**Hypothesis**

**Theoretical Tinnitus Multimodality Framework: A Neurofunctional Model**

Iman Ghodratitoostani1*, Alexandre C.B. Delbem1, Mohammad Torabi-Nami2,3,4, Bahador Makkabiadi5,6, Hamid Jalilvand7, Tanit Ganz Sanchez8,9

1USP-Institute of Mathematics and Computer Science, Universidade De São Paulo, São Carlos, SP, Brazil 2Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran 3Sleep Disorders Laboratory, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran 4Shiraz Neuroscience Research Center, Shiraz University of Medical Sciences, Shiraz, Iran 5Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran 6Research Center for Biomedical Technologies and Robotics (RCBTR), Institute for Advanced Medical Technologies (IAMT), Tehran, Iran 7Department of Audiology, School of Rehabilitation Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran 8University of São Paulo, Medical School, São Paulo, Brazil 9Instituto Ganz Sanchez, São Paulo, Brazil

*Corresponding author: Iman Ghodratitoostani, USP-Institute of Mathematics and Computer Science, Universidade De São Paulo, São Carlos, SP, Brazil iman.ghodrati@usp.br

Received: 19.02.2016 Revised: 22.03.2016 Accepted: 02.04.2016

**Abstract**

Our knowledge about subjective tinnitus physiopathology has improved in the last decades, while information to understand the main mechanisms that transform a neutral phantom sound to tinnitus distress appear to be inadequate. The current review presents evidence from several studies using neuroimaging, electrophysiology and brain lesion techniques aiming at hypothesizing a new realistic multimodality tinnitus framework which can better explain the structural and functional brain connectivity in different stages of tinnitus development. Further to the present work, a full review of the entire literature should be prompted to discuss evidence to more comprehensively investigate the relationship between structural and functional connectivity of tinnitus. Progresses in such framework will shed lights to the tinnitus neurofunctional model and further evidence-based treatment modalities.

**Introduction**

With the earlier functional and structural neuroimaging techniques including the quantitative electroencephalography (qEEG), magneto encephalography (MEG) and animal lesion studies, following areas have been implicated in tinnitus: the peripheral auditory system, the thalamus (reticular, medial geniculate and dorsal nuclei), auditory cortex, the limbic system (anterior cingulate cortex, amygdala), brainstem (raphe nucleus), subcallosal and paralimbic areas which include basal ganglia (ventral palladium), striatum (nucleus accumbens) and ventromedial prefrontal cortex (1-3). Figure 1 provides a schematic overview of the tinnitus-involved network through integrating data from SPECT, PET, fMRI and MEG studies in tinnitus.

The current review addresses tinnitus structural and functional brain network connectivity which may provide insights into a testable tinnitus framework and signal/information flows.
Some additional structural/functional data are discussed below.

**Thalamic regions**

The Thalamic Reticular nucleus (TRN) is located between the thalamus and cortex regions. TRN receives excitatory inputs from all cerebral cortices and their associated thalamic nuclei and sends inhibitory projections particularly to the thalamus (4). TRN is connected with a particular dorsal thalamic nucleus (4). It is also partitioned into seven different sectors considered to be independently involved with specific sensorial processing (4). Five sections are sensory (auditory, gustatory, somatosensory, visceral and visual), one is motor and the last is the Limbic (4). TRN is also associated with the visual area and its lesion alters the orientation of attention (5, 6). Considering its association with the dorsal thalamus and the prefrontal cortex (PFC), TRN receives excitatory inputs from the PFC and sends inhibitory projections to the dorsal thalamus (7). A mapping study of sensorial responses on TRN showed that some of its cells correspond to multimodal sensory neurons (8). Moreover, it has been shown that TRN mediates cross-modal effects of visual stimulation on auditory response in the MGB (9). It has further been demonstrated that some auditory cells in the TRN, project to the somatosensory and not to the auditory thalamic nuclei (10). These findings suggest the participation of the TRN cross-modal sensorial processing via the loop-connectivity between the cortex and the thalamus.

