Auditory and Vestibular Research

Abnormal slow electroencephalography activity in open and close eye conditions as an optimal index for Tinnitus

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Highlights:

- Eyes condition for electroencephalography analysis is important in tinnitus patients
- Alpha power decrease with delta increase in closed to open eye may indicate tinnitus
- DAR and DTABR indexes change in closed to open eye can use as biomarkers in tinnitus

Abstract

Background and Aim: Recent studies try to clarify the difference of neuro-physiological responses of subject with tinnitus. Quantitative electroencephalography (QEEG) analysis is different on eyes close or open. The recording of brain activities must be clarified by eyes condition. This study aimed to investigate this further in terms of differences in electroencephalography activity between closed and open eyes condition in resting position of tinnitus patients.

Methods: QEEG was analyzed in 46 subjects with tinnitus (34 men and 12 women), in two eye conditions (close/open) for 3 minutes at resting position. Relative power of delta, theta, alpha, beta and gamma bands estimated. Paired T-test analysis for comparison of Delta/Alpha (DAR), Delta+Theta/Alpha+Beta (DTABR) between close/open eyes were done.

Results: In closed to open eyes condition DAR and DTABR increased significantly ($p=0.009$ and $p=0.016$). Power of delta increased in open eyes whereas, alpha reduced significantly ($p<0.001$).

Conclusion: Subjects with tinnitus indicate difference electroencephalography activities at two eyes conditions. Delta band is completely revers in comparison to normal subjects that documents at previous researches. Increase

of relative power of delta in closed to open eyes condition with reduce of alpha may be indicate sever tinnitus based on QEEG data. It seems that is better to select open eyes condition for electroencephalography analysis. Increase of DAR index is a good variable in open eye condition and this study suggest the use of it as a potential biomarker for comparison of the severity of tinnitus.
Keywords: Tinnitus, quantitative electroencephalography, delta to alpha ratio, biomarker

Introduction

In previous research it was thought that subjective tinnitus was only a problem related to the peripheral auditory system [1, 2], but the current researches widely accepted view is that this auditory phantom perception is the result of failed compensatory mechanisms in the brain and it does not seem to follow only inner ear receptor damage [3,4].

Also, recording of electroencephalography (EEG) have led to the identification of tinnitus-related abnormalities in spontaneous brain activity at rest position. These studies indicate in the resting state, activity of delta (0.5-4 Hz) and gamma (35.5-45 Hz) frequency bands increased, whereas a reduction of alpha oscillations (8.5-12 Hz) in temporal regions may be occurred [5, 6]. The reasons and theoretical frameworks on which these findings are based are the thalamocortical dysrhythmia model (TCD) [7] and synchronization with loss of inhibition model (SLIM) [6]. In the TCD model, it has been 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. An increase in the gamma frequency range may be the result of 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 pattern of low alpha, high delta, which is usually found in EEG data in the resting state of tinnitus patients [7].

There are few studies that suggest the EEG with close and open eyes at rest position are different. The most of these studies show an increase of delta and alpha power in close eyes in compared to open eyes, while the beta band may increase in the open eyes state between gender matched young and healthy old subjects [8,9].

In open eye condition, higher alpha power is usually observed specially in the posterior regions. This finding associated with reduced relaxed attention and sensory perception [8,10]. While, in closed eye condition alpha power decreased and beta activity increased specially in the frontal areas that are associated with increased arousal and visual processing [8]. In closed eye condition greater activity have recorded in sensory network such as; sensorimotor and visual network while in open eye condition higher activities have recorded which related to default mode network, salient 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 frequency 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 resting position EEG was used as frequency of sensory (audio-visual) tasks [15]. Alpha band activity has been associated with a wide range of processes encompassing memory, perception, decision and cognitive functioning. IAF is a specific parameter for the alpha activity [16]. The closing and opening of the eyes at rest can affect IAF in subject with tinnitus due to cognitive and perceptual consequences of tinnitus.

The aim of this study is to compare the power of delta, alpha band frequencies in subjects with tinnitus at resting position with close and open eyes. The delta/alpha ratio is a good variable because of compare these two power frequency and may detect the eye effects in subjects with Tinnitus.

Although the apparent mechanism of deviation of 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]. The aim of this study is to detect the relation between close and open eyes conditions in tinnitus by DAR and DTABR.

