Vagus nerve stimulation for tinnitus: A review and perspective

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Abstract

Vagus nerve stimulation is a promising new tool in the treatment of chronic tinnitus. Current protocols involve pairing sounds, which exclude the tinnitus frequency, with simultaneous vagus nerve stimulation (VNS). This is based on extensive preclinical animal studies that demonstrate that pairing non-tinnitus sounds with VNS results in a tonotopic map plasticity. It is thought that by expanding the non-tinnitus sound representation, it is possible to overturn the expanded tonotopic map associated with the tinnitus frequency in these animal models. These findings have been translated into a clinical approach, where a clinically significant, but moderate improvement, in tinnitus distress and a modest benefit in tinnitus loudness perception has been shown. Yet, pairing tinnitus matched sound to VNS may produce tinnitus improvement by Pavlovian conditioning, in which the distressful tinnitus sound becomes associated with a relaxing "rest and digest" response from activation of the vagus nerve. If this hypothesis is correct, beneficial effects should be achieved with paired sounds that resemble the tinnitus sounds as much as possible.

In conclusion, although the potential to use VNS to drive neural plasticity to reduce or eliminate the neural drivers of ongoing tinnitus is exciting, much work is needed to more completely understand the neural basis of tinnitus and to develop tailored therapies to address the suffering caused by this heterogeneous condition. Whether pairing of the vagus stimulation with non-tinnitus or tinnitus-matched sounds is essential is still to be determined.

Keywords

Tinnitus, Vagus, Vagal, Nerve, Stimulation, Paired

1 Background: Rationale for vagus nerve stimulation for tinnitus

Tinnitus can be defined as the conscious awareness of a non-complex sound for which there is no identifiable corresponding external sound source. Tinnitus has a similar prevalence rate of 10–15% worldwide, including the USA, Europe, Asia and Africa (Axelsson and Ringdahl, 1989; Khedr et al., 2010; Kim, 2018; Lasisi et al., 2010; Michikawa et al., 2010; Shargorodsky et al., 2010). Whereas 80% of the patients with tinnitus do not suffer from it, 20% of the patients are severely distressed by the tinnitus (Axelsson and Ringdahl, 1989), i.e. 2–3% of the total population (Axelsson and Ringdahl, 1989). Tinnitus with associated suffering can be called tinnitus disorder (see chapter "Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal)" by De Ridder).

Tinnitus is comparative by clinical, pathophysiological and treatment analogies with phantom pain (De Ridder et al., 2011a; Moller, 1997; Tonndorf, 1987; Vanneste et al., 2019b) but also with other diseases such as Parkinson's disease, major depressive disorder, and slow wave epilepsy, which are grouped under the name of thalamocortical dysrhythmias (De Ridder et al., 2011b, 2015b; Llinas et al., 1999; Vanneste et al., 2018). The thalamocortical dysrhythmias are rooted in deafferentation, i.e. sensory, motor, or emotional deprivation. Physiological auditory deprivation or auditory deafferentation should be differentiated from clinical hearing loss, as tinnitus without hearing loss does not exclude auditory deafferentation (Weisz et al., 2006). Indeed, part (up to 50%) of the auditory nerve can be surgically transected without an associated hearing loss, both in animals (Schuknecht & Woellner, 1953) and humans (Dandy, 1941). This can be explained by the overlap of different frequencies, resulting from the V-shaped tuning curves of auditory neurons: at low stimulus intensities the neurons are tuned in a very discrete and selective way, and anatomically the neighboring frequencies are processed in adjacent areas, in an orderly fashion, resulting in a tonotopic map. However, at higher amplitudes the tuning becomes less selective, both at the level of the cochlea and more centrally up to the auditory cortex, and thus starts to overlap. This means that a specific tone presented at a high amplitude can be processed by adjacent neurons, allowing them to fill in the missing information. There exists a phenomenon of "hidden hearing loss," which has been linked to cochlear synaptopathy, defined as the loss of inner hair cell synapses without any evidence of increased hearing thresholds (Kujawa and Liberman, 2009). Cochlear synaptopathy can be detected by a loss of peak I in the ABR (Kujawa and Liberman, 2009) and by the summating potential/action potential (SP/AP) ratio of electrocochleography (Liberman et al., 2016), both of which are abnormal in tinnitus (Bramhall et al., 2019; Kara et al., 2020). Moreover, anatomical "dead regions" have been described in the cochlea. Dead regions are regions in the cochlea where inner hair cells or neurons are not functioning, and may occur in patients with cochlear synaptopathy or may result from cochlear damage due to noise or ototoxicity (Kara et al., 2020). Dead regions may be detected by the threshold equalizing noise (TEN) test, which has been shown to be

abnormal in 75% of tinnitus patients (Kara et al., 2020). This primary neural degeneration causes deafferentation without affecting hearing thresholds, thus likely contributing to problems understanding speech in difficult listening environments, and putatively being important in the generation of tinnitus (Kujawa and Liberman, 2015).

Tinnitus is often caused by loud occupational or leisure related sounds (Axelsson and Prasher, 2000; Gilles et al., 2012) which can result in transient or permanent damage to the inner hair cells and synapses of the cochlea (Morest et al., 1998; Mulroy et al., 1998; Nordmann et al., 2000). Indeed, hearing loss in musicians and soldiers is very common (Di Stadio et al., 2018), with up to 38.6% of musicians presenting with hearing loss, more so in rock (63.5%) than classical musicians (32.8%) (Di Stadio et al., 2018). However, the relationship between hearing loss and tinnitus is not straightforward. Not everybody with hearing loss develops tinnitus and not all tinnitus patients have abnormal audiograms (Langguth et al., 2013). The prevalence of tinnitus in musicians is double the 15% prevalence in the general population, amounting to 26% (Di Stadio et al., 2018), similar to what is noted in other occupational noise exposure (Phoon et al., 1993) and deployed military personnel (30%) (Theodoroff et al., 2015).

