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A comparison of P-300 study in subjective tinnitus with normal hearing patients and normal hearing adults

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Abstract

Tinnitus can occur in normal hearing subjects and interfere with daily life and well-being. The P300 auditory evoked potential is used to demonstrate the cortical pathway of the auditory system. This study aimed to compare P300 characteristics between tinnitus patients with normal hearing and healthy subjects and explore the relationship between P300 characteristics and tinnitus severity. This study included 18 tinnitus patients with normal hearing and 18 healthy subjects. Each group was divided into two age groups: 18-40 and 41-60. All subjects with a bilaterally normal pure tone threshold and type A tympanogram were included. The mini-cog screening test and a structured interview (M.I.N.I.) were used to evaluate cognitive impairment and psychiatric disorders. In healthy volunteers, a trend of longer latency and smaller amplitude of P300 was found as age increased. However, no significant difference between the two age groups was noted. When compared between tinnitus and healthy subjects, there was a significantly delayed latency of P300 in age groups of 18-40 years and 41-60 years ($p<0.05$), whereas P300 amplitude did not differ. We discovered a delayed result of P300 latency in subjective tinnitus in both two age groups ($p=0.03$ and $p<0.01$, respectively) and a relationship between tinnitus sufferers and altered P300 characters. Hence, P300 may be an objective measurement for diagnosing tinnitus patients.

Keywords: Cognition, Normal hearing, P300, Tinnitus.

1. Introduction

Tinnitus is the sense of sound without environmental or external sound [1]. The prevalence is ranged from 5.1 to 42.7% [2]. Pathology is linked to abnormalities in the central or peripheral auditory system and is associated with the failure of habituation when individuals are not accustomed to a stimulus [3]. Cochlear damage from presbycusis, noise-induced hearing loss, and ototoxic drugs frequently cause tinnitus. Most cases of tinnitus are associated with hearing loss and underlying medical illness. However, it can be presented with a normal audiogram [4]. Therefore, a medical history, tinnitus severity assessment, and audiological testing of hearing function are required to make a diagnosis [5]. The most frequent type of tinnitus can be perceived only by affected individuals. It is called 'subjective tinnitus' and is challenging to diagnose when it exists without an underlying illness or hearing impairment.

The severity of tinnitus varies from person to person. Apart from psychological distress, the cognitive deficit from tinnitus-related attention and working memory impairment can significantly impact the quality of life of some people. To measure cognitive efficiency, the P300 evoked potential is an objective measurement for electrophysiological neural responses that are generated by both cortical and subcortical structures, including the primary auditory cortex, prefrontal cortex, medial temporal lobe, and limbic system [6], which are associated with auditory discrimination, cognitive performance such as memory and focus. The P300 amplitude measures the brain activity required in processing incoming information, which combines the memory of the stimulus and the distinguishment of the context in which the stimulus occurs. Therefore, the P300 amplitude represents the working memory performance. The larger the amplitude of P300, the superior the memory performance is. The P300 latency is the processing time required for the brain to generate and respond to the target sound. P300 appears at 300 msec in normal people. The shorter the latency, the faster the central processing is [7]. The reduced amplitude and prolonged latency of P300 are the most frequent alterations to indicate slowed cognitive processing [8] that is related to decreasing working memory and attention level in tinnitus patients. The pathology of tinnitus is associated with neuronal changes in the central auditory system and overlaps with P300 regions. Therefore, the P300 abnormalities in tinnitus patients may be linked to fewer responding neurons [9,10], neuronal hypoactivity in the auditory system [11], and increased desynchronization from trial to trial.

A systematic review and meta-analysis of late auditory evoked potentials showed P300 can be a potential biomarker for subjective tinnitus [11]. However, they could not identify evidence of whether the difference component of P300 is covarying with tinnitus severity or not. There were studies comparing the P300 characteristics between chronic subjective tinnitus patients with normal hearing and normal hearing subjects [12,13,14]. Participants were matched by age and gender in the studies of Najafi and Rouzbahani [12] and Elmorsy and Abdeltawwab [13] but were not matched in the study of Asadpour et al. [14]. In the study of Elmorsy and Abdeltawwab [13], tinnitus subjects were excluded if they had a history of psychological or neurological problems. However, they did not use acceptable screening tools such as the Mini International Neuropsychiatric Interview (M.I.N.I) for psychological disorders or the Mini-Cog test for cognitive problems. The factors of age, psychiatric disorders, and cognitive impairment can affect P300 characteristics. In addition, the results of Najafi and Rouzbahani [12] and Elmorsy and Abdeltawwab [13] found that tinnitus subjects tended to have longer latency and lower amplitude than normal subjects, but there were not statistically significant differences, and tinnitus subjects tended to have lower amplitude in the study of Asadpour et al. [14], which may be due to the presence of confounding variables in these studies. The primary objective of this study was to evaluate the P300 characteristics of patients with subjective tinnitus compared to healthy subjects. The secondary objective was determining the relationship between P300 characteristics and tinnitus severity.

