Chapter 20
A Global Brain Model of Tinnitus

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Keypoints

1. Subjective tinnitus is characterized by the perception of a phantom sound in the absence of any physical source.
2. While transient tinnitus usually lasts only a couple of seconds to a few hours, chronic tinnitus is an ongoing conscious perception of sound for more than 6 months with low incidence of spontaneous remissions.
3. Empirical studies in animals and humans often show enhancement of cortical excitability in the auditory areas associated with the tinnitus.
4. Theoretical and experimental studies suggest an additional involvement of extra-auditory cortical regions, especially the frontal cortex, the parietal cortex, and the cingulum.
5. Using magnetoencephalograpic recordings, we found that these areas are functionally connected with each other and form a global fronto–parietal–cingulate network.
6. The top–down influence of this global network on auditory areas is associated with the distress that is perceived by many individuals with tinnitus.
7. We suggest that both entities – the enhanced excitability of the central auditory system and the integration with a global cortical network – are important to generate and maintain a conscious percept of tinnitus.
8. This chapter will concentrate on how a conscious perception of tinnitus is formed and maintained throughout a lifetime.

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Abbreviations

ACC	Anterior cingulate cortex
AM	Amplitude modulation
dB	Decibel
DPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
ERS	Event-related synchronization
Hz	Hertz
MEG	Magnetoencephalography
OF	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PDC	Partial directed coherence
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
SLIM	Synchronization by loss of inhibition model
SPL	Sound pressure level
SSR	Steady state response

Introduction

Subjective tinnitus is characterized by a conscious perception of a sound in the absence of any physical source. This sound is typically described as a tone, a hissing or roaring noise, and in some cases as a combination of several sounds. Transient tinnitus, a phenomenon perceived by a large percentage of the population at least once in a lifetime, typically lasts a few seconds to a few hours. A far smaller percentage (5–15%) of people in western societies reports hearing their tinnitus constantly for more than 6 months [1]. Such an

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ongoing perception of tinnitus has the potential to impair the ability to concentrate, to disturb sleep, to affect social interactions, and it may even cause psychiatric problems. Indeed, about 1–3% of the general population reports that their tinnitus adversely affects their quality of life [2].

In this chapter, we will concentrate on how a conscious perception of tinnitus is formed and maintained in the brain. In general, our sensory systems constantly receive an overwhelming amount of sensory input, which – although being processed within the nervous system e.g., primary sensory regions – does not enter our consciousness completely. In fact, most of the stimuli remain unconscious and our conscious perception is limited to only a few sensory events. In recent years, several studies have investigated the neural mechanisms for the conscious perception of sensory stimuli [3–6] and with the Global Neural Workspace Hypothesis, Dehaene et al. proposed a model for conscious visual perception that explains several empirical findings and observations [3, 4]. In short, this model points out two requirements for conscious perception: (1) activation of the respective sensory area and (2) the entry of this activity into a global network of long-range cortical couplings. In light of this view, we want to review the current knowledge about chronic tinnitus and suggest a model for the perception of tinnitus.

In the following chapter, we will summarize the findings of altered activity in the central auditory and nonauditory regions as well as the cross-talk between auditory and nonauditory areas in tinnitus. We will give a short overview of the studies on conscious perception of external stimuli. Finally, we suggest a model for tinnitus perception that has the potential to explain several tinnitus phenomena and propose new methods of tinnitus therapy.

Increased Excitability of the Central Auditory System

Many individuals with tinnitus are able to localize their tinnitus to one or both ears. In most cases, the tinnitus sensation is accompanied by an audiometrically measurable damage to the cochlea. Thus, one may think that the tinnitus is generated within the ears; however, this is most likely not the case. If the phantom sound was generated within the ears, a transection of the auditory nerve would reliably eliminate the ongoing perception of the tinnitus sound. To date, there is much evidence refuting this view. There are only a small percentage of patients in whom the auditory nerve section leads to relief from tinnitus. The majority of patients still experience tinnitus after surgical sectioning of the auditory nerve [7, 8]. Furthermore, if tinnitus was generated in the periphery, a systematic enhancement of spontaneous activity in auditory nerve fibers would be present. As summarized by Eggermont and Roberts [9], changes in the spontaneous firing rate of the auditory nerve are rather unsystematic. When tinnitus is induced experimentally in animals, spontaneous auditory nerve activity may be enhanced, reduced, or even remain the same. Thus, the tinnitus perception is elicited irrespective of the utilized technique and the accordant changes in auditory nerve activity. These results suggest that for the majority of individuals, the sensation of tinnitus originates from central rather than peripheral parts of the auditory system. There is a large body of studies demonstrating the importance of central structures in tinnitus. Tinnitus-related changes of spontaneous activity can be found throughout the central auditory system. The spontaneous firing rate is enhanced in the dorsal cochlear nucleus [10], the inferior colliculus, and the primary and the secondary auditory cortex [9].

