ORIGINAL ARTICLE

Gap Pre-pulse Inhibition of the Cortical Auditory Evoked Potentials as a Possible Objective Tinnitus Assessment Tool

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Abstract

Objectives

The objective assessment tests overcome the variability of subjective methods. Cortical recordings with gap pre-pulse inhibition of the acoustic startle reflex stimulus have been used as objective tinnitus assessments in humans. This study aims to investigate this possible objective tinnitus test and compare gap-induced inhibition in different stimulus parameters and brain regions.

Materials & Methods

Twenty People (18-50 years old) without hearing loss and tinnitus were included. The sound stimuli consisted of continuous background noise with a loud startle tone preceded by a silent gap (20 and 40 ms duration, 120 and 150 ms distance from the startle). The N1-P2 complex amplitude and topoplot maps were extracted in 27-channel cortical response recording after signal processing. Four brain regions of interest (ROI) of anterio-frontal, centro-frontal, right, and left temporal were investigated.

Results

The results showed that the maximum inhibition occurred in a 40 ms gap duration and 150 ms distance in all 4 ROIs. In comparing ROIs, the centro-frontal and left temporal regions revealed the most inhibition ($p<0.05$). The decrease in the amplitude of the N1 and P2 in that region could also be traced in the 100 and 200 ms topoplots.

Conclusion

Gap-induced inhibition was observed in all gap-embedded stimuli and all ROIs. However, the 40-150 mode and centro-frontal and

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left temporal regions had maximum inhibition in normal subjects. It provides a promising tool for objectively assessing tinnitus in humans with particular implications in children.

Keywords: Gap Pre-pulse Inhibition, Acoustic Startle Reflex Inhibition, Objective Tinnitus Assessment, Cortical Auditory Evoked Potentials
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Introduction

Subjective assessment methods have always been at risk of bias and inter-and intra-individual variability, specifically in children who cannot give reliable answers. In addition to overcoming these limitations, the objective tests facilitate investigating neurophysiological hypotheses that lead to efficacious therapeutic solutions. Tinnitus is a condition currently lacking a universally recognized, objective method for diagnosis. Tinnitus is a common ear pathology with a prevalence of 10-15%(1), occurring at any age, even in children(2). Besides, it has no eliminative treatment (3, 4) because of tinnitus heterogeneity and measuring limitations(5). The gap pre-pulse inhibition of the acoustic startle reflex (GPIAS) is the most widely objective method for detecting tinnitus in animals (6-10). The original idea of GPIAS is that tinnitus "fills in" a silent gap embedded in background noise, so this gap (gap pre-pulse) cannot inhibit the acoustic startle reflex (ASR) to the subsequent loud sound (pulse). This inhibition deficit occurs only when the background noise frequency matches the tinnitus frequency(6). GPIAS is currently being studied in humans via electromyography (EMG) of eye blink(11, 12), psychoacoustic gap detection tasks(13), post-auricular muscle response (PAMR)(14), and cortical auditory evoked potentials (CAEP)recordings(15). The human studies examining GPIAS provided evidence contradicting the gap-filling assumption because of deficient gap pre-pulse inhibition (GPI) in both low and high background frequency noise in tinnitus patients(11).

Auditory evoked potentials (AEPs) are an electroencephalogram (EEG) that arise from thalamocortical auditory pathways following sound stimulus and can be recorded objectively from the scalp. The voltage changes that occur 80 to 500 ms in response to time-varying acoustic cues are known as CAEP, and the auditory and frontal cortex are involved in its complex processing(16). The successful recording of CAEP (N1-P2 complex) with the GPIAS stimuli in previous studies (15, 17, 18) and the following arguments have allowed researchers to agree on a standard way of assessing humans tinnitus. The first superiority of CAEP over other methods of GPIAS measurement in humans is that the involuntary nature of these obligatory responses overcomes the limitation of manipulating reflexive or cognitive responses by the individual's intention. Second, common anatomical regions exist between the tinnitus and GPIAS modulators. The GPIAS is processed through the cortico-striatal-pallido-thalamic circuit in which the thalamus and striatum

(putamen, globus pallidus, caudate nucleus, and nucleus accumbens) make connections with the temporal, frontal, and prefrontal cortices (19-21). Several auditory and non-auditory neural networks are responsible for perceptual and psychological aspects of tinnitus based on integrative or global workspace models (22). Since the auditory cortex is one of the essential hubs involved in both tinnitus networks(23) and temporal resolution ability (24), changes in the dynamic properties of auditory cortical responses (spatial distribution, amplitude, and latency of components) can be utilized as objective diagnostic tools in tinnitus, exclusively with gap included stimulus paradigm.

It is appropriate to determine the parameters causing the most inhibition in ordinary adults before performing further comparative studies in tinnitus or pediatric populations to apply the cortical responses with the GPIAS. Among the many factors that affect GPIAS processing(25), previous studies have emphasized the role of gap duration, gap distance from startle name as inter stimulus interval (ISI), and background noise frequency(15, 26). In the previous study recorded with cortical responses, parameters of background noise frequency (600 and 8000 Hz), gap duration (20, 50, 100, and 200 ms), ISIs (20, 50, 100, and 200 ms), and intensities of background noise (5, 20, and 35 dB SL) were investigated(15).

Since no definite information is available about the gap duration of 20 and 40 ms and the ISIs of 120 and 150 ms, the closest values to that cause the most inhibition(25), this study aims to investigate the most influential parameters causing maximum inhibition. Furthermore, to further investigate the filling-in hypothesis and minimize the effect of background frequencies on gap processing(26), the background noise frequency of 1000 Hz was used as a non-matched tinnitus frequency. The frequency of 10, 000 Hz was used as the matched-tinnitus frequency to create a more accurate match with the tinnitus frequency because high-frequency hearing loss and high-pitch tinnitus are common in tinnitus sufferers(27, 28). In previous similar studies, the parameters mentioned above should have been discussed(15, 17). Correspondingly, cortical responses were recorded in two channel in previous study (17), not providing spatial information. In the present study, a 27-channel EEG recording was used to observe the activity distribution on the head and compare the amount of inhibition in different brain regions of interest (ROI). Then, 4 ROI were considered in the CAEP and GPIAS processing (anterior-frontal, centro-frontal, right temporal, and left temporal). By averaging the waveform of the electrodes of each ROI, the inhibition of the N1-P2 complex amplitude was compared in different stimulation paradigms and ROIs in healthy individuals without tinnitus.

