European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):136-144.
https://doi.org/10.58600/eurjther1925

Original Research

Investigation of the Effect of Tinnitus and Hearing Loss on Hippocampus Volume

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Received: 2023-11-10 **Accepted:** 2024-02-24 **Published Online:** 2024-02-25

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ABSTRACT

Objective: This study aims to compare hippocampal changes with a correlation of audiological testing results in patients suffering from tinnitus.

Methods: Patients diagnosed with tinnitus in the university hospital between February 2021 and March 2022 were prospectively included in the study by performing magnetic resonance imaging. The volume was determined by manually tracing the hippocampus' margins on the images using the Vitrea2® workstation (Canon Medical Systems Vital Images, Minnesota, USA). Statistics were used to assess the correlation between the parameters of the hearing test.

Results: The distribution of the patient group (21 males, 19 females) and control group (15 males, 15 females) was uniform, and the mean ages of the two groups were 50.23±12.09 and 32.30±7.97, respectively. Significant statistical differences existed in the mean ages of the groups ($p<0.05$). Bilateral hippocampal volumes, right bone, and air conduction all differed significantly ($p<0.05$). The median values in the patient group were as follows: right HC 2620 mm3 (range 1600-3610), left HC 2450 mm3 (range 1610-3990), right air conduction 20 dB (range 10-61), left air 21 dB (range 11-65), and right bone 13.5 dB (range 8-49). Age was positively correlated with bilateral measurements of air and bone hearing levels (p 0.05; right air r=0.513, right bone r=0.438, left air r=0.589, left bone r=0.487). Between the 30-39 and 60-69 age groups, there was a significant difference in bone and air conduction levels ($p<0.05$).

Conclusion: In this study, it was found that the hippocampus volumes of healthy hearing people with tinnitus complaints were significantly higher in MRI examinations compared to the control group. In addition, in cases of tinnitus accompanied by bone conduction hearing loss, hippocampus volumes were found to be less than those of tinnitus alone, but not less than in the control group. It is suggested that chronic acoustic stimulation caused by tinnitus causes an increase in hippocampus volume and that problems in sensorineural integrity prevent this increase.

Keywords: Hearing loss, Hippocampus, Magnetic resonance imaging, Tinnitus, Volume

INTRODUCTION

Tinnitus is one of the most prevalent hearing disorders defined by the perception of a sound, such as a voice or noise, when there is no external sound origin. It is experienced by 17% of the general population and 33% of the elderly [1, 2]. An estimated 1% of the adult population suffers from tinnitus annually, of

which a severe form affects 2% of individuals and all adults experience tinnitus. There is no evidence that the prevalence of tinnitus varies between the sexes; nevertheless, it does increase with age (10 percent of young adults, 14 percent of middle-aged people, and 24 percent of the elderly) [3]. Tinnitus is a social challenge in aging populations.

Symptoms can be acute (within <3 months) or chronic (typically <12 months). It appears to be linked to hearing loss in many cases, as both symptoms frequently coexist. Approximately ninety percent of chronic tinnitus sufferers also have hearing loss. High-frequency hearing loss is frequently correlated with high-pitched tinnitus [1, 4, 5].

Several factors, including age, medications, head or neck trauma, otological problems, and general medical conditions (hypertension, cardiovascular disease, and Meniere's disease), have been implicated in the development of tinnitus. Nevertheless, exposure to loud noises is believed to be the primary cause of hearing loss [1].

Numerous studies have established a close association between tinnitus and both maladaptive neuroplasticity and attention-cycle disorder. According to functional neuroimaging studies, several regions beyond the central auditory system, including the frontal cortex, parahippocampus, insula, cerebellum, and thalamus, have been implicated in tinnitus perception and accompanying suffering. Also, recent studies have found that subcortical nuclei such as the amygdala, thalamus, hippocampus, insula, and basal ganglia exert a significant influence on tinnitus [6-10].

Functional imaging research has identified specific regions within the limbic system (hippocampus) and central auditory pathway (auditory cortex, medial geniculate body) that exhibit activity in patients experiencing somatic tinnitus when they adjust the volume of the phantom sound by moving their face, jaw, or upper torso. Somatic tinnitus appears to arise from somatosensory system invasion of deafened auditory cortical areas. It has also been demonstrated that tinnitus sufferers have a considerable loss in hippocampus gray matter. It has also been demonstrated that in the tinnitus group, subcortical and cortical auditory areas, as well as sound detection regions (posterior insula, hippocampus), respond with decreased, rather than increased, blood oxygenation level-dependent (BOLD) activity [4, 11].