2. Materials and methods

This research is a cross-sectional study conducted between May 2022 and February 2023 at the outpatient clinic of the Department of Otorhinolaryngology, Srinagarind Hospital, Khon Kaen University, Thailand. The sample size calculation for two independent groups with 95% type-I error, 80% power, and 10% drop-out used means from the study of Gabr et al. in 2011 [15].

2.1 Participants

Thirty-six volunteers aged 18 to 60 years old were recruited (18 patients with subjective tinnitus and 18 healthy subjects as control) and divided by age into groups of 18-40 and 41-60 years old (9 participants in each age group) because age is a variable factor that affects the P300 characteristics. As the age increases, particularly above 40, the latency is longer, and the amplitude is smaller than that of younger [16]. All participants underwent standard otologic examination to confirm normal hearing by otoscopy and audiometry with a type A tympanogram with frequencies between 250 and 8000 Hz. At least three months, otolaryngologists had to diagnose patients with tinnitus, whether unilateral or bilateral subjective tinnitus. The severity of tinnitus was assessed using the Tinnitus Handicap Inventory; a score less than 16 indicates "no or slight handicap," 18 to 36 "mild," 38 to 56 "moderate," 58 to 76 "severe," and a score over 78 as "catastrophic handicap [17].

The exclusion criteria included taking psychotropic medication, major neurocognitive disorders, and psychiatric disorders were screened by the Thai version of Mini-Cog (a total score of 5 indicates no cognitive impairment) and the Mini International Neuropsychiatric Interview (M.I.N.I), respectively.

2.2 Hearing evaluation

Using an AC40 or GSI61 audiometer, pure tone audiometry was carried out using the air conduction (AC) and bone conduction (BC) pathways, with frequencies ranging from 250 to 8000 Hz and 500 to 4000 Hz, respectively. Both AC and BC have normal hearing thresholds (≤25 dBHL) and no significant air-bone gap. The GSI tympStar Pro tympanometer was used to measure the acoustic immittance, which includes acoustic reflexes. The P300 evoked potentials were assessed following tympanometry and audiometry. The Tinnitus Handicap Inventory (THI) was used to categorize the severity of tinnitus in study individuals. Also, after a P300 investigation, tinnitus patients underwent tinnitus matching testing and tinnitus masking therapy. Audiologists conducted all the auditory evaluations.

2.3 P300 procedure

All patients underwent testing for P300 evoked potentials. The parameter recording is 75 dBnHL using an oddball paradigm. Table 1 displays the settings for the acquisition parameter and the stimulus parameter. Participants were instructed to count only the target stimulus or infrequent stimulus when they heard it and to ignore the standard stimulus or frequent stimulus while they were seated comfortably in a quiet room. Four electrode sites were cleaned with Nuprep gel: ground electrode (FpZ), active electrode (Fz), and reference electrode (M1, M2). Each electrode has an impedance of less than 5 kΩ, and the difference between each electrode does not exceed 2 kΩ.

Table 1 P300 response test parameter.

P300 parameter	value
Transducer	ER 3A insert earphones with foam tips
Type of stimuli	Tone burst 1000 Hz (standard) 2000 Hz (target)
Type of oddball paradigm	Two stimuli
Electrode montage	FpZ-ground electrode/Fz-active electrode/ mastoid M1 M2-reference electrode
Rate of stimuli	1.1/sec
Intensity	75 dBnHL
Polarity	Alternating
Probability	20 (target): 80 (standard)
Filter	1-30 Hz
Number of stimuli	150-250

The statistical analysis was conducted using IBM SPSS Statistics 28.0.0.0. Numerical data was presented as mean±SD (standard deviation) or median, while non-numerical data was presented as proportions. The normal distribution was determined using the Kolmogorov-Smirnov test. Independence and paired sample t-test, Chi-square test, and Mann-Whitney U test were performed to explore significant differences between the two groups. Spearman's correlation was used to examine the correlation between the P300 characteristics and the THI score. The *p*-value was set at less than 0.05 for statistical significance.

