Thalamus, Hippocampus, Amygdala in Patients With Chronic Subjective Tinnitus: Volume Analysis

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Abstract

Background and Purpose: This study aimed to investigate the relationship between the existence and degree of chronic subjective tinnitus of unknown origin and the volumetric size of thalamus, hippocampus, amygdala.

Methods: 100 patients who complaint of chronic subjective tinnitus applied to …. Hospital between 01.01.2020 and 31.12.2021 were included in the study. With volBrain system, thalamus, hippocampus and amygdala was measured. THI was performed on all patients and scores and grades were recorded. According to THI, patients were divided into 5 groups as Slight, Mild, Moderate, Severe, and Catastrophic.

Results: Of the 100 patients participating in the study, 56 (56%) were female and 44 (44%) were male. The ages of the patients ranged from 20 to 72, with a mean of 45.52. Tinnitus Handicap Inventory (THI) was performed and their scores and degrees were checked. Scores range from 12 to 88, with an average of 47.44. Catastrophic tinnitus is statistically significantly higher in patients whose hippocampus, thalamus, amygdala volume/total brain volume ratio is less than the normal range for their age group ($p<0.001$). When the amygdala, thalamus and hippocampus volumes of patients with tinnitus were compared with the data of healthy patients in the volbrain system, they were found to be statistically significantly lower (respectively $p<0.001$, $p=0.039$, $p=0.001$).

Conclusion: There is a need to focus more on additional neuropsychiatric assessment scales and volumetric measurement methods in patients with chronic subjective tinnitus and to elucidate unknown points in the etiopathogenesis of tinnitus

Main Points

- The volumetric dimension of thalamus, hippocampus, amygdala are closely related to the existence and degree of tinnitus in patients with chronic subjective tinnitus of unknown cause.
- More anatomical, radiological, functional studies are needed to clearly elucidate the etiopathogenesis of chronic subjective tinnitus
- A multidisciplinary approach should be used for the patients with chronic subjective tinnitus

Introduction

Tinnitus is the perception of a ringing or non-metallic sound coming from the head or ears in the absence of an external auditory stimulus. Tinnitus is a symptom (not a disease) and therefore reflects an underlying abnormality [1]. In studies conducted in various parts of the world, it affects people at percentages ranging from 8–22% [2–5]. Most often, tinnitus is associated with a sensorineural hearing loss, but tinnitus types such as pulsatile tinnitus, tinnitus with vertigo, fluctuating tinnitus or unilateral tinnitus should be investigated thoroughly [1]. Tinnitus can be caused by some reasons; *Otological, Neurological, Traumatic*, *Other medical comorbidities* (hypertension, diabetes, rheumatoid arthritis),

Psychological, Lifestyle, *Ototoxic medications* [6] or it may also present as *idiopathic tinnitus* for which no organic cause can be found by anamnesis, physical examination, laboratory and imaging methods [7]. Further references to tinnitus in this article pertain to tinnitus of the subjective type, which is by far the most common type of tinnitus [1].

Subjective tinnitus is the result of the brain's response to a lack of input from the auditory environment. In the healthy auditory system, there is a regular tonotopic frequency map from the auditory environment (cochlea) throughout the midbrain to the auditory cortex. When a region of the cochlea is damaged, the subcortical and cortical projections adapt to this chronic lack of output (plasticity) and the tonotopic organization changes. After cochlear injury, neurons in the auditory pathway show 2 important changes: an increase in spontaneous firing rate and an increase in the frequency representation of neurons bordering the injury site [8].

These findings are explained by a) loss of central inhibition in the damaged areas and b) cortical plasticity of the still active adjacent areas of the cortex. Therefore, the neurophysiology of tinnitus is associated with deleterious cortical adaptation to the deprivation of input from the sensory periphery [8].

