

# Electrophysiological differences in sensorineural hearing loss patients with and without problem-tinnitus

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## Objects

Problem-tinnitus refers to tinnitus that is sufficiently severe to produce a major disruption in the patient's life; tinnitus of such severity involves a number of regions of the auditory system and other brain systems may also play an essential role. Auditory brainstem responses (ABR) and event-related potentials (ERP) were recorded from sensorineural hearing loss (SNHL) patients with problem-tinnitus and were then compared with responses from normal hearing and hearing loss tinnitus-free patients.

## Aim

To study whether differences exist in ABR and/or ERP parameters in SNHL patients with and without problem-tinnitus when matched as closely as possible for hearing loss, age, and sex to investigate the mechanism responsible for tinnitus.

## Materials and Methods

Ninety participants were included in this study. They were divided into two groups: the study group included 66 participants with bilateral symmetrical SNHL that did not exceed a moderate degree. The study group was divided into two subgroups: 36 patients had problem-tinnitus and 30 patients were tinnitus-free (SNHL, age, and sex matched). Participants in each of these subgroups were compared with each other and were also compared with 24 healthy individuals in the control group (age and sex matched with the study group). All participants were subjected to a basic audiological evaluation and electrophysiological tests (ABR and ERP).

## Results

This work had shown a higher prevalence of ABR abnormalities in tinnitus patients in comparison with either the control group or the SNHL tinnitus-free group. Statistically significant differences were found in III–V and I–V interpeak latencies and in the V/I amplitude ratio in problem-tinnitus female patients compared with tinnitus-free female patients. Meanwhile, in problem tinnitus male patients when compared with tinnitus-free male patients at III–V interpeak latencies and at VI amplitude ratio.

As regards the results of ERP in this work, an increase in latency and amplitude reduction were found. Statistically significant differences were observed regarding both the mean latency values of waves N1, P2, and P300 and the amplitude mean values of P2 and P300 when we compared the problem-tinnitus subgroup with either the tinnitus-free subgroup or the control group (both female and male patients).

## Conclusion

A variety of ABR and ERP components are altered in tinnitus patients; this would indicate impairment in both the central auditory pathway and central auditory processing. Thus, it is suggested that this form of ABR, ERP testing could be considered as an objective measure to complement behavioral, audiological, and other physiologic methods of assessing tinnitus, rather than a single definitive tinnitus measure in an attempt to supplement and thereby extend knowledge of the nature and origins of tinnitus. Furthermore, these results provide the basis for future neurofeedback-based tinnitus therapies aiming at maximizing the ability to shift attention away from the tinnitus.

## Keywords:

auditory brainstem responses, event-related potentials, sensorineural hearing loss, tinnitus

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## Introduction

Problem-tinnitus refers to tinnitus that is sufficiently severe to produce a major disruption in the patient's

life [1,2]. Melcher *et al.* and [3] Lockwood *et al.* [4] reported that tinnitus of such severity involves a number of regions of the auditory system and that other brain systems may also play an essential role.

Although tinnitus is commonly associated with hearing loss, other etiological factors have emerged from the widest epidemiological studies of tinnitus prevalence and actually they were considered as potential causes of tinnitus and/or cofactors. As reported by Hoffman, these factors include conditions such as vascular disease, diabetes, hypertension, autoimmune disorders, and degenerative neural disorders [5–7].

The high incidence of cochlear damage led many to suggest that tinnitus arises in this organ. Previously, tinnitus localized to a specific ear was considered sufficient evidence for a peripheral origin [6–9]. Later, Dauman and Tyler [9] argued that the distinction between peripheral, neural, and central cannot be maintained. Kenmochi and Eggermont [10] also suggested a central effect of salicylates and quinine in addition to their peripheral ototoxic effects. Also, the gradual reorganization of the central nervous system (CNS) after, for example, noise-induced, peripheral lesions also suggested that the distinction of peripheral versus central tinnitus is likely not very relevant.

Eggermont [8] reported that the reduced spontaneous activity for nerve fibers with characteristic frequency (CFs) in the hearing loss range may result in a reduction in lateral inhibition at more central levels (e.g. in the dorsal cochlear nucleus (DCN) or the inferior colliculus) as the auditory system is a reentrant system characterized by multiple, loosely interconnected, regional feedback loops [11]. This reduced lateral inhibition of neurons with CFs close to the edge frequency of the audiogram induces hypersensitivity and hyperactivity in these neurons.

Chronic tinnitus is often accompanied by hearing impairment, but it is still unknown whether hearing loss can actually cause tinnitus. The association between the pitch of the tinnitus sensation and the audiogram edge in patients with high-frequency hearing loss suggests a functional relation, but a large fraction of patients with hearing loss do not present with symptoms of tinnitus [12]. Lockwood *et al.* [13] demonstrated a higher prevalence of hearing loss compared with tinnitus. It is therefore unclear as to which factors of hearing loss contribute to the occurrence of tinnitus.

Numerous studies have shown that tinnitus often has a central rather than a peripheral origin. The most direct evidence for this is clinical studies showing that tinnitus frequently persists following transection of the auditory nerve ipsilateral to the tinnitus. The percentage of patients not experiencing relief from tinnitus after eighth nerve section ranges across studies from 38 to 85% [14,15].

This difficult state of affairs with respect to central tinnitus is complicated by the interconnected nature of complex systems such as the auditory system. Disturbances in one part of the system are reflected in altered functional properties in other parts of the system. The complex causality associated with central tinnitus may be a consequence of such system properties [16].

Thus, as recognized before [17,18], the whole brain may somehow be involved in the sensation of tinnitus, specifically through the closed loop-type interaction between the periphery and the CNS, potentially amplified by the action of the sympathetic nervous system [19,20]. Lockwood *et al.* [13] reported that the complexity of the changes in the nervous system associated with tinnitus may explain why it is so resistant to treatment.

Eggermont [8] summarized tinnitus as a central phenomenon similar to all other perceptions. Its potential cure then requires foremost changes in the CNS. A first step may be to find a way to modify the reorganized tonotopic maps back to normal.

Tinnitus begins as an auditory disorder, but in its clinically significant form, it has two other important components. The persistent auditory percept is often associated with attentional problems: the tinnitus becomes the focus of too much attention and sufferers often have difficulties concentrating [21–24]. The percept(s) of tinnitus can also have undesirable emotional components such as persistent annoyance, frustration, anger, anxiety, and depression [25]. These attentional and emotional disturbances are the aspects of tinnitus that affect sleep patterns and ultimately have the most impact on quality of life.

Persistent tinnitus may rapidly become a source of serious disturbance and handicap at psychological and socio-professional levels; in fact, in 1–3% of the general population, tinnitus affects quality of life, involving sleep disturbance, work impairment, and psychiatric distress [26].

In most cases, despite appropriate medical examination, the origin of tinnitus is unknown. In most cases, acute tinnitus symptoms remain untreated, and after 3 months of persistent symptoms, the chronic state is reached (duration more than 3 months [27]). Once the chronic state has been reached, there is no known treatment that can completely relieve the symptoms.