Main Points:

- Tinnitus patients had significant hippocampal changes compared to non-tinnitus patients.
- Tinnitus caused a significant increase in hippocampal volume.
- Hearing loss reduces hippocampal volume, which rises with tinnitus.

The importance of the hippocampus in learning, memory formation, and spatial navigation has been the subject of much research [12]. Nonetheless, because it receives information from the thalamus and auditory cortex, the hippocampal region is also intimately linked to the auditory system [13]. Due to these connections, the hippocampus can perform vital functions linked to auditory processing, such as differentiating sounds, integrating auditory data with other sensory inputs, and creating memories associated with auditory events [14]. According to research, the hippocampus is involved in the creation of episodic memories that are related to specific auditory cues [15]. Numerous cognitive deficiencies, such as issues with memory formation, spatial navigation, and auditory information processing, can result from hippocampal dysfunction. Volumetric changes in the hippocampus and its subdivisions, which play an important role in the formation and retrieval of memories, have been associated with epilepsy, Alzheimer's disease, and other disorders [16]. For these reasons, the hippocampal region seems important for auditory and cognitive activities.

Magnetic resonance imaging (MRI), which has a very important place in soft tissue examination, is one of the primary tools used to examine the brain in the diagnosis and monitoring of various neurological and psychiatric diseases. MRI, which enables detailed examination and measurement of structures of different sizes in the brain with different sequences and examination options, provides clinicians with highly accurate and reliable information in monitoring the progression of diseases and monitoring their response to treatment. In this context, MRI-based measurement methods are of great importance for clinical and research purposes in brain diseases [17].

This study aims to investigate the correlation of clinical and audiological data and radiological findings in patients diagnosed with tinnitus and compare hippocampal volumetric changes in tinnitus.

MATERIALS AND METHODS

Ethical Consideration

The non-interventional clinical research ethics committee of the medical faculty approved the study protocol (a prospective case-control study, permission number: 2021.141.05.14). All patients reviewed and signed the informed consent form. The people participating in the study were treated in accordance with the 1964 Declaration of Helsinki and its amendments.

Study Population

Patients aged between 18-65 years and diagnosed with tinnitus between February 2021 and March 2022 were prospectively included in the study by performing MRI.

Patients were categorized into groups including: 1) control group (n=30), without tinnitus and/or hearing loss (0-25 decibels hearing level; dBHL), 2) tinnitus group (n=25), without hearing loss (0-25 dBHL), and 3) mild-to-moderate hearing loss associating tinnitus group (n=15, 26-60 dBHL).

Hippocampus (HC) volumes and hearing test metrics, including bilateral assessments of air and bone conduction, were compared between groups.

Inclusion and Exclusion Criteria

Patients aged 18-65 years, who had audiometric tests and MRI of optimum quality, were included in the study. Patients with previous surgery, trauma history, and malignancy were excluded.

The study subjects comprised individuals who presented with sensorineural hearing loss and an air-bone gap of less than 10 dB.

Image Ocquisition

MR images were obtained using T1-weighted imaging (WI), T2-WI, FLAIR, and postcontrast-T1-WI 3D Cube sequences on a 1.5 Tesla device (GE Healthcare Signa, Philips Ingenia) using a receive-only, eight-channel, phased-array head-neck coil.

Scan Parameters

- 3D Cube T1-WI parameters: TR (repetition time), 600 ms; TE (effective echo time) 29 ms; flip angle 8; matrix size 250x250; 1 mm slice thickness; NEX 1 and 250 mm FOV.
- 3D Cube FLAIR parameters: TR 4800 ms; TE 306 ms; TI (inversion time), 1660 ms; flip angle 90; echo-train length 125; matrix size 250x250; slice thickness 1 mm; FOV 250 mm and NEX 1.
- 3D Cube T2-WI parameters: TR 2800 ms; TE 275 ms; flip angle 40; matrix size 250x250; slice thickness 1 mm; FOV 250 mm and NEX 1.
- 3D Cube Postcontrast T1-WI: The same parameters used as T1-WI. MRI contrast material (Gadoterate meglumine, 0.1 mmol/kg, intravenous injection rate 2-3 ml/sec) was used for evaluation.

Postcontrast T1-WI MR images were employed in the assessment and reconstruction of the 3D hippocampus volume (Figure 1).

