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Quantitative analysis of white matter brain changes in tinnitus patients with normal hearing: a case-controlled study with diffusion tensor imaging

Amira Eltabbakh^{1*} and Nashwa Nada²

Abstract

Background This research aimed at assessing the white matter microstructural (WM) brain changes in tinnitus patients with bilateral normal peripheral hearing using diffuse tensor imaging to test whether, tinnitus alone without hearing loss can cause WM brain changes or not.

Patients and materials Twenty-eight patients were enrolled in this research, 14 patients with bilateral tinnitus without hearing loss (audiometrically proven) and 14 normal hearing controls. All subjects underwent a full basic audiological evaluation, tinnitus matching, and were asked to fill the Tinnitus Handicap Inventory (THI) questionnaire. They underwent diffusion tensor brain imaging, mean diffusivity (MD) and fractional anisotropy (FA) values were measured at special parts of central auditory pathway, and parts of limbic system. A comparison between study and control groups was held as regards MD and FA at different brain sites using an independent sample Student t-test or Mann–Whitney U test. Furthermore, the relationship between THI scores and the MD/FA measures was examined by correlation tests.

Results As regards FA values, some regions as [lateral lemniscus (LL), inferior colliculus (IC), frontal arcuate fasciculi (AF) and parahippocampus] showed statistically significant decreased FA values in the tinnitus group compared to Normal Hearing (NH) group ($p < 0.05$). As regards MD values, tinnitus patients showed significantly higher MD values at (auditory cortex, amygdala, and AF) compared to control group ($p < 0.05$). As regards correlations, THI scores showed statistically significant positive correlation with MD values measured at Rt Amygdala ($r = 0.55, p = 0.04$).

Conclusions The central auditory pathway affection is proved in tinnitus patients with normal hearing (as least as evidenced by conventional audiological examinations) and the auditory-limbic association is proved so far. The involvement of IC confirms the subcortical auditory centres involvement in the generation of the tinnitus. Auditory associations are also significantly impacted by the effect of tinnitus.

Keywords Auditory, DTI, Hearing loss, Limbic, Normal hearing, Tinnitus

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Background

Tinnitus is an auditory problem characterized by a hissing, tonal, or buzzing sound in the absence of any physical sound source [1].

The usual clinical assessment of tinnitus involves tinnitus matching, measurement of tinnitus distress, assessment of mood (emotional component) as well



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as assessment of the underlying hearing level, which is a common comorbidity with tinnitus [1, 2].

A few studies using electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), and magnetic encephalogram (MEG) have unanimously agreed on the functional changes in the brain caused by tinnitus and their relation to the types of tinnitus and the degree of hearing loss [2]. Diffusion tensor imaging (DTI) is a recently developed MR acquisition modality that enables the measurement of the structural organization of tissues [3, 4]. As a powerful and non-invasive technique for in vivo exploration of human tissues, DTI is widely used in various medical fields, especially in brain imaging [5, 6]. DTI is based on the diffusion properties of water molecules in the white matter of the brain. The diffusion is limited by the fibrous nature of white matter: the well-organized axon structure, axon membranes, neurofilaments and overall myelin coating surrounding the neurons induce the displacement of water molecules to occur preferentially along the axon fibers rather than perpendicularly to them [7]. This anisotropic diffusion of water molecules can be measured by an MR scanner, allowing us to infer information on white matter connectivity.

In our research, we studied the characteristics of white matter fiber tracts defining the (classical) auditory pathway, especially the pathways from the Lateral Lemniscus (LL) and inferior colliculi (IC) to the medial geniculate body (MGB) up to the auditory cortex. We also investigated the connections between the auditory system and the limbic system (amygdala, hippocampus, and parahippocampus). Furthermore, we measured the intracerebral connection as arcuate fasciculus (AF) and intercerebral connections as corpus callosum (CC). As in most of previous research [8–10], the confounding effect

of underlying hearing loss contaminated the results, hereby, we focus on tinnitus patients without hearing loss to eradicate the effect of hearing loss.

Methods

Subjects

A total of 28 subjects were recruited for our study. Fourteen patients with bilateral untreated persistent idiopathic tinnitus with normal hearing were included as a study group. Fourteen right-handed healthy volunteers were recruited as healthy controls with normal hearing (NH). All the patients met the inclusion criteria: persistent idiopathic tinnitus (≥ 3 months persistently) without any history of associated brain diseases confirmed by conventional MRI, no pre-existing mental illness or cognitive disorder affecting the structural outcome, and no contradictions to MRI. Based on the audiogram results Fig. 1, all the subjects were without hearing loss, which was defined as more than 25 dB hearing loss at frequencies ranging from 0.25 to 8 kHz (0.25, 0.5, 1, 2, 4, and 8 kHz) in a pure tone audiometry (PTA) examination. Patients who met the following criteria weren't included in the study: having [pulsatile tinnitus, hyperacusis, any kind of hearing loss (*conductive, sensorineural, or mixed hearing loss*) or any other neurological conditions]. All the patients were asked to fill in the tinnitus handicap inventory (THI) to assess the severity of disease at the time of MRI acquisition and tinnitus matching for pitch and loudness was done for all tinnitus patients (Table 1).