Auditory brainstem response (ABR) testing in tinnitus patients was an attempt to objectify a subjective complaint by the identification of an electrophysiological correlate for tinnitus [28–30]. ABR is a useful tool in investigating the anatomical and functional characteristics of the auditory pathway from the end organ to the inferior colliculus and in detecting lesions even if the auditory threshold is unaffected [31,32].

The application of this technique was based on the hypothesis that tinnitus, a neurotological disorder, was a reflection of dyssynchrony in the neuronal firing and transmission in the pathways of the auditory system (peripheral, central, or both). Maurizi *et al.* [33] reported that ABR may aid in the differentiation of central versus peripheral tinnitus. Thus, ABR may contribute to clarification of the origin of tinnitus in normal listeners. Systematic analyses of the cumulative effects of age, hearing loss, sex, and tinnitus on ABR are not common in the clinical literature.

In studies of patients with tinnitus, for example, ABR has shown quantitative increases in latency and poor reproducibility [21]. However, these reports did not state whether increases in tinnitus latencies were greater than those associated with sex, age, or hearing loss.

Filha and Matas [34] reported that the alterations in auditory event-related potentials (ERP) in individuals with tinnitus are suggestive of dysfunction in the central auditory pathways at a cortical level. Gabr *et al.* [35], also, reported that the mean latency of P300 was significantly delayed when compared with the normal group. Meanwhile, Attias *et al.* [36] reported that ERP amplitudes (waves N1, P2, and P3) in tinnitus patients were significantly lower than in controls in all testing paradigms. No differences were found in ERP peak latencies, ABR, reaction time, or response scoring. The lower ERP amplitudes may indicate attenuated or 'abnormal' auditory central processing in noise-induced hearing loss tinnitus patients.

Aims of the work:

- (1) To study whether differences exist in ABR and/or ERP parameters in a group of sensorineural hearing loss (SNHL) patients with problem-tinnitus when closely matched with a second group of SNHL without problem-tinnitus.
- (2) To investigate the mechanism responsible for tinnitus.

## Patients and methods

This work was carried out at the Audiology unit, Department of Otolaryngology – Head and Neck Surgery in University Hospitals in the period from February 2009 to January 2011. Informed consents were obtained from all individuals who participated in this study after explaining the nature and purpose of this work according to the principles of the Ethical Committee of Assiut University.

Ninety participants were included in this study. They were divided into two groups: the study group included 66 participants with bilateral symmetrical SNHL that did not exceed a moderate degree. This group was divided into two subgroups according to the presence or absence of tinnitus into a tinnitus-free subgroup, which included 30 participants with complaints of SNHL only (16 women and 14 men), and a problem-tinnitus subgroup, which included 36 participants with SNHL and tinnitus (19 women and 17 men); their age ranged from 18 to 45 years. The control group included 24 participants (14 women and 10 men), age range 20–43 years, with normal hearing and no tinnitus, age and sex matched to the study group.

### Inclusion criteria

- (1) Patients with tinnitus were included in the study if they presented with subjective, chronic bilateral tinnitus, that is, tinnitus was a permanent sensation, stable, and spontaneous (not occurring only during

exposure to noise or immediately after), tinnitus was perceived in both ears with similar pitch, and had persisted for at least 1 year.

We noted that the duration of hearing loss and tinnitus could not always be reliably determined, as hearing loss may be slowly progressing, and tinnitus often develops from occasional episodes to a permanent sensation.

- (2) In addition, only patients with moderate-to-severe and disabling tinnitus were included. Walpurger [37] reported that when participants felt subjectively severely impaired by the tinnitus sounds in situations where they were distracted from the tones (e.g. work, hobbies) and in situations where they were not distracted (e.g. going to sleep), they were classified as 'tinnitus complainers'.

### Exclusion criteria

- (1) Patients with unilateral tinnitus to eliminate possible confounding factors that could arise from assigning the two ears of a single patient to two different groups in the analysis [38,39].
- (2) Patients using a hearing aid, as hearing aids can reduce tinnitus [40,41] and are used in tinnitus therapy [42].
- (3) Patients afflicted with definite middle or inner ear pathology (such as basic chronic otitis media, otospongiosis, Meniere's disease, with noise exposure or acoustic trauma) were excluded, as in those conditions, the origin of tinnitus may be reasonably related to the primary disease.
- (4) Patients who had complaints of cardiovascular neurological, psychiatric, behavioral dysfunctions, tinnitus patients who were free from medication for at least 1 month before the study; these data were obtained during the medical interview. All participants were right-handed [36].

After collection of personal data, all patients were subjected to a careful assessment of general medical history to identify tinnitus-related pathologies and other health diseases; this was followed by an audiological history and an otological examination. As for the analysis of data collected, the following parameters were considered: age, sex, and tinnitus duration.

### Audiological evaluation

For basic audiological evaluation, pure tone audiometry was performed using a clinical audiometer (Madsen audiometer OB 822, headphones TDH 39P, GN Otometrics, Copenhagen, Denmark) calibrated to accepted standards [43]. Speech audiometry, speech recognition threshold, and the speech discrimination scores were also evaluated in an acoustically designed booth. Tympanometric measurements were obtained using an Interacoustics AZ-26 Impedancemeter, headphones TDH 39P calibrated daily according to the manufacturer's instructions in order to evaluate the integrity of the tympano-ossicular system through a tympanometric curve and also through acoustic reflex measurements.

### Electrophysiological evaluation:

*Auditory brainstem-evoked potentials (auditory brainstem responses):*

After the audiological evaluation, electrophysiological evaluations (ABR and ERP) were carried out on selected individuals.

First, the ABR recordings were obtained at the initial 12 ms using Nicolit Spirit equipment, USA. Patients lay supine in a silent, electrically shielded room and were requested to remain awake and relaxed throughout the recording session. Silver–silver chloride (Ag–Ag Cl) surface electrodes were applied to the scalp: the active electrode was placed on the forehead, the reference electrode was placed on the mastoid of the tested ear, and the ground electrode was placed on the contralateral mastoid; the electrode impedance should not exceed the desired impedance limit of 5 k $\Omega$ . A total of 1000–2000 alternating polarity clicks at a 90-dB hearing level were delivered for each test using a low repetition rate (RR) of 21 clicks per second and then a high RR of 61.1 clicks per second through the earphones TDH 39. The click duration was 100  $\mu$ s.

The responses were recorded differentially between the vertex electrode and the contralateral and ipsilateral mastoid electrode. The responses were filtered (100–3000 Hz) and computer averaged.

Each ear was tested individually, and the parameters studied were the absolute latency of waves I, III, V, and VII and the intervals between the different waves, interpeak latencies (IPLs) I–III, I–V, and III–V. The amplitude ratio between waves V and I and the interaural latency difference in wave V were also studied. The prevalence of normal and abnormal results for each parameter measured was calculated for each patient group.

