REVIEW ARTICLE

Applications of auditory evoked potentials in tinnitus: a review

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Abstract

Background and Aim: Subjective tinnitus is a phantom auditory perception caused by different factors and affects the patient's quality of life. The tinnitus pathophysiology is not fully understood; therefore, there is no effective treatment for tinnitus. Along with other methods, auditory evoked potentials (AEPs) may be helpful in understanding this condition and the involved structures. This study aimed to review the applications of AEPs in tinnitus studies.

Recent Findings: The studies investigating tinnitus were categorized into three groups of tinnitus pathophysiology, pre- or post-treatment/ intervention evaluation of tinnitus, and objective diagnosis of tinnitus. Contradictory and unrepeatable findings were observed in each group.

Conclusion: Discrepancies in the results of AEPs studies can be due to between-group and within-group differences, lack of proper matching in terms of tinnitus etiology and hearing loss, and difference in neurophysiologic models of tinnitus.

Keywords: Auditory evoked potentials; tinnitus; gap-prepulse inhibition; auditory brainstem response; middle latency responses; late latency response

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Introduction

Tinnitus is a subjective and involuntary sound perception in the absence of an external auditory stimulus. Different factors such as aging, ototoxic drugs, exposure to noise, and some ear diseases can result in sensorineural hearing loss (SNHL) by causing damage to cochlear hair cells and/or auditory neurons. Hearing loss can often cause tinnitus, which has significant negative effects on the patient's social interactions and quality of life [1,2]. Tinnitus is estimated to affect 12−30% of the world's population [3] and its impact on the patients' life ranges from a mild to a severe disturbance. About 2.4 million of the world's population suffer from the most severe type of tinnitus that is usually associated with sleep disturbance, depression, and anxiety [4]. Despite its high prevalence, significant economic burden, and negative impacts on the quality of life, there is no Food and Drug Administration-approved treatment options for tinnitus [1]. For treatment, it requires a complete and accurate understanding of the pathophysiology of this disorder. Damage to the peripheral auditory system is often considered as the main cause of tinnitus [5]. Studies have even shown that subjects with tinnitus and apparently normal hearing probably have minor auditory problems resulting in tinnitus [1,6]. Therefore, early tinnitus models have suggested that tinnitus occurs due to a spontaneous pathological increase in the neural

activity of the peripheral sensory receptors or auditory nerve [7,8]. However, these models are not consistent with experimental findings [9,10]. Physiological studies, using most recent imaging methods, have demonstrated that despite cochlear lesions, tinnitus results from incompatibility of the central auditory system with peripheral lesion [1,11]. In this regard, several neurophysiologic causes have been proposed for tinnitus, including tonotopic expansion/reorganization [12], enhanced neural synchrony [13], increased spontaneous activity [14], and aberrant filtering of auditory information by limbic regions [1]. Although tinnitus has a central origin, there is no consensus on generating mechanisms or locations. While central gain enhancement is observed in several auditory areas, it is not clear where this hyperactivity starts, how it is transmitted between regions, and what is the contribution of each area to the change in overall activity [1].

During auditory stimulation, the electroencephalogram (EEG) undergoes changes that are related to changes in the sound in a time-locked fashion. These simultaneous EEG changes are known as auditory evoked potentials (AEPs) which are divided into short-latency, middle-latency, and long-latency components [15]. Short-latency AEPs result from the electrical processes within the inner ear and action potentials in the auditory nerve. Other components of AEPs that are generated within the brain stem reflect action potentials and postsynaptic potentials from the auditory pathway and cochlear nuclei to the inferior colliculus [16]. Middle-latency AEPs (10−50 ms latency) are generated in the thalamus and the primary auditory cortex (AC) [17]. Finally, the long-latency AEPs (> 50 ms latency) are probably generated in the secondary AC [18]. Therefore, any changes in the stimuli, age or plasticity due to hearing loss or rehabilitation can affect the amplitude of AEPs [19]. Considering the above materials, it seems that AEPs can improve our understanding of the enhanced sounds coding as well as the physiological changes in the auditory pathways of tinnitus patients. This study aimed to review the role of AEPs in tinnitus with a focus on tinnitus pathophysiology, post-treatment assessment and follow-up, and diagnosis.