The loss of auditory input may induce a cascade of neurophysiological changes in the central auditory system sometimes culminating in the perception of a phantom sound. Neurophysiological changes likely result from the imbalance between excitation and inhibition that can lead to map reorganization and increased synchronous firing of auditory neurons (Eggermont and Roberts, 2004). Auditory deprived neurons respond to the same frequencies as neighboring neurons still receiving input from undamaged parts of the cochlea (Dietrich et al., 2001; Rajan et al., 1993; Syka, 2002). This results in reorganization of the tonotopic map in the cortex, and an increase in the number of neurons generating synchronous activity might ultimately be responsible for the tinnitus perception (Eggermont and Roberts, 2004; Muhlnickel et al., 1998; Moller, 2006a).

This tonotopic map reorganization as a neural correlate of tinnitus has been the foundation on which vagus nerve stimulation paired with sound stimulation excluding tinnitus tones was based (Engineer et al., 2011).

Tonotopic map reorganization, however, may be more related to auditory deafferentation and potential hearing loss than to the tinnitus percept (Langers et al., 2012), analogous to what has been noted in the somatosensory system (Makin et al., 2013). Indeed, limited deafferentation can occur without detectable tonotopic map reorganization. This has been explained by a multiphase response to auditory deafferentation (De Ridder et al., 2014b), in which wider bandwidth deafferentation is characterized by progressively more complex involvement of the auditory cortex.

2 Vagus nerve stimulation for tinnitus

Vagus nerve stimulation is a neuromodulation technique that exerts an effect on the brainstem and brain. Using functional imaging it has been shown that vagus stimulation modulates activity in the auditory system (including superior temporal

gyrus, Heschl's gyrus, planum porale, and planum temporale) (Lehtimaki et al., 2013; Yakunina et al., 2018) and limbic system (amygdala) (Yakunina et al., 2018). Furthermore, the parahippocampus is also modulated by vagus nerve stimulation (Yakunina et al., 2018). All these areas are implicated in tinnitus (De Ridder and Vanneste, 2014; De Ridder et al., 2006; Maudoux et al., 2012; Song et al., 2012). In the brainstem the locus coeruleus and nucleus tractus solitarius are modulated as well, which are connected to the dorsal cochlear nucleus (Kaltenbach, 2006). Vagus nerve stimulation is approved as a treatment for depression, a co-morbidity commonly encountered in tinnitus (Dobie, 2003; Joos et al., 2012; Langguth et al., 2007, 2011; Pattyn et al., 2016). Thus the application of vagus nerve stimulation in tinnitus intuitively makes sense, as it modulates brain areas involved in the emotional, auditory and mood components of tinnitus (Elgoyhen et al., 2015; Langguth et al., 2013).

Yet, vagus nerve stimulation can also be paired with external stimuli, driving neuroplasticity by resetting dysfunctional circuits through cortical map expansion. This provides a form of replication with variation that supports a Darwinian mechanism to select the most behaviorally useful circuits (Kilgard, 2012).

Vagus nerve stimulation can be clinically performed in 2 ways: non-invasively, i.e. non-surgically and invasively, i.e. surgically. Non-surgical vagus nerve stimulation can be performed by electrically stimulating the superficial vagal branches at the external ear canal at the area of the concha or tragus, or by electrical stimulation in the neck. Different commercially available devices exist to electrically stimulate the vagus nerve. Invasive vagus stimulation is routinely used for epilepsy and major depressive disorder (Cristancho et al., 2011; Daban et al., 2008). Using a direct surgical approach a coil electrode is attached to the vagus nerve and connected to a programmable internal pulse generator.

Vagus nerve stimulation for tinnitus has been performed in either of two ways: paired to non-tinnitus sounds, or vagus nerve stimulation without paired sounds, as often is the case in the setting of depression or epilepsy, two FDA approved indications for vagus nerve stimulation.

2.1 Sound paired vagus nerve stimulation for tinnitus

2.1.1 Initial animal sound-paired vagus nerve stimulation studies

Up until recently, all kinds of invasive neuromodulation were performed in a simple way, in which the electrical stimuli were applied to the target tissue without any associated external stimuli. However, recently a new neuromodulation method was introduced that can drive auditory cortex plasticity in a controlled and therapeutic direction by pairing repeated short-term simulation of the vagus nerve with simultaneously presented tones that fall outside the tinnitus frequency (Engineer et al., 2011, 2013; Hays et al., 2013; Kilgard, 2012; Kilgard and Merzenich, 1998, 1999, 2002). It was shown that repeatedly pairing a brief burst of vagus nerve stimulation (VNS) with a 9 kHz tone in normal rats causes a dramatic expansion of the region of primary auditory cortex that responds to 9 kHz (Engineer et al., 2011).

Tinnitus is associated with a similar overrepresentation of the tinnitus-matched frequency (Engineer et al., 2011). To treat tinnitus in noise-exposed rats, VNS is paired with a variety of tones that exclude the tinnitus frequency, thereby eliminating the behavioral and physiological manifestations of tinnitus in a rat model (Engineer et al., 2011).

2.1.2 Human sound-paired vagus nerve stimulation studies

These results have been translated in two human studies. Repeated short duration vagus nerve simulation was paired with non-tinnitus tones, excluding the tinnitus frequency, in 10 patients with chronic tinnitus in a first open label pilot study (De Ridder et al., 2014a). This was followed by a second larger placebo-controlled study involving 30 patients (Tyler et al., 2017). All stimulation and auditory presentation parameters were kept as close as possible to the seminal animal study (Engineer et al., 2011). Half-second bursts of VNS were delivered at an intensity of 0.8 mA, 100 μs pulse width at 30 Hz, every 30 s. If desired, for comfort, the output current (0.8 mA) was reduced in 0.05 mA steps. The stimulation intensity was lower and pulse width shorter than what is typically delivered for epilepsy (Amar et al., 1998; Lundgren et al., 1998; Lundy et al., 1993). As patients received VNS only during 2.5 h per day, the total time of stimulation (150 s per day) was dramatically less than the approximately 8600 s/day of VNS typically delivered for epilepsy. This equates to around 2% of the time for epilepsy. A pure tone was paired with each vagus nerve stimulation pulse. Each tone frequency was delivered to both ears via headphones (see Fig. 1). VNS was delivered 150 ms prior to each tone and both the tone and VNS train duration were 0.5-s-long. Patients underwent ~2.5 h of daily VNS tone pairing for 20 days, 5 days a week (i.e. Monday through Friday) for 4 weeks. Tone frequencies ranged from 170 to 16,000 Hz. Tones half an octave on either side of the tinnitus frequency were excluded from the stimulus set.