#### *Event-related potentials*

We excluded from this investigation those patients with a poor ABR morphology [36].

The acoustic stimulus used was pure tone at 80 dB HL, at frequencies of 1 kHz (frequent stimulus) and 2 kHz (rare stimulus), randomly introduced by the computer. The rare stimulus was between 15 and 20% from the total of 300 stimuli. Active participation of the patients (in an odd-ball paradigm) was required; thus, the patients were instructed to keep their attention focused on the rare stimuli that randomly appeared among a series of frequent stimuli, and they were asked to count out loud the number of times the rare event happened. P300 was recorded through four electrodes placed at Fz (+ve electrode), Fpz (ground electrode), M1, and M2 (mastoids) as reference electrodes. The total number of stimuli ranged from 200 to 300; we checked the presence and absence of these potentials, and their latency and amplitude of components N1, P2, and P300 were also calculated and later on the types of alterations found were described.

All the tests were carried out in the morning, before the individual went to work, thus ensuring that the individual was not tired at the time of the test and that he/she would maintain attention during the ERP recording.

### Statistical analysis and comparisons

The statistical package for SPSS (Version 17.0, Chicago, Illinois, USA) was used for statistical evaluation. Student's *t*-test was used to compare the results between the two groups. A *P*-value of less than 0.05 was considered as statistically significant.

## Results

In the present study, the age of the individuals in the study group varied between 18 and 45 years (mean =  $28.35 \pm 3.71$  years), and in the control group, it varied between 21 and 45 years (mean =  $29.72 \pm 4.34$  years). Sex distribution in the study group and the control group is illustrated in Table 1.

We did not find statistically significant differences between the groups in relation to age or sex.

For participants with tinnitus, the mean reported duration of hearing loss was  $4.83 \pm 1.33$  years, and for tinnitus-free participants, it was  $5.1 \pm 1.71$  years; the difference was not significant ( $P = 0.372$ ).

All tinnitus participants had tinnitus for more than 1 year, with a mean reported duration of  $4.67 \pm 1.19$  years. The duration of tinnitus was not significantly different from the duration of hearing loss ( $P = 0.635$ ).

### Results of basic audiological evaluation

The ABR of men and women evolved differently from the age of 30 years, the latencies of I–III and I–V in men lengthening with age and those of women tending to shorten [44]; therefore, the patient groups were compared with a control group of the same sex in all test results in this study. Thus, the study and the control groups were classified according to their sex type and then each sex type was further classified into two subgroups according to the absence or presence of problem-tinnitus, resulting in two subgroups for female patients 'a' and 'b' and two subgroups 'c' and 'd' for male patients.

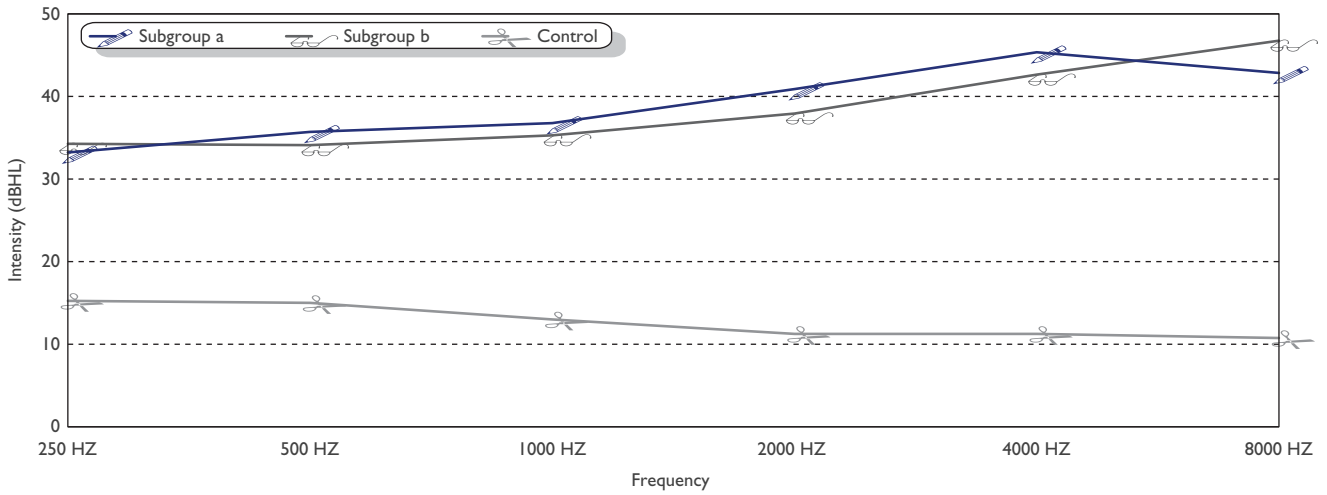
Comparison of pure tone average (PTA) results at different frequencies was carried out between tinnitus-free and problem-tinnitus subgroups (a, b) and (c, d) women and men, respectively, and the control group of each sex separately. PTA results were elevated in both subgroups (the problem-tinnitus subgroup and the tinnitus-free subgroup) when compared with the control group of the same sex, with a statistically highly significant difference at all frequencies, but with no statistically significant difference between the females' two subgroups 'a' and 'b' (Fig. 1) or the males' two subgroups 'c' and 'd' (Fig. 2).

Clearly, the duration of hearing loss in the tinnitus-free and problem-tinnitus subgroups was not statistically

**Table 1 Demographic data of the participants in the control group and the two study subgroups**

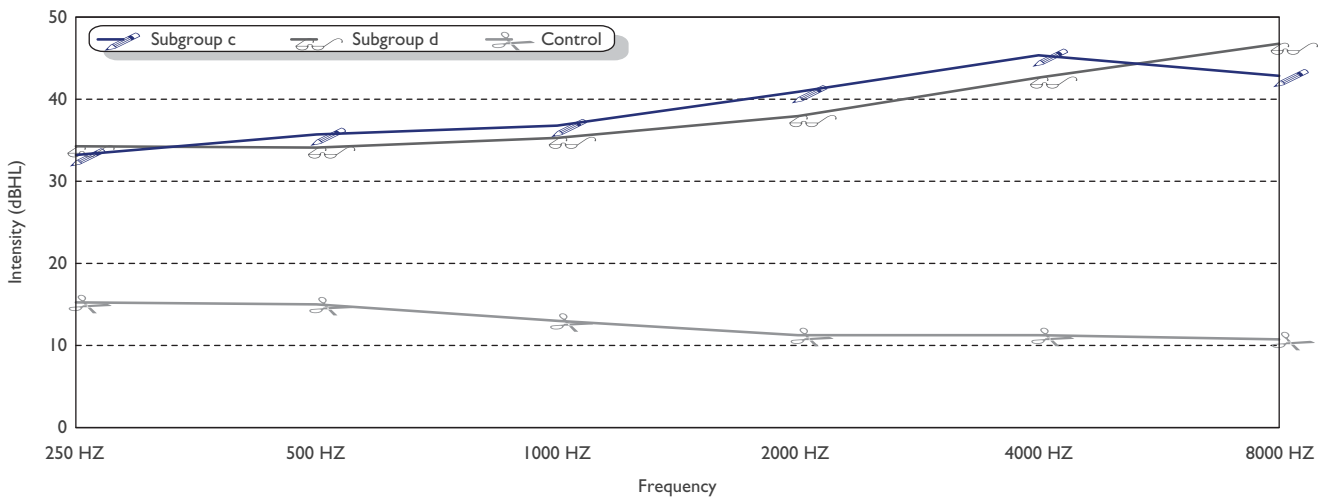
Control group (N=24)		Study group (N=66)			
		Females N=35		Males N=31	
Females	Males	Subgroup 'a'	Subgroup 'b'	Subgroup 'c'	Subgroup 'd'
14 (58.33%)	10 (41.16%)	16 (45.7% <sup>1</sup> )	19 (54.28%)	14 (45.16%)	17 (54.83%)