Methods

Forty-six subjects with tinnitus (34 men and 12 women) with mean age of 46.6 + 5.9 years, participated after obtaining informed concept in this study. All of subjects will be recruited from the tinnitus part of the audiology clinic of the Rofeideh rehabilitation hospital in the first 6 months of 2023. This study performed after gained approval from the Ethics Committee. The ethics number is IR.USWR.REC.1401.230

Inclusion criteria

Subjects with the following conditions were included in this study: Chronic tinnitus for more than 6 months, age between 30 and 60 years, the existence of tonal and subjective tinnitus, tinnitus sensation in one or both ears, absence of pulsating and multi-tonal tinnitus, absence of Meniere's disease or fluctuating hearing level, the absence of cerebellopontine angle tumors or any diagnosed neurological disease, absence of any history of cardiovascular disease, absence of severe to profound hearing loss, absence of obvious complaints of hyperacusis symptoms, no use hearing aids, absence of receiving any tinnitus treatment, the average hearing threshold at the frequency 2000-8000 is between 20 dB and 60 dB, total Tinnitus-Handicap-Index (THI) score at the initial assessment (mild-sever), moderate score in Hospital-Anxiety-and-Depression-Scale (HADS) questionnaire, no use of sedatives drugs, absence of epilepsy and convulsions diagnosed by a neurologist or psychiatrist.

Exclusion criteria

Subjects with the following conditions were excluded in this study: Failure to noise-free records of brain activity during three minutes of recording, report of increased tinnitus during brain activity recording, occurrence of fatigue in subjects in the form of non-cooperation during recording of brain activity, eating caffeine (tea, coffee) at least 4 hours before recording brain activity, washing hair with shampoo at least 4 hours before brain activity recording.

Measurements

Persian version of THI and Visual-Analog-Scale (VAS) were completed by participants, before electroencephalography (EEG) recording [18].

The brain activity was estimated with quantitive EEG, and was recorded (bandwidth is 0.2–70 Hz, the impedance is less than 20 kHz, and the sampling rate is 1024 Hz) with 64 channel amplifiers (Ant Neuro by, Hengelo, Netherlands) according to the international 10/20 system, from 30 Ag/AgCl surface electrodes and a diameter of 8 mm electrode sites distributed throughout the whole head of the participants. The 30 electrodes were placed in central and bilateral places in regions of F,C,T,P and O. A reference electrode was placed on the mastoid process and a ground electrode is placed on the right-hand wrist. To record vertical and horizontal electrooculogram, a pair of electrodes above and below the right eye and another pair were placed on either side of each eye. We utilized the standardized Low-Resolution Brain Electromagnetic Tomography Analysis (sLORETA) provided by the KEY Institute for Brain-Mind Research (https://www.uzh.ch/keyinst/loreta.htm) to estimate the intracerebral neural brain responsible for the recorded scalp electrical activities. The sLORETA calculates electrical neural activity by measuring absolute and relative power. The sLORETA solution space comprises 6239 voxels with a voxel size of 5 x 5 x 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).

Thalamo Cortical Dysrhythmia (TCD) were calculated and frequency ranges of delta, theta, alpha, beta, and gamma by sLORETA software and the relative power levels of each rhythm was evaluated. With the electrooculogram of the O1 and O2 electrodes, blinking and eye movement artifacts are controlled. EEG were recorded for two eye conditions (close and open), at rest sitting position in silent room for three minutes.

The DAR and DTABR as a specific variable measured and compare between close and open eyes conditions.

Data analysis

Analysis of EEG data were offline with band pass filtered between 1 to 70 Hz and re-referenced to linked earlobes and then send into the EEG Lab toolbox favored by MATLAB software. Independent Component Analysis (ICA) was applied to eliminate residual artifacts caused by muscle movement, eye blinks and electrocardiography (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), relative power of each frequency band was measured at each electrode by sLORETA software as below equation:
R(h) = 100* E(h)/ E total. R(h); Relative power, E (h); the absolute power in each frequency band, E total; the sum of the powers in all frequency bands.
DAR and DTABR were measured by average of all area for each condition in resting position (Fig1).

Statistical methods

Statistical methods for outcomes analysis were performed using SPSS (version 17). Variables described with means and standard deviations. Normal distribution test Kolmogorov-Smirnov was normal for all outcomes whereas beta and gamma relative power didn't have normality distribution in some area. We used Paired T-test for parametric variables and Wilcoxon test for non-parametric variables depended to normal distribution.
To recognize potential differences in source localization of brain electrical activity in two different conditions, the current density distributions were contrasted by using sLORETA. Nonparametric permutation tests of sLORETA images (statistical nonparametric mapping: (SnPM) were conducted for each contrast via sLORETA's built-in voxel with a threshold $P < 0.05$.