3. Results

The 36 participants were screened, and they all passed the inclusion criteria. The mean age of tinnitus patients vs. healthy controls was 27.56±6.75 vs. 27.89±4.10 years in the aged 18-40 years group and 50.33 ±5.12 vs. 46.00±4.77 years in the aged 41-60 years group, respectively. There were no significant differences in terms of age, gender, or handedness in both age groups ($p>0.05$). The tinnitus patients in a 41–60-year group had underlying diseases (allergy, hypertension, hyperlipidemia, thyroid disease, etc.) significantly higher (88.88%) than healthy controls (44.44%; $p<0.01$). The participants' characteristics were presented in Table 2.

Table 2 Characteristic of participants between normal and tinnitus groups in 18-40 years and 41-60 years.

Characteristics	The group of subjects of 18-40 years (n=18)		*p*-value	The group of subjects of 41-60 years (n=18)		*p*-value
	Normal groups (n=9)	Tinnitus groups (n=9)		Normal groups (n=9)	Tinnitus groups (n=9)	
1. Age (y)*	27.89 ±4.10	27.56 ±6.75	0.90	46.00 ±4.77	50.33 ±5.12	0.08
2. Gender, male (%) **	44.44	33.33	0.63	44.44	22.22	0.32
3. Right handedness (%) **	100	88.88	0.30	100	100	>0.99
4. Underlying disease (%) **						
No	66.66	77.77	0.59	55.55	11.11	0.04[a]
Yes	33.33	22.22	0.59	44.44	88.88	<0.01[a]
Disease (%) **						
Hyperlipidemia	0	0	>0.99	33.33[b]	11.11	0.26
Allergy	33.33	11.11[b]	0.26	11.11[b]	44.44[b]	0.11
Thyroid	0	11.11[b]	0.30	0	11.11	0.30
Hypertension	0	0	>0.99	0	22.22[b]	0.13
Others	0	11.11	0.30	11.11	11.11	>0.99
5.Tinnitus handicap inventory mean±SD	-	48.22±29.54	-	-	31.11±10.87	-

[a] significant
[b] subject found over 1 underlying disease *Independent t-test **Chi-square test

Most tinnitus sufferers (61.11%) had reported the THI score as a mild level of handicap. In the 18-40 years group, the mean THI score was 48.22±29.54, and in the 41-60 years group was 31.11±10.87. However, no significant correlation was found between tinnitus duration and severity (r=-0.20, *p*=0.42) by Spearman's correlation. There also was no statistically significant difference, with *p*-values >0.05, observed in the duration of tinnitus (median in 18-40 years group=6 months vs. 41-60 years group=12 months; *p*>0.99), tinnitus lateralization (unilateral in 18-40 years group=33.33% vs. 41-60 years group=55.55%, bilateral in 18-40 years group=66.66% vs. 41-60 years group =44.44%; *p*>0.05), or THI score (mean in 18-40 years group=48.22±29.54 vs. 41-60 years group=31.11±10.87; *p*=0.12) in both age groups. Moreover**,** most people in the 18-40 years group have bilateral tinnitus, but most people in the 41-60 years group have unilateral tinnitus.

When comparing the hearing threshold between a tinnitus and a control group, no significant difference was observed at the frequency of 250-6000 Hz either on the same side or in both ears. However, it was found that the hearing threshold of the tinnitus group was significantly lower (mean in right and left=9.72±8.30, 7.78±9.11, respectively) than that of the control group (mean in right and left =15.56±6.15, 13.89±5.83, respectively; *p*=0.02) at the frequency of 8000 Hz in both ears (Table 3). No significant differences in acoustic reflex threshold and decay between the two groups in either ear (*p*>0.05).

Table 3 compares the hearing threshold from 250-8000 Hz in both ears between normal and tinnitus groups.