Data acquisition

The diffusion images as well as usual brain MRI studies were acquired on a 1.5-T General Electric scanner (GE Medical Systems, Milwaukee).

Hearing Threshold (dB) at Different Frequencies in Both Groups

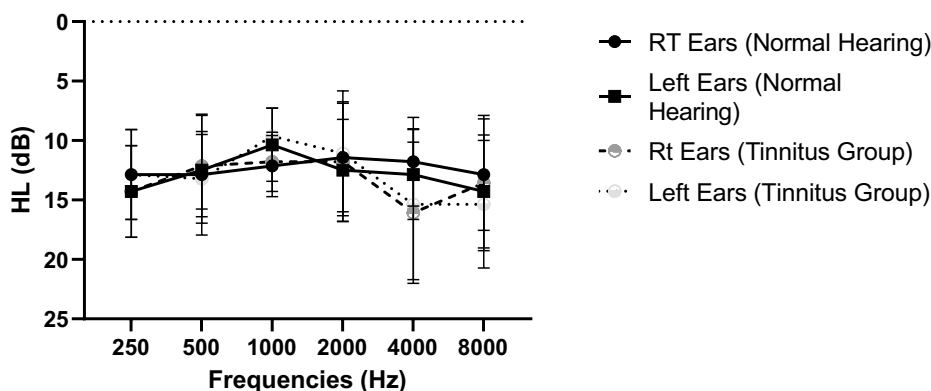


Fig. 1 Hearing thresholds measured at different frequencies from right and left ears in both groups. Rt: right, HL dB: hearing level in decibel, Hz: Hertz

For DTI performed in the axial plane with the following parameters: field of view=240×240 mm; matrix size=128×128; no. of slices=50 each 2.2 mm thick without gaps; imaging resolution=1.85×1.85×2 mm³. DTI diffusion was measured along 60 non-collinear directions. For each slice and each gradient direction, two images with no diffusion weighting (b=0 s/mm²) and diffusion weighting (b=1000 s/mm²) were acquired. The in-plane resolution was 1 mm. The slice thickness was 4 mm. All our patients were examined in the supine position using the head coil.

For clinical evaluations and for exclusion of any coincidental brain findings, all patients also had a MRI scan of whole brain that included an axial T1-weighted sequence, an axial and coronal T2-weighted image, an axial and sagittal FLAIR images. The imaging parameters for the spin echo (SE) axial spin echo T2-weighted images was (repetition time [TR] 2000 ms, echo time [TE] 20/100 ms; matrix size 256×256; field of view [FOV] 240 mm; slice thickness 5 mm), and T2-FLAIR (TR 8000 ms, TE 50/158 ms; matrix size 256×256; FOV 240 mm; slice thickness 5 mm, inversion time, 2200 ms). Axial T1-weighted MR images (TR=600 ms, TE = 10 ms, axial slices 5 mm).

All tensor imaging processing were carried out on independent workstation (DSI studio, version 0.59). The circular (ROI) region of interest was implemented at each anatomical location on both sides and the mean FA and MD values within the ROI were measured (Figs. 2, 3, 4).

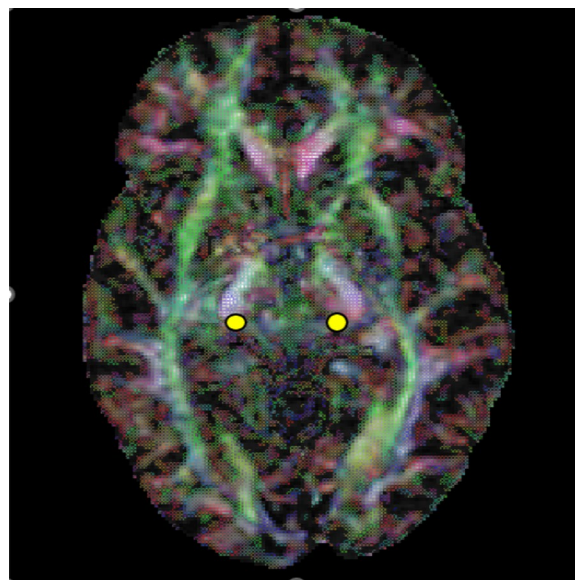


Fig. 3 The regions-of-interests (ROIs) were drawn manually on the axial images for medial geniculate bodies bilaterally

3D FIESTA images were used for anatomical reference and ROIs were drawn manually on the axial images for the lateral lemniscus, inferior colliculus (Fig. 2), the medial geniculate body (Fig. 3), amygdala, hippocampus, Para hippocampal region, the auditory cortex, mid splenium (Fig. 4), and mid genu (Fig. 4) of the corpus callosum.

