Research Article

Abnormal Slow Electroencephalography Activity in Eyes-Open and Eyes-Closed Conditions as an Optimal Marker for Tinnitus

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Short running title: Abnormal slow electroencephalography…

Highlights:
- Eyes open/closed conditions in EEG recording is important for tinnitus patients
- Changes in alpha and delta power in eyes open/closed conditions may indicate tinnitus
- The delta+theta/alpha+beta ratios can be an indicator of tinnitus

ABSTRACT
Background and Aim: Recent studies try to clarify the difference of neuro-physiological responses of people with tinnitus. Quantitative Electroencephalography (QEEG) analysis is different in the eyes-closed or eyes-open conditions. This study aimed to compare the EEG activity of tinnitus patients between eyes-closed and eyes-open conditions at rest position.
Methods: Participants were 46 people with tinnitus (34 males and 12 females). Their QEEG was recorded in two eye conditions (close/open) for three minutes at resting position. Relative power of delta, theta, alpha, beta and

gamma bands were estimated. Paired t-test was used for comparison of Delta/Alpha Ratio (DAR), and Delta+Theta/Alpha+Beta Ratio (DTABR) between the two eye conditions.
Results: The DAR and DTABR ratios were significantly higher in the eyes-open condition compared to the eyes-closed condition ($p=0.009$ and $p=0.016$, respectively). The delta power increased and alpha power decreased significantly in the eyes-open condition compared to the eyes-closed condition ($p<0.001$).
Conclusion: People with tinnitus have different EEG activities in eyes open/closed conditions. Increased delta power and decreased alpha power in the eyes-open condition may be an indicative of severe tinnitus. It seems better to record EGG activity with eyes open. Increased DAR is a good indicator in the eyes-open condition which is recommended to be used as a potential biomarker for comparing the severity of tinnitus.
Keywords: Tinnitus; quantitative electroencephalography; delta to alpha ratio; biomarker

Introduction

Previously, it had been thought that subjective tinnitus problem is only related to the peripheral auditory system [1, 2], but currently there is a widely accepted view that this auditory phantom perception is the result of failed compensatory mechanisms in the brain and it does not seem to cause only inner ear receptor damage [3, 4]. The Electroencephalography (EEG) studies have led to the identification of tinnitus-related abnormalities in spontaneous brain activity at rest position. These studies indicate that, in the resting state, activity of delta (0.5–4 Hz) and gamma (35.5–45 Hz) frequency bands increase, whereas alpha oscillations (8.5–12 Hz) in temporal regions may decrease [5, 6]. These findings are based on the Thalamocortical Dysrhythmia (TCD) model [7] which was further expanded to the Synchronization-by-Loss-of-Inhibition-Model (SLIM) [6]. In the TCD model, it is proposed that the spontaneous firing of thalamic fibers appears due to the deprivation of auditory input, and this phenomenon is proposed as a necessary factor for the occurrence of tinnitus [7].
In fact, following the deprivation of thalamic relay cells from inner ear excitatory inputs, the cell membrane becomes hyperpolarized, and these neurons generate low-threshold calcium bursts in slow wave mode. Thalamocortical feedback loops lead to this slow wave rhythm in cortical neurons that can be recorded as delta activity on the scalp. The increase in the gamma frequency range may be caused by a decrease in lateral inhibition in the auditory cortex due to a decrease in the activity of inhibitory neurons [6]. Therefore, this imbalance between inhibition and stimulation in the cerebral cortex is a theoretical explanation for the low alpha/ high delta pattern, which is usually found in the resting state EEG data of tinnitus patients [7].
There are few studies that suggest that the resting state EEG with eyes closed and open are different. Most of these studies have shown the increased delta and alpha power in the eyes-closed condition compared to the eyes-open condition, while some studies have shown increased beta band in the eyes-open condition in young and healthy old people [8, 9]. In the eyes-open condition, higher alpha power is usually observed specially in the posterior regions. This finding associated with reduced relaxed attention and sensory perception [8, 10]. In the eyes-closed condition, alpha power decrease and beta activity increase specially in the frontal lobes that are associated with increased arousal and visual processing [8]. In this condition, greater activity have recorded in sensorimotor and visual networks, while in the eyes open condition higher activities have recorded in the default mode, salience, and frontoparietal networks [11, 12]. According to above mentioned findings based on neural network, EEG recording in different eye condition leads to different recording, analysis and interpretations [13, 14].
The rhythm and power of neural oscillations in the alpha band have been recently proposed as marker for the temporal resolution of visual perception. The Individual Alpha Frequency (IAF) peak in the resting state EEG has been used as frequency of sensory (audio/visual) tasks [15]. Alpha band activity is associated with a wide range of processes encompassing memory, perception, decision and cognitive functioning. IAF is a specific parameter for the alpha activity [16]. Closing or opening eyes at rest position can affect IAF in people with tinnitus due to cognitive and perceptual consequences of tinnitus. Although the apparent mechanism of deviation in the Delta/Alpha Ratio (DAR) and Delta-Theta/Alpha-Beta Ratio (DTABR) in tinnitus is still uncertain, researchers have suggested that delta/alpha tends to increase in tinnitus, without specific underlying documentation and only used for neurofeedback therapy [17]. This study aimed to compare the power of delta and alpha band frequencies in people with tinnitus at resting position with eyes closed or open and assess the relationship between eyes-closed and eyes-open conditions in tinnitus by the DAR and DTABR.

