Research Article

Investigating the Feasibility of Gap Prepulse Inhibition by Auditory Middle Latency Responses in Healthy Subjects

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Highlights

- AMLR amplitudes in the gap prepulse paradigm can indicate inhibition
- GPI related to the Na-Pa and Pb-Nc amplitudes creates greater inhibition

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ABSTRACT

Background and Aim: Gap Prepulse Inhibition (GPI) is a type of Prepulse Inhibition (PPI) in which a gap is used as a prepulse. This study was conducted to investigate the silence gap effect on Auditory Middle Latency Response (AMLR) inhibition in normal subjects.

Methods: In this study, 25 participants with normal hearing and no history of tinnitus were included. AMLR was recorded in response to stimuli with gap and without gap in two background noises of 2 and 8 kHz at two electrode locations Fz and Cz and then, gap prepulse inhibition for Na-Pa, Pa-Nb, Nb-Pb and Pb-Nc amplitude with Use of responses to stimuli with and without gap was calculated.

Results: The results showed that the mean amplitudes of all four AMLR indices decreased in response to the stimuli with gap and this decrease was more and statistically significant in 8 kHz background noise ($p \leq 0.001$).

Conclusion: According to the results of this study, it seems that in future studies, PPI of Na-Pa and Pb-Nc amplitudes can be used as main indicators and PPI of Pa-Nb and Nb-Pb amplitudes as alternative indicators in the PPI paradigm in tinnitus diagnosis.

Keywords: Prepulse inhibition; tinnitus; auditory middle latency responses

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Introduction

Prepulse Inhibition (PPI) is a general neurological phenomenon in which the response to a main stimulus or pulse (acoustic or tactile pulse) is reduced when a weaker or prepulse stimulus (acoustic, visual, or tactile prepulse) is presented 30 to 500 milliseconds before it [1], and by increasing the intensity of the pre-pulse stimulus, the amount of inhibition also increases [2]. Gap-Prepulse Inhibition (GPI) is a special method for investigating PPI, in which a silence gap embedded in the background noise is used as a prepulse, and it was invented to assess tinnitus objectively. This method hypothesizes that if tinnitus partially or completely fills the gap and disrupts the perception of the gap, inhibition does not occur, but in normal subjects, inhibition occurs due to the perception of the gap. Turner et al. proposed the use of Gap-Prepulse Inhibition of the Acoustic Startle reflex (GPIAS) to assess tinnitus in animal studies, based on the hypothesis of a PPI deficit in tinnitus [3]. Fournier and et al attempted to implement the GPIAS method in humans using the eyeblink startle response [4]. However, it seems that behavioral responses such as acoustic startle reflex or eyeblink startle reflex have limitations for clinical diagnosis [5-7]. These patterns have not been successfully replicated in humans. Therefore, the presence of an electrophysiological method capable of examining neural responses to gaps has gained attention [8]. In recent years, studies have been conducted on both humans and animals to investigate PPI using cortical auditory evoked responses, often utilizing Auditory Late-Latency Responses (ALLR) [9-12]. However, it appears that the use of LLR is associated with challenges, including the significant impact of attentional states on the N1 and P2 amplitudes, which can influence their results and interpretations. Moreover, due to the strong correlation of these components with higher-level cognitive processes, their use is not recommended, especially for gating functions [13]. Additionally, given that the neural circuitry controlling GPI is not entirely clear, the role of the auditory cortex and LLR in these findings remains uncertain [8]. Conversely, many studies have reported that the basis of the PPI circuitry is located in the brainstem, and subcortical circuits play a crucial role in PPI [14, 15]. Auditory Middle Latency Response (AMLR) is one of the best options for objective assessment of the auditory function at higher levels and provides valuable information about the thalamic function and thalamocortical pathways in both children and adults [16]. The generators of AMLR have long been suggested to include the auditory cortex with a high likelihood of participation from the brainstem and thalamus [17]. Additionally, unlike late-latency cortical responses, studies have shown that AMLRs are relatively stable and exhibit greater stability in response to changes in the individual's state and attention [18]. To the best of our knowledge, no study has been conducted to investigate GPI on AMLR peaks in both animals and humans. Since understanding the characteristics of GPI in healthy individuals and optimizing it in participants with normal hearing is essential before conducting studies on GPI indices in patients with tinnitus, the aim of this study was to examine GPI in relation to AMLR peaks in individuals with normal hearing without tinnitus. If our hypothesis is confirmed, the indices that demonstrate significant inhibition in normal individuals can be compared with patients suffering from tinnitus in future studies.