In summary, this study aims to introduce a possible objective tool for tinnitus detection. In this regard, this study intends to find the stimulus parameter creating the most inhibition in normal people and the ROI that better reflects the gap-induced inhibition. This information is supportive for future comparative studies in particular pathologies and populations.

Materials & Methods

The study was approved by the Research Ethics Committees of the Iran University of Medical Sciences (approval ID: IR. IUMS. REC. 1399. 813) on the 11th of November, 2020. The participants received written and oral information about the study and consented to participate by completing

the personal consent questionnaire. Participants had the option to withdraw if they chose not to continue with the study.. This study was conducted in the brain mapping laboratory of the Audiology Clinic of Iran University of Medical Sciences. The study included twenty participants, aged between 18 and 50. Eligibility was determined by the absence of severe hearing issues, permanent tinnitus, ear diseases, and neurological or cardiovascular disorders. Additionally, those who were on sedative drugs were excluded from the study. After essential hearing evaluation, CAEP was recorded for those whose hearing thresholds were less than 25 dBHL in the frequency range of 250 to 4000 Hz and less than 40 dBHL in the 4000 to 10000 Hz range. Each participant underwent a comprehensive evaluation during a two-hour session, including an otoscopic examination (Econom 2050, RIESTER, Germany), tympanometry and ipsilateral acoustic reflex (Clarinet, Inventis, Denmark), pure tone audiometry, and 27-channel EEG recording (Brain Quick LTM, Micro Med, Italy). Pure tone audiometry was performed using the conventional modified Hughson-Westlake method (29) to determine air and bone conduction thresholds (in frequencies from 250 to 12500 Hz) in an acoustic chamber.

Sound stimuli

The stimuli used for EEG recording were made in Adobe Audition software (2021-14.4.0.38 version, Adobe Inc., CA, USA) in wave format and presented by Cogent plugin (2000 v 1.33) in Matlab software(R-2016-b, MathWorks, Natick, MA, USA). Stimuli consisted of continuous background noise with a loud, startling tone preceded by a silent gap. Stimuli were presented in two general conditions with and without gaps. In the no-gap mode, only the background noise frequency was manipulated, and two types of stimuli were presented with the background noise frequency of 1 KHz and 10 KHz. In stimuli with gaps in each background noise frequency, two characteristics of gap duration (20 and 40 ms) and inter-stimulus interval (ISI) (defined as the distance between gap termination and the onset of startle) (120 and 150 ms) were manipulated.

In this way, ten stimulus paradigms were created. The startle stimulus was a 1000 Hz pure tone, with a 20 ms duration and an intensity of 65 dB SL. The startling intensity was adjusted according to each person's hearing threshold at 1000 Hz through an audiometer connected to the computer. As background noise, not matched with the tinnitus frequency, a narrow band noise with a 1000 Hz center frequency and a critical bandwidth of 160 Hz (920-1080 Hz) was used, and for a matched-tinnitus frequency, a narrow band noise with 10000 Hz center frequency with a bandwidth of 500 Hz (9500-12000 Hz) was used(30). The intensity of background noise was 20 dBSL, considered according to the hearing threshold of people at frequencies of 1000 and 10000 Hz. Since there was the possibility of high-frequency hearing loss up to 40 dB in the frequencies of 4000 to 10000 in participants, the researchers had to provide 10000 Hz background noise at 20 dB SL for each person. For this purpose, three different types of stimuli were previously constructed for the hearing threshold of 20, 30, and 40 dB at the frequency of 10000 Hz. For each individual, stimuli with 10000 Hz background noise frequency were selected among these three stimuli corresponding to the hearing threshold of 10, 000 Hz.

The intensity level of the stimuli was calibrated using a sound level meter (B&K Type 2250-L

Sound Level Meter / Analyzer - Brüel & Kjær) and a two cc coupler (IEC Ear Simulator RA0045, G.R.A.S. Sound & Vibration, Holte, Denmark) in an acoustic room. Stimuli were presented to the right ear with the ER-3A insert earphone (Etymotic Research INC., Elk Grove Village, IL)., the stimuli were presented randomly and with an inter-trial interval (ITI) (defined as the distance between the offset of each stimulus and the onset of the next) between three and ten seconds to reduce the person's prediction. Besides, the order of presenting stimuli with and without gaps was random. The duration of each stimulus was 600 ms with 100 ms pre-stimulus time. In each trial, fifty stimuli were introduced. The induced response was obtained through a process of averaging and further processing these stimuli.

CAEP measurement

Behavioral and CAEP measurements were recorded simultaneously in one session for two hours. After conducting the behavioral tests, the necessary preparation was given to the subjects to record the electrophysiological response. The subjects were asked to sit quietly inside the acoustic chamber, to be awake and alert, and to avoid excessive eye and body movements during the recording. Since direct attention increases GPIAS and attention processes lead to false results, the passive listening protocol is more appropriate in humans (31), so subjects were asked not to pay attention to the stimuli and watch the muted video presented by the monitor inside the acoustic chamber. The video was about bird research and had subtitles and no emotional impact. The ongoing EEG was acquired via a 32-electrode cap (Brain Quick LTM, Micro Med, Italy). The electrodes placed on FP1, FP2, FPZ, F3, F4, F7, F8, Fz, FC3, FC4, CP3, CP4, CP5, CP6, Cz, C3, C4, C5, C6, T7(T3), T8(T4), P7(T5), P8(T6), Pz, P3, P4 and Oz according to international 10–20 system. The reference was set on the right and left ear lobule (A1 and A2) and the ground on the forehead —two electrodes above and under the left canthus controlled eye movement. Thirty-two electrodes were recorded, but five electrodes of these 32 electrodes were reference and eye electrodes, and the EEG data was obtained on 27 electrodes. The impedance was under ten kOhm, and the impedance difference between electrodes was under two kOhm with a sampling rate of 512 Hz and an online bandpass filter of 0.016-120 Hz.