Methods

Participants

Forty-six people with tinnitus (34 males and 12 females) participated in this study after declaring informed consent. They were recruited from the audiology clinic of Rofeideh Rehabilitation Hospital, Tehran, Iran, during the first 6 months of 2023. The inclusion criteria were: Chronic tinnitus for more than 6 months, age 30–60 years, existence of tonal and subjective tinnitus, tinnitus sensation in one or both ears, no pulsating and multi-tonal tinnitus, no Meniere's disease or fluctuating hearing level, no cerebellopontine angle tumors or any diagnosed neurological disease, no any history of cardiovascular diseases, no severe to profound hearing loss, no obvious complaints of hyperacusis symptoms, no use of hearing aids, not receiving any tinnitus treatment, an average hearing threshold of 20–60 dB at 2000–8000 Hz frequency, mild to severe score for total Tinnitus Handicap Index (THI) at the initial assessment, moderate score in the Hospital Anxiety and Depression Scale (HADS), no use of sedatives drugs, no epilepsy and convulsions according to a neurologist or psychiatrist. The exclusion criteria were: Failure to noise-free recording of brain activity during three minutes of recording, report of increased tinnitus during brain activity recording, occurrence of fatigue in the form of non-cooperation during brain activity recording, caffeine use (tea, coffee) at least four hours before recording brain activity, washing hair with shampoo at least four hours before brain activity recording.

Measurements

Persian versions of the THI and the Visual Analog Scale (VAS) were completed by participants before EEG recording [18]. The EEG activity was recorded quantitatively (bandwidth of 0.2–70 Hz, impedance <20 kHz, and a sampling rate of 1024 Hz) with a 64-channel amplifier (ANT Neuro, Hengelo, Netherlands) according to the international 10–20 system using 30 Ag/AgCl surface electrodes with 8-mm diameter distributed over the head of the participants. The electrodes were placed in central and bilateral places in F, C, T, P and O areas. A reference electrode was placed on the mastoid process and a ground electrode was placed on the right hand's wrist. To record vertical and horizontal electrooculogram, a pair of electrodes were placed above and below the right eye and another pair on either side of each eye. We utilized the KEY Institute's standardized Low-Resolution Brain Electromagnetic Tomography Analysis (sLORETA) method to estimate the intracerebral neural brain responsible for the recorded electrical activities. The sLORETA calculates electrical activity by measuring absolute and relative power. The sLORETA solution space comprises 6239 voxels with a voxel size of 5×5×5 mm, and is limited to cortical gray matter, hippocampi, and amygdala. The coordinates of the electrodes are based on a probabilistic brain volume defined by the Montreal neurological Institute. We exported the EEG data that were free from artifacts in ASCII format from MATLAB to sLORETA software. Using this software, we calculated EEG cross-spectrum and sLORETA transformation matrix across five frequency bands (delta, theta, alpha, beta and gamma).

The TCD state was measured and the frequency ranges of delta, theta, alpha, beta, and gamma (by sLORETA software) and the relative power of each rhythm was evaluated. With the electrooculogram of O1 and O2 electrodes, blinking and eye movement artifacts were controlled. EEG activity was recorded in two eye conditions (closed and open) at rest (sitting) position in a silent room for three minutes. The DAR and DTABR as a specific variable were measured and compared between the two eyes-closed and eyes-open conditions.

