Tinnitus and Multimodal Cortical Interaction

OPEN ACCESS

Authors

Christian Dobel[1], Markus Junghöfer[2], Birgit Mazurek[3], Evangelos Paraskevopoulos[4], Joachim Groß[2]

Affiliations

1 Dept. of Oto-Rhino-Laryngology, University Hospital of Jena, Germany
2 Institute for Biomagnetism and Biosignal Analysis, University of Münster, Germany
3 Tinnitus Center, Charité – University Medicine of Berlin, Germany
4 Department of Psychology, University of Cyprus, CY, Nicosia, Cyprus

Key words

Tinnitus, comorbidity, imaging techniques, functional MRI, electroencephalography, magnet encephalography

Bibliography

Laryngo-Rhino-Otol 2023; 102: S59–S66

DOI 10.1055/a-1959-3021

ISSN 0935-8943

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Univ. Prof. Dr. Christian Dobel
Dept. of Oto-Rhino-Laryngology
Am Klinikum 1
07747 Jena
Germany
christian.dobel@med.uni-jena.de

ABSTRACT

The term of subjective tinnitus is used to describe a perceived noise without an external sound source. Therefore, it seems to be obvious that tinnitus can be understood as purely auditory, sensory problem. From a clinical point of view, however, this is a very inadequate description, as there are significant comorbidities associated with chronic tinnitus. Neurophysiological investigations with different imaging techniques give a very similar picture, because not only the auditory system is affected in chronic tinnitus patients, but also a widely ramified subcortical and cortical network. In addition to auditory processing systems, networks consisting of frontal and parietal regions are particularly disturbed. For this reason, some authors conceptualize tinnitus as a network disorder rather than a disorder of a circumscribed system. These findings and this concept suggest that tinnitus must be diagnosed and treated in a multidisciplinary and multimodal manner.

Contents

1. Introduction

Subjective tinnitus describes the perception of a tonal and more complex sound without the presence of an external source. Therefore, it is often referred to as a phantom noise, in analogy to phantom pain. A description as a circumscribed phenomenon of the auditory pathway or auditory system therefore seems obvious. Tinnitus can occur as a result of any injury to the auditory pathway, such as hearing loss or presbycusis. Likewise, injury to the auditory nerve, such as from a vestibular schwannoma, can cause tinnitus. These impairments lead to changes in cortical activity and ultimately to perception of tinnitus. However, the correlation of lesion or hearing loss and tinnitus is complex. Hearing loss does not necessarily lead to tinnitus, and not every patient with chronic tinnitus has an abnormal hearing threshold. Therefore, it has been assumed that any combination of an alteration in auditory or somatosenory input together with altered central nervous activity or structures may produce tinnitus [1]. Based on neurophysiological studies, it has been suggested that, as a consequence of altered activity, tinnitus is associated with reorganization of tonotopic maps [2]. Tonotopic organization is a hallmark of the auditory system in mammals, originating in the cochlea and continuing to the neocortex in humans [3, 4].

Already this brief overview shows that tinnitus is a very heterogeneous disorder. In addition to the above-mentioned impairment of the auditory pathway (see also the current S3 guideline [5]), chronic tinnitus (persisting for more than 3 months) is accompanied by significant cognitive and affective disorders in most cases. In the cognitive domain, abnormalities are most notable in attention [6–8], executive functions, and memory functions. These impairments of central processes can also be the cause of disorders of language comprehension. A recent study revealed that the perception of linguistic signals is impaired, but not the perception of speakers or voices [9]. Thus, the impairment of perception cannot be explained by a too weak or unclear presentation of the auditory signal per se.

Besides these abnormalities of cognition, affective disorders in particular are observed in tinnitus (see Mazurek et al.; further presentation for the DGHNO meeting in 2023). A recent study compared four groups with regard to psychopathological impairments: decompensated tinnitus patients, compensated tinnitus patients, patients with major depression without tinnitus, and unimpaired control subjects [10]. Evaluated questionnaires on anxiety, depressive and psychosomatic symptoms were collected from all groups. The four groups could be classified using a canonical discriminant analysis based on two factors. Factor 1 was termed “general psychopathology” because most questionnaires responded strongly to this factor. With regard to this factor, patients with decompensated tinnitus and patients with major depression were equally and more impaired than patients with compensated tinnitus, while the latter were also significantly more impaired than healthy controls. Both tinnitus groups (compensated and decompensated) scored higher than the other two groups on factor 2, “somatization”. Consistent with previous trials, this study could demonstrate the strong psychopathological burden in compensated, but especially in decompensated tinnitus. By the quantitative approach, the increased burden could also be revealed in compensated tinnitus patients, even if they were not clinically conspicuous in the actual sense.