Methods

Subjects

The participants in this study included 25 normal individuals (12 males, 13 females) aged between 20 and 40 years (mean age 26.48±5.68). The lack of a history of tinnitus or other neurological diseases was confirmed by questionnaire form and medical examination. Tympanometry and pure tone audiometry were performed for all subjects in a soundproof booth using standard audiometric procedures before the experiment, and considering that the stimulus intensity was based on dB HL, to prevent issues related to the overall sensitivity reduction associated with hearing background noise and the main stimulus (pulse), only individuals with normal hearing who had a hearing threshold of 0 dB HL at frequencies of 1 kHz, 2 kHz, and 8 kHz (and hearing thresholds≤25 dB HL in other frequencies) were included in the study. Informed consent was obtained from all participants before the study.

Stimulus

The stimulus, as shown in Figure 1, consisted of a background noise and a pulse stimulus. The background noise was a pure tone of 8 kHz or 2 kHz at an intensity

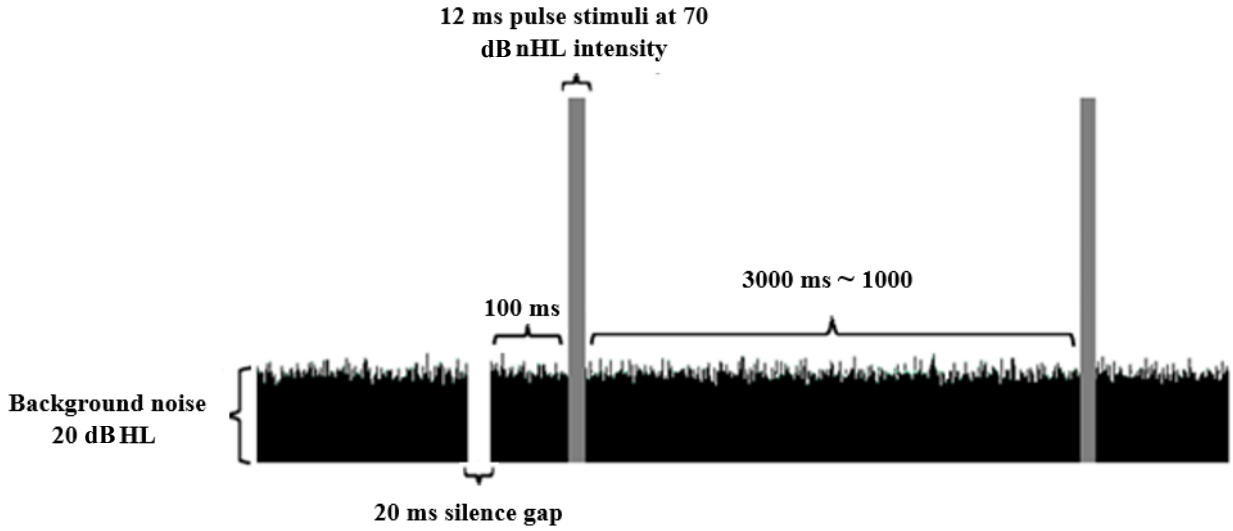

Figure 1. Schematic view of the stimulus used in this study, including tone burst with and without gap

of 20 dB HL. This means that two stimuli were created, one with background 8 kHz and one with background 2 kHz. The pulse stimuli were 1000 Hz tone bursts with a duration of 12 ms, including a one-cycle rise and fall time, and a 10-cycle plateau at an intensity of 70 dB nHL. Before half of them, a silent gap of 20 ms duration was randomly embedded. An Interstimulus Interval (ISI) of 100 ms was considered between the offset of the silent gap and the onset of the pulse stimulus. The Inter-Trial Interval (ITI) between pulse stimuli varied randomly between 1 to 3 seconds to prevent habituation of GPI and P50 and to reduce the predictability of the individuals. The number of trials for each type of pulse stimulus was set to 250. Thus, it took approximately 17 minutes to perform the test with each type of background. The stimulus components were created in MATLAB 2021b (Math Works Inc., Natick, MA, USA) at a sampling frequency of 44,100 Hz and a resolution 16 bits per sample. They were combined and ultimately played in MATLAB software. All acoustic signals were calibrated using the 2250 Bruel & Kjær sound level meter (Bruel & Kjær, Denmark) in the experimental environment.