Neuroimaging studies in humans also suggest a hyperactive auditory cortex in tinnitus. In some individuals, tinnitus can temporarily be suppressed by masking or lidocaine application. Mirz et al. [11] used this effect to investigate changes in regional cerebral blood flow (rCBF) during tinnitus suppression in the positron emission tomograph (PET). They reported a significant reduction of rCBF in the right temporal lobe during tinnitus suppression. However, changes in nonauditory structures were also observed, which will be discussed in the next section. In another PET study, individuals with tinnitus were distracted from their symptoms with the serials seven test (counting silently backwards in steps of seven), which led to a reduction of rCBF in the left and the right auditory cortices [12]. Neuroimaging recordings of tinnitus patients during resting state differ from recordings of individuals who do not have tinnitus inasmuch as the individuals with tinnitus experience an ongoing phantom sound. Using magnetoencephalography (MEG) in resting state recordings, Weisz et al. [13] reported a significant enhancement of delta (1–4 Hz) activity and a concomitant reduction of alpha (8–12 Hz) activity in individuals with tinnitus. These changes were most prominent in

the temporal regions and correlated with the subjective rating of tinnitus distress. A later analysis on an extended dataset also showed a significant increase of gamma frequencies (40–90 Hz) in the left and right temporal lobe of the tinnitus group [14]. These results fit well into a recently proposed framework that explains enhanced synchronization of auditory activity by a reduction of cortical inhibition ("Synchronization by Loss of Inhibition Model," SLIM, [15]). Synchronized alpha activity is often assumed to be an indicator for active cortical inhibition mechanisms: A decrease in alpha power is associated with an increase in cortical excitability [16–18], while an increase in alpha power (also called Event-Related Synchronization, ERS) reflects inhibition [16]. The alpha desynchronization, as observed in chronic tinnitus, reflects a release of inhibition and thus favors the synchronization of neuronal activity. Altogether, the elevated rCBF (in PET), the enhancement of gamma band synchronization (in MEG), and the augmented spontaneous firing rate (single-unit recordings in animals) all act as an indicator for increased excitability of the auditory cortex in tinnitus.

Integration of Auditory and Nonauditory Brain Activity

Changes in brain activity accompanying tinnitus are not restricted to the auditory cortices. In the study by Mirz et al. referred to above, tinnitus suppression was accompanied by a reduction of rCBF in the temporal lobe, but also in the frontal lobe and posterior brain regions [11]. The MEG study by Weisz et al. [13] demonstrates alpha power decrease and delta power increase mainly located in the temporal lobe, but also extending into frontal and parietal sites.

Furthermore, there are also reports of structural changes in gray and white matter regarding chronic tinnitus. In a voxel-based morphometry study, Mühlau displayed a decrease of gray matter density in subcollosal regions and a gray matter increase in the posterior thalamus, and the medial geniculate body for tinnitus patients compared with healthy controls [19].

These results suggest an involvement of extra-auditory brain regions in the generation and/or perception of the phantom tinnitus sound. As hypothesized earlier by Jastreboff, the neural activity that causes tinnitus is generated within the auditory system, while nonauditory regions are involved in encoding the conscious percept as well as the emotional evaluation of it [20]. This hypothesis is supported by a study conducted in the 1960s, which revealed that a disconnection of the prefrontal cortex resulted in a reduction of tinnitus annoyance in most of the surviving patients [21]. Also, almost all clinicians are aware of anecdotal evidence that chronic tinnitus patients are often not aware or disturbed by their tinnitus (e.g., when distracted), but it can become the focus of attention or brought back into conscious awareness at any time. Based on these results and theoretical considerations, we postulate the existence of a widespread tinnitus network functionally connecting auditory and nonauditory brain regions. If such a network existed, there should be a considerable difference in the long-range cortical networks between participants with tinnitus and control participants who do not report an ongoing perception of tinnitus. Furthermore, if the connectivity between auditory and nonauditory regions encodes tinnitus distress, a correlation between the functional inter-regional connectivities and tinnitus distress should be revealed. We challenged these suppositions in three studies with MEG recordings in tinnitus and nontinnitus control participants.