In summary, it can already be seen from these examples that tinnitus is an extremely heterogeneous disorder that affects different physical, emotional, and cognitive domains. To briefly anticipate what is to come, current neurophysiological findings point in the same direction. These findings were obtained by means of various methods, their strengths and weaknesses will be described in the following section.

2. Neurological, neurophysiological, and neurocognitive examination methods

Neurophysiological imaging methods can basically be described on two dimensions, temporal and spatial. Current examination procedures show their strengths and weaknesses on these dimensions. Magnetic resonance imaging (MRI), as a method for detecting structural and functional properties of the brain, has very high spatial accuracy and allows localization of structures and corresponding activation in the cubic millimeter range at typical magnetic field strength to 1.5–3 Tesla. MRI is one of the most commonly used noninvasive methods, but it is expensive and requires specially trained staff. Using voxel-based morphometry (VBM), the entire brain can be depicted in volumetric pixels (voxels), allowing morphometric differences to be mapped individually or across groups and quantified for statistical analysis. The necessary structural images in the MRI scanner usually take only a few minutes. Diffusion tensor imaging (DTI) methods can also be performed based on such structural images. This allows diffusion movements of water molecules in the brain to be imaged and quantified. Frequently, DTI is used to determine the course, strength, and effectiveness of large nerve fiber bundles. Commonly used measures include fractional anisotropy (FA, the directionality of white fiber matter) and axial diffusivity (AD, the strength of diffusion in fiber direction) and radial diffusivity (RD, the strength of diffusivity perpendicular to the principal direction). These measures can be used to detect the integrity or affectedness of axons and their myelination.

In addition to structural measurements, MRI also allows the determination of functional neuronal activity. This is based on the “blood oxygenation level dependent” (BOLD) effect, with which the regional distribution of highly oxygenated blood in the brain, and thus the activity, can be measured. While the spatial accuracy is also very high, the temporal resolution is in the range of several seconds. Measurements in MRI scanners involve considerable noise exposure, which can be quite stressful for tinnitus patients.

Electroencephalography and magnet encephalography (EEG and MEG) are methods that record the synchronized activity of larger cell clusters directly and completely non-invasively. The spatial accuracy for determining the origin of the signal can be measured less precisely than with MRI but increases with the number of sensors used. The localization of activity is based on mathematical modeling techniques that incorporate, for example, head shape, electrical conductivity properties in the head, and the underlying number or neuronal sources. In contrast to the rather limited spatial resolution capability, the temporal resolution is in the range of milliseconds. In particular, EEG is a very widely used technique that is inexpensive and requires few staff.

The aforementioned methods for measuring brain activity allow the recording of spontaneous activity, i. e., without external stimuli and without the subjects being involved in a task to be performed (so-called "resting state" activity), as well as the recording of evoked activity. Evoked activity measures the brain's responses to a sensory stimulus that may be associated with the performance of a task (e. g. key press).

3. Structural changes in tinnitus

Structural changes have been reported in tinnitus not only in auditory and sensory, but also in limbic areas [11, 12]. However, different areas with increased or decreased gray matter volume (GMV) were found in different studies. GMV in Heschl's gyrus and superior temporal gyrus showed changes in both directions in tinnitus patients compared to healthy controls [13–16], while inferior colliculus volume (Landgrebe et al., 2009) was decreased and medial geniculus volume (Muhlau et al., 2006) was increased in these patients. As for the non-auditory limbic brain structures, decreased GMV was reported in the ventromedial (vmPCF) and dorsomedial (dmPFC) prefrontal cortex, nucleus accumbens, anterior (ACC), posterior cingulate cortex, hippocampus, and supramarginal gyrus [15, 17–19]. However, the changes in some of these areas were modulated by hearing loss [13, 14, 20]. In some studies, regional volumes have been associated with depressive and affective comorbidity, such as insula, cerebellum, and ACC [19, 21].

A recent study investigated the issue of psychiatric comorbidity in relation to structural changes in the brain caused by tinnitus (see Besteher et al., 2019, parallel to Ivansic et al., 2019). While hypothesis-based (region of interest-based) analysis of brain areas involved in tinnitus (specifically parahippocampal cortex, ACC, and superior temporal/transverse temporal cortex) showed main effects of tinnitus in parahippocampal cortex and trend-level findings in ACC and superior/transverse temporal cortices, several other findings at the whole-brain level (e. g. in the precuneus) did not survive a more conservative correction for multiple statistical comparisons. A reduction in parahippocampal matter was also found in a comparative analysis of tinnitus patients without psychiatric comorbidity compared with health controls, supporting the findings described above. This means that even if patients do not meet the diagnostic criteria for a psychiatric disorder, they are still more distressed than healthy controls. The most important finding of this study concerning the brain structural associations of this condition in tinnitus patients appears to be the particular importance of limbic structures (anterior and posterior cingulate gyri and parahippocampal gyri).