Applications of auditory evoked potentials in evaluation of tinnitus pathophysiology

Study of the pathophysiology of tinnitus may play an important role in its treatment. The most recent pathophysiologic theory of tinnitus suggest that the central nervous system (CNS) is the source or the generator of this disorder [20,21]. However, despite the importance of the central mechanisms in tinnitus, it seems that many of these mechanisms are secondary to decreased cochlear activity [22]. The central gain which was first proposed by Jastreboff [7], is another hypothesized mechanism which argues that tinnitus results from the hyperactivity or reduced inhibition in the central auditory system in response to decreased input to the peripheral auditory system [23]. Cochlear damage can lead to decrease in the neural output from the cochlea to the brain, and can potentially activate the compensatory mechanisms in the brain [24]. All of these processes can be studied histologically in rodents, but they cannot be easily observed in human studies due to difficulties in accessing the involved tissues.

The auditory brainstem response (ABR) test is one of the techniques for assessing the neural activity of the auditory pathway (from the vestibulocochlear nerve to the cochlear nuclei and inferior colliculus), and measures the synchronous neural activity along this pathway [16]. The ABR test is widely used for localizing the lesions affecting peripheral or central auditory systems [25]. Many studies investigated the ABR in tinnitus patients and reported contradictory results. Attias et al. compared ABR between 13 noise-induced tinnitus patients with hearing thresholds of 20−45 dB at the frequency range of 2−8 kHz and 11 age- and hearing-matched controls. Their results showed a significant enhancement in the amplitude of wave III in the tinnitus group with no significant difference in latency of the waves [26]. In another study, Kim et al. assessed the ABR test results of 123 tinnitus patients divided into three audiogram groups (flat, high-frequency gently sloping, and high-frequency steeply sloping). Their results showed an increase in the latencies of waves I, III, and V in the high-frequency steeply sloping group, but not in

the amplitudes of the waves. This study employed no control group [27]. Goljanian et al. Compared the ABR test results of 30 tinnitus patients with hearing loss and 30 tinnitus patients with no hearing loss (no control group), and found the prolongation of waves I and V latencies in tinnitus patients with hearing loss [28]. Although it seems that tinnitus is usually accompanied by hearing loss and is less common in subjects with normal hearing [5], few studies evaluated the ABR characteristics in tinnitus patients suffering from hearing loss; the majority of studies have been conducted on tinnitus patients with normal hearing. This may be due to prevent the known confounding effects of hearing loss on ABR [29]. Dos Santos-Filha et al. compared the ABR test results of 30 patients with noise-induced tinnitus and normal hearing and 30 controls that were matched for age, gender, and hearing thresholds. Their results showed no significant difference between the two groups [30]. Hannah Guest et al. found no significant difference in the ABR test results between 22 tinnitus patients with normal hearing and 22 controls [31]. Gu et al. compared the ABR test results of 15 tinnitus patients and 21 normal hearing subjects matched for age, gender, and hearing thresholds. Their results showed reduced amplitude of wave I and increased amplitude of wave V [32]. Schaette and McAlpine compared the ABR test results of 15 tinnitus patients with normal hearing and 18 controls and reported a decrease in the amplitude of wave I, but no change in wave V [33]. The last two mentioned studies reported that the reason for the decrease in the amplitude of wave I was the reduced output of the auditory nerve resulted directly from decreased activity of neural fibers with low spontaneous firing rates (SRs) interpreted as synaptopathy. The increased wave V amplitude in Gu et al.'s study and the unchanged wave V amplitude along with decreased wave I amplitude in Schaette and McAlpine's study was because the CNS enhanced its neural response to compensate for the reduced auditory nerve activity. The reviewed studies are summarized in Table 1. The results of review indicated that the tinnitus types had less been studied; in most of them, the etiology and psychoacoustic characteristics of tinnitus as well as hearing thresholds above 8 kHz were not reported and a control group was not used or did not properly matched with the study groups. However, changes in wave I may indicate peripheral damage, and changes in the next waves may suggest compensatory mechanisms such as enhanced neural synchrony in tinnitus. Nevertheless, changes in waves III and V amplitude may occur independent of wave I changes [29].

