

Evaluation of Possible Alterations in The Auditory Evoked and Event-Related Potentials in Patients with Tinnitus

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ABSTRACT

Objective: Tinnitus is a very common health problem and is reported in all age groups. The ability to objectively assess tinnitus complaints could provide significant benefits to treat or prevent its progress. In this study, we aimed to identify reliable electrophysiological biomarkers for tinnitus comparing by auditory evoked potential (AEPs), auditory event related potentials (AERPs), and mismatch negativity (MMN) responses between patients with tinnitus and healthy controls.

Materials and Methods: This study included ten subjects with tinnitus and ten age and sex-matched healthy controls. All participants gave informed consent forms and were evaluated through basic audiology evaluation, the Tinnitus Handicap Inventory for a structured diagnostic interview and tinnitus severity, and electrophysiological tests. Electrophysiological data were collected from 32 surface scalp electrodes using different frequencies of stimulus for AEPs and the oddball paradigm for AERPs and MMN.

Results: The components of AEPs for auditory stimulus with different frequencies, the components of AERPs for standard (StbD) and deviant (Dev) tones, and the difference wave (MMN) were compared between the two groups. Neither AEPs components in auditory stimulus with different frequencies, nor the AERPs components for StbD and Dev tones were affected by tinnitus ($p>0.05$ for all comparisons). However, the MMN amplitude was significantly decreased in the tinnitus group compared to the control group on the left front ($p<0.001$), right front ($p<0.01$), and left back ($p<0.01$) brain regions, while no significant changes were observed in MMN latency between the two groups.

Conclusion: Our results indicate that tinnitus leads to a deficit in the neural networks of the auditory sensory memory, and the MMN amplitude may serve as an objective biomarker for assessing tinnitus.

Keywords: Tinnitus, auditory sensory processing, evoked and event-related potentials, MMN

INTRODUCTION

Tinnitus is generally defined as the perception of various sounds in the absence of an exogenous sound source (1). Tinnitus may be an indication of auditory damage that may be accompanied by hearing loss and vertigo, and may occur even in the absence of clinical symptoms such as hearing loss. In addition, an increased neuronal activity at diverse parts of the auditory pathway may also trigger tinnitus. Studies show that tinnitus is observed in approximately 20-30% of the world's population, but only a minority of cases seek medical attention (2). Although it was widely accepted that tinnitus was caused by the degeneration of cochlear hair cells and/or auditory nerve until the 2000s, today there are studies with conflicting results and the pathophysiological events underlying tinnitus

have not yet been fully explained. Recent studies show that besides acoustic trauma, depression and long-term exposure to a stressful environment can also be effective in triggering tinnitus (3). Additionally, it has been reported in the literature that there is a relationship between tinnitus and changes in cognitive functions (4). Based on these findings, it could be said that the peripheral auditory system is not the only source of tinnitus, but the central auditory system may also play an important role in the development of tinnitus.

The electrical signals produced after the mechano-electrical cycle are transmitted to the brain via the auditory nerve and are perceived as sound after being processed here. Time-locked responses to the auditory stimuli occur in the brain, which can be recorded via disc electrodes placed on the scalp (5, 6). We

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think that these responses of the nervous system to auditory stimuli, also called auditory evoked and/or auditory event-related potentials (AEP and AERP, respectively), may provide a great advantage to examine possible changes that may occur at the cortex level in individuals with tinnitus. For this reason, in our planned study, AEPs were recorded in individuals with tinnitus using auditory stimuli consisting of 7 different frequencies, 0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz, at a constant 85 dB sound intensity. And also, we recorded the AERPs using the oddball paradigm. By comparing the auditory evoked and auditory event-related potentials obtained from the age-matched control group without any hearing problems and individuals with tinnitus and normal hearing, we tried to define possible electrophysiological changes that may have occurred at the cortex level.

MATERIALS AND METHODS

Subjects

This study was conducted at the Akdeniz University Medical School, Department of Biophysics, after obtaining ethical approval from the Akdeniz University Local Ethics Committee (Approval date and number: KAEK-561 and 18.08.2021).