**Figure 1**



Mean hearing level in the control and (a, b) subgroups (women).

**Figure 2**



Mean hearing level in the control and (c, d) subgroups (men).

significantly different, which would seem to rule out hearing loss as a primary cause of tinnitus; this was found in both the female and male patients.

As a statistically significant difference was not found between the average pure tone thresholds of the right and left ears at all frequencies in the control and both

female (a, b) and male (c, d) subgroups, accordingly, the right and the left ears were grouped together in all subsequent analyses.

All participants had speech discrimination scores that were proportionate with the PTA results.

Tympanometric findings were similar in both groups (all within the normal type 'A' tympanogram), reflecting bilateral normal middle ear function and proportionate acoustic reflex test results.

### Results of auditory brainstem responses

After audiological evaluation, the selected individuals were subjected to an electrophysiological evaluation (ABR).

The parameters studied were (a) occurrence of waves I, III, and V; (b) absolute latency values of waves I, III, V, and VII; (c) IPL values III-I, V-III, and V-I; (d) amplitude ratio between waves V and I; and (e) interaural latency difference in wave V. The prevalence of normal and abnormal results for each parameter measured was calculated for each patient group.

### Qualitative analysis of the results

The occurrences of normal and altered results for the latency of wave I, III, and V components in the control, female subgroups 'a' and 'b' and male subgroups 'c' and 'd' are summarized in Table 2, which are presented in the following.

#### Occurrence of waves I, III, and V

- (1) Poor morphology (poorly defined ABR waveforms) [45].
- (2) Absent wave I.
- (3) Absent wave III.
- (4) Absent wave V.

### Quantitative analysis of the results:

#### Absolute latency values of waves I, III, and V

The mean ( $\pm$  SD) absolute latency values of waves I, III, and V, VII in the female study (a, b subgroups) and the control group are given in Table 3. Statistically significant increases were found in the following:

- (1) The latencies of waves I, III, V, and VII in the study subgroup 'b' compared with the control group ( $P = 0.005, 0.008, 0.001, \text{ and } 0.03$ ), respectively.
- (2) Meanwhile, when study subgroup 'b' was compared with subgroup 'a,' statistically significant differences were found in the latency of waves V and VII.

However, the mean ( $\pm$  SD) values for absolute latencies of waves I, III, V, and VII in the male study subgroups (c, d)

and the control group are presented in Table 4. Statistically significant increases were found only between

- (1) The tinnitus subgroup 'd' when compared with the control group in the latencies I, V, and VII ( $P = 0.029, 0.044, \text{ and } 0.012$ ), respectively.

The finding of a significant latency difference in wave VII between the problem-tinnitus subgroup 'd' either with the control or the tinnitus-free subgroup 'c' extend the diverse latency findings for waves I-V to include this later wave [46-48].

#### Interpeak latency values III-I, V-III, and V-I

Table 3 shows the mean ( $\pm$  SD) IPL values I-III, III-V, and I-V in the study female (a and b subgroups) and the control group. Statistically significant increases were found for:

- (1) The interpeaks III-V ( $P = 0.028$ ) and I-V ( $P = 0.008$ ) when comparing the study subgroup 'b' with the control group.
- (2) Also, on comparing the study subgroup 'b' with the subgroup 'a,' a statistically significant increase was found for interpeaks III-V ( $P = 0.044$ ) and I-V ( $P = 0.001$ ).

However, in Table 4, it was found that the only statistically significant increase in the interpeak III-V ( $P = 0.042$ ) was between the male tinnitus subgroup 'd' and the control group.

An increased latency of the III-V IPL usually reflects an increased neural conduction time in the brainstem [49].

#### Amplitude ratio between waves V and I

The study of a wave's amplitudes is used less in clinical practice than the absolute latencies and IPLs in the detection of brainstem auditory pathway problems because the amplitudes are extremely variable. Hall [50] considered the analysis of the V/I amplitude ratio to be one of the most important parameters in ABR recording; for this reason, in this study, the amplitude ratio was evaluated instead of the individual amplitude.

In this work, there was a statistically significant increase in the study female subgroup 'b' when compared with either the control group or the subgroup 'a'.

Also, a statistically significant increase was found in the amplitude ratio between the study male subgroup 'd'

**Table 2 Distribution of the occurrence of normal and altered results for the latency of wave I, III, and V components in the control, female subgroups 'a,' 'b' male subgroups 'c,' 'd'.**

	Study group					
	Control group		Females		Males	
	Females N=28 ears	Males N=20 ears	Subgroup 'a' N=32 ears	Subgroup 'b' N=38 ears	Subgroup 'c' N=28 ears	Subgroup 'd' N=32 ears
Poor morphology	1	0	2	5	4	6
Absent wave I	0	0	5	4	4	5
Absent wave III	0	0	1	2	1	3
Absent wave V	0	0	0	0	0	0

**Table 3 Mean  $\pm$ SD of nine auditory brainstem response of different parameters on using low repetition rate (21.1 s) in women of control and both subgroups in the study group (tinnitus-free patients subgroup 'a' and problem-tinnitus patients subgroup 'b').**

