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REVIEW ARTICLE

An overview of the tinnitus network activity and its clinical implications

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Abstract

Background and Aim: Tinnitus, the phantom perception of sound, in which many cortical and subcortical areas are involved has become one of the popular subjects of neuroscience research. Neuroimaging studies have introduced the tinnitus network model to explain the involvement of auditory and non-auditory areas in this perception. In such a model, the cognitive and emotional aspects of tinnitus can be interpreted conveniently. Therefore, this paper aimed to review the neural basis of tinnitus networks, including data from neuroimaging studies, and discuss the clinical implication of this concept, as well.

Recent Findings: The data from neuroimaging studies were reviewed and discussed in order to complete the overall image of tinnitus network and its correlates such as the distress network, attentional network and other cognitive mechanisms. In addition to the auditory system, the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) were considered to be important hubs in tinnitus distress network, especially for having important connectivity with the other networks like attention and salience networks. Moreover, the top-down control of DLPFC over the other brain areas was regarded as the most important brain area to be targeted using the non-invasive interventions and the results were compelling.

Conclusion: Understanding the network model has helped in optimizing the neuromodulation protocols like electrical stimulation techniques. Thus, the clinical implications of this model can be generalized to the other types of treatments and the outcomes might be satisfying.

Keywords: Tinnitus; tinnitus network; distress network; attention network; functional connectivity

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Introduction

Tinnitus is the phantom perception of sound, generated inside the auditory system, in the absence of any external sound source [1,2]. Tinnitus has a high incidence rate of 15% of the adult's population, 6-25% of them have serious distressful and problematic symptoms [3,4]. Chronic tinnitus is characterized by the persistent conscious perception of sound with much distress and a resistance to treatment approaches. Such a scenario might be attributed to the

prevention of habituation which makes the situation more complicated [5,6]. Due to its high prevalence and substantial distress, tinnitus has become one of the popular subjects of medical, behavioral and neuroscience studies [7].

The most common cause of tinnitus is the central auditory deafferentation due to a cochlear damage. It is proposed that tinnitus is generated to reduce the uncertainty of the auditory environment caused by this deafferentiation [8]. Many neurophysiological models were proposed for tinnitus generation mechanisms, such as the increased spontaneous activity in the auditory cortex [9], tonotopic map re-organization [10], and enhanced neural synchrony [11]. Moreover, the involvement of the efferent auditory system was also discussed [12]. And the recent model has introduced the activation of overlapped co-operable networks between auditory and non-auditory areas in the brain as such integrative model [13,14]. The heterogeneity of tinnitus and the variety of its related symptoms like sleep disorders, functional and cognitive problems have encouraged much research on the neurophysiological model. Neuroimaging reports highlighted the inevitable role of the multi-regional coupling and reciprocal interactions introduced in the concept of tinnitus network [15-17]. Therefore, this paper aimed to review the neural basis of tinnitus networks, including data from neuroimaging studies, and discuss the clinical implication of this concept, as well.

How does the brain work as a network?

The simplest way to explain the brain function is to have a specified function for each area: the one-to-one or area-function mapping model. However, the actual image is more sophisticated and a mapping of many-to-many area-function couplings can be expected; in such a model, several areas can contribute in one function, or vice versa, where one area is involved in multiple functions [18]. The basic framework of the model is supposed to have the network interactions, while its phenotype is well represented by the perceptual, cognitive, emotional, and other functions of the brain [19]. Each brain network consists of multiple nodes or areas between which, different types of structural and functional connectivity are existing. The node with the high functional connectivity is called the "rich hub" [20]. Thus, by determining the connectivity of the hub, its impact on the behavior can be predicted. From the "graph theoretical" concept [21], there are two types of hubs: the "provincial" hub which takes a central position in the network, and the "connector" hub which links the separated networks together [22]. For instance, the posterior cingulate cortex (PCC) is a connector hub between the default mode and the cognitive networks [23].