Results

Forty-six voluntary tinnitus subjects participated at this study at age range of 30 to 56 years (46.6 ± 5.9), (Male = 34, Female = 12) and THI score (46.52 ± 1.84), VAS (5.65 ± 0.83). based on our aim to compare the EEG activities of tinnitus sufferers in two conditions of open and close eyes, the secondary depended variables compared between conditions at two approaches:
a) Parametric and Nonparametric tests for relative power of all electrodes and DAR, DTABR by SPSS software (Table 1, Fig 2).
b) Nonparametric permutation tests of sLORETA images statistical nonparametric mapping: (SnPM) were conducted for each contrast via sLORETA's built-in voxel wise randomization tests (5000 permutations) with a threshold $P < 0.05$ (Fig 1).
Comparison of the relative power of delta between eye closed and eye open EEG recording showed significant difference ($t=6.379$, $p< 0.001$). Comparison of the relative power of alpha between two conditions of record, also showed significant difference ($t=-7.941$, $p< 0.001$). Both ratios; DAR and DTABR, between two conditions of records have shown significant difference (mean diff=9.68±4.83, mean diff=6.2±3.08, $p< 0.001$). It seems that these two quantitative electroencephalography scales are appropriate ones for the current study aim to investigate different neuro-physiologic activity of tinnitus sufferers in resting EEG with open and close eyes. Comparison of sLORETA images (brain mapping between all frequencies rhythms at two different conditions was significant ($t = 5.504$, $p<0.001$).
There is significant negative correlation between DAR, DTABR and THI in closing eye condition due to increase of alpha peak (DAR - THI, $r = -0.728$, $p<0.001$), (DTABR - THI, $r = -0.527$, $p<0.001$). Also, there is significant positive correlation between DAR, DTABR and THI in opening eye condition due to increase of delta and reduce of alpha peaks (DAR - THI, $r = 0.466$, $p=0.001$), (DTABR - THI, $r = 0.413$, $p=0.004$). But about VAS scale there was no correlation between DAR, DTABR and VAS. These results are in line to the current study secondary aim for check the correlation between EEG activities with the amounts of tinnitus annoyance in sufferers.

Discussion

In previous studies, decrease power of delta and alpha in closed to open eye condition in normal subjects were reported [9]. The current study findings indicate that subjects with tinnitus have reverse EEG activities at two eyes conditions. In the current study a significant increase in relative power of delta in closed to open eyes conditions indicated the reduced motor responses preparation, brain's tendency to this engage from external stimuli and increased attention processing, and these findings are relevant with the results of previous study [19, 20, 21]. But another study had reverse results [8].
The relative power of alpha also showed a significant decrease in closed to open eye condition. This finding is in line with studies that consider the higher activity of the alpha band in the posterior regions in closed eyes, reflect reduced sensory input [19,22] or associated with tinnitus distress [23,24]. Higher power of alpha in closed eye 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 associated with abnormal brain activity patterns, including changes in the power of alpha and delta bands [21,27]. Previous studies on neurofeedback approaches as a treatment or managing method in tinnitus patients showed that alpha/ delta ratio was effective in reducing on unpleasant psychologic emotional and perceptual consequences of tinnitus. This result 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 over the course of training compared to beta/theta ratio neurofeedback [28].

In our study we compared between tow eye conditions of EEG recording (open eye Vs. close eye) for DAR and DTABR in tinnitus patients. In close eyes condition DAR and DTABR reduced significantly in comparison to open eyes. Power of delta increased in open eyes whereas, alpha reduced significantly. On base of previous reports and the current study findings, it seems that DAR is a good index in the open eye condition for EEG scope in tinnitus.

Negative correlation between THI with DAR and DTABR in the eye closed condition due to the increase in alpha power and positive correlation between DAR and DTABR with THI in the open eyes condition due to the increase in delta power was one of the findings of this study. These findings may indicate that these indexes could express the level of distress and annoyance of tinnitus to some extent. In addition, some studies showed that neurofeedback based on the ratios of bands power, especially alpha-delta has been more effective in reducing distress and intensity of tinnitus in follow up. For THI results they expressed no interaction effect but significant time/ group interaction for Tinnitus Magnitude Index (TMI) were showed. It seems that a special combination of increasing of alpha and reducing of beta is more effective in reducing distress and intensity of tinnitus [28]. These connections between objective findings in EEG/QEEG with subjective or self-report questionnaire scores in tinnitus sufferers, shed a light for new evaluation, treatment approach and follow up techniques in tinnitus studies. QEEG findings in close eye may be increase alpha and beta power markedly and it may produce a source of error, so it is better open eyes selected for EEG analysis in these subjects.