Parameter	Control group N=27 ears	Subgroup 'a' N=30 ears	P-value (Control and a)	Subgroup 'b' N=33 ears	P-Value (Control and b)	P-Value (a and b)
Absolute latency						
Wave I	1.66 $\pm$ 0.16	1.71 $\pm$ 0.086	0.343	1.82 $\pm$ 0.13	0.005	0.08
Wave III	3.67 $\pm$ 0.19	3.78 $\pm$ 0.230	0.156	3.84 $\pm$ 0.15	0.008	0.394
Wave V	5.51 $\pm$ 0.23	5.61 $\pm$ 0.253	0.28	5.95 $\pm$ 0.18	0.001	0.299
Wave VII	6.8 $\pm$ 0.410	7.0 $\pm$ 0.283	0.16	7.8 $\pm$ 0.35	0.002	0.03
Interpeak latency						
I-III	1.98 $\pm$ 0.20	2.017 $\pm$ 0.090	0.118	2.02 $\pm$ 0.09	0.508	0.122
III-V	1.85 $\pm$ 0.16	1.904 $\pm$ 0.224	0.495	2.35 $\pm$ 0.44	0.028	0.044
I-V	3.84 $\pm$ 0.25	3.856 $\pm$ 0.181	0.869	4.27 $\pm$ 0.17	0.008	0.02
V/I amplitude ratio	2.43 $\pm$ 1.20	2.334 $\pm$ 1.20	0.831	3.74 $\pm$ 0.19	0.03	0.02
Interaural latency difference of wave V	0.12 $\pm$ 0.06	0.13 $\pm$ 0.074	0.433	0.15 $\pm$ 0.05	0.311	0.395

**Table 4 Mean  $\pm$ SD of nine auditory brainstem response of different parameters on using low repetition rate (21.1 s) in men of the control group and both subgroups in the study group (tinnitus-free patients subgroup 'c' and problem-tinnitus patients subgroup 'd').**

Parameter	Control group N=20 ears	Subgroup 'c' N=24 ears	P-value (Control and c)	Subgroup 'd' N=26 ears	P-value (Control and d)	P-value (c and d)
Absolute latency						
Wave I	1.75 $\pm$ 0.136	1.87 $\pm$ 0.17	0.061	1.99 $\pm$ 0.179	0.029	0.701
Wave III	3.83 $\pm$ 0.117	3.89 $\pm$ 0.27	0.286	3.97 $\pm$ 0.241	0.097	0.618
Wave V	5.71 $\pm$ 0.162	5.80 $\pm$ 0.203	0.39	5.99 $\pm$ 0.313	0.044	0.563
Wave VII	7.12 $\pm$ 0.23	7.2 $\pm$ 0.28	0.844	7.9 $\pm$ 0.35	0.012	0.200
Interpeak latency						
I-III	2.04 $\pm$ 0.24	2.08 $\pm$ 0.17	0.548	2.06 $\pm$ 0.243	0.522	0.857
III-V	1.83 $\pm$ 0.12	1.90 $\pm$ 0.19	0.744	2.45 $\pm$ 0.244	0.042	0.03
I-V	3.90 $\pm$ 0.190	4.03 $\pm$ 0.22	0.780	4.10 $\pm$ 0.288	0.958	0.840
V/I amplitude ratio	2.32 $\pm$ 0.82	2.17 $\pm$ 0.834	0.874	3.57 $\pm$ 1.9	0.03	0.02
Interaural latency difference of wave V	0.14 $\pm$ 0.079	0.16 $\pm$ 0.081	0.451	0.17 $\pm$ 0.057	0.325	0.402

when compared with the control group ( $P = 0.03$ ) and subgroup 'c' ( $P = 0.02$ ), Table 4.

But this isolated finding does not support any conclusion. ABR should be analyzed with all parameters together. Other investigations should be performed to better understand this finding.

*Interaural difference in the latency of wave V was also studied*  
On comparing the mean ( $\pm$ SD) interaural latency difference in wave V calculated individually for all participants in the female subgroups (a, b), male subgroups 'c' 'd,' and the control group, we found that the following:

No statistically significant difference was found in this parameter as presented in Tables 3, 4.

An abnormal result for this ABR parameter was found only in three out of 36 patients (15.78%) in subgroup 'b' and four ears (2%) in the tinnitus subgroup 'd'.

#### Results of auditory brainstem response on using a high repetition rate

Higher statistically significant difference values were found only between the female subgroup 'b' and subgroup 'a' on using a high RR in wave III and V absolute latencies, which were not observed on using a low RR.

(1) Among men, higher statistically significant difference values were found between subgroup 'c' and subgroup 'd' for both wave V absolute latency and I-V IPL than found on using a low RR.

#### Results of quantitative analysis of auditory brainstem response parameters in women

As can be seen from Table 3, no statistically significant difference was found in any recorded parameter of ABR between the female subgroup 'a' and the control group. But, on comparing tinnitus subgroup 'b' with the control group for different components of ABR, there were statistically significant increases in the absolute latencies of waves I, III, and V and in I-V and III-V IPL values; there was also a statistically significant increase in the V/I amplitude ratio. Meanwhile, although there were increases in all ABR components between a and b subgroups, statistically significant differences were found in I-V and III-V IPLs and in the V/I amplitude ratio.

#### Results of quantitative analysis of auditory brainstem response parameters in men:

As can be seen from Table 4, there was no statistically significant difference in any recorded parameter between the subgroup 'c' and the control group. There was a statistically significant difference between the subgroup 'd' and the control group in wave I, V, and VII absolute

latencies and III-V IPL and the VI amplitude ratio. Although there were increases in all ABR components in the male subgroup 'd' when compared with subgroup 'c,' there was a statistically significant difference in both III-V IPL and the VI amplitude ratio in c and d subgroups.

**Results of event-related potential N1, P2, and P3**

*Qualitative analysis of the results*

ERP responses were present in all the individuals in the control group and absent in four women (two each in the 'a' and 'b' subgroups, respectively) and four men (one and three in the 'c' and 'd' subgroups, respectively).

In the rest of the individuals with a preserved response, the occurrences of normal and altered results for each potential from the ERP for both latency and amplitude were analyzed, Table 5.

We must emphasize that in this work, two types of alterations were observed: one was the increased latency type and the other was reduction of the amplitude.

In the tinnitus-problem subgroups of both women and men, there were the highest percentages of altered results in P2, P3 latency and P3 amplitude components when compared with the control group of the same sex.

The problem-tinnitus groups of both female and male subgroups had a higher percentage of altered ERP components than these tinnitus-free subgroups. The highest percentage of abnormalities had been found in P2 latency, P3 latency, and P3 amplitude test components.

*Quantitative results*

Latency analysis:

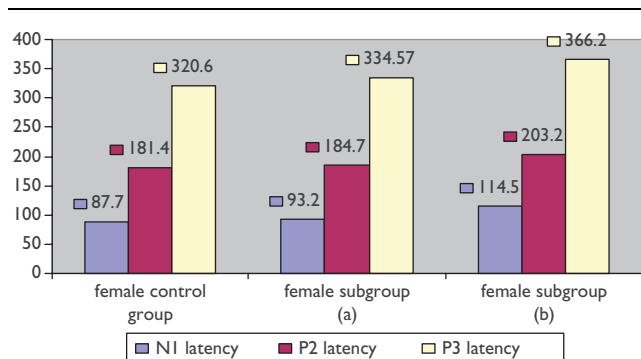
*In women:* in the present study, although there were no statistically significant differences between subgroup 'a' and the control group in the latency values (N1, P2, N2, P3), we observed that subgroup 'b' showed higher mean latency values in all the components that were assessed when compared with the control group, with statistically significant differences ( $P = 0.002, 0.000, 0.01,$  and  $0.01$ ), respectively, but, on comparing subgroup 'a' and tinnitus subgroup 'b,' there were statistically significant differences in the latencies of N1, P2, and P300 ( $P = 0.01, 0.02,$  and  $0.03$ ), respectively. (Fig. 3).

