Hypothesis

Theoretical Tinnitus Multimodality Framework: A Neurofunctional Model

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Received: 19.02.2016
Revised: 22.03.2016
Accepted: 02.04.2016

Keywords: Tinnitus; Neurofunctional model; Neuroimaging; Electrophysiology; Functional connectivity; Structural Connectivity

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.

https://doi.org/10.18869/nrip.jamsat.2.1.181

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) . Figure1 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 palladium (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 wean 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 sensory 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 sensorial systems to the cortex. The POFC 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 POFC 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 coinsidental 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 whas been 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.

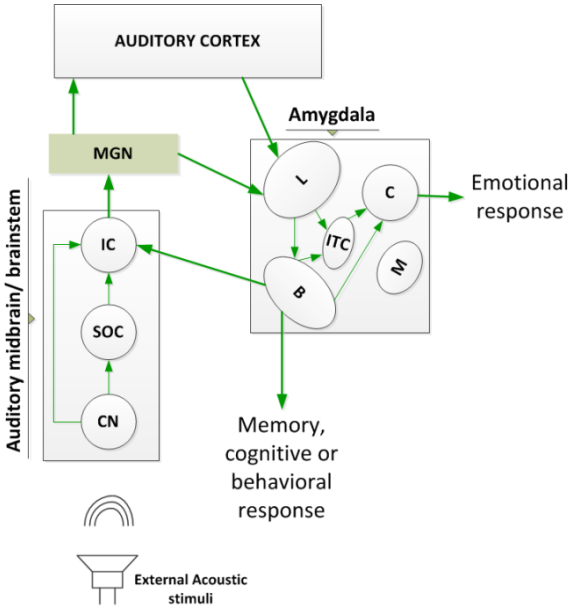

Figure 1. Auditory midbrain/ brainstem, and Amygdala divisions and connections in auditory system. The lateral Amygdala receives neuronal input from auditory thalamus (medial geniculate nucleus) and auditory cortex (primarily association areas) The basal Amygdala projects to inferior colliculus to generate 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 (dlPFC), 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 more synchronization 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 parabrachial 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

1. *Seydell-Greenwald A, Leaver AM, Turesky TK, Morgan S, Kim HJ, Rauschecker JP. Functional MRI evidence for a role of ventral prefrontal cortex in tinnitus. Brain research. 2012;1485:22-39.*
2. *Seydell-Greenwald A, Raven EP, Leaver AM, Turesky TK, Rauschecker JP. Diffusion imaging of auditory and auditory-limbic connectivity in tinnitus: preliminary evidence and methodological challenges. Neural plasticity. 2014;2014:145943.*
3. *Rauschecker JP, Leaver AM, Mühlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron. 2010;66:819-26.*
4. *Pinault D. The thalamic reticular nucleus: structure, function and concept. Brain research Brain research reviews. 2004;46(1):1-31.*
5. *Weese GD, Phillips JM, Brown VJ. Attentional orienting is impaired by unilateral lesions of the thalamic reticular nucleus in the rat. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1999;19(22):10135-9.*
6. *Baldauf ZB. Dual chemoarchitectonic lamination of the visual sector of the thalamic reticular nucleus. Neuroscience. 2010;165(3):801-18.*
7. *Zikopoulos B, Barbas H. Circuits formultisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. Reviews in the neurosciences. 2007;18(6):417-38.*
8. *Shosaku A, Sumitomo I. Auditory neurons in the rat thalamic reticular nucleus. Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale. 1983;49(3):432-42.*
9. *Yu XJ, Xu XX, Chen X, He SG, He JF. Slow Recovery From Excitation of Thalamic Reticular Nucleus Neurons. Journal of neurophysiology. 2009;101(2):980-7.*
10. *Kimura A, Imbe H, Donishi T, Tamai Y. Axonal projections of single auditory neurons in the thalamic reticular nucleus: implications for tonotopy-related gating function and cross-modal modulation. Eur J Neurosci. 2007;26(12):3524-35.*
11. *Krause M, Hoffmann WE, Hajos M. Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. Biological psychiatry. 2003;53(3):244-53.*
12. *Mayo JP. Intrathalamic mechanisms of visual attention. J Neurophysiol. 2009;101(3):1123-5.*
13. *Zikopoulos B, Barbas H. Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2006;26(28):7348-61.*
14. *Torres-Garcia ME, Solis O, Patricio A, Rodriguez-Moreno A, Camacho-Abrego I, Limon ID, et al. Dendritic morphology changes in neurons from the prefrontal cortex, hippocampus and nucleus accumbens in rats after lesion of the thalamic reticular nucleus. Neuroscience. 2012;223:429-38.*
15. *Churchill L, Zahm DS, Kalivas PW. The mediodorsal nucleus of the thalamus in rats--I. forebrain gabaergic innervation. Neuroscience. 1996;70(1):93-102.*
16. *Churchill L, Zahm DS, Duffy P, Kalivas PW. The mediodorsal nucleus of the thalamus in rats--II. Behavioral and neurochemical effects of GABA agonists. Neuroscience. 1996;70(1):103-12.*
17. *Zahm DS, Williams E, Wohltmann C. Ventral striatopallidothalamic projection: IV. Relative involvements of neurochemically distinct subterritories in the ventral pallidum and adjacent parts of the rostroventral forebrain. The Journal of comparative neurology. 1996;364(2):340-62.*
18. *O'Donnell P, Lavin A, Enquist LW, Grace AA, Card JP. Interconnected parallel circuits between rat nucleus accumbens and thalamus revealed by retrograde transynaptic transport of pseudorabies virus. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1997;17(6):2143-67.*
19. *Kimura A, Yokoi I, Imbe H, Donishi T, Kaneoke Y. Auditory thalamic reticular nucleus of the rat: anatomical nodes for modulation of auditory and cross-modal sensory processing in the loop connectivity between the cortex and thalamus. The Journal of comparative neurology. 2012;520(7):1457-80.*
20. *Zikopoulos B, Barbas H. Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2012;32(15):5338-50.*