In our study, brain mapping analysis indicate reduce of activation for delta in occipital area and theta in central and frontal areas whereas alpha power is more increase in central and parietal cortex in close eyes condition. This finding is in line with previous study [19].

Roseman et al. expressed that superior parietal with bifrontal cortex and supramarginal gyrus are involved in compensatory process attenuating tinnitus perception [29]. Reduce activity of theta in frontal area and increased activity of alpha in parietal may suggest the compensatory processing efforts to attenuate the tinnitus perception. Based on our current findings, there are significant changes in alpha and delta powers in two conditions (open and close eyes). DAR and DTABR scales can be used as biomarkers for detection of eye effect in tinnitus subjects and also attention to the reported correlations with THI scores, seems that they may be useful biomarkers for follow-up the intervention effects in tinnitus patients at least based on our study participants.

The present study has limitations that need consideration. First, with attention to heterogeneous nature of the tinnitus, the sample size was relatively small for generalizability of the findings. Second, EEG recordings only in the resting state don't present a complete understanding of tinnitus neural network and connections between the hubs in this networks.

For the future studies, record 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. In order to more stimulate alpha rhythm, use of light stimulation is recommended. Use of the suggested biomarkers in this study for intervention output follow-ups in decreasing tinnitus annoyance/distress in line with the tinnitus questionnaires is recommended, too. It seems that these biomarkers can use in follow-up stages for any tinnitus interventions through cognitive-behavioral therapy or tinnitus retraining therapy to any neuromodulator techniques.

Conclusion

The findings of the present study can be only being sited within the scope of this study and cannot simply be generalized to all tinnitus population. Subjects with tinnitus indicate difference EEG activities at two eyes conditions in comparison to the usual reported in normal populations without tinnitus. These changes, especially in delta band increase from closed to open eye is completely revers in comparison to previous researches findings in normal subjects. It seems that increase of DAR in closed to open eye condition is a good marker for detection

of tinnitus. It seems that DAR and DTABR can be more valuable biomarkers in interpreting the perception and experiencing the consequences of tinnitus or intervention outcomes in this population.

Contribution of authors:
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.

Acknowledgment
We would like to thank the participated patients in the present study and the audiology department of Asma rehabilitation center and the clinical research development unit of Rofeideh rehabilitation hospital.

Conflict of interest:
The present study has no conflict of interest.

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Table 1) Significant differences in mean relative power between close and open eyes in resting position in total area and difference cortex areas for five frequency rhythms.

Frequency band	Region	Eyes-open		Eyes-closed		t*/z**-Statistic	P-value
		Mean(%)	SD	Mean(%)	SD		
Delta	Total Area	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 (Lt)	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 (Rt)	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 Area	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 (Lt)	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 (Rt)	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 Area	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 (Lt)	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 (Rt)	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 Area	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 (Lt)	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 (Rt)	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 Area	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 (Lt)	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 (Rt)	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