Recording procedures

For ERP recording, participants were comfortably seated on a chair and asked to look at a computer screen in front of them displaying a plus sign at the eye level. They were instructed to remain as relaxed and motionless as possible and not to pay attention to the stimuli. Each participant underwent the test twice, once with a stimulus with an 8 kHz background noise, and after a five-minute rest, once with a stimulus with a 2 kHz background noise.

The stimuli were delivered monaurally through ER-3A insert earphones (Etymotic Research, Elk Grove Village, IL, USA), and triggers were sent simultaneously to the recording system using a parallel port method. To record electrical activities, the g.HIamp system (g.Tec, GmbH, Austrian) was utilized. The non-inverting electrodes were placed using an electrode cap at the positions Fz, and Cz in accordance with the international 10-20 system. The ground electrode was placed at FPZ, and the inverting electrodes were positioned at A1 and A2. To monitor eye movements and blinking, electrodes placed above and below the right eye and at the outer canthi of both eyes were used. The sleepiness of participants was monitored through visual observation and EEG control. The sampling rate was set at 1200 Hz.

Preprocessing was performed in MATLAB using the EEGLAB and ERPLAB toolboxes. The data were offline-referenced to the average of the left and right (A1 and A2) earlobe and filtered with a frequency range of 1.0 to 200 Hz. Trials containing artifacts (±50 μV) were removed from the analysis before averaging. Moreover, the ANC (Adaptive Noise Cancellation) technique was utilized to remove blink artifacts. Epochs were defined in the range of –10 ms (prestimulus time) to 100 ms after the onset of the pulse stimulus. Finally, two averaged waveforms were obtained for stimuli with and without gaps for each electrode site and for each background noise frequency, individually for each participant.

Data analysis

After averaging, the Na-Pa, Pa-Nb, Nb-Pb, and Pb-Nc components in different channels were visually inspected and analyzed for stimuli with and without gaps. The Na component was identified as the trough in the range of approximately 12 to 21 ms, Pa as the positive peak in the range of approximately 21 to 38 milliseconds, Nb as the trough in the range of approximately 25 to 50 milliseconds, and Pb as the positive peak in the range of approximately 40 to 80 milliseconds. Additionally, to compare responses related to gaps in the 2 kHz and 8 kHz background noises, the Na-Pa and Nb-Pb components were calculated in response to the onset of gaps.

GPI was calculated using the following formula:

$$gPPI = \frac{\text{no gap\_gap}}{\text{no gap}}$$

The significance level was set at 0.05. Paired t-tests and Wilcoxon tests were utilized for data analysis using the SPSS 17 software.

Results

Amplitudes of auditory middle latency response to the pulse stimuli

Figure 2 illustrates the grand average of AMLR waves in response to stimuli with and without gaps for 8 kHz and 2 kHz background noises at the Fz and Cz electrode positions. As seen in the figure, the amplitude of the waves was larger in both background noises and electrode positions in response to stimuli without gaps compared to stimuli with gaps. For a more detailed comparison of the Na-Pa, Pa-Nb, Nb-Pb, and Pb-Nc amplitudes between stimuli with and without gaps under background noise conditions and different electrode positions, paired t-test was used. The results are presented in Table 1.

Next, the amplitude of the recorded waves from both types of stimuli with and without gaps at the Fz and Cz electrode positions was compared between the two background noise conditions, 8 kHz and 2 kHz. As seen in Figure 3, the amplitudes were larger in the 8 kHz background noise compared to 2 kHz. The results of the paired t-test for comparing between the 2 kHz and 8 kHz background noise are also presented in Table 2.