In the first study, we employed auditory steady-state responses (SSR) to entrain the tinnitus network and investigated long-range functional connectivity across various nonauditory brain regions [22]. We presented amplitude-modulated (AM) tones of three different carrier frequencies to 22 participants (12 individuals with tinnitus and 10 controls). One of these stimuli was designed to match the individual tinnitus sound and the two other were control tones that were 1.1 and 2.2 octaves below the frequency of the tinnitus. Cortical connectivity was analyzed by means of phase synchronization in the participants with tinnitus and in healthy controls. We found a deviating pattern of long-range functional connectivity in tinnitus that was strongly correlated with individual ratings of tinnitus intrusiveness. Phase couplings between the anterior cingulum and the right frontal lobe as well as phase couplings between the anterior cingulum and the right parietal lobe demonstrated significant *condition* times *group* interactions. They were correlated with individual tinnitus distress ratings in the tinnitus condition. This study provided the first evidence for tinnitus-related alterations in the long-range synchronization between distant brain regions outside auditory areas.

The second study aimed to investigate the cortical networks in the resting state [23]. The analysis was based on a sample of 41 participants: 21 individuals with chronic tinnitus and 20 healthy control participants who did not have tinnitus. Cortical coupling was again analyzed by means of phase-locking analysis between distant brain regions. We found a significant decrease of inter-areal coupling in the alpha (9–12 Hz) band and a significant increase of inter-areal coupling in the 48–54 Hz gamma frequency range for the tinnitus group. Furthermore, an inverse relationship ($r=-0.71$) of the alpha and gamma network coupling was observed for all participants. Discrimination analysis revealed a separation of 83% between the tinnitus and the control group based on the alpha and gamma couplings. Post hoc analysis showed an influence of tinnitus manifestation on gamma coupling. In the participants who had a short tinnitus history, the left temporal cortex was predominant in the gamma network, whereas in the participants who had a longer tinnitus duration, the gamma network was more widely distributed across the cortex.

This study demonstrated disturbances in the long-range cortical coupling in individuals with tinnitus under resting conditions. The resting state is of particular interest for tinnitus research since individuals with this condition typically report an enhanced perception of the tinnitus when they are in a quiet surrounding. The results of the second study are in line with several other findings demonstrating the emergence of functional connectivity across widely distributed brain areas, in association with a conscious perception of the stimulus [3, 4, 6, 24, 25]. This connectivity may be an important mechanism of the brain in binding different features of the stimulus to form a comprehensive perception. Additionally, this connectivity might serve as an amplifier that enhances the neuronal activity in sensory areas (e.g., [3]).

In a recently published framework on chronic tinnitus, Weisz et al. proposed a top–down influence of higher order brain areas on the cortical activity in the auditory cortex [15]. With the third study [26] we specifically aimed to assess this top–down influence using partial directed coherence (PDC) – a measure that is based on the concept of Granger causality and allows for investigating the directionality of information flow between distant brain regions in the frequency domain.

Using MEG, we investigated the long-range cortical networks of individuals with chronic tinnitus ($n=23$) and healthy controls ($n=24$) in the resting state. A beam-forming technique was applied to reconstruct the brain activity at source level, and the directed functional coupling between all voxels was analyzed by means of Partial Directed Coherence. Within a cortical network hubs are brain structures that either influence a great number of other brain regions or are influenced by a great number of other brain regions. A strong outflow in this context indicates that this brain area considerably influences the activity of other brain structures. In the tinnitus group, two brain regions were identified with stronger outflow and one site with a weaker outflow. Stronger outflows were located in the prefrontal cortex and in the posterior part (parieto-occipital/occipital) of the brain. The weaker outflow was found in the orbitofrontal cortex (OFC). All these changes in the outflow behavior were found for the gamma frequency band above 30 Hz. A strong inflow means that this brain area is strongly driven by other brain regions.

With respect to the inflow characteristics, we found two sites with significant group differences. The OFC received more inflow in the high-frequency gamma range in the tinnitus group compared to the control group. Posterior parts of the cortex received less inflow from other brain areas in a broad frequency range, including slow waves, alpha, low beta, and gamma frequencies. Furthermore, we found the inflow to the temporal cortices correlated positively with subjective ratings of tinnitus distress: the more the activity in the temporal cortices was driven by other brain regions, the stronger the subjective distress reported by the participants. Additionally, we demonstrated that the inflow to the temporal cortex mainly originates from the prefrontal cortex and the posterior part of the brain; both are structures that we have characterized with a strong outflow within this network.