In the first study, the therapy safety and feasibility was demonstrated (Fig. 1B): the surgery and stimulation was well tolerated and no patients withdrew from the study due to complications or side effects (De Ridder et al., 2014a). Four of the 10 patients exhibited clinically meaningful improvements in their tinnitus, both for the affective component, as quantified by the Tinnitus Handicap Inventory (THI), and for the sound percept, as quantified by the minimum masking level (MML). These improvements were stable for more than 2 months after the end of therapy. Of the 10 patients, 5 were on medications that included muscarinic antagonists, norepinephrine agonists and GABA agonists, thereby possibly interfering with acetylcholine and norepinephrine release induced by VNS and essential for inducing plasticity. The medicated patients had no improvement whereas the four treatment responders were all medication-free patients. This study confirmed that VNS paired with tones, excluding the tinnitus matched frequency, is safe and feasible in humans, yet good outcomes may be prevented by medications that interfere with VNS effects (De Ridder et al., 2014a).

In the second larger placebo-controlled study, medication was excluded, as to prevent its influence on stimulation induced map plasticity. In this study, patients

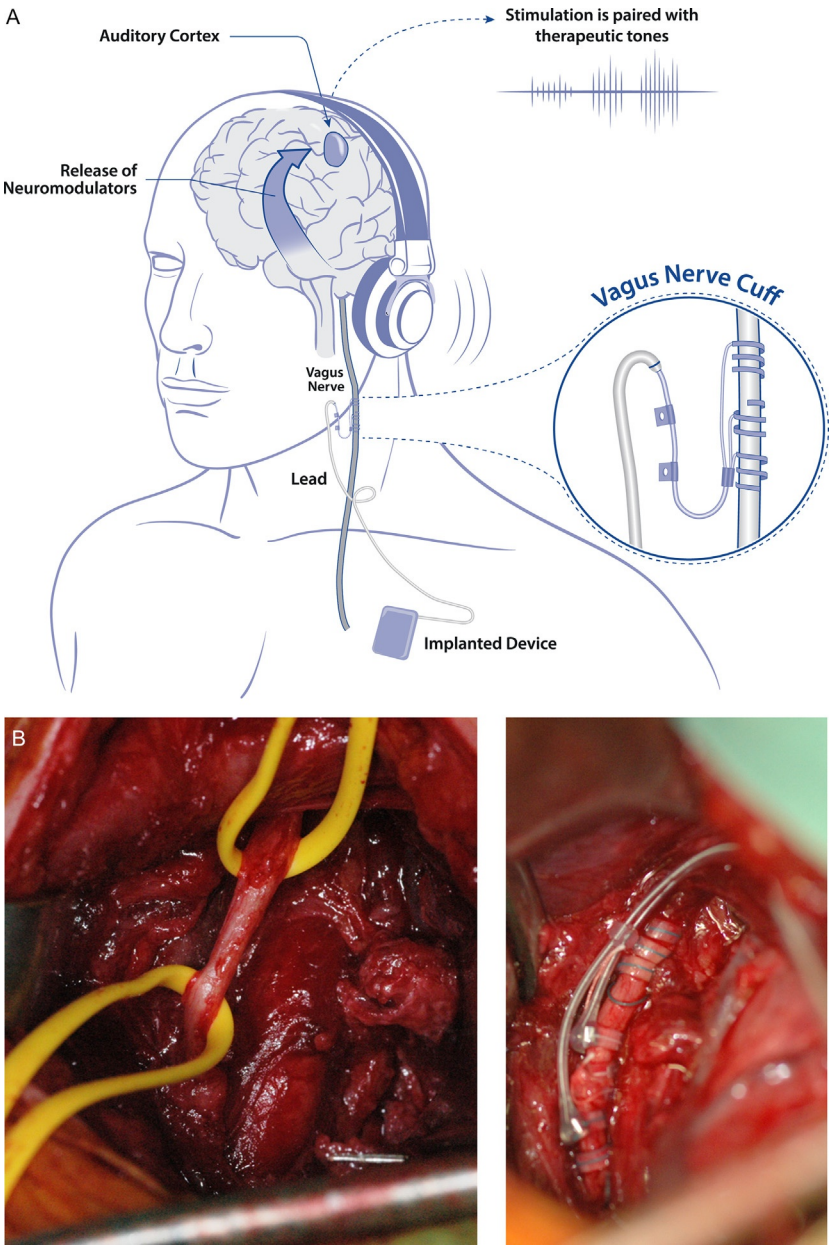

FIG. 1

(A) Sound paired vagus nerve stimulation consists of pairing non-tinnitus sounds with electrical stimuli of the left vagus nerve (with permission from Microtransponder). (B) Intraoperative picture of vagus nerve before (left) and after application of the coil-electrode (right).

were randomized to either VNS with paired auditory stimuli (active group), or to a control condition, where VNS and auditory stimulation were offered separately. The stimulation parameters were identical to the first study (15 pulses at 0.8 mA, constant current, charge balanced with 100 μs pulse width at 30 Hz. The duration of the VNS pulse train was 0.5 s. Each pulse train was delivered approximately every 30 s for 2.5 h). The paired group improved more than the control unpaired group on the THI (10-points difference). Both paired and unpaired groups, however, had a clinically meaningful difference, which is defined as more than 7-point improvement (Zeman et al., 2011): 17.7 points for the paired group, which was statistically significant, vs 7.7 for the control group (statistically non-significant). Yet, for all other outcome parameters including the Tinnitus Handicap Questionnaire (THQ), Tinnitus Functional Index (TFI), loudness severity, loudness match, and minimal masking levels (MML), there was no statistically significant difference between the paired group and the control group. After 6 weeks all patients were unblinded and switched to paired stimulation. After one-year THI, THQ, TFI and loudness severity improved significantly, in contrast to loudness matching and MML. The treatment had better efficacy in tonal tinnitus than in noise-like tinnitus and in non-blast induced tinnitus with 70% response rate at 1 year. Thus, it was concluded that paired VNS may be particularly beneficial for tonal, non-blast induced tinnitus in patients without interfering medication use (Tyler et al., 2017). Why blast injury and non-tonal tinnitus may respond worse is unknown.

