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AUDITORY EVOKED POTENTIAL P300 IN TINNITUS PATIENTS WITH NORMAL HEARING

By

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ABSTRACT

Background: Tinnitus is defined as the perception of sound in the absence of acoustic events. This sound perception or noise emanating from the ears or head ranges from a barely noticeable annoyance to a debilitating chronic condition.

Objective: To assess the P300 response in subjects with tinnitus and normal hearing and compare that response with normal hearing subjects without tinnitus.

Patients and Methods: In this study we assessed P300 in 20 normal hearing subjects and compared their results with the results of P300 in 20 tinnitus subject with normal hearing. All study subjects underwent full history taking, otological examination, basic audio logical evaluation, otoacoustic emission and electrophysiological test (P300). No significant difference was found between both groups as regard hearing threshold, speech audiometry, immittancemetry and otoacoustic emission.

Results: Tinnitus patients had longer P300 latencies than normal subjects which was not significant, and lower P300 amplitude which was significant. These results reflected that tinnitus patients have poor attention ability as the components of long latency auditory evoked potential were influenced by the degree of attention to the stimulus, involvement of the central auditory nervous system, suggesting a participation of the auditory cortex in the generation, and/or tinnitus maintenance.

Conclusion: P300 test may be a useful tool for objective assessment of tinnitus patient and to evaluate the neurocognitive status of tinnitus patient.

Keywords: Tinnitus, auditory evoked potential, central auditory nervous system.

INTRODUCTION

Tinnitus is defined as a sound perception in the absence of a sound source *(Azevedo et al., 2020).* Epidemiologic studies have shown that on average, 17.5% of the world populations have tinnitus with 5.3% having severe tinnitus, which reduces the quality of life *(Najafi and Rouzbahani, 2020).*

There are several risk factors for tinnitus identified in the biomedical literature, such as age or medication, frequent loud noise exposure, otologic diseases such as otosclerosis, otitis media, presbycusis, sudden deafness, Ménière's disease, and acoustic schwannoma *(Le´ger et al., 2014).*

Although tinnitus is usually associated with hearing loss, it also may occur with normal hearing because normal hearing thresholds do not necessarily indicate the absence of cochlear damage or complete organization of central auditory system

(Le´ger et al., 2014). The presence of OAE is a strong evidence of cochlear structural integrity and their lack could indicate a cochlear lesion due to the link with OHC activity *(Gentil et al., 2015).*

Some studies have suggested that various networks are involved in perception and generation of tinnitus, such as frontal cortex and limbic system, which may be responsible for distress and attention disorders in patients with tinnitus. Tinnitus may have impact on different types of attention e.g. dividing attention and working memory *(Shakarami et al., 2015).*

Different subjective and objective tests have been introduced for assessment of auditory attention. In recent years, objective tests such as auditory P300 test have been more common *(Huang et al., 2015).*

The P300 is an endogenous response and depends on cognitive processes like attention. Some different cortical and subcortical regions are involved in P300 generation. The P300 test has two standard and target stimuli; for better and reliable recording, attention to target stimuli was necessary *(Najafi et al., 2017).*

Some studies showed affection of cognitive function in people suffering from tinnitus in compare to people without tinnitus suggesting that tinnitus patients have a slower processing speed and poor attention.

However, many studies haven't found conclusive and common results regarding the impairment of cognitive function in tinnitus subjects with normal hearing. Accordingly, this study was conducted to compare patients with tinnitus and normal hearing to those without tinnitus using auditory P300 response.

The present work aimed to assess the P300 response in subjects with tinnitus and normal hearing, and compare that response with normal hearing subjects without tinnitus.