TRN is involved in sensory gating (11), attentional modulation (12, 13) and is also responsible for the generation of sleep spindles (14). TRN affects the activity in the dorsomedial (DM) thalamus. Lesions of TRN may influence the activity of the dorsomedial thalamus neurons through two possible pathways. One is the loss of the inhibitory input from the TRN due to excitatory neurons of the DM thalamus. The second is where PFC-NAc-VP pathway enhances the inhibitory action on DM thalamus by decreasing the excitatory pathway of the PFC to the neurons of NAc. This action reduces the inhibitory function of the NAc to the excitatory neurons of the ventral pallidum (VP), resulting in an inhibition of the DM thalamus (15-18). Therefore, lesion to TRN results in a dysfunctional control of the DM thalamus (13) where TRN receives projections from the PFC (13) and retains bidirectional connectivity with the dorsal thalamus (7).

The PFC-TRN circuit can enhance the motivation of dominant stimuli and also establish pathways to the cortex and enhance the motivation of reticular neurons to forcefully suppress distractors (7). The PFC-MD thalamus pathway, which maps via the same TRN prefrontal pathways, strengthen transmissions of relevant signal and weaken those of distractors, “lateral inhibition” (7).

The auditory component of TRN has a gating role in the control of auditory stimuli that are relayed from the thalamus to cortex (19). The gating TRN involvement in cross-modal stimuli processing for attention has been demonstrated. Evidence suggest that the cortical afferents from the temporal cortex, which enclose the primary and anterior auditory regions, topographically coincide with thalamic afferents from the ventromedial division of the medial geniculate nucleus at the auditory TRN (19).

Recently, a robust pathway from the amygdala to the TRN was discovered, which had only been exhibited in humans (20). It was shown that networks originated from the basal nuclei and the cortical nuclei of the amygdala, follow different paths within the thalamus, while subjected to coincidental terminal distributions in TRN. The majority of the fibers of both networks excite the amygdala anteriorly and localize dorsally toward the inferior thalamus peduncle or the external capsule and mainly enter the thalamus anteriorly (20). External stimuli with emotion values are transferred by the sensory systems to the cortex. The POF and the amygdala receive inputs from higher-order association cortices (21). Both areas project to the TRN via sensorial cortices and their thalamic nuclei (7). Thus, the POF and amygdala are found as optimal spots to direct attention to affective external stimuli through the posterior TRN.

**The auditory cortex**

Despite the prior empirical evidences, it was shown that the abnormal activity in auditory system can generate tinnitus (22). Animal studies demonstrated an enhancement of spontaneous and sound-evoked neuronal activity at several regions of the auditory pathways. However, whether the observed abnormal activity is related to tinnitus or hyperacusis (which is coincidental with tinnitus in most cases) remains as an open discussion (23). According to the intrinsic technique of fMRI, it is not feasible to detect the absolute blood oxygenation, while relative blood oxygenation between conditions can be compared (24, 25).

The influences of the top-down attention modulation on related neural activity was detected as approximated tinnitus effect in auditory cortex hyperactivity (26).
Limbic system

The limbic system’s involvement in tinnitus pathology is demonstrated in several studies, however, its specific role remains uncertain (27-47). Rauschecker (2010) proposed that the corticostriatal circuit can cause the chronic tinnitus resulting in the disturbance leading to permanent eruption of the gain control of the phantom sound perception as chronic tinnitus (3, 37). Furthermore, the corticostriatal network eruption has been illustrated in evaluation of reward, emotion, cognition and aversion in other domains (27-32).

The vmPFC and the nucleus accumbens (NAc) are components of the cortico-striatal thalamic circuit, whereby vmPFC sends excitatory projections to the NAc (48-50). Studies have shown a reduction in gray matter of the vmPFC in tinnitus patients against the control group representing a reduced neural activity output (51). On the other hand, the enhancement noted in the NAc activity can represent disinhibition of NAc by reducing vmPFC input to local inhibitory interneurons (51).

The amygdala

The Amygdala can be classified into lateral, basal, central and medial nucleus and interacted inhibitory cells. The lateral amygdala plays a sensory gateway role and receives neuronal inputs originated from the thalamic and cortical areas, hence associated with several sensory functions (auditory, visual, somatosensory, gustatory and olfactory) (52). The basal amygdala receives inputs from polymodal memory and high-level cognitive association cortices. Internally, information flows from the lateral and basal nucleus directly to the central nucleus and indirectly via the inhibitory central nucleus. The lateral nucleus of the amygdala receives direct neuronal input from the auditory thalamus (medial geniculate body) as well as the auditory cortex (52, 53). Output from the central nucleus is related to numerous autonomous functions. Excitatory projections from the thalamus to the hypothalamus stimulate the sympathetic nervous system to release corticosteroid hormone via the hypothalamic-pituitary gland, modulating the arousal and stress state. It has also been revealed the projections from basal amygdala are related to memory (hippocampus) and high-level cognition (prefrontal and associative cortices)(54).