21. Barbas H, Zikopoulos B, Timbie C. Sensory pathways and emotional context for action in primate prefrontal cortex. Biological psychiatry. 2011;69(12):1133-9.
22. Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: the neuroscience of tinnitus. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010;30(45):14972-9.
23. Gu JW, Halpin CF, Nam EC, Levine RA, Melcher JR. Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity. J Neurophysiol. 2010;104(6):3361-70.
24. Logothetis NK. What we can do and what we cannot do with fMRI. Nature. 2008;453(7197):869-78.
25. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nature reviews Neuroscience. 2001;2(10):685-94.
26. Seydell-Greenwald A, Leaver AM, Turesky TK, Morgan S, Kim HJ, Rauschecker JP. Functional MRI evidence for a role of ventral prefrontal cortex in tinnitus. Brain research. 2012.
27. Bar M. A cognitive neuroscience hypothesis of mood and depression. Trends in cognitive sciences. 2009;13(11):456-63.
28. Blood AJ, Zatorre RJ, Bermudez P, Evans AC. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat Neurosci. 1999;2(4):382-7.
29. Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron. 2001;30(2):619-39.
30. Kable JW, Glimcher PW. The neurobiology of decision: consensus and controversy. Neuron. 2009;63(6):733-45.
31. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci. 2007;10(9):1116-24.
32. Sotres-Bayon F, Quirk GJ. Prefrontal control of fear: more than just extinction. Current opinion in neurobiology. 2010;20(2):231-5.
33. Langguth B. A review of tinnitus symptoms beyond 'ringing in the ears': a call to action. Current medical research and opinion. 2011;27(8):1635-43.
34. Halford JB, Anderson SD. Tinnitus severity measured by a subjective scale, audiometry and clinical judgement. The Journal of laryngology and otology. 1991;105(2):89-93.
35. Halford JB, Anderson SD. Anxiety and depression in tinnitus sufferers. Journal of psychosomatic research. 1991;35(4-5):383-90.
36. Robinson S. Antidepressants for treatment of tinnitus. Prog Brain Res. 2007;166:263-71.
37. Muhlau M, Rauschecker JP, Oestreicher E, Gaser C, Rottinger M, Wohlschlager AM, et al. Structural brain changes in tinnitus. Cereb Cortex. 2006;16(9):1283-8.
38. Langguth B, Kleinjung T, Landgrebe M. Tinnitus: the complexity of standardization. Evaluation & the health professions. 2011;34(4):429-33.
39. Moller AR. Pathophysiology of tinnitus. Otolaryngol Clin North Am. 2003;36(2):249-66, v-vi.
40. Moller AR. Neural plasticity in tinnitus. Prog Brain Res. 2006;157:365-72.
41. Mahlke C, Wallhausser-Franke E. Evidence for tinnitus-related plasticity in the auditory and limbic system, demonstrated by arg3.1 and c-fos immunocytochemistry. Hear Res. 2004;195(1-2):17-34.
42. Landgrebe M, Langguth B, Rosengarth K, Braun S, Koch A, Kleinjung T, et al. Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. NeuroImage. 2009;46(1):213-8.
43. Lanting CP, de Kleine E, van Dijk P. Neural activity underlying tinnitus generation: results from PET and fMRI. Hear Res. 2009;255(1-2):1-13.
44. Kaltenbach JA, Godfrey DA. Dorsal cochlear nucleus hyperactivity and tinnitus: are they related? American journal of audiology. 2008;17(2):S148-61.
45. Shulman A. A Final Common Pathway for Tinnitus - The Medial Temporal Lobe System. Int Tinnitus J. 1995;1(2):115-26.
46. De Ridder D, Vanneste S, Congedo M. The distressed brain: a group blind source separation analysis on tinnitus. PloS one. 2011;6(10):e24273.
47. Rauschecker JP, Leaver AM, Muhlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. Neuron. 2010;66(6):819-26.
48. Divac I, Mogensen J, Marinkovic S, Martensson R. On the projections from the neostriatum to the cerebral cortex: the "displaced" neurons. Neuroscience. 1987;21(1):197-205.
49. Ferry AT, Ongur D, An X, Price JL. Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. The Journal of comparative neurology. 2000;425(3):447-70.
