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Published in:
Hearing Research

DOI:
10.1016/j.heares.2021.108280

Publication date:
2021

Hearing Research 407 (2021) 108280

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Review Article

The thalamus and tinnitus: Bridging the gap between animal data and findings in humans

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ARTICLE INFO

Article history:
Received 12 February 2021
Revised 26 April 2021
Accepted 27 May 2021
Available online 13 June 2021

Keywords:
Auditory processing
Thalamus
Tinnitus
Connectivity
Neuroimaging

ABSTRACT

The neuronal mechanisms underlying tinnitus are yet to be revealed. Tinnitus, an auditory phantom sensation, used to be approached as a purely auditory domain symptom. More recently, the modulatory impact of non-auditory brain regions on the percept and burden of tinnitus are explored. The thalamus is uniquely situated to facilitate the communication between auditory and non-auditory subcortical and cortical structures. Traditionally, animal models of tinnitus have focussed on subcortical auditory structures, and research with human participants has been concerned with cortical activity in auditory and non-auditory areas. Recently, both research fields have investigated the connectivity between subcortical and cortical regions and between auditory and non-auditory areas. We show that even though the different fields employ different methods to investigate the activity and connectivity of brain areas, there is consistency in the results on tinnitus between these different approaches. This consistency between human and animals research is observed for tinnitus with peripherally instigated hearing damage, and for results obtained with salicylate and noise-induced tinnitus. The thalamus integrates input from limbic and prefrontal areas and modulates auditory activity via its connections to both subcortical and cortical auditory areas. Reported altered activity and connectivity of the auditory, prefrontal, and limbic regions suggest a more systemic approach is necessary to understand the origins and impact of tinnitus.

1. Introduction

Tinnitus, commonly known as 'ringing in the ears', is a sensation of sound attributed to a location inside the head, to both ears, or to one ear. Tinnitus can be defined as the conscious perception of a sound that cannot be attributed to any physical source inside or outside the body.

Current animal research related to tinnitus is primarily concerned with subcortical structures, notably the cochlear nucleus, the inferior colliculus, and the thalamus. Most of these studies perform behavioral tests for tinnitus, employing innate auditory reflexes or paradigms that involve training an animal to respond to the absence or presence of sound stimuli. This is in contrast to human research, where researchers rely on self-report measures of tinnitus. Initially, the majority of human research on tinnitus has focused on cortical activity both from auditory and non-auditory structures. Lately, the interest in the functional connectivity between those structures is growing, and human research has expanded to the subcortical structures and their connectivity. Even though human and animal research on tinnitus used to work at different ends of the auditory pathway, this gap is bridged in more recent work. In light of this development, the thalamus is of specific interest due to its unique position to facilitate communication between subcortical and cortical structures.

The thalamic nucleus that is dedicated to auditory processing is the medial geniculate body (MGB). In mammals, the principal source of ascending inputs to the ventral divisions of the medial geniculate body (MGBv) is the central nucleus of the tonotopically organized inferior colliculus (ICc), which is part of the primary (lemniscal) ascending pathway. The dorsal divisions (MGBd) mainly receive inputs from the dorsal cortex (DC) and lateral nuclei of the inferior colliculus, although the rostral MGBd divisions also receive inputs from the ICc. These non-central divisions of the IC are part of the non-tonotopic or diffuse ascending pathway. The magnocellular division (MGBm) receives inputs from all three of these IC divisions and is generally thought to receive ad-

Abbreviations: SFR, Spontaneous firing rates; TTS, Temporary threshold shift; PTS, Permanent threshold shift; ALFF, amplitude of low-frequency fluctuation; TRN, thalamic reticular nucleus.

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https://doi.org/10.1016/j.heares.2021.108280

Table 1
SFR and burst-firing, central gain, and tinnitus.

Structure	Agent	PTS	TTS	SFR	Bursting	Gain	Behavior
ANF	Noise	✶		↓≈[1]	↑[1]		
ANF	Salicylate		✶			↓[21]	⊙[21]
VCN	Noise	✶		↑[23,30]		↑[18,30]	⊙[30]
DCN	NoiseNoise	✶	✶	↑[2]↑[4,27]	↑[2,3]↑[4]		⊙[4,27]
DCN	Salicylate		✶	↑[13]			⊙
ICC	NoiseNoise	✶	✶	↑[5]↑[6,7,24]	↑[5]↑[6] ≈ [7]	↑[15,16]	⊙[5]⊙[6]
ICC	Salicylate		✶	↓[7]		↓[19]≈[28]	⊙[19]
ICX	Salicylate		✶	↑[8]	↑[8]		⊙[8]
MGBv	NoiseNoise	✶	✶✶	↑[9]≈[14]	↑[9,12]↓[14]	↑[9]	⊙[9,12]⊙[14]
MGBv	Salicylate		✶	≈[29]		↑[21,28,29]	⊙[21,28,29]
A1	Noise		✶	≈ →↑[10]	↑→ ≈[10]	↑[17,20]	⊙[20]
A1	Noise	✶		↑[11,25,26]	≈[11]		⊙[25]
A1	Salicylate		✶	↓[22]≈[29]		↓[19]↑[21,22,28]	⊙[19,21,28,29]