Data analysis

Analysis of EEG data were done offline with band pass filtered (1–70 Hz) and re-referenced to linked earlobes and then imported into the EEG Lab toolbox of MATLAB software. Independent Component Analysis (ICA) was applied to eliminate residual artifacts caused by muscle movement, eye blinks and ECG components, subsequently exploiting a fast Fourier transform for the distinct frequency bands: delta (0.2–4 Hz), theta (5–7 Hz), alpha (8–12Hz), beta (13–30 Hz), and gamma (31–45 Hz). The relative power of each frequency band was measured at each electrode in sLORETA software using the following equation: R(h)=100*E(h)/E total, where R(h) is the relative power, E(h) is the absolute power in each frequency band, and E total is the sum of powers in all frequency bands. The DAR and DTABR were measured from the average power of all brain areas for each condition (open/close eyes) in resting position.

Statistical analysis

Statistical analyses were performed in SPSS v.17. The variables were described using means and standard deviations. According to the Kolmogorov-Smirnov test, data distribution was normal for all study outcomes whereas beta and gamma relative power were abnormal in some areas. Therefore, we used paired t-test for parametric variables and Wilcoxon test for non-parametric variables. To recognize potential differences in source localization of brain electrical activity in two different eye conditions, the current density distributions were contrasted by using the sLORETA method. The Statistical Nonparametric Mapping (SnPM) of sLORETA images was conducted for each contrast using sLORETA's built-in voxel-wise randomization tests (5000 permutations) with a threshold p<0.05.

Results

The participants were 34 males and 12 females with tinnitus aged 30–56 years with a mean age of 46.6+5.9 years, a THI score of 46.52±1.84, and a VAS score of 5.65±0.83. The results of comparing the relative power of frequency bands between two eye conditions are presented in Table 1 and the DAR and DTABR comparison are illustrated in Figure 1. The results of comparing the relative power between two eye conditions based on the SnPM of sLORETA images are illustrated in Figure 2.
There were significant differences in the relative power of delta (t=6.379, p<0.001) and alpha (t=–7.941, p<0.001) between eye-closed and eye-open conditions (Table 1). Also, there were significant differences in both DAR and DTABR between two conditions (mean difference=9.68±4.83 and 6.2±3.08, respectively, p<0.001; see Figure 1. Therefore, these two quantitative electroencephalography scales were appropriate to investigate different neuro-physiologic activity of tinnitus sufferers in resting EEG with eyes open or close eyed. Comparison of sLORETA images showed that the SnPM of all frequencies between two eye conditions was statistically significant (t=5.504, p<0.001; see Figure 2).
There was a significant negative correlation between DAR and THI score (r=–0.728, p<0.001) and between DTABR and THI score (r=–0.527, p<0.001) in the eyes-closed condition due to increase of alpha peak, while there was a significant positive correlation between DAR and THI score (r=0.466, p=0.001) and between DTABR and THI score (r=0.413, p=0.004) in the eyes-open condition due to the increase of delta peak and reduction of alpha peak. However, the VAS score had no significant correlation with DAR or DTABR.

Discussion

In previous studies, decreased power of delta and alpha in the eyes-open condition compared to the eyes-closed condition in healthy people have been reported [9]. In the current study, the findings indicated that people with tinnitus had different EEG activities in eyes open/closed conditions. There was a significant increase in the relative power of delta band in the eyes-open condition compared to the eyes-closed condition, indicating the reduced motor preparation due to external stimuli and increased attention processing. This finding is consistent with the results of other studies [19-21], although one study had contrasting results [8]. In our study, there was a significant decrease in the relative power of alpha band in the eyes-open condition compared to the eyes-closed condition. This finding is in line with the results of other studies that considered the higher activity of alpha band in the posterior regions in eyes-closed condition is a reflective of reduced sensory input [19, 22] or is associated with tinnitus distress [23, 24]. Higher alpha power in the eyes-closed condition in tinnitus patients leads to engagement of attentional selection for internal imagery process which subsequently leads to chronic auditory phantom perception [25, 26]. The process of perceiving the tinnitus is associated with abnormal brain activity patterns, including changes in the power of alpha and delta bands [21, 27].
A previous study on neurofeedback as a method for treatment or management of tinnitus showed that alpha/delta ratio neurofeedback was effective in reducing unpleasant psychologic emotional and perceptual consequences of tinnitus, indicating that both alpha/delta ratio neurofeedback and beta/theta ratio neurofeedback reduced tinnitus intensity. Analysis of EEG data showed a consistent pattern for the alpha/delta ratio neurofeedback over the course of training compared to beta/theta ratio neurofeedback [28]. In our study, we compared the DAR and DTABR parameters between two eyes open/closed conditions of EEG recording in tinnitus patients. In the eyes-closed condition, DAR and DTABR were significantly lower in comparison with the eyes-open condition. Based on previous reports and the current study, it seems that increased DAR is a good indicator of tinnitus in EEG recording with eyes open.
Negative correlation of the THI score with DAR and DTABR in the eye-closed condition (due to the increase in alpha power) and positive correlation between them in the eyes-open condition (due to the increase in delta