50. Jayaraman A. Anatomical evidence for cortical projections from the striatum in the cat. Brain research. 1980;195(1):29-36.
51. Schlee W, Mueller N, Hartmann T, Keil J, Lorenz I, Weisz N. Mapping cortical hubs in tinnitus. BMC biology. 2009;7:80.
52. LeDoux J. The amygdala. Current biology : CB. 2007;17(20):R868-74.
53. Sah P, Lopez De Armentia M. Excitatory synaptic transmission in the lateral and central amygdala. Annals of the New York Academy of Sciences. 2003;985:67-77.
54. Kraus KS, Canlon B. Neuronal connectivity and interactions between the auditory and limbic systems. Effects of noise and tinnitus. Hear Res. 2012;288(1-2):34-46.
55. Rasia-Filho AA, Londero RG, Achaval M. Functional activities of the amygdala: an overview. Journal of psychiatry & neuroscience : JPN. 2000;25(1):14-23.
56. Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron. 2005;48(2):175-87.
57. Davis M, Whalen PJ. The amygdala: vigilance and emotion. Molecular psychiatry. 2001;6(1):13-34.
58. Baxter MG, Murray EA. The amygdala and reward. Nature reviews Neuroscience. 2002;3(7):563-73.
59. Sander D, Grafman J, Zalla T. The human amygdala: an evolved system for relevance detection. Reviews in the neurosciences. 2003;14(4):303-16.
60. Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. Brain research Brain research reviews. 2003;41(1):88-123.
61. Pessoa 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.
62. Compton RJ. The interface between emotion and attention: a review of evidence from psychology and neuroscience. Behavioral and cognitive neuroscience reviews. 2003;2(2):115-29.
63. Compton RJ, Banich MT, Mohanty A, Milham MP, Herrington J, Miller GA, et al. Paying attention to emotion: an fMRI investigation of cognitive and emotional stroop tasks. Cognitive, affective & behavioral neuroscience. 2003;3(2):81-96.
64. 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.
65. Murray EA. The amygdala, reward and emotion. Trends in cognitive sciences. 2007;11(11):489-97.
66. Bechara A, Damasio H, Damasio AR. Role of the amygdala in decision-making. Annals of the New York Academy of Sciences. 2003;985:356-69.
67. Balleine BW, Killcross S. Parallel incentive processing: an integrated view of amygdala function. Trends Neurosci. 2006;29(5):272-9.
68. Pessoa L. Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?". Neuropsychologia. 2010;48(12):3416-29.
69. Salzman CD, Fusi S. Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. Annual review of neuroscience. 2010;33:173-202.
70. Maren S. What the amygdala does and doesn't do in aversive learning. Learn Mem. 2003;10(5):306-8.
71. Maren S. Synaptic mechanisms of associative memory in the amygdala. Neuron. 2005;47(6):783-6.
72. Weinberger NM. The medial geniculate, not the amygdala, as the root of auditory fear conditioning. Hear Res. 2011;274(1-2):61-74.
73. Armony JL, Quirk GJ, LeDoux JE. Differential effects of amygdala lesions on early and late plastic components of auditory cortex spike trains during fear conditioning. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1998;18(7):2592-601.
74. Pedemonte M, Pena JL, Velluti RA. Firing of inferior colliculus auditory neurons is phase-locked to the hippocampus theta rhythm during paradoxical sleep and waking. Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale. 1996;112(1):41-6.
75. Ising H, Kruppa B. Health effects caused by noise: evidence in the literature from the past 25 years. Noise & health. 2004;6(22):5-13.
76. Czisch M, Wehrle R, Stiegler A, Peters H, Andrade K, Holsboer F, et al. Acoustic oddball during NREM sleep: a combined EEG/fMRI study. PloS one. 2009;4(8):e6749.
77. Boso M, Politi P, Barale F, Enzo E. Neurophysiology and neurobiology of the musical experience. Functional neurology. 2006;21(4):187-91.
78. Limb CJ. Structural and functional neural correlates of music perception. The anatomical record Part A, Discoveries in molecular, cellular, and evolutionary biology. 2006;288(4):435-46.