It is thought that tinnitus may be associated with mood and emotional stress in patients with normal audiological examinations. The role of the limbic system, which has functions such as mood, memory, and processing of received signals, in tinnitus is emphasized. It supports various functions such as emotion, behavior, long-term memory, and smell. The limbic system, which has a primitive structure, is involved in the sequential emotional processing of input from the sensory systems and consists of the amygdaloid nucleus complex (amygdala), mammillary bodies, stria medullaris, central gray and dorsal and ventral nuclei of Gudden.[1] Brain functional changes can be observed in the case of tinnitus, in the limbic system organs, especially in the amygdala. The organization of the tonotopic map of the cerebral cortex may also change. Some researchers have advocated the creation of new tonotopic maps in the case of chronic tinnitus. The changes in the central nervous system in tinnitus patients were similar to the changes in the central nervous system in chronic neuropathic pain patients [1, 8, 9].

Our aim in this study is to investigate the relationship between the volumetric dimension of thalamus, hippocampus, amygdala with the existence and degree of tinnitus in patients with chronic subjective tinnitus of unknown cause.

Materials And Methods

100 tinnitus patients who applied to …. Hospital between 01.01.2020 and 31.12.2020 were included in the study. All of the patients applied with the complaint of chronic subjective tinnitus. Otoscopic examination of the patients was normal. Patients with a pure tone mean of 20 dB or less in the audiometry test were included in the study. Complete blood count, biochemistry parameters, thyroid function tests, iron panel, lipid panel, vitamin 12 and folic acid levels were within normal limits. None of the patients participating in the study had a psychiatric disorder or a history of psychiatric drug use. All patients underwent Temporal

Computed Tomography (CT), Temporal Magnetic Resonance Imaging (MRI), Brain MRI and Diffusion Brain MRI examinations. All examination and anamnesis information, CT and MRI results were recorded.

The volBrain system automatically calculated whether the ratio of the thalamus, hippocampus, amygdala volumes to the total brain volume was among the reference values according to the patients' age group and gender. We did not need a control group because the volBrain program uses its own database and compares with patients.

The Tinnitus Handicap Inventory (THI), which was created by Kuk et al. [10] in 1990 and adapted into Turkish by Aksoy et al. [11] in 2007, score was the sum of the 25 answers where a weight of 4 was given to the answer “Yes,” a weight of 2 to the answer “Sometimes,” and a weight of 0 to the answer “No.” Thus, the range of scores was between 0 and 100, where 100 was the maximum score that could be obtained for the sum of the 25 questions. Levels of handicap are estimated as follows: Grade 1 – slight handicap (THI 0–16), Grade 2 – mild handicap (THI 18–36), Grade 3 – moderate handicap (THI 38–56), Grade 4 – severe handicap (THI 58–76), Grade 5 – catastrophic (THI 78–100): Ability to carry out a normal life is seriously impaired. THI was performed on all patients and scores and grades were recorded. According to THI, patients were divided into 5 groups as Slight, Mild, Moderate, Severe, and Catastrophic.

Informed consent were obtained from patients who participated in clinical investigations.

Approval was obtained for the study from the … Clinical Research Ethics Committee (Meeting Number: 70, Decision Number: 1148, Date: 18 Nov 2020).

MRI Examination

Brain MRI images of the patients included in the study were obtained on the Philips Ingenia 1.5 T (Eindhoven, Netherlands) device. The parameters used are T1WI FOV: 24x24 cm, TE 3.4 ms, TR 7.3 ms; T2W FOV: 24x24 cm, TE 245 ms, TR 1500 ms, FLAIR: FOV 23x24 cm, TR 11,000 ms, TE140 ms, Slice 4 mm, Gap 1mm.