↑, increase; ↓, decrease; ≈ →↑ change from no effect to increase; ↑→ ≈ change from increase to no effect; ✶, indicates type of trauma, ⊙, behavioral signs of tinnitus.[1]Liberman and Kiang (1978) cat
[2]Finlayson and Kaltenbach (2009) hamster
[3]Pilati et al. (2012) rat.
[4]Wu et al. (2016) guinea pig.
[5]Bauer et al. (2008) chinchilla.
[6]Coomber et al. (2014) guinea pig.
[7]Ma et al. (2006) CAB/J mice.
[8]Chen and Jastreboff (1995) rat.
[9]Kalappa et al. (2014) rat.
[10]Noreña and Eggermont (2003) cat.
[11]Norena and Eggermont (2006) cat. [12]Sametsky et al. (2015) rat. [13]Martel et al. (2019) guinea pig.
[14]Barry et al. (2019).
[15]Salvi et al. (1990) chinchilla.
[16]Wang et al. (2002) chinchilla.
[17]Norena et al. (2003) cat.
[18]Cai et al. (2009) rat.
[19]Sun et al. (2009) rat.
[20]Sun et al. (2012) rat.
[21]Chen et al. (2015) rat.
[22]Noreña et al. (2010).
[23]Vogler et al. (2011) guinea pig.
[24]Vogler et al. (2014) guinea pig.
[25]Basura et al. (2015) guinea pig.
[26]Seki et al. (2003) cat.
[27]Brozoski et al. (2002) rat.
[28]Wong et al. (2020) rat.
[29]Vianney-Rodrigues et al. (2019) rat,[30]Martel and Shore (2020) guinea pig.
ANF, auditory nerve fibers. VCN, ventral cochlear nucleus. DCN, dorsal cochlear nucleus, ICC, central nucleus of the inferior colliculus. ICX, external nucleus of the inferior colliculus, MGBv, ventral nucleus of the medial geniculate body. A1, primary auditory cortex. SFR, spontaneous firing rate' PTS, permanent threshold shift; TTS, temporary threshold shift. Modified and updated from Eggermont (2020).

ditional inputs from vestibular, somatosensory, and possibly visual systems (Hackett, 2011). Note that the mean spontaneous firing rate of the MGBv in anesthetized mice is much higher (8.8 spikes/second) than both the MGBd (2.2 s/s) and MGBm (2.6 s/s) divisions (Anderson and Linden, 2011).

2. The classical auditory network and tinnitus

The classical auditory network -from cochlear nucleus to auditory cortex (ACx)- has been extensively studied in animal models, typically in rodents for subcortical structures and in rodents and cats for ACx. A consistent finding is that after noise trauma, the spontaneous firing rate (SFR) is increased in all the classical auditory structures. For the rodent studies, this increase in SFR is accompanied by behavioral signs of tinnitus. Animal (post temporary threshold shift, TTS; (Qu et al., 2019), as well as human studies in patients with tinnitus (e.g., Berlot et al., 2020), have shown decreased functional connectivity between the MGB and the primary auditory cortex (A1). Therefore, it appears that the increased SFR in AC is not simply inherited from the MGB. This deduction suggests either an additional source for the increased SFR in AC (1), or that functional connectivity changes based on low-frequency fluctuations in the BOLD response do not apply to spontaneous spiking activity (2), or that animal data do not predict human findings (3). We will first review some pertinent findings in animal studies involving noise exposure and then argue that functional connectivity (FC) findings based on low-frequency fluctuations in the BOLD response apply to population spike activity; we also note that related findings in rodents likely apply to humans as well. Finally, we identify potential sources of increased SFR in auditory cortex that argue for concurrent decreased FC between MGB and A1.

2.1. Findings in noise-exposed animals with regard to spike firing

We combined extensive literature data on central gain changes, exemplified in driven firing rates, and local field potentials (LFPs), both following noise exposure and salicylate administration, as well as SFRs and burst firing in Table 1. Note that increases and decreases in SFR are nearly always accompanied by similar changes in central gain. Interestingly, the SFR and gain changes are the same in temporary (TTS) and permanent threshold shift (PTS) inducing noise exposures. Furthermore, changes in SFR and gain induced by salicylate produce findings opposite to the changes observed following noise exposure. Even though the studies that re-

ported these changes in spike firing use various experimental animals, the results appear to be species independent. Similarly, there are no clear differences between the different animal models in terms of the effect of noise exposure on the classical auditory areas.

We highlight a few exemplary studies. In the guinea pig DCN, under anesthesia, increased spontaneous firing rates (SFR) and burst firing was induced by a TTS-inducing noise-exposure protocol consisting of a 1/4 octave bandwidth stimulus (6.4–7.6 kHz, 2 h) with a root mean square level of 97 dB SPL (Wu et al., 2016). Furthermore, a different noise-exposure paradigm (116 dB, centered on a 16 kHz octave band, 1 h) in rats enhanced spontaneous firing, altered burst properties (increased burst rate in MGBv, MGBm, and MGBd), and increased the rate-level function slope when driven by broadband noise and tones at the unit's characteristic frequency in awake animals (Kalappa et al., 2014). The results of these two types of noise-exposure protocols in two different animal models were very similar. In both studies, the normalized behavioral scores suggesting tinnitus were based on the gap-induced inhibition of the acoustic startle reflex (GPIAS). Burst-firing properties in subcortical structures in relation to tinnitus have been discussed in a recent publication (Eggermont, 2020). Contrasting the findings of Kalappa et al. (2014), Barry et al. (2019) reported no differences in SFR in MGB neurons (areas not specified) between trauma groups, with and without behavioral evidence of tinnitus, and a sham group. In their study, noise was applied at much higher levels and longer durations (2 h, 10 kHz, 124 dB SPL). In addition, acoustic trauma resulted in a significant *decrease* in the percentage of neurons showing burst firing, and this effect was similar in anesthetized animals with and without behavioral signs of tinnitus. Within the bursting neurons, the number of spikes occurring in a burst and the number of bursts per minute were also significantly reduced compared to the sham group (Barry et al., 2019).