Gap prepulse inhibition results

Considering values higher than zero, in the 8 kHz background noise and at electrode site Fz, 25 participants (100%) for Na-Pa amplitude, 23 participants (92%) for Pa-Nb amplitude, 22 participants (88%) for Nb-Pb amplitude, and 23 participants (92%) for Pb-Nc amplitude demonstrated GPI or inhibition of amplitude

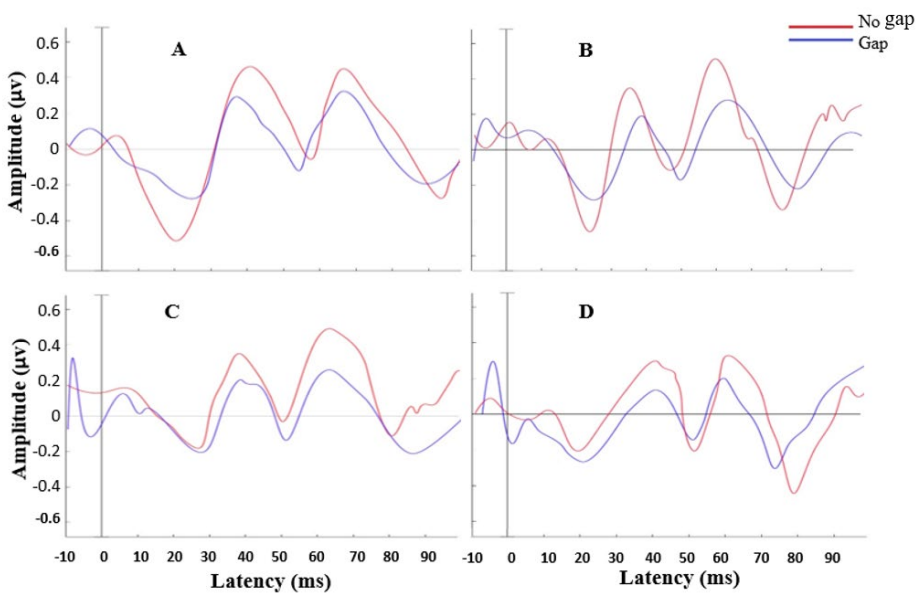

Figure 2. Grand averaging of auditory middle latency response waveforms in response to sound stimuli without gap (red line) and with gap (blue line) (A) at the Fz electrode and 8 KHz background frequency (B) at the Cz electrode and 8 KHz background frequency (C) at the Fz electrode and 2 kHz background frequency and (D) at the Cz electrode and 2 KHz background frequency

Table 1. Paired t-test results to compare Na-Pa, Pa-Nb, Nb-Pb and Pb-Nc amplitudes between pulse stimuli without gap and with gap, at Cz and Fz electrodes, separated by background noise

	Fz				Cz			
	8 kHz		2 kHz		8 Khz		2 kHz	
	t (24)	p	t (24)	p	t (24)	p	t (24)	p
Na-Pa	10.87	<0.000**	3.36	0.003**	7.63	<0.000**	1.29	0.206
Pa-Nb	6.02	<0.000**	2.12	0.044*	4.81	<0.000**	1.48	0.152
Nb-Pb	3.77	0.001**	1.99	0.057	–8.08	<0.000**	4.21	<0.000**
Pb-Nc	–6.5	<0.000**	5.54	<0.000**	–14.44	<0.000**	14.81	<0.000**