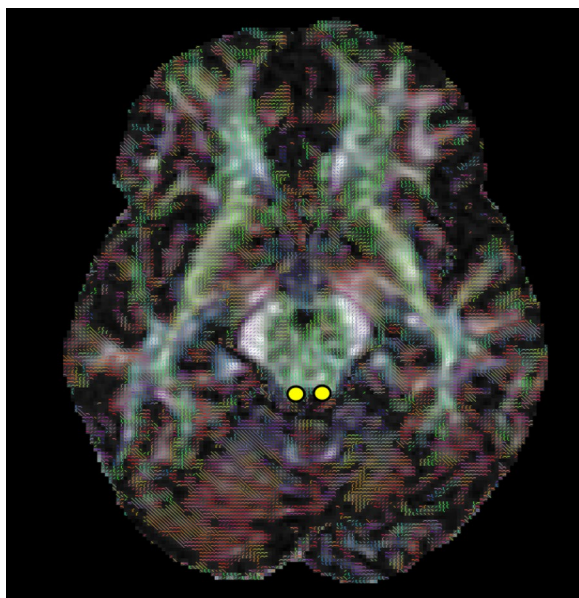


Fig. 2 The regions-of-interests (ROIs) were drawn manually on the axial images for inferior colliculus bilaterally

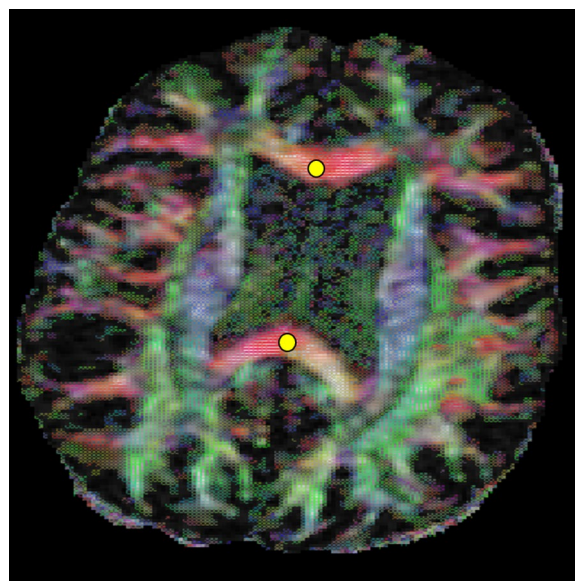


Fig. 4 The regions-of-interests (ROIs) were drawn manually on the axial images for mid genu and mid splenium of corpus callosum

Table 1 Tinnitus type, matching (pitch and loudness), laterality, Tinnitus handicap inventory score (THI) among tinnitus patients

Tinnitus patients	Matched frequency (KHz)	Loudness level (dB SL)	Type of tinnitus NBN versus pure tone	Laterality	THI score
No 1	3	20	NBN	Bilateral more at Rt	66
No 2	1.5	20	Tonal	Bilateral more at left	64
No 3	2	30	Tonal	Bilateral more at Rt	80
No 4	6	40	NBN	Bilateral more at Rt	82
No 5	12	30	Tonal	Bilateral equal	56
No 6	8	60	NBN	Bilateral more at left	62
No 7	4	40	Tonal	Bilateral equal	80
No 8	3	30	Tonal	Bilateral more at Rt	60
No 9	2	25	Tonal	Bilateral more at left	50
No 10	8	30	Tonal	Bilateral equal	82
No 11	10	20	NBN	Bilateral equal	70
No 12	4	40	NBN	Bilateral more at left	72
No 13	3	50	NBN	Bilateral equal	68
No 14	6	30	Tonal	Bilateral equal	78

KHz: kilohertz, No: Number of patient, NBN: narrow band noise, THI: tinnitus handicap inventory

Statistical analysis of the collected data

Results were collected, tabulated, and statistically analysed by Prism 8 (GraphPad software) version 8.0.2 (263).

Two types of statistical analysis were done:

- a) Descriptive statistics were expressed in Number (No), percentage (%) mean (\bar{x}), standard deviation (SD), median and interquartile range
- b) Analytic statistics e.g.
 - Unpaired t-test was employed to compare different readings of normally distributed data while Mann Whitney test was used for data that did not follow normal distribution.
 - Fisher’s exact test was utilized to compare the sex distribution between distinct groups.
 - p value < 0.05 was considered statistically significant.
 - The normality of distribution parameters was evaluated by Kolmogorov–Smirnov test.
 - Correlation between MD and FA measured values and THI score was applied. Pearson correlation test was used for normally distributed data, spearman test was used when normal distribution not proved.
 - Graphical art was made with Prism 8 (GraphPad software).

Results

Twenty-eight subjects were enrolled at this study, 14 tinnitus patients with normal hearing and 14 normal hearing controls. The group of healthy volunteers consisted of 9 male and 5 females, their age varied from 18 to 55 years, with a mean \pm SD (37 \pm 9). The tinnitus patients were (4 men and 10 women) with ages varying from 18 to 53 years, with a mean \pm SD (38 \pm 13). All the subjects were right-handed. All our patients suffered from bilateral tinnitus. Both groups were matched for age and gender. Tinnitus description, laterality, and tinnitus matched frequency are illustrated in Table 1. The frequency and loudness level of tinnitus were determined by a matching procedure. Figure 1 shows the hearing levels of the tinnitus patients and control NH at different frequencies.

