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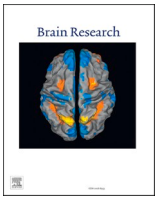

The role of the medial geniculate body of the thalamus in the pathophysiology of tinnitus and implications for treatment

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ABSTRACT

Tinnitus is an auditory sensation in the absence of actual external stimulation. Different clinical interventions are used in tinnitus treatment, but only few patients respond to available options. The lack of successful tinnitus treatment is partly due to the limited knowledge about the mechanisms underlying tinnitus. Recently, the auditory part of the thalamus has gained attention as a central structure in the neuropathophysiology of tinnitus. Increased thalamic spontaneous firing rate, bursting activity and oscillations, alongside an increase of GABAergic tonic inhibition have been shown in the auditory thalamus in animal models of tinnitus. In addition, clinical neuroimaging studies have shown structural and functional thalamic changes with tinnitus. This review provides a systematic overview and discussion of these observations that support a central role of the auditory thalamus in tinnitus. Based on this approach, a neuromodulative treatment option for tinnitus is proposed.

1. Introduction

Tinnitus is the sensation of a sound in the absence of an external sound source. Globally, it affects more than one in ten persons, and has a severe impact on the quality of life in approximately 3% of affected persons (Kim et al., 2015; McCormack et al., 2016). Moreover, tinnitus has a high comorbidity with depression and anxiety (Bhatt et al., 2017). Current treatments mainly focus on hearing restoration and psychological coping strategies (Cima et al., 2012). While these can alleviate tinnitus, many persons remain refractory to the available treatment options. As a result, tinnitus represents a great social and economic burden (Maes et al., 2013). In order to enable the development of effective treatments, further insight into the underlying pathophysiology of tinnitus is essential.

The dominant origin of tinnitus is thought to be hearing loss, which leads to peripheral deafferentation. This results in neural plasticity within a brain network that includes auditory as well as non-auditory (e.g. limbic) regions (Shore et al., 2016). In tinnitus, this plasticity may be maladaptive, resulting in pathological neuronal activity (Sedley 2019). As a mandatory station in the ascending auditory pathway, the medial geniculate body (MGB), the auditory part of the thalamus, plays an important role in auditory processing (Chen et al., 2019; Lee 2013; Moerel et al., 2015). One potential role of MGB in tinnitus pathology has been outlined by Leaver and colleagues (Leaver et al., 2011;

Abbreviations: AC, auditory cortex; CN, cochlear nucleus; DCN, dorsal cochlear nucleus; DBS, deep brain stimulation; IC, inferior colliculus; ICC, central part of inferior colliculus; ICx, external cortex of the inferior colliculus; non-PAC, non-primary auditory cortex; tDCS, transcranial current stimulation; MGB, medial geniculate body; MGD, dorsally located subdivision of the MGB; MGM, medial part of the MGB; NAc, nucleus acumbens; PAC, primary auditory cortex; MGV, ventral part of the MGB; STN, subthalamic nucleus; TMS, transcranial magnetic stimulation; TRN, thalamic reticular nucleus; VIM, ventral intermedius thalamic.

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Rauschecker et al., 2010). The MGB is thought to gate and transform auditory information as it is passed to the auditory cortex (AC) (Brinkmann et al., 2021; Sherman 2012). The MGB also extensively connects with limbic structures that are likely impacting emotional responses to tinnitus (LeDoux 2007). In this review we integrate the existing evidence on the central role of the auditory thalamus in tinnitus pathology. This knowledge may then guide the development of focussed tinnitus treatment strategies intervening at the level of the auditory thalamus.