*In men:* there were significant statistically differences on comparing the male problem-tinnitus subgroup 'd' with the control group in all auditory ERP latency values N1, P2, N2, and P3 with ( $P = 0.007, 0.009, 0.04,$  and  $0.01$ ), respectively. Also, when this was compared with subgroup 'c,' we found significant statistically higher mean latency values for (N1, P2, and P3) ( $P = 0.001, 0.03,$  and  $0.003$ ), respectively. (Fig. 4).

Amplitude analysis:

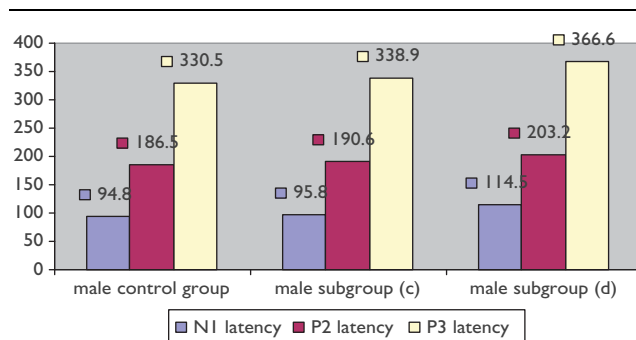
*In women:* no statistically significant differences in the amplitude values were found between the control group and subgroup 'a'. Meanwhile, subgroup 'b' of tinnitus patients had statistically significantly reduced P2 and P3 amplitudes compared with the control group ( $P = 0.04$  and  $0.001$ ), respectively. Also, in the present work, it was found that the tinnitus subgroup 'b' had a lower P300

**Figure 3**



The mean latency values (ms) of wave (N1, P2, P3) in women of the control group and study subgroups 'a' and 'b'.

**Figure 4**



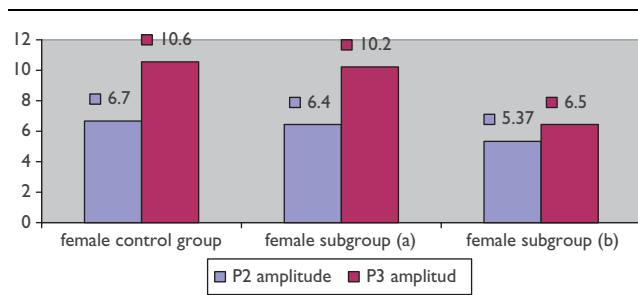
The mean latency values of wave (N1, P2, P3) in millisecond in men of the control group and study subgroups 'c' and 'd'.

**Table 5 Distribution of the occurrence of altered results for the latency and amplitude of event-related potential N1, P2 and P300 components, in the control and study groups**

Components	Control group		Study group			
	Females N=27 ears	Males N=20 ears	Subgroup 'a' N=30 ears	Subgroup 'b' N=33 ears	Subgroup 'c' N=24 ears	Subgroup 'd' N=26 ears
Poor Morphology	2 (7.4%)	1 (5%)	2 (7.14%)	3 (9.09%)	4 (16.6%)	4 (15.38%)
N1 latency	0 (0%)	0 (0%)	6 (21.42%)	10 (33.3%)	4 (20%)	10 (45.45%)
P2 latency	2 (7.4%)	0 (0%)	8 (28.57%)	20 (66.6%)	2 (20%)	16 (72.72%)
P3 latency	4 (16%)	4 (21.5%)	4 (14.28%)	18 (60%)	6 (30%)	14 (63.63%)
P3 amplitude	4 (16%)	3 (15.78%)	6 (21.42%)	18 (60%)	7 (29.16%)	12 (54.54%)

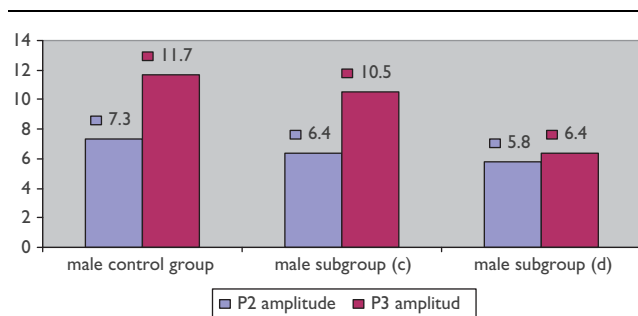


Figure 5



The mean amplitude values ( $\mu\text{V}$ ) of P2 and P3 in women of the control group and study subgroups 'a' and 'b'.

Figure 6



Shows the mean amplitude values in ( $\mu\text{V}$ ) of P2, P3 in females of the control group and study subgroups 'c' & 'd'.

mean amplitude value compared with the tinnitus-free subgroup 'a,' with a statistically significant difference ( $P = 0.001$ ). (Fig. 5).

*In men:* no statistically significant differences in the amplitude values were found between the control group and subgroup 'c'. Meanwhile, problem-tinnitus subgroup 'd' had significantly reduced P2 and P3 amplitudes compared with the control group ( $P = 0.001$  and  $0.000$ ), respectively. Also, in this study, it was found that the tinnitus subgroup 'd' had a statistically significant lower P300 mean amplitude value compared with the tinnitus-free subgroup 'c' ( $P = 0.000$ ). (Fig. 6).

#### Correlation between auditory brainstem response and event-related potential

Abnormal P300 prolonged latency was statistically significantly correlated with both wave V absolute latency and III-V IPL. However, abnormal P300 prolonged latency was not statistically significantly correlated with tinnitus duration, in both the female and the male subgroups.

#### Discussion

Hypothesizing that peripheral and/or central tinnitus is due to a functional alteration in nerve fibers, auditory-evoked potentials could be used in detecting them. Differences in the brainstem responses between tinnitus

patients and controls have been observed and replicated in several studies [1,21,44], whereas differences in brainstem potentials and middle latency responses [51] give rise to the suggestion that there is an underlying pathological process for the perception of tinnitus.

In this study, the tinnitus-problem female subgroup presented a statistically significant increase in the latencies of waves I, III, and V when compared with the control group and this was only for waves I and V in the male tinnitus-problem subgroup on comparing the problem-tinnitus subgroup with the tinnitus-free subgroup; although the absolute latency of all waves was high, there was no statistical significantly increase on using a low RR, Tables 3,4, whereas on using a high RR, both III and V in female patients and only wave V absolute latency were significantly increased in male patients. It has been proposed that the absence of extreme values in the ABR parameters in patients with tinnitus might be owing to the stimulus masking the abnormal activity in the central pathways, thus changing the expected ABR results [52].