Ear	Subjects	Hearing threshold (dBHL) in 250-8000 Hz							
		250	500	1000	2000	3000	4000	6000	8000
Right	Normal	11.94±4.89	13.61±3.34	13.89±5.01	14.44±5.39	13.06±5.97	14.17±6.24	13.61±7.23	15.56±6.15
	Tinnitus	11.67±5.14	12.78±4.91	14.44±6.61	14.44±6.39	14.44±5.39	14.72±5.8	10.56±5.39	9.72 ±8.30
	p-value*	0.87	0.56	0.78	>0.99	0.47	0.78	0.16	0.02[a]
Left	Normal	10.00±4.53	10.83±4.28	11.11±4.71	11.11±4.71	12.78±4.91	12.78±5.99	12.50±7.12	13.89±5.83
	Tinnitus	11.39±4.79	9.72±4.36	11.11±4.71	11.39±6.37	14.44±7.45	13.06±5.72	10.83±7.71	7.78 ±9.11
	p-value*	0.38	0.45	>0.99	0.88	0.43	0.89	0.50	0.02[a]

[a]significant
*Independent t-test

For normal groups, there is no significant difference in latency/amplitude was found between age groups based on gender /sides (Table 4). When age is increasing, P300 latency is longer and P300 amplitude is smaller, but there is no significant difference between the younger and older groups in both latency and amplitude (*p*=0.23 and *p*=0.91, respectively).

Table 4 The comparison of P300 characteristics between two ears and gender in normal groups.

Factors		P300 components in normal groups, mean (SD)			
		The group of subjects of 18-40 years (n=18 [a])		The group of subjects of 41-60 years (n=18[a])	
		Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)
1. Between two ears	Right ear	304.33±27.72	6.02±3.27	329.89±27.20	6.16±2.20
	Left ear	314.22±36.78	6.87±2.54	320±26.42	6.22±2.86
	p-value*	0.08	0.12	0.19	0.38
2. Gender	Male	308.12±31.05	5.83±2.61	312.62±19.22	6.14±1.14
	Female	310.20±34.83	6.94±3.06	334.70±19.75	6.43±2.94
	p-value**	0.93	0.58	0.14	0.86

[a] number of ears
*Paired t-test **Independent t-test

Table 5 The comparison of P300 characteristics between normal and tinnitus groups in 18-40 years and 41-60 years.

P300 components	The group of subjects of 18-40 years				The group of subjects of 41-60 years			
	Normal groups (n=18[a])	Tinnitus groups			Normal groups (n=18[a])	Tinnitus groups		
		Bilateral (n=16[a])	Affected ear (n=14[a])	Unaffected ear (n=2 [a])		Bilateral (n=17[a])	Affected ear (n=12[a])	Unaffected ear (n=5[a])
1. Latency (ms), 95%CI	309.28 ±31.13, (285.34 to 333.21) *	366.78 ±39.52 [b], (336.40 to 397.15) *	366.44 ±39.91 [b], (335.76 to 397.13) *	318.00 ±15.56, (178.23 to 457.77) *	324.89 ±21.66, (308.24 to 341.54) *	373.33 ±17.81 [b], (359.64 to 387.02) *	370.81 ±19.15 [b], (354.80 to 386.83) *	382.00 ±28.84 [b], (346.18 to 417.81) *
2. Amplitude (μV), median	6.44±2.76, 6.21	9.87±7.50**, 7.11	9.86±7.50**, 6.62	8.42±0.74*, 8.42	6.30±2.20, 6.32	7.58±3.67**, 6.61	8.33±5.61**, 6.44	8.21±2.52*, 8.82

Bilateral is the bilateral ear in tinnitus patients.
Affected ear is an ear with tinnitus in tinnitus patients.
Unaffected ear is an ear without tinnitus in tinnitus patients.
[a] number of ears
[b] significant
*Independent t-test **Mann-Whitney U test

The P300 waveform in the one-sided ear of three tinnitus patients was excluded due to poor waveform morphology. The P300 latency in tinnitus patients is longer than those of control groups. A significant difference in P300 latency between the controls (mean in latency=309.28±31.13) and the tinnitus group of age 18-40 years either with one affected ear (mean in latency=366.44±39.91; $p<0.01$) or bilateral affected ears (mean in latency=366.78±39.52; $p=0.03$). Meanwhile, a group of age 41-60 years found significant difference between control (mean in latency=324.89±21.66) and tinnitus patients on affected (mean in latency= 370.81±19.15; $p<0.01$), unaffected (mean in latency=382.00±28.84; $p<0.01$), and bilateral ears (mean in latency=373.33±17.81; $p<0.01$). However, the P300 amplitude in controls is smaller than in tinnitus patients, but no significant difference was observed in P300 amplitude in both age groups ($p>0.05$), as shown in Table 5.