2. The functional anatomy of the auditory thalamus

The MGB is centrally positioned in the auditory network, conveying auditory information to the primary auditory cortex (PAC) (Calford and Aitkin 1983). In the lemniscal pathway the MGB receives ascending input from both the inferior colliculus and the cochlear nucleus (CN). Axons from the cochlear nerve terminate in the CN, but also receive non-auditory sensory input. The CN primarily conveys auditory information to the inferior colliculus (IC), but has also direct efferents to the MGB (Malmierca et al., 2002). The MGB receives descending inputs from the PAC and non-primary AC (non-PAC), thalamic reticular nucleus (TRN), and limbic structures (Fig. 1) (Bajo et al., 1995; LeDoux et al., 1991; Lee and Winer 2008; Mellott et al., 2014). Descending cortical axons projecting to thalamus are more numerous than ascending projections (Ojima and Rouiller, 2011). The cytoarchitecture of the MGB reveals three major subdivisions: dorsal, medial, and ventral division (Hashikawa, et al., 1991). The ventral part of the MGB (MGV) is part of the lemniscal auditory pathway. It is a fast transmission station of ascending auditory information received from the central part of the IC. Neurons in the MGV are sharply tuned for sound frequency and fast temporal modulation of sounds. The MGV mainly projects to the PAC (Lennartz and Weinberger, 1992). The dorsally located subdivision of the MGB (MGD) integrates auditory input from the dorsal cortex of the IC with non-auditory signals (Bartlett 2013). In contrast to the MGV, the MGD projects to the non-PAC and the amygdala (De La Mothe et al., 2006). The amygdala is thought to be related to the emotional response of tinnitus (Davies et al., 2017) and has projections to the nucleus accumbens (NAc) and hippocampus, which both have been linked to tinnitus (Rauschecker et al., 2010; Salvi et al., 2011). While it is historically considered a non-lemniscal structure, the medial part of the MGB (MGM) has, compared to the rest of the MGB, the best physiological response properties (Anderson and Linden 2011). In addition to responding to auditory input, its neurons can be driven by visual and somatosensory stimuli (Bartlett 2013). The MGM sends projections to both PAC and non-PAC, as well as subcortical structures such as the amygdala (Bartlett 2013; Doron and Ledoux 2000).

The TRN is situated at the lateral border of the thalamus. It contains an auditory division that receives excitatory input from both the PAC and MGB, and sends inhibitory feedback to the MGB (Pinault 2004; Shosaku and Sumitomo 1983; Villa 1990). The TRN strongly inhibits the MGB and, when deactivated, a substantial increase of MGB neuronal responses to auditory stimuli is observed (Yu et al., 2009; Zhang et al., 2008). The TRN also receives input from limbic structures (O'Donnell et al., 1997; Yu et al., 2009). The amygdala and NAc activate the TRN, resulting in a suppression of the spontaneous firing rate of MGB and PAC neurons (Aizenberg et al., 2019; Barry et al., 2015). The prominent role in auditory processing and connectivity to the limbic system make the MGB a structure of particular interest for exploring treatment options for tinnitus.

3. Thalamic alterations in tinnitus

Two prominent theories suggest a central role for the MGB in tinnitus. The thalamocortical dysrhythmia model states that a prolonged hyperpolarization in MGB neurons, following deafferentation, results in aberrant cortical oscillations (Llinas et al., 2005). These oscillations are proposed to underlie the tinnitus percept. Alternatively, the noise cancellation hypothesis states that while in normal condition the TRN gates MGB activity, this gating mechanism fails in tinnitus (Rauschecker