power) was other findings of this study. These findings may indicate that these indicators can show the level of distress and annoyance in tinnitus to some extent. A neurofeedback study found no significant interaction effect of time×group for the THI score but reported a significant interaction effect for the Tinnitus Magnitude Index (TMI). According to this study, alpha/beta ratio neurofeedback was more effective in reducing distress and tinnitus intensity [28]. The relationship between objective EEG findings and subjective findings (score of a self-report questionnaire) in tinnitus sufferers can be useful for new evaluations, treatment approaches, and follow up techniques in tinnitus studies. Quantitative EEG recording with eyes closed may increase alpha and beta power and lead to errors; therefore, it is better to record the EEG activity of tinnitus people with their eyes open.

In our study, brain mapping analysis indicated a reduced delta power in the occipital area, a reduced theta power in the central and frontal areas, and increased alpha power in the central and parietal areas in the eyes-closed condition. This finding is in line with the results of a previous study [19]. According to Roseman et al., superior parietal along with bifrontal cortex and supramarginal gyrus are involved in compensatory process attenuating tinnitus perception [29]. Reduced theta activity in the frontal area and increased alpha activity in the parietal area may suggest the compensatory processing efforts to attenuate the tinnitus perception.

Based on our findings, it can be said that there are significant differences in alpha and delta powers between two eyes open/closed conditions in tinnitus patients. DAR and DTABR scales can be used as biomarkers for detection of eye effect on the EGG activity of tinnitus people. Also, considering their reported correlations with the THI score, it seems that they may be useful biomarkers in the follow-up of the intervention effects in tinnitus patients.

The present study had some limitations. The sample size was relatively small to generalize the findings. The findings of the present study cannot be generalized to all tinnitus population. The EEG recording only in the resting state cannot present a complete understanding of tinnitus neural network and connections between the hubs in this network. For the future studies, recording of the EEG or evoked responses by presenting the triggers with focusing on the central auditory processing for complete understanding of tinnitus neural network and the connection between the hubs in this network is recommended. To more stimulate alpha rhythm, the use of light stimulation is recommended. Moreover, we recommend the use of biomarkers suggested in this study for the follow-up of intervention output in reducing tinnitus annoyance/distress along with the tinnitus questionnaires. It seems that these biomarkers can use in follow-up stages for any tinnitus interventions including cognitive behavioral therapy, tinnitus retraining therapy, or neuromodulator techniques.

Conclusion

People with tinnitus have different electroencephalography activities, especially in delta band, in the eyes open/closed conditions, compared to the similar electroencephalography activity reported for people without tinnitus. It seems that the increased DAR in the eyes-open condition compared to the eyes-closed condition is a good marker for the detection of tinnitus. It seems that delta/alpha ratio and delta+theta/alpha+beta ratio can be more valuable biomarkers in interpreting the perception and experience of tinnitus or intervention outcomes in people with tinnitus.

Ethical Considerations

Compliance with ethical guidelines

This study has ethical approval from the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences (Ethical code: IR.USWR.REC.1401.230).

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Authors' contributions

MS: Study design, acquisition of data, interpretation of the results, statistical analysis, and drafting-editing the manuscript; YL: Study design, drafting the manuscript; ST: Study design, interpretation of the results, EEG analyzing and drafting the manuscript; EB: Statistical analysis, methodology, drafting the manuscript; MJ: Supervision, methodology, study design, interpretation of the results, and drafting-editing the manuscript.

Conflict of interest

The present study has no conflict of interest.