PATIENTS AND METHODS

This study included 2 groups:

1. **Healthy comparative group (control group):** consisted of 20 adults with age range from 40-60 years old with the following criteria: No complaints about tinnitus, no hearing complaints or difficulties reported by the patients, normal hearing sensitivity not exceeding 25 dB in the frequency range 250- 8000 Hz, normal middle ear functions as evidenced by otological examination, tympanometry and acoustic reflex threshold and no history of chronic diseases or noise exposure.
2. **Tinnitus group** consisted of 30 adults with age range from 40-60 years old with the following criteria: Bilateral or unilateral tinnitus for at least 3 months, no hearing complains or difficulties reported by the patients, normal hearing sensitivity not exceeding 25 dB in the frequency range 250 -8000 Hz, normal otoacoustic emission, normal middle ear functions as evidenced by otological examination, tympanometry and acoustic reflex threshold, no history of chronic diseases.

Exclusion criteria: History of hearing loss, individuals who less than 40 years

old or older than 60 years old, abnormal immittancemetry, history of local ear diseases and history of chronic medical diseases affecting hearing.

Equipment: Two channels pure tone audiometer (Piano), sound treated room (I.A.C), immittancemeter (Maico, MI 44), otoacoustic emission (Madsen, Capella), and electrophysiologic measures (Interacoustic Eclipse EP25).

Methods:

All subjects of the study were subjected to the following:

Full history taking including personal, medical and otological history, otological examination to exclude external or middle ear disease, basic audio logical evaluation including pure tone audiometry including air conduction for octave frequencies 250Hz through 8000Hz and bone conduction for octave frequencies 500Hz through 4000Hz, speech audiometry including speech recognition threshold (SRT) test using Arabic Bisyllabic Words *(Qasim et al., 2021),*word discrimination score (WD) test using Arabic monosyllabic Phonetically Balanced Words *(Najem and Marie, 2021),* immittancemetry including tympanometry at varying pressure ranging from +200 to -400 mmH2O to evaluate the middle ear pressure and its compliance , and acoustic reflex thresholds determination ipsilaterally and contraletrally using pure tones of 500, 1000, 2000 and 4000Hz.

Transient Evoked Otoacoustic emission:

The test was conducted in a quiet room. The patients sit calmly and instructed not to talk or move. The probe was firmly inserted into subject's ears and it was tested for probe fitting before the start of the test. TEOAEs were elicited using non-linear click stimuli at stimulus intensity 60 dB peak equivalent sound pressure level and rejection level 45dB. TEOAEs were recorded as present or absent. To be classified as present, the recording has to show a whole wave reproducibility of 75% or more and a signal to noise ratio of greater than or equal to +3 dBSPL in at least three frequency bands. TEOAEs stimuli were presented to the subject through miniature transducer housed in a probe fitted in the subject's external ear canal. The stimulus level in the ear canal was measured using a miniature microphone also housed in the ear probe. TEOAEs were analyzed by recording 1000 sweeps in one session within a time window of 3-18 msec and averaged within 5 frequency bands centered at (1, 1.5, 2, 3, 4 KHz).

Auditory evoked potentials (P300):

Skin preparation: The skin at the places of the electrodes was prepared through cleaning with gauze soaked with alcohol to reduce electrode impedance, disposable electrodes were used.

Recording parameters were according to *(Shalaby et al. (2017),* Transducer: insert earphones. Band pass filter: 1-30 Hz. Stimulus: 1 and 2 kHz tone bursts, 1 kHz represented non targeted stimuli (80%) and 2 kHz represented targeted stimuli (20%). Stimuli intensity: 70dBnHL. Sweeps number: 300. Polarity: Rarefaction. Rate: 0.5 per second. Analysis time: 500ms.

Electrode montage and test position was according to *Lasheen et al. (2019),*

Two reference electrodes (non-inverting) were placed over the right and left mastoid. The active electrode (inverting electrode) was placed at high frontal Fz and the ground electrode was placed at low frontal FPz In the sitting position, the subjects were asked to identify the rare stimulus by counting when target sounds occur. The time of recording for each individual was about 10-15 minutes.

The P300 was identified as a large broad positivity in the wave of deviant stimulus (rare stimulus) with latency of about 380 milliseconds post stimulus onset.