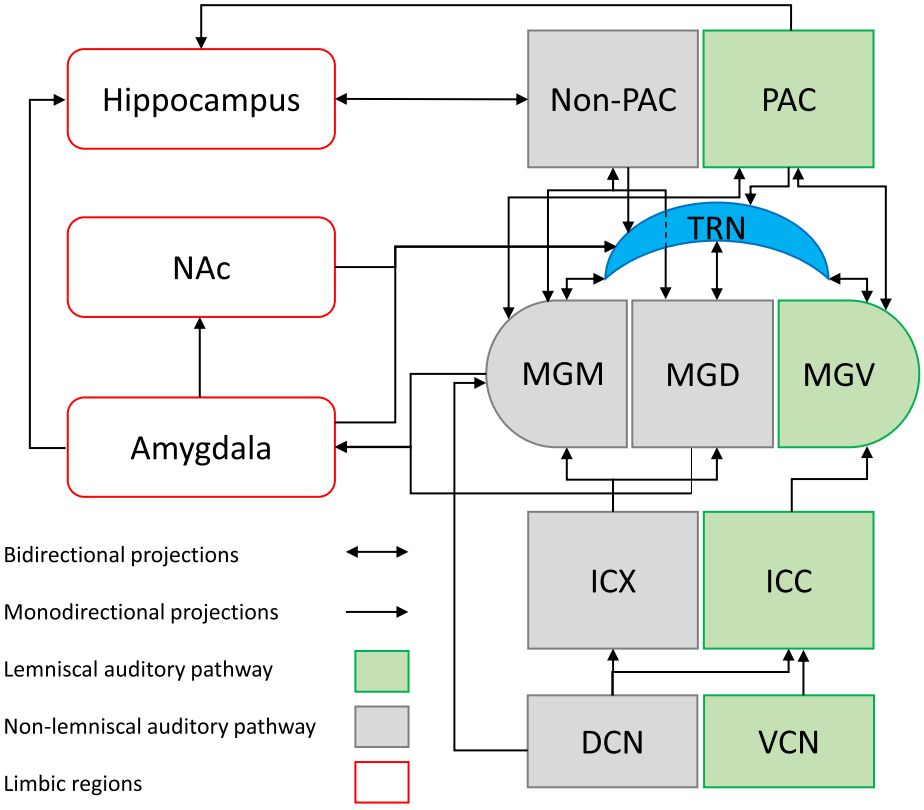

Fig. 1. Auditory and limbic anatomical connections of the MGB. The ventral part of the MGB (MGV) receives lemniscal input from the central part of inferior colliculus (ICC) and sends it to the primary auditory cortex (PAC). The IC (inferior colliculus) receives ascending input from the DCN (dorsal cochlear nucleus) and VCN (ventral cochlear nucleus). Dorsal and medial parts of the MGB (MGD, MGM) receive non-lemniscal input from the external cortex of the inferior colliculus (ICX) and project to the non-primary AC (non-PAC). The MGM also has a direct connection with the DCN and PAC. Both MGD and MGM send projections to the amygdala, which projects to the nucleus acumbens (NAc) and hippocampus. The thalamic reticular nucleus (TRN) receives excitataory input from PAC, MGB, amygdala, and NAc and sends inhibitory input to the MGB.

et al., 2010). The tinnitus percept is proposed to result from MGB hyperactivity, and subsequent PAC hyperactivity, caused by TRN-driven disinhibition of the MGB (Leaver et al., 2011; Rauschecker et al., 2010). Below we review evidence in support of alterations at the level of the MGB in tinnitus pathology, including findings from electrophysiological, neurochemical, and neuroimaging studies.

4. Electrophysiological findings

The use of electrophysiological measurements of deep brain structures for research purposes in humans is limited due to self-evident ethical considerations. Animal models for tinnitus are used as an alternative. Two methods are applied to induce tinnitus-like behavior in animals. First, the application of ototoxic drugs (e.g. sodium salicylate, quinine) can lead to acute and temporary tinnitus. Alternatively, acoustic trauma through loud noise exposure is employed, leading to chronic tinnitus (Eggermont 2013). It is important to note that potential confounding factors are hearing loss, hyperacusis and stress in these models.

In the rodent MGB, there are morphologically different cell types (Clerici and Coleman 1990). GABAergic neurons are low in number, likely less than 1% in the MGB of the rodent (Winer and Larue 1996). Thus, most recorded neurons in the studies below are probably glutamatergic. In an initial study using brain slices, about 80% of the MGB neurons altered the firing rate during salicylate application. The altered neuronal activity consisted of both increased (52.4%) and decreased activity (47.6%) (Basta et al., 2008). Whole-cell patch-clamp recordings demonstrated that administering high doses of sodium salicylate decreases the excitability of MGB neurons, leading to a hyperpolarization of the resting state potential (Su et al., 2012; Wang et al., 2016). The intrinsic properties of MGB neurons were altered and reduced synaptic transmission was observed after salicylate application (Su et al., 2012). The authors speculated that it is likely that salicylate alters the intrinsic properties of MGB neurons through its actions on the membrane ion channels expressed in the MGB neurons, resulting in a hyperpolarized state. This would lead to reduced thalamic input to the auditory cortex, fitting to the cortico-thalamic dysrhythmia model. A study that acquired multi-unit activity in the MGB showed an increased firing to tone bursts in animals that were exposed to sodium salicylate (Chen et al., 2013). A shift towards a hyperactive state of the multiunit activity was observed over a broad range of frequencies. The authors suggested that systemic salicylate administration results in a sound-evoked hyperactivity in the MGB supporting the noise cancellation hypothesis. Important to note is that the hyperactive state could also be related to hyperacusis, as it is known that salicylates increase the startle amplitude, which can be interpreted as hyperacusis (Sun et al., 2009).