This exposure-level effect might relate to the behavioral findings of Turner and Larsen (2016), who exposed rats to noise of various levels, duration, and spectrum. Rats were behaviorally tested for tinnitus and hyperacusis using the GPIAS and pre-pulse inhibition using 60-dB SPL before noise exposure and at regular intervals. Twelve months after noise exposure, the middle-aged rats were then tested again for tinnitus and hyperacusis before collecting ABR thresholds, which suggested that no hearing loss was present for frequencies < 32 kHz. GPIAS reflexes *"suggesting tinnitus 12-months after noise exposure were significant in groups receiving the four least intense noise doses (110-dB for 30, 60 and 120* min*, and 116-dB for 30* min*), while some of the significant rates of hyperacusis occurred in groups receiving more intense or longer exposures; 122 dB, 60* min*; 116 dB 120* min*."* These results suggest that low-to-moderate noise exposures like in the Wu et al. (2016) and Kalappa et al. (2014) studies may result in the greatest likelihood of producing tinnitus behavior.

Anesthetics that are widely used in animal research are known to affect the spiking activity of thalamocortical neurons, decreasing the number of active single units and altering burst firing properties (Britvina and Eggermont, 2008a; Deane et al., 2020; Hentschke et al., 2017; Raz et al., 2014). Furthermore, the anesthetic-related changes in the activity of auditory thalamocortical neurons are influenced by sound stimulation (Britvina and Eggermont, 2008b). Yet, the aforementioned studies of Wu et al. (2016) and Barry et al. (2019) compared the electrophysiological recordings of the noise-exposed group to a sham group. Both the noise-exposed and the sham group had undergone the same anesthetic protocol and sound stimulation, suggesting that the noise trauma or tinnitus behavior and not the anesthetic related to the observed group differences. Moreover, the tinnitus-related findings in awake animals (Kalappa et al., 2014) are comparable to the results obtained with a similar protocol but in anesthetized animals (Wu et al., 2016), although at different levels of the auditory pathway. Overall, it appears that noise exposure protocols with more moderate noise intensities or shorter duration are most likely to result in changes in SFRs and bursting, correlates that have been linked to tinnitus behavior.

Whereas the above measurements were performed days to weeks after the noise exposure, here we present the acute changes in A1 of 16 ketamine-anesthetized cats occurring after a 1-h exposure to a 120-dB SPL pure tone (5 or 6 kHz) from the study by Noreña and Eggermont (2003). The changes in A1 were recorded with two 8-micro-electrode arrays, and care was taken to record from the same waveform-sorted units before and up to 8 h after the trauma. The exposure resulted in an ABR threshold increase that stabilized after a few hours to, on average, 40 dB in the frequency range of 6–32 kHz. There was a significant increase in the maximum of driven spike-firing rate (Noreña et al., 2003). Changes in spontaneous activity from the same neurons were recorded over 15-min periods before, immediately after (After 1), and more than two hours after (After 2) an acute acoustic trauma. This study reported on the SFR, the peak cross-correlation coefficient (ρ) and burst-firing activity (Noreña and Eggermont, 2003; Fig. 1). SFRs were not changed within 15 min after the noise exposure, whereas neural synchrony and burst firing both increased. Two hours after cessation of the noise, the SFRs were significantly increased, the cross-correlation coefficient for spontaneous firing was further increased, but spontaneous burst firing returned to normal. This contrasts with the subcortical findings by Kalappa et al. (2014) and Wu et al. (2016), which showed increased bursting months after the noise exposure. Seki and Eggermont (2003) reported no changes in spontaneous burst firing up to 4 months after the trauma. Still, they did report an increase in SFR that was significant up to 45 days after noise trauma, after which it leveled off.

Whereas increased SFRs are reliably reported in animals with behavioral evidence of tinnitus, it is preceded by changes to burst firing and neural synchrony, which can be taken as the initial correlates of tinnitus and possibly hyperacusis. It is worth pointing out that the induction of tinnitus in animals is almost exclusively accompanied by impaired sensitivity of the auditory periphery, either transient or permanent. Therefore, it should be considered that the neurophysiological changes attributed to the percept of tinnitus may reflect different degrees of deafferentation or other changes to the inner ear structures that correlate with but are not necessarily causative of tinnitus.

2.2. Connectivity studies between IC, MGB, and A1 based on BOLD responses

The subcortical and cortical correlates of tinnitus have been investigated in a localized manner, as described in the previous paragraph, and as the interaction between these areas: at the network level. We include here only those studies that estimated functional connectivity between subcortical and cortical auditory areas (Table 2). This was the case in two animal studies; Chen et al. (2015) used salicylate to induce tinnitus in rats, and Qu et al. (2019) used a TTS-inducing noise exposure protocol in mice. The reported activity and connectivity were based on the amplitude of the low-frequency fluctuation (ALFF). In contrast to studies using noise-exposure-induced changes in spike firing (Table 1), the salicylate-induced ALFF in A1 increases, whereas the TTS noise-induced ALFF decreased. Similarly, the FC between the MGB and A1 increases in salicylate-treated animals, whereas it decreases after noise exposure. Thus, similar to reports on SFR, the effect of salicylate and noise exposure on connectivity are in opposite directions.