Volumetric and Segmentation Reporting

A compressed T1WI dataset in NIFTI (Neuroimaging Informatics Technology Initiative) format was uploaded to the online MRI-T1WI system at www.volbrain.com (VolBrain version 1.0 for whole-brain segmentation and HIPS version 1.0 hippocampus segmentation). When automated processing is complete, a PDF report is generated with volumetric data on gray matter, white matter, CSF and subcortical gray matter, and hippocampus segmentation. We validate NIFTI files for all cases using ITK-SNAP Version 3.4.0 software. When the process was finished, we were notified by email so that we could download a package containing some image files and two reports that collect all the volumetric values calculated from the segmentations. The report also includes several snapshots of different labeling results as quality control. All volumes are presented as an absolute value (measured in cm3) and relative value. The volumes of the thalamus, hippocampus, amygdala were measured. In each patient, the ratio of

these regions to their brain volumes and whether this ratio was within the reference values according to their age-sex group were examined (classified as normal, less, or more according to the reference values).

With volBrain system, the intracranial cavity; tissue volumes; brain, cerebellum, and brainstem volumes; the volumes of the lateral ventricles and subcortical structures (putamen, caudate, pallidum, thalamus, hippocampus, amygdala, and nucleus accumbens) can be measured [12]. The volBrain system is an online system, and after uploading the data you have to the system, it can quickly give you the volume of the desired brain region in a few steps **(fig. 1,2)**

Image Analysis

The traditional assessment was done using Philips ISP (Intellispace portal) for primary reporting. Patients with a mass, cyst, previously operated on extensive ischemic sequelae in conventional brain MRI examinations were not included in the study.

Statistical analysis

In the study, summary statistics of categorical variables were given in terms of frequency and percentage, while mean ± standard deviation was used for continuous variables. The conformity of the continuous variables to the normal distribution was tested with the Shapiro-Wilk and Kolmogorov Smirnov tests. The Chi-square test was used for the analysis of categorical variables. An independent t-test was used for the variables in the independent structure with two groups. In cases where the number of groups was more than two, a one-way analysis of variance was used together with Bonferroni's post-hoc analysis. The statistical significance level (p-value) of the study was determined as 0.05. Analyzes were made using the Statistica 13 package program.

Results

Of the 100 patients participating in the study, 56 (56%) were female and 44 (44%) were male. The ages of the patients ranged from 20 to 72, with a mean of 45.52.

Thalamus, amygdala, hippocampus values measured by the volbrain system; The thalamus volume of the patients ranged from 7-12.24 cm^3, and the mean volume was 9.23 cm^3. The thalamus volume/total brain volume ratio ranged from 0.55–0.83%, with an average of 0.68%. The hippocampus volume of the patients ranged between 3.87–10.51 cm^3, and the mean volume was 7.40 cm^3. The hippocampus volume/total brain volume ratio ranged from 0.26–0.66%, with an average of 0.55%. The amygdala volume of the patients ranged between 0.48–2.14 cm^3, and the mean volume was 1.31 cm3. The amygdala volume/total brain volume ratio ranged from 0.03–0.15%, with an average of 0.10%.

Accordingly, the volumetric ratio of the thalamus was found to be normal in 48 (48%) patients and less than normal in 52 (52%) patients. The volumetric ratio of the hippocampus and amygdala was normal in 76 (76%) patients, less than normal in 20 (20%) patients, and more than normal in 4 (4%) patients.

Tinnitus Handicap Inventory (THI) was performed and their scores and degrees were checked. Scores range from 12 to 88, with an average of 47.44. The grades were Slight in 16 (16%) patients, Mild in 24 (24%) patients, Moderate in 20 (20%) patients, Severe in 20 (20%) patients and Catastrophic in 20 (20%) patients.

Catastrophic tinnitus is statistically significantly higher in patients whose hippocampus, thalamus, amygdala volume/total brain volume ratio is less than the normal range for their age group ($p < 0.001$). When the amygdala, thalamus and hippocampus volumes of patients with tinnitus were compared with the data of healthy patients in the volbrain system, they were found to be statistically significantly lower (respectively $p < 0.001$, $p = 0.039$, $p = 0.001$) (Table 1).