ABR test is also used to detect noise-induced hidden hearing loss. Exposure to excessive noise results in an excessive release of glutamate from inner hair cell (IHC) ribbon synapses that can cause inflammation and swelling of dendrites, leading to hearing loss at certain frequencies due to partial disconnection between IHCs and afferent neurons [34]. Because of the repair properties of the auditory system, the nerve endings can regrow towards sensory cells resulting in hearing restoration through re-establishing functional connections [35]. However, in some cases, despite the growth of nerve terminals, synaptic connections may remain incomplete due to ribbon loss [36]. It seems that this damage selectively affects the cochlear neurons with low activity that are responsible for high thresholds and coding of sounds with moderate to high intensities [37]. The term synaptopathy describes damage to cochlear synapses with intact hair cell populations resulting in hidden hearing loss (a functional hearing impairment with no increase in hearing thresholds) [38].

As mentioned earlier, Schaette and McAlpine [33] and Gu et al. [32] reported a similar decrease in wave I amplitude at high intensity levels in tinnitus patients with normal hearing compared to controls and due to decreased activity of auditory nerve fibers with low SRs resulting in synaptopathy. However, transient-evoked ABR may cause little sensitivity to synaptopathy in humans. Moreover, ABR amplitudes are varied and affected by factors such as head size, cochlear dispersion, and skull thickness [39-41], which can obscure the effects of synaptopathy. Bourien et al. conducted a study on gerbils and Guinea pigs exposed to ototoxic agents. Their results showed that low-SR fibers did not contribute to

Table 1. Population demographics and results in the yielded studies of auditory brainstem response in tinnitus patient

| Author (s) | Sample size | | Tinnitus etiology | Hearing thresholds | Results | |
	Tinnitus group	Control group			Latency	Amplitude
Attias et al. [26]	13	11	Noise-induced	Normal hearing (≤ 20 dB HL, frequencies: 0.25−2 kHz); Hearing loss (20−45 dB HL, frequencies: 2−8 kHz)	No differences	Enhanced wave III amplitude
Schaette and McAlpine [33]	15	18	-	Normal hearing (≤ 20 dB HL, frequencies: 0.25−8 kHz); high frequency tested (up to 16 kHz)	-	Reduced wave I, but no change in wave V
Gu et al. [32]	15	21	-	Normal hearing (≥ 20 dB HL, frequencies: 0.25−8 kHz); high frequency tested (up to 16 kHz)	No differences	Reduced wave I and enhanced wave V
Santos-Filha et al. [30]	30	30	Noise-induced	Normal hearing (< 25 dB HL, frequencies: 0.25−8 kHz)	No differences	-
Kim et al. [27]	123	-	Heterogeneous	Audiometric configurations: 1) flat, 2) high frequency gently sloping, 3) high frequency steeply sloping	Prolonged latencies for waves I, III and V in high frequency steeply sloping group	-
Guest et al. [31]	20	20	-	≤ 20 dB HL at 0.25−8 kHz	No differences	No differences
Goljanian et al. [28]	30 with hearing loss, 30 without hearing loss	-	-	Normal hearing (≤ 25 dB HL); hearing loss (20−45 dB HL)	Prolonged wave III and V for hearing-loss group	No differences

the compound action potential (CAP) equivalent to ABR wave I, and had relatively weak onset responses that limited their contribution to ABR [42]. On the other hand, low-SR fibers are better in synchronizing to amplitude-modulated stimuli compared high SR-fibers [43] and, therefore, can contribute more to subscortical envelope following response (EFR). In an animal study, Shaeen et al. used optimized EFR stimuli for the increase of auditory nerve contribution and showed that the EFR amplitude was more sensitive to noise-induced cochlear synaptopathy in rats compared to ABR amplitude [44]. In another study, Bharadwaj et al. argued that the stimuli at high intensities and shallow modulations are encoded weakly in synaptopathic ears due to the saturation of high-SR fibers and reliance on low-SR fibers. Therefore, they calculated the slope of the function relating EFR amplitude to stimulus modulation depth as an additional strategy for sensitivity enhancement [45]. Hannah Guest et al. [31] studied the relationship between

electrophysiological measures of synaptopathy and duration of noise exposure through evaluating subcortical EFRs using different modulation depths (0 dB and 6 dB) in 30 tinnitus patients with normal hearing (Mean age = 25.7 years) and 30 completely matched healthy controls. The history of lifetime noise exposure was provided using the procedure described by Lutman et al. [46]. Their results showed that the measures were associated neither with tinnitus status nor with lifetime noise exposure. They concluded that tinnitus in young adults with normal audiograms may not be related to synaptopathy, indicating other effects of noise exposure [31]. However, efforts to find measures that are sensitive to synaptopathy are ongoing. Batrel et al. invented a method known as Cochlear Mass Potentials considering the importance of low-SR fibers in speech perception in noise as well as the dynamic-range encoding and the low sensitivity of ABR wave I and CAP to decrease in these fibers [47]. However, this method requires more human and animal studies to be applicable as a potential diagnostic tool.