A recent study [23] investigated structural changes after auditory training and compared patients who improved with those who did not benefit from training. Compared to patients with improvement, patients without benefit had a significant decrease in gray matter volume in the right middle frontal gyrus (MFG) as well as the right precentral gyrus (PreCG). Thus, improvement in auditory perception is particularly associated with changes in frontal rather than typically auditory structures. A very recent meta-analysis compared groups of patients with and without tinnitus in whom hearing loss was or was not measurable [24]. The authors reported a minor reduction in gray matter in the left inferior temporal gyrus in normal-hearing tinnitus patients compared with groups of hearing subjects without tinnitus. In contrast, tinnitus was associated with increased gray matter in the bilateral lingual gyrus and bilateral precuneus in the groups with hearing loss. This study suggests that changes in gray matter in individuals with and without tinnitus are driven by hearing loss.

4. Changes of the white fiber matter in tinnitus

A first DTI study found reduced FA in the right prefrontal area, the left inferior and superior longitudinal fasciculus, and the anterior thalamic radiation in tinnitus patients compared to healthy control subjects [25]. In contrast, other authors showed increased FA in similar regions such as the inferior longitudinal fasciculus and anterior thalamic radiation [26], as well as in auditory and limbic areas [27]. Other DTI studies dealt with the correlation between perceived loudness of tinnitus and measures of white matter integrity. A positive correlation between perceived loudness and FA and a negative correlation between loudness and RD and AD were reported in the anterior thalamic radiation and ventromedial prefrontal cortex [19, 28]. An increase in RD at the level of the lateral lemniscus and inferior colliculus indicated the presence of demyelination processes [29]. This study emphasized that hearing loss but not tinnitus per se was associated with white matter changes (Lin et al., 2008). An increase in AD in the left superior, middle, and inferior temporal white matter similarly indicated axonal degeneration in tinnitus patients compared with control subjects [30]. Overall, recent DTI trials emphasize that the differences between tinnitus patients and controls are less due to the tinnitus itself, but can be mainly explained by age and an altered hearing threshold of the patients [31]. These factors, as well as experienced tinnitus distress and existing comorbidities, may at least partially explain the above contradictory results and should be captured in future studies to elucidate the anatomical heterogeneity of tinnitus patients (Schmidt et al., 2018). A recently published trial with a very tight control of these aspects failed to detect changes in white matter that correlate with perceived loudness of tinnitus. However, the severity of hearing loss and tinnitus distress did correlate with changes in acoustic radiation and arcuate fasciculus [32].

5. Functional changes in tinnitus

Magnetic resonance imaging (MRI) studies of tinnitus patients have also been used to depict functional changes (fMRI) that allow determination of dysfunctional network activity. Compared to all other methods, fMRI is the most commonly used imaging technique. Also due to the short duration and simplicity of the examination, "resting-state fMRI" (rs-fMRI) represents a very commonly used method in which the subject is not involved in a task. These rs-fMRI scans allowed the identification of several so-called resting-state networks across studies populations, analysis methods, and recording protocols: sensorimotor network, auditory network, limbic network, visual and extrastriate visual network, insular-temporal/anterior cingulate salience network (ACC), left and right lateralized frontoparietal network (attention), dorsal and ventral atten-

tion networks, default mode network (DMN), and a network for frontal executive functions [33]. Based on six available studies, an earlier review [34] came to the conclusion that the limbic DMN and auditory-limbic functional connectivity in particular are increased in resting state of tinnitus. A very recent paper [35] provides a review of 29 studies, 26 of which report abnormalities in tinnitus patients compared to controls in resting state networks. They include the auditory network (19 studies), DMN (17 studies), visual network (14 studies), dorsal (7 studies) and ventral (1 study) attention network, the executive function network (9 studies) and the limbic system (8 studies). The authors emphasized that the findings depended on the regions of interest (ROIs), i. e. whether or not a priori specific regions were included in the analyses. The authors therefore suggested that future studies should prioritize replicability of outcomes. In the peer-reviewed studies, strong heterogeneity was again evident and confounding variables were not adequately controlled. Nonetheless, the overall results suggest that multiple overlapping networks are involved in tinnitus. However, it remains unclear which changes are primarily due to tinnitus and which may be secondary to tinnitus.