FMRI-based FC studies between auditory areas in humans have suggested reduced FC between the thalamus and ACx based on the

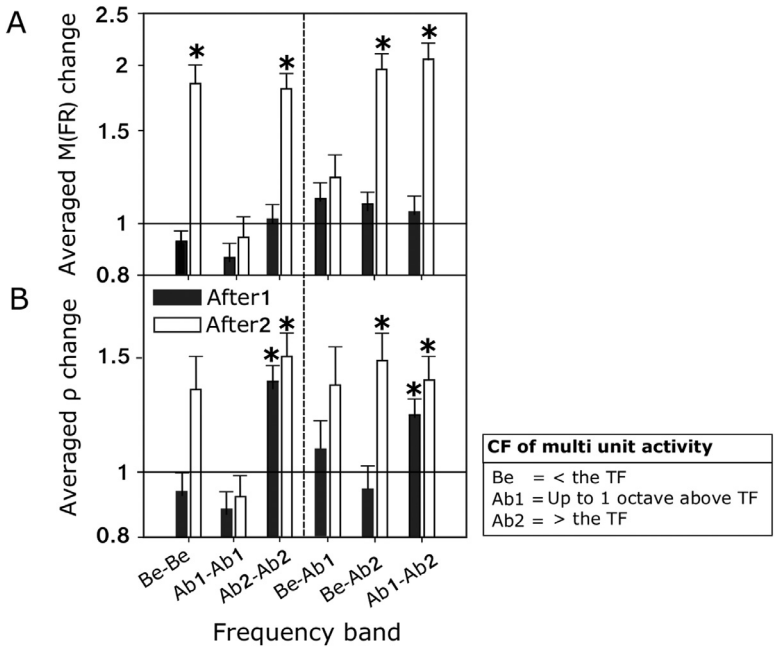

Fig. 1. Effect of the acoustic trauma on SFR and neural synchrony (ρ). (**A**) Change in averaged SFR (geometric mean) based on multi-unit responses grouped according to different CFs, M(FR). (**B**) Change in averaged spike-pair cross-correlation coefficient ρ (geometric mean) for units with different CFs. The black bars indicate the responses immediately after the noise trauma (After1), and the white bars indicate the responses a few hours (After2) after the acoustic trauma ($\pm$S.E.M., $^*P < 0.0083$). Neural units with a CF below the trauma-tone frequency (TF) were labeled as Be, those with a CF within 1 octave above the TF were labeled as Ab1, and those with a CF more than 1 octave above the TF were labeled as Ab2. On the left side of both panels are the within frequency band comparisons depicted, showing the difference in responses immediately after versus several hours after the noise trauma. On the right side of both panels are the between frequency band comparisons depicted. For example, Be-Ab1 indicates the average comparison of a unit with a CF below the TF to one unit with a CF within 1 octave above the TF. Immediately after the acoustic trauma (black bars), ρ is significantly increased in the Ab2 within frequency band comparison, whereas M(FR) is not. Similarly, ρ is significantly increased in the between frequency band comparison Ab1-Ab2 and M(FR) is not. In both cases, the M(FR) increase is present several hours after the noise trauma but not immediately after. Adapted from Noreña and Eggermont (2003).

Table 2
Functional connectivity and activity involving the thalamus.

	IC	MGB	A1
IC	$\uparrow^{2}$	$\uparrow^{2} \approx^{5}$	$\Downarrow^{6} \Downarrow^{7} \approx^{8}$
MGB	$\uparrow^{2} \approx^{5}$	$\uparrow^{2}$	$\uparrow^{2} \downarrow^{3} \Downarrow^{4} \Downarrow^{5} \approx^{7}$
A1	$\Downarrow^{6} \Downarrow^{7} \approx^{8}$	$\uparrow^{2} \downarrow^{3} \Downarrow^{4} \Downarrow^{5} \approx^{7}$	$\uparrow^{2} \downarrow^{3}$

$\uparrow \sim \downarrow$ animal data; $\Uparrow \approx \Downarrow$ human data. On the diagonal, the activity within a structure is presented and off-diagonal the connectivity between structures. [2]Chen et al. (2015) fMRI, salicylate.
[3]Qu et al. (2019) fMRI, TTS.
[4]Zhang et al. (2015).
[5]Berlot et al. (2020).
[6]Boyen et al. (2014).
[7]Lanting et al. (2014).
[8]Leaver et al. (2016).

connectivity reduction between IC and ACx (Boyen et al., 2014). The same group (Lanting et al., 2014) also found a similar reduction in connectivity between IC and A1 but could not substantiate this for the MGB and A1. Zhang et al. (2015) reported decreased functional connectivity between the thalamus and primary and associative auditory cortex. This was recently corroborated by a 7T fMRI study (Berlot et al., 2020) that measured the various tuning properties in ACx in great detail. This study also reported the FC between the IC, tonotopic MGB, and A1 and between the primary and higher-order auditory cortex. The connectivity between IC and MGB was unchanged in tinnitus patients compared to matched controls. However, the connectivity between the MGB and A1 was reduced, as was that between A1 and higher-order auditory cortex. Furthermore, Zhang et al. (2015) found that the decrease in connectivity was significantly correlated with tinnitus duration and scores on the tinnitus handicap questionnaire (THQ). In addition, Leaver et al. (2016) identified a resting-state network (RSN) in tinnitus patients that was not apparent in control data. This tinnitus RSN included IC and medial Heschl's gyrus, with no significant connectivity change between them-, and classically non-auditory regions:the mediodorsal nucleus of the thalamus, striatum, lateral prefrontal, and orbitofrontal cortex. The majority of these findings thus points towards altered connectivity between MGB and A1, although part of the evidence comes from decreased connectivity between IC and ACx in humans with tinnitus. A consistent finding in both human and animal studies is the reduced connectivity between MGB and A1 in those with tinnitus and peripherally instigated hearing loss.