White matter changes in Tinnitus Patients compared to healthy control group

As regard FA

Statistically significant decreased values in the tinnitus group compared to NH group were detected at the following regions: Left LL and right IC (p values = 0.0381 and 0.0213 respectively), right AF and left AF with (p value = 0.0016 and p value = 0.0057 respectively). There was also statistically significant difference measured at left para hippocampus with reduced FA level in tinnitus

Table 2 Comparison between study (Tinnitus) and control (normal hearing) group as regards fractional anisotropy (FA) measured at different brain sites

FA	Tinnitus group Mean ± SD	Control group Mean ± SD	Tinnitus group median (IQ range)	Control group median (IQ range)	p value	Parametric (t) test/ nonparametric Mann–Whitney (U)
Rt LL	0.4086 ± 0.08883	0.4193 ± 0.1277	0.4100 (0.3125–0.4900)	0.4500 (0.2675–0.5225)	0.7986	t = 0.2578
Lt LL	0.3500 ± 0.1054	0.4757 ± 0.1578	0.3150 (0.2875–0.4050)	0.4950 (0.3350–0.5525)	0.0381	U = 53
Right IC	0.4243 ± 0.09036	0.5579 ± 0.2073	0.4500 (0.4000–0.4700)	0.6400 (0.4000–0.7325)	0.0213	U = 48.50
Left IC	0.4779 ± 0.08145	0.5157 ± 0.2239	0.4400 (0.4000–0.5600)	0.5450 (0.3475–0.7125)	0.5573	t = 0.5946
Right MGB	0.3614 ± 0.1104	0.3571 ± 0.1774	0.3400 (0.2800–0.4850)	0.3650 (0.2100–0.4025)	0.7946	U = 92
Left MGB	0.3729 ± 0.1086	0.4164 ± 0.1649	0.3550 (0.3100–0.4350)	0.3700 (0.3300–0.4625)	0.5032	U = 83
Right AC	0.2886 ± 0.06479	0.3571 ± 0.1467	0.3100 (0.2400–0.3300)	0.3550 (0.2625–0.4950)	0.1272	t = 1.600, df = 17.88
Left AC	0.2614 ± 0.1066	0.3250 ± 0.1746	0.2300 (0.1500–0.3800)	0.2950 (0.1775–0.5425)	0.2554	t = 1.163, df = 26
Right AMG	0.1700 ± 0.02987	0.1757 ± 0.08178	0.1700 (0.1400–0.1900)	0.1550 (0.1100–0.2000)	0.4433	U = 81
Left AMG	0.1686 ± 0.02905	0.2593 ± 0.2717	0.1600 (0.1500–0.1800)	0.1650 (0.1175–0.2275)	0.8999	U = 93
Right hippocampus	0.3171 ± 0.1401	0.2750 ± 0.1360	0.3700 (0.1500–0.4000)	0.2500 (0.1550–0.3650)	0.4266	t = 0.8077, df = 26
Left hippocampus	0.3143 ± 0.1233	0.2929 ± 0.1459	0.3500 (0.1600–0.4300)	0.2500 (0.1575–0.4475)	0.6581	U = 88
Right para hippocampus	0.1500 ± 0.02418	0.2529 ± 0.2260	0.1500 (0.1300–0.1600)	0.2000 (0.1300–0.2675)	0.0986	U = 62
Left parahippocampus	0.1471 ± 0.03024	0.1786 ± 0.03570	0.1300 (0.1300–0.1900)	0.1850 (0.1450–0.2100)	0.0185	t = 2.513, df = 26
Right frontal AF	0.3243 ± 0.05515	0.4814 ± 0.1458	0.3300 (0.3000–0.3700)	0.4600 (0.3650–0.5400)	0.0016	t = 3.773, df = 16.65
Left frontal AF	0.3471 ± 0.09840	0.4786 ± 0.1303	0.3300 (0.2300–0.4300)	0.4450 (0.3825–0.5850)	0.0057	t = 3.012, df = 26
Right parietal AF	0.4186 ± 0.06163	0.4593 ± 0.1824	0.4400 (0.3700–0.4600)	0.4250 (0.3475–0.6025)	0.4360	t = 0.7911, df = 26
Left parietal AF	0.4100 ± 0.1129	0.4550 ± 0.1718	0.3800 (0.3100–0.4800)	0.4250 (0.3450–0.4700)	0.6263	U = 78
Splenium	0.7229 ± 0.2023	0.7686 ± 0.1558	0.8000 (0.7100–0.8500)	0.8100 (0.7200–0.8850)	0.2393	U = 72
Genu	0.6500 ± 0.2028	0.6400 ± 0.2200	0.6900 (0.6400–0.7900)	0.7300 (0.4925–0.8000)	0.6584	U = 88

Areas that showed significant levels of changes between two groups are expressed in bold

AC: auditory cortex, AF: arcuate fasciculus, AMG: amygdala, FA: fractional Anisotropy, IC: inferior colliculus, LL: lateral lemniscus, Lt: left, MGB: medial geniculate body, Rt: right

patients compared to control with good level of significance (*p value* = 0.0185) (Table 2, Fig. 5).

compared to control group with (*p values levels* = 0.018, 0.0325 and 0.0113 respectively) (Table 3, Fig. 5).