Despite the large number of tinnitus studies using electrophysiological tests, there were little information about auditory middle latency responses (MLRs) [48]. MLR test is an electrophysiological method that has not been frequently used for the evaluation of central auditory pathways in individuals suffering from tinnitus. There are debates over the role of cortical and subcortical auditory structures in tinnitus generation and maintenance; however, some studies used middle latency auditory evoked potential (MLAEP) in tinnitus patients to identify the structures involved in tinnitus and to diagnose tinnitus, expand available treatment options, and develop more effective treatments. Gerken et al. conducted one of the few MLR studies on tinnitus patients. They divided the patients into four groups of tinnitus (N = 9, mean age = 45.7 years), normal hearing without tinnitus (N = 11, mean age = 28 years), hearing loss without tinnitus (N = 8, mean age= 40.9 years), and older patients without tinnitus (N = 7, mean age = 63.6 years). Baseline analyses showed no significant difference in MLR results between the groups, but further

analysis showed that the MLR amplitude of 5 out of 9 patients with tinnitus (56%) had an increase by 3 standard deviations or more compared to participants with normal hearing, which was not directly related to age or hearing loss. Therefore, they concluded that there may be different types of tinnitus in the affected individuals and the MLR amplitude may be increase in some types [49]. In another study, Theodoroff et al. evaluated the MLR in 40 patients with severe tinnitus aged 20−61 years (Mean age = 50.3 years) and 40 subjects without tinnitus aged 25−65 years (Mean age = 40.5 years) as controls. Their hearing threshold was < 5 dB at 0.25 kHz and < 30 dB at 3 kHz. The results showed that although tinnitus patients were older and had more hearing loss compared to controls, there was no significant differences in the recorded MLRs between them [48]. Dos Santos Filha et al. studied the MLR of 60 participants, 30 with and 30 without tinnitus aged 27−50 years (mean age = 41 years, hearing threshold < 25 dB at frequencies 0.25−8 kHz) exposed to occupational noise (> 85 dB). The amplitude and latency of Na and Pa waves were recorded for the ipsilateral (C3/A1 and C4/A2) and contralateral (C3/A2 and C4/A1) modes. Quantitative analysis of MLAEP showed no significant difference in the amplitude and latency of Na and Pa waves between the two groups. However, their values were greater in the tinnitus group. The authors attributed it to the lack of significant within-group and between-group differences in the mean latency and amplitude of MLR components [50].

MLR test is also used to evaluate auditory sensory gating. As mentioned earlier, one of the theories about tinnitus pathophysiology is nerve fiber differentiation resulting from cochlear damage that can cause decreased inhibition in the central auditory nervous system [51]. Auditory sensory gating is a measure of inhibitory function in the central auditory nervous system. Auditory sensory gating is defined as the ability of CNS to filter irrelevant information and involves temporofrontal, hippocampal, and frontal cortical networks [52,53]. In healthy individuals, when a paired-click stimuli (Interval about 500 ms) are presented, the second stimulus usually

elicits a much smaller amplitude response for the P50 [54,55]. It seems that this mechanism is impaired in tinnitus patients [56]. Campbell et al. evaluated the auditory sensory gating in 15 patients with mild tinnitus and 18 with no tinnitus (aged 18−30 years) using cortical auditory evoked potential (CAEP) paired-tone paradigm. The hearing threshold of both groups was < 20 dB HL from 250 Hz to 8000 Hz. Their hearing thresholds were assessed at 10, 12.5, and 16 kHz. Their results showed expected amplitude suppression of P50 and reduced N1 latency for the second CAEP response in non-tinnitus adults. On the contrary, adults suffering from tinnitus showed no significant difference between the waveforms of the first and second CAEP responses, indicating the absence of typical inhibitory processes. The changes in Pa component were also analyzed in their study. The results showed a moderate correlation only between the gating difference value of the Pa component and the tinnitus handicap inventory (THI) score. Accordingly, tinnitus patients were divided to two groups with high and low suppressors. In low suppressors, the Pa amplitude increased or remained unchanged in response to the second stimulus. Therefore, they concluded that the Pa amplitude difference may act as a biomarker of tinnitus severity in this population [57]. Studies showed the role of emotional neuronal networks of the non-auditory brain areas including the prefrontal cortex, and their effect on central and peripheral circuits during tinnitus [58,59]. On the other hand, there were reports on the suppression of the Pa component in healthy people and lack of its suppression in patients with prefrontal lesions [60]. Hence, the changes in Pa component may indicate the involvement of neural relays in areas such as prefrontal cortex.