The response parameters measured were latency which was measured from the stimulus onset to the maximum positive peak of the wave , and amplitude which was measured from the highest point of the P300 wave form to the following most negative excursion.

Statistical Analysis:

The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 20). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics: Mean, Standard deviation (± SD) for numerical data, Frequency and percentage of non-numerical data.

Analytical statistics: Student t test was used to assess the statistical significance of the difference between two study group means. Chi-square test was used for comparison between groups regarding qualitative data.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant when P-value < 0.05

RESULTS

There was no statistically significant difference between control group and tinnitus group as regard age and gender **(Table 1)**.

Table (1): Comparison between control group and tinnitus group as regard age and gender

Parameters \ Groups		Control group No. = 20		Tinnitus group No. = 30		P-value
Age (years)	Mean ± SD	50.40 ± 7.15		51.90 ± 5.45		0.45
Gender	Female	10	50.0%	11	37.0%	0.3
	Male	10	50.0%	19	63.0%	

Mean tinnitus duration was 2.20 ± 1.13, and 33.3% of patients had Rt tinnitus, 33.3% of patients had Lt tinnitus, and 33.3% of patients had bilateral tinnitus **(Table 2)**.

Table (2): Duration of tinnitus and laterality

Tinnitus group No. =30	**Duration of tinnitus (years)**	**Mean ± SD**	**2.20 ± 1.13**
	Laterality	**No.**	**%**
	Right	10	33.3%
	Left	10	33.3%
	Bilateral	10	33.3%

There was no statistically significant difference between right and left ears of control group as regard P300 latency and P300 amplitude **(Table 3)**.

Table (3): Comparison between right and left ears of control group as regard P300 latency and P300 amplitude

Control group		**Right**	**Left**	**P-value**
		No. = 20	**No. = 20**	
Latency	Mean ± SD	377.05 ± 9.83	381.69 ±8.04	0.11
Amplitude	Mean ± SD	12.14 ± 2.74	11.95 ± 3.34	0.84

There was no statistically significant difference between right and left ears of tinnitus group as regard P300 latency and P300 amplitude **(Table 4)**.

Table (4): Comparison between right and left ears of tinnitus group as regard P300 latency and P300 amplitude

Tinnitus group		**Right**	**Left**	**P-value**
		No. = 30	**No. = 30**	
Latency	Mean ± SD	379.20 ± 11.4	382.90 ±10.01	0.08
Amplitude	Mean ± SD	10.40 ± 1.89	9.83 ± 1.72	0.11

There was no statistically significant difference between females and males of control group as regard P300 latency and P300 amplitude **(Table 5)**.

Table (5): Comparison between females and males of control group as regard P300 latency and P300 amplitude.

Gender / Control group	**Females**	**Males**	**P value**
	No. = 10	**No. = 10**	
Rt latency	375.65 ± 10.02	378.45 ± 9.96	0.539
Lt latency	380.28 ± 7.21	383.10 ± 8.96	0.448
Rt amplitude	12.33 ± 2.71	11.94 ± 2.90	0.761
Lt amplitude	12.52 ± 3.42	11.38 ± 3.33	0.457

There was no statistically significant difference between females and males of tinnitus group as regard P300 latency and P300 amplitude **(Table 6)**.

Table (6): Comparison between females and males of tinnitus group as regard P300 latency and P300 amplitude

Gender / Tinnitus group	Females	Males	P value
	No. = 11	No. = 19	
Rt latency	375.61 ± 9.68	379.11 ± 11.08	0.304
Lt latency	381.10 ± 7.84	383.18 ± 9.82	0.476
Rt amplitude	11.67 ± 2.63	10.76 ± 2.50	0.271
LT amplitude	11.28 ± 3.08	10.18 ± 2.77	0.323

There was no statistically significant difference between control and tinnitus group as regard P300 latency **(Table 7)**.