The tinnitus pitch matching is 55% of high pitch, 20% of mid-pitch, and 25% of low pitch, respectively. Additionally, the mean loudness matching is 31.94±12.62 dBHL. Regarding tinnitus masking, half of people with tinnitus had less tinnitus, and 34.03% had the same level.

4. Discussions

The P300 reflects brain processes that affect cognitive function, including attention and memory processes. In this study, we excluded participants with psychiatric disorders and/or cognitive impairments because these factors affected P300 characteristics. We found increased latency and decreased amplitude of P300 with increasing age in healthy controls which may be because of the age-related cognitive impairment in information processing [6], even though no significant difference ($p>0.05$). Also, the comparison of the P300 latency and amplitude between sex and side did not show a significant difference ($p>0.05$). However, it was noticed that the P300 amplitude in females was higher than in males because of the bigger size of the grey matter structure than in males [18]. Hypertension was found in one-third of the tinnitus patients [19] and may be linked to P300 abnormality due to the association with cognitive impairment, which is related to the duration of hypertension, treatment, or any co-morbidities [20]. In this study, there were more frequent underlying diseases, such as allergy and hypertension, in tinnitus patients than in healthy controls in the group aged 41-60 years ($p<0.01$). However, the sample size of our study was small and did not record the cognition-related factors for participants with hypertension.

Numerous variables impacted tinnitus severity, including sociodemographic, tinnitus features, and co-morbid medical conditions [21]. We found the difference in tinnitus localization among age groups, as most subjects in the 18-40 years group have bilateral tinnitus, while most of those in the 41-60 years group have unilateral tinnitus in this study. Bilateral tinnitus has more physical symptoms than unilateral tinnitus, which may indicate a higher discomfort level or tinnitus severity [22]. The subjects in 18-40 years group tended to report a worse THI score than in 41-60 years group, but it is not statistically significant. For the hearing threshold at 8000 Hz, the tinnitus group has a significantly lower hearing threshold than the normal group, even normal hearing threshold (<25 dBHL) in both groups. The better hearing ability at 8000 Hz of tinnitus patients may reflect greater sensitivity to abnormal sound than those of normal control. However, we did not perform tinnitus matching and evaluate the hearing threshold above the 8000 Hz. This postulated explanation needs confirmation in the future.

The P300 waveform in the one-sided ear of three tinnitus patients was excluded due to poor waveform morphology, which affected the lower sample size. One possible reason may be the difficulty in differentiating target stimuli from ringing in the ear. The other reason may be the resemblance of the target stimulus and the tinnitus sound [23]. Tinnitus patients in this study had significantly prolonged latency compared with normal controls ($p<0.05$) and higher P300 amplitude but no significant difference in both the age 18-40 years group and the age 41-60 years group. Similar to the findings from a study in 2020 by Najafi and Rouzbahani [12], which found a larger amplitude in patients with mild severity of tinnitus than in normal subjects at Cz electrode placement with no significant difference, the result was reversed when placed electrode at Fz site and reflects the effects of electrode placement site toward P300 characteristics. When analyzing the affected and unaffected ears in patients with tinnitus separately, we found factors such as a longer duration and a number of affected ears associated with longer latency and reduced amplitude of P300, even though no significant difference was found regarding duration or severity of tinnitus. The possible causes related to changes in P300 latency in tinnitus patients were (1) the tinnitus masking effect [24], (2) the reduction in the number of working neurons/ neuronal activity [10], (3) the mismatching of the neuronal firings [10], (4) the impairment of attention [24] , and (5) the tinnitus-related pathology which impaired the cognitive function [25].

All subjects were screened for cognitive function with a mini cog that combines memory, visuospatial, and executive function test. Tinnitus patients with a mild level of attentional impairment may be missed when diagnosed with a full score of mini-cog screening and need a specialized assessment for attention. The prolonged latency of P300 in tinnitus patients reflects slower and more challenging discrimination of whether the target stimulus is an important stimulus or not, and it is associated with reduced attention level. Moreover, we found that tinnitus patients tend to have higher P300 amplitude than normal patients, but it is not statistically significant. The prior studies by Mannarelli et al. [26] and Shalaby et al. [27] hypothesized that lower P300 amplitude in tinnitus patients reflects tinnitus-related cognitive process impairment as the result of the reduced number of working neurons or the abnormality in auditory brainstem pathway or higher neural structure [10]. The potential reasons for the inconsistent results of our study may be due to the small sample size or may be the lower performance on working memory and attention in healthy controls which the Mini-cog screening test couldn't detect.