3. Contradiction between increased spike firing and decreased connectivity?

The increased spike firing and decreased connectivity appear to be at odds with one another, as is illustrated in Fig. 2. Whereas there is a consistent increase of SFR in all auditory areas following noise exposure, tinnitus present or not, the ALFF-based connectivity between MGB and A1 is decreased. We recall that this suggests either an additional source, uncorrelated to the MGB, driving SFR in A1, or that the ALFF-based connectivity does not apply to spontaneous neuronal spiking. Alternatively, this discrepancy may indicate that animal-based measures are not translatable to humans. The latter can be ruled out by direct evidence since the FC measures in mice and humans are similar. Therefore, we will now focus on the remaining two options and investigate this discrepancy based on strictly neural signals. To compare the findings based on human and animal studies, the focus in this review is on local field potentials (LFP). LFPs represent the low frequency (< 100 Hz) fluc-

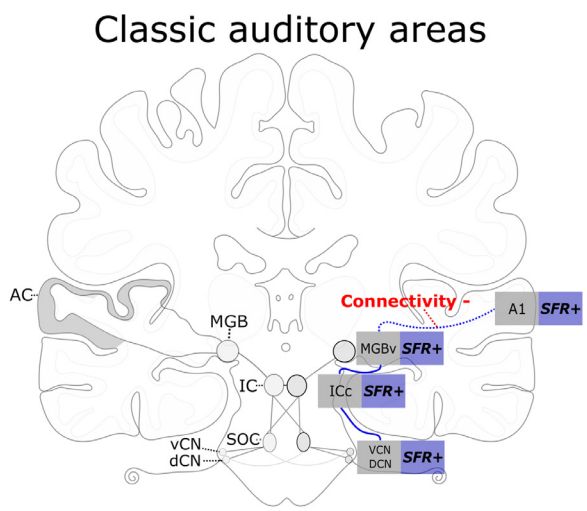

Fig. 2. For noise-exposed animals, the SFR increases compared to controls or pre-exposure levels from the cochlear nucleus to the primary auditory cortex. Yet, the amplitude of the low-frequency fluctuation (ALLF) based connectivity decreases between MGBv and A1.

tuations of the extracellularly recorded signals, which strongly correlate with the BOLD response.

3.1. Spike firing and LFP based connectivity for salicylate

Vianney-Rodrigues et al. (2019) were the first to simultaneously measure thalamic and cortical oscillatory activity and coupling in the MGBv and A1 of anesthetized rats before and after salicylate application. In MGBv and A1, salicylate increased the stimulus-driven activity with shorter latencies, especially in A1. In the MGB, salicylate reduced the SFR, spontaneous theta, alpha, and beta frequency LFP oscillations. It also decreased the coherence (synchrony) between electrode pairs in theta, alpha, and beta bands but increased coherence in the gamma band. Within A1, salicylate significantly increased gamma oscillations, decreased theta power, and decreased coherence between electrode pairs in theta and alpha bands but increased coherence in the gamma band. When coherence was measured between one electrode in the MGB and another in A1, salicylate decreased coherence in beta, alpha, and theta bands but increased coherence in the gamma band. There was also an increased theta phase (in MGBv) to gamma amplitude (in A1) coupling which supports the thalamocortical dysrhythmia model for tinnitus in humans (Llinás et al., 1999). In general, salicylate decreases the oscillations, coherence, and SFR in the beta, alpha, and theta bands of the MGB and the alpha and theta bands of A1. In concert, it increases the coherence of activity within and between the MGB and A1 in the gamma band. These similarities suggest that connectivity results obtained with animal models and human models of tinnitus do not necessarily contradict each other.

Normally, the theta and gamma oscillatory activity are not temporally coherent since they reflect different thalamocortical functional states (Llinás and Steriade, 2006). The thalamocortical dysrhythmia theory states that these frequency bands become coupled in conditions that are associated with co-occurring negative and positive symptoms. Tinnitus is a prime example of such a condition, where a loss of peripheral sensitivity (negative symptom) is associated with the presence of a phantom sound (positive symptom). This theory has further been corroborated in humans for other conditions that involve deafferentation and a phantom percept, such as chronic pain and Charles Bonnet syndrome (eg., (Llinás et al., 1999; Tu et al., 2020)). Important to the questions posed in this review, the theory proposes that both deafferentation and inhibitory action of other brain regions on the thalamus can instigate this dysrhythmia. According to the dysrhythmia theory, the negative symptoms are related to continuous thalamic hyperpolarization, either initiated by deafferentation or sustained inhibition, resulting in the de-inactivation of T-type Ca^{2+} channels, thereby increasing oscillations in the theta range as well as bursting activity (Llinás and Steriade, 2006). The positive symptoms result from these low-frequency theta oscillations that decrease lateral inhibition in the auditory cortex, resulting in high-frequency gamma activation (Llinas et al., 2005). In line with the dysrhythmia theory, salicylate application relates to increased gamma activity and the coupling of theta and gamma-band activity in A1. In contrast to the dysrhythmia theory, theta-band power in the MGB and A1 is decreased in salicylate-induced tinnitus (Vianney-Rodrigues et al., 2019). Interestingly, both salicylate and noise-induced tinnitus in humans and animal models of tinnitus have been associated with increased gamma-band activity in A1 (Adamchic et al., 2014; van der Loo et al., 2009; Vianney-Rodrigues et al., 2019).

