and healthy young subjects from their rsEEG recordings. Our results demonstrated that Alzheimer's disease patients had lower gamma dominant peak frequency than healthy elderly and young subjects. Also, the gamma dominant peak frequency of healthy elderly was lower than those of healthy young subjects. Specifically, the gamma dominant peak frequencies across groups were approximately 33 Hz in Alzheimer's disease patients, 35 Hz in healthy elderly subjects and 37 Hz in healthy young subjects. These results suggest that decreases in the gamma dominant peak frequency can be seen both with age progression and cognitive decline.

In the literature, gamma oscillations have been associated with memory, attention and perception mechanisms especially at the hippocampal regions (Jensen et al. 2007). On the other hand, hippocampal atrophy and declined performances in various cognitive domains such as memory, attention and perception, have previously been reported in Alzheimer's disease pathology (Frisoni et al. 2010; Frankó and Joly 2013) and healthy aging processes (Pelletier et al. 2013; Svenningsson et al. 2019). In addition to these structural and behavioral alterations, we found a decrease in the resting state EEG gamma dominant peak frequency of diagnosed Alzheimer's patients and healthy elderly participants.

In recent years, studies on gamma entrainment have indicated that 40 Hz visual and auditory gamma entrainment application may have a curative effect on Alzheimer's disease (Iaccarino et al. 2016; Martorell et al. 2019; Adaikkan et al. 2019; Garza et al. 2020). However, in another study conducted in the light of these findings, Lee and colleagues (2021) showed that the optimal gamma entrainment application was in the 34–38 Hz range and with 400 cd/m^2 white light on healthy young participants. Therefore, on one hand, in studies that focus on the gamma entrainment application side, further investigations are necessary to identify the optimal frequency value within the different frequencies of gamma frequency entrainment applications. On the other hand, in studies investigating the current situation, Murty and colleagues (2020) demonstrated that the gamma center frequency of healthy elderly subjects is lower than the younger subjects in their study in which they investigated the changes of the oscillations during normal aging. In addition to all these studies, to our knowledge, our study is the first study in terms of showing the gamma dominant peak frequency differences between Alzheimer's disease patients, healthy elderly, and healthy young subjects for a better understanding of the current situation and demonstrating the current status of Alzheimer's disease patients compared to healthy elderly and healthy young people. Specifically, according to our findings, the gamma dominant peak frequency of Alzheimer's disease patients was around 33 Hz, while it was around 35 Hz for healthy elderly and 37 Hz for healthy young subjects, respectively. Taking these results into consideration, applying gamma entrainment to Alzheimer's disease patients at 35 Hz, which was the gamma dominant peak frequency of healthy elderly participants, as opposed to current gamma entrainment studies that use 40 Hz (Iaccarino et al. 2016; Ismail et al. 2018; Adaikkan et al. 2019; Jones et al. 2019; Martorell et al. 2019; Garza et al. 2020; He et al. 2021), may yield better results at the beginning of the therapy. It would also be in the optimal frequency range (34–38 Hz) proposed by Lee and colleagues (2020). In other words, we may see better curative effects of gamma entrainment on Alzheimer's disease if we entrain the gamma dominant peak frequency of AD patients to 35 Hz as an initial stage of the treatment process and increase the frequency value of the application step by step towards 37 Hz.

On the other hand, the results of the power analyses revealed that AD patients had higher power values compared to healthy subjects, as opposed to previous studies that reported decreased power in AD patients and multiple AD mice models (Herrmann and Demiralp 2005; Verret et al. 2012; Gillespie et al. 2016; Palop and Mucke 2016; Martinez-Losa et al. 2018). The reason for this inconsistency could be attributed to the patients' varying disease durations in these studies. As previously mentioned in the methods section, the data of Alzheimer's disease patients that we included in our retrospective analysis belonged to early stage AD patients. To clarify, differences in power values of patients at different stages of the disease may be explained by differences in pathophysiological and behavioral features observed across the Alzheimer's disease continuum (Sperling et al. 2011). Increased power in rsEEG gamma oscillations in preclinical AD subjects (Gaubert et al. 2019) and mild AD patients (Van Deursen et al. 2008; Wang et al. 2017) may have occurred as a possible compensatory mechanism in the early stages of Alzheimer's disease pathology, which is consistent with our findings. On the other hand,

this increase in power could have been caused by a disruption in hippocampal parvalbumin positive inhibitory interneurons (PV cells) (Verret et al. 2012; Goutagny and Krantic 2013; Xu et al. 2020), which are selectively vulnerable to Alzheimer's disease pathophysiology (Brady and Mufson 1997). Impairment of these inhibitory interneurons has been shown to disrupt the balance of excitatory and inhibitory activities, which is essential for the generation of hippocampal gamma oscillations, and lead to aberrant network activity (Stargardt et al. 2015; Rey et al. 2019). Together with these disruptions, the fact that there were also epileptic seizures in AD mouse models gives the idea that there could be a connection between these aberrant network activities and epileptic seizures in AD (Palop et al. 2007). In line with this idea, there were epileptiform activities in AD patients in the early stage of the disease as well (Vossel et al. 2013, 2016). As a result, our findings regarding the increased power in rsEEG gamma oscillations may be explained by observations of epileptiform activity reported in AD patients (Palop et al. 2007; Palop and Mucke 2009), particularly in the early stages of the disease (Palop and Mucke 2010b; Palop et al. 2006; Vossel et al. 2013). Moreover, related to their roles in generating hippocampal gamma rhythms, PV cells have been suggested to be involved in the cross-frequency coupling between theta and gamma oscillations as well. In genetically modified mice (Wulff et al. 2009), removing fast synaptic inhibition of PV cells have resulted in significantly reduced theta-gamma coupling, which have demonstrated the importance of an intact network of GABA-ergic interneurons underlying this process. Overall, the various causes mentioned above as potentially underlying the lower frequency and higher power findings in rsEEG gamma activity in AD patients were speculations. Future studies are necessary to test and validate these hypotheses before making confident statements about the effects of these variables on our findings.