Based on these studies, another model, so-called “triple network model” suggests that the default mode network and the executive function network are anti-correlated in acute tinnitus. In chronic tinnitus, this anti-correlation disappears, and a dysfunctional triple network emerges consisting of the DSM, executive, and salience networks underlying tinnitus-associated distress and cognitive executive impairments [36].

A recent study investigated tonotopic changes in tinnitus and, in this context, did not evaluate resting-state activity but brain activity in response to sinusoidal tones with frequencies between 0.25 and 8 kHz [37]. Subjects with and without tinnitus, but all with bilateral hearing loss, and a control group were evaluated. Activity in bilateral regions of the auditory cortex was higher in the groups with hearing loss compared to the control group. This was most evident in the group without tinnitus. Similarly, the tonotopic maps of the group with hearing loss without tinnitus did not differ from the controls. These results indicate that higher activation and reorganization of tonotopic maps are a feature of hearing loss and not of tinnitus.

6. Evidence by electro and magnetic encephalography for presentation of dysfunctional network activity in tinnitus

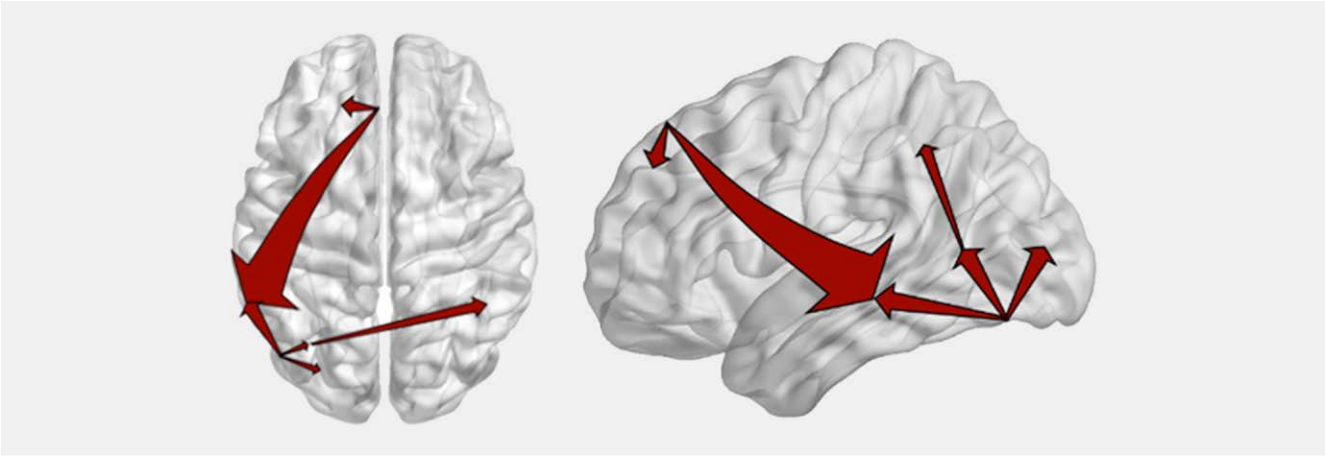
Complementary to resting-state in tinnitus patients using fMRI, EEG and MEG studies achieved comparable conclusions. An MEG study with source localization investigated extended cortical connections in tinnitus patients compared to controls [38]. The study looked for so-called “hubs” within ramified networks connecting different regions. The prefrontal cortex, orbitofrontal cortex, and parieto-occipital regions were shown to be central structures in the tinnitus network, and the information flow toward the temporal cortex correlated with the severity of tinnitus distress. Changes in functional connectivity were demonstrated in an EEG study [39] that investigated the role of stress in the perception of tinnitus. This emphasized the role of the parahippocampus as the node of a network that additionally included the posterior and anterior cingulate cortex, insula, and auditory cortex regions. In another EEG trial, a reorganization of the entire tinnitus network was observed, reflected by a decrease in the strength and efficiency of information transfer between fronto-limbic and medial temporal regions [40]. These regions also represented the main nodes of the tinnitus network. Parts of this network, and specifically the connections from the left hippocampus/parahippocampus to the subgenual anterior cingulate cortex, were strongly correlated with tinnitus distress.

An MEG study yielded very similar results but could show, using more complex connectivity measures that the role of the left parahippocampal area is modulated by the dorsomedial prefrontal cortex, a region typically attributed to the dorsal attention network and involved in the regulation of emotional processing [41]. In addition, this method of analysis across the entire cortex provided new insight into the role of the left inferior parietal cortex, which modulated the activity of the right superior temporal gyrus (see ▶ **Fig. 1**).