A total of 10 patients with tinnitus (mean age = 40.8±9.86 years) and 10 healthy controls (mean age = 36.7±6.95 years) gave informed consent and participated in the study. Six men and four women participated in each group. The inclusion criteria consisted of bilateral moderate or severe tinnitus and normal audiologic presentations (hearing threshold at 0.25 – 8 kHz < 25 dB HL). All patients were interviewed using a structured diagnostic interview, and the Tinnitus Handicap Inventory (THI) was used to determine the tinnitus severity (7). In addition, the following procedures were performed on the patients; inspection of the external auditory canal using

a Heine otoscope, and pure-tone air audiometry over 0.25-8 kHz frequencies to evaluate hearing levels of patients. In order to provide more homogeneous experimental groups, patients with chronic otitis media, otosclerosis, acoustic tumor, Meniere’s disease, history of ear surgery and neuropsychiatric diseases were excluded from this study.

Electrophysiological Recordings and Analysis

The electroencephalography (EEG) activity was recorded with 32 Ag/AgCl electrodes mounted in an elastic cap (Easy-cap) according to the international 10–20 system, and two linked earlobe electrodes (A1 + A2) served as references. A ground electrode was also placed on the back of the left ear. All electrode impedances were less than 10 kOhm. The EEG signal was amplified (Brainamp EEG/EP Amplifier, Brain Products, Munich, Germany), band-pass filtered (0.1-250 Hz) and digitized at a 1000 Hz sampling rate (Brainvision Recorder, Brain Products, Munich, Germany).

Auditory evoked potentials (AEPs)

Auditory evoked potentials (AEPs) were recorded using stimuli of 0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz at the 85 dB sound pressure level (SPL). The duration of the 85-dB tones was 50 ms, and the tones were presented through an earphone.

The AEPs data were processed in 500 ms epochs. The averaging of 80 responses was performed with Brainstorm (8), which is documented and freely available for download online under the GNU general public license. Peak latencies of the components (first positive peak P1, second positive peak P2, first negative peak N1 and second negative peak N2) were measured from the stimulus artifact to the peak in milliseconds. The amplitudes were measured as the voltage between successive peaks.

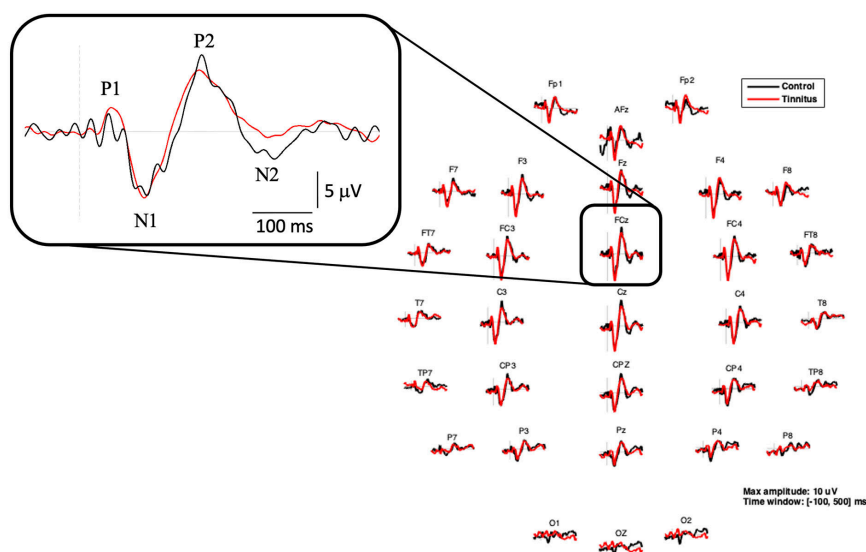


Figure 1: The grand average of AEPs evoked by 2000 Hz-auditory stimuli in the control (black) and tinnitus (red) groups. Waveforms obtained from 31 EEG channels are shown, and AEP response from FCz channel is shown in expanded format at the upper left. There are no significant differences in peak-to-peak amplitude and latency values of AEP components between groups.