The other findings of P300 studies by Elmorsy and Abdeltawwab [13], Najafi and Rouzbahani [12], and Asadpour et al. [14] revealed no statistically significant differences in the latency of P300, which was inconsistent to our results. Also, there is no difference of P300 amplitude between the tinnitus patients and the controls. In studies by Gabr et al. [15], Attias et al. [10], and Mannarelli et al.[26] revealed the factor as cognition impairment and psychiatric problems can affect the P300 characteristics. The researcher compared articles with P300 characteristics between normal and tinnitus groups as the forest plot shown in Figures 1 and 2. Tinnitus sufferers were shown to have longer P300 latency than normal groups (mean difference = 22.35, P=0.01) and reduced P300 amplitude (mean difference = -1.87, *p*<0.01).

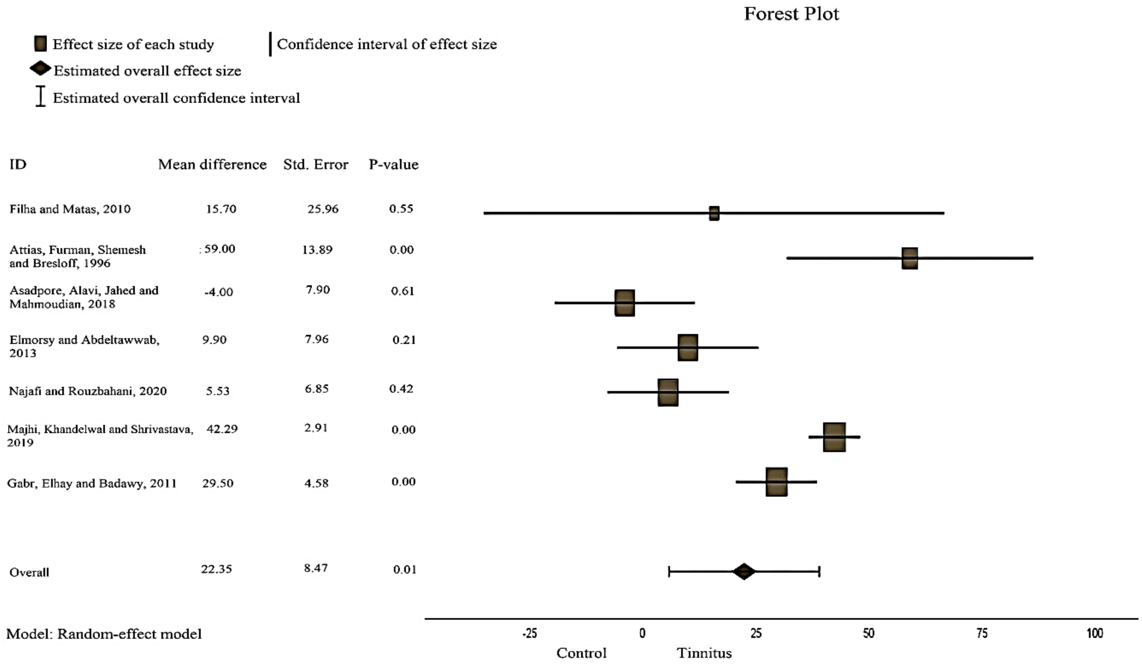

Figure 1 7 model result of a forest plot of P300 latency [9, 28, 14, 13, 12, 29, 15].