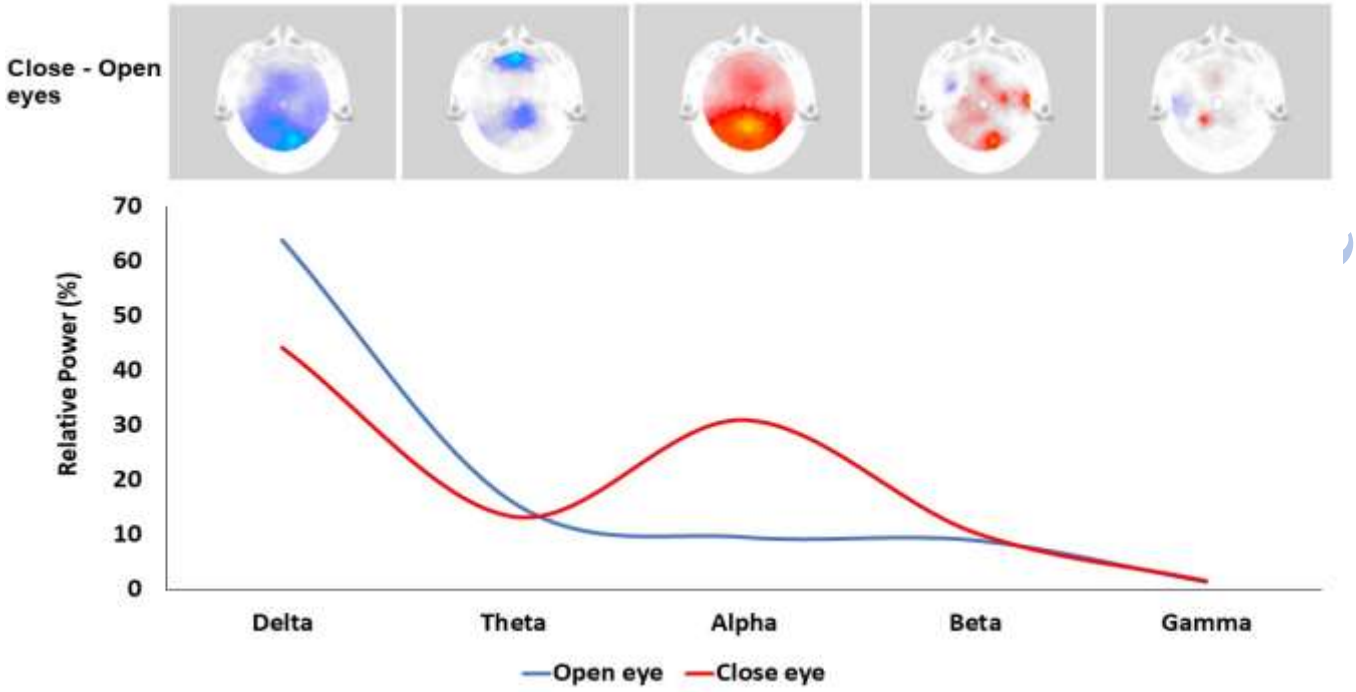

Figure 1) Relative power of subject's EEG rhythms with tinnitus at two eye conditions. Alpha rhythm increased in close eye whereas delta rhythm reduced markedly. The difference between open and close eyes by brain mapping shows that relative power at close eyes reduce at delta and theta (blue mapping areas) whereas increase at alpha and beta rhythms (yellow and red mapping areas).

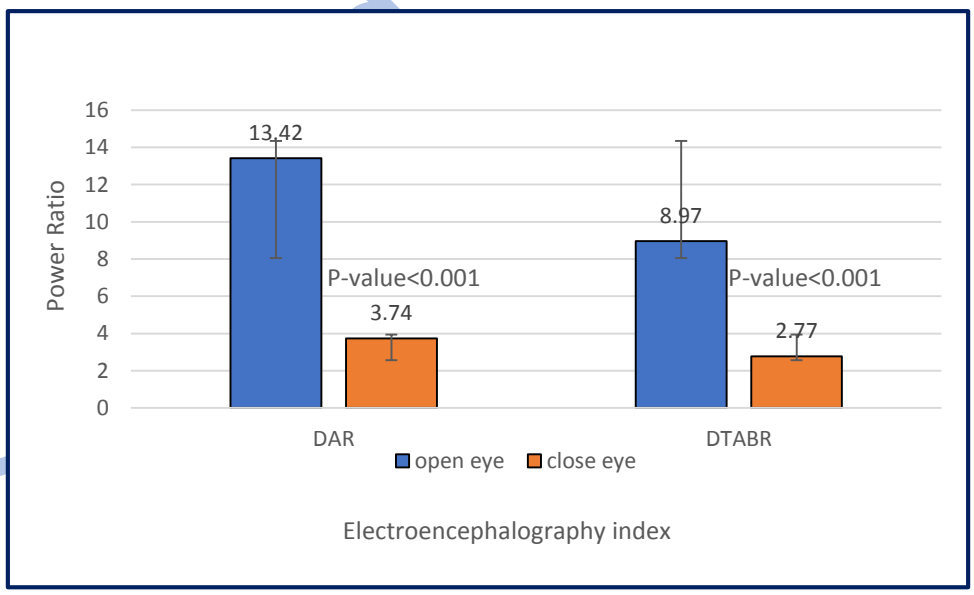

Figure 2) Comparison of Delta/Alpha Ratio (DAR), Delta+Theta/Alpha+Beta Ratio (DTABR) between open/close eyes condition in tinnitus patients.