In the sound exposed animal model an elevation in the spontaneous firing rate and burstiness of neurons in the MGB was described in awake animals implanted with a tetrode (Kalappa et al., 2014). The authors also showed steeper rate-level functions to broad band noise (BBN) and tones in the characteristic frequency of the neuron. The unit discharge properties of the MGB were correlated with the tinnitus scores, suggesting that features of MGB unit activity functionally related to tinnitus and not necessarily the other confounding factors such as hearing loss or hyperacusis after noise trauma. In another study conducted under anesthesia with urethane the spontaneous firing rate remained unaffected after noise trauma in the MGB, while the burstiness of neurons decreased (Barry et al., 2015). These findings were, however, seen in all animals after noise trauma and not solely in animals which showed a behavioural phenotype of tinnitus. These findings could thus also be related to hearing loss or hyperacusis. We also studied the neural firing properties of MGB neurons under anesthesia with ketamine and xylazine after noise trauma, and identified different types of response patterns to sounds: i) fast response, ii) sustained response, iii) suppressed response, iv) no response (van Zwieten et al., 2021). First, a reduction in the number of fast responding neurons and a corresponding increase in non-responsive neurons after noise-exposure was seen. Next, an increased spontaneous firing of sustained and suppressed response type neurons without influencing the responsiveness to stimuli was observed. Third, fast responding neurons in noise-exposed animals showed an increased threshold without a change in the spontaneous firing rate. As stressed above, the findings described in the animal studies above should be interpreted cautiously, since not all studies adequately differentiated between tinnitus, hearing loss and hyperacusis, and experimental conditions largely differed ranging from ex-vivo studies in tissue slides to in vivo recordings under anesthetized or awake conditions.

Aberrant neural oscillations in the central auditory system are also postulated to contribute to the perception of tinnitus, but the exact nature of these changes is still poorly understood (Llinas et al., 1999; Llinas et al., 2005; Sedley et al., 2012; Weisz et al., 2007). One of the most consistent findings is an increased gamma band activity in tinnitus patients (Hartmann et al., 2014; Sedley et al., 2012), but also changes in the theta band have been described in an MEG study in which persons experienced tinnitus and this was suppressed when tinnitus was masked (Llinas et al., 2005). In animals, recording of oscillations depends on the state of consciousness and the type of (anesthetic) drugs the animals are exposed to. In animals under pentobarbital or urethane anesthesia, or high doses of diazepam cortical oscillations were composed of both stimulus-locked and non–stimulus-locked oscillations, whereas in unanesthetized animals they were only composed of non-stimulus locked oscillations. In this study, the authors were unable to observe oscillatory activity in the MGB (Cotillon-Williams and Edeline 2003). Earlier studies described by the same group showed reliable oscillations induced by tone presentations in only a relatively small proportion of recorded neurons in the MGB under pentobarbital anesthesia (Cotillon and Edeline 2000; Cotillon et al., 2000). The oscillatory activity disappeared and spontaneous neural activity reduced after local muscimol injection (Cotillon and Edeline 2000). In a study in a sodium salicylate rat model of tinnitus under anesthesia with ketamine and xylazine in which simultaneous recordings from the MGB and PAC were obtained the power and coherence in the low-frequency bands (theta, alpha, and beta) was reduced in the MGB (Vianney-Rodrigues et al., 2019). In the PAC, reduced theta power and reduced coherence in the theta and alpha bands was seen. In both MGB and PAC, power was increased in the gamma band, and the cross-frequency coupling of theta and gamma activity increased as well. Although this study supports most aspects of the thalamocortical dysrhythmia model, the reported decreased theta power conflicts with its predictions (Ashton et al., 2007; De Ridder et al., 2015; Lorenz et al., 2009; Ortmann et al., 2011; Van Der Loo et al., 2009; Weisz et al., 2007; Zhang et al., 2021). In a recent study in sound-exposed animals, we have shown that deep brain stimulation (DBS, 100 Hz, 60 μs pulse width and 100 μA) of the MGB disrupts thalamocortical synchronization under ketamine and xylazine anesthesia (van Zwieten et al., 2021).