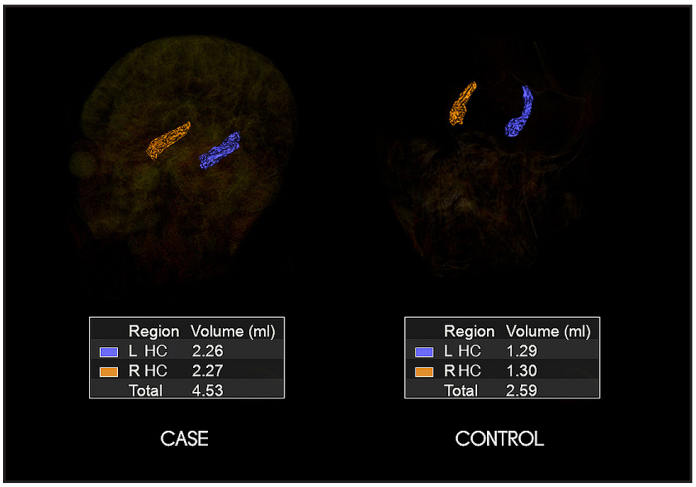

Figure 1. 3D reconstruction images show bilateral hippocampal volumes of case and control groups (HC: hippocampus).

Measurement and Imaging Analysis

The volume and segmentation were determined by manually tracing both hippocampus margins on the MR images with the Vitrea2 ® workstation (Canon Medical Systems Vital Images, Minnesota, USA). Volume and segmentation were determined by manual tracing of both hippocampus edges on MR images with the Vitrea2 ® workstation (Canon Medical Systems Vital Images, Minnesota, USA). The segmentation and measurement procedures were performed by a highly experienced radiologist and an anatomist in accordance with the scientific method based on mutual consultation and current studies in the literature.

The selection process for segmenting the anatomical borders of the hippocampus followed the methodology outlined by McHugh et al. [18] (Figure 2). In the presence of mammillary bodies in the coronal slice, which served as a demarcation line between the amygdala and the hippocampus, the anterior boundary of the

hippocampus was delineated. Defined at the section where the fornix appeared as a continuous tract, the posterior demarcation was established. The inferior horn of the lateral ventricle was encompassed within the gray matter-described superior border of the hippocampus. By means of the collateral white matter of the parahippocampal gyrus, the inferior border was developed. The segmentation process additionally included the subiculum and uncal sulcus.

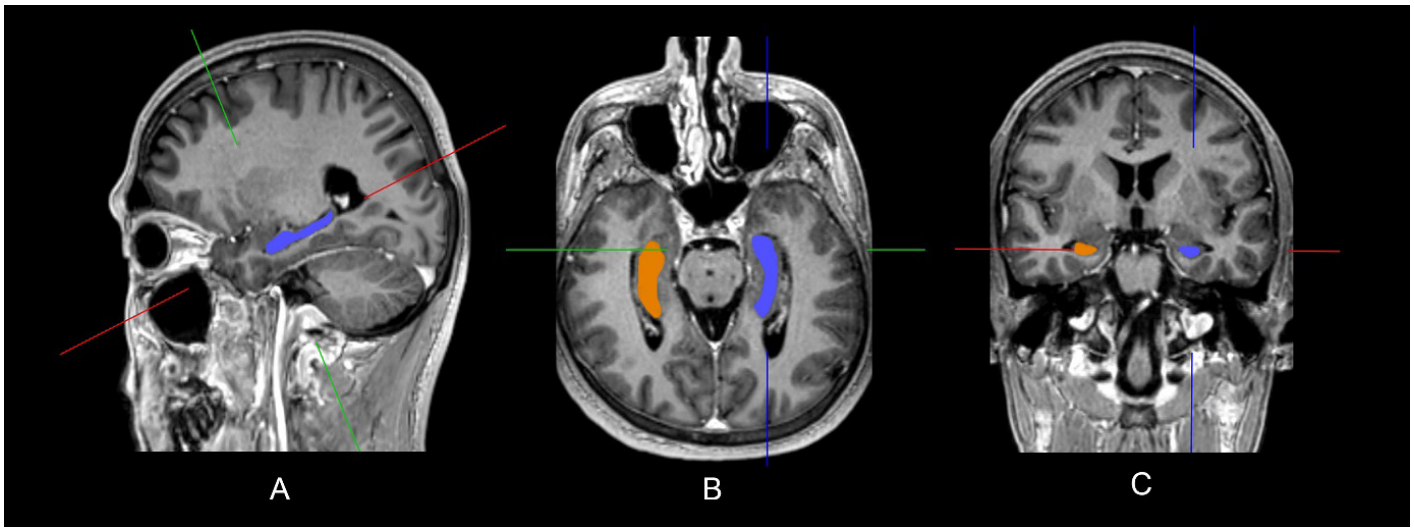

Figure 2. Multiplan demonstration of determined hippocampus borders in the long axis on the MR images.