Table (7): Comparison between control group and tinnitus group as regard P300 latency

Latency	Control group	Tinnitus group	P-value
	No. = 20	No. = 30	
Rt	377.05 ± 9.83	379.20 ± 11.40	0.24
Lt	381.69 ± 8.04	382.90 ± 10.01	0.67

There was a statistically significant difference between control and tinnitus group as regard P300 amplitude **(Table 8)**.

Table (8):Comparison between control group and tinnitus group as regard P300 amplitude

Amplitude	Control group	Tinnitus group	P-value
	No. = 20	No. = 30	
Rt	12.14 ± 2.74	10.40 ± 1.89	0.011*
Lt	11.95 ± 3.34	9.83 ± 1.72	0.002**

DISCUSSION

Patients with tinnitus may suffer from several problems in their daily life *(Shakarami et al., 2015)*. In some cases, tinnitus may affect attention. Several tests have been proposed for assessment of auditory attention. One of them is P300 test. The P300 is an endogenous response which depends on several factors, like attention *(Mohamad et al., 2016)*.

Tinnitus could be central in origin. Auditory evoked potentials (AEPs) are used to examine the synchronous discharge of fibers in the auditory pathway and identify the presence of abnormal neuronal activity. The auditory long latency event related potential is one of the most common protocols for evaluation of the auditory cortical areas. The insula and auditory cortical areas of the superior temporal lobe are major sites of generation of the auditory P300

response *(Elmorsy and Abdeltawwab, 2013).*

In present study, we assessed P300 response in tinnitus patients with normal hearing and compared their results with the response of normal hearing subjects without tinnitus.

We evaluated 30 subjects with normal hearing and tinnitus with no history of systemic diseases, their mean age was 51.90 ± 5.45, 11(37%) subjects were females and 19 (63%) were males. The mean duration of tinnitus was (2.20 year ± 1.13). Ten (33.3%) subjects had Rt side tinnitus, ten (33.3%) subjects had Lt side tinnitus, and ten (33.3%) subjects had bilateral tinnitus.

We compared their results with 20 normal hearing subjects with no complain of tinnitus nor systemic diseases, their mean age was 50.40 ± 7.15, 10 (50.0%) subjects were females and 10 (50.0%) subjects were males.

There was no significant difference between tinnitus and control group as regard age and gender.

Both groups had bilateral normal hearing threshold, with no significant difference between both groups. This agreed with *Elmorsy and Abdeltawwab (2013)* and *Gilles et al. (2016)* who found non statistical significant difference between tinnitus patients and normal hearing subjects without tinnitus as regard hearing threshold despite higher threshold level for the tinnitus group. *Gilles et al. (2016)* who suggested that tinnitus may occur in the absence of measurable peripheral damage and might cause more central plasticity than expected.

Both groups had bilateral normal OAE, and there was no significant difference between control group and tinnitus group. This agree withd *Gilles et al. (2016)* and *Kara et al. (2020)* who found non-significant difference between tinnitus and non-tinnitus subjects as regard TEOAE. These results suggested that in both groups outer hair cell functions were similar and outer hair cell dysfunctions were not contributing to tinnitus.

The mean of P300 latency was (377.05 ± 9.83) in Rt ears and (381.69 ± 8.04) in Lt ears of control group. The mean of P300 latency was (379.20 ± 11.4) in Rt ears and (382.90 ± 10.01) in Lt ears of tinnitus group.

There was no significant difference between Rt and Lt ears of control group and no significant difference between Rt and Lt ears of tinnitus group as regard P300 latency and P300 amplitude.

As regard to gender there was no significant difference between males and females of control group and there was no significant difference between males and females of tinnitus group but males tend to have longer P300 latency and lower amplitude than females. This agreed with the result of *Puttabasappa et al. (2017)* who reported non-significant differences between males and females as regard P300 amplitude and latency.

Melynyte et al. (2018) reported that the P300 amplitude could be significantly modulated by gender, with greater amplitude in females relative to males. He also reported that gender has a minimal effect on the P300 latency, and it is often comparable between males and females. He also found longer latencies in females, included only young female subjects (age

range: 18–29 years). They also revealed that 13 out of 31 studies reported larger P300 amplitudes in females. Only one study out of 24 studies reported longer P300 latencies in females, and all other studies found no gender-related effect on P300 latencies.