Late latency response (LLR) test is another physiological test for evaluation of the pathophysiological changes in tinnitus. From a neurophysiological point of view, tinnitus is a sound perception that occurs in cortical regions [61]. Since LLR is generated from the primary and secondary AC and beyond them, it can be used to assess the integrity of auditory system beyond the brainstem level [62]. Some studies were conducted on LLR reporting different results including increased N1 latency [63], abnormal P2 latency [64], or increased P1 amplitude [65]. Jacobson and McCaslin conducted a study to evaluate the difference in N1 potential between 31 controls (Mean age = 39 years) and 32 tinnitus patients (Mean age = 46 years). Their hearing threshold was ≤ 20 dB HL from 250 Hz to 8000 Hz and ≤ 20 dB HL from 250 Hz to 2000 Hz, respectively. Tinnitus subjects showed various degrees of hearing loss at frequencies above 2000 Hz and reported a mean THI score of 39. Both passive and selective auditory attention paradigms were used in this study. The results showed no significant difference in N1 latency between the two groups in any paradigms; however, the N1 amplitude showed a significant decrease in the tinnitus group compared to the control group, indicating adaptive brain processes in tinnitus patients. Moreover, they suggested that tinnitus, as a continuous afferent signal, may place the N1 potential generators into a relative refractory state in which they are unable to respond completely to a transient auditory stimuli, which can decrease the N1 amplitude [66]. Bramhall et al. evaluated the ABR, MLR, and LLR results of 65 participants aged 19−35 years divided to three groups of non-veterans, veterans with tinnitus, and veterans without tinnitus. The hearing threshold of all participants was < 20 dB from 250 Hz to 8000 Hz and distortion product otoacoustic emissions were normal in all subjects. Their results showed a moderate decrease in the ABR wave I amplitude in response to 4 kHz tone-burst stimuli in veterans with and without tinnitus compared to the control group, and a similar wave V amplitude in all three groups. Moreover, the MLR test showed a decrease in both veteran groups, especially those with tinnitus, compared to the control group. Click-evoked LLR was not reduced in veterans compared to non-veterans, while veterans suffering from tinnitus had significantly larger LLR. The authors argued that reduced peripheral auditory input can result in a compensatory gain in the central auditory system even in subjects with normal audiograms affecting auditory perception [67].

Some studies provided evidence for frequency-related reorganization of the AC [68]. Moreover, comparison of different brain regions between tinnitus patients and controls using electrophysiological tests showed considerable differences [69,70]. One of these differences was related to the hyperactivity of the gamma frequency range in the temporal cortex of tinnitus patients [69]. Therefore, most of the cochlear nuclei in the auditory pathway can be affected during tinnitus. It seems that these compensatory mechanisms are related to lack of GABAergic inhibition and reduced activity of specific potassium channels (Kv7.2/3) [71,72]. Therefore, it is possible that the decreased input to the auditory nerve can result in decreased synaptic transmission strength in the cochlear nucleus [73] and changes in the balance of central excitatory and inhibitory inputs, leading to hyperactivity and increased bursting and neural synchrony [74].

In general it seems that The discrepancy in AEP test results in tinnitus patients can be explained by different neurophysiological models of tinnitus perception including tonotopic reorganization of the auditory cortex [71,75], increased spontaneous firing rates of auditory neurons [76], and increased neural synchrony [77]; all resulting in changes in neural processing [49]. However, since it is believed that neural synchrony is necessary for the formation of an auditory object that transforms to a conscious perception, neural synchrony may a potential candidate for tinnitus perception [78-80].