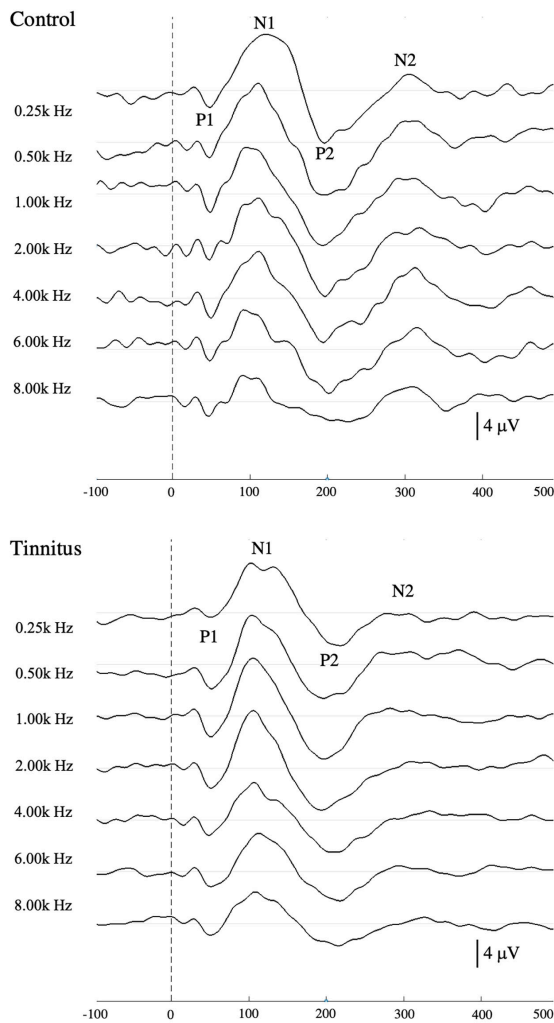


Figure 2: The grand average of AERPs in the control (top) and tinnitus (bottom) groups. Traces are prepared by averaging AERPs over F3, Fz, F4, FC3, FCz, and FC4 region evoked by 85 dB SPL stimulus at different frequencies (0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz).

Auditory event-related potentials (AERPs)

Auditory event-related potentials (AERPs) were recorded using the oddball condition. In the oddball condition for auditory stimuli, frequencies of standard and deviant tones were 2000 and 2500 Hz, respectively. Deviant tones were pseudorandomized to occur at a 20% probability in a sequence of standard tones presented at the inter-stimulus interval (ISI) of 1000 ms. The tones were ordered pseudo-randomly in their series with the restriction that there were no less than two standards between consecutive deviants.

AERPs data were processed in 800 ms epochs using Brainstorm (8). AERPs were digitally filtered (0.1–40 Hz), segmented (for each deviant and standard before deviant), and baseline corrected (-100 ms). Before the averaging procedure, the epochs with artifacts were rejected by an off-line technique. The following averaged curves were computed for each

participant and then for the two groups: Standard before deviant (StbD) (AERPs to standard tones preceding deviant tones), Deviant (Dev) (AERPs to all deviant tones during the oddball paradigm) and difference wave (Dev minus StbD). Electrode positions selected as regions of interest were left front (F3, F7, FT7 and FC3), right front (F4, F8, FT8 and FC4), left back (TP7, CP3, P7 and P3), right back (TP8, CP4, P8 and P4), Fz, FCz, Cz, CPz and Pz, and mismatch negativity (MMN) amplitude and latency were calculated and averaged over these electrode positions (F, frontal; FT, fronto-temporal; FC, fronto-central; T, temporal; TP, temporo-parietal; C, central, CP, centro-parietal, P, parietal). Odd and even numbers indicate left hemisphere and right hemisphere, respectively.

Statistical Analysis

To determine the sample size for this study, we utilized the G*Power free software. The power analysis indicated that each group should have 10 participants, with a type I error level of 5% and a power of 80% to detect a minimal and significant difference between groups. The statistical analysis of the obtained data was performed with the SPSS 18.0 (SPSS, Chicago, IL, USA) software for Windows. A student t test was used to compare demographic characteristics. The peak-to-peak amplitudes and latencies of AEP components were analyzed in a Three-way mixed ANOVA including the between subject factor groups (control vs. tinnitus) and the within subject factor locations (F3, Fz, F4, FC3, FCz, and FC4 electrode regions), and stimulus (0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz). The peak-to-peak amplitudes of P1, N1, P2 and N2 of AERPs were analyzed in a Three-way mixed ANOVA including the between subject factor groups (control vs. tinnitus) and the within subject factor locations (left front, right front, left back, right back, Fz, FCz, Cz, CPz and Pz) and stimulus (StbD and Dev). MMN amplitudes and latencies were analyzed in a Two-way mixed ANOVA using 2 groups (control vs. tinnitus) x 9 electrode regions (left front, right front, left back, right back, Fz, FCz, Cz, CPz and Pz). Post-hoc comparisons were analyzed with the Bonferroni test. All results are expressed as mean±standard deviation (SD). Significance levels were set at $p < 0.05$.