Pure Tone Audiometry (PTA)

All participants underwent PTA as well. The same audiometrist conducted the operation in accordance with international standards using a two-channel audiometer (Interacoustics A/S, Denmark). For each ear, thresholds for frequencies ranging from 250 Hz to 8 kHz were examined. The average PTA thresholds were calculated from threshold levels of 500, 100, and 2000 Hz. A diagnosis of auditory dysfunction was made for individuals whose hearing threshold exceeded 25 dBHL [19].

Statistical Evaluation

The statistical analysis was conducted utilizing version 18.0 of SPSS. To determine whether the data were normally distributed, the Kolmogorov-Smirnov normality test was applied. In the process of evaluation, parametric or non-parametric tests were employed. In order to analyze demographic data, including marital status, age, and gender, descriptive tests were utilized. To compare groups with normally distributed data, the independent sample T-test was applied; for non-normally distributed data, the Mann-Whitney U test was utilized; and for categorical data, the chi-square test was applied. The correlation study utilized the Pearson test to assess the distribution of normally distributed data and Spearman's rho test to investigate data that was not normally distributed. P was set at a level of statistical significance below 0.05.

Statement

The authors employed a paraphrasing technology (QuillBot AI) to paraphrase the text while writing this paper. After utilizing this tool/service, the authors examined and modified the text as needed and accepted full responsibility for the publication's content.

RESULTS

The gender, age, hippocampal volume (HV), and hearing test results of the participants in the study are summarized in Table 1. The difference in mean age between the groups was statistically significant ($p<0.05$). HVs and hearing test metrics, including bilateral assessments of air and bone conduction, were compared between groups. Bilateral HVs and mean air-bone metrics differed significantly ($p< 0.05$).

Age was positively correlated with bilateral measurements of air and bone hearing levels ($p< 0.05$; right air $r=0.513$, right bone $r=0.438$, left air $r=0.589$, left bone $r=0.487$). Between the 30-39 and 60-69 age groups, there was a significant difference in bone and air hearing metrics ($p<0.05$, Figure 3).

A statistically significant difference was found between the control group (0-25 dBHL) and patients with tinnitus – without hearing loss (cases, 0-25 dBHL), and patients with tinnitus and

hearing loss (26-60 dBHL) in the comparison of air level and bilateral HVs ($p<0.05$, Figure 4).

There was a statistically significant difference between the control group (0-25 dB) and the patients with tinnitus without hearing loss (cases, 0-25 dBHL) in the comparison of bone level metric and both HV ($p<0.01$). In the comparison of the control group (0-25 dBHL) and patients with tinnitus and hearing loss (26-60 dBHL), the bone level metric and only the right HV were found to be statistically significant ($p<0.01$, Figure 4).

Although HVs increased compared to the control group, in bone level metrics HVs showed a decrease among the tinnitus groups (Figure 4). In the patient group with hearing loss, the air-bone gap was 6.5 dBHL on average.