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Table 1. The mean relative power (%) of five frequency bands in two eyes-closed and eyes-open conditions in resting position for different brain areas and their comparison

Frequency band	Brain region	Mean(SD)		t/z statistic	p
		Eyes open	Eyes closed		
Delta	Total	63.84(18.99)	44.27(17.89)	t=6.379	<0.001[*]
	Frontal	64.21(19.75)	50.84(21.03)	t=4.293	<0.001[*]
	Temporal (left)	62.24(20.83)	46.18(18.60)	t=5.092	<0.001[*]
	Central	65.07(22.17)	44.20(19.21)	t=5.945	<0.001[*]
	Temporal (right)	63.01(21.51)	44.10(18.31)	t=5.676	<0.001[*]
	Parietal	62.92(21.05)	41.08(20.87)	t=5.564	<0.001[*]
	Occipital	66.75(19.98)	39.17(20.69)	t=7.426	<0.001[*]
Theta	Total	16.06(8.74)	13.42(7.49)	t=1.797	0.079[*]
	Frontal	18.87(10.96)	13.55(10.16)	t=2.650	0.011[*]
	Temporal (left)	15.53(9.13)	13.22(7.57)	t=1.627	0.111[*]
	Central	15.61(10.21)	14.29(7.52)	t=0.824	0.414[*]
	Temporal (right)	13.98(8.71)	13.70(7.01)	t=0.191	0.849[*]
	Parietal	17.37(10.11)	12.25(8.08)	t=2.885	0.006[*]
	Occipital	16.08(10.59)	13.53(9.26)	t=1.318	0.194[*]
Alpha	Total	9.71(7.80)	31.05(17.65)	t=–7.941	<0.001[*]
	Frontal	8.45(7.75)	26.43(18.86)	t=–6.360	<0.001[*]
	Temporal (left)	9.73(8.36)	28.72(17.07)	t=–7.508	<0.001[*]
	Central	9.50(7.36)	29.17(16.93)	t=–8.026	<0.001[*]
	Temporal (right)	10.36(8.70)	29.24(17.73)	t=–6.921	<0.001[*]
	Parietal	10.70(9.03)	36.49(20.94)	t=–7.558	<0.001[*]
	Occipital	9.01(9.20)	37.44(21.89)	t=–8.441	<0.001[*]
Beta	Total	9.14(8.77)	10.47(6.54)	z=–2.48	0.013[**]
	Frontal	7.31(9.45)	8.32(6.24)	z=–2.38	0.017[**]
	Temporal (left)	10.58(8.89)	10.82(6.68)	z=–0.77	0.441[**]
	Central	9.66(9.33)	12.00(8.53)	z=–2.82	0.005[**]
	Temporal (right)	10.33(9.96)	11.47(7.19)	z=–1.84	0.066[**]
	Parietal	7.75(7.81)	9.72(6.44)	z=–2.56	0.010[**]
	Occipital	7.30(8.75)	9.63(7.23)	z=–2.93	0.007[**]
Gamma	Total	0.89(1.09)	1.68(4.02)	z=–0.72	0.468[**]
	Frontal	0.64(0.87)	1.57(4.18)	z=–1.06	0.289[**]
	Temporal (left)	1.40(2.00)	1.85(3.94)	z=–0.24	0.806[**]
	Central	0.94(1.10)	1.49(3.39)	z=–0.64	0.523[**]
	Temporal (right)	1.46(2.13)	2.15(5.00)	z=–0.37	0.714[**]

	Parietal	0.45(0.51)	1.51(5.35)	z=–1.28	0.201**
	Occipital	0.40(0.38)	1.24(2.94)	z=–2.12	0.034**