In addition, amygdala processes emotions (55, 56) like fear and anger (57, 58) and drives external sensorial stimuli to behavioral and autonomic responses. The Amygdala detects the relevant stimuli (59, 60), bottom-up attention processes (61-63), anticipatory and arousal reactions (64, 65) and plays a vital role in motivation and decision-making (61, 66). The stimuli evaluation and motivation processing are more related to the basolateral and central nucleus, respectively (67). In conjunction, their association to cognition (56, 68, 69) influence decision-making and behavior. Furthermore, amygdala plays a role in fear-related classical conditioning (70, 71). Anatomical evidence shows the lateral convergence of the auditory thalamus, auditory cortex, somatosensory thalamus and associative cortices (72). Lesion studies have demonstrated that the medial geniculate body and the adjacent posterior intralaminar nucleus are important for association of the two stimuli and long-term potentiation (72). Lesion to the rat’s amygdala showed impaired responses to acoustic stimuli (73). The amygdala responses to sensory stimuli are not always accompanied by conscious or even an awake state (74). Sensory evaluation during sleep is a useful feature for surviving dangerous conditions (75) and EEG and fMRI studies showed that sound presented during NREM sleep phase could decrease the amygdala sensitivity to other stimuli, possibly as a sleep protective mechanism (76). The amygdala also responds to music (77, 78). Neuroimaging techniques in humans have exhibited that music is processed in several areas of brain related to emotional processing, including the amygdala (77). The amygdala responds to pleasant and unpleasant music and even unexpected musical events (79). Rodent studies have demonstrated that fear-conditioning can activate the amygdala and may improve tonotopic map plasticity in the auditory cortex. The receptive fields for frequencies of unconditioned stimuli were enhanced by co-activity of the basal forebrain and auditory cortex (80-83). It was also demonstrated that stimulation of the lateral amygdala can inhibit the primary auditory cortex response to sound by means of GABA receptors (84). Additionally, amygdala neurons project directly to the inferior colliculus, which modulates emotion processing and plays a role as a thalamo-cortical feedback at a low-level of the ascending auditory pathway (85).

The hippocampus

The hippocampus receives sensory auditory input directly or indirectly from auditory association cortices via the para-hippocampal cortex, the perirhinal cortex and other forebrain areas including the medial frontal cortex, insula, and amygdala (86, 87). The auditory association cortex receives inputs
from the hippocampus via parahippocampal and perirhinal cortices (88).

The hippocampus is associated with explicit and declarative memory (89, 90) and also episodic memory, while the right hippocampus is specifically associated with spatial memory (91). The dorsal hippocampus participates in primary cognitive information processes, while the ventral hippocampus is involved in emotional tasks for memory and learning. The amygdala can modulate hippocampal memory; the hippocampus formed memory can modulates amygdala response to emotional stimuli (92, 93). The amygdala contribution to hippocampus increases emotional value of the stimuli, which in turn facilitates hippocampal memory-consolidation (94). Moreover, amygdala and hippocampus collaboration can contribute to long-term consolidation of emotional events (95). The main function of the hippocampal auditory component is the formation of long-term memories. Music memory retrieval activates mainly the right, but not left hippocampus hemisphere (96). The hippocampus is also involved in emotional music processing. Functional-MRI studies have shown that the activity of the right hippocampus and amygdala are enhanced upon listening to sad, but not neutral or pleasant music (97). Additionally, there is evidence supporting that hearing-loss is linked with degeneration in the hippocampus (98). Given such observations, and despite hippocampus’ role in normal auditory system illustrated in Figure 1, it is suggested that hippocampus can play a role in a particular type of tinnitus which involves emotional processes such as sound-blast, which has not covered in our proposed neurofunctional model.

**Prefrontal Cortex**

The prefrontal cortex (PFC) is thought to participate in high-level control of behavior generation (99). PFC is highly interconnected with the brain, including extensive connections with cortical, subcortical and brainstem sites (100). The dorsal prefrontal cortex is especially interconnected with brain regions involved in attention, cognition and action, while the ventral prefrontal cortex interconnects with brain regions involved in emotion (101). PFC receives excitatory inputs (102, 103) from the hippocampus, basolateral amygdala (BLA), nucleus accumbens (NAc) and other limbic cortices by means of intracortical projections (104, 105). The BLA and hippocampal have control over the PFC cells (106, 107). Synapses from the hippocampus to the PFC are able to change and articulate several types of plasticity in cognitive processes (108, 109).