Based on these studies (Engineer et al., 2011), non-invasive stimulation methods have also been tested in tinnitus patients with (Lehtimaki et al., 2013) or without (Kreuzer et al., 2012, 2014) sound therapy. These methods employ electrical stimulation of the outer ear because there is some evidence that the nerve fibers in the tragus join the vagus nerve. While outer ear stimulation is insufficient to stimulate the entire vagus nerve, there is growing evidence that the technique is safe (Kreuzer et al., 2012), and induces alterations of brain activity resembling the effects of invasive vagus nerve stimulation (Kraus et al., 2013). Transcutaneous VNS (tVNS) alone (without paired auditory stimulation) had no relevant effects on tinnitus complaints but reduced subjectively reported depressive symptoms (Kreuzer et al., 2014). A pilot study investigating seven 45 min sessions of tVNS paired with sounds (classical music), omitting one octave surrounding the patient's tinnitus frequency, showed improvements in both mood and tinnitus handicap (Lehtimaki et al., 2013).

2.2 How does sound paired VNS exert its clinical benefit?

Exposure to intense noise degrades the frequency tuning of auditory cortex neurons and increases cortical synchronization (Engineer et al., 2011). Repeatedly pairing tones with brief pulses of vagus nerve stimulation (Borland et al., 2016, 2018; Loerwald et al., 2018) completely eliminates the physiological and behavioral correlates of tinnitus in noise-exposed rats (Engineer et al., 2011). In addition to well-studied changes in primary auditory cortex, a recent study has confirmed that

VNS paired with tones is also sufficient to alter frequency tuning in lower auditory stations including the inferior colliculus and higher auditory stations, including secondary auditory cortex. Pairing tones with VNS reduces neural synchronization in a rat model of tinnitus (Engineer et al., 2011).

Thus, the hypothesis is that pairing sounds with VNS can result in a desynchronization of highly correlated activity within human auditory cortex. This is confirmed in EEG analysis, which demonstrates that gamma band activity, itself correlated to tinnitus loudness perception (De Ridder et al., 2015a; van der Loo et al., 2009), is decreased after sound paired VNS. The power in sensor space or current density in source space depends on the synchronization of the activity of underlying or source-localized neurons respectively (Moller, 2006b).

As mentioned before tinnitus can be considered as an emergent property of multiple overlapping and dynamically changing networks, generating a unified percept, including a loudness, location, and affective components (De Ridder et al., 2014c). This network has been proposed to use theta as a carrier wave and gamma as an information wave (De Ridder et al., 2015c; Vanneste et al., 2018). Thus, the theta frequency links the medial and lateral pathway, which encode the motivational, affective component and the loudness discriminatory component respectively. Sound paired with VNS reduces the functional connectivity between the dorsal anterior cingulate cortex and the auditory cortex in the theta frequency band. Sound paired with VNS also reduces functional connectivity between the descending noise canceling pathway hubs of the subgenual anterior cingulate cortex and parahippocampus. Furthermore, it has been shown that the subgenual anterior cingulate cortex and parahippocampus form a general aversive network (Moulton et al., 2011), which is confirmed in tinnitus (Vanneste et al., 2013).

Clinically, this reduction in functional connectivity is expected to dissociate the normally present correlation between subjective loudness perception (lateral pathway) and distress (medial pathway), because the decreased communication between the pathways decreases the salience, encoded by the medial pathway (Seeley et al., 2007), from the tinnitus sound. The decreased functional connectivity with the parahippocampus and subgenual anterior cingulate cortex permits the noise canceling system to function more effectively, and thus decrease the loudness and percentage of the time the tinnitus is present (Song, 2015). As expected, sound paired vagus nerve stimulation indeed seems to dissociate the normally present correlation between subjective loudness perception and distress (Vanneste et al., 2017).

Yet, the question may be raised whether this is a pure VNS effect or whether the pairing is crucial? The results from the paired versus unpaired stimulation are unclear, in that pairing seems to be better for the THI, but not for the THQ, TFI, loudness severity, loudness matching and MML. Thus, the question arises whether VNS in itself may be beneficial, i.e. the hypothesis can be raised that the improvement is mainly due to an anti-depressant-like effect resulting from vagus nerve stimulation (Cristancho et al., 2011; Daban et al., 2008).

2.3 Vagus nerve stimulation and tinnitus

Vagus nerve stimulation is clinically used for major depressive disorder (Daban et al., 2008) and epilepsy (Englot et al., 2011). This makes it possible to evaluate whether VNS alone has an effect on tinnitus. In a retrospective study of a population of epilepsy patients, the tinnitus loudness was evaluated in a retrospective telephone survey using a VAS (Wichova et al., 2018). Out of the 56 patients with epilepsy who underwent VNS, 20 patients (35%) reported the presence of pre-operative tinnitus. This is twice the prevalence of a non-epilepsy population. The tinnitus positive group was significantly older, consistent with the age-related prevalence in tinnitus (Shargorodsky et al., 2010). Of the 20 pre-operative epilepsy patients with tinnitus, all patients continued to have tinnitus post-operatively. Four (20%) noted no changes in VAS of tinnitus loudness while 16 (80%) improved with at least a one-point decrease. The mean difference between pre- and 1 year post-operative VAS of loudness was 2.05, which was statistically significant, and the same amount as obtained after 1 year with paired stimulation, in which the subjective loudness perception improvement was 1.94 (Tyler et al., 2017), also significant. After shorter duration of sound paired VNS results are less pronounced, both in paired and unpaired stimulation (Fig. 2).