In addition to these studies based on resting-state measurements, a number of trials have been published that focused on brain activity as an evoked response to auditory stimulation. Repeatedly, a tinnitus-related increase in neuronal excitability was reported, reflected for example in the amplitude of the auditory N1 component. In this context, this early auditory evoked component is often used to objectively assess stimulus-associated EEG/MEG signals or as a biomarker to indicate typical and atypical cortical development (for a review, see Tomé et al., 2015; Foxe et al., 2011). Tinnitus patients had higher N1 amplitude in response to a frequency-specific tone outside the area of hearing loss, typically 500 Hz or 1 kHz, compared to healthy controls (Pantev, 1989; Hoke et al., 1998; Weisz et al., 2005), or even in response to tinnitus frequency tones (Kadner et al., 2002; Pineda et al., 2008). In contrast, however, other authors demonstrate significantly smaller N1 amplitudes in tinnitus patients compared to normal-hearing controls [45, 46] or showed no response to a 1-kHz tone [47, 48]. The inconsistency of these results may be due to the relatively small sample sizes (< 30 subjects) and different methodological strategies, such as different and/or varying number of a priori defined ROIs, or by constraints on a small number of sources in brain activity modeling. When source modeling methods were used that allowed for a large number of possible sources, an interaction of temporal, frontal, and parietal regions was reported within the N1 time window [49, 50].

7. Conclusion and outlook

Tinnitus is a common symptom with a prevalence in Europe of about 15 %, with 1–2 % of the population suffering from severe tinnitus [51]. The aging of societies and the associated hearing loss are expected to lead to a further increase in prevalence. The resulting healthcare expenses are already substantial [52, 53] and will continue to increase. In particular, tinnitus of high severity is characterized by high comorbidity, which can manifest in diverse physical, emotional, and cognitive symptoms. Already for this reason, it is obvious that tinnitus cannot be conceptualized as a narrowly defined purely auditory phenomenon. The results using the neuro-



▶ **Fig. 1** Significantly higher connectivity in tinnitus patients compared to control subjects. The arrows represent connections between areas with greater connectivity in tinnitus patients, with the thickness of the arrows representing the strength of connectivity. These results show that there is a cluster of connections in the dorsal prefrontal cortex, left medial cortex, parahippocampal regions, left inferior temporal gyrus, lateral occipital gyrus, and right intraparietal lobe (for details [41]).

physiological methods described here allow very similar conclusions to be drawn. Regardless of the methods used, the analysis procedures, the heterogeneity of the samples, the involvement of subjects in tasks, it was shown that tinnitus is characterized by complex dysfunctional network activity. In addition to auditory temporal regions, parietal, frontal, and especially limbic systems are particularly frequently affected. Whereas earlier analysis methods could only detect simultaneous activation, newer methods allow establishing correlations between specific activation patterns and regions, so that the direction of connectivity can be determined. It has been emphasized several times in this review article that in order to understand chronic tinnitus, a number of confounding variables must be controlled, including especially hearing loss and comorbid symptomatology. It would be desirable for future studies to focus on replication, an appropriate number of subjects, and comprehensive interdisciplinary diagnostics [54].

This review article was intended to provide a synopsis of the most common non-invasive procedures. Those techniques have in common the ability to capture the structural and functional properties of the brain over as large an area as possible. Near-infrared spectroscopy (NIRS) is another non-invasive technique that measures electromagnetic radiation in the infrared range. This method is used to determine blood volume and blood flow as well as oxygen content of various tissues such as the brain. Similar to EEG and MEG, the temporal resolution is very high, and the spatial resolution is rather moderate (again depending on the number of sensors applied). Compared to the above methods, NIRS is new and has been little used, especially in research on chronic tinnitus. Currently, the number of sensors used is relatively small, so that a priori decisions must be made as to which regions' activity will be recorded and evaluated. Initial studies indicate that cortical changes in tinnitus are not limited to auditory regions [55], but also affect emotion-relevant regions [56].

To determine the causal role of specific areas and networks on the development of chronic tinnitus, longitudinal studies and especially studies on the transition from an acute to a chronic state in patients are desirable. Currently, these studies are lacking, which is also a major gap in the literature from a clinical perspective. A combination of neurophysiological procedures would also be desirable, e. g. to exploit the advantages of different procedures. This would allow conclusions about spatial and temporal aspects of brain activation. Another gap in the literature is longitudinal studies in the course of therapeutic interventions. Since in particular cognitive behavioral therapy is recommended according to the S3 guideline for the treatment of chronic tinnitus, it seems obvious to investigate the neurophysiological changes in the course of this therapeutic procedure.