Extraction of CAEP from EEG

In offline processing, the independent component analysis (ICA) method removed cardiac and eye movement artifacts using MATLAB and EEGLab software (toolbox 14-1-1b). The data were filtered by an offline FiltFilt digital filter with an order of 5 and a bandpass of 1 to 35 Hz and measured compared the average response obtained from A1 and A2. Time windows with voltage changes less than 0.1 or more than 50 μV were excluded from the analysis process. The 600 ms time windows with 100 ms pre-stimulus time were extracted and averaged for the detected target stimuli. The output of these processes was seen in the intended channels. In each individual, the peak amplitude of the CAEP waves evoked by the target stimuli was detected as the most prominent signal relative to the baseline at time intervals of 80-150 ms (N1) and 150-200 ms (P2) were determined at the every electrode location(32). The amplitude and latency of the waves were selected manually from every intended channel by visual inspection. The peak-to-trough method was used to calculate the amplitude

of the N1-P2 complex. The amount of startle inhibition caused by the gap was calculated by comparing the amplitude of the N1-P2 complex in two conditions with and without a gap in the same background noise frequency and by this formula: Inhibition ratio= amplitude of N1-P2 complex in Gap condition/amplitude of N1-P2 complex in No Gap condition. The value of this ratio is between zero and one. The closer this ratio is to one, the less inhibition by the gap in the startle, indicating an inhibition deficit. The smaller the ratio, less than one, indicates more significant inhibition for stimuli with a gap. Recognizing which brain region best reflects gap-induced inhibition in cortical responses would be helpful in future comparative studies. Since the auditory and frontal cortices are involved in both the modulation of cortical waves and the GPIAS, the inhibition ratio of the N1-P2 complex amplitude was compared in the 4 ROIs. The response of the anterior-frontal ROI included the average response from the F3, F4, Fz, F7, and F8 electrodes. The response of the centro-frontal ROI included the average response from the Cz, FC3, and FC4 electrodes. The response of the right temporal ROI included the average response from the C4, C6, and T8 electrodes. The response of the left temporal ROI had the average response from the C3, C5, and T7 electrodes.

The topoplot maps (the spatial distribution of activity in 27 electrode locations at a specific time) extracted by separate codes were written in MATLAB by an expert programmer. For this purpose, a grand average wave was first obtained from the averaging waves of all people, and then the brain map of the activity at the time defined in the codes was displayed in the study electrode montage. Because the gap-induced inhibition effect was investigated in the amplitude of the N1-P2 complex, the specified times for extracting the topoplot map followed the expected time for appearing the N1 and P2 waves, i.e., 100 and 200 ms, respectively. Each electrode's activity at any defined time is displayed with a color spectrum where warm colors indicate positive activity (positive peak) in that brain area, and cold colors indicate negative activity (negative peak). Green or yellow indicates neutral activity around the baseline (no peak). Increasing the amplitude of the negative peak enhances the vibrancy of cool colors, while amplifying the positive peak accentuates the intensity of warm colors.

Data analysis

The average ratios in different stimulation modes of each frequency (1000 and 10000 Hz) in each ROI were compared using repeated measures analysis with within-group measures to investigate the effect of stimulation parameters on inhibition ratio. Mauchly's Test of Sphericity was first investigated to compare the stimulation modes. Greenhouse-Geissers was then reported in the lack of sphericity assumption to distinguish the difference among stimulation modes. The LSD post hoc test assessed pairwise comparisons. Similarly, a comparison of the inhibition caused by each stimulation mode between four brain regions was also made using repeated measures analysis with within-group measures. If the results were significant, a pairwise comparison was created with the LSD post hoc test.

Results

The participants in the study included eight women and 12 men with a mean age of 38.10 years old and a standard deviation (SD) of 8.38. The mean and SD of Hearing thresholds of subjects at measured frequencies in the right ear were as follows:

6.91(5.1) dB at 500 Hz, 7.75(4.12) dB at 1000 Hz, 11.25 (4.83) dB at 2000 Hz, 16.25 (6.66) dB in 4000 Hz, 22.25 (8.18) dB in 8000 Hz, 26.50 (9.04) dB in 10000 Hz, and 32.25 (14.18) dB in 12500 Hz.

Effects of stimulus parameters on inhibition in each ROI

The mean and SD of inhibition ratios of different stimulation modes are shown in Table 1. In this and subsequent figures and tables, 0 ms is the startle onset, and all reported latencies are relative to the startle onset for all stimuli conditions Gap-induced inhibition was observed in all considered ROIs (Figure 1). The lowest amount of inhibition, or in other words, the most significant inhibition ratio, occurred in the stimulation mode with a gap duration of 20 ms and ISI of 120 ms. The highest amount of inhibition (the smallest ratio) was related to the stimulation mode, including a gap with a duration of 40 ms and ISI of 150 ms. This situation was observed in both background noise frequencies of 1000 and 10000 Hz and all four ROIs. However, the difference between the minimum and maximum inhibition ratios differed between different brain regions. As shown in Table 1, the most significant difference between inhibition ratios of stimulus modes occurred in the central and left temporal regions. In the anterior-frontal and right temporal regions, a more negligible difference between inhibition ratios was observed, so the difference between these two regions and the two central and left temporal regions can be argued from the effect size values.

Comparing different stimulus modes of each background noise frequency in each ROI by repeated measures analysis (Table 1) showed that ratios of various parameters had significant differences in inhibition ratio with each other($p<0.05$). Thus, the stimulation modes were compared pairwise with the LSD post hoc test in each frequency and ROI. As seen in Table 2, in the paired comparison of stimulation modes of each frequency, the highest number of significant differences between the two stimulus modes was obtained in the central and left temporal regions. Likewise, another essential finding was that in comparing the two stimulation modes of 20-120 and 40-150, a significant difference in the inhibition ratio was seen in both frequencies of 1000 and 10000 Hz and all regions (except for the insignificant difference between two modes at the frequency of 10000 Hz in the anterior-frontal region).

Gap duration effect on inhibition

In investigating the gap duration effect on the inhibition ratio, the result of comparing two durations of 20 and 40 ms at the ISI of 120 (i.e., comparing the inhibition ratio between the two modes of 20-120 and 40-120) showed a significant difference in the inhibition ratio between these two modes in the anterior-frontal and central regions at the frequency of 1000 Hz. While at the frequency of 10000 Hz, a significant difference between the two modes was observed in the right and left temporal and central regions (Table 2).

In comparing two gap durations at a distance of 150 (i.e., comparing the inhibition ratio between the two modes of 20-120 and 40-120) at a frequency of 1000 Hz in all four regions and at a frequency of 10000 Hz in the central, right and left temporal regions, a significant difference found between these two modes.

In conclusion, comparing the two gap duration indicated that the gap duration of 40 ms creates more inhibition than the gap duration of 20 ms.