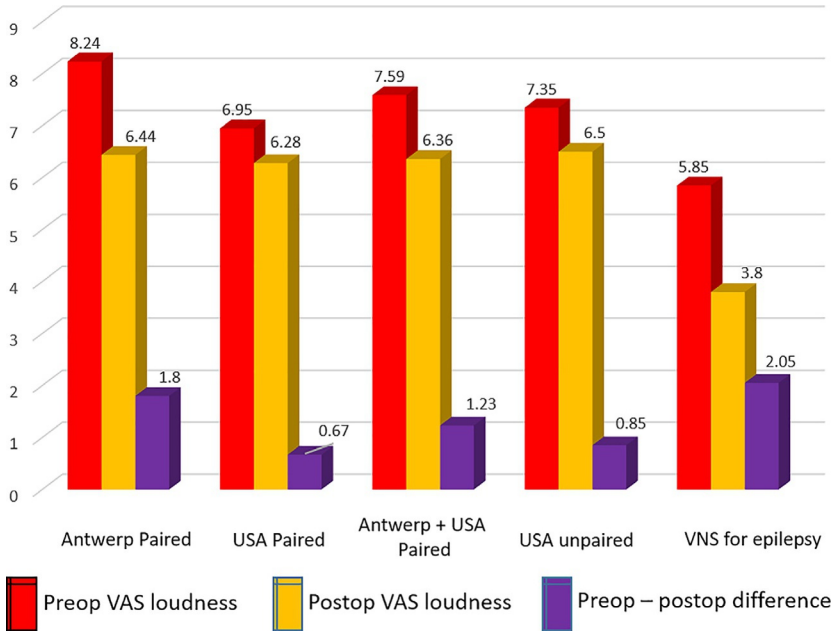

FIG. 2

Summary of outcomes of sound paired stimulation, sound unpaired stimulation and pure VNS based on De Ridder et al. (2014a); Tyler et al. (2017); Wichova et al. (2018).

These results suggest the possibility that VNS may reduce tinnitus severity via two distinct mechanisms. VNS triggers release of neuromodulators including norepinephrine, acetylcholine and serotonin, which desynchronizes the cortex and improves mood. When paired with specific events VNS also drives long lasting neural plasticity, which can restore function in animal models of tinnitus, stroke, spinal cord injury and peripheral nerve damage (Ganzer et al., 2018). It is possible that the targeted plasticity produced by pairing VNS with particular events also benefits from non-specific actions, including effects on mood (Elger et al., 2000).

The dual action of VNS is perhaps best documented in rat models of post-traumatic stress disorder (PTSD). VNS engenders highly specific changes in emotional responses and in amygdala gene expression when stimulation is paired with sounds conditioned to produce fear (Alvarez-Dieppa et al., 2016). In conjunction with these biochemical changes, delivery of VNS paired with sounds also generates long-lasting plasticity in the connection from prefrontal cortex to the amygdala that regulates fear and anxiety. Independent of these central effects, VNS also produces a short-acting reduction in anxiety even when not paired with any sound (Noble et al., 2019). There is growing evidence that central and peripheral effects of VNS work together to enhance recovery in animal models of PTSD (Noble et al., 2018). It is not yet clear whether these two pathways function synergistically or independently to benefit tinnitus patients.

For tinnitus, it is much less clear what experiences should be paired with VNS for maximal benefit. It is known that the interval between VNS-sound pairings determines the degree of plasticity produced (Borland et al., 2018). However, many other aspects of VNS-sound therapy have not been explored in a systematic manner. Pairing VNS with fast or slow trains of tones can increase or decrease the maximum rate that cortical neurons can respond to sound (Shetake et al., 2012). Delivery of equivalent VNS paired with speech sounds selectively alters the cortical response to the paired sounds, highlighting the importance of the paired event (Engineer et al., 2015). It is not yet known how these different forms of plasticity might be optimally used to reduce tinnitus symptoms. It remains a possibility that the effectiveness of VNS-sound pairing could be enhanced by selecting the appropriate sounds. Given the heterogeneous nature of tinnitus etiology and symptoms, it is likely that the neural basis of tinnitus differs significantly across individuals (Lee et al., 2017; Vanneste et al., 2019a). Thus, the most effective application of targeted plasticity therapy may require that different sounds are selected for each individual and paired with VNS to reduce the activity of the neural generators and reduce tinnitus severity.

2.4 A third potential mechanism in pairing vagus nerve stimulation to sounds?

The mechanism of action of paired VNS is based on the concept that pairing non-tinnitus sounds to VNS results in a tonotopic map plasticity, expanding the non-tinnitus sound representation. This expansion of the non-tinnitus frequencies in the tonotopic map could overturn the expanded tonotopic map associated with

the tinnitus frequency, thereby normalizing tonotopy. Whereas initial studies highlighted the correlation between tinnitus and tonotopic map reorganization, even in humans (Muhlnickel et al., 1998), analogous to what was demonstrated for phantom pain (Flor et al., 1995), later studies demonstrated that in tinntus patients with little or no detectable hearing loss there is no detectable tonotopic map reorganization (Langers et al., 2012), similarly to what was demonstrated in pain (Makin et al., 2013). In both tinnitus and pain, it was concluded that the tonotopic map reorganization and somatotopic map reorganization respectively are linked to the deafferentation, i.e. the hearing loss and the sensory deprivation, rather than the tinnitus and pain percept (Langers et al., 2012; Makin et al., 2013). As the preclinical data (Engineer et al., 2011) that generated the human trials (De Ridder et al., 2014a, 2015a; Tyler et al., 2017) were dependent on this map plasticity and gap detection test (Turner et al., 2006), which has also become criticized (Boyen et al., 2015), it shows the limits of animal testing in the field of tinnitus studies.