79. Jentschke S, Koelsch S, Friederici AD. Investigating the relationship of music and language in children: influences of musical training and language impairment. Annals of the New York Academy of Sciences. 2005;1060:231-42.
80. Morris JS, Friston KJ, Dolan RJ. Experience-dependent modulation of tonotopic neural responses in human auditory cortex. Proceedings Biological sciences / The Royal Society. 1998;265(1397):649-57.
81. Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. Biological psychiatry. 2003;53(6):494-501.
82. Weinberger NM. Associative representational plasticity in the auditory cortex: a synthesis of two disciplines. Learn Mem. 2007;14(1-2):1-16.
83. Froemke RC, Martins AR. Spectrotemporal dynamics of auditory cortical synaptic receptive field plasticity. Hear Res. 2011;279(1-2):149-61.
84. He DF, Chen FJ, Zhou SC. GABA mediaties the inhibitory effect of lateral amygdaloid nucleus stimulation on the acoustic response of neurons in A l cortex: An in vivo microiontophoretic study. Sheng li xue bao : [Acta physiologica Sinica]. 2004;56(3):374-8.
85. Marsh RA, Fuzessery ZM, Grose CD, Wenstrup JJ. Projection to the inferior colliculus from the basal nucleus of the amygdala. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2002;22(23):10449-60.
86. Mohedano-Moriano A, Pro-Sistiaga P, Arroyo-Jimenez MM, Artacho-Perula E, Insausti AM, Marcos P, et al. Topographical and laminar distribution of cortical input to the monkey entorhinal cortex. Journal of anatomy. 2007;211(2):250-60.
87. Munoz-Lopez MM, Mohedano-Moriano A, Insausti R. Anatomical pathways for auditory memory in primates. Frontiers in neuroanatomy. 2010;4:129.
88. O'Mara S. The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. Journal of anatomy. 2005;207(3):271-82.
89. Eichenbaum H. Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron. 2004;44(1):109-20.
90. DeVito LM, Eichenbaum H. Distinct contributions of the hippocampus and medial prefrontal cortex to the "what-where-when" components of episodic-like memory in mice. Behavioural brain research. 2010;215(2):318-25.
91. Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. Neuron. 2002;35(4):625-41.
92. Phelps EA. Human emotion and memory: interactions of the amygdala and hippocampal complex. Current opinion in neurobiology. 2004;14(2):198-202.
93. Richter-Levin G. The amygdala, the hippocampus, and emotional modulation of memory. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry. 2004;10(1):31-9.
94. Abe K. Modulation of hippocampal long-term potentiation by the amygdala: a synaptic mechanism linking emotion and memory. Japanese journal of pharmacology. 2001;86(1):18-22.
95. Richter-Levin G, Akirav I. Amygdala-hippocampus dynamic interaction in relation to memory. Molecular neurobiology. 2000;22(1-3):11-20.
96. Watanabe T, Yagishita S, Kikyo H. Memory of music: roles of right hippocampus and left inferior frontal gyrus. NeuroImage. 2008;39(1):483-91.
97. Mitterschiffthaler MT, Fu CH, Dalton JA, Andrew CM, Williams SC. A functional MRI study of happy and sad affective states induced by classical music. Human brain mapping. 2007;28(11):1150-62.
98. Angelucci F, Fiore M, Ricci E, Padua L, Sabino A, Tonali PA. Investigating the neurobiology of music: brain-derived neurotrophic factor modulation in the hippocampus of young adult mice. Behavioural pharmacology. 2007;18(5-6):491-6.
99. Warden MR, Selimbeyoglu A, Mirzabekov JJ, Lo M, Thompson KR, Kim SY, et al. A prefrontal cortex-brainstem neuronal projection that controls response to behavioural challenge. Nature. 2012;492(7429):428-32.
100. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. Neuropsychology review. 2006;16(1):17-42.