A Short Notion on Long-Range Cortical Networks

Long-range synchronization of distant brain regions has been first reported by Gray et al. [27]. They revealed synchronized oscillatory responses between neighboring columns in the visual cortex of the cat. Based on this finding, they proposed that synchronization combines different features of the visual pattern, which is

processed in different specialized columns of the visual cortex to form a common percept of the visual scene. While Gray et al. reported synchronization between cortical columns within the visual cortex, further studies demonstrated synchronization also over longer distances in the brain using noninvasive recording techniques: Miltner et al. [28] revealed long-range synchronization between the visual cortex and somatosensory areas during an associative learning task. Hummel and Gerloff [29] showed that successful performance in a visuotactile discrimination task significantly correlates with long-range coherence between the visual and the sensorimotor cortex. Melloni et al. [6] used different masks to manipulate whether a test stimulus was visible or invisible to the participants. They found significantly different gamma phase locking across widely separated regions of the brain for the "visible" and the "invisible" condition. Supp et al. [30] visually presented familiar and unfamiliar objects and revealed different patterns of long-range coupling between frontal, temporal, and parietal areas. This leads to the assumption that successful communication between widely distributed brain areas depends on long-range synchronization (also called "long-range coherence" or "long-range coupling"). Furthermore, in the "Communication Through Coherence" model, Pascal Fries also suggested that the absence of synchronization between distant brain regions prevents communication between them. Hence, irritations in the synchronization pattern can lead to major disturbances of brain functions.

Indeed, abnormal patterns of long-range functional coupling were reported in several pathologies. For instance, Uhlhaas and Singer [31] investigated schizophrenic patients during a Gestalt perception task and discovered a reduction of beta-band phase synchrony that might be related to their impairment in grouping stimulus elements to form a coherent percept. A reduction of long-range synchronization has also been detected in Alzheimer's disease [32] and autism [33, 34]. Le van Quyen et al. [35] reported a decrease of long-range synchrony for the preictal phase in epilepsy with the epileptic focus. This isolation was accompanied by an increase of local synchrony within the epileptic focus. Silberstein et al. [36] discovered an increase of cortico-cortical coupling in Parkinson's disease that correlated with the strength of Parkinsonism. Therapeutic interventions like the application of L-dopa or electrical stimulation of the subthalamic nucleus resulted in a reduction of the cortico-cortical coupling and Parkinson symptoms.

The theoretical framework on conscious perception suggested by Dehaene et al. asserts the existence of a global neuronal workspace that is distributed over the whole cortex. It is mainly located in the parietal lobe, the frontal lobe, the cingulate cortex, and the sensory systems [3, 4]. In order to form a conscious percept of a stimulus, two conditions are required: first, neuronal activity of the sensory cortex of the respective modality and second, an entry into the global neuronal workspace and thus long-range coupling between the widely distributed workspace neurons. According to this model, bidirectional coupling between this fronto–parietal–cingulate network and the sensory areas is needed for conscious perception (i.e., awareness of the stimulus). Activity of sensory areas without this coupling would remain preconscious. Furthermore, Dehaene and colleagues proposed that top–down influence from the global workspace on sensory areas enhances the neuronal activity therein.

Altogether, long-range connectivity might serve two important roles in brain function: First, the long-range connectivity might be a way to bind various stimulus features and integrate information from different brain regions to form a conscious perception of the (usually) external stimulus. Second, it is suggested that higher order brain regions might influence the excitability in sensory regions via long-range connections (so-called top–down modulation, [15]).

A Global Brain Model of Tinnitus

In this chapter, we propose a model for the conscious perception of the tinnitus sound, which is based on the above-mentioned studies on long-distance cortical coupling and extends earlier tinnitus models by Jastreboff [20], Eggermont and Roberts [9], and Weisz et al. [15]. Two levels of tinnitus-related neuronal processing are distinguished in this framework: the *local* (or *sensory*) level refers to the activity in the auditory areas. The *global* level refers to long-range cortical network of functionally connected brain areas.