The differences between females and males were due to that the human cortex to differ in thickness, brain wiring and different patterns between hemisphere connections *(Ingalhalikar et al., 2014)*. Thus, the electrophysiological assessment of processing of the stimuli in the brain, including observed higher P300 amplitudes in females, can be influenced by the wider range of structural and physiological aspects. For example, the grey matter volume in the parietal lobe was shown to be thicker in females and the volume of grey matter was correlated with P300 amplitudes to the rare-target stimuli Similarly, larger sizes of the corpus callosum in females were reported *(Ritchie et al., 2017)*. There was no statistically significant difference between control group and tinnitus group as regard P300, but tinnitus group had longer latencies.

This was in agreement with the results of *Elmorsy and Abdeltawwab (2013), Houdayer et al., (2015)* and *Najafi and Rouzbahani (2020)* who found non-significant delay in latency of P300 in tinnitus patient with normal hearing compared with non-tinnitus group with normal hearing.

dos Santos Filha et al., (2010) and *Lima et al., (2020)* reported a statistically significant delay in P300 latency between tinnitus and non-tinnitus group.

There was significant lower amplitude in tinnitus group when compared with control group. This war in agreement with *Hong et al. (2016)* and *Asadpour et al. (2018)* who reported significant lower amplitude in tinnitus group than healthy group.

Elmorsy and Abdeltawwab (2013) and *Najafi et al., (2020)* reported lower P300 amplitude in tinnitus group than P300 amplitude in normal subjects which was non-significant.

Houdayer et al. (2015) found non-significant differences in P300 amplitude between tinnitus group with normal hearing and normal hearing non tinnitus group.

The two major neurophysiological markers of cognitive function are latency and amplitude. Latency is a reliable indicator of the speed of information processing in the brain. Prolonged latency presents prolonged information processing time. On the other hand, reduced of the amplitude reflected disruption in the activities of some generators (frontal and parietal cortex, thalamus and temporal dispersion of information processing in the cortex). For the diagnosis of cognitive dysfunction pathology only one of the parameters is sufficient prolonged P300 latency and/or reduced P300 amplitude *(Faber et al., 2012).*

Based on functional imaging studies, it is generally accepted that tinnitus is associated with maladaptive neuroplasticity because of impairment in the auditory system *(Faber et al., 2012)*. Tinnitus can be attributed to hyperactivity and reorganization in the auditory central nervous system with coactivation of non-auditory brain structures such as the

dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) *(Vanneste et al., 2010).*

The DLPFC is essential for higher order cognitive control functions and goal-directed behaviors *(McNamee et al., 2015),* and the ACC executes top-down inhibitory control *(Silton et al., 2010).* These prefrontal areas have also been found to be involved in auditory attention *(Toarmino et al., 2017).*

Although it has been reported that tinnitus influences auditory selective attention, with patients reporting concentration difficulties due to their tinnitus *(Heeren et al., 2014),* uncertainty still exists regarding the direction of causation between tinnitus and cognitive processes of attention *(Mohamad et al., 2016).* While some studies showed that tinnitus leads to altered performance on attention-related tasks, others have suggested that these alterations might rely on reduced top-down executive control *(Waechter et al., 2021).*

Haider and Fazel-Rezai (2017) reported that the increase in latency or reduction in amplitude in the LLAEP is associated with clinical and subclinical problems. He also reported that a deficit in some central auditory processing skill, with a reduction in the auditory attention, memory deficit and difficulties in frequency discrimination can cause changes in the LLAEP components in individuals with tinnitus.