Application of auditory evoked potentials in assessment of tinnitus treatment methods

The effectiveness of tinnitus treatment methods is usually assessed by subjective tests that are unable to accurately reflect the patient's progress [81]. In addition to the roles discussed in previous section, AEPs can be used to evaluate the effectiveness of tinnitus treatment methods. Although the neural generators of AEPs are not clearly identified, monitoring of the neural electrical activity can be an interesting method for objective assessment of tinnitus treatment methods, since a possible cause of tinnitus is neural hyperactivity in the auditory nervous system.

Based on this assumption, some studies used AEPs before and after the intervention to confirm the changes in the auditory pathways [81]. Zeng et al. conducted a study on a 46-year-old male musician with a 1.5-year history of tinnitus. The symptoms were resistant to habituation therapy and medications such as high doses of benzodiazepines, antidepressants, and other hypnotics. Despite normal hearing in the left ear (< 20 dB HL), the right ear of patient had profound idiopathic sudden SNHL. Cochlear implantation was done in the right ear to control tinnitus with electrical stimulation. After low-rate electrical stimulation (< 100 Hz) tinnitus was fully suppressed. The cortical N100 response was recorded in tinnitus-present and tinnitus-suppressed states. The results showed reduced amplitude and increased latency of the cortical N100, and increased spontaneous alpha power during tinnitus suppression compared to the tinnitus-present state as evidence for a normal cortical state [82]. In another study, Tugumia et al. evaluated the effect of auditory training on perception of tinnitus-related symptoms in 12 patients aged ≥ 18 years (six patients and six controls) with constant unilateral or bilateral tinnitus for more than two years. Participants were randomly divided into two groups, including the study and control groups. After initial electrophysiological assessments using P300, the study group underwent auditory training for eight weeks. Comparison of the test results before and after training showed that, although P300 latency decreased in the study group after auditory training compared to baseline, the difference was not statistically significant [83]. Yang et al. conducted a study to evaluate the effects of repetitive transcranial magnetic stimulation (rTMS) on the AC activities, and compare the components of AEPs before and after rTMS. Participants were 20 tinnitus patients (ten male and ten female, aged 31−60 years) and 16 healthy controls (ten female and six male, aged 20−45 years). Patients had a mild hearing loss (pure tone threshold ranged 21−40 dB HL) while the hearing threshold in controls was normal (< 20 dB HL). Event-related potential (ERP) results were compared between the two groups and also before and

after treatment for each group. The results showed a larger N1 response to target stimuli compared to standard stimuli in the control group. On the other hand, the N1 response to standard stimuli was larger in the tinnitus group before intervention compared to its response to target stimuli. This can be due to increased neural synchrony resulted from the reorganization of cortical tonotopic maps and/or weak neuronal adaptation in the temporal lobe. The tinnitus group in Yang et al.'s study showed a larger mismatch negativity (MMN) amplitude after treatment compared to pre-treatment phase and also in comparison with the control group [84]. Mahmoudian et al. conducted a study to investigate alterations in auditory change detection and auditory sensory memory related to residual inhibition (RI) induced by auditory electrical stimulation (AES) using MMN with multiple deviants in frequency, intensity, duration, location, and silent gap duration in participants with tinnitus. Participants were 28 people with tinnitus aged 22−45 years (eighteen men and ten women). Their hearing threshold was ≤ 20 dB HL from 250 to 2000 Hz, and ≤ 40 dB HL at 4 and 8 kHz frequencies. Participants were allocated randomly into groups of AES and placebo. Following AES, participants were categorized into two groups of RI and no RI. Then, MMN was recorded before and after AES and placebo electrical stimulation for all groups. The results showed that AES recovered the MMN amplitude and area under the curve for all deviations except for the gap. They concluded that the presence of RI can reestablish change-detection mechanisms in the central auditory pathways, and MMN can be a useful technique for monitoring the effects of treatments and rehabilitation [85].