The Sensory Level

Tinnitus is frequently associated with hyperactivity and enhanced synchronization of neuronal activity in the auditory cortex. Animal studies have shown a systematic

enhancement of spontaneous neuronal activity of the dorsal cochlear nucleus, the inferior colliculus, the primary auditory cortex, and the secondary auditory cortex (see [9] for a review). Moreover, studies in humans with chronic tinnitus revealed tinnitus-related changes in oscillatory activity of the temporal cortex [13, 14, 37, 38]. In a very recent study, we investigated rock musicians who perceived a transient tinnitus after a loud (~120 dB SPL for ~2 h) band practice. Resting-state activity in the MEG was recorded at two time points: immediately after the practice and at a second day without exposure to loud music. We found a strong enhancement of gamma frequency power (55–85 Hz) in the right temporal cortex during the perception of transient tinnitus, which was also observed on the single participant level in 13 of 14 participants and, importantly, was not correlated with the degree of hearing loss (Ortmann et al., submitted).

The hyperactivity in auditory areas (i.e., enhanced spontaneous firing rate as observed in animal studies) and the stronger synchronization of neuronal activity (as observed through an increase of oscillatory power in the gamma frequency range) both argue for an enhanced excitability of the auditory cortex in tinnitus [9]. The absence of an alpha effect in our transient tinnitus study could imply that a down-regulation of inhibition sets in after synchronization of excitatory neurons and could play a crucial role in the transition to chronic tinnitus. A down-regulation of inhibition would require less excitatory activity to ignite a tinnitus-related cell assembly, putatively evolving into "spontaneous synchronization" (i.e., where spontaneous activity (firing) of neurons suffices for synchronization of excitatory neurons [15]). We suggest that the enhanced spontaneous synchronization of circumscribed tonotopically organized regions of the central auditory system is one necessary prerequisite for the perception of tinnitus.

The Global Level

A second requirement for the conscious perception of tinnitus is the activation of a global network characterized by long-range coupling between distant cortical regions. The brain contains a highly organized pattern of functional connectivity for which we report multiple evidence of disturbance in cases of tinnitus. Based on our studies, we suppose the tinnitus-related global network to spread over the entire cortex. However, four core regions are emphasized particularly: (a) the dorsolateral prefrontal cortex (DPFC), (b) the orbitofrontal cortex (OFC), (c) the anterior cingulate cortex (ACC), and (d) the precuneus/posterior cingulate cortex (PCC). Furthermore, top–down influence of these higher order regions on the auditory cortices modulates the neuronal activity therein. The prefrontal cortex and the precuneus/PCC regions are the main areas for this top–down modulation. This idea of a tinnitus-related global network is an application of the global workspace hypothesis as suggested by Dehaene et al. onto chronic tinnitus [3, 4]. They postulated the existence of global workspace neurons that are distributed over distant areas of the cortex, characterized by a disproportionally large amount of long-range excitatory connections. Information that is processed within this network can easily be accessed by various brain systems; hence, it is hypothesized that this workspace is the basis for conscious perception. People with chronic tinnitus report an ongoing perception of the tinnitus sound. Thus, we propose that the tinnitus sound is constantly kept in the global workspace.

Furthermore, we suppose a top–down influence from the fronto-parietal-cingulate network on the temporal cortices that enhances the neuronal excitability therein. The magnitude of this influence is mediated by the subjectively perceived tinnitus distress. Support for this assumption comes from the above-described study in which we demonstrated significant correlations between the strength of the inflow hubs and the tinnitus distress. As outlined above, we presume that desynchronized alpha activity reflects a state of reduced intracortical inhibition and enhanced neuronal excitability. In a previous MEG-study [13], we demonstrated that the decrease of alpha power in temporal regions correlated strongly with the tinnitus distress as reported by the participants in our study. Two mechanisms are likely to influence alpha power decreases in the resting state:(1) a profound hearing loss that is frequently associated with the occurrence of tinnitus might lead to loss of lateral inhibition in the tonotopically ordered auditory cortex and thus increase the excitability of the auditory cortex and (2) a top–down influence from higher order brain regions on the temporal cortex might further affect the cortical excitability. Here, we assert that the later mechanism plays the more prominent role in tinnitus of the chronic state. This is largely supported by the fact that temporal alpha desynchronization