RESULTS

Demographics

In the present study, the age of the individuals in the tinnitus group varied between 26 and 53 years (mean age = 40.8 ± 9.86 years), and in the control group, it varied between 24 and 47 years (mean age = 36.7 ± 6.95 years). Sex distribution in tinnitus and control groups was 4 females and 6 males for each group. We did not observe statistically significant differences between the groups in relation to age or sex ($p > 0.05$ for each condition). The tinnitus localization of the patients is bilateral, and out of the 10 tinnitus patients, 6 patients had moderate tinnitus, while the others had severe tinnitus as per the THI grading score (Grading scores of patients for THI vary between 38 and 66).

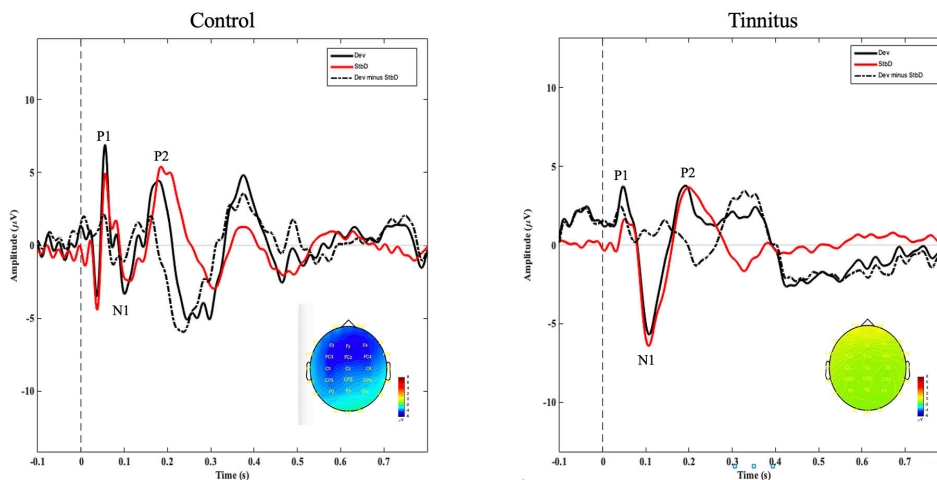


Figure 3: The grand average of auditory event related potentials (AERPs) recorded in the control and tinnitus patients. AERPs to standards (StbD, red line), deviants (Dev, black line) and difference waves (Dev minus StbD, black dash-dot line) are demonstrated for the region of interest (left front; averaged over F3, F7, FT7 and FC3). At the right bottom corner of each panel, topographies at MMN peak maximum are illustrated for each group. Difference waveforms (Dev minus StbD) were obtained by subtracting StbD responses from Dev ones and averaging across all deviation magnitudes (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Auditory evoked potentials (AEPs)

Topographic maps of AEPs for both experimental groups are presented in Fig. 1 for 2000 Hz and the AEP traces with grand averaged over F3, Fz, F4, FC3, FCz, and FC4 electrode regions of both groups for each stimulus frequency are presented in Fig.2. Measurements were made on two negative and two positive potentials, which were seen in all of the groups. The grand average means and SD of peak latencies of AEPs components (P1, N1, P2, and N2) in F3, Fz, F4, FC3, FCz, and FC4 electrode regions of both groups are shown in Table 1. We did not observe any significant differences between groups in terms of latencies of AEP components for each stimulus condition ($p>0.05$), and there is no significant effect of electrode localization on the latencies of AEPs between regions of interest ($p>0.05$) either.

The grand average means and SD of peak-to-peak amplitude of AEPs components (P1N1, N1P2, and P2N2) in F3, Fz, F4, FC3, FCz, and FC4 electrode regions of both groups are shown in Table 2. We did not observe any significant differences between groups in terms of peak-to-peak amplitudes of AEPs for each stimulus condition ($p>0.05$).