One of the most recent relevant fMRI studies, using a voxel-based morphometry analysis, showed gray matter reduction of subcallosal regions (37), particularly in the vmPFC in tinnitus sufferer (110, 111). Furthermore, a MEG study in tinnitus patients showed that vmPFC activity is positively correlated with resting-state cortical networks, however results were not duplicated in control subjects (51). It was shown that in tinnitus subjects, medial prefrontal cortex activity was vigorously altered by activity in other regions of the brain, and weakly influenced activity in other brain regions (26). It also demonstrated functional differences in the vmPFC between tinnitus patients and a control group. The study observed a positive correlation between BOLD responses in the vmPFC and psychoacoustic tinnitus parameters, such as loudness and duration.

![Figure 1](image.png)

Figure 1. Auditory midbrain/brainstem, and Amygdala divisions and connections in auditory system. The lateral Amygdala receives neuronal input from auditory thalamus (medial geniculate nucleus) and auditory cortex (primarily association areas) The basal Amygdala projects to inferior colliculus to generate an amygdalar-auditory feedback loop; B, basal Amygdala; C, central Amygdala; CN, cochlear nucleus; IC, inferior colliculus; L, lateral Amygdala; MGN, medial geniculate nucleus; SOC, superior olivary complex. Modified from (54).

Other variables related to tinnitus, including tinnitus handicap inventory scores, hearing loss, noise sensitivity, anxiety and depression showed weak or no correlations with the BOLD signal (26). The observed activity in the vmPFC represents an effort to suppress the perceived sound to be able to perform the required experimental task. The positive correlation of the vmPFC activity with
psychoacoustic parameters is an indication that this neural activity shows specific relation with conscious awareness (26).

The particular projection observed in the dorsolateral prefrontal cortex (dPFC), posterior orbitofrontal cortex (pOFC), vmPFC as part of pOFC, and their associated mediodorsal thalamic nucleus (MD) depicts a crucial role in cognition, emotion and memory (20) in addition to tasks such as intrusive thoughts and emotions (113). These findings would therefore suggest that LPFC performs an important role in cognitive evaluation, which is a finding in agreement with top-down attention regulation processes.

**The subcallosal area and paralimbic system**

Thalamus reticular nucleus and dorsal thalamus are triggered by the serotonergic neurons which receive projects from DRN, nucleus accumbens and paralimbic area (18, 114). GABAergic neurons of TRN are stimulated by serotonin (115, 116) which results in inhibition of thalamic relay in sensory sectors (117). The TRN inhibition may shift between tonic and burst firing mode of the thalamo-cortical relay (118, 119).

Leaver et al (2011) proposed that the NAc hyperactivity enhances appraisal of the phantom sound perception. The vmPFC also projects to the TRN, manifesting its auditory distribution (13), which inhibits communication between the auditory cortex and medial geniculate nucleus (MGN). Therefore, deficient vmPFC output could further inhibit the phantom sound at the MGN (110). Based on the evidence, patients with better preserved gray matter in the vmPFC had less hyperactivity in NAc and mHG, suggesting that the vmPFC is able to apply inhibitory influence on the auditory system (110). It was suggested that dysregulation of the limbic and auditory networks may be at the heart of chronic tinnitus (110). Rauschecker et al proposed a noise cancelling mechanism involvement based on the studies which found notable subcallosal volume loss in tinnitus patients (37, 42). Subcallosal activation correlates at varying degrees with the unpleasant effects of dissonant music (28) and is altered by the perception and expectation of pain (120). Moreover, abnormal activity levels in the subcallosal area are observed in certain depressive disorders patients (121, 122). Additionally, the posterior portion of subcallosal area is projected to the NAc, which is an important component of the ventral striatum (123, 124). The ventral striatum has strong interconnectivity with subcallosal area (125, 126). NAc has a critical role in reward behavior and avoidance learning by means of dopaminergic pathways (127) and plays a regulatory role in several emotion-related systems via serotonergic neurons (128).

