ORIGINAL ARTICLE

Brainstem auditory evoked potential: an analysis of central gain in adults with chronic tinnitus

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ABSTRACT

Objective: To evaluate whether the presence of chronic tinnitus alters the amplitudes and wave III/I and V/I ratio responses in the Auditory Brainstem Evoked (ABR) with click stimulus in young adults. **Methods:** This was an analytical, cross-sectional, and quantitative study. The sample included individuals aged 19 to 30 years, divided into two groups: the study group, comprising individuals with chronic tinnitus, and the control group, consisting of typical individuals. The evaluation included the following procedures: anamnesis, basic audiological assessment, transient otoacoustic emissions, behavioral assessment of central auditory processing, and ABR-click. **Results:** A total of 51 ears were included in the study, with 25 ears in the study group and 26 ears in the control group. Significant differences were observed between the groups only for wave I amplitudes, which were higher in individuals with tinnitus. Additionally, the study group exhibited higher average responses for wave I/III ratios and lower averages for wave V/I ratios. **Conclusion:** Chronic tinnitus leads to increased wave I amplitude and altered wave III/I and V/I ratios in ABR-click assessments. These findings suggest a promising analytical approach, potentially indicative of increased central gain.

Keywords: Tinnitus, Evoked potentials, Adults, Central nervous system, Brainstem.

INTRODUCTION

Chronic tinnitus is an otological symptom characterized by the perception of sound in the absence of an external acoustic stimulus. This condition affects more than 740 million adults worldwide and negatively impacts quality of life[1,2]. Thus, conducting detailed audiological evaluations, such as high-frequency audiometry, electroacoustic measurements (otoacoustic emissions), and especially electrophysiological assessments, is crucial for optimizing its management. These evaluations address the need to investigate the central auditory nervous system in this population[3].

Recent studies have shown that tinnitus is frequently observed in individuals with alterations in their auditory thresholds. However, there are also reports of its occurrence in individuals with normal hearing thresholds[4]. Several theories have been proposed to understand the pathophysiology of tinnitus. One of these is the central gain model, which focuses on neural deafferentation mechanisms and suggests that minor changes in input to the auditory pathway lead to widespread alterations across various regions of the central auditory nervous system (CANS)[5,6]. It is believed that these changes can induce a reorganization of neuroplasticity in the auditory pathway, in-

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creasing its neural responsiveness to compensate for reductions in peripheral auditory input. This leads to an increase in spontaneous neural activity, which is considered the primary neurophysiological mechanism underlying the generation of tinnitus[7].

According to the central gain theory, individuals with chronic tinnitus experience alterations in neuroelectric function within the CANS and reorganization of the cortical tonotopic map. There is thalamo-cortical hyperactivity and increased neural synchrony. This central gain model is the most widely accepted hypothesis for explaining the perception and persistence of the symptom[7,8].

To investigate the underlying mechanism of tinnitus, some studies have used Auditory Brainstem Evoked (ABR) with click stimuli in individuals with tinnitus perception. Findings in the specialized literature indicate a reduction in wave I amplitude, presumably due to a decrease in neural fibers, as well as a change in the relationship between the amplitude of wave I and wave V. This demonstrates an increase in neural responsiveness at the level of the lateral lemniscus, reflecting central gain in the higher regions of the brainstem[6,9]. One study suggests that the relationship between the amplitudes of the waves can be used as a reliable metric to objectively identify tinnitus and as a biomarker for neuroelectric changes in central plasticity resulting from different treatments[9].

The present study aims to use ABR-click to investigate the responses of the CANS by analyzing the wave amplitudes. Thus, the goal is to determine whether this exam can be used as a potential tool for diagnosing individuals with tinnitus. Additionally, this study is justified by the lack of research with more stringent methodological controls that use ABR-neurodiagnosis with the parameters adopted in this research, as well as those that exclude individuals with central auditory processing disorders, thus accurately measuring central gain at different levels of the brainstem without the influence of other variables.

In this research, the objective is to analyze the amplitude of the waves and the relationships between waves III/I and V/I in the ABR-click of young adults with and without the perception of chronic tinnitus.

METHOD

Study design

This was an analytical, cross-sectional, and quantitative study carried out in accordance with resolution Nº. 466/12 and approved by the Human Research Ethics Committee under protocol number 56038322100005346.