This difference did not depend on the background noise frequency; a similar pattern occurred at both frequencies. Furthermore, the contrast from these two durations was more visible at the ISI of 150 ms than at 120 ms. On the other hand, the central and left temporal regions better reflected the difference between the two durations at different ISIs and frequencies. These two regions were common in all pairwise comparisons of two durations and showed significant differences between the two modes (except for the comparison of 20-120 and 40-120 at the frequency of 1000 Hz, where no significant difference was observed in the left temporal region). Furthermore, the two anterior-frontal and right temporal regions revealed differences in some cases of comparing the two durations, and in some comparisons, no significant difference was observed.

ISI effect on inhibition

In comparing the effect of ISI on the inhibition, when this study considers the constant gap duration of 20 ms (i.e., comparing the inhibition ratio between the two modes of 20-120 and 20-150) at the frequency of 1000 Hz, no significant difference was observed between the two modes in any of the regions. Nevertheless, at 10000 Hz, all ROIs showed a significant difference between these two stimulation modes.

When two ISIs were compared at a fixed gap duration of 40 ms, only the central region at the frequency of 1000 Hz and only the central and left temporal regions at 10000 Hz showed a significant difference in the inhibition ratio between these two stimulation modes.

From the inhibition ratio values presented in Tables 1 and 2, evidently, during a gap duration of 20 ms, the impact of increasing the ISI from 120 to 150 is not isolated to a particular brain region. Instead, it depends on the frequency. This is because an increase in inhibition correlated with a rising ISI was solely observed at the 10, 000 Hz frequency. However, in a gap duration of 40 ms, ISI 150 produced more inhibition than 120, and central and left temporal regions better reflected the inhibition effect caused by increasing ISI, regardless of frequency. Another point already mentioned is that the impact of increasing the ISI on the increase of inhibition was better visible in long gaps because the ISI of 150 in the 40 ms gap duration created smaller inhibition ratio values (more inhibition) compared to the 20 ms gap duration.

Effect of ROI on each parameter

The inhibition ratio caused by each stimulation mode was compared between four brain regions to address which ROI best exhibits gap-induced inhibition in the amplitude of the N1-P2 complex.

The comparison results of inhibition ratio in each parameter among 4 ROIs using repeated measures showed that only in the stimulation mode of 4--150 (in both frequencies of1000 and 10000 Hz) different ROIs made a significant difference in inhibition ratio ($p<0.05$ in Mauchly's test of sphericity). A large effect size was also obtained in these two modes: 0.27 for 1000-40-150 and 0.22 for 10000-40-150). In other stimulation modes, no significant difference was observed between the inhibition ratios of each mode in four ROIs ($p>0.05$). However, the largest effect size was related to the mode of 1000-40-120 in the medium range. The effect sizes of 1000-20-120 were in the weak range, and 1000-20-150 were in the non-significance area. The values were as follow for each mode: $p=0.21$, $\eta=0.07$ for 1000-20-120, $p=0.96$, $\eta=0.005$ for 1000-20-150, $p=0.15$, $\eta=0.09$

for 1000-40-120, p=0.94, η=0.006 for 10000-20-120, p=0.36, η=0.05 for 10000-20-150, p=0.95, η=0.06 for 10000-40-120. Differences in stimulus modes in each ROI can be seen in Figure 1.

As it is clear from the values of the inhibition ratio in Figure 2, in the two modes of 1000-40-150 and 10000-40-150, where a significant difference was observed in the inhibition ratio of four regions, the highest inhibition (in other words, the smallest inhibition ratio), occurred in the centro-frontal and left temporal regions, and less inhibition occurred in the anterior-frontal and right temporal regions.

Moreover, as the results of LSD post hoc analysis for those two modes demonstrated (Table 3), the two left temporal and centro-frontal regions had similar inhibition ratios, and the two anterior-frontal and right temporal regions had similar values, i.e., the inhibition ratios of these two regions were not significantly different from each other. In comparison, the paired comparison of other regions with each other showed a significant difference in the inhibition ratio of that state between different regions ($p<0.05$). The visual representation of this finding is presented in Figure 2.

Topoplot

The topoplot map shows the activity of the whole brain at a specific time with a color spectrum indicating the positive and negative peaks of CAEP. The display of maps obtained at 100 and 200 ms (equivalent to the approximate time of occurrence of N1 and P2 waves) in different stimulation modes is shown in Table 4. Due to the subtle differences in the amplitude and the lack of noticeable change in the spatial distribution of the activity in the plots in different stimulation modes, the average voltage of each peak (N1, P2, and N1-P2 complex) in different regions was mentioned separately. These numbers were obtained from the grand averaging wave of all subjects, and in each ROI, the result was the average activity recorded from the electrodes of that region. As can be inferred from the average voltage of the peaks, with the addition of the gap to the stimuli, the amplitudes decreased compared to the state without the gap (inhibition caused by the gap occurred).

Regarding the changes in the N1 wave following the addition of the gap, the most voltage changes were observed in the centro-frontal, left temporal, anterior-frontal, and right temporal regions, respectively (in both 1000 and 10000 Hz). These findings can be seen in the 100 ms plot, as gradually fading dark blue areas in the centro-frontal and left temporal regions.

Regarding the P2 voltage changes, the average amplitudes and the 200 ms plot showed that, like the N1, the amplitude of this wave decreased with the addition of a gap, mostly in the centro-frontal and left temporal regions, and the colorful hot spots observed in the state without a gap, in the gap-included stimuli gradually became lighter in these regions.

In general, the pattern and broad view of the activity in the plots have no noticeable visual change, but the dimming of the hot-colored areas, a sign of a decrease in amplitude, occurred in stimulations with a gap compared to the no gap mode, expressly in the centro-frontal and left temporal ROIs. Among the different stimulus modes with a gap, the most distinct plot compared to those without was related to the modes of 40-150 (both at 1000 and 10000 Hz frequencies).

Table 1 . Comparison of inhibition ratio in each ROI using repeated measures.