Altogether findings obtained from electrophysiological studies in animal models of tinnitus provide evidence that is in line with the postulated theories. The observed hyperpolarized state supports the cortico-thalamic dysrhythmia model (Llinas et al., 1999). The reported upregulation in firing can be considered as a compensatory central mechanism, referred to as central gain, resulting from increased spontaneous activity as a response to the decreased peripheral input. This is in line with predictions of the noise cancellation hypothesis (Leaver et al., 2011; Rauschecker et al., 2010). It is important to note that all observations described above need further confirmation in future studies that control for confounding effects of hearing loss and hyperacusis. It would also be desirable that specific cell types are identified to elucidate the changes across MGB neuronal subtypes that are linked to tinnitus, hearing loss and/ or hyperacusis. It should also be stressed that studies in humans are warranted to confirm the findings from preclinical studies.

5. The role of GABAergic signalling

GABAergic synapses are abundant throughout the auditory pathway (Mugnaini 1985; Prieto et al., 1994; Schofield and Beebe 2019; Watanabe et al., 2002), and GABA signalling has accordingly been hypothesized to be crucial for healthy audition. For example, GABAergic inhibition may underlie the sharpening of frequency tuning in the thalamus and PAC compared to earlier auditory relays (Bartlett 2013). GABAergic inhibition potentially also enhances the contrast between acoustic signals against ongoing background signals (Ebert and Ostwald 1995). At the thalamic level, GABA-mediated inhibition modulates and resets distribution of the ongoing thalamocortical rhythmic oscillations. Excessive thalamic inhibition or deafferentation of the auditory thalamus is proposed as the ultimate origin of the pathologically increased thalamic hyperpolarization, causing corticothalamic dysrhythmia (Llinas et al., 2005).

Compared to other auditory regions, the MGB shows a high sensitivity for GABA (Cai et al., 2014). Internally generated GABAergic input exists in the MGB, arising from an interneuron population whose number varies substantially across species (from less than 1% in rats and bats to 25% in cats and monkeys (Winer and Larue 1996). Most GABAergic MGB input, however, arises from neurons outside the MGB that originate predominantly in the TRN and IC (Richardson et al., 2021). MGB neurons have a high expression of GABAA receptors. GABAA receptors are ligand-gated anion channels composed of pentameric subunits. In the MGB, two main types of GABAA receptors are present that are composed of 2α, 2β and either δ or γ subunits (Caspary and Llano 2017). The GABAA extrasynaptic receptors containing δ subunits have great affinity to GABA and desensitize slowly, producing long-lasting tonic inhibition of MGB neurons. This subtype seems to be more abundant in the MGB than the type containing γ subunits which produce fast phasic inhibition (Richardson et al., 2011; Wisden et al., 1992). Interestingly, the response mode of MGB neurons depends on their state. By applying hyperpolarizing current pulses the extrasynaptic GABAA receptors can be switched from tonic inhibition into burst mode (Cope et al., 2005). That is, if GABAA receptors are hyperpolarized, MGB neurons will respond with bursts of activity upon stimulation. Instead, without hyperpolarization, stimulation of MGB neurons will result in regular tonic firing. It has been suggested that the switch from tonic to burst mode, referred to as thalamocortical dysrhythmia, results in aberrant activity in the auditory cortex underlying the tinnitus percept (Cope et al., 2005; De Ridder et al., 2015; Llinas et al., 1999).

Using ex-vivo spectroscopy measurements of the auditory pathway in animal models with chronic tinnitus, a reduction in GABA level was only observed within the MGB (Brozoski et al., 2012). This finding is in sharp contrast to the thalamocortical dysrhythmia model, according to which elevated GABA in the MGB would be expected. The reduction of GABA was not replicated using microdissection mapping procedure combined with high-performance liquid chromatography. Interestingly, this study showed an increase in (excitatory) aspartate and a decrease in (inhibitory) taurine levels in the MGB (Godfrey et al., 2012). Although no significant changes in the GABA levels were found in this study, taurine can activate GABA receptors. This might result in a reduced thalamocortical relay excitability (Jia et al., 2008). Taurine supplements have proven their efficacy in alleviating tinnitus in animal models as well (Brozoski et al., 2010). Important to note is that the studies presented by Brozoski et al. and Godfrey. et al. do not distinguish between intra- and extracellular neurotransmitter (GABA) levels. It would be helpful to conduct an in vivo study that measures extracellular GABA levels in a tinnitus animal model at the level of the MGB that could provide insight on the extracellular GABA levels in relation to tinnitus and controlling for hearing loss and hyperacusis. In an in vitro study, animals with tinnitus did show increased tonic GABAA currents and an increase in the number of spikes per burst (Sametsky et al., 2015). This suggests a shift towards increased tonic inhibition, which could be a possible factor initiating thalamocortical dysrhythmia. In the same study, an increase in the mRNA expression of the δ-subunit of the extrasynaptic GABAA receptors in ventral and dorsal MGB contralateral to the noise-exposed ear was found, which is in accordance with their first finding.