Human studies do not have the resolution to investigate changes in oscillatory frequency bands between specific regions but report on brain changes that can be roughly localized to originate from a specific cortical area. Similar to the findings of increased gamma-band power in salicylate induced tinnitus behavior in animals (Vianney-Rodrigues et al., 2019), human EEG and MEG studies report increased cortical gamma oscillations in tinnitus patients (e.g., Vanneste et al., 2010; Weisz et al., 2011; De Ridder et al., 2014). Moreover, gamma-band power is positively correlated with tinnitus loudness (Adamchic et al., 2014; van der Loo et al., 2009; Vanneste et al., 2019). Whereas in mild hearing loss there was a positive correlation between tinnitus loudness and current density in the gamma frequency band over the ACx, in severe hearing loss tinnitus loudness correlated with an increase in the gamma band current density over the parahippocampal area (Vanneste and De Ridder, 2016).

3.2. What is the correlation between spike firing, LFP, and ALFF?

The BOLD-response appears most similar to LFPs (Heeger et al., 2000; Rees et al., 2000), and it has been proposed that BOLD-responses reflect synaptic processing rather than spiking output (Logothetis et al., 2001). The BOLD-based resting-state FC is not directly coupled with SFRs and may not reflect spontaneous activity at the neuronal level. In human ACx, Nir et al. (2007) found that when there was a strong spike-spike correlation, there was also a strong spike-BOLD coupling and a strong gamma-BOLD coupling. Overall, the results of Nir et al. (2007) showed a wide range of coupling levels between the firing rates of individual neurons and gamma LFP power. However, they observed a strong spike-gamma coupling that was present only when the firing-rate correlations of neighboring neurons were high. This phenomenon occurred during both sensory stimulation and spontaneous activity. In addition, they found that gamma LFP was well coupled to BOLD measured across different individuals. By contrast, the coupling of single units to BOLD was highly variable and, again, tightly related to inter-neuronal firing-rate correlations. Nir et al. (2007) offer a resolution to a central controversy regarding the coupling between neurons, LFP, and BOLD signals by suggesting that "*gamma LFP and BOLD signals are coupled to the correlated firing rate in a local population but not necessarily to the firing rate of single units*, which are often uncorrelated with the averaged behavior of the local population."

Elaborating, whereas the coupling of the spike correlations with the gamma LFP and BOLD response likely reflects the activity of a local subset of neurons, we just established that it does not reflect single-unit activity, and it is unlikely to represent global fluc-

Table 3
Functional connectivity of auditory cortex with limbic areas.

	Auditory cortex	Amygdala	Parahippocampus
Auditory cortex	$\uparrow^{1}\downarrow^{2}\Downarrow^{4}\uparrow^{8}$	$\downarrow^{2}\Uparrow^{3}\Downarrow^{4}\Downarrow^{5}\uparrow^{8}\Downarrow^{9}$	$\Uparrow^{6,7}\sim^{8}$
Amygdala	$\downarrow^{2}\Uparrow^{3}\Downarrow^{4}\Downarrow^{5}\uparrow^{8}$	$\sim^{1}\uparrow^{2}\uparrow^{8}$	
Parahippocampus	$\Uparrow^{6,7}\sim^{8}$		$\downarrow^{8}$

$\uparrow \sim \downarrow$ animal data; $\Uparrow \approx \Downarrow$ human data.
[1]Chen et al. (2016) noise SFR.
[2]Qu et al. (2019) noise ALFF.
[3]Chen et al. (2017).
[4]Hofmeier et al. (2018).
[5]Cai et al. (2020).
[6]Schmidt et al. (2013).
[7]Schmidt et al. (2017).
[8]Chen et al., 2015).
[9]Zhang et al. (2015), salicylate, ALFF.

tuations (Cohen and Kohn, 2011). This indicates that both LFP and BOLD coupling to spike correlations are well poised to investigate tinnitus since the impact of tinnitus is unlikely the result of a single rogue neuron, nor is it a state likely to affect the entire brain. Interestingly, tinnitus in animals is strongly correlated with increased pair-wise neural spike correlation in DCN (Wu et al., 2016), MGB (Kalappa et al., 2014), and A1 (Noreña and Eggermont, 2003).

4. Impact of non-auditory regions on auditory processing

4.1. Involvement of limbic structures

It should be considered that limbic structures, which may be involved in the emotional aspects or the burden of tinnitus, exert their effect by changing the resting-state activity in the ACx, thereby decreasing thalamocortical FC. An overview is presented in Table 3.

4.1.1. Animal studies

Important for cortico-thalamic interactions is the inhibitory reticular nucleus of the thalamus (TRN), which is part of the auditory forebrain circuitry. The TRN contains GABAergic neurons that project to dorsal thalamic neurons, including the MGB. The TRN receives input from, among others, branches of thalamocortical axons, branches from corticothalamic axons, as well as projections from the basal forebrain, amygdala, prefrontal cortex, and cholinergic brainstem fibers (Caspary and Llano, 2017). Thus, limbic structures have the ability to impact ACx activity via their connections to the TRN, which, in turn, has a modulatory effect on the MGB. For example, activation of basolateral amygdala projections that terminate in the TRN suppress spontaneous activity but enhance sound-evoked responses in ACx (Aizenberg et al., 2019). Thereby, the TRN plays a pivotal role in controlling thalamocortical gain.

In a resting-state fMRI study of salicylate-induced tinnitus in rats, Chen et al. (2015) found hyperactivity in the auditory network -IC, MGB, and ACx- with side branches to, among others, the amygdala. When the seed region was in ACx, there were significant bilateral increases of FC in large clusters located in the MGB, IC, and amygdala. After noise-induced tinnitus in rats, Chen et al. (2016) found that noise trauma significantly elevated the SFR in ACx, whereas SFR in the lateral amygdala were only slightly increased across all frequencies. In mice, Qu et al. (2019) had found decreased ALFF in ACx and increased ALFF in the amygdala at day 28 post-noise exposure in mice exhibiting tinnitus behavior, combined with decreased FC of the MGB and ACx with the amygdala and hippocampus.