Auditory event related potentials (AERPs) and MMN response

Figure 3. illustrates the components of AERPs responses to StbD and Dev tones in the oddball paradigm for both experimental groups. Difference waveforms (Dev minus StbD) obtained by subtracting StbD responses from Dev ones are also indicated in the Fig. 3. The analysis of latencies of AERPs components in response to StbD and Dev tones indicated that there is no

Table 1: The mean and standard deviations of peak latencies of AEP components in the tinnitus and control groups. There was no main group effect in terms of peak latencies of AEP components between the two groups.

	Groups	P1(ms)	N1(ms)	P2(ms)	N2(ms)	p-value
F3	Control	47.1 ±2.24	103.5±10.62	194±7.07	304.5±18.73	> 0.05
	Tinnitus	51.1±4.9	109.8±14.8	206.9±24.3	306.7±31.0	
Fz	Control	46.5±2.60	104.5±9.84	194.5±6.22	3304±19.44	
	Tinnitus	51.3±4.7	108.8±14.9	207.3±24.1	206.3±31.0	
F4	Control	46.8±2.60	104±10.2	194.25±5.76	302±22.41	
	Tinnitus	50.9±5.2	109.3±15.1	207.3±24.2	307±31.0	
FC3	Control	47.75±2.49	105.6±10.2	195±4.58	304.5±18.73	
	Tinnitus	51.1±4.9	109.8±14.2	207.3±23.3	306±30.1	
FCz	Control	46.5±2.60	104.5±9.84	195±4.58	303.5±20.17	
	Tinnitus	52.7±7.7	109.5±14	207.8±24.2	300.7±22.1	
FC4	Control	46.0±2.45	104.5±10.62	196.5±2.60	301.5±23.17	
	Tinnitus	51.9±6.3	109.8±14.8	207.3±24.1	306.3±31.2	

AEP: Auditory evoked potential; F3: left frontal; Fz: midline frontal; F4: right frontal; FC3: left fronto-central; FCz: midline fronto-central; FC4: right fronto-central

Table 2: The means and standard deviations of peak-to-peak amplitudes of AEP components in the tinnitus and control groups. There was no main group effect in terms of peak-to-peak amplitudes of AEP components between the two groups.

Groups		P1N1(V)	N1P2(V)	P2N2(V)	p-value
F3	Control	10.97±3.52	-15.47±3.68	10.93±5.54	>0.05
	Tinnitus	9.80±2.46	-11.83±4.95	5.94±2.54	
Fz	Control	11.62±3.72	-16.60±3.91	12.52±6.90	
	Tinnitus	10.52±2.82	-13.44±15.52	7.19±2.70	
F4	Control	10.91±3.55	-14.74±3.47	10.43±5.72	
	Tinnitus	10.09±2.82	-12.57±5.35	6.22±2.60	
FC3	Control	11.10±3.54	-17.31±4.19	11.52±45.82	
	Tinnitus	9.93±2.68	-12.56±4.98	6.58±2.46	
FCz	Control	12.06±3.91	-19.52±4.96	14.88±7.86	
	Tinnitus	10.86±2.90	-15.30±5.64	8.80±3.03	
FC4	Control	11.00±3.42	-16.70±4.11	11.38±5.96	
	Tinnitus	10.01±2.85	-12.90±5.35	6.62±2.43	

AEP: Auditory evoked potential; F3: left frontal; Fz: midline frontal; F4: right frontal; FC3: left fronto-central; FCz: midline fronto-central; FC4: right fronto-central

Table 3: The mean and standard deviations of peak-to-peak amplitudes of AERP components in response to standard (StbD) and deviant (Dev) tones in the tinnitus and control groups. There was no main group effect in terms of peak-to-peak amplitudes of AERP components between the two groups.