Yet, the dual mechanism involved may theoretically even have a third component, which is that paring the tinnitus-matched sound to simultaneous vagus nerve stimulation may be effective in reducing the tinnitus loudness and distress via Pavlovian reconditioning. The parasympathetic nervous system, including its main component, the vagus nerve, have been called the "rest, digest and restore" system, in balance with the sympathetic "fight and flight" system. When presenting a distressful tinnitus sound with simultaneous relaxing and mood improving vagus nerve stimulation, this may result in Pavlovian reduction of tinnitus intrusiveness via reduction of the tinnitus related distress network. This tinnitus-matched sound-paired VNS stimulation has not yet been performed in humans, however, it is not inconceivable that this may underlie the benefits noted in VNS in epilepsy patients, as the constant phantom sound may progressively become associated to the "rest and digest" vagus nerve stimulation. A study should be performed with tinnitus-matched sound paired vagus nerve stimulation, as the pairing is more obvious for the brain when the tinnitus matched sound is temporally also matched (Fig. 3).

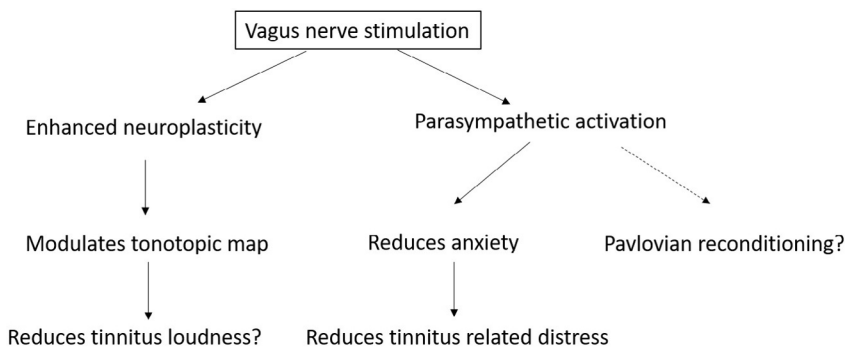

FIG. 3

Vagus nerve stimulation improves the efficacy of sound exposure therapy by enhancing the central release of neuromodulators and by reducing anxiety through the activation of the parasympathetic system. A third mechanism may involve Pavlovian reconditioning.

3 Conclusion

Vagus nerve stimulation is a promising new tool for the treatment of chronic tinnitus. Current protocols produce a clinically significant but moderate improvement in tinnitus distress and a modest benefit in tinnitus loudness perception. Although the potential to use neural plasticity to reduce or eliminate the neural drivers of ongoing tinnitus is exciting, much work is needed to more completely understand the neural basis of tinnitus and to develop tailored therapies to address the suffering caused by this heterogeneous condition. Whether pairing of the vagus stimulation with non-tinnitus or tinnitus-matched sounds is essential is still to be determined. Current evidence for paired or unpaired vagus nerve stimulation in the setting of tinnitus is insufficient for FDA approval.

References

Alvarez-Dieppa, A.C., Griffin, K., Cavalier, S., McIntyre, C.K., 2016. Vagus nerve stimulation enhances extinction of conditioned fear in rats and modulates arc protein, CaMKII, and GluN2B-containing NMDA receptors in the basolateral amygdala. Neural Plast. 2016, 4273280.

Amar, A.P., Heck, C.N., Levy, M.L., Smith, T., DeGiorgio, C.M., Oviedo, S., et al., 1998. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome. Neurosurgery 43, 1265–1276, (discussion 76–80).

Axelsson, A., Prasher, D., 2000. Tinnitus induced by occupational and leisure noise. Noise Health 2, 47–54.

Axelsson, A., Ringdahl, A., 1989. Tinnitus—a study of its prevalence and characteristics. Br. J. Audiol. 23, 53–62.

Borland, M.S., Vrana, W.A., Moreno, N.A., Fogarty, E.A., Buell, E.P., Sharma, P., et al., 2016. Cortical map plasticity as a function of vagus nerve stimulation intensity. Brain Stimul. 9, 117–123.

Borland, M.S., Engineer, C.T., Vrana, W.A., Moreno, N.A., Engineer, N.D., Vanneste, S., et al., 2018. The interval between VNS-tone pairings determines the extent of cortical map plasticity. Neuroscience 369, 76–86.

Boyen, K., Baskent, D., van Dijk, P., 2015. The gap detection test: can it be used to diagnose tinnitus? Ear Hear. 36 (4), e138–e145.

Bramhall, N.F., McMillan, G.P., Gallun, F.J., Konrad-Martin, D., 2019. Auditory brainstem response demonstrates that reduced peripheral auditory input is associated with self-report of tinnitus. J. Acoust. Soc. Am. 146, 3849.

Cristancho, P., Cristancho, M.A., Baltuch, G.H., Thase, M.E., O'Reardon, J.P., 2011. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. J. Clin. Psychiatry 72, 1376–1382.

Daban, C., Martinez-Aran, A., Cruz, N., Vieta, E., 2008. Safety and efficacy of vagus nerve stimulation in treatment-resistant depression. A systematic review. J. Affect. Disord. 110, 1–15.

Dandy, W., 1941. Surgical treatment of Ménières disease. Surg. Gynaecol. Obstet. 72, 421–425.

De Ridder, D., Vanneste, S., 2014. Targeting the parahippocampal area by auditory cortex stimulation in tinnitus. Brain Stimul. 7 (5), 709–717

De Ridder, D., Fransen, H., Francois, O., Sunaert, S., Kovacs, S., Van De Heyning, P., 2006. Amygdalohippocampal involvement in tinnitus and auditory memory. Acta Otolaryngol. Suppl. 50–53.

De Ridder, D., Elgoyhen, A.B., Romo, R., Langguth, B., 2011a. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc. Natl. Acad. Sci. U. S. A. 108, 8075–8080.

De Ridder, D., van der Loo, E., Vanneste, S., Gais, S., Plazier, M., Kovacs, S., et al., 2011b. Theta-gamma dysrhythmia and auditory phantom perception. J. Neurosurg. 114, 912–921.

De Ridder, D., Vanneste, S., Engineer, N.D., Kilgard, M.P., 2014a. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. Neuromodulation 17, 170–179.

De Ridder, D., Vanneste, S., Freeman, W., 2014b. The Bayesian brain: phantom percepts resolve sensory uncertainty. Neurosci. Biobehav. Rev. 44C, 4–15.