This agrees with Ikner and Hassen [46], who compared patients with tinnitus with patients without tinnitus. Female patients with tinnitus and normal hearing had significant prolonged latencies for waves I, III, and V. Rosenhall and Axelsson [47] found prolongation of wave I accompanied by a prolongation of waves III and V, findings that are consistent with a lesion in the peripheral auditory system that occurs most often in tinnitus patients or in individuals with normal hearing or slight hearing loss.

Also, Lemaire and Beutter reported that [44] the latency of wave I was significantly increased in patients with tinnitus when they studied a large group of patients with tinnitus. Shulman and Seitz [28] reported that tinnitus with a peripheral lesion might show normal peak latency values, with wave I slightly affected.

This is in disagreement with the results of Attias *et al.* [36], who reported that no differences were found in peak latencies of Brainstem auditory evoked potentials.

This is also in disagreement with the results of Maurizi *et al.* [33], who reported that the latency values of waves I and III were essentially identical in both tinnitus and tinnitus-free ears, whereas the latency values of wave V were higher only in ears with tinnitus that had no residual inhibition, due to a slight increase in the I-III interval values ( $P < 0.2$ ).

In the present work, a significant latency difference in wave VII was found between problem-tinnitus in control and tinnitus-free groups in both female and male patients. Tables 3 and 4 extend the diverse latency findings for other ABR absolute latencies to include this later wave, which agrees with [48,53,54].

Furthermore, the interpeak I-III, interpeak III-V, and I-V values were found to be higher, but both interpeak III-V and I-V values were significantly higher in the female tinnitus group compared with either the control group or the tinnitus-free group matched in sex, age, and

hearing loss; meanwhile, on comparing the male tinnitus group with the control group and the tinnitus-free group, only interpeak III–V was significantly higher on using a low RR (Tables 3 and 4), whereas on using a high RR, both interpeak III–V and I–V values were significantly increased.

This is in agreement with Rosenhall and Axelsson [47], who reported two patterns of abnormalities: prolongation of wave I accompanied by a prolongation of waves III and V, findings that are consistent with a lesion in the peripheral auditory system, and a lengthening of the III–V IPL, indicating a dysfunction in the brainstem. Both patterns occurred most often in tinnitus patients with normal hearing or with a slight hearing loss.

Also, Ikner and Hassen [46] found a prolonged III–V IPL. Lemaire and Beutter [44], who studied a large group of patients with tinnitus, reported that the I–V IPL was either decreased or increased, and Cassvan *et al* [55] reported that abnormalities in the III–V or I–V IPLs occurred in many patients with tinnitus. However, in those reports, most patients experienced vertigo as well as tinnitus.

But this is in disagreement with Maurizi *et al.* [21], who reported a slight increase in the I–III interval values and found that in tinnitus ears, the III–V interval is normal, and also in disagreement with Cassvan *et al.* [55] who reported an abnormality in the I–III interval value.

This indicates probably more than one site for the origin of tinnitus or the initial cochlear dysfunction, leading to a brainstem abnormality wherein more abnormal results may be found in at least one of the nine parameters evaluated. Rosenhall and Axelsson [47] and Kehrle *et al.* [51] reported two patterns of abnormalities: prolongation of wave I accompanied by a prolongation of waves III and V, findings that are consistent with a lesion in the peripheral auditory system, and a lengthening of the III–V IPL, indicating a dysfunction in the brainstem. Both patterns occurred most often in tinnitus patients with normal hearing or a slight hearing loss. In this study, these two patterns of abnormalities were also found between the problem-tinnitus subgroup and the control group; meanwhile, the main difference between the problem-tinnitus subgroup and the tinnitus-free subgroup was the lengthening of the III–V IPL, indicating a dysfunction in the brainstem.

In this study, a statistically significant increase in the V/I amplitude ratio was found in the problem-tinnitus subgroups, both women and men, compared with either the control group or the tinnitus-free group, Tables 3, 4; this may be due to a lower wave I amplitude, which is in agreement with Lemaire and Beutter [44], and/or a high wave V amplitude (loss of lateral inhibition) in the tinnitus group when compared with either the control group or the tinnitus-free group. This isolated finding cannot support any conclusion, thus indicating that additional studies should be performed. ABR should be analyzed with all parameters together. Other investigations should be performed to better understand this

finding; the presence of an abnormality in only one parameter evaluated does not lead to a specific site of alteration.

This agrees with Kehrle *et al.* [51], who also found a statistically significant increase in this ratio in the tinnitus study group compared with the control group. However, Maurizi, *et al.* [33] reported that V/I amplitude ratios were almost normal in tinnitus ears.

The evaluation of the interaural difference in the latency of wave V in this study did not show significant differences in patients with tinnitus in relation to the control group, which is in agreement with Hood [56], who found that there was no interaural latency significant difference (wave V) in patients with tinnitus in relation to the control group.

The relationship between ABR activity and tinnitus is probably result when reduced spontaneous activity for nerve fibers with CFs in the hearing loss range may result in a reduction of lateral inhibition at more central levels (e.g. in the DCN or inferior colliculus). induces hypersensitivity and hyperactivity in these neurons [8].

Kaltenbach [25] reported the DCN as a possible source of tinnitus-generating signals. In addition, the DCN hypothesis of tinnitus can now be expanded to include possible involvement in other, nonauditory components of tinnitus. It will be shown that the DCN has direct connections with nonauditory brainstem structures (such as reticular formation), which are implicated in the control of attention and emotional responses. A probable hypothesis may be that attentional and emotional disorders, such as anxiety and depression, which are commonly associated with tinnitus, may result from an interplay between these nonauditory brainstem structures and the DCN. Implicit in this hypothesis is that attempts to develop effective antitinnitus therapies are likely to benefit from a greater understanding of how the levels of activity in the DCN are influenced by different states of activation of these nonauditory brainstem structures and vice versa.

Shulman and Goldstein [57] reported that tinnitus may originate as an initial dyssynchrony in presynaptic or postsynaptic neuronal transmission within the peripheral or the CNS (cortical or subcortical). Meanwhile, Lemaire and Beutter [44], suggested that these ABR abnormalities in tinnitus patients may be due to efferent system dysfunction.

According to Jastreboff [58,59], the auditory pathway plays only a secondary role, whereas the limbic system is responsible for the impairment experienced by tinnitus patients. In his model, Jastreboff emphasized the role of the limbic system in affecting a participant's attention, memory, detection, and processing of auditory stimuli. Recently, Landgrebe *et al.* [60] described structural alterations in the CNS detected in tinnitus patients by voxel-based morphometry: significant gray matter decreases in the right inferior colliculus and in the left hippocampus confirm the important role of the limbic

system in the pathophysiology of tinnitus. This could explain the abnormal P300 findings in tinnitus patients as the limbic system and, in particular, the hippocampus, may be involved in the generation and modulation of the P300 wave [61].