101. Price JL. Prefrontal cortical networks related to visceral function and mood. Annals of the New York Academy of Sciences. 1999;877:383-96.
102. Sesack SR, Pickel VM. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. The Journal of comparative neurology. 1992;320(2):145-60.
103. Vertes RP. Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. Neuroscience. 2006;142(1):1-20.
104. Jay TM, Witter MP. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. The Journal of comparative neurology. 1991;313(4):574-86.
105. Lewis DA, Anderson SA. The functional architecture of the prefrontal cortex and schizophrenia. Psychological medicine. 1995;25(5):887-94.
106. O'Donnell P, Grace AA. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1995;15(5 Pt 1):3622-39.
107. Goto Y, O'Donnell P. Network synchrony in the nucleus accumbens in vivo. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2001;21(12):4498-504.
108. Silva-Gomez AB, Rojas D, Juarez I, Flores G. Decreased dendritic spine density on prefrontal cortical and hippocampal pyramidal neurons in postweaning social isolation rats. Brain research. 2003;983(1-2):128-36.
109. Kolb B, Forgie M, Gibb R, Gorny G, Rowntree S. Age, experience and the changing brain. Neurosci Biobehav Rev. 1998;22(2):143-59.
110. Leaver AM, Renier L, Chevillet MA, Morgan S, Kim HJ, Rauschecker JP. Dysregulation of limbic and auditory networks in tinnitus. Neuron. 2011;69(1):33-43.
111. Leaver AM, Seydell-Greenwald A, Turesky TK, Morgan S, Kim HJ, Rauschecker JP. Cortico-limbic morphology separates tinnitus from tinnitus distress. Frontiers in systems neuroscience. 2012;6:21.
112. Tomasi D, Caparelli EC, Chang L, Ernst T. fMRI-acoustic noise alters brain activation during working memory tasks. NeuroImage. 2005;27(2):377-86.
113. Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, et al. Neural circuitry underlying voluntary suppression of sadness. Biological psychiatry. 2003;53(6):502-10.
114. Brown P, Molliver ME. Dual serotonin (5-HT) projections to the nucleus accumbens core and shell: relation of the 5-HT transporter to amphetamine-induced neurotoxicity. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2000;20(5):1952-63.
115. McCormick DA, Wang Z. Serotonin and noradrenaline excite GABAergic neurones of the guinea-pig and cat nucleus reticularis thalami. The Journal of physiology. 1991;442:235-55.
116. Pape HC, McCormick DA. Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. Nature. 1989;340(6236):715-8.
117. Guillery RW, Sherman SM. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. Neuron. 2002;33(2):163-75.
118. Llinas R, Jahnsen H. Electrophysiology of mammalian thalamic neurones in vitro. Nature. 1982;297(5865):406-8.
119. Sherman SM. A wake-up call from the thalamus. Nat Neurosci. 2001;4(4):344-6.
120. Ploghaus A, Becerra L, Borras C, Borsook D. Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. Trends in cognitive sciences. 2003;7(5):197-200.
121. Drevets WC, Price JL, Simpson JR, Jr., Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997;386(6627):824-7.
122. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651-60.
123. Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc Natl Acad Sci U S A. 2001;98(20):11818-23.
124. Gruber AJ, Hussain RJ, O'Donnell P. The nucleus accumbens: a switchboard for goal-directed behaviors. PloS one. 2009;4(4):e5062.
125. Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, Katz E, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. Cereb Cortex. 2008;18(6):1374-83.
126. Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex. 2000;10(3):206-19.
127. McCullough LD, Sokolowski JD, Salamone JD. A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. Neuroscience. 1993;52(4):919-25.