De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Elgoyhen, A.B., et al., 2014c. An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks. Neurosci. Biobehav. Rev. 44, 16–32.

De Ridder, D., Congedo, M., Vanneste, S., 2015a. The neural correlates of subjectively perceived and passively matched loudness perception in auditory phantom perception. Brain Behav. e00331.

De Ridder, D., Kilgard, M., Engineer, N., Vanneste, S., 2015b. Placebo-controlled vagus nerve stimulation paired with tones in a patient with refractory tinnitus: a case report. Otol. Neurotol. 36, 575–580.

De Ridder, D., Vanneste, S., Langguth, B., Llinas, R., 2015c. Thalamocortical dysrhythmia: a theoretical update in tinnitus. Front. Neurol. 6, 124.

Di Stadio, A., Dipietro, L., Ricci, G., Della Volpe, A., Minni, A., Greco, A., et al., 2018. Hearing loss, tinnitus, hyperacusis, and diplacusis in professional musicians: a systematic review. Int. J. Environ. Res. Public Health 15.

Dietrich, V., Nieschalk, M., Stoll, W., Rajan, R., Pantev, C., 2001. Cortical reorganization in patients with high frequency cochlear hearing loss. Hear. Res. 158, 95–101.

Dobie, R.A., 2003. Depression and tinnitus. Otolaryngol. Clin. North Am. 36, 383–388.

Eggermont, J.J., Roberts, L.E., 2004. The neuroscience of tinnitus. Trends Neurosci. 27, 676–682.

Elger, G., Hoppe, C., Falkai, P., Rush, A.J., Elger, C.E., 2000. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res. 42, 203–210.

Elgoyhen, A.B., Langguth, B., De Ridder, D., Vanneste, S., 2015. Tinnitus: perspectives from human neuroimaging. Nat. Rev. Neurosci. 16, 632–642.

Engineer, N.D., Riley, J.R., Seale, J.D., Vrana, W.A., Shetake, J.A., Sudanagunta, S.P., et al., 2011. Reversing pathological neural activity using targeted plasticity. Nature 470, 101–104.

Engineer, N.D., Moller, A.R., Kilgard, M.P., 2013. Directing neural plasticity to understand and treat tinnitus. Hear. Res. 295, 58–66.

Engineer, C.T., Engineer, N.D., Riley, J.R., Seale, J.D., Kilgard, M.P., 2015. Pairing speech sounds with vagus nerve stimulation drives stimulus-specific cortical plasticity. Brain Stimul. 8, 637–644.

Englot, D.J., Chang, E.F., Auguste, K.I., 2011. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J. Neurosurg. 115, 1248–1255.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., et al., 1995. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 375, 482–484.

Ganzer, P.D., Darrow, M.J., Meyers, E.C., Solorzano, B.R., Ruiz, A.D., Robertson, N.M., et al., 2018. Closed-loop neuromodulation restores network connectivity and motor control after spinal cord injury. Elife, 7.

Gilles, A., De Ridder, D., Van Hal, G., Wouters, K., Kleine Punte, A., Van de Heyning, P., 2012. Prevalence of leisure noise-induced tinnitus and the attitude toward noise in university students. Otol. Neurotol. 33, 899–906.

Hays, S.A., Rennaker, R.L., Kilgard, M.P., 2013. Targeting plasticity with vagus nerve stimulation to treat neurological disease. Prog. Brain Res. 207, 275–299.

Joos, K., Vanneste, S., De Ridder, D., 2012. Disentangling depression and distress networks in the tinnitus brain. PLoS One 7, e40544.

Kaltenbach, J.A., 2006. The dorsal cochlear nucleus as a participant in the auditory, attentional and emotional components of tinnitus. Hear Res. 216–217, 224–234.

Kara, E., Aydin, K., Akbulut, A.A., Karakol, S.N., Durmaz, S., Yener, H.M., et al., 2020. Assessment of hidden hearing loss in normal hearing individuals with and without tinnitus. J. Int. Adv. Otol. 16, 87–92.

Khedr, E.M., Ahmed, M.A., Shawky, O.A., Mohamed, E.S., El Attar, G.S., Mohammad, K.A., 2010. Epidemiological study of chronic tinnitus in Assiut, Egypt. Neuroepidemiology 35, 45–52.

Kilgard, M.P., 2012. Harnessing plasticity to understand learning and treat disease. Trends Neurosci. 35, 715–722.

Kilgard, M.P., Merzenich, M.M., 1998. Plasticity of temporal information processing in the primary auditory cortex. Nat. Neurosci. 1, 727–731.

Kilgard, M.P., Merzenich, M.M., 1999. Distributed representation of spectral and temporal information in rat primary auditory cortex. Hear. Res. 134, 16–28.

Kilgard, M.P., Merzenich, M.M., 2002. Order-sensitive plasticity in adult primary auditory cortex. Proc. Natl. Acad. Sci. U. S. A. 99, 3205–3209.

Kim, J.S., 2018. Association between tinnitus and mental health among Korean adolescents: the Korea National Health and nutrition examination survey. Cent. Eur. J. Public Health 26, 65–70.

Kraus, T., Kiess, O., Hosl, K., Terekhin, P., Kornhuber, J., Forster, C., 2013. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal—a pilot study. Brain Stimul. 6, 798–804.

Kreuzer, P.M., Landgrebe, M., Husser, O., Resch, M., Schecklmann, M., Geisreiter, F., et al., 2012. Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. Front. Psych. 3, 70.

Kreuzer, P.M., Landgrebe, M., Resch, M., Husser, O., Schecklmann, M., Geisreiter, F., et al., 2014. Feasibility, safety and efficacy of transcutaneous vagus nerve stimulation in chronic tinnitus: an open pilot study. Brain Stimul. 7, 740–747.

Kujawa, S.G., Liberman, M.C., 2009. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. J. Neurosci. 29, 14077–14085.

Kujawa, S.G., Liberman, M.C., 2015. Synaptopathy in the noise-exposed and aging cochlea: primary neural degeneration in acquired sensorineural hearing loss. Hear. Res. 330, 191–199.