In the present study, patients with SNHL who were tinnitus-free showed normal results of ERP as compared with the results from healthy controls both in the female and the male groups, which was in agreement with other studies [62,63]. Meanwhile, statistically significant alterations were found in tinnitus-problem in the latencies and amplitude of components N1, P2, and P3 in relation to the tinnitus-free or the control group, both women and men. This was in agreement with Norena *et al.* [64] and Jacobson and McCaslin [65] who also suggested that alterations in the electrophysiological abnormalities in the long latency auditory-evoked potential (LLAEP) may be found in individuals with tinnitus.

Picton [66] reported that the increase in latency or reduction in amplitude in the LLAEP may be associated with clinical and subclinical problems. Clinical and subclinical problems, having said that, it is believed that a deficit in some central auditory processing skill, with a reduction in the auditory attention [8,67], memory deficit [68,69], Bellis [70] reported that changes on the characteristics of the LLAEP components in individuals with tinnitus.

According to Coelho *et al.* [71], patients with tinnitus frequently complain of concentration difficulties in daily activities, which could be higher or lower, according to the attention paid to this symptom. It is known that components N1, P2, and P300 are influenced by the degree of attention paid to the stimulus. If the stimulus is ignored, the wave shapes are damped and very likely delayed [6]. Another factor that must be taken into account is the fact that tinnitus has a masking effect on the acoustic signals presented to these individuals [66]. Thus, one could infer that an increase in ERP latency in less attentive individuals from the study group, very likely due to the presence of tinnitus, may have been because of this reduced attention.

However, Attias *et al.* [36] observed that the latencies from components N1, P2, and P300 in individuals with tinnitus remained unaltered.

In this study, statistically significant differences were found between the control and the tinnitus-problem study subgroup in the amplitude of components P2 and P300. This agrees with Attias *et al.* [36], who found a marked reduction in the amplitude of these components. Other authors have also reported a reduction in N1, P2, and P300 amplitudes in the group with tinnitus [72].

Attias *et al.* [48] found significantly lower P3 amplitudes in tinnitus patients and no differences between patients and controls with regard to the N1 and P2 components. They also reported that it is still unclear whether the underlying process for the development of a severe tinnitus complaint is a high degree of self-attentiveness (a specific personality trait), because of which the patient

is unable to habituate to uninformative and repetitive stimuli [73], or whether the neurophysiological disturbance is the reason for the inability to habituate as noted by Shulman and colleagues [57–59] and leads to heightened self-attentiveness. Their results, however, support the notion of a neurophysiological deficit in an individual with tinnitus [74,75]. These authors report that the lower ERP amplitudes may indicate attenuated or 'abnormal' auditory central processing in noise-induced hearing loss tinnitus patients; they suggested that this dysfunction reflects an adaptive brain process response to the tinnitus and points to auditory central involvement in tinnitus sensation.

This disagree with Filha and Matas [34] who observed only type of alteration in tinnitus patients: an increase in N1, P2, and P300 component latencies. Jacobson *et al.* [21], also reported that the latency increase in components N1 and P2 was the most commonly found alteration in patients with tinnitus. This also disagreed with others who have reported an increase in the amplitude of N1 and P2 in tinnitus patients in event-related electrical or magnetic potentials [76].

In this work, P300 results showed that tinnitus patients might have an impairment in cognitive performance. This impairment appeared as a prolonged P300 latency in these patients when compared with controls with normal hearing.

Filha and Matas [34] observed that the ERP alterations seen in individuals with tinnitus show an involvement of the central auditory nervous system, suggesting a participation of the auditory cortex in the generation and/or tinnitus maintenance. Thus, the ERP is a useful tool to investigate the mechanism responsible for this symptom.

In addition, P300 recording requires the participants' attention on the deviant stimuli. As attention is affected in tinnitus patients [17,57], abnormal P300 results were found.

Alster *et al.* [75], suggested that, therefore, it is unclear whether or not these ERP changes are specific to tinnitus or occur as a consequence of subclinical psychiatric.

Other possible factors that may be associated with the changes seen in the LLAEP in individuals with tinnitus are the possibility of a reduction in the number of working neurons, a reduction in neural activity, and/or a greater mismatch of the firings of the neurons involved [36].

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## Conclusion

There is no single pathophysiological pathway to explain the production of subjective tinnitus. All structures of the auditory system have been suggested as possible sites for the generation of tinnitus, from the periphery to the auditory cortex.

In this study, using carefully matched participants with regard to hearing sensitivity, age, sex, and duration of hearing loss, it was found that although the presumed tinnitus site of the lesion in this study is 'peripheral,' the only observed difference seemed to be in the central measures in problem-tinnitus patients when compared

with tinnitus-free patients (statistical significantly increase on using a high RR at both III and V in female patients and only in wave V absolute latency in male patients, and also a lengthening of the III-V IPL in the problem-tinnitus subgroup in comparison with the tinnitus-free subgroup).

Also, statistically significant alterations were found in the tinnitus-problem in the latencies and amplitude of components N1, P2, and P3 in relation to the tinnitus-free or the control group, both women and men.

The presence of abnormal results in ABR and ERP in problem-tinnitus patients may indicate that there are different sensibilities in the central pathways toward the cochlear dysfunction or that tinnitus may be centrally from the start as a lesion in the brain stem and/or due to a high degree of self-attentiveness (a specific personality trait), because of which the patient is unable to habituate to uninformative and repetitive stimuli [20]. It is not clear whether the neurophysiological disturbance is the reason for the inability to habituate [56,58,59,73] and leads to heightened self-attentiveness or whether these electrophysiologic changes are specific to tinnitus or occur as a consequence of subclinical psychiatric symptomatology.

This was confirmed from the presence of SNHL in tinnitus-free subgroup patients whatever their duration of hearing loss; they did not develop tinnitus, whereas some patients had complaints of tinnitus from the start even they were not aware of the presence of hearing loss, which was confirmed by the presence of abnormal results in ABR and ERP in tinnitus patients with normal hearing sensitivity in other studies.

Thus, it is suggested that these kinds of electrophysiological studies (AEP and/or ERP) may provide an objective basis for classifying different forms of problem-tinnitus; ERP testing may be used to complement behavioral, audiologic, and other physiologic methods [6,70-72,74] of assessing tinnitus that help to determine the site of the lesion for tinnitus origin.

Neurofeedback-based tinnitus therapies recommend maximizing the ability to shift attention away from the tinnitus; also, cognitive and psychological conditions in tinnitus patients should be considered in their evaluation and management [36].

Fioretti *et al.* [77] reported that transcranial magnetic stimulation induces neurostimulation of specific brain regions potentially involved in the pathophysiology of tinnitus. This might represent a new promising approach for the treatment of tinnitus on the basis of the involvement of dysfunctional neuroplastic processes in the brain. A growing number of studies have demonstrated a reduction of tinnitus after repeated sessions of repetitive low-frequency transcranial magnetic stimulation.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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