Table 1
THI Grade and Variables

	THI Grade					
Variables	Sligth	Mild	Moderate	Severe	Catastrophic	P Value
Age	48,00 ± 9,77	37,83 ± 16,75	43,20 ± 11,00	50,00 ± 10,78	50,60 ± 5,01	0.002
Patient's Thalamus Volume	9,12 ± 1,43	9,49 ± 1,62	9,17 ± 0,77	8,62 ± 1,22	9,08 ± 1,85	0.039
Patient's Thalamus Volume / Total Brain Volume	0,64 ± 0,06	0,69 ± 0,08	0,71 ± 0,07	0,68 ± 0,04	0,70 ± 0,04	< 0.001
Patient's Hippocampus Volume	8,71 ± 0,84	7,06 ± 2,09	8,07 ± 0,80	6,78 ± 1,72	6,73 ± 2,24	0.001
Patient's Hippocampus Volume/Total Brain Volume	0,61 ± 0,03	0,52 ± 0,15	0,62 ± 0,03	0,53 ± 0,12	0,50 ± 0,17	< 0.001
Patient's Amygdala Volume	1,49 ± 0,17	1,03 ± 0,40	1,45 ± 0,33	1,29 ± 0,46	1,39 ± 0,16	< 0.001
Patient's Amygdala Volume/Total Brain Volume	0,11 ± 0,01	0,08 ± 0,03	0,11 ± 0,02	0,10 ± 0,03	0,10 ± 0,02	< 0.001

Discussion

The idea that the thalamus, amygdala, hippocampus play a role in hearing and studies emphasizing this is a relatively new situation. The amygdaloid complex, a subunit of the limbic system, is associated with processing important information that crosses the threshold for emotional impact. This effect can be auditory stimuli. The amygdala is closely related to several behavioral functions, psychiatric disorders, and related tinnitus. The hippocampus, which is in contact with the limbic system, is known to play a role in learning and the formation of new memories. It has been shown that hippocampal synaptic integrity is also impaired by hearing loss and hippocampal neurogenesis is reduced by acoustic trauma. Like the

amygdala, the hippocampus responds to sound directly or indirectly from a variety of inputs. There are direct connections from the hippocampus to the auditory cortex, as well as to the primary A1 (auditory region 1) region, which is involved in the formation of long-term auditory memories. The hippocampus is also indirectly linked to the auditory cortex. It also has indirect connections through the anterior medial cortex, insula, and amygdala [1]. Patient with idiopathic chronic subjective tinnitus was included in our study. The volumes of the thalamus, amygdala, hippocampus of these patients were measured with the volBrain system.

In a study conducted by Chen et al. in a year with patients with right-sided chronic tinnitus, connections from the right amygdala and hippocampus to hearing-related or other unrelated areas such as the superior temporal gyrus were observed with functional MRI [13].

Seydell et al., it was emphasized that while hearing loss is associated with the loss of neuronal connections in the auditory pathway, tinnitus may be associated with an increase in signaling in the neuronal pathway in the auditory and limbic systems [14]. In the study of Sedley et al., an increase in signal was detected in the limbic system and auditory cortices in patients describing intracranial tinnitus in an EEG-like study [15].

Tae et al. showed that patients with right-sided tinnitus suffered from atrophy in the basal and lateral nuclei of the right-sided amygdala compared to controls. In patients with reduced limbic regional volume compared to the normal population; They are more prone to tinnitus or certain auditory pathologies [16].

Neuroimaging studies using connectivity modalities such as resting-state fMRI (functional MRI) and diffusion MRI continue to reveal tinnitus-related abnormalities in the auditory, limbic, and other brain systems [17]. Leaver et al., when viewed with fMRI, tinnitus patients showed a higher fMRI signal, especially in the nucleus accumbens, compared to controls. When the sounds of tinnitus frequencies were given, this signal difference became more evident. No signal difference was detected in patients with tinnitus compared to control patients, including the MGN (medial geniculate nucleus) in the auditory cortex in the masked analysis. This showed that auditory transmissions returned to normal when the tinnitus was suppressed externally. Overall, their data suggest that both auditory and limbic regions are involved in tinnitus, and interactions between the limbic corticostriatal network and the primary auditory cortex may be key to understanding chronic subjective tinnitus [18].