The eligibility criteria were: aged between 18 and 30 years, pure tone auditory thresholds within normal ranges (250 to 8000Hz), normal mobility of the tympanic-ossicular system (type A tympanometric curves), presence of contralateral stapedial acoustic reflexes at normal levels[10], integrity in cochlear functioning (presence of Transient Otoacoustic Emissions), and normal synchrony of the auditory pathway at the level of the brainstem bilaterally. For both groups, the exclusion criteria were the use of continuous medication (including people undergoing pharmacological treatment for tinnitus), occupational noise exposure, complaints of dizziness, objective tinnitus or evidence of a vascular component (pulsatile tinnitus), as well as overt or diagnosed neurological, psychiatric, or cognitive impairment. It is important to note

that individuals with a SARS-CoV-2 infection were not included.

Participants

The sample consisted of research participants selected by convenience at the audiology clinic of the Federal University of Santa Maria, during the period from July 2021 to May 2022. Young adult individuals of both sexes participated in the study and were divided into two groups:

- Control Group (CG), composed of typical individuals without the perception of tinnitus.
- Study Group (EG), composed of individuals with complaints of subjective chronic tinnitus, that is, those with continuous tinnitus perception for more than 6 months[8].

Procedures for sample composition

All participants underwent a semi-structured anamnesis, basic audiological assessment (tonal audiometry - 250 to 8000 Hz, speech audiometry, and immittance measures, tympanometry, and contralateral acoustic reflex testing), and transient otoacoustic emission (TOAE).

TOAEs were recorded with the Intelligent Hearing Systems (IHS) using a non-linear click stimulus, with a window of 20 ms, 1024 stimuli, at an intensity of 80 dBSP. Up to 15% of artifacts were accepted, provided the screening protocol showed normal outer hair cells (that is, a response at 3 of the 5 evaluated frequencies – 1, 1.5, 2, 3, and 4 kHz – at a signal/noise ratio > 3 dB[12]. A neurodiagnostic ABR was then performed on all subjects[13].

We also performed central auditory processing tests[14]. The following tests were performed: Frequency Pattern Test (FPT), Masking Level Difference (MLD)[16], Dichotic Digit Test (DDD), Speech-in-Noise Test (SIN) (ipsilateral competitive noise at a S/N ratio of +5 dB[17], and a monaural Gap In Noise (GIN) test[18]. Such evaluations were selected with the aim of achieving the minimum suggested test battery, according to the recommendations of the Brazilian Academy of Audiology[19]. In the CG, individuals needed to show, in addition to normality in the aforementioned assessments, normal responses in the V/I wave amplitude ratio[15].

All behavioral tests were carried out in an acoustically treated cabin, using supra-aural headphones (Telephonics TDH39), a two-channel audiometer (Interacoustics AD629B) connected to a notebook.

Search procedure

To compare the two groups, ABR neurodiagnosis was performed. The aim was to record central gain in terms of the amplitudes (in microvolts) and ratios of waves III/I and V/I in young adults who had no audiological alterations. To record potentials, participants were seated in a comfortable chair and instructed to keep their eyes closed throughout the capture. Before the examination, the skin was cleaned with gauze and abrasive paste, and the electrodes were fixed using conductive paste and adhesive tape.

The electrophysiological evaluation was carried out using the SMART-EP equipment from IHS, in which the electrodes were attached following the 10–20 stan-

dard established by the International Electrode System (IES) (2016)[20]. Thus, the active electrode was placed in the fronto-polar region along the midline (Fpz), the ground electrode at the midline of the frontal region (Fz), and the reference electrodes on the right (A2) and left (A1) earlobes. Intra-aural headphones (EAR-Tone ER•3C) were used. The impedance of the electrodes was maintained below 3 kΩ and the interelectrode impedance below 2 kΩ. Two scans were performed for each ear, accepting a maximum of 10% of artifacts[13].

The parameters used for the neurodiagnostic ABR are set out in Table 1.

Table 1. Parameters used for the acquisition of ABR clicks, following Webster (2017).

type of stimulus	click
stimulated ear	RE/LE (monaural)
stimulus intensity	80 dBHL
presentation	27.7/sec
polarity	rarefaction
sweep	2048
high pass filter	100 Hz
low pass filter	3000 Hz
gain	100K
analysis time	12 ms

Key: RE: right ear; LE: left ear; dBHL: decibel hearing level; sec: seconds; Hz: hertz; ms: milliseconds.

The auditory pathway synchrony was considered normal when the latency of waves I, III, and V, their interpeak intervals I–III, III–V, and I–V, and the interaural difference of wave V latency were within normal limits (2 standard deviations), as suggested by Webster[13]. For the measurement of the ratios of waves III/I and V/I, the amplitudes of waves I, III, and V were marked (i.e, from the peak of the wave to the next valley, as shown in Figure 1).