4.1.2. Human recordings

Connectivity between auditory and limbic areas has been investigated with functional (FC) and effective, or directional, connectivity (EC) with contradictory results. Studies on FC in tinnitus patients with normal audiometric thresholds report a decrease in FC between the thalamus and amygdala, and between the thalamus and auditory cortex (Zhang et al., 2015) as well as between the amygdala and the auditory cortex (Hofmeier et al., 2018). A similar decrease in FC between the amygdala and the auditory cortex was reported for tinnitus patients with sensorineural hearing loss (Cai et al., 2020). Furthermore, Hofmeier et al. (2018) found that whereas the amygdala activity was no longer correlating with the ACx, it was positively connected to lower-level auditory brainstem regions in the tinnitus group. Thus, both human and animal work on tinnitus and peripherally instigated hearing loss indicate decreased functional connectivity between the amygdala and ACtx. In contrast, studies that used Granger-causality analysis reported enhanced EC of the amygdala with the primary and association auditory cortex in tinnitus patients with normal and elevated audiometric thresholds (Cai et al., 2020; Chen et al., 2017). In the study of Chen et al. (2017), this increased connectivity was positively correlated with THQ scores, and thereby with tinnitus distress. Interestingly, Chen et al. (2017) did not find enhanced EC between the amygdala and the thalamus, but only between the amygdala and auditory cortex.

The interpretation of Granger causality in fMRI time series is tricky since it assumes the complete absence of noise in the measured responses and consequently no variability in the hemodynamic response function, whereas measurement noise can reverse the estimation of causality direction (Smith et al., 2011). In summary, whereas it is reported that the coherence between auditory cortex and amygdala activation decreases in tinnitus, the influence of the amygdala on the auditory cortex appears to be increased. The direct connectivity of the amygdala with the ACx is subserved by structural connections only for the secondary auditory cortex (Tsukano et al., 2019). It is important to consider that models of effective connectivity that rely on structural priors have more evidence than those that do not (Stephan et al., 2009). Further, the amygdala's influence on the primary auditory cortex (A1) takes place via the modulatory influence of the TRN on the MGB (Aizenberg et al., 2019; Zikopoulos and Barbas, 2012). Additionally, there are direct projections from the amygdala to the IC (Marsh et al., 2002), and in turn, the amygdala receives input from the MGBm (Turner and Herkenham, 1991). Therefore, there are direct and indirect pathways via which the amygdala can influence auditory cortex activity.

Hofmeier et al. (2018) and Koops et al. (2020) found that subcortical and cortical auditory regions responded with reduced BOLD activity in the tinnitus group, emphasizing reduced stimulus-evoked central neural gain, which corresponds to the reported decrease in spontaneous low-frequency fluctuations (ALFF) in tinnitus animals (Qu et al., 2019). Interestingly, a specific reduction in ACx activity at the tinnitus frequency was observed in patients with additional hyperacusis (Koops and van Dijk, 2021), which contrasted with the enhanced responses to all other frequencies. This reduced responsiveness to the tinnitus frequency was not related to a difference in the reported tinnitus characteristics (frequency and loudness), highlighting that auditory cortex activity in response to a tinnitus-like sound is not a straightforward method to probe brain activity relating to the tinnitus percept. The reported reduction in neural gain in tinnitus, based on the BOLD signal, may relate to the reduced coherence of activity between the amygdala and ACx (Cai et al., 2020; Hofmeier et al., 2018; Zhang et al., 2015), with the TRN-mediated amygdala activation no longer enhancing the sound-evoked responses in ACx. A decoupling of the basolateral amygdala and ACx could result in the observed enhanced spontaneous activity and decreased sound-evoked responses in ACx in tinnitus, as implicated by the findings of Aizenberg et al. (2019). Lower sound-evoked activity in high-

frequency regions of ACx in humans with hearing loss and additional high-frequency tinnitus (Koops et al., 2020) may reflect that the TRN reduces the gain for these frequencies, as proposed by Rauschecker et al. (2010). Alternatively, the observed increase in spontaneous ACx activity may be invoked by sources other than the amygdala. For instance, the enhanced SFR in ACx could potentially be supplied by the parahippocampus, which shows increased FC with ACx in tinnitus patients (Maudoux et al., 2012; Schmidt et al., 2017, 2013).

4.2. Prefrontal influence

Neuroimaging studies on tinnitus subscribe the notion that tinnitus perception involves both auditory and non-auditory brain areas (Eggermont, 2021). Prefrontal cortex (PFC) stimulation alters the SFR of MGB neurons and can thereby modulate auditory activity (Barry et al., 2017). The PFC can modulate auditory activity via direct projections of the OFC to A1 (Winkowski et al., 2018) and the anterior PFC to the association auditory cortex (Barbas et al., 2005; Medalla and Barbas, 2014). Alternatively, the dorsolateral and medial PFC can influence auditory processing via its projections to the TRN, arising from both layers V and VI of the PFC (Zikopoulos and Barbas, 2006). Furthermore, the PFC can modulate auditory activity via frontostriatal circuits that show altered connections to the NAc in animals with behavioral evidence of tinnitus (Hullfish et al., 2019; Leaver et al., 2016; Xu et al., 2019). In turn, the NAc core projects to the TRN (O'Donnell et al., 1997), and via this route, the PFC can affect the ACx via the modulatory effect of the TRN on the MGB. The notion of the PFC as integration site is enhanced by its interconnections via intracortical glutamatergic projections with the hippocampus, basolateral amygdala, and nucleus accumbens (Torres-García et al., 2012). Both the PFC and hippocampal formation send excitatory projections to the NAc and are interconnected with the amygdala. This route is in line with the proposal of Leaver et al. (2011) that decreasing activity in the VMPFC could disinhibit the action of the thalamic reticular nucleus (TRN) on the ventral part of the medial geniculate body (MGBv), thereby allowing spontaneous subcortical activity more access to the auditory cortex (ACx) (Eggermont, 2021).