ROI	Background noise frequency	gap duration-ISI	Inhibition ratio		Mauchly's Test of Sphericity	Mean square	F statistics	p-value	Effect size
			Mean	SD					
Anterio-frontal	1000	20-120	0.92	0.08	21.39**	0.05	5.74	0.006	0.23
		20-150	0.90	0.06					
		40-120	0.85	0.11					
		40-150	0.82	0.09					
	10000	20-120	0.93	0.05	4.95	0.05	5.96	0.001	0.24
		20-150	0.86	0.11					
		40-120	0.85	0.09					
		40-150	0.80	0.10					
Central	1000	20-120	0.91	0.06	6.75	0.09	17.53	< 0.001	0.48
		20-150	0.88	0.07					
		40-120	0.82	0.11					
		40-150	0.76	0.07					
	10000	20-120	0.93	0.04	11.05	0.12	15.55	< 0.001	0.45
		20-150	0.85	0.08					
		40-120	0.85	0.09					
		40-150	0.74	0.12					
Right temporal	1000	20-120	0.91	0.07	3.57	0.06	4.19	0.01	0.18
		20-150	0.89	0.07					
		40-120	0.87	0.07					
		40-150	0.83	0.08					
	10000	20-120	0.92	0.06	4.95	0.04	6.84	0.001	0.26
		20-150	0.87	0.09					
		40-120	0.86	0.10					
		40-150	0.81	0.10					
Left temporal	1000	20-120	0.88	0.10	3.45	0.094	16.37	< 0.001	0.46
		20-150	0.89	0.08					
		40-120	0.83	0.08					
		40-150	0.74	0.08					
	10000	20-120	0.92	0.07	10.40	0.091	12.81	< 0.001	0.40
		20-150	0.83	0.12					
		40-120	0.85	0.07					
		40-150	0.76	0.11					

Table 2. Pair comparison of stimuli in each ROI by LSD post hoc test.

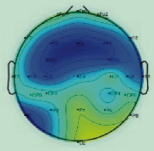
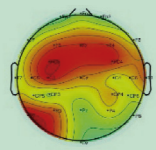
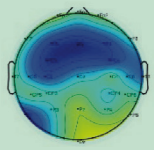
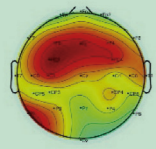
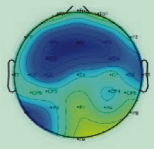
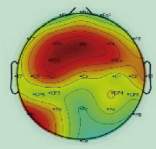
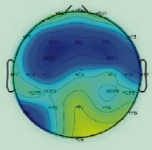
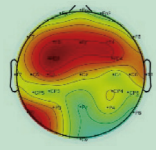
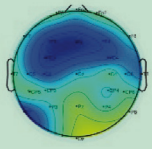
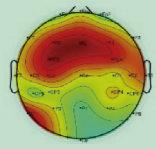
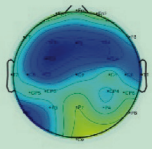
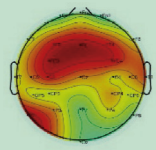
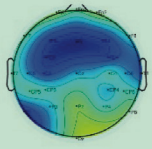
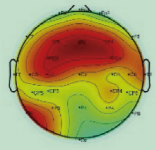
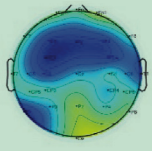
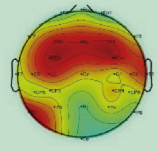
stimuli			**ROI**							
			Anterio-frontal		**Centro-frontal**		**Right temporal**		**Left temporal**	
Background noise freq	gap duration-ISI		Mean diff	P value	Mean diff	P value	Mean diff	P value	Mean diff	P value
1000	20-120	20-150	0.025	0.06	0.029	0.14	0.02	0.41	-0.008	0.72
		40-120	0.072	0.04	0.092	0.004	0.04	0.14	0.047	0.116
		40-150	0.098	0.001	0.155	<0.001	0.078	0.004	0.142	<0.001
	20-150	40-120	0.047	0.09	0.063	<0.001	0.028	0.28	0.055	0.019
		40-150	0.073	0.012	0.126	0.007	0.06	0.013	0.15	<0.001
	40-120	40-150	0.027	0.036	0.063	0.032	0.038	0.124	0.094	0.002
10000	20-120	20-150	0.064	0.02	0.079	0.002	0.055	0.015	0.09	0.01
		40-120	0.078	0.004	0.080	0.001	0.065	0.014	0.071	<0.001
		40-150	0.124	0.001	0.19	<0.001	0.115	<0.001	0.164	<0.001
	20-150	40-120	0.014	0.611	0.002	0.95	0.009	0.73	-0.019	0.48
		40-150	0.061	0.103	0.11	0.009	0.06	0.02	0.074	0.017
	40-120	40-150	0.047	0.19	0.10	0.001	0.05	0.13	0.10	0.002

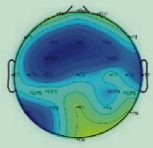
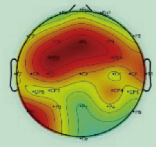
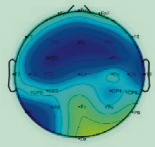
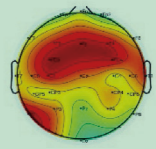
Table 3. Pair comparison of ROIs in each stimulus mode by LSD post hoc test.