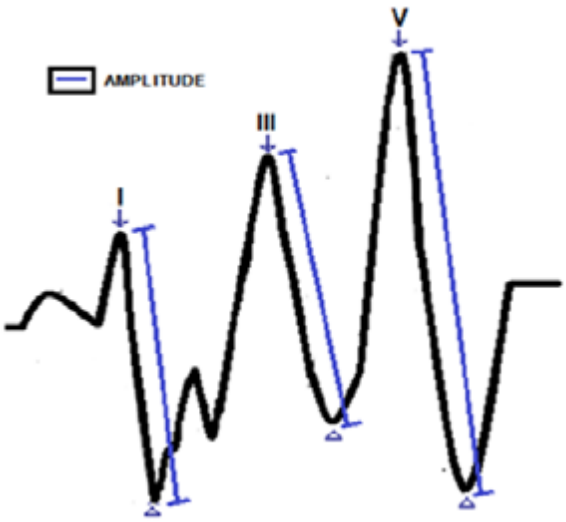

Figure 1. graphic representation of wave amplitude marking

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 21.0 for Windows. For sample size calculation (number of ears required for the study), a confidence level of 0.05, a margin of error of 0.5, and a standard deviation of 0.99, as observed in the V/I ratio of a previous study[11], were used, which required a total of 22 ears per group. After data collection, the data were entered into an Excel spreadsheet for statistical analysis. The normality of the variables was assessed using the Shapiro-Wilk test. Subsequently, a Mann-Whitney U test was applied to check for data homogeneity, as well as to compare the amplitudes of waves I, III, and V and the ratios of waves III/I and V/I for ears with and without tinnitus. A significance level of 5% (i.e., $p<0.05$) was adopted for comparison and statistical differences between the groups.

RESULTS

A total of 63 individuals were tested during the available collection period. Of these, 33 individuals were excluded: 23 due to alterations in the central auditory processing tests, 1 due to sensorineural hearing loss, 2 due to isolated frequency hearing loss, 2 due to middle ear alteration (type C tympanometric curve), 1 due to the perception of pulsatile tinnitus, 2 due to retrocochlear alteration (absence of wave I in the ABR), and 2 due to not returning to finalize the evaluations.

As a result, the sample consisted of 30 individuals. Considering the presence of unilateral tinnitus, the analysis performed for both groups was by ear, i.e., ears with tinnitus and ears without tinnitus. Thus, due to the presence of unilateral tinnitus, there were differences between the groups regarding the total number of ears included in the study.

Sample Analysis

For the control group (CG), 13 right ears and 13 left ears were included, totaling 26 ears. For the study group (EG), 12 right ears and 13 left ears with tinnitus were included, totaling 25 ears in this group. It is noteworthy that among the subjects in the EG with subjective tinnitus, 10 perceived it in both ears, accounting for 20 ears with tinnitus, 3 perceived it only in the left ear, and 2 perceived it only in the right ear.

In the analysis of the sample variables related to age (CG = 22.77, EG= 26.66; p-value = 0.457) and sex (CG = 6 men and 20 women, EG= 10 men and 16 women; p-value = 0.197), no statistical differences were observed between the groups.

Analysis of the Research Procedure

When comparing the amplitudes of waves I, III, and V, as well as the III/I and V/I ratios between right and left ears, no statistically significant differences were observed for both the CG and EG (Table 2). Therefore, the right and left ears were grouped together for subsequent comparisons.

Table 2. Comparison between typical and tinnitus groups for amplitudes and relations of waves III/I and V/I in ABR between ears.

ABR CG	Variables	Ears	*n*	Mean	Median	Mín	Max	DP	*p*-value
(μV)	amp I	RE	13	0,33	0,27	0,08	0,70	0,18	0,369
		LE	13	0,27	0,24	0,08	0,65	0,14	
	amp III	RE	13	0,27	0,23	0,08	0,48	0,14	0,281
		LE	13	0,21	0,22	0,08	0,37	0,09	
	amp V	RE	13	0,45	0,48	0,19	0,66	0,13	0,411
		LE	13	0,45	0,46	0,19	1,00	0,19	
	ratio III/I	RE	13	1,04	1,00	0,25	2,05	0,64	0,626
		LE	13	0,85	0,77	0,40	1,70	0,37	
	ratio V/I	RE	13	1,66	1,51	0,78	2,91	0,63	0,898
		LE	13	1,58	1,55	0,63	2,34	0,46	