Given the observed neurochemical changes in the MGB with tinnitus, GABAA extrasynaptic receptors in the MGB might be a relevant (pharmaceutical) target to treat tinnitus (Richardson et al., 2011; Richardson et al., 2012). Muscimol is a potent, selective agonist for the GABAA receptors. As discussed above, the local application of muscimol alleviates tone induced oscillations both in the auditory cortex as well as in the MGB and neural activity is suppressed (Cotillon-Williams and Edeline 2003). Also the oscillations in the auditory cortex diminished after muscimol injection into the MGB. It could be postulated that administration of GABA agonists may potentially ameliorate the tinnitus percept by reducing aberrant cortico-thalamic oscillatory activity. In a systematic review of the efficacy of GABA agonists, clonazepam has proven to be the most effective drug so far (Jufas and Wood 2015). It is important to note that neither clonazepam or other GABA agonists have thus far been approved by the European Medicines Agency (EMA) or the US Food Drug Administration (FDA) to treat tinnitus (Richardson et al., 2011; Richardson et al., 2012). Therefore a GABA agonist should not yet be considered as a regular therapy. GABAA receptors in the MGB should however be considered a potential target for pharmacological treatment of tinnitus.

6. Neuroimaging of the auditory thalamus

Neuroimaging, and specifically magnetic resonance imaging (MRI), is widely used to study changes in brain anatomy (i.e., grey and white matter alterations) as well as function in persons suffering from tinnitus. Below, we discuss evidence of changes in brain anatomy and function with tinnitus in turn. An increased grey-matter volume of the MGB (Muhlau et al., 2006) and other thalamic nuclei (Tae et al., 2018) was reported in tinnitus patients. However, these results were not replicated by other research groups (Boyen et al., 2013; Chen et al., 2014; Landgrebe et al., 2009; Leaver et al., 2011; Zhang et al., 2015). While some studies of white matter modifications in tinnitus reported a reduction of the MGB (Allan et al., 2016) and anterior thalamic radiation white matter integrity (Aldhafeeri et al., 2012), these findings were likely related to hearing loss rather than tinnitus (Husain et al., 2011; Seydell-Greenwald et al., 2014). Instead, when controlling for hearing loss via standard audiometric testing, increases in white matter integrity between regions in the auditory pathway (Crippa et al., 2010) and auditory-limbic connectivity are reported (Benson et al., 2014; Seydell-Greenwald et al., 2014). However, these results need to be interpreted with caution as hyperacusis and hearing loss are potential confounding factors. That is, even when elevated auditory thresholds cannot be observed, hearing loss can still be present at frequencies higher than those tested with standard audiometry. Moreover, cochlear dead regions (Weisz et al., 2006) as well as hair cell damage (Kujawa and Liberman 2009) can exist even without resulting in elevated thresholds. In sum, due to confounds between tinnitus, hearing loss and hyperacusis, results from MRI research on changes in brain anatomy with tinnitus are still inconclusive.

Although these cautionary notes apply to earlier functional MRI (fMRI) studies of tinnitus as well, many recent fMRI studies are carefully controlled for confounds. While earlier studies reported subcortical hyperactivity in tinnitus, including in the MGB (Lanting et al., 2008; Melcher et al., 2009), these findings do not hold when correcting for hearing loss and hyperacusis (Koops et al., 2020). More recent studies that implemented corresponding control measures have reported no difference in the sound-evoked BOLD response strength in subcortical auditory structures (Berlot et al., 2020; Davies et al., 2014) or even showed a decrease compared to controls (Hofmeier et al., 2018; van Gendt et al., 2012). No effect of hearing loss in MGB activity was observed, which might also be related to the low number of participants