Langers, D.R., de Kleine, E., van Dijk, P., 2012. Tinnitus does not require macroscopic tonotopic map reorganization. Front. Syst. Neurosci. 6, 2.

Langguth, B., Kleinjung, T., Fischer, B., Hajak, G., Eichhammer, P., Sand, P.G., 2007. Tinnitus severity, depression, and the big five personality traits. Prog. Brain Res. 166, 221–225.

Langguth, B., Landgrebe, M., Kleinjung, T., Sand, G.P., Hajak, G., 2011. Tinnitus and depression. World J. Biol. Psychiatry 12, 489–500.

Langguth, B., Kreuzer, P.M., Kleinjung, T., De Ridder, D., 2013. Tinnitus: causes and clinical management. Lancet Neurol. 12, 920–930.

Lasisi, A.O., Abiona, T., Gureje, O., 2010. Tinnitus in the elderly: profile, correlates, and impact in the Nigerian study of ageing. Otolaryngol. Head Neck Surg. 143, 510–515.

Lee, S.Y., Nam, D.W., Koo, J.W., De Ridder, D., Vanneste, S., Song, J.J., 2017. No auditory experience, no tinnitus: lessons from subjects with congenital- and acquired single-sided deafness. Hear. Res. 354, 9–15.

Lehtimaki, J., Hyvarinen, P., Ylikoski, M., Bergholm, M., Makela, J.P., Aarnisalo, A., et al., 2013. Transcutaneous vagus nerve stimulation in tinnitus: a pilot study. Acta Otolaryngol. 133 (4), 378–382.

Liberman, M.C., Epstein, M.J., Cleveland, S.S., Wang, H., Maison, S.F., 2016. Toward a differential diagnosis of hidden hearing loss in humans. PLoS One 11, e0162726.

Llinas, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P.P., 1999. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc. Natl. Acad. Sci. U. S. A. 96, 15222–15227.

Loerwald, K.W., Buell, E.P., Borland, M.S., Rennaker 2nd, R.L., Hays, S.A., Kilgard, M.P., 2018. Varying stimulation parameters to improve cortical plasticity generated by VNS-tone pairing. Neuroscience 388, 239–247.

Lundgren, J., Amark, P., Blennow, G., Stromblad, L.G., Wallstedt, L., 1998. Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia 39, 809–813.

Lundy, D.S., Casiano, R.R., Landy, H.J., Gallo, J., Gallo, B., Ramsey, R.E., 1993. Effects of vagal nerve stimulation on laryngeal function. J. Voice 7, 359–364.

Makin, T.R., Scholz, J., Filippini, N., Henderson Slater, D., Tracey, I., Johansen-Berg, H., 2013. Phantom pain is associated with preserved structure and function in the former hand area. Nat. Commun. 4, 1570.

Maudoux, A., Lefebvre, P., Cabay, J.E., Demertzi, A., Vanhaudenhuyse, A., Laureys, S., et al., 2012. Connectivity graph analysis of the auditory resting state network in tinnitus. Brain Res. 1485, 10–21.

Michikawa, T., Nishiwaki, Y., Kikuchi, Y., Saito, H., Mizutari, K., Okamoto, M., et al., 2010. Prevalence and factors associated with tinnitus: a community-based study of Japanese elders. J. Epidemiol. 20, 271–276.

Moller, A.R., 1997. Similarities between chronic pain and tinnitus. Am. J. Otol. 18, 577–585.

Moller, A.R., 2006a. Neural plasticity in tinnitus. Prog. Brain Res. 157, 365–372.

Moller, A., 2006b. Intraoperative Neurophysiological Monitoring, Second ed. Humana Press, Totowa, New Jersey.

Morest, D.K., Kim, J., Potashner, S.J., Bohne, B.A., 1998. Long-term degeneration in the cochlear nerve and cochlear nucleus of the adult chinchilla following acoustic overstimulation. Microsc. Res. Tech. 41, 205–216.

Moulton, E.A., Elman, I., Pendse, G., Schmahmann, J., Becerra, L., Borsook, D., 2011. Aversion-related circuitry in the cerebellum: responses to noxious heat and unpleasant images. J. Neurosci. 31, 3795–3804.

Muhlnickel, W., Elbert, T., Taub, E., Flor, H., 1998. Reorganization of auditory cortex in tinnitus. Proc. Natl. Acad. Sci. U. S. A. 95, 10340–10343.

Mulroy, M.J., Henry, W.R., McNeil, P.L., 1998. Noise-induced transient microlesions in the cell membranes of auditory hair cells. Hear. Res. 115, 93–100.

Noble, L.J., Souza, R.R., McIntyre, C.K., 2018. Vagus nerve stimulation as a tool for enhancing extinction in exposure-based therapies. Psychopharmacology (Berl) 236 (1), 355–367.

Noble, L.J., Meruva, V.B., Hays, S.A., Rennaker, R.L., Kilgard, M.P., McIntyre, C.K., 2019. Vagus nerve stimulation promotes generalization of conditioned fear extinction and reduces anxiety in rats. Brain Stimul. 12, 9–18.

Nordmann, A.S., Bohne, B.A., Harding, G.W., 2000. Histopathological differences between temporary and permanent threshold shift. Hear. Res. 139, 13–30.

Pattyn, T., Van Den Eede, F., Vanneste, S., Cassiers, L., Veltman, D.J., Van De Heyning, P., et al., 2016. Tinnitus and anxiety disorders: a review. Hear. Res. 333, 255–265.

Phoon, W.H., Lee, H.S., Chia, S.E., 1993. Tinnitus in noise-exposed workers. Occup. Med. (Lond.) 43, 35–38.

Rajan, R., Irvine, D.R., Wise, L.Z., Heil, P., 1993. Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex. J. Comp. Neurol. 338, 17–49.

Schuknecht, H.F., Woellner, R.C., 1953. Hearing losses following partial section of the cochlear nerve. Trans. Am. Laryngol. Rhinol. Otol. Soc. 58, 369–93