ABR EG	Variables	Ears	*n*	Mean	Median	Mín	Max	DP	*p*-value
(μV)	amp I	RE	12	0,33	0,31	0,04	0,51	0,13	0,586
		LE	13	0,35	0,38	0,09	0,52	0,11	
	amp III	RE	12	0,30	0,21	0,07	0,61	0,19	0,957
		LE	13	0,28	0,27	0,05	0,63	0,15	
	amp V	RE	12	0,47	0,48	0,21	0,72	0,13	0,288
		LE	13	0,41	0,39	0,19	0,67	0,15	
	ratio III/I	RE	12	1,17	0,90	0,30	3,75	1,00	0,463
		LE	13	1,28	1,28	0,13	2,33	0,55	
	ratio V/I	RE	12	1,73	1,51	0,91	4,82	1,01	0,082
		LE	13	1,23	1,20	0,56	2,18	0,43	

Key: CG = Control Group; EG= Study Group; RE= Right ear; LE: Left ear; μV = microvolts; n = number of ears; Min = minimum; Max = maximum; SD = standard deviation; Statistical analysis was performed using the Mann-Whitney U test.

In comparisons between all ears with and without tinnitus, it was found that there was a significant difference only for the amplitude of wave I (Table 4). However, the qualitative analysis of the averages stands out, from which it was possible to observe higher wave III/I ratios for the EG.

Table 4. Total comparison between groups for the amplitudes and relationships of waves III/I and V/I in ABR.

ABR	Variables	Groups	*n*	Mean	Median	Mín	Max	DP	*p*-value
(μV)	amp I	CG	26	0,29	0,26	0,08	0,70	0,16	**0,044***
		EG	25	0,33	0,34	0,04	0,52	0,12	
	amp III	CG	26	0,24	0,23	0,08	0,48	0,12	0,402
		EG	25	0,29	0,26	0,05	0,63	0,17	
	amp V	CG	26	0,45	0,47	0,19	1,00	0,16	0,932
		EG	25	0,43	0,46	0,19	0,72	0,14	
	ratio III/I	CG	26	0,94	0,78	0,25	2,05	0,52	0,231
		EG	25	1,22	1,25	0,13	3,75	0,78	
	ratio V/I	CG	26	2,54	1,53	0,63	2,91	0,54	0,107
		EG	25	1,47	1,40	0,56	4,82	0,79	

Caption: CG = control group; EG = study group; μV = microvolts; *n* = total number of ears; SD = standard deviation; Min = minimum values; Max = maximum values; * = Statistically significant difference; Statistical analysis by Mann–Whitney *U*-test

When the amplitudes and the amplitude ratios of the waves were plotted, it showed that wave III amplitudes and wave III/I ratios were greater for the EG (Figure 2).

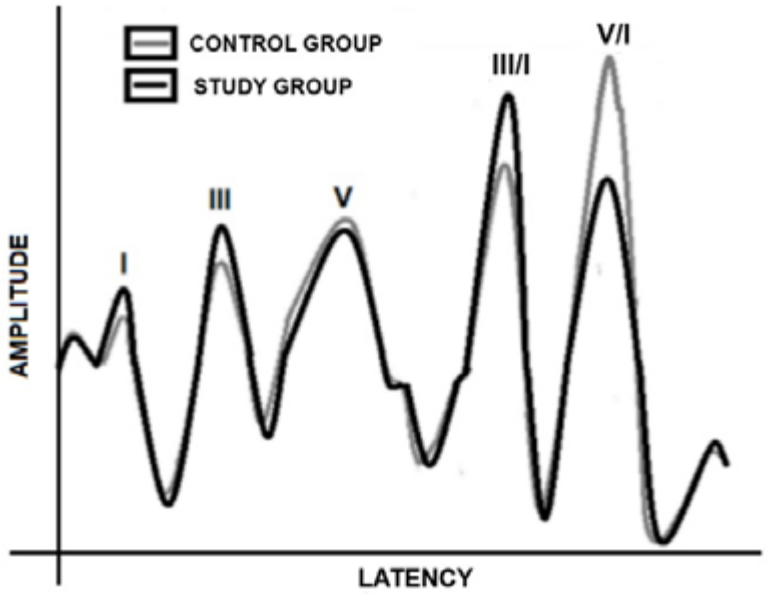

Figure 2. graphic representation of findings between groups

DISCUSSION

The trends of the present study are in agreement with the literature[3,6,9]. The current theory is that the central gain in patients with subjective tinnitus is elevated, and this is supposed to underlie the pathophysiological mechanism which generates the symptom[7]. In our work it was possible to observe similar changes in ABR amplitude and wave ratios in individuals with chronic tinnitus.

Recent research has shown changes only in ABR latency in individuals with chronic tinnitus[21,22]. Based on the theory of increased central gain in this population, it also seems important to analyse the amplitudes and ratios of waves III/I and V/I in ABR. It seems that these parameters can be modified by a number of neural components which are activated by stimulation and synchronization between them[7]. Thus, our findings suggest it might be possible to measure changes in the auditory pathway resulting from tinnitus, and that such an analysis might be useful to demonstrate an increase in neural responsiveness[9].