included (Boyen et al., 2014; Gu et al., 2010). While other studies did find an effect of hearing loss in cortical activity (Koops et al., 2020). Based on these fMRI studies, it could be postulated that MGB activity decreases in human tinnitus, independent of the hearing threshold. Thalamic hypoactivity is in line with predictions of the thalamocortical dysrhythmia model, but not the noise cancellation model (Leaver et al., 2011; Llinas et al., 1999; Rauschecker et al., 2010; van Gendt et al., 2012). Note that these results from fMRI studies do not match with the electrophysiological findings that suggest neural hyperactivity. This mismatch could be explained by the lack of control for confounds (hearing loss, hyperacusis) in the animal literature or the difference in methodology between the animal and human literature. Functional MRI provides an indirect measure of neural activity, and operates at the spatial scale of (hundreds of) thousands of neurons. Consequently, any difference in tinnitus-related responses across neural subtypes, as revealed through animal models of tinnitus (van Zwieten et al., 2021), will not be picked up by fMRI studies (Ojemann et al., 2013). A way forward to match these results would be to use optical imaging in animal models (bringing the measured signal closer to that observed with fMRI) (Bruns et al., 2017) while carefully controlling for hearing loss and hyperacusis.

Resting-state functional MRI (rs-fMRI) measures the correlation between signals across brain areas in the absence of a stimulus, resulting in an estimate of functional connectivity. Using rs-fMRI to explore functional connectivity, several studies have found decreased connectivity between the thalamus and cortical areas in persons with tinnitus with and without hearing loss (Berlot et al., 2020; Hofmeier et al., 2018; Leaver et al., 2016; Zhang et al., 2015). This reduction in connectivity was not specific to locations with a frequency preference corresponding to the tinnitus pitch, as shown by a recent ultra-high field fMRI study (Berlot et al., 2020). Additionally, tinnitus attenuation by sound or pharmacological therapies was accompanied by normalization of thalamic functional connectivity (Han et al., 2019; Lv et al., 2020; Searchfield et al., 2020). While reduced functional connectivity with tinnitus thus seems to be a consistent result from the functional imaging literature, it does not allow discriminating between the two MGB tinnitus theories. The noise cancellation model of tinnitus (Leaver et al., 2011; Rauschecker et al., 2010) predicts MGB disinhibition, but does not make specific predictions on the thalamocortical connectivity strength. Likewise, the thalamocortical dysrhythmia hypothesis predicts that the nature of thalamocortical connectivity changes with tinnitus (from tonic to bursting firing mode), but does not state the implications of this mode change on functional connectivity.

7. Neuromodulation

Multiple invasive and non-invasive neuromodulation techniques have been used with the objective to reduce the loudness of the tinnitus percept and alleviate distress. Here, we will focus on neuromodulation of the (auditory) thalamus.

Neuromodulation by chronically implanted electrodes, known as DBS, is preceded by lesioning surgeries. Stereotactic lesions of the thalamus have been performed as an (experimental) treatment for neuropathic pain, epilepsy, neuropsychiatric disorders, movement disorders, and even for tinnitus. The effect of medial thalamotomies under local anaesthesia has been described in 104 patients (Jeanmonod et al., 1996). Six patients were primarily treated for tinnitus. The thalamotomy was restricted to the medial thalamus including the central lateral nucleus, the centre median, the parafascicular nucleus, the ventromedial nucleus, and the posterior thalamic complex, which included the suprageniculate-limitans complex and the posterior nucleus. In three out of six patients with tinnitus a 50–100% relief was achieved, with a complete recovery in one patient (Jeanmonod et al., 1996). Important to note is that the blinding procedure, complications and adverse effects of the lesion were not reported.