Groups		P1N1(V)		N1P2(V)		P2N2(V)	
		StbD	Dev	StbD	Dev	StbD	Dev
Left front	Control	7.85±2.75	8.55±2.07	7.87±2.72	8.88±4.40	6.16±4.08	7.15±3.72
	Tinnitus	6.97±1.79	8.00±2.52	8.24±2.26	7.97±2.09	4.76±1.49	6.46±1.88
Right front	Control	7.73±2.44	8.38±1.48	7.47±2.98	7.14±3.63	6.32±4.35	6.51±2.73
	Tinnitus	7.04±1.77	7.69±3.17	8.13±2.99	8.05±2.78	4.72±1.48	7.24±2.48
Left back	Control	5.53±2.08	7.37±2.09	4.59±1.97	6.54±4.09	3.76±1.95	5.77±3.33
	Tinnitus	3.33±1.31	3.48±1.11	3.67±2.22	4.54±1.76	2.64±1.56	4.61±1.32
Right back	Control	4.35±1.72	6.15±1.68	3.98±1.95	5.39±3.74	3.93±2.00	5.65±2.92
	Tinnitus	2.75±0.92	3.55±1.29	2.99±1.70	4.41±1.63	2.12±0.96	6.66±1.61
Fz	Control	9.14±3.06	10.40±2.35	10.47±4.06	11.59±5.74	10.24±6.98	12.41±4.92
	Tinnitus	9.07±2.10	10.24±3.51	11.16±3.30	10.45±3.48	6.98±1.88	9.40±2.70
FCz	Control	8.85±3.67	9.91±2.58	11.42±4.85	13.12±7.01	11.27±7.84	13.15±5.66
	Tinnitus	9.45±2.75	10.17±4.58	11.85±3.53	11.79±4.85	7.95±1.76	10.98±3.33
Cz	Control	7.42±3.95	8.68±2.19	9.91±5.44	12.11±7.76	9.64±7.84	11.26±5.76
	Tinnitus	8.57±2.99	9.31±4.62	10.87±4.05	11.39±5.59	7.54±1.97	10.73±3.31
CPz	Control	5.92±3.54	8.20±2.79	7.57±4.94	10.04±6.90	7.19±5.59	8.61±3.62
	Tinnitus	6.42±2.43	7.44±2.98	7.88±3.75	9.21±4.68	5.85±1.85	8.96±2.43
Pz	Control	5.18±2.80	7.72±2.56	5.76±3.40	8.42±5.91	5.71±3.25	7.77±2.33
	Tinnitus	4.31±1.41	5.02±1.96	4.94±2.76	6.97±3.17	3.99±1.93	6.55±2.02

AERP: Auditory event related potential; Fz: midline frontal; FCz: midline fronto-central; Cz: midline central; CPz: centro-parietal midline; Pz: parietal midline.

statistically significant difference between groups. Mean±SD of peak-to-peak amplitudes (P1N1, N1P2, and P2N2) in response to StbD and Dev tones are shown in Table 3. When we examined the peak-to-peak amplitudes, there was a significant effect in both electrode location ($F_{2,286,132.6}=131, p<0.001$) and electrode location x group interaction ($F_{88,464}=1.421, p<0.05$). However, there is no significant group effect ($F_{711,58}=0.66, p=0.72$) for the amplitudes of AERPs.

Mean±SD of MMN amplitudes and latencies in each electrode region (left front, right front, left back, right back, Fz, FCz,

Cz, CPz and Pz) are shown in Table 4. There was no main group effect ($F_{1,10}=0.63, p=0.45$) and no significant interaction of electrode region x group ($F_{8,80}=1,13, p=0.35$) on MMN latency. However, when we examined the MMN amplitudes, a significant group effect [$F_{1,22}=15, p<0.001$] was observed. Post-hoc comparisons showed that MMN response was significantly decreased in the tinnitus group in comparison to the control group over regions of left front ($p=0.0005$), right front ($p=0.008$), and left back ($p=0.003$). This result has indicated that the most robust decrement of MMN amplitude occurred in the left hemisphere.

Table 4: The mean and standard deviations of MMN latency and amplitude in the control and tinnitus groups. There was no main group effect in terms of MMN latency between the two groups, while statistically significant differences were observed between the two groups in terms of MMN amplitude in the left front, right front, and left-back brain regions.