Qu et al., ABR (Auditory Brainstem Response) was performed in mice with tinnitus and the rhythm of the 1st and 5th waves and the ratio of these waves were examined. They found an abnormal connection between the limbic system and the auditory cortex on the 28th day in noise-induced tinnitus. In tinnitus mice, 1st wave with decreased amplitude and 5th wave with increased amplitude were observed [19].

Ouyang et al., Manganese Enhanced MRI data revealed a bilateral increase in activity along the auditory pathway and certain limbic regions of rats with tinnitus compared to age-matched controls. In addition, anxiety symptoms were also observed in patients with blast-induced tinnitus. Taken together, our data

suggest that blast-induced tinnitus may play a role in auditory and limbic hyperactivity, while the non-auditory effects of blast and potential traumatic brain injury may also affect [12].

The limitations of our study are that all subunits of the limbic system were not evaluated in the volBrain system and there was no healthy control group without tinnitus.

Conclusion

In our study, we found that the amygdala, hippocampus and thalamus volumes in bilateral idiopathic chronic subjective tinnitus patients were smaller than the normal population, and they were significantly smaller in patients with catastrophic tinnitus according to THI, compared to patients with less complaints.

Declarations

Ethics approval and consent to participate

Informed consent were obtained from patients who participated in clinical investigations. Approval was obtained for the study from the … Clinical Research Ethics Committee (Meeting Number: 70, Decision Number: 1148, Date: 18 Nov 2020).

Consent for publication

Not applicable.

Availability of data and materials

All data and material are in accordance with standards and can be shared.

Competing interests

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Authors' contributions

All authors contributed equally to this work.