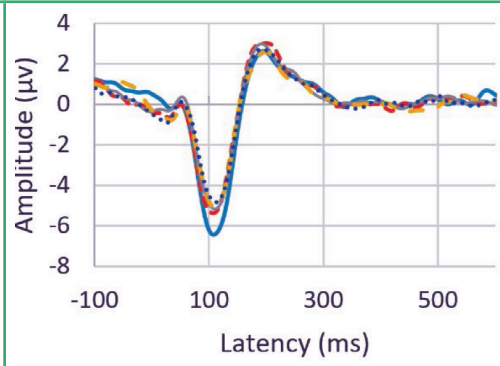
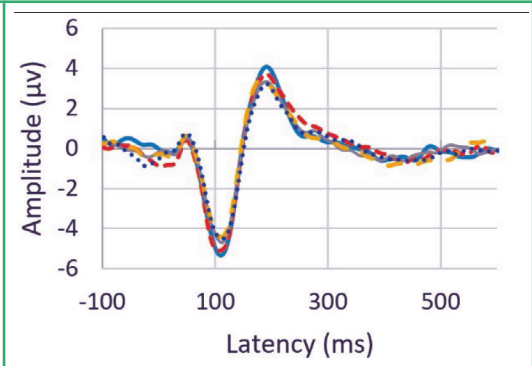
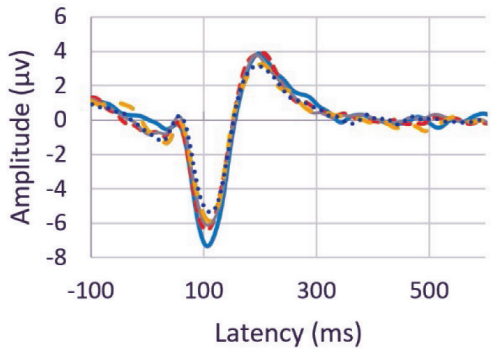
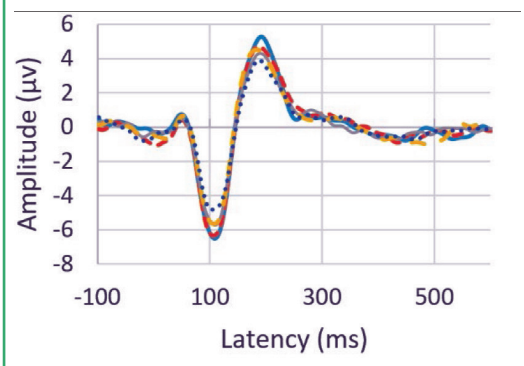
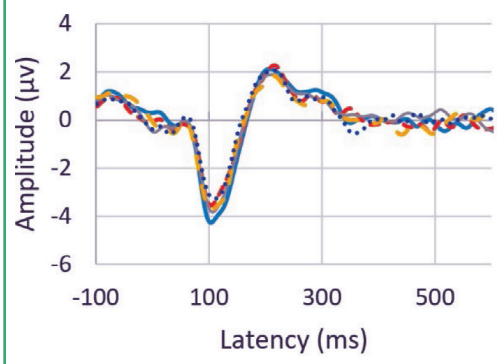
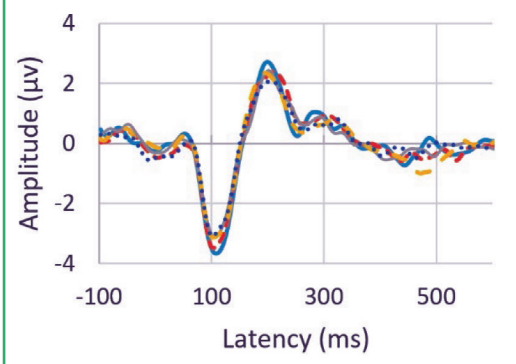
stimuli	**ROI**						
						95 CI	
	i	j	MD(i-j)	SE	P-value	LB	WEB
1000-40-150	Anterio-frontal	Centro-frontal	0.064	0.021	0.008	0.019	0.109
	Anterio-frontal	Right temporal	-0.010	0.027	0.71	-0.066	0.046
	Anterio-frontal	Left temporal	0.084	0.031	0.015	0.019	0.150
	Centro-frontal	Right temporal	-0.074	0.018	0.001	-0.112	-0.036
	Centro-frontal	Left temporal	0.020	0.023	0.384	-0.028	0.069
	Right temporal	Left temporal	0.095	0.027	0.002	0.039	0.150
10000-40-150	Anterio-frontal	Centro-frontal	0.064	0.021	0.006	0.020	0.109
	Anterio-frontal	Right temporal	-0.005	0.019	0.778	-0.046	0.035
	Anterio-frontal	Left temporal	0.048	0.022	0.036	0.003	0.094
	Centro-frontal	Right temporal	-0.070	0.022	0.005	-0.116	-0.024
	Centro-frontal	Left temporal	-0.016	0.019	0.417	-0.056	0.024
	Right temporal	Left temporal	0.054	0.022	0.026	0.007	0.101

MD: Mean Difference; SE: Standard Error; CI: Confidence Interval; LB: Lower Band; UB: Upper Band

Table 4. Plots of 100 and 200 ms and amplitude of waves at different ROIs and stimuli modes.

stimulus	time		N1-P2 complex amp (N1 amp, P2 amp)			
	100 ms	200 ms	anterio-frontal	centro-frontal	Right temp	Left temp
1000-NG			9.05 (-6.42, 2.62)	11.2 (-7.32, 3.87)	6.4 (-4.27, 2.12)	7.66 (-4.98, 2.67)
1000-20-120			8.39 (-5.37, 3.01)	10.31 (-6.4, 3.9)	5.84 (-3.55, 2.28)	6.82 (-4.08, 2.73)
1000-20-150			8.15 (-5.15, 2.99)	9.95 (-6.13, 3, 81)	5.72 (-3.83, 1.88)	6.86 (-4.35, 2.5)
1000-40-120			7.67 (-5.06, 2.6)	9.13 (-5.85, 3.27)	5.58 (-3.74, 1.83)	6.41 (-4.08, 2.32)
1000-40-150			7.54 (-4.81, 2.72)	8.52 (-5.36, 3.15)	5.35 (-3.26, 2.08)	5.69 (-3.49, 2.19)
10000-NG			9.41 (-5.33, 4.07)	11.77 (-6.51, 5.25)	6.4 (-3.67, 2.72)	8.1 (-4.44, 3.65)
10000-20-120			8.79 (-5.08, 3.7)	11.02 (-6.31, 4.7)	5.88 (-3.48, 2.39)	7.51 (-4.08, 3.42)
10000-20-150			8.05 (-4.7, 3.34)	10.02 (-5.72, 4.29)	5.57 (-3.13, 2.43)	6.73 (-3.99, 2.73)

10000-40-120			7.91 (-4.43, 3.47)	10.15 (-5.64, 4.5)	5.5 (-3.13, 2.36)	6.84 (-3.86, 2.97)
10000-40-150			7.75 (-4.51, 3.23)	8.74 (-4.83, 3.9)	5.19 (-3.09, 2.09)	6.19 (-3.37, 2.81)

ROI	Background noise frequency	
	1000	10000
Anterio-frontal		
Centro-frontal		
Right temporal		