As regard MD

Tinnitus patients showed significantly higher MD values in (Rt Auditory cortex, right amygdala, and right AF)

Correlation

THI scores showed a strong positive correlation with MD values measured at Rt Amygdala (*r* = 0.55, *p* = 0.04) (Fig. 6).

Comparison between study and control groups as regards FA/MD

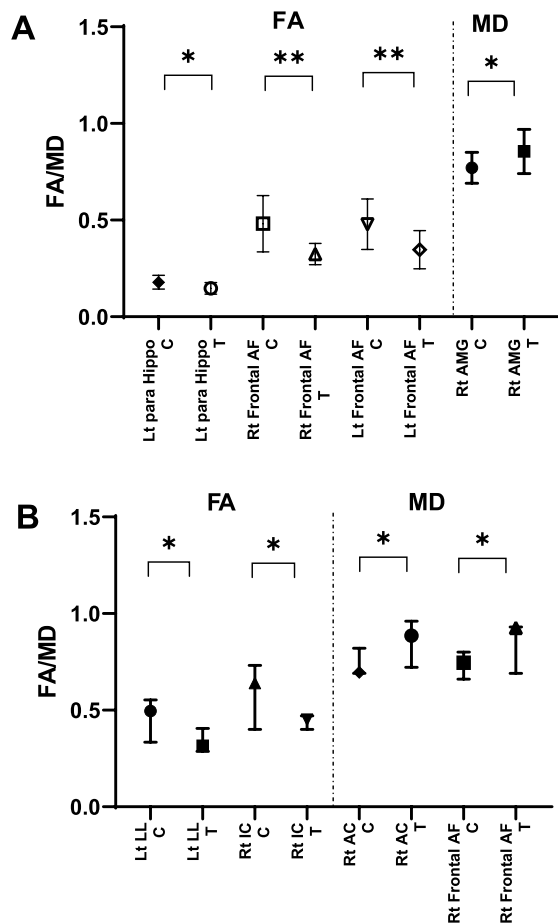


Fig. 5 Comparison between control and tinnitus as regards FA and MD values measured at different anatomical brain regions. **A** student t test for normally distributed data (data are expressed as a mean ± SD). **B** Mann Whitney U test for data did not follow normal distribution (data are expressed as a Median & IQ range). (Statistical significance if $p < 0.05$). AF: Arcuate Fasciculus, AMG: amygdala, C: control, IC: inferior colliculus, FA: fractional anisotropy, LL: lateral lemniscus, Lt left, MD: mean diffusivity, Para Hippo: Para hippocampus, Rt: right, SD: standard deviation, T: tinnitus

Discussion

“Tinnitus is the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source” [11]. Although most incidences of tinnitus are temporary, chronic subjective tinnitus occurs in 4–15% of the general population, with an increasing prevalence in populations with an age more than 50 years to almost 20% [12]. Although tinnitus is usually linked to presence of hearing loss, 8% of patients with tinnitus had normal hearing thresholds (defined

as better than or equal to 20 dB HL) up to 8000 Hz [13] and others reported that more than 60% of people with normal hearing (based on tonal audiometry) have tinnitus [14, 15]. Norena [16] proposed three distinct subtypes of tinnitus: cochlear tinnitus, peripheral dependent central tinnitus, and peripheral-independent central tinnitus [16]. Cochlear tinnitus refers to the tinnitus that originates from aberrant inner ear activity [16]. Peripheral dependent central tinnitus refers to a tinnitus associated with cochlear spontaneous activity, while peripheral independent central tinnitus refers to a tinnitus that is independent from cochlear spontaneous activity [16].

The auditory nerve (AN), which transmits action potentials in response to stimulation of the hair cells in the cochlea, is where the central auditory system begins. The auditory system’s cochlear nucleus (CN), which receives information from the ipsilateral cochlea, is the first auditory system nucleus. The auditory message then travels from LL to IC before being projected to (MGB) of the thalamus. MGB is a relay station of several types of information of which the auditory pathway is only one. Fibers leaving the MGB project to the primary auditory cortex (AC). In addition to this classical auditory pathway, connections between the auditory system and the limbic system are also found [12]. The limbic system is involved in motivation, mood, and emotion [17], and consists of many subsystems, including the hippocampus, the amygdoid complex [18]. Typical complaints attached to tinnitus such as anxiety, depression, and emotions such as fear indicate the association of the limbic system with tinnitus.

Previous research in this issue dealt with people complaining of combined tinnitus and hearing loss as Aldhafeeri et al. [8] & Lee et al. [9] and Ahmed et al. [19], so, the results of DTI studies were contaminated by the presence of hearing loss. So, the significant findings in those works were not accounted for tinnitus alone in the presence of the other confounding factor i.e., hearing loss.

In this research we studied the characteristics of WM fiber tracts defining the (classical) auditory pathway, especially the pathways from the Lateral Lemniscus (LL) and Inferior Colliculi (IC) to the Medial Geniculate Body (MGB) up to the auditory cortex. We also investigate the connections between the auditory system and the limbic system (amygdala, hippocampus, and parahippocampus). Furthermore, we measured the intracerebral connection as Arcuate Fasciculus (AF) and intercerebral connections as Corpus Callosum (CC). As most of previous research as that held by Aldhafeeri et al. [8] & Lee et al. [9] and Crippa et al. [10] the confounding effect of underlying hearing loss contaminated the results, hence, we focused on tinnitus patients without hearing loss (audiometric basis) to eradicate the effect of hearing loss.