Auditory evoked potentials as an objective measure of tinnitus

There is a lack of consensus on an objective test for measurement of tinnitus. Questionnaires and psychometric tests are usually used to evaluate tinnitus in clinical settings where the tinnitus severity and pitch are matched to a stimulus. The problem with these subjective methods is that,

regardless of their questionable reliability which is still a matter of debate [86], they cannot be used in patients with low behavioral or cognitive abilities, children with prelingual hearing loss, and malingerers [87]. There is also a need for objective methods in animal studies to extrapolate the animal results to humans. Turner et al. proposed the gap-prepulse inhibition (GPI) of the acoustic startle (GPIAS) reflex method for animal studies [88]. This method is elicited by presenting a startling sound following a silence gap embedded in the background noise. The silence gap acts as a predictor and produces the inhibition of the startle response. In Turner et al.'s study, the rats with salicylate-induced tinnitus showed little startle response inhibition compared to normal rats, especially when the background noise matched for the possible tinnitus frequency. Therefore, it was hypothesized that the gap was probably filled with noise and rats were unable to hear it [88]. Fournier and Hébert applied the GPIAS method on humans using the eye-blink startle reflex. Their results were similar to those of Turner et al., however, despite a high-frequency tinnitus, a lack of startle response inhibition was observed at low- and high-frequency background noises [89]. Since the neural cycle controlling GPIAS is not fully known, there are doubts about the contribution of factors other than tinnitus in this method. Moreover, this method has not been re-used correctly in humans [87]. Studies showed that AEPs can be used for monitoring gap process in stimuli with a long duration [90,91]. Accordingly, another role of AEP reported mostly in recent studies is the objective assessment of tinnitus. Ku et al. [92] conducted a study on 20 patients with constant unilateral or bilateral tinnitus (Pitch = 8 kHz) and 20 healthy subjects to evaluate the effect of tinnitus on the N1-P2 complex in the GPI paradigm. Two background noises at 8 kHz and 600 Hz were used to evaluate the effect of matching background noise with tinnitus frequency. Moreover, 20, 50, and 100 ms gap durations were used to investigate the effect of gap length before presenting the stimulus. Their results showed a decreased GPI in the N1-P2 complex for a background noise of 8 kHz (matched to tinnitus

pitch) only in the tinnitus group using a 20-ms gap. For a background noise of 600 Hz (not matched to tinnitus pitch), both groups showed decreased GPI using a 20-ms gap. This may be due to factors other than tinnitus such as intrinsic effects of low frequencies on the gap processing [93]. Ku et al. suggested frequencies above 1 kHz to minimize the intrinsic effects of background frequencies on the gap processing [92]. Berger et al. found that a gap in a continuous background noise could inhibit cortical evoked potentials to a startling stimulus in guinea pigs in a manner similar to GPIAS termed gap-induced reductions in evoked potentials (GIREP) [94]. They conducted another study on nine guinea pigs to provide an objective method for tinnitus assessment using the GIREP. In guinea pigs, the tinnitus was induced by exposure to narrowband noise (8−10 kHz) at sound levels of 105 and 120 dB SPL. The stimuli were broadband noise bursts of 20 ms duration embedded in five different background noise conditions including broadband noise and narrowband noise centered at 5, 9, 13, and 17 kHz. Gaps with 50 ms duration started 100 ms before presenting the stimulus. Evoked potentials were recorded on ipsilateral and contralateral sides of the AC using two electrocorticographic arrays. Their results showed a significant reduction in GIREP for the contralateral AC in the 120 dB exposed pigs, particularly at the noise exposure frequency (8−10 kHz) [95]. A similar paradigm of response to tinnitus frequency was observed in a study by Ku et al. [92]; however, contrary to the results of Burger et al. [94], this response occurred in a 20-ms gap which can be due to differences in the effective duration for eliciting a response between animal and human subjects [87].

Conclusion
A review of the auditory evoked potential (AEP) studies in tinnitus patients suggests that the AEP test as an electrophysiological test can be used in three areas including tinnitus pathophysiology, post-treatment evaluation and follow-up, and objective diagnosis. The studies have reported different results; although many of them have found differences between tinnitus and non-tinnitus patients, there is a lack of reproducibility. The discrepancy in AEP test results in tinnitus patients can be explained by different neurophysiological models of tinnitus perception However, it seems that, neural synchrony may a potential candidate for tinnitus perception. Another reason for discrepancy in the results of studies investigating AEPs in tinnitus may be the difference in selecting and screening subjects based on tinnitus etiology and severity, lack of attention to matching for gender, age, and degree of hearing loss, and the difference in stimulation paradigms and acquisition parameters. Although the AEP test is an accessible, non-invasive low cost method, more in-depth studies are needed before recommending it as a potential clinical diagnostic tool in tinnitus studies.

Conflict of interest
The authors declared no conflicts of interest.

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