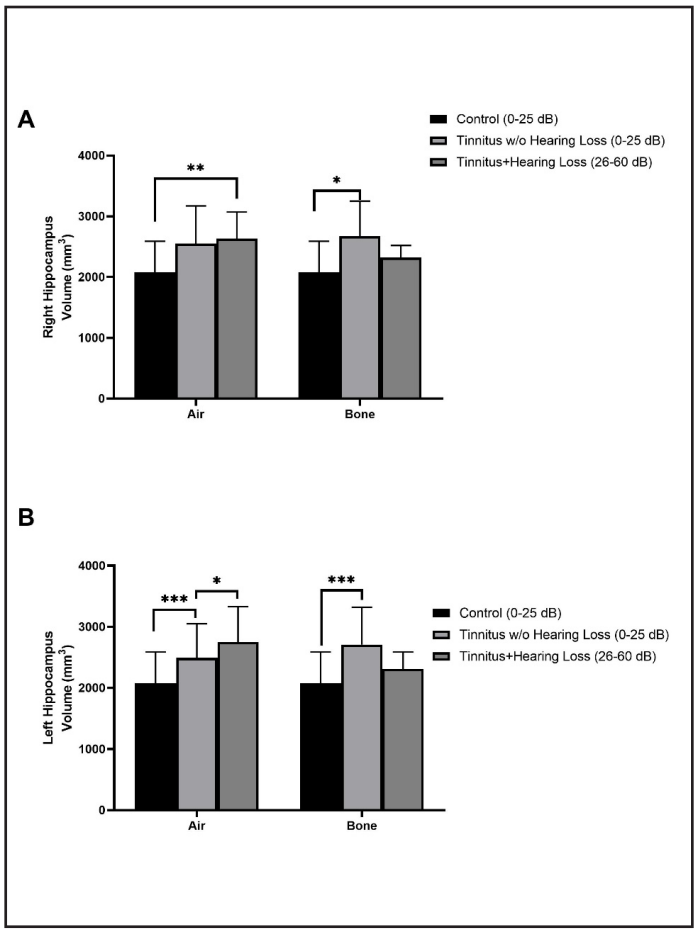

Figure 4. Hippocampal volume changes in the control group and tinnitus patients based on hearing loss groupings with air and bone conduction (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$).

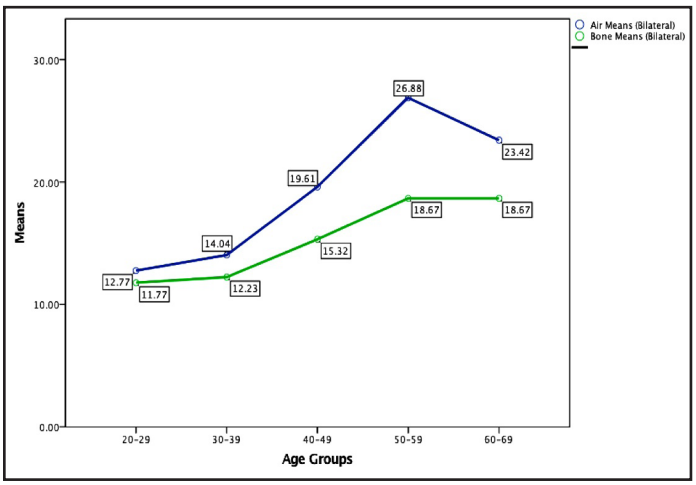

Figure 3. A significant difference in bone and air hearing metrics between the 30-39 and 60-69 age groups ($p<0.05$).

DISCUSSION

Tinnitus has a significant negative impact on patients' lives (emotional distress, cognitive dysfunction, social withdrawal, and impaired work performance) [20, 21], and the disease's causes and treatments are still unknown [22]. However, neurological approaches to the etiology of tinnitus have expanded the scope of tinnitus research [23]. The integrity of the complete hearing system, from the external ear to the auditory brain, is evaluated using air conduction testing. Bone conduction testing evaluates the sensorineural structures' integrity (cochlea, eighth nerve, brainstem nuclei, and relays to the auditory cortex). The integration of these two assessments enables the doctor to classify the patient's hearing as being within the expected range by utilizing essential physiological data [24].

The hippocampus, which is located in the temporal lobe of the central nervous system where hearing is processed, is assumed to play a role in the processing of auditory input, episodic memory, spatial navigation, and their reflection on actions [25, 26]. Noise exposure and tinnitus, for example, have been found to have an effect on hippocampal development and function [27]. Hearing loss and dementia are also investigated in the context of the hippocampus-auditory process link [28].

Tinnitus patients' left hippocampus was shown to be smaller than the control group paired for hearing loss [29]. Hippocampal surface area, on the other hand, was adversely connected negatively correlated with tinnitus handicap inventory scores which is specifically designed to evaluate the effect of tinnitus

in daily life and to document the results of tinnitus treatment by Newman et al. [7]. The right and left hippocampus volumes in both the patient and control groups were found to be the same in our investigation, and the difference between the two sides identified in prior studies was not seen in the current study.

The increased connection between the hippocampus and auditory cortex is related to louder tinnitus percepts and longer tinnitus duration in resting-state fMRI studies [8, 30]. It appears that, as compared to the control group, the left hippocampus is a key essential structure in chronic tinnitus patients [31].