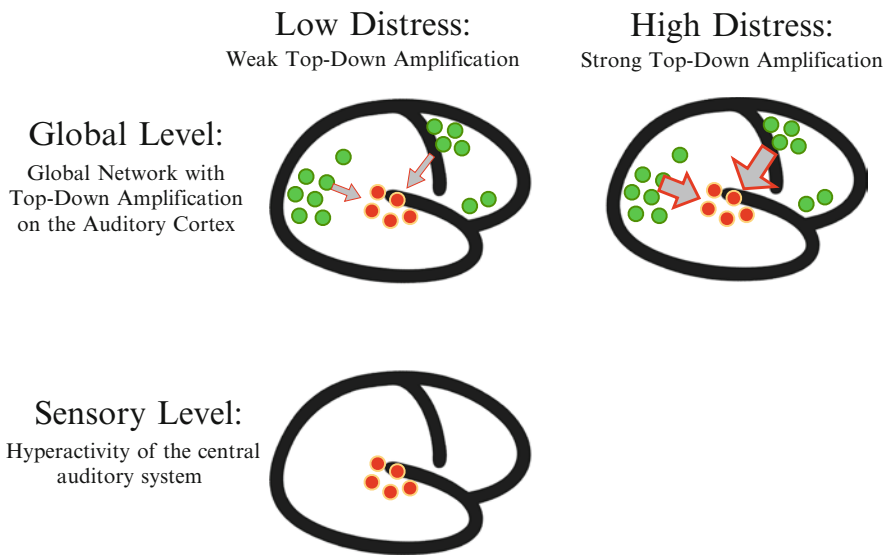

Fig. 20.1 Global Brain Model of Tinnitus. Abnormal activity sensory level and at the global level is required for a perception of tinnitus. The global network amplifies the neuronal activity by top–down influence. Higher tinnitus distress is associated with stronger top–down amplification

correlates well with the tinnitus distress ratings, but not with hearing loss (Fig. 20.1).

In summary, the models state that there are two processes that modulate excitability in the auditory cortices: at the sensory and the global level. The explanation at the sensory level takes into account that chronic tinnitus is usually associated with a profound damage to the hearing system (ear or auditory nerve). The reduced sensory input leads to a decrease of inhibitory mechanisms in the central auditory system and ultimately to an enhancement of cortical excitability therein (and favors the synchronization of spontaneous neuronal activity). We assume that this is the central mechanism in the generation of the phantom sound at tinnitus onset. The second explanation emphasizes a top–down influence of the global tinnitus network on the auditory cortices. We suggest that tinnitus-related information is processed in the globally extended fronto–parieto–cingulate network with influence on the auditory cortex. The magnitude of this influence is positively associated with the strength of the perceived tinnitus distress. Stronger tinnitus distress is characterized by stronger top–down influence leading to a marked alpha desynchronization, which is a neuronal signature of reduced cortical inhibition. We suppose that this mechanism is especially involved in the maintenance of the tinnitus-related enhancement of neuronal excitability in later periods of the tinnitus history. This is supported by the fact that we found significant correlations between tinnitus distress and top–down connectivity, but no results for the bottom–up connectivity.

Implications of the Model for the Treatment of Tinnitus

The proposed model explains the partial success of current therapies for tinnitus like Neurofeedback (see Chap. 87), transcranial magnetic stimulation (TMS), and cognitive therapies (see Chap. 73). Repetitive transcranial magnetic stimulation (rTMS) (see Chap. 88) aims to reduce the enhanced excitability in the auditory cortex, which leads to a reduction of tinnitus loudness [39–43]; however, a complete relief of tinnitus is rare. Regarding the global brain model of tinnitus, this is not surprising. Even if rTMS successfully reduces the enhanced excitability in the auditory cortices, the amplification by the global network would constantly fight against it. On the other hand, it has been shown that cognitive therapies also reduce tinnitus symptoms to some extent [20, 44]. In our proposed framework, we speculate that cognitive therapies are able to alter the tinnitus-related global network by changing the conscious elaboration of the tinnitus percept. This can potentially reduce the top–down amplification of the global network on the temporal lobe and thus lower the enhanced excitability therein, though there is still an untreated abnormal pattern of spontaneous activity in the temporal cortex that results from damage to the peripheral hearing system. If this abnormal spontaneous activity reaches a certain threshold, it can enter the global network again by means of the "bottom–up mode" as explained above.

Therefore, we stress the importance of a combination of both branches in tinnitus therapy: reducing the enhanced excitability in the auditory cortex on the one hand (e.g., via rTMS), and changing the global network on the other hand (e.g., via cognitive therapies). We strongly suggest combining both treatment approaches and expect synergy effects that improve the benefit from current tinnitus therapies.

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