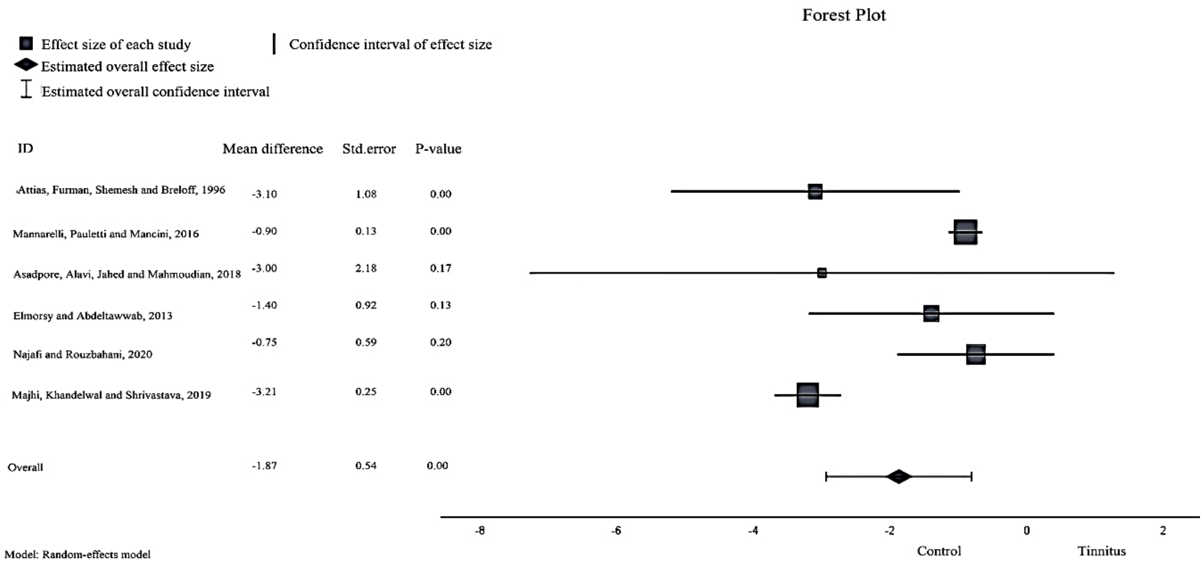

Figure 2 6 model results of a forest plot of P300 amplitude [28, 26, 14, 13, 12, 29].

The majority of tinnitus severity is a mild to moderate handicap for this study, which agreed with Urnau and Tochetto [30] and Mavrogeni et al. [31]. We found two subjects who suffered from catastrophic handicap, and they had acute tinnitus, but P300 characteristics did not differ from those of with mild to moderate tinnitus severity. According to Zhang et at. [32], acute tinnitus has a higher tinnitus severity than chronic tinnitus (26 % vs 5.7%, respectively). The cause of higher tinnitus severity in acute tinnitus is the onset of tinnitus, which reflects poorer adaptability [33]. Other factors, including a difference in personality traits, also influence the perception of tinnitus and might cause higher distress. In this investigation, we did not screen for personality differences.

Wang et al. [34] discovered a significant positive correlation between P300 latency and tinnitus severity (r=0.345). Nonetheless, this study is consistent with studies by Najafi and Rouzbahani [12], which had not found any correlation between the P300 characteristics and the severity of tinnitus. We assumed that individuals with mild to moderate tinnitus severity and people of normal hearing could distinguish between the standard and target stimuli easily. It could be implied that people with tinnitus are less attentive and have lower cognitive performance. The possible factors that influenced P300 characteristics were underlying diseases, mental disorders, some medications, and personality traits which we need to control in further studies carefully.

In this study, most tinnitus pitch matching occurs at a high frequency, about 55%, and most of pitch is over 3000 Hz [35]. Regarding tinnitus matching, we discovered two tinnitus patients who were confused between tinnitus frequency and the stimulus frequency that may be caused by multiple frequency tinnitus or no tinnitus during tinnitus matching processing. Sound masking is more useful in about 66.67% of acute tinnitus cases, especially in younger people. Younger patients may have shorter durations. This study agrees with Aytac et al. [36] We can utilize the normative P300 characteristics in normal participants obtained from this study in clinical applications. Patients with longer latency or smaller amplitude than normal may be caused by cognitive impairment. The limitation of this study is the small sample size, and it does not control factors that impact P300, such as personality traits, mental problems, or some medications. Further studies with a larger number of subjects are needed to reveal the significant difference in P300 characteristics with interesting factors to support the usefulness of P300.

5. Conclusions

According to this study, people who suffered from tinnitus had a prolonged latency of P300 and showed a relationship between the source of P300 and tinnitus. There is no correlation between tinnitus severity and P300 characteristics. Further studies with a larger number of subjects are needed to reveal the significant difference of P300 characteristics with interesting factors to support the usefulness of P300 study as may be an effective tool for diagnosis and proper measurements of tinnitus.

6. Ethical approvals

The study was reviewed and approved by the Khon Kaen University Ethics Committee in Human Research (HE651068) and registered in Thai Clinical Trial Registry (TCTR20220430002).

7. Acknowledgements

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8. Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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