Moreover, theta-gamma coupling has been linked to working memory performance in the literature. To put it more explicitly, theta-gamma phase-amplitude coupling theory claims that the number of gamma cycles within a theta cycle would predict working memory capacity (Lisman and Idiart 1995; Sauseng et al. 2010, 2019). According to this theory, slower theta oscillations with lengthier cycles would allow a greater number of gamma cycles nested within them and since each gamma cycle suggested to represent a memory item (Axmacher et al. 2010), slowing down theta oscillations with external modulation would result in higher working memory capacity (Alekseichuk et al. 2016; Wolinski et al. 2018). Furthermore, when compared to MCI subjects and healthy controls, Alzheimer's disease patients had reduced theta-gamma coupling levels and poorer working memory performance (Goodman et al. 2018; Lahijanian et al. 2021). Taking these findings into consideration, we think that decreased gamma dominant peak frequency in AD patients may be contributing to the decreases in theta-gamma coupling levels and working memory performance of these patients. In other words, we suggested that decreases in the working memory performance related to the number of gamma cycles within a theta phase may have occurred due to the decreased gamma dominant peak frequency of AD patients in the progression of the pathology. However, assuming such an intricate relationship as this one requires further evidence. As a result, future research could look into changes in theta band dominant peak frequency and working memory performance in AD patients, in addition to their altered gamma dominant peak frequency and theta-gamma coupling to explore the relationship we proposed.

Lastly, our results should be interpreted considering the possible effects of scale-free property activity which is arrhythmic and has a trend in which lower frequency brain signals have higher power values than higher frequency brain signals (Keil et al. 2022). Brain signals comprise both scale-free and oscillatory activity. Because of their different spatiotemporal characteristics, it is possible to distinguish them with further analyses (He, 2014). Moreover, some physiological and psychological factors such as aging have been shown to affect the characteristics of scale-free activity, particularly the power values across frequencies (Ao et al. 2022; Smit et al. 2011). Taken all this together, it could be expected this activity to differentially affect the power values of different age groups in our dataset. On the other hand, our findings revealed significantly higher power values in AD patients but similar power values in healthy young and healthy elderly groups. But still, a careful distinction between scale-free and oscillatory activity may provide a better understanding of the changes in EEG brain oscillations. Future studies could separately examine the effects of scale-free and oscillatory activities on EEG gamma oscillations (28–48 Hz) in healthy people and in Alzheimer's disease patients to identify aging as well as pathology-related changes in these activities.

Conclusion

In conclusion, these findings demonstrated that the decreased gamma dominant peak frequency could be a new diagnostic criteria of Alzheimer's disease as a non-invasive biomarker. Further empirical support regarding the decreased rsEEG gamma oscillation frequency in Alzheimer's disease patients compared to healthy elderly and young controls will strengthen the accuracy of this electrophysiological biomarker in determining the presence of AD related pathology. We think that a gradual decrease of the gamma

dominant peak frequency across healthy young, healthy elderly, and Alzheimer's disease patients groups could be a sign of the progression of the disease. In other words, the decrease in the gamma dominant peak frequency could be a marker for the standpoint of the patient in the spectrum which starts from the preclinical Alzheimer's Disease stage and ends with the severe Alzheimer's disease. Therefore, further longitudinal or between subject studies could compare patients from the preclinical, early, and late stages of Alzheimer's disease in order to gain a better understanding of the alterations in the gamma dominant peak frequency characteristics of patients throughout the progression of the disease.

Our results demonstrated the step by step decrease in the gamma dominant peak frequency as approximately 37 Hz for healthy youngs, 35 Hz for healthy elderly, and 33 Hz for Alzheimer's disease patients, respectively. Therefore, we suggest that recent gamma entrainment applications should use 35 Hz in the entrainment applications as opposed to current gamma entrainment applications which use 40 Hz because entraining the Alzheimer's disease patients gamma dominant peak frequency to the healthy elderly's could be a better application as opposed to 40 Hz as an initial stage of the entrainment therapy. Also, as the gamma entrainment therapy progresses, the applied frequency can be increased towards 37 Hz, which is the gamma dominant peak frequency of healthy young people.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11571-022-09873-4.

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Data Availability The data supporting the findings of the article is available in the Resting-state EEG Gamma in Alzheimer at https://osf.io/5sfa4/ (Güntekin et al. 2022).

Declarations

Ethics approval and consent to participate For all participants included in this retrospective analysis, an informed consent form was obtained at the time of data collection. Ethical approval for this study was obtained from the ethics committee of Istanbul Medipol University (no: E-10840098-772.02-5002).

Conflict of interest Authors declare having no conflict of interest.

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