More broadly, some regions of the brain have a high-level functional connectivity with the majority of other regions. The higher the functional connectivity of the region, the greater impact on behavior it should have [20]. That is, a lesion in such area may lead to a wide spectrum of behavioral disorders. On the other hand, targeting this area with neuromodulation techniques can be more advantageous than targeting the other hubs in the same network. Lastly, even the rich hub of the network can be affected or modulated by the function of another node/hub on the same network or another connected network. For example, the dorsal anterior cingulate cortex (dACC) is a provincial hub in the distress network while its function can be modulated by the function of the dorsolateral prefrontal cortex (DLPFC), the latter is a rich hub in many other networks like attention network [24-26].

Tinnitus perception network and its correlates

It is axiomatic that the auditory network (the auditory cortex) is involved in tinnitus generation and perception. However, the role of the peripheral auditory system, the sub-cortical regions, as well as the primary and secondary auditory cortex and their correlates is not completely understood [27]. De Ridder et al. introduced a proposed tinnitus core network consisted of the auditory cortex, ventromedial prefrontal cortex (vmPFC), inferior parietal area and the parahippocampus (Fig. 1) [16]. These regions represent the minimal amount of brain

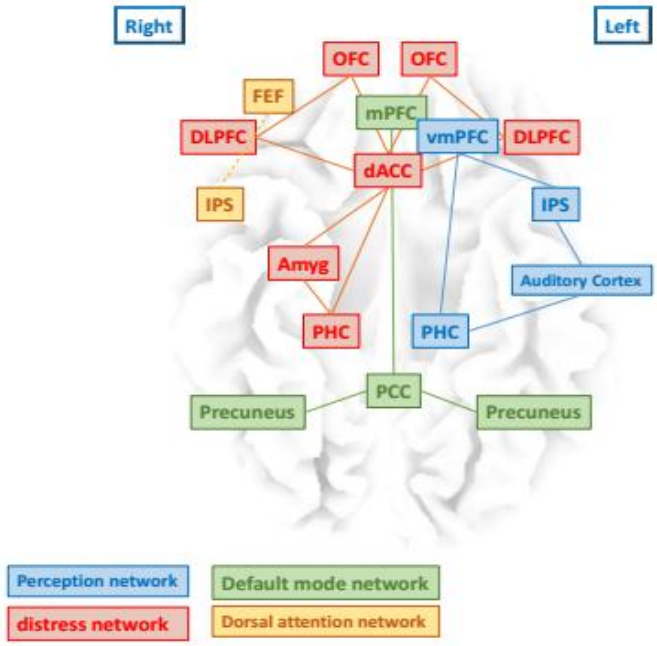

Fig. 1. Brain networks involved in generating and modulating tinnitus perception and related distress. Tinnitus perception network consists of the auditory cortex, the infra-parietal sulcus (IPS), the ventromedial prefrontal cortex (vmPFC) and the parahippocampus (PHC). Tinnitus distress network consists of the dorsal anterior cingulate cortex (dACC), amygdala (Amyg), parahippocampus and the right DLPFC and OFC for stress processing and left DLPFC and OFC for depressive feelings. The dorsal attention network shows activated connectivity between the frontal eye fields (FEF) and the right infra-parietal sulcus. The default mode network shows disruption of functional connectivity between the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC) and the bilateral precuneus.

areas required for tinnitus generation and perception [16]. Electroencephalography (EEG) studies have revealed increased oscillatory power in theta band in the auditory cortex nested in gamma band hyperactivity [28-30]. The differentiation of the central auditory structures arising from the cochlear nerve injury would trigger important alterations in the auditory pathways and can lead to the sensation of tinnitus [31]. The pathological theta–gamma rhythm has been attributed to this differentiation leading to a prediction error between the sensed and perceived auditory input and gives rise to the tinnitus perception [32]. Moreover, a reduced alpha power has been frequently reported in tinnitus EEG studies [33,34]. On the other hand, the prediction error has been linked to the decreased alpha power and the later has been linked to the decrease in sensory updating that leads to such error [32,35]. Thus, the auditory network is involved in generating the phantom percept of sound which needs to be brought into consciousness in order to reach the cognitive processing cycles; and these processing cycles give to the phantom percept its loudness, annoyance, and related-distress. Thereby, a network that consists of the posterior cingulate cortex (PCC), insular cortex and amygdala is called the salience network [36], which receives the phantom percept and yields its saliency then introduce it to the attention network through the PCC connections [23].