Acknowledgements

The authors' research on chronic tinnitus is supported by the German Research Foundation (Deutsche Forschungsgemeinschaft; DO 711/10–1, 10–3; GR 2024/10–3; JU 445/10–3)

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Langguth B, Kreuzer PM, Kleinjung T et al. Tinnitus: causes and clinical management. Lancet Neurol 2013; 12: 920–930. doi:10.1016/s1474-4422(13)70160-1

[2] Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends in neurosciences 2004; 27: 676–682. doi:10.1016/j.tins.2004.08.010

[3] Rauschecker JP, Tian B, Hauser M. Processing of complex sounds in the macaque nonprimary auditory cortex. Science 1995; 268: 111–114. doi:10.1126/science.7701330

[4] Brugge JF, Merzenich MM. Responses of neurons in auditory cortex of the macaque monkey to monaural and binaural stimulation. J Neurophysiol 1973; 36: 1138–1158. doi:10.1152/jn.1973.36.6.1138

[5] Mazurek B, Hesse G, Dobel C et al. Chronic Tinnitus. Dtsch Arztebl Int 2022; 119: 219–225. doi:10.3238/arztebl.m2022.0135

[6] Andersson G, McKenna L. The role of cognition in tinnitus. Acta Otolaryngol Suppl 2006. doi:10.1080/03655230600895226: 39-43. doi:10.1080/03655230600895226

[7] Mohamad N, Hoare DJ, Hall DA. The consequences of tinnitus and tinnitus severity on cognition: A review of the behavioural evidence. Hear Res 2016; 332: 199–209. doi:10.1016/j.heares.2015.10.001

[8] Tegg-Quinn S, Bennett RJ, Eikelboom RH et al. The impact of tinnitus upon cognition in adults: A systematic review. Int J Audiol 2016; 55: 533–540. doi:10.1080/14992027.2016.1185168

[9] Zäske R, Frisius N, Ivansic D et al. Phonetic perception but not perception of speaker gender is impaired in chronic tinnitus. Prog Brain Res 2021; 260: 397–422. doi:10.1016/bs.pbr.2020.12.003

[10] Ivansic D, Besteher B, Gantner J et al. Psychometric assessment of mental health in tinnitus patients, depressive and healthy controls. Psychiatry research 2019; 281: 112582. doi:10.1016/j.psychres.2019.112582

[11] Adjamian P, Hall DA, Palmer AR et al. Neuroanatomical abnormalities in chronic tinnitus in the human brain. Neurosci Biobehav Rev 2014; 45: 119–133. doi:10.1016/j.neubiorev.2014.05.013

[12] Simonetti P, Oiticica J. Tinnitus Neural Mechanisms and Structural Changes in the Brain: The Contribution of Neuroimaging Research. Int Arch Otorhinolaryngol 2015; 19: 259–265. doi:10.1055/s-0035-1548671

[13] Boyen K, Langers DR, de Kleine E et al. Gray matter in the brain: differences associated with tinnitus and hearing loss. Hear Res 2013; 295: 67–78. doi:10.1016/j.heares.2012.02.010

[14] Husain FT, Medina RE, Davis CW et al. Neuroanatomical changes due to hearing loss and chronic tinnitus: a combined VBM and DTI study. Brain Res 2011; 1369: 74–88. doi:10.1016/j.brainres.2010.10.095

[15] Mahoney CJ, Rohrer JD, Goll JC et al. Structural neuroanatomy of tinnitus and hyperacusis in semantic dementia. J Neurol Neurosurg Psychiatry 2011; 82: 1274–1278. doi:10.1136/jnnp.2010.235473

[16] Mühlau M, Rauschecker JP, Oestreicher E et al. Structural brain changes in tinnitus. Cereb Cortex 2006; 16: 1283–1288. doi:10.1093/cercor/bhj070

[17] Landgrebe M, Langguth B, Rosengarth K et al. Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. Neuroimage 2009; 46: 213–218. doi:10.1016/j.neuroimage.2009.01.069

[18] Leaver AM, Renier L, Chevillet MA et al. Dysregulation of limbic and auditory networks in tinnitus. Neuron 2011; 69: 33–43. doi:10.1016/j.neuron.2010.12.002

[19] Leaver AM, Seydell-Greenwald A, Turesky TK et al. Cortico-limbic morphology separates tinnitus from tinnitus distress. Front Syst Neurosci 2012; 6: 21. doi:10.3389/fnsys.2012.00021