Abbas et al. (2019) reported that tinnitus patients have poor attention ability. The components of LLAEP are influenced by the degree of attention to the stimulus. If the stimulus is ignored, the wave shapes are damped and possibly delayed. It is also believed that tinnitus has a masking effect on the acoustic signals presented to tinnitus individuals. Therefor it can be inferred that individuals in tinnitus group were less attentive during the test due to the presence of tinnius *(Lima et al., 2020).* Other possible factors that can be attributed to the increased P300 wave latency in individuals complaining of tinnitus are the possibility of a reduction in the number of functioning neurons, a decrease in neural activity and/or DE synchronization in the affected neurons *(Azevedo et al., 2020).*

dos Santos Filha et al. (2010) reported that the LLAEP alterations seen in individuals with tinnitus show an involvement of the CANS, suggesting a participation of the auditory cortex in the generation and/or tinnitus maintenance. Thus, the LLAEP is a useful tool to investigate the mechanism responsible for this symptom. *De Ridder et al. (2011)* suggested that the reason for lower amplitude in tinnitus group may be the input processing disorder and frontal lobe involvement, because dorsolateral prefrontal cortex (DLPFC) has an important role in auditory attention and has a direct connection with primary auditory cortex; involvement of DLPFC may cause the reduction of amplitude in tinnitus group.

Seraji et al., (2021) explained that reduction in LLAEP amplitude without changes in latency could be assigned to a reduction in the number of neurons responding to a reduction on neural activity and/ or a larger mismatch of the firings of the neurons involved.

Elmorsy and Abdeltawwab (2013) showed that despite the P300 peak

amplitudes were overall reduced for idiopathic subjective tinnitus subjects than normal subjects; P300 peak latencies were of statistically non-significant values. They reported that these findings are consistent with the hypothesis that tinnitus patients differ in their response to auditory stimuli. Possible mechanism includes the possibilities of central origin of tinnitus that causes different response to auditory tone burst and a processing of selective attention associated with it. On the other hand, they explained the no statistical significant difference that was found as regards the auditory P300 latencies that those patients do not have auditory problems at the level measured by P300 and so casting the doubt on affection of the hypothized origin of P300 mainly auditory cortical area for tinnitus origin.

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الجهد السمعي المثار (P300) في الأشخاص الذين يعانون من الطنين وطبيعي السمع

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خلفية البحث: يُعرَّف طنين الأذن بأنه إدراك الصوت في غياب الأحداث الصوتية. هذا الإدراك الصوتي أو الضوضاء الصادرة من الأذنين أو الرأس تتراوح من إزعاج بالكاد إلى حالة مزمنة منهكة.

الهدف من البحث: تقييم استجابة P300 في الأشخاص الذين يعانون من طنين الأذن وطبيعي السمع.

المرضى وطرق البحث: في هذه الدراسة قمنا بتقييم P300 في 20 شخصًا طبيعي السمع وقارنا نتائجهم بنتيجة P300 في 20 حالة لديهم طنين وطبيعي السمع. خضع جميع الخاضعين للدراسة لأخذ التاريخ الكامل، وفحص الأذن، والتقييم السمعي الأساسي، والانبعاثات السمعية واختبار الفسيولوجيه الكهربية (P300).

نتائج البحث: فيما يتعلق بمرضى الطنين P300 كان لديهم زمن انتقال P300 أطول من الأشخاص العاديين والذي لم يكن ذو دلالة احصائية، وسعة P300 أقل والتي كانت ذات دلالة احصائية. وتبين هذه النتائج أن مرضى طنين الأذن يعانون من ضعف في القدرة على الانتباه لأن مكونات هذا الاختبار تتأثر بدرجة الانتباه إلى المنبه. وقد يكون ذلك راجعا الي مشاركة الجهاز السمعي المركزي، مما يشير إلى مشاركة القشرة السمعية في انشاء و/ أو استمرارالطنين.

الاستنتاج: قد يكون اختبار P300 أداة مفيدة للتقييم الموضوعي لمريض طنين الأذن ولتقييم الحالة الإدراكية العصبية لمريض طنين الأذن.

الكلمات الدالة: الطنين، الجهد السمعي المثار، الجهاز العصبي السمعي المركزي.