The role of attention in the modulation of tinnitus perception

The attention network, in turn, is involved in

alerting and orienting the patient`s attention towards the sound ringing in his head, and regulates its emotional response through connections to the tinnitus distress network, that impede the habituation process; such functional connectivity is guaranteed by the parahippocampus [17]. Two important networks are involved in the modulation of tinnitus perception, they are the default mode network (DMN) and the dorsal attention network (Fig. 1) [37]. The default mode network consists of the medial prefrontal cortex, the posterior cingulate cortex, and the precuneus; while the dorsal attention network consists of the frontal eye fields and the right infra-parietal cortex [17]. The two networks have an anti-correlated relationship that is: when the DMN network becomes active the dorsal attention network is deactivated, and vice versa [38]. Some studies revealed a connectivity disruption between the DMN important hubs that means: the tinnitus patients cannot reach the actual resting state and instead they have a constant activation of the dorsal attention network that impels them attending to their tinnitus [39]. Modulating such abnormal functional connectivity can be surprisingly helpful.

Tinnitus distress network

The recent EEG studies have used sLORETA, standardized low-resolution brain electromagnetic tomography analysis, for source analysis and defining the functional connectivity between the brain regions of interest [40]. The results of these studies alongside the functional magnetic resonance imaging (fMRI) studies revealed the relation between tinnitus related-distress and the increased power of beta band in the anterior cingulate cortex (ACC), in addition, the amount of distress was correlated to the alpha band activity in several brain areas that form the distress network [40]. This network consists of the amygdala [41], ACC [42], insula [43] and parahippocampus [44]. These hubs are interconnected and overlapped functionally with the previously discussed networks [45]. Moreover, other studies have reported increased beta band connectivity between the precuneus and the orbitofrontal cortex (OFC) and also DLPFC [46,47]. These frontal areas showed some laterality for emotional processing: the right OFC and DLPFC related to the distress network while the left side linked to the depression network [48]. As a conclusion, there is a defined network for emotional processing in tinnitus patients known as the tinnitus distress network. This network demonstrated two processing lines: one for the stressful feelings and the other for the depressive ones. The overlapping hubs in the two lines are the parahippocampus, amygdala, and the ACC, while they dissociate in the right and left frontal areas (Fig.1).

The dorsal anterior cingulate cortex is involved in the negative effects caused by tinnitus [24], chronic pain [49,50] and also the post-traumatic stress disorder [51]. Furthermore, the DLPFC has modulatory top-down effects on auditory processing [52,53], auditory memory [54,55], and attention [26]. It has been demonstrated that the impaired top-down cognitive control of DLPFC may have a key role in tinnitus persistence and interfere with habituation mechanisms leading to increased tinnitus distress [56]. In addition, significant positive correlations were obtained between the activity of these hubs and the subjectively perceived distress using tinnitus questionnaire (TQ) [24], and tinnitus handicap inventory (THI) [57]. Thus, the ACC and DLPFC seem to be the key hubs in tinnitus distress network, especially for having important connectivity with the other networks involved like the attention network and the auditory processing network. It is notable that the top-down control of the DLPFC over the other regions makes it the most important connecting area between tinnitus related networks and consequently introduces it as the area of choice to be targeted using the non-invasive neuromodulation techniques [56,58].