[20] Melcher JR, Knudson IM, Levine RA. Subcallosal brain structure: correlation with hearing threshold at supra-clinical frequencies (>8 kHz), but not with tinnitus. Hear Res 2013; 295: 79–86. doi:10.1016/j.heares.2012.03.013

[21] Schecklmann M, Lehner A, Poeppl TB et al. Cluster analysis for identifying sub-types of tinnitus: a positron emission tomography and voxel-based morphometry study. Brain Res 2012; 1485: 3–9. doi:10.1016/j.brainres.2012.05.013

[22] Besteher B, Gaser C, Ivanšić D et al. Chronic tinnitus and the limbic system: Reappraising brain structural effects of distress and affective symptoms. Neuroimage Clin 2019; 24: 101976. doi:10.1016/j.nicl.2019.101976

[23] Chen Q, Lv H, Wang Z et al. Outcomes at 6 months are related to brain structural and white matter microstructural reorganization in idiopathic tinnitus patients treated with sound therapy. Hum Brain Mapp 2021; 42: 753–765. doi:10.1002/hbm.25260

[24] Makani P, Thioux M, Pyott SJ et al. A Combined Image- and Coordinate-Based Meta-Analysis of Whole-Brain Voxel-Based Morphometry Studies Investigating Subjective Tinnitus. Brain Sci 2022; 12. doi:10.3390/brainsci12091192

[25] Aldhafeeri FM, Mackenzie I, Kay T et al. Neuroanatomical correlates of tinnitus revealed by cortical thickness analysis and diffusion tensor imaging. Neuroradiology 2012; 54: 883–892. doi:10.1007/s00234-012-1044-6

[26] Benson RR, Gattu R, Cacace AT. Left hemisphere fractional anisotropy increase in noise-induced tinnitus: a diffusion tensor imaging (DTI) study of white matter tracts in the brain. Hear Res 2014; 309: 8–16. doi:10.1016/j.heares.2013.10.005

[27] Crippa A, Lanting CP, van Dijk P et al. A diffusion tensor imaging study on the auditory system and tinnitus. Open Neuroimag J 2010; 4: 16–25. doi:10.2174/1874440001004010016

[28] Seydell-Greenwald A, Raven EP, Leaver AM et al. Diffusion imaging of auditory and auditory-limbic connectivity in tinnitus: preliminary evidence and methodological challenges. Neural Plast 2014; 2014: 145943. doi:10.1155/2014/145943

[29] Lin Y, Wang J, Wu C et al. Diffusion tensor imaging of the auditory pathway in sensorineural hearing loss: changes in radial diffusivity and diffusion anisotropy. J Magn Reson Imaging 2008; 28: 598–603. doi:10.1002/jmri.21464

[30] Ryu CW, Park MS, Byun JY et al. White matter integrity associated with clinical symptoms in tinnitus patients: A tract-based spatial statistics study. Eur Radiol 2016; 26: 2223–2232. doi:10.1007/s00330-015-4034-3

[31] Yoo HB, De Ridder D, Vanneste S. White Matter Changes in Tinnitus: Is It All Age and Hearing Loss. Brain Connect 2016; 6: 84–93. doi:10.1089/brain.2015.0380

[32] Ahmed S, Mohan A, Yoo HB et al. Structural correlates of the audiological and emotional components of chronic tinnitus. Prog Brain Res 2021; 262: 487–509. doi:10.1016/bs.pbr.2021.01.030

[33] van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010; 20: 519–534. doi:10.1016/j.euroneuro.2010.03.008

[34] Husain FT, Schmidt SA. Using resting state functional connectivity to unravel networks of tinnitus. Hearing research 2014; 307: 153–162. doi:10.1016/j.heares.2013.07.010

[35] Kok TE, Domingo D, Hassan J et al. Resting-state Networks in Tinnitus: A Scoping Review. Clin Neuroradiol. 2022. doi:10.1007/s00062-022-01170-1. doi:10.1007/s00062-022-01170-1

[36] De Ridder D, Vanneste S, Song JJ et al. Tinnitus and the Triple Network Model: A Perspective. Clin Exp Otorhinolaryngol 2022; 15: 205–212. doi:10.21053/ceo.2022.00815

[37] Koops EA, Renken RJ, Lanting CP et al. Cortical Tonotopic Map Changes in Humans Are Larger in Hearing Loss Than in Additional Tinnitus. J Neurosci 2020; 40: 3178–3185. doi:10.1523/jneurosci.2083-19.2020