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Figures

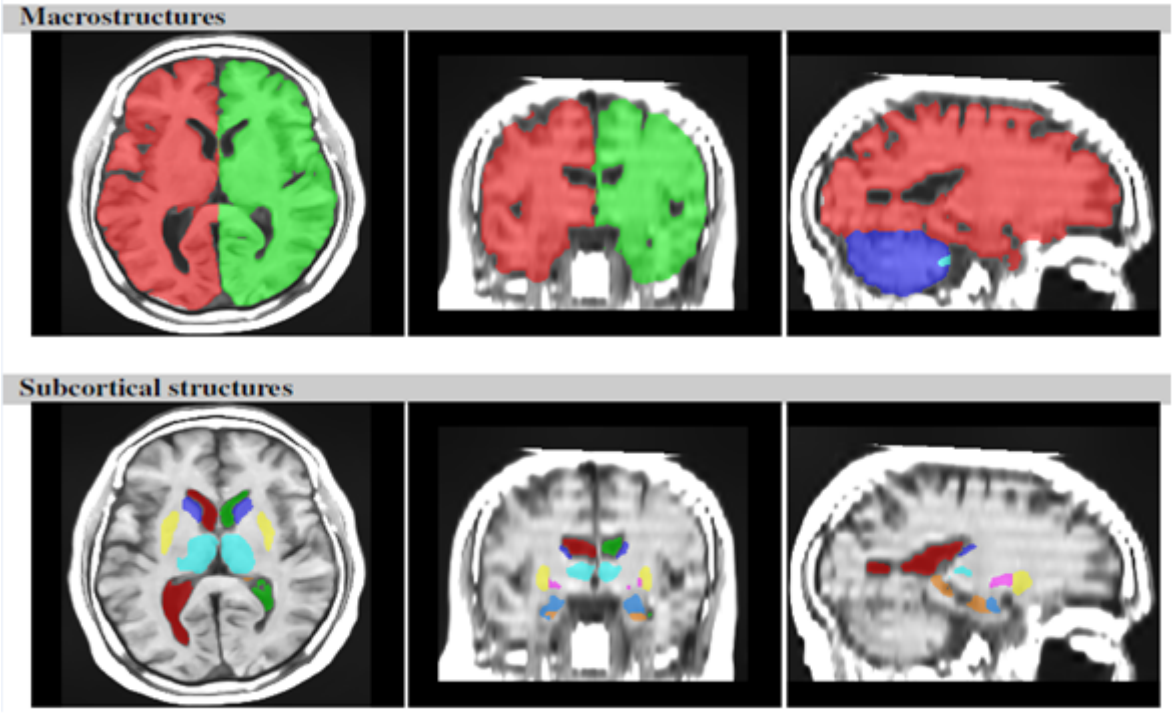

Figure 1

volBrain And Brain

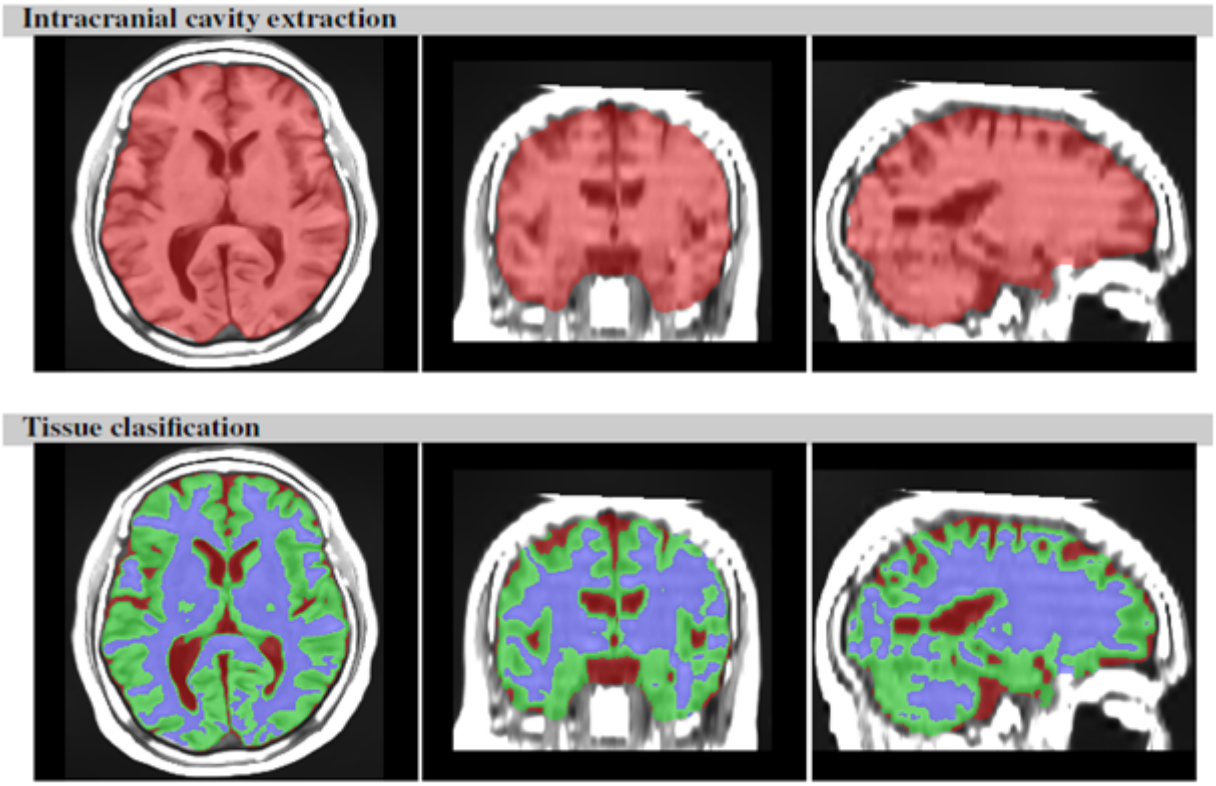

Figure 2

volBrain and Volumetric Calculation