128. Ambroggi F, Ishikawa A, Fields HL, Nicola SM. Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. Neuron. 2008;59(4):648-61.
129. Hoffman HJ, Reed GW. Epidemiology of tinnitus. Tinnitus: Theory and Management2004. p. 16e41.
130. Levine RA, Abel M, Cheng H. CNS somatosensory-auditory interactions elicit or modulate tinnitus. Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale. 2003;153(4):643-8.
131. Alster J, Shemesh Z, Ornan M, Attias J. Sleep disturbance associated with chronic tinnitus. Biological psychiatry. 1993;34(1-2):84-90.
132. Folmer RL, Griest SE. Tinnitus and insomnia. Am J Otolaryngol. 2000;21(5):287-93.
133. Hallam RS. Correlates of sleep disturbance in chronic distressing tinnitus. Scandinavian audiology. 1996;25(4):263-6.
134. Kaltenbach JA. Neurophysiologic mechanisms of tinnitus. J Am Acad Audiol. 2000;11(3):125-37.
135. Eggermont JJ. Correlated neural activity as the driving force for functional changes in auditory cortex. Hear Res. 2007;229(1-2):69-80.
136. Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends in neurosciences. 2004;27(11):676-82.
137. Norena AJ, Eggermont JJ. Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. Hearing research. 2003;183(1-2):137-53.
138. Kaltenbach JA, Zacharek MA, Zhang J, Frederick S. Activity in the dorsal cochlear nucleus of hamsters previously tested for tinnitus following intense tone exposure. Neurosci Lett. 2004;355(1-2):121-5.
139. Seki S, Eggermont JJ. Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. Hear Res. 2003;180(1-2):28-38.
140. Muhlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci U S A. 1998;95(17):10340-3.
141. Eggermont JJ. Cortical tonotopic map reorganization and its implications for treatment of tinnitus. Acta oto-laryngologica Supplementum. 2006(556):9-12.
142. Rajan R, Irvine DR. Neuronal responses across cortical field A1 in plasticity induced by peripheral auditory organ damage. Audiology & neuro-otology. 1998;3(2-3):123-44.
143. Langguth B, Landgrebe M, Kleinjung T, Sand GP, Hajak G. Tinnitus and depression. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2011;12(7):489-500.
144. Lenhardt ML, Shulman A, Goldstein BA. The role of the insula cortex in the final common pathway for tinnitus: experience using ultra-high-frequency therapy. Int Tinnitus J. 2008;14(1):13-6.
145. Robinson SK, Viirre ES, Stein MB. Antidepressant therapy in tinnitus. Hear Res. 2007;226(1-2):221-31.
146. Zenner HP, Pfister M, Birbaumer N. Tinnitus sensitization: Sensory and psychophysiological aspects of a new pathway of acquired centralization of chronic tinnitus. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2006;27:1054-63.