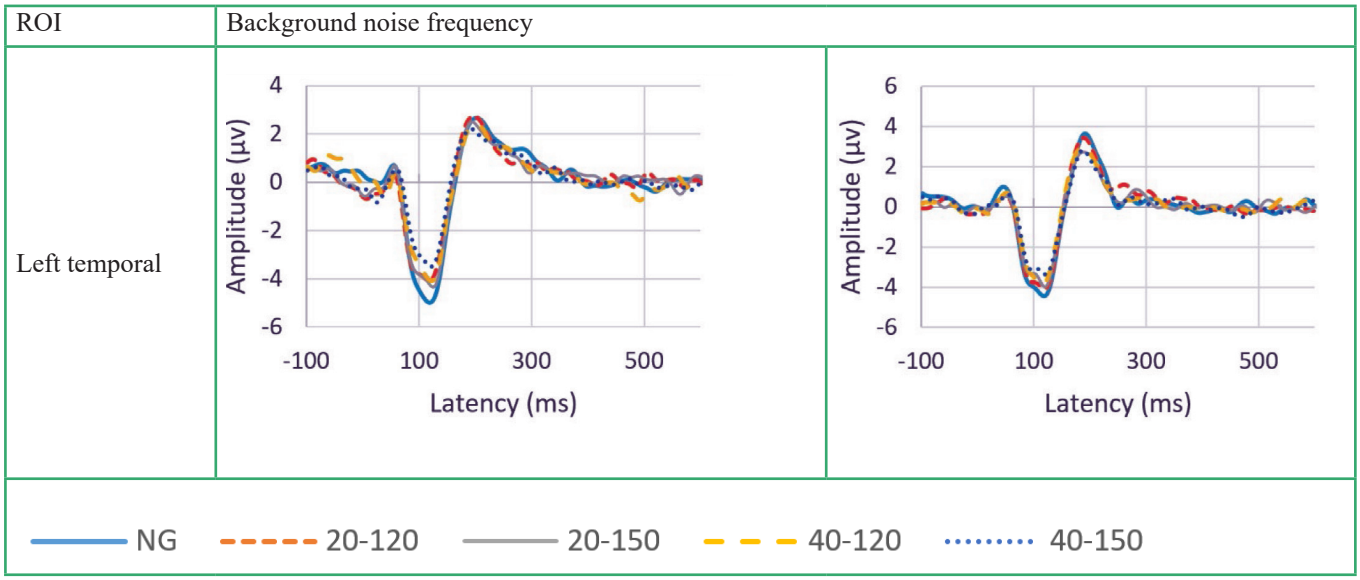


Figure1. ***Grand*** *averaging waveforms of the CAEP in different ROIs in response to with and without gap stimuli with the 1000 and 10000 Hz background noise frequency.*

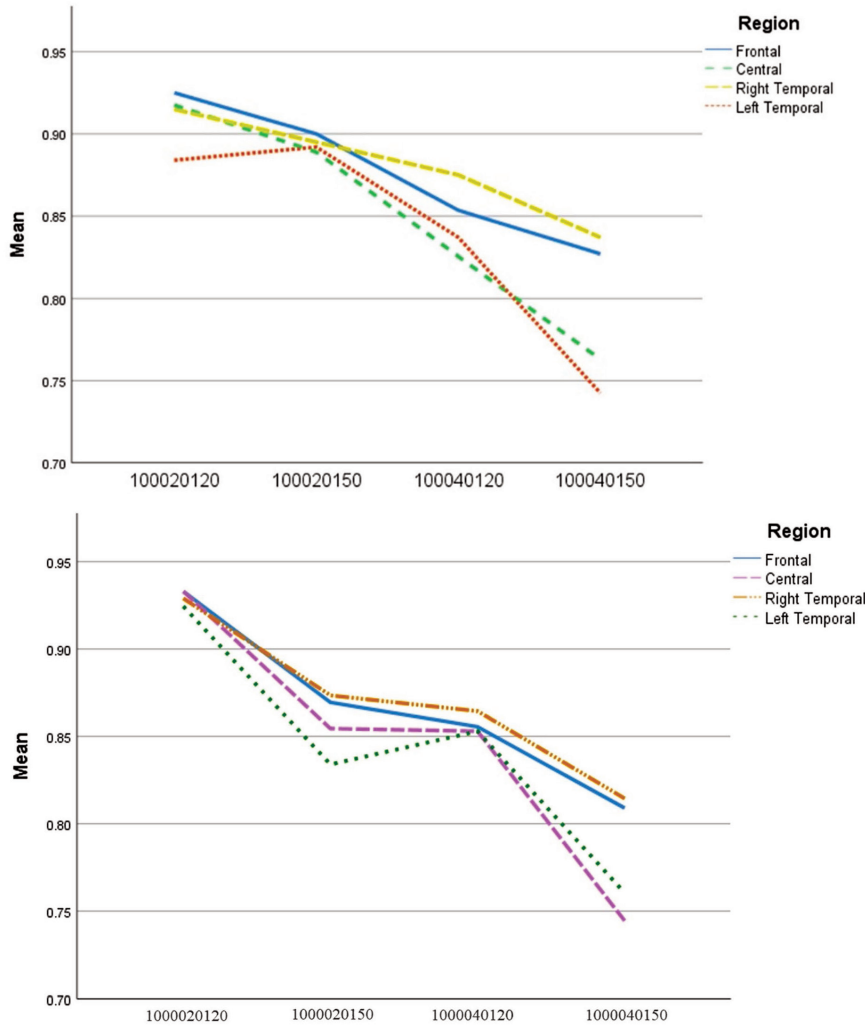


Figure 2. *Inhibition ratio comparison of each stimulus mode between ROIs.*

Discussion

Here, the present study introduces a possible objective method for tinnitus assessment and presents the results of comparing evoked potential biomarkers with GPIAS stimuli between different stimulus parameters and ROIs in normal hearing subjects. For this purpose, the parameters of background noise frequency (1000 Hz as non-tinnitus-matched frequency and 10000 Hz as tinnitus-matched frequency), gap duration (20 and 40 ms), and ISI (120 and 150 ms) were manipulated. In addition, the amount of inhibition caused by the gap in the amplitude of the N1-P2 complex was compared in different stimulus modes and four different ROIs (anterior-frontal, centro-frontal, left, and right temporal). In both frequencies and all four ROIs, the inhibition caused by the gap in the amplitude was observed. The comparison of different stimulation modes in each ROI showed that the lowest amount of inhibition occurred in 20-120 and the highest inhibition occurred in 40-150. The most significant difference between the largest and the smallest inhibition ratio was observed in the centro-frontal and left temporal regions. These findings were also confirmed by comparing each parameter in four different ROIs. Besides, the results showed a significant difference between four ROIs only in 40-150 mode (in both frequencies). The centro-frontal and left temporal regions had the smallest inhibition ratio in this simulation mode. Examining the topoplot maps at 100 and 200 ms, the reduction of the amplitude of the waves was also visible with the gradual fading of the hot blue and red colored regions, specifically in the centro-frontal and left temporal areas.