In the study conducted by Tae et al. [7], a non-significant increase in left hippocampus volume was observed in patients with tinnitus (n=53) compared to the age and sex-matched control (n=52) group (3.67±0.46 ml and 3.57±0.47 ml, respectively), while a very small non-significant decrease in right hippocampus volume was observed (3.80±0.50 ml and 3.84±0.55 ml, respectively). Another study found that tinnitus increased the volume of the hippocampus and amygdala while hearing loss had no effect on the volume of either region. However, it has been noted that the duration and severity of tinnitus have no effect on this volumetric change. It is stated that the lateralization is primarily on the right side [32]. As a result of the region of interest analysis conducted in another study, a significant decrease in gray matter concentration in the left hippocampus was reported [6]. In the current study, both hippocampi volumes were shown to be higher in patients with tinnitus than in the control group. This also demonstrates that the HVs may show variation depending on the region and country. The findings of this study revealed that HVs were higher in the tinnitus-only group compared to control group patients, but HVs were lower in the tinnitus group with hearing loss. We suggest that chronic acoustic stimulation caused by tinnitus causes an increase in hippocampus volume and that problems in sensorineural integrity prevent this increase. The review by Zhang et al (2022) discusses possible mechanisms that may support this hypothesis and is recommended for those who want to have detailed information [33].

In the comparison with the literature, the mean HVs showed variation between 3076 ± 472 mm^3 (minimum) and 3573 ± 630 mm^3 (maximum) (Supplementary Table 1). The mean HV in the current study was 2304 ± 599 mm^3 which shows the variation in HV according to the regions and populations.

Tinnitus is exacerbated by age, which causes cortical thinning and the most significant changes in the frontal and temporal cortices (hippocampal areas) and deeper structures (putamen, thalamus, nucleus accumbens). Aging causes changes in many brain areas that aren't directly related to age-related sensory degeneration (presbycusis, presbyopia) [34, 35]. After average hearing loss was taken into account, it was discovered that age had a negative link with the gray matter volume of the bilateral amygdalae, hippocampi, nucleus accumbens, and thalami. Hearing loss was substantially associated with bilateral nucleus accumbens and thalamus volume, but not with amygdala or hippocampus volume [36]. In the current study, tinnitus showed a positive correlation with increasing age.

Table 1. Shows the age of participants, hippocampus volume, and hearing test metrics.

Parameters	Subgroups	Control	Tinnitus without Hearing Loss	Tinnitus with Hearing Loss
Age (years)	All	32.30±7.98	47.12±12.47	53.33±8.67
Gender	Male	15	13	8
	Female	15	12	7
Bone conduction (dB)	Right	11.53 ± 1.69	11.28±2.44	24.47±10.58
	Left	11.70 ± 1.78	12.04±2.30	24.67±12.86
Air conduction (dB)	Right	11.73 ± 1.66	14.68±3.95	35.80±12.97
	Left	11.73 ± 1.61	16.64±4.83	36.80±13.30

Mean values are provided.

Limitations

The limitations in the current study can be listed as being a single-center study, the number of patients admitted during the study period is limited, and low voluntary participation in the study is low. Another issue with our study is that the total volume measurement values we acquired from the MR imaging system and the software we utilized for the measurement were low in comparison to other studies in the literature. The reason for this is assumed to be connected with slice thickness and post-processing, which can be corrected by a variety of formulas. To retain the data's authenticity, the results obtained from measurements taken under identical conditions were compared. There is no reason to be concerned about the reliability and accuracy of our data in the present situation.

CONCLUSION

In conclusion, tinnitus induced a substantial increase in bilateral hippocampi volume, and the hearing loss that accompanies tinnitus generated a less significant increase in patients suffering from tinnitus alone compared to the control group. Future research should look into whether the hippocampus volume increase, which we believe is caused by tinnitus, regresses with the emergence of hearing loss, or whether these two factors, which occur concurrently, restrict the increase in volume.

Acknowledgments: None.

Conflict of interest: No conflicts of interest are disclosed by the authors.

Acknowledgments: None.

Conflicts of interest statement and funding: The authors declare no competing interests.

Institutional ethics review committee's approval: Tekirdag Namık Kemal University, Faculty of Medicine, Non-interventional clinical research ethics committee, Approval No: 2021.141.05.14.

Authorship Contributions: HS: Conceptualization, Design, Supervision, Materials, Data collection and processing, Analysis and/or Interpretation, Literature review, Writing, Critical Review. MO: Analysis and/or Interpretation, Literature review, Writing. TE: Conceptualization, Design, Materials, Data collection and processing, Critical Review.

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How to Cite;

Sasani H, Ozkan M, Ersozlu T (2024) Investigation of the Effect of Tinnitus and Hearing Loss on Hippocampus Volume. 30(2):136-144. Eur J Ther. https://doi.org/10.58600/eurjther1925