Table 3 Comparison between study (Tinnitus) and control (NH) group as regards mean diffusivity (MD) measured at different brain sites

MD	Tinnitus group Mean ± SD	Control group Mean ± SD	Tinnitus group median (IQ range)	Control group median (IQ range)	p value	Parametric (t) test /nonparametric Mann-Whitney (U)
Rt LL	0.8064 ± 0.2593	0.9557 ± 0.7473	0.8100 (0.5850–0.8350)	0.7950 (0.6450–0.9450)	0.9367	U = 96
Lt LL	0.7657 ± 0.08455	0.7643 ± 0.07079	0.7300 (0.6975–0.8450)	0.7750 (0.7350–0.8300)	0.6423	U = 87.5
Right IC	1.040 ± 0.9507	0.8686 ± 0.2043	0.7750 (0.5750–0.9200)	0.8200 (0.7400–0.9250)	0.3944	U = 79
Left IC	0.8321 ± 0.1683	0.8336 ± 0.1280	0.7600 (0.6950–1.008)	0.8050 (0.7375–0.8750)	0.6587	U = 88
Right MGB	1.023 ± 0.2721	0.9857 ± 0.3440	0.9950 (0.8300–1.238)	0.9450 (0.8000–1.043)	0.7539	t = 0.3168, df = 26
Left MGB	0.9171 ± 0.05663	0.9014 ± 0.1490	0.9150 (0.8575–0.9700)	0.8750 (0.7950–0.9525)	0.2402	U = 72
Right AC	0.8393 ± 0.1228	0.7314 ± 0.06792	0.8850 (0.7225–0.9600)	0.6950 (0.6900–0.8200)	0.0181	U = 47.5
Left AC	0.7836 ± 0.1035	0.7729 ± 0.09911	0.7700 (0.6850–0.9025)	0.8000 (0.6675–0.8600)	0.7819	t = 0.2797, df = 26
Right AMG	0.8550 ± 0.1140	0.7707 ± 0.08052	0.8350 (0.7700–0.9700)	0.7950 (0.6950–0.8400)	0.0325	t = 2.260, df = 26
Left AMG	0.8514 ± 0.08356	0.9493 ± 0.2464	0.8400 (0.7875–0.9000)	0.8600 (0.7600–1.070)	0.1785	t = 1.407, df = 15.95
Right hippocampus	0.8771 ± 0.2060	0.8093 ± 0.3012	0.8650 (0.6200–1.0480)	0.8350 (0.6725–1.043)	0.4928	t = 0.6958, df = 26
Left hippocampus	0.8171 ± 0.1176	0.8407 ± 0.1015	0.8600 (0.7475–0.9325)	0.8450 (0.7800–0.8975)	0.5751	t = 0.5677, df = 26
Right para hippocampus	0.8521 ± 0.09341	0.8871 ± 0.1941	0.8400 (0.7725–0.9500)	0.7950 (0.7375–1.058)	0.8829	U = 94.50
Left para hippocampus	0.8386 ± 0.1762	0.9021 ± 0.1549	0.7950 (0.7000–0.9400)	0.9000 (0.7575–1.050)	0.3201	t = 1.014, df = 26
Right frontal AF	0.8571 ± 0.1466	0.7393 ± 0.09499	0.9250 (0.6900–0.9300)	0.7450 (0.6600–0.8000)	0.0113	U = 44
Left frontal AF	0.7386 ± 0.08565	0.7336 ± 0.1137	0.7400 (0.7050–0.8050)	0.7000 (0.6575–0.7925)	0.8965	t = 0.1314, df = 26
Right Parietal AF	0.7700 ± 0.1766	0.7779 ± 0.1044	0.7400 (0.6000–0.9400)	0.7600 (0.6950–0.8225)	0.8872	t = 0.1433, df = 26
Left parietal AF	0.7657 ± 0.08821	0.7336 ± 0.08509	0.7800 (0.7500–0.8300)	0.7050 (0.6500–0.8325)	0.3003	U = 75
Splenium	0.8957 ± 0.2631	0.8164 ± 0.1294	0.8200 (0.7400–0.9700)	0.8300 (0.7350–0.8900)	0.7946	U = 92
Genu	0.8014 ± 0.1019	0.9607 ± 0.3256	0.7900 (0.7000–0.9100)	0.8650 (0.7300–1.103)	0.1004	t = 1.747, df = 15.52

Areas that showed significant levels of changes between two groups are expressed in bold

AC: auditory cortex, AF: arcuate fasciculus, AMG: amygdala,, IC: inferior colliculus, LL: lateral lemniscus, Lt: left, MD: mean diffusivity, MGB: medial geniculate body, Rt: right

Our results revealed *significant decrease in the FA values* in study group compared to normal healthy pears in the following regions (Left Lateral Lemniscus, Rt inferior colliculus, Rt Frontal arcuate Fasciculus, Left Frontal arcuate fasciculus, and left Para hippocampus). While there was *significant increase in MD* values in the study group compared to the control group in the following areas (Rt Broadman area, Rt amygdala and Rt frontal arcuate fasciculus). Moreover, we found statistically

significant positive correlation between THI scores and the MD values at (Rt amygdala).