	Groups	MMN Latency (ms)	MMN Amplitude (V)
Left front	Control	213.18±36.77	4.97±1.53
	Tinnitus	216.50±25.44	2.07±0.91***
Right front	Control	226.83±11.51	4.18±0.88
	Tinnitus	231.83±32.97	2.47±1.27**
Left back	Control	225.67±26.84	5.08±1.21
	Tinnitus	231.17±31.33	2.97±1.18**
Right back	Control	210.17±26.18	4.09±1.25
	Tinnitus	237.33±47.20	3.91±1.46
Fz	Control	223.33±16.81	4.28±1.25
	Tinnitus	225.67±27.05	2.68±1.39
FCz	Control	220.00±20.20	3.53±1.10
	Tinnitus	224.33±26.15	3.66±1.68
Cz	Control	216.33± 23.27	4.13±1.17
	Tinnitus	223.33±27.18	3.97±1.94
CPz	Control	208.33±37.08	3.98±1.53
	Tinnitus	227.34±23.04	4.21±1.70
Pz	Control	203.00±34.38	3.80±1.38
	Tinnitus	228.67±21.30	3.45±1.64

MMN: mismatch negativity; Fz: midline frontal; FCz: midline fronto-central; Cz: midline central; CPz: centro-parietal midline; Pz: parietal midline. Bold indicates significant differences versus Control group. For left front, ***p < 0.001; right front, **p < 0.01; and left back, ** p < 0.01.

DISCUSSION

In this study, we compared the components of auditory evoked potentials (AEPs) and auditory event-related potentials (AERPs) among individuals with tinnitus and age-matched normal individuals. We found that tinnitus has no effect on the components of AEPs. However, in this study, we observed that tinnitus has led to a significant decrement in the amplitude of mismatch negativity (MMN), but has not induced any prolongation of the MMN latency.

As known, it is possible to define that AEPs are the electrical current fluctuations in the peripheral and central nervous system in response to external auditory stimuli, and can be recorded from the scalp in a non-invasive way (9). The earlier responses of long-latency AEPs (P1, N1, P2 and N2) generally provide valuable information about the physical properties of auditory stimuli such as early sensory functions, spectral and temporal characteristics of the stimulus (10), while the later responses reflect the processing and interpretation of auditory information resulting from higher neural processes in response to the task-dependent events (11, 12). From these properties of the AEP components, several studies have highlighted that AEPs might be considered as a possible biomarker for evaluating tinnitus complaints (13, 14).

In a study, the N1-P2 peak-to-peak amplitude was specifically evaluated since it has been more reliable than the N1 and P2 analyzed independently. Researchers reported N1-P2 amplitude was highly affected by tinnitus, and also N1

latency was shorter in the tinnitus group than in the control group. In addition to this, they showed that there might be differences among different types of tinnitus. Thus, it was concluded that auditory cortical processing differed between tinnitus and normal subjects in terms of stimuli intensity-dependence (14). In contrast to this study, it has been reported that the latencies of the components N1 and P2 were higher in the tinnitus patients than in those obtained from the control group, while there were no significant changes in the N1-P2 amplitude between groups (15). In another study, it was indicated that there is a significant difference between tinnitus and control groups in terms of N1 amplitude, identifying lower amplitudes in tinnitus patients compared to control (16). In addition, researchers, investigating electrophysiological differences among tinnitus with sensorineural hearing loss, sensorineural hearing loss without tinnitus and normal individuals, have reported that the tinnitus group had a higher prevalence in auditory brainstem response abnormalities (17). These results demonstrated tinnitus complaints arise independently from hearing loss. In contrast to these studies, we also aimed to evaluate late-latency AEPs evoked by various stimuli with different frequencies (starting from 250 Hz to 8000 Hz). When we evaluated the components of AEPs for each stimulus frequency, we did not observe any significant changes in both latency and peak-to-peak amplitude of AEPs. Our results pointed that the earlier components of AEPs had not been affected by tinnitus. Therefore, from these observations, it is possible to say that tinnitus does not lead to any significant changes in the early cortical sensory processing, specifically related to stimulus frequency in our

experimental condition.