The PFC is, via its direct connections and as part of frontal-auditory networks, ideally situated to influence gating of thalamic output to the auditory cortex. It becomes apparent that we cannot hope to understand tinnitus without incorporating the impact of frontal networks on thalamic areas, such as the TRN, which can directly modulate the activity and, potentially, the functional connectivity of the auditory system.

5. Discussion

As is known from cross-correlation studies in animal cortex (Eggermont, 1992), increased and uncorrelated noise, potentially the result from a noise source outside of the auditory pathway, might be the reason for reduced functional connectivity between the thalamus and the auditory cortex reported in both human and animal studies on tinnitus. In addition to changes in functional connectivity , correlations or coherence based on the low-frequency fluctuations in the BOLD response are similarly affected (Bijsterbosch et al., 2020; Duff et al., 2018).

In the case of noise-exposure-induced tinnitus in animals and tinnitus with mild hearing loss in humans, the FC between MGBv and A1 is reduced. It is clear that the ALFF-based connectivity estimate may apply to correlated SFRs and even more to gamma oscillations in the LFPs. Consequently, due to this uncoupling of MGBv and A1 activity, the increased SFRs in A1 are likely not transmitted from the MGBv, and hence must have another source. The source of this increased spontaneous activity could originate within the auditory cortex itself, and it could be provided by a release from lateral inhibition in A1 (Lakunina et al., 2020; Sanes and Kotak, 2011; Seki and Eggermont, 2003), which may convert even reduced SFR transfer from the thalamus into increased SFRs in A1. This is consistent with the findings of van Gendt et al. (2012), who used fMRI to show that "gaze-induced tinnitus was associated with reduced inhibition of the ACx, increased activity of the CN and IC, and inhibition of activity in the MGB." A substrate for increased resting-state activity in A1 could result from decreased GABA concentration in A1 itself in tinnitus patients, as demonstrated with MRI spectroscopy (Sedley et al., 2015). The decrease in GABA points towards dysfunctioning of the cortical inhibitory interneurons. In line with the reported increased SFRs in A1, increased central noise has been proposed as the mechanism responsible for tinnitus in an active loudness model (Zeng, 2013; Zeng et al., 2020). This model attributes central gain to hearing loss and hyperacusis but distinctly couples tinnitus to increased central noise. The increase in neural noise, or background activity, can alter the propagation mode through the different cortical layers and may activate neural networks (Hasanzadeh et al., 2020; van Rossum et al., 2002). Overall, the reduced connectivity between the MGB and ACx can indicate that increased SFRs originate in ACx itself.

Alternatively, non-auditory cortical and subcortical areas can drive or modulate the increased SFRs that are observed in the auditory system in tinnitus. Whereas there is an uncoupling of the MGB and ACx, we would like to reiterate that the gain of the MGB, in turn, is controlled not only by direct input from the IC but is modulated by the TRN. Therefore, this uncoupling of the MGB and ACx can be driven by areas outside of the ascending auditory pathway. Whereas the MGBv is part of the lemniscal pathway and forms the gateway and transformer between the ICc and A1, all divisions of the MGB receive collaterals from the TRN (Bartlett, 2013). The TRN is integrating input from prefrontal and limbic areas and can synchronize or inhibit MGB activity. The findings on tinnitus relating to limbic structures suggest that the enhanced SFRs in ACx could potentially be supplied by the parahippocampus, which shows increased FC with ACx in tinnitus patients. This would imply the parahippocampus as a tinnitus generator (De Ridder et al., 2014) or the maintainer of the subjective phenomenon of tinnitus. Alternatively, the decreased coherence between the amygdala and ACx (Cai et al., 2020; Hofmeier et al., 2018; Zhang et al., 2015) may result in a release from basolateral amygdala mediated suppression of spontaneous activity in ACx, corresponding to the increased SFRs reported in animal studies on tinnitus. Simultaneously, this can result in the reduced sound-evoked responsiveness of ACx reported in human studies on tinnitus. Whereas a reduction in the coherence of amygdala and ACx activity is observed in tinnitus, hyperacusis may relate to increased coherence of amygdala and AC activity, a feat that has been observed in auditory fear conditioning (Aizenberg et al., 2019).

Lastly, the TRN has been implicated as the driver of attention towards salient stimuli, per the 'attentional searchlight' hypothesis (Crick, 1984). Since the brain does not appear to habituate to the tinnitus sound, the tinnitus sound is almost constantly drawing the attention of the patient. The TRN is well situated to mediate this process. The increased SFRs in the auditory subcortical system are not simply relayed to the ACx via the MGB but are processed by the thalamus and influenced by non-auditory areas. We conclude that even though the thalamus is not the source of the increased noise, it plays a pivotal role in the altered activity of the auditory system in tinnitus.

Declaration of Competing Interest

The authors declare no conflict of interest or competing financial interest.

Acknowledgment

We thank Pim van Dijk for constructive comments on an earlier version of this manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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