Our results agreed with Aldhafeeri et al.[8], Lee et al. [9], Ahmed et al. [19] & Chen et al. [20]who found decreased FA in AF in the tinnitus group. However, in the 1st three studies, the tinnitus was contaminated with HL While the latter conducted their studies on tinnitus with normal hearing. On concordance with our study, Gunbey et al. [21], found statistically significant decrease in

Correlation between MD values measured at Rt AMG and THI scores

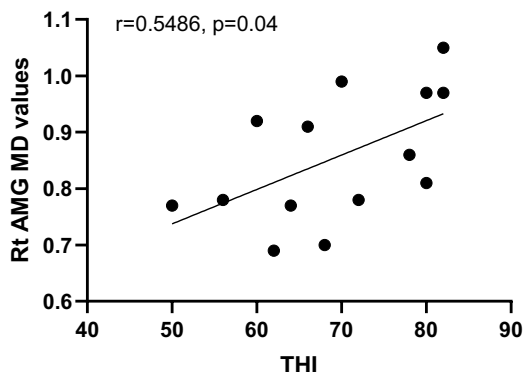


Fig. 6 Correlation between MD measured from Rt AMG, and THI score showed statistically significant positive correlation ($p=0.04$). MD: mean diffusivity; RT AMG: right amygdala; THI: tinnitus handicap inventory

FA at IC and Amygdala in tinnitus compared to control group Also, FA significantly decreased in LL in tinnitus with normal hearing compared to control group. According to Ryu et al. [22] research the tinnitus group with hearing loss also exhibited increased MD in WM under the auditory cortex and limbic system. Hereby, we also found significant increase in the MD in the Rt AC and Rt Amygdala.

On the other hand, other studies as Schmidt et al. [23] found no differences in diffusion indices in patients when compared with controls, and the severity and duration did not affect FA values as well. They considered this due to the differences in imaging parameters, which did not have the sensitivity to detect the changes. Most recently Khan et al. [24] who had their studies on tinnitus group with normal hearing and tinnitus with hearing loss and normal hearing control, found no significant alteration in FA values in tinnitus group with normal hearing compared to normal hearing controls.

According to the earlier tinnitus model, the tinnitus signal is generated at the periphery (linked to the periphery of auditory system) and is detected and processed by the subconscious centers of the auditory pathways. Finally, it is interpreted at the highest level of the auditory system (the secondary auditory cortices). The person’s reaction and thoughts determine the tinnitus signal spread. The tinnitus signal may be constrained inside the auditory pathways if a person only detects tinnitus without experiencing any unpleasant effects from it. However, if this activity spreads to the limbic and autonomic nervous systems by specifically activating the sympathetic part of the autonomic system, it elicits several unfavourable responses, such as irritation, anxiety and panic, and

triggers the survival reflexes, which results in a decreased ability to enjoy life’s activities [1].

While all our cases were without hearing loss (*audiometric basis*), the central auditory system was significantly affected (*LL and IC*). This usually happened in cases of the peripheral theory of tinnitus i.e., cochlear pathology. Our explanation for this entity is that, (1) it might be peripheral independent central tinnitus as described earlier by Noreña [16] (2) Or, possibly, these parts might be affected because they part of descending auditory pathway (the noise reduction pathway). The top-down noise suppressing system may not be working properly, which can result in the perception of sound. An imbalance between the bottom-up ascending auditory pathways and the noise suppressing descending pathways can generate tinnitus [25–27]. Specifically, that, inferior colliculus is an obligatory synaptic station in the descending auditory pathways [28] and according to our results the FA was significantly affected at this part of the auditory pathway. However, as we didn’t perform any audiological tests to assess the concomitant affection of the descending pathway, so, it is hard to confirm this theory 3) The third explanation is the *deafferentation theory*. Deafferentations of the cochlea yielded hyperexcitability in the ascending auditory pathway thus being consistent with the idea that central changes and tinnitus may be initially triggered by peripheral auditory system deficits. Although our study was done on tinnitus patients with normal hearing, the presence of hidden hearing loss is still a factor. Before pure tone audiometry can detect the hearing loss, the OHCs can be damaged by up to 30% [29]. A state that is recently described as hidden hearing loss (HHL). Such hearing loss that is not detectable with conventional audiometric tests (pure tone audiometry) [30]. The damage to the synaptic ribbons involving pre and post dendritic synapses is another possible pathophysiology of HHL [31, 32]. Recently, Wan and Corfas [33] reported the third mechanism for underlying HHL. The authors discovered that temporary Schwann cell demyelination causes a persistent disruption of the cochlear hemi nodal, which produces in long-term auditory impairments that are indicative of HHL. Taken together, these findings suggest that deafferentation-induced reorganization model is still a suggested theory.