As the prevalence of tinnitus increases nowadays, it becomes a highly important topic for researchers who wish to evaluate how tinnitus affects auditory processing in higher brain function and its possible mechanisms. AEPs are generally associated with the physical properties of the stimulus and do not require a high cognitive skill. However, considering tinnitus leads to problems at the psychological and socio-professional levels, it might be inevitable for individuals with tinnitus to have a deterioration in higher cognitive functions. In this condition, the possible alterations in higher brain function could be examined by relevant methods such as event-related potentials using the oddball paradigm. In generally, P300 or MMN responses are used to evaluate higher brain functions. P300 is a cognitive ERP component reflecting voluntary attention processing (18, 19). In this context, evaluating the studies in the literature, we see that there are some variable results, showing significant delays of the P300 latency (4, 15), or no changes of the P300 component (20, 21). In the study performed by Houdayer et al. 2015, it was reported that tinnitus patients had shorter N1 and P2 latency of AERPs, but no changes in the P300 component. In addition to these findings, they also showed a reduced current density in the left inferior and parietal cortical sources of several cortical rhythms in tinnitus patients in resting state EEG (20). But, Gabr et al. 2011 reported that a significant prolongation of the P300 component was observed in the patients with tinnitus, and this prolongation is highly correlated with psychiatric evaluations conducted by using the Hamilton depression and Hamilton anxiety scales (4). In a more detailed study, researchers have investigated to ascertain any significant difference in P300 latency and amplitude between tinnitus patients and the control group. They showed a significant increase in latency and a decrease in amplitude of P300 component on increasing severity of tinnitus. However, a limitation of this study is that tinnitus patients also have sensorineural hearing loss, and therefore, it is difficult to say that the findings are only related to tinnitus (22). It is possible to explain these contradictory results by considering the P300 component requires voluntary attention, as well as may be affected by individuals' psychiatric conditions.

On the other hand, MMN is related to involuntary attention and reflects the brain capacity to discriminate the sounds in the absence of any prior instruction regardless of the individual's attentional and behavior capacity (23). Therefore, the commonly accepted mechanism for the generation of MMN response is a pre-attentive sensory memory mechanism that automatically compares present auditory input and memory traces of previous sounds. Considering these advantages, it emerges as a much better candidate than the P300 component to be a possible biomarker for objectively evaluating complaints related to tinnitus. However, few studies have investigated the possible changes of MMN response in tinnitus patients. In one of these studies, it was noted that tinnitus patients have significantly more negative N1 components for standard

stimuli and have a significantly lower MMN amplitude, and the MMN latency is approximately 20 ms delayed compared to the control group, but not reached statistically significant levels, stating that MMN amplitude may become a useful biomarker to evaluate the prognosis and treatment effects of tinnitus (24). Mahmoudian et al. 2013 reported that MMN amplitude on the frontocentral regions, but not latency, was significantly affected by tinnitus (25) In another study, researchers showed that the patients with chronic tinnitus had lower the MMN amplitudes compared to the control group at the Fz region for all deviant types without affecting MMN latency and no correlation between THI and MMN responses (26). These findings indicate that the pre-attentive and automatic central auditory processing is impaired in individuals with chronic tinnitus. In contrast to these studies, El-Minawi et al. 2018 also reported tinnitus induced a significant decrement in both MMN amplitude and latency (27). On the other hand, we also evaluated the possible changes in the MMN amplitude and latency between tinnitus patients and normal healthy controls. Partly in agreement with these studies, we also determined that MMN amplitude was significantly lower in the patients with tinnitus compared to those in the control group over the left front, right front and left back electrode regions, but no significant changes were observed in the MMN latency. We can say that this decrease observed in MMN amplitude is probably due to the interaction of the sounds that tinnitus patients sense constantly and the sounds presented during the paradigm. Based on these findings, we may conclude that, while the effects of tinnitus on the early components of event-related potentials remain unclear, it has a masking effect on the MMN amplitude.

Limitation

The limitation of our study is the sample size in the patient group. Although it meets the desired power value (80%), it remains low. Further studies with a large sample size are needed to elucidate the tinnitus related alterations on AERPs with high accuracy.

CONCLUSION

Evaluation of both auditory potentials in different stimulus frequencies and auditory event-related potentials within the same study groups revealed that the alterations observed in AERPs occur independently in the physical properties of the auditory stimulus, because tinnitus does not have any effect on the components of AEP, which is mostly related to the physical properties of the stimulus, and without any requirement of high-order functioning. In addition, it is possible to say that it disturbs the neural networks of auditory discrimination and sensory memory involvement in the MMN generation, without affecting the timing of the sensory processing because no changes were observed in the MMN latency.

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Informed Consent: Written informed consent was obtained.

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