In the present research, reduced wave I amplitudes were not observed in the EG, but statistically significant differences between the groups, with higher means for individuals with chronic tinnitus, corroborating a recent study[11] that also observed similar amplitudes. These findings are justified by the possibility that these subjects may exhibit reduced amplitudes of wave I, as its limited clinical applicability as a biomarker for the symptom has already been demonstrated, due to the high variability in response[22]. Thus, these individuals may exhibit changes in the amplitudes of waves III and V, which can occur independently of changes in wave I[11,21]. Based on these findings, it becomes possible to infer that the compensations found at the brainstem level are not necessarily due to the loss of neural fibers of the 8th cranial nerve, but probably due to the presence of chronic tinnitus[11].

Recent studies have shown that the amplitude ratio of waves V/I can be used as a promising analysis for assessing central gain in individuals with chronic tinnitus[9,11,22,23]. However, for such compensations, it is necessary to analyze the amplitude of wave I, that is, it is important to observe if the increase in neural responsiveness comes from the reduced output at the level of the VIII cranial nerve or if this occurs due to the increase in neural recruitment in the brainstem structures[24]. In this context, in the present study, only an increase in the mean responses of the amplitude ratio of waves III/I and decreases in the mean responses of the ratio of waves V/I were evidenced, evidencing a greater neural responsiveness at the level of the cochlear nucleus. It can also be inferred that this is not due to a reduction in peripheral auditory input (wave I with larger amplitudes), but rather as a result of the presence of the symptom, which causes an increase in neural responsiveness in this region.

In the analysis of the wave ratios, although no statistically significant differences were observed between the groups, higher mean responses were observed in the amplitude ratio of waves III/I for the EG. These findings corroborate recent studies, which reported an increase in the amplitude ratio of waves III/I, a decrease in the ratio of waves V/I, as well as a reduction in symptom perception with the use of drugs that were used with the objective of inhibiting a subgroup of neurons in the cochlear nucleus, which demonstrated that it plays a significant role in tinnitus maintenance[4,25,26].

Thus, such findings demonstrate that individuals without reduced output of the auditory nerve have greater neural responsiveness at the level of the cochlear nucleus and that this neural increase decreases at higher levels of the brainstem, as a result of compensations in the previous stages of the auditory pathway.

Chronic tinnitus in young adults, with preserved peripheral auditory acuity, seems to present changes in central gain as a pathophysiological mechanism, which makes it possible to characterize it as a neuroplasticity disorder[4,25]. In addition, recent animal model studies have observed a possible influence of the cochlear nucleus and glutamatergic interneurons in the cerebellum on the persistence of the symptom. This is justified by the difficulties in synaptic remodeling that occur in the gain modulation circuit[27,28]. Thus, the influences of this structure on the perception of the symptom are observed, through the increase in neural responsiveness at the beginning of the brainstem, which are maintained due to the way the individual reacts and registers such perception.

Taking all of the above into account, the findings of the present study point to the importance of wave amplitude. This measure goes beyond those of latency, interpeak intervals, and interaural differences in patients with chronic tinnitus[21]. It is possible that the amplitude values and, perhaps, the ratios of waves III/I and V/I, could provide a clear clinical differentiation when evaluating this population. If so, this would help us understand the pathophysiological mechanisms involved in tinnitus, and direct clinical management towards possible interventions. The idea is to employ auditory rehabilitation so as to neuroplastically reorganize the auditory pathway, with the ultimate aim of remission of symptoms[29].

Study limitations

Finally, we emphasize the need to carry out more studies along the same lines as done here, with a larger and more representative sample so as to confirm the results. At the same time, peripheral auditory acuity and the efferent pathway should also be investigated using high frequency audiometry, distortion product otoacoustic emissions, and suppression, the aim being to rule out cochlear synaptopathy and possible hidden hearing losses at supra-threshold levels. Such changes affect cochlear integrity, and can cause subtle changes in auditory inputs and neural responsiveness in order to compensate for reductions in peripheral auditory information[30,31].

CONCLUSION

Chronic tinnitus results in an increase in the amplitude of wave I and in the ratio of waves III/I and V/I in ABR-click, in young adults (ages 20 to 30). Thus, this analysis is promising, as it may demonstrate an increase in central gain.

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Contributions from each author:

HGM, DRT participated in data collection, as well as in the conception of writing the article

VCM participated in the general review and writing of the manuscript, as well as updating its literature

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