The role of memory mechanisms

As the attentional and emotional processing was proposed to be mandatory in tinnitus persistence and suffering, the memory mechanisms as other aspects of cognition are likewise of crucial importance. The parahippocampus is involved in the prevention of the natural habituation process

through a constant updating of the phantom percept [44]. The memory network consists of the parahippocampus, hippocampus and the amygdala [36]. It has important overlap with the auditory perceptual network and the distress network, in addition to rich functional connectivity with the ACC, DLPFC, insula and auditory cortex, which might interpret the relation between the hippocampal area and the cognitive dysfunction in tinnitus [59]. On the other hand, the functional connectivity analysis revealed the relation between the hippocampus/parahippocampus and the hypothalamus [60]. Such connections with the autonomic nervous system centers can interpret the role of this system in modulating some of the functional and emotional components of tinnitus distress and also explain how the patient can control this distress by controlling the autonomic system through relaxation strategies for example [36].

Discussion and clinical implications

Our previous review has pointed out the role of neuroimaging techniques in optimizing the use of non-invasive neuromodulation, transcranial electrical stimulation in particular, for the management of tinnitus [61]. In this review, we discussed tinnitus networks in sight of neuroimaging results and demonstrated how the brain areas are functioning in the network manner. Rich hubs in the auditory system, limbic system, and the frontal cortex are interconnected with each other and proposed to contribute to the tinnitus perception and its cognitive aspects.

As the brain is working as a complex network, it is beneficial to treat the brain functional disorders in the light of the network model. The clinical implications of this model are very important. The goal is to modulate the abnormal activity of the tinnitus networks. This goal can be achieved through neuromodulation techniques or other approaches. Based on the principle of the network science we can expect that targeting any hub in a network may be useful in modulating the whole system [62]. Moreover, by targeting the rich hub or provincial hub in the network the results may be much desirable through modulating more than one involved network. The reports from the transcranial magnetic stimulation [58,63] and transcranial electrical stimulation [64,65] studies had corroborated this notion. Furthermore, the multisite approach may also be the best choice for treating distressful tinnitus; for instance, targeting the prefrontal and auditory cortex in sequence, have reported being more effective in reducing both tinnitus loudness and distress in comparison to the stimulation of prefrontal tDCS, transcranial direct current stimulation, alone [66], or auditory tRNS, transcranial random noise stimulation alone [67]. The ultimate role is to find the appropriate region to be targeted depending on the neuroimaging data. As a future perspective, in order to utilize such important findings, further studies should provide a user-friendly tool for clinicians as an objective diagnostic tool; in which the clinician can find out which features are necessary for tinnitus assessment and consequently choosing the best intervention by recording EEG from the least number of electrodes, six electrodes for example two frontal, two parietal and two auditory like the neurofeedback montage. However, to reach this goal much causal research is needed and the study of effective connectivity is highly recommended. Effective connectivity modeling enables one to define the direction of effect between regions and thereupon attains the improved vision of the flow of signals through these networks.

Finally, the network model has been well correlated with the non-invasive neuromodulation techniques, and the results are compelling. We hope to generalize this concept to the other models of treatment and we expect to have satisfying outcomes. For example, we can target the distress and emotional network activity by means of counseling or cognitive behavioral therapy. Also, it is rational that relaxation techniques can regulate the autonomic nervous system and thereupon the distress network through its connection to the limbic system. Lastly, the modulation of attention networks by means of integrative and distractive strategies is another example which has been investigated in

many studies with significant results, such strategies can be applied simply through modifying the patient lifestyle to be more active and engaging [68]. However, in order to set up the guidelines for such algorithms, more studies are still needed.

Conclusion

Understanding the tinnitus network model can be helpful in optimizing the treatment strategies. The involvement of auditory areas in connection with the prefrontal area, the cingulate cortex, and the limbic system makes it necessary to consider all these systems in the management approach.

Conflict of interest

The study was not supported by any grants and the authors have no conflicts of interest to be declared.

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