[38] Schlee W, Mueller N, Hartmann T et al. Mapping cortical hubs in tinnitus. BMC Biol 2009; 7: 80. doi:10.1186/1741-7007-7-80

[39] Vanneste S, De Ridder D. Stress-Related Functional Connectivity Changes Between Auditory Cortex and Cingulate in Tinnitus. Brain Connect 2015; 5: 371–383. doi:10.1089/brain.2014.0255

[40] Mohan A, Davidson C, De Ridder D et al. Effective connectivity analysis of inter- and intramodular hubs in phantom sound perception – identifying the core distress network. Brain Imaging Behav 2020; 14: 289–307. doi:10.1007/s11682-018-9989-7

[41] Paraskevopoulos E, Dobel C, Wollbrink A et al. Maladaptive alterations of resting state cortical network in Tinnitus: A directed functional connectivity analysis of a larger MEG data set. Sci Rep 2019; 9: 15452. doi:10.1038/s41598-019-51747-z

[42] Tomé D, Barbosa F, Nowak K et al. The development of the N1 and N2 components in auditory oddball paradigms: a systematic review with narrative analysis and suggested normative values. J Neural Transm (Vienna) 2015; 122: 375–391. doi:10.1007/s00702-014-1258-3

[43] Foxe JJ, Yeap S, Snyder AC et al. The N1 auditory evoked potential component as an endophenotype for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives, first-episode, and chronic schizophrenia patients. Eur Arch Psychiatry Clin Neurosci 2011; 261: 331–339. doi:10.1007/s00406-010-0176-0

[44] Weisz N, Wienbruch C, Dohrmann K et al. Neuromagnetic indicators of auditory cortical reorganization of tinnitus. Brain 2005; 128: 2722–2731. doi:10.1093/brain/awh588

[45] Attias J, Urbach D, Gold S et al. Auditory event related potentials in chronic tinnitus patients with noise induced hearing loss. Hear Res 1993; 71: 106–113. doi:10.1016/0378-5955(93)90026-w

[46] Jacobson GP, McCaslin DL. A reexamination of the long latency N1 response in patients with tinnitus. J Am Acad Audiol 2003; 14: 393–400

[47] Jacobson GP, Ahmad BK, Moran J et al. Auditory evoked cortical magnetic field (M100-M200) measurements in tinnitus and normal groups. Hear Res 1991; 56: 44–52. doi:10.1016/0378-5955(91)90152-y

[48] Colding-Jørgensen E, Lauritzen M, Johnsen NJ et al. On the evidence of auditory evoked magnetic fields as an objective measure of tinnitus. Electroencephalogr Clin Neurophysiol 1992; 83: 322–327. doi:10.1016/0013-4694(92)90091-u

[49] Stein A, Engell A, Lau P et al. Enhancing inhibition-induced plasticity in tinnitus – spectral energy contrasts in tailor-made notched music matter. PLoS One 2015; 10: e0126494. doi:10.1371/journal.pone.0126494

[50] Stein A, Engell A, Junghoefer M et al. Inhibition-induced plasticity in tinnitus patients after repetitive exposure to tailor-made notched music. Clin Neurophysiol 2015; 126: 1007–1015. doi:10.1016/j.clinph.2014.08.017

[51] Biswas R, Lugo A, Akeroyd MA et al. Tinnitus prevalence in Europe: a multi-country cross-sectional population study. Lancet Reg Health Eur 2022; 12: 100250. doi:10.1016/j.lanepe.2021.100250

[52] Trochidis I, Lugo A, Borroni E et al. Systematic Review on Healthcare and Societal Costs of Tinnitus. Int J Environ Res Public Health 2021; 18:. doi:10.3390/ijerph18136881

[53] Tziridis K, Friedrich J, Brüeggemann P et al. Estimation of Tinnitus-Related Socioeconomic Costs in Germany. Int J Environ Res Public Health 2022; 19. doi:10.3390/ijerph191610455

[54] Elgoyhen AB, Langguth B, De Ridder D et al. Tinnitus: perspectives from human neuroimaging. Nat Rev Neurosci 2015; 16: 632–642. doi:10.1038/nrn4003

[55] San Juan JD, Zhai T, Ash-Rafzadeh A et al. Tinnitus and auditory cortex: using adapted functional near-infrared spectroscopy to measure resting-state functional connectivity. Neuroreport 2021; 32: 66–75. doi:10.1097/wnr.0000000000001561

[56] Huang B, Wang X, Wei F et al. Notched Sound Alleviates Tinnitus by Reorganization Emotional Center. Front Hum Neurosci 2021; 15: 762492. doi:10.3389/fnhum.2021.762492