In the current study, CAEPs were investigated with the GPIAS stimuli. Previous studies have proposed the successful recording of cortical responses (P1, N1, and P2 components) with the GPIAS(15, 17) and gap in noise(GIN)(33) paradigms as a possible tool for the objective detection of tinnitus in humans. Common neural areas exist in the PPI/GPIAS and tinnitus network. The extensive anatomical overlap between the PPI/GPIAS regulatory circuits and the tinnitus networks supports that tinnitus, as a deficit of sensory-gating disorder, can affect the GPIAS and that cortical recordings can trace these effects. Multi-channel EEG recording allows viewing the spatial distribution of activity on the head. The N1 and P2 amplitudes investigated inhibition because these components are the obligatory responses of the auditory system caused by the primary and secondary auditory cortex, influenced by physical and sensory factors(16, 32). Since the early cortical responses have the largest amplitude in the frontocentral electrodes (unlike late components (like P3), prominent in the parietal electrodes) (34, 35), the role of auditory and anterior-frontal cortices in the GPIAS circuit(21), the four ROIs of anterior-frontal, centro-frontal, right and left temporal (36) were considered to observe the inhibition effect on the amplitudes.

In examining the effect of gap duration and ISI in a pairwise comparison between stimulus modes, observingly, regardless of the background noise frequency, 40 ms duration compared to 20 ms duration and 150 ISI compared to 120 caused more inhibition. This pattern was visible in all comparisons in the centro-frontal and left temporal regions, but in the anterior-frontal and right temporal regions, all comparisons did not follow this pattern.

The GPIAS stimulus has a complex processing that simultaneously contains several types of auditory

stimuli, including low-intensity background noise, a silent gap, and a strong startle stimulus. More inhibition occurred in 40 ms duration than 20 ms because in longer gaps, two cues of the onset and termination of the gap are available, and it becomes easier to detect the silent gap in the noise. Increased inhibition with increasing gap duration has been proven in some studies(17, 37). Short gaps provide less time for high-level cortical processing and top-down modulation of the GPIAS(18). The result of a previous CAEP study with GPIAS suggested that a 20 ms gap duration can differentiate tinnitus from normal better than 50 ms, although this difference was observed only at the tinnitus-matched background noise frequency (17). Likewise, in investigating the relationship between people's age and the gap-induced inhibition, a relation was observed in the 20 ms gap, but the inhibition decreased with increasing age at the 50 ms gap (18).

On the contrary, in the study of the relevance of hearing loss and inhibition, observingly, hearing loss affects the detection of short gaps, but it has no impact on gaps longer than 30 ms, except for more than 60 dB of hearing loss (13). The ability to detect a gap in a continuous signal is one of the ways to investigate temporal resolution, depending on the intensity and spectral characteristics of the background signal and the duration of the gap(38, 39). Studies have demonstrated that the detection of short gaps (less than 50 ms) is done unconsciously(40) by the auditory cortex, while in longer gaps, subcortical areas also play a role in addition to the auditory cortex(24). The GPIAS paradigm reflects pre-attentive gap detection and sensory filtering. Although ASR can be modulated by attention, it causes more inhibition(31). The cortical neurons constantly compare the activity before and after the gap and respond to the end of the gap with gap termination responses (GTR). GTR, the neural manifestation of the detection of short gaps, increases with the increase of gap duration(24).

Additionally, the greater the distance between the gap and Startle, the more time is available to compare the responses before and after the gap, making the gap more accessible to percept. For this reason, in the results of this study, more inhibition was observed at the ISI of 150 than at 120. In studies, an ISI of 30 to 240 ms is usually used, but the optimal inhibition often occurs at an ISI of 120 ms(41). Undeniably, the ISI affects the conscious perception of the pre-stimulus gap. In short intervals of 30 to 500 ms, people cannot voluntarily and consciously do behavioral inhibition(42). In this regard, a study suggests that in the ISI of 60 ms, pre-discovery of the stimulus and evaluation occurs; in the ISI of 120, differentiation of the stimulus and allocation of more attention occurs, and in the ISI of 240, a change from evaluation of the stimulus to judgment occurs(43).

Regarding the effect of frequency on inhibition, as expected, inhibition did not differ in two frequencies of 1000 and 10000 Hz in the normal group without tinnitus. These results will help future comparative studies more closely examine the filling-in hypothesis. According to this hypothesis, unlike the normal group, the tinnitus group may show different inhibition in two frequencies, and inhibition deficiency is observed in tinnitus-matched frequency.

In this study, the inhibition effects caused by the gap in the amplitude of the N1 and P2 waves could be traced more precisely in the centro-frontal and left temporal regions. These results can be due to the direction of dipoles generating these waves,

and it is consistent with the results of dipole source localization analysis studies. The N1 dipoles are tangential, showing the activity of the primary auditory cortex, and can be recorded from midline locations. In contrast, radial dipoles show the activity of the secondary auditory cortex in the more lateral regions of the temporal areas(44). Studies employing both EEG and MRI has discovered that the temporal, parietal, and cingulate regions are instrumental in processing new auditory stimuli. However, the prefrontal cortex (PFC) also contributes by suppressing these stimuli in sensory gating mechanisms. (45).

Plots of 100 and 200 ms and the average voltage of N1 and P2 components showed that with a gap to the stimuli, the N1 amplitude changed more than P2. Thus, N1 was more effective in determining the amplitude of the N1-P2 complex and calculating the inhibition ratio. It indicates unconscious selective attention and bottom-up processing of auditory stimuli. Due to its exogenous nature, it is more sensitive to the characteristics of the acoustic changes in stimulus. While the P2 occurs at the start of the top-down processes and the interaction of the top-down and bottom-up processes, the nature of the components is endogenous. The contribution of N1 and P2 components to the amplitude of the N1-P2 complex will probably be different from normal in the case of tinnitus because the results have shown that tinnitus affects the later components of the CAEPs (like P3) (46).

In conclusion

Recording CAEPs with the GPIAS method provides a tool for objectively diagnosing human tinnitus. The validity of this method needs to be proved due to the inherent variability of the startle reflex and scant studies about it. Before conducting comparative studies in tinnitus, it is helpful to investigate which stimulus parameter creates the most inhibition and which ROI better reflects the gap-induced inhibition in normal people. The study results indicated a gap duration of 40 ms induced more inhibition compared to 20 ms and an ISI of 150 ms compared to 120 ms. Furthermore, the centro-frontal and left temporal brain regions reflect the inhibition pattern more accurately. These findings have implications for the commissioning and designing of services for childhood tinnitus. Parameters should be tested in a further study and reframed if necessary in the pediatric population.

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Authors' Contribution

Authors attest that all persons designated as authors qualify for authorship, and all those who qualify are listed. All authors contributed to the study's conception and design. All authors read and approved the final manuscript.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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