* p<0.05, ** p<0.01

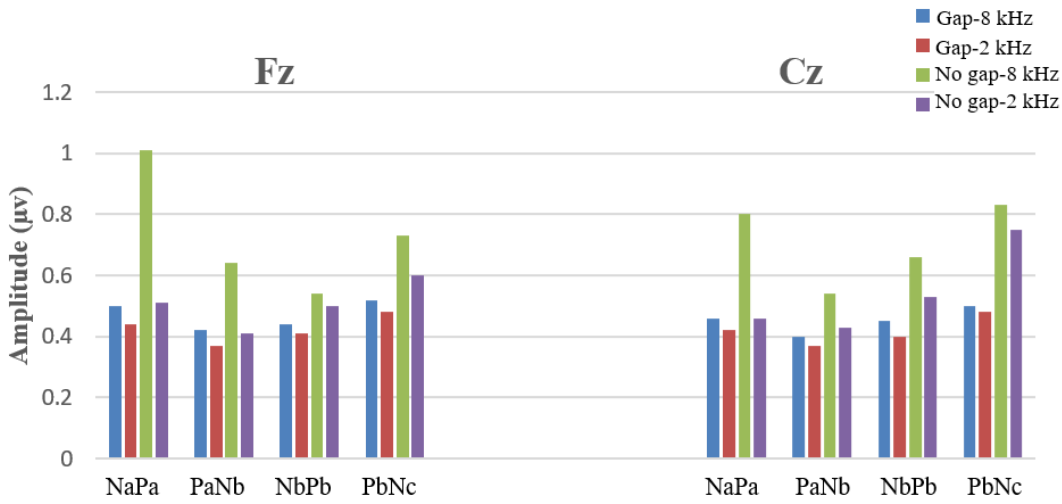

Figure 3. Comparisons of the mean amplitudes to the gap and no gap pulse stimulus recorded at the Fz and Cz electrodes between 2 and 8 kHz background noise

in response to the gap stimulus. In electrode site Cz, the corresponding numbers were 22 participants (85%) for Na-Pa, 21 participants (84%) for Pa-Nb, 20 participants (80%) for Nb-Pb, and 24 participants (96%) for Pb-Nc.

In the 2 kHz background noise and at electrode site Fz, 16 participants (64%) for Na-Pa amplitude, 17 participants (68%) for Pa-Nb amplitude, 16 participants (64%) for Nb-Pb amplitude, and 21 participants (84%) for Pb-Nc amplitude demonstrated GPI or inhibition of amplitude in response to the gap stimulus. At electrode site Cz, the corresponding numbers were 15 participants (60%) for Na-Pa, 18 participants (72%) for Pa-Nb, 19 participants (76%) for Nb-Pb, and 23 participants (92%) for Pb-Nc.

The GPI values obtained from each of the four indices Na-Pa, Pa-Nb, Nb-Pb, and Pb-Nc for both background noises (8 and 2kHz) and both electrode positions (Fz and Cz) are shown in Figure 4. The GPI values for all four indices were larger in the 8 kHz background noise compared to the 2 kHz background noise.

However, the results of the Wilcoxon test showed that this difference was statistically significant for the Na-Pa index at Fz (Z=–2.16, p=0.030) and Cz (Z=–2.05, p=0.040), as well as the Pa-Nb index at Fz (Z=–2.65, p=0.008). However, it was not statistically significant for PaNb at Cz (Z=–0.55, p=0.581), and also for Nb-Pb at Fz (Z=–0.68, p=0.493) and Cz (Z=–1.17, p=0.242), and for Pb-Nc at Fz (Z=–1.44, p=0.150) and Cz (Z=–1.81, p=0.069).

Next, the GPI values for all four indices were compared between electrode locations Fz and Cz. The Wilcoxon test results showed that the GPI related to the

Table 2. Paired t-test results to compare Na-Pa, Pa-Nb, Nb-Pb and Pb-Nc amplitudes between 8 and 2 kHz background noise at Cz and Fz electrode locations, separated by gap and No gap stimulus

	Fz				Cz			
	No gap		Gap		No gap		Gap	
	t (24)	p	t (24)	p	t (24)	p	t (24)	p
Na-Pa	9.52	<0.000**	1.06	0.290	8.12	<0.000**	0.79	0.430
Pa-Nb	3.63	0.001**	1.09	0.285	2.90	0.008**	0.77	0.449
Nb-Pb	1.53	0.189	0.56	0.580	2.92	0.007**	1.57	0.129
Pb-Nc	2.86	0.008**	1.63	0.116	2.94	0.007**	0.85	0.404