DBS has a similar clinical effect as lesioning, but has the advantage that the effects are reversible. Stimulation parameters can be adjusted to obtain the maximal reduction of symptoms and avoid or minimize side-effects. To provide DBS treatment, electrodes are stereotactically implanted in a specific brain structure. These electrodes are connected subcutaneously to an internal pulse generator. DBS has proven to be an effective therapy for patients suffering from essential tremor and Parkinson's disease (Lozano et al., 2019). Several human and animal studies have shown that DBS might also be effective in treating tinnitus. Human evidence stems from questionnaires in tinnitus patients who underwent DBS for treatment of other co-existing diseases (mostly movement disorders). Three out of seven patients who reported to have tinnitus prior to DBS reported a decrease in tinnitus loudness during VIM DBS. From this patient cohort, two out of four patients where DBS was turned off and on reported a decrease in tinnitus if DBS was switched on (Shi et al., 2009). In another questionnaire study, a significant decrease of tinnitus handicap was experienced by DBS in the subthalamic nucleus (STN) and a near-statistically significant, but larger decrease, in the VIM. The retrospective character of this study could be prone to recall bias thus conclusions need to be tempered (Smit et al., 2016a). The exact mechanism of the positive effect of VIM and STN DBS on tinnitus remains speculative. The STN and VIM could directly attenuate tinnitus, or more likely, current could have spread to the MGB, or efferent or afferent fibers of the MGB (Shi et al., 2009).

Subcortical auditory targets, including the MGB (van Zwieten et al., 2019b), have been tested in preclinical studies. In all of them, a clear reduction of tinnitus-like behaviour in the noise-trauma tinnitus animal model was found (Luo et al., 2012; Smit et al., 2016b; van Zwieten et al., 2019a; van Zwieten et al., 2019b). As results are similar throughout the subcortical auditory pathway, any of these brain regions represents a potentially suitable target for DBS. However, in selecting the most suitable target for DBS, several characteristics beyond tinnitus suppression must be considered. For example, the chance of inducing side effects and the ease of the stereotactic approach are crucial. The MGB is considered the most accessible target among the subcortical auditory regions from a surgical point of view (van Zwieten et al., 2016). Furthermore, side effects of stimulation are expected to be minimal, as no hearing loss or other side-effects were observed in the animal model (van Zwieten et al., 2019b). We therefore postulate that the MGB is a suitable target for DBS.

Although the exact functional mechanism of DBS remains unknown, several theories have been postulated. DBS may cause soma inhibition, in combination with axonal activation (McIntyre et al., 2004). Furthermore, DBS may reduce the neuronal firing rate and exert inhibitory effects via the activation of GABAA receptors, which are highly available in the MGB (Moser et al., 2003). These effects are similar to the effects of GABAA agonist described above. Thereby this postulated DBS mechanism might contribute to the reduction of aberrant cortico-thalamic oscillations. In line with this it has already been suggested that changes in the firing pattern and neuronal oscillations could explain the therapeutic effect of DBS (Hahn and McIntyre 2010). In a rodent animal model, MGB DBS suppresses thalamocortical synchronization in the beta and gamma bands (van Zwieten et al., 2021). Another theory is that DBS results in a large-scale release of neurotransmitters at the stimulation site, which results in a dissociation of the input and output of the stimulation nucleus. As a result, abnormal neuronal activity is disrupted (Chiken and Nambu 2016). The complete working mechanism of DBS effect is likely complex, possibly comprising multiple of the proposed mechanisms and affecting a network of brain regions (McIntyre and Hahn 2010). Given that the functional mechanism of DBS remains unknown, it is impossible to predict the exact effect of thalamic DBS on thalamocortical connectivity. DBS may further reduce thalamocortical functional connectivity (e.g. by reducing the firing rate of the MGB, or adding neural noise to the system), but it may also disrupt abnormal neural activity or oscillations (restoring "healthy" connectivity). The positive effect of MGB DBS in animal models, where it was shown that DBS relieved tinnitus symptomatology (van Zwieten et al., 2021) is

promising. If MGB DBS also successfully relieves symptoms in humans, additional research will be needed to understand the mechanism underlying the beneficial effect of DBS.

8. Conclusion

The MGB is centrally located in the auditory circuit, where it forms a hub connecting limbic regions with the auditory network. Current knowledge on alterations of the MGB obtained in animal studies as well as human studies suggest that the MGB plays an important role in the tinnitus neuropathophysiology. The exact changes in tinnitus at the biohistochemical and neuronal level are not fully unravelled. More research is also required in order to localize alterations to specific subregions of the MGB, and for gaining knowledge on its connectivity with other structures, specifically with the limbic system. Nonetheless, the proposed changes at the neurotransmitter level and altered neural activity as evidenced by diverse electrophysiological as well as functional neuroimaging studies provide a strong rationale to target the MGB in the search for an effective treatment for tinnitus.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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