It is well known that the limbic and paralimbic systems serve as a crucial link between the auditory system and the emotional processing system [22]. The limbic system’s emotional and cognitive abilities may be impacted by tinnitus, and the limbic system itself may play a role in the emergence and maintenance of tinnitus. The amygdala, one of the major components of the limbic system, has the capacity to modulate the activity and plasticity of the AC with direct neural input received from the

MGB, as it also receives direct input from the AC [34]. FMRI research has provided evidence of altered interactions between multiple auditory and limbic related brain structures in tinnitus [35–38]. Contrary to those using BOLD fMRI, only a few studies as Aldhafeeri et al. [8], Lee et al., [9], Seydell-Greenwald et al. [39] and Gunbey et al. [21] have examined structural changes in the brain in tinnitus. The structural changes that take place as part of the pathophysiological mechanism of tinnitus have been usefully described by these structural studies. Functional network studies in tinnitus patients have revealed the greater interaction of auditory network and limbic systems [38, 40]. Volumetric imaging studies such those held by Chen et al. [41], Schlee et al. [42], Maudoux et al. [43], have demonstrated that tinnitus patients had structural abnormalities in both the central auditory and limbic systems. In the current study we found a significant decrease of FA at the left parahippocampus and a significant increase in MD at the Rt amygdala which confirms the limbic system affection. Furthermore, a positive correlation was found between the MD values at the Amygdala and THI scores which in turn confirms the theory. However, in this study, the involvement of the hippocampus, which is the second major area of the limbic system, was not documented. Crippa et al. [10] demonstrated that the tracts connecting the AC, the amygdala and the MGB to each other belong to the non-classical auditory pathways and showed the connection between hearing and the limbic system. According to Gunbey et al. [21], FA reduced in the amygdala, which may be a sign of early DTI findings in tinnitus sufferers. They also found a significant correlation between FA values at amygdala and THI scores. Also, Ryu et al. [22] found a significant alteration in WM in both auditory cortex and limbic system in tinnitus patients. The Para hippocampal area was hypothesized to play a vital role in transporting information to the areas of the hippocampus associated with remembering, and a dysfunction of this mechanism was presumed to be an explanation of complex auditory imaginary perceptions, such as auditory hallucinations [44]. The Para hippocampal area is involved in tinnitus and tinnitus-related stress [45]. Together with some previous research, all these findings support the hypotheses that the limbic system plays a significant role in the generation of tinnitus, and that tinnitus can stress and change neuronal activity and plasticity in the limbic system [20].

Finally, the prefrontal cortex is a critical area that is responsible for attention, speech in noise listening and the cocktail party effect (noise reduction) [21]. Arcuate fasciculi are an important connection between this critical area and the auditory areas. With affection of these

important connections, a suggested cognitive affection will be postulated. In the current study we found a significant decrease of FA in both Rt and Left frontal arcuate fasciculi.

Knowing the exact underlying pathology or affected sites of tinnitus determine the future therapeutic modality for tinnitus management.

Conclusions

From this study we conclude that tinnitus alone might be responsible for WM microstructure abnormalities. The auditory-limbic association of the tinnitus pathway in patients without HL (audiometric basis) has been proved so far. The deafferentation theory of tinnitus is still questionable, as hidden hearing loss is still postulated as a peripheral cause of the tinnitus. The involvement of IC confirms the subcortical auditory centers involvement in generation of tinnitus and/or the descending pathway affection. Secondary auditory cortices and auditory associations are both significantly impacted by the effect of tinnitus.

Limitations and recommendations

Several issues should be noticed in the future. First, the sample size was relatively small. Second, as we could not exclude the effect of hidden hearing loss as a possible cause, and we rely on conventional hearing tests, in the future research other tests to detect the hidden hearing loss should be applied. Lastly, we did not perform any audiological tests to assess cognitive dysfunction in this group of patients.

Abbreviation

AC	Auditory cortex
AF	Arcuate fasciculus
AMG	Amygdala
AN	Auditory nerve
CAP	Central auditory pathway
CC	Corpus callosum
CN	The cochlear nucleus
DTI	Diffusion tensor image
EMG	Electroencephalogram
FA	Fraction anisotropy
FMRI	Functional MRI.
IC	Inferior colliculus.
LL	Lateral lemniscus.
MD	Mean diffusivity
MEG	Magnetic encephalogram
MGB	Medial geniculate body
NH	Normal hearing.
PTA	Pure tone audiometry.
ROI	Region of interest
THI	Tinnitus handicap inventory
VAS	Visual analogue scale
WM	White matter

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Author contributions

NN proposed the idea, collected and interpreted the data, referred the patients from the audio vestibular unit and contributed to writing the original draft. AE made the radiological test analysis and contributed to writing and reviewing the article. Both authors have read approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [ethical/privacy issues] but are available from the corresponding author on reasonable request.

Declarations**Ethical consent and approval to participate**

This is a prospective observational study comprising 28 subjects that was conducted at a Tanta university hospital, between April 2022 to September 2022. Tanta university research ethics committee review board has approved the study with approval report code 35755. This study conforms to the Declaration of Helsinki. Informed consents were obtained from all participants in this study.

Consent for publication

All participants included in the research gave written consent to publish the data included in the study. Authors accepted to publish the paper.

Competing interests

Authors declare no competing interests.

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