Between 20 to 40% of the patients who suffered noise-induced hearing loss also developed chronic tinnitus (129). Moreover, patients with somatic tinnitus are capable of modulating the loudness and pitch of the phantom sound by movements of the eyes, neck or jaw (130). Indicative alteration will happen in tinnitus level for instance secondary to sleep deprivation or stress (131-133). The phantom sound might completely disappear for one day or more and then return as loud as before. This intermittent perception could reflects the perception suppression actions of inhibitory gating mechanisms (3).

**Aberrant tinnitus-related plasticity in the auditory and limbic systems**

Three types of experimental brain plasticity are observed in conjunction with tinnitus.

First is alterations in the level of spontaneous neural activity in the central auditory system (134, 135) such as noise exposure and ototoxic drugs modulation (136) which could lead to changes in spontaneous activity in different auditory brain areas. Noise exposure of any kind reduces spontaneous firing rate of the eighth cranial nerve which terminates in magnifying spontaneous firing rate at several level of auditory brain cortex (137, 138).

Next, changes in temporal pattern of spontaneous neural activity could modulate moreynchronization of activities across auditory neurons (135, 139). In general, changes can occur via external auditory sound stimulation so differences in neural synchrony may also be perceived as a tinnitus. Burst-firing and neural synchrony could materialize in tinnitus patients (137, 139). Apparently, peripheral hearing-loss reduces the afferent inputs to brainstem which in turn contributes to changes in neural activity of the central auditory system thereby causing tinnitus.

Finally, reorganization of tonotopic maps can also cause tinnitus (139-141). These readjustments may not directly correspond to tinnitus, while they can influence abnormal neural activity such as cortical reorganization, which can cause over-description of frequencies at the edge of peripheral hearing-loss (141, 142).

Tinnitus studies have demonstrated that auditory thalamus projection to the amygdala may generate an emotional reflex to the phantom sound (54). Experimentally-induced tinnitus established the
correlation between the auditory cortex and amygdala activation (41). Tinnitus is related with gray matter deficiency in auditory system (inferior colliculus), in hippocampus which regulates tinnitus pathophysiology (42, 43) and in subcallosal region including nucleus accumbens, which is connected with amygdala and emotion (37). The dorsal cochlear nucleus is over-activated in the presence of tinnitus (44). Furthermore, tinnitus may alter attention and emotion via affecting the locus coeruleus, the reticular formation and the raphe nuclei (33, 143). Activities observed in many types of tinnitus indicate the significant roles of amygdala and hippocampus (45) along with parabulbar nucleus and insula (144). Developing a learning mechanisms which creates awareness of the phantom-sound and involves the role of a distress network consisting of anterior cingulate cortex, anterior insula and amygdala has been proposed (46). Similar to the externally-induced noises, internally-generated tinnitus can cause emotional distress resulting in mood disorders such as depression. Stress or depression may further induce tinnitus (145). There is also evidence that pathways including the limbic system may apply to noise cancellation mechanisms. A feedback network from amygdala to the auditory system can suppress the tinnitus signal at a subcortical level before it reaches the auditory cortex and induces conscious perception (47). Amygdala neurons project to the nucleus accumbens, consequently connect to inhibitory neurons in thalamic reticular nucleus, which synapse on ascending neurons in medial geniculate body via lateral inhibition mechanism, preventing signal to reach auditory cortex. Limbic system and associated areas play an important role in tinnitus generation/suppression and can be vital in future tinnitus treatments. Treatment procedure of cognitive level may need to shift the attention away from undesired phantom sound (146).

Concluding remarks

The knowledge of structural and functional brain network connectivity is necessary and yet insufficient to project tinnitus development frameworks. Exploring the exact role of bottom-up and top-down cognitive processes is essential for arriving at a realistic tinnitus model. Furthermore, investigating the relation between tinnitus and prevalent related comorbidities may lead to better insights into the tinnitus functional network.

Eventually, projecting novel animal and clinical models can make distinction between different paradigms and improve our perception about tinnitus, its pathophysiological underpinnings and evidence-base treatment modalities.

References


43. Pessa L. Reprint of: Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?". Neuropsychologia. 2011;49(4):681-94.


46. Murray EA, Wise SP. What, if anything, can monkeys tell us about human amnesia when they can't say anything at all? Neuropsychologia. 2010;48(8):2385-405.


50. Pessa L. Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?". Neuropsychologia. 2011;49(4):681-94.


52. Weinberger NM. The medial geniculate, not the amygdala, as the root of auditory fear conditioning. Hear Res. 2011;274(1-2):601.