* p<0.05, ** p<0.01

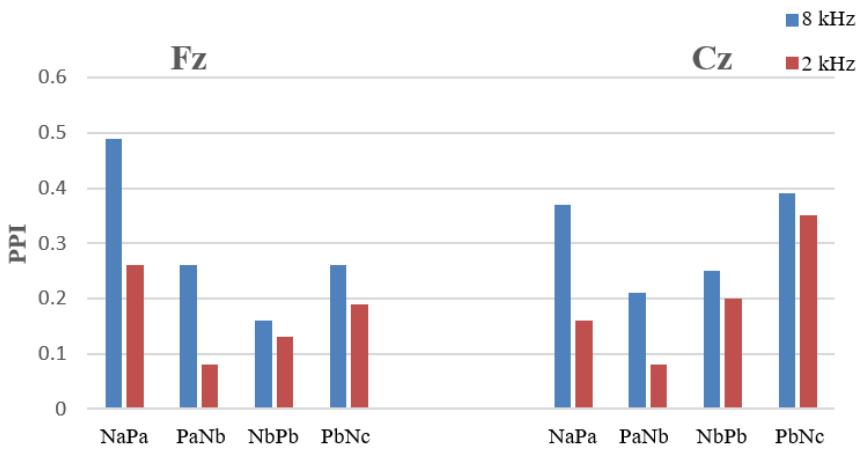

Figure 4. Comparison of the mean gap prepulse inhibition obtained from different amplitude indices, between 2 and 8 kHz background noise in Fz and Cz electrodes. PPI; prepulse inhibition

Pa amplitudes was greater at electrode Fz compared to Cz, and this difference was statistically significant for the Na-Pa index in both 8 kHz (Z=–2.57, p=0.010) and 2 kHz (Z=–2.54, p=0.011) background noises. However, for the Pa-Nb index, this difference was not statistically significant for 8 kHz (Z=–1.46, p=0.143) and 2 kHz (Z=–0.175, p=0.861) background noises. Additionally, as for the GPI related to Pb amplitudes, the GPI for both indices was greater at electrode Cz than Fz. However, this difference was not statistically significant for the Nb-Pb index in 8 kHz (Z=–1.44, p=0.150) and 2 kHz (Z=–0.175, p=0.861) background noises. On the other hand, for the Pb-Nc index, this difference was statistically significant for both 8 kHz (Z=–2.301, p=0.021) and 2 kHz (Z=–2.914, p=0.004) background noises.

Discussion

The main objective of this study was to investigate changes in the amplitude of AMLR waves in response to stimuli with gaps compared to stimuli without gaps in normal individuals. The research aimed to answer the question of whether AMLR responses could be used as a measure in the GPI method or not. To the best of our knowledge, no study has examined changes in AMLR amplitudes in the GPI paradigm in humans or animals.

In this study, in order to achieve more indices and the best index for evaluating GPI, the amplitudes of Na-Pa, Pa-Nb, Nb-Pb, and Pb-Nc were analyzed. Due to large baseline fluctuations and the difficulty in obtaining a stable baseline, the peak-to-peak criterion was used to calculate the amplitude. These large fluctuations may result from responses evoked by background noise and silent gap stimuli. Labeling of response peaks is based on our knowledge from previous electrophysiology articles and AEP waveforms recorded with common stimuli such as clicks and tone bursts (e.g., [19, 20]).

Our hypothesis was that the peak amplitudes of AMLR in individual's normal, in response to the main stimulus (tone burst) presented after a silent gap, would decrease compared to the amplitudes in response to the stimulus without a gap. As a result, we compared the amplitudes with and without gaps and found that AMLR was inhibited by a pre-pulse gap, supporting our hypothesis. The data analysis showed that the amplitude of all four indices was larger in response to stimuli without gaps, in both background noises and electrode positions, compared to the amplitude of AMLR components in response to stimuli with gaps. Although no study so far has investigated the effect of GPI in AMLR, in a study conducted by Alhussaini and et al in the year of 2018, they showed that AMLR is evoked by the stimulus of the silence gap, which confirms our hypothesis that in normal subjects, Gap is recognized as a pre-pulse [21].