* Paired t-test; ** Wilcoxon test

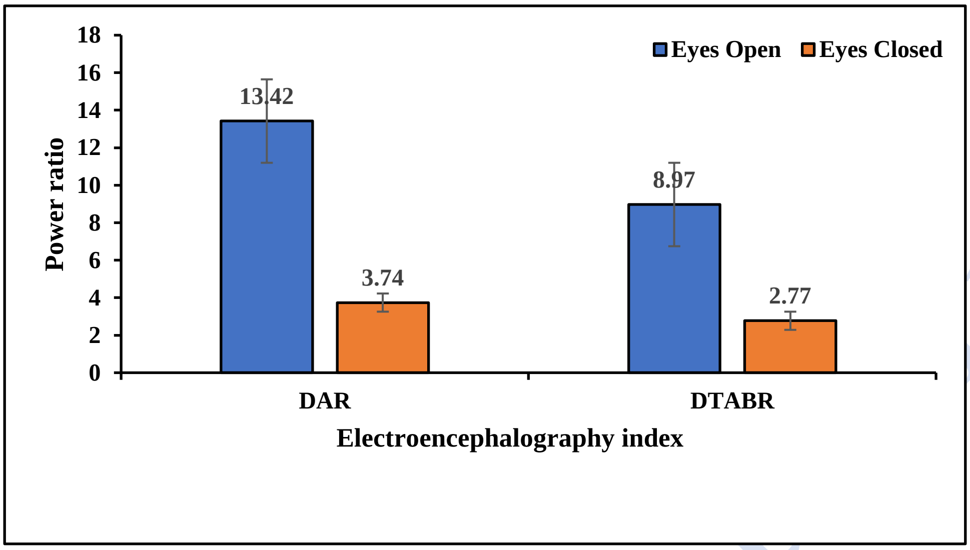

Figure 1. Comparison of delta/alpha ratio and delta+theta/alpha+beta ratio between eyes open/closed conditions in tinnitus patients. DAR; delta/alpha ratio, DTABR; delta+theta/alpha+beta ratio

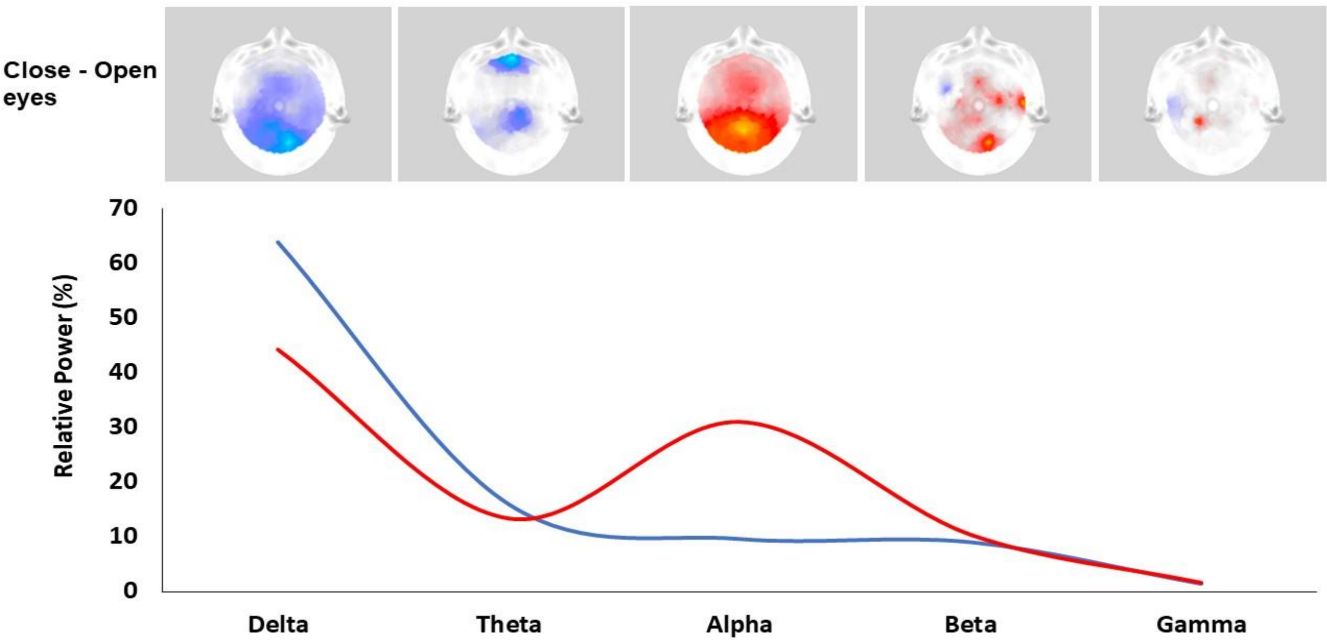

Figure 2. Relative power of electroencephalography bands at two eye conditions based on the statistical nonparametric mapping of standardized low-resolution brain electromagnetic tomography analysis images. Alpha power increased and delta power reduced in the eyes-closed conditions (Eyes open in blue line and Eyes closed in red line). The brain mapping shows that relative power at the eyes-closed condition reduced at delta and theta bands (blue areas) but increased at alpha and beta bands (yellow and red areas)