In terms of inhibiting the Pb or P50 amplitude, numerous studies have introduced it as an indicator of sensory gating using the paired-click paradigm [16, 22, 23]. Additionally, if P1 can be equated to Pb, some studies in the field of GPI have reported amplitude inhibition in response to pre-pulses [24, 25]. However, the Pa amplitude has not been considered as an indicator for gating and inhibition assessment, and few studies have made reference to it [26, 27]. Given that the anatomical generators of the Pa, with midline montage, are related to thalamocortical pathways and the mesencephalic reticular formation, as well as the primary auditory cortex, the inhibition of Pa amplitudes can have associated with all three of these elements and the Raphe nucleus in the mesencephalic reticular formation, which could play a significant role in PPI [27, 28].

Then, GPI was calculated using amplitudes with and without gaps. The results indicated that the mean GPI values at both electrode sites were larger for the 8 kHz background noise compared to the 2 kHz background noise. This difference was significant for the GPI related to the Na-Pa amplitude at both electrodes and for the Pa-Nb amplitude at the Fz electrode. the Minimal Detectable Gap (MDG) decreases with an increase in background noise frequency, suggesting that auditory filtering mechanisms may have different functions at frequencies above 4 kHz and below that [29]. Moreover, in high-frequency carriers, due to non-linearity, narrower regions on the basal membrane are occupied. As a result, tuning occurs with higher intensity, creating sharper and more focused inhibition [12]. Finally, a greater perceptual separation occurs between the prepulse and background noise, and the prepulse is identified as a stronger stimulus, leading to greater inhibition and, consequently, a larger GPI [30]. On the other hand, the perceptual separation effects mentioned in the context of gap detection also apply to the main stimulus, which is a 1000 Hz tone bursts. Therefore, the 1 kHz stimulus may generate smaller amplitudes in the 2 kHz background noise compared to the 8 kHz background noise. The significant difference in the amplitudes without gaps between the two backgrounds and in both electrodes, as shown in Table 1, could be for the same reason.

Subsequently, the magnitude of GPI was compared between Fz and Cz electrodes. The results showed that GPI related to Pa amplitude in the Fz electrode and GPI related to Pb amplitude in the Cz electrode were larger, and this difference was more salient for GPI related to Na-Pa and Pb-Nc. Although the effects of electrode placement on GPI are not clearly defined, some studies have indicated that Pa amplitudes in Fz and Pb amplitudes in Cz are slightly larger, and it has been stated that these differences are not clinically significant [31] and are related to the placement, orientation, and distance of these electrodes relative to the neural generators responsible for the waves. However, ultimately, it seems that GPI related to Na-Pa and Pb-Nc amplitudes is larger and more stable in both electrodes, and may serve as a better indicator for evaluating GPI. Furthermore, the results of this study indicated that although the amplitudes and the GPI related to Pa-Nb and Nb-Pb are less stable, possibly due to the high variability of Nb [32], they might be suitable alternatives for calculating GPI in the absence of Na-Pa and Pb-Nc waves. According to the results of this study and the advantages mentioned in the introduction section for AMLR, it is suggested that in future studies, the effects of tinnitus and its pitch in the paradigm of GPI in AMLR be investigated.

Conclusion

The findings of this study demonstrated that the auditory middle latency response amplitudes decrease due to Gap Prepulse Inhibition (GPI) in response to stimuli with gaps compared to stimuli without gaps. This

inhibition was more pronounced in the high-frequency background noise compared to the low-frequency background noise. Considering the analysis of gap-related responses, this is likely because embedded gaps in the higher-frequency background noise are identified as stronger prepulses, leading to greater inhibition. Furthermore, although GPI was observed for all four indices (Na-Pa, Pa-Nb, Nb-Pb, and Pb-Nc), it appears that GPI related to the Na-Pa and Pb-Nc amplitudes creates greater inhibition in both electrode locations and is a more stable index, especially for Na-Pa in Fz and Pb-Nc in Cz.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by Ethic Committee of Tehran University of Medical Science (Code: IR.TUMS.FNM.REC.1401.101).

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Authors' contributions

HS: Study design, acquisition of data, interpretation of the results, statistical analysis, and drafting the manuscript; GM: Study design, drafting the manuscript, supervising the manuscript; MRA: Study design, drafting the manuscript.

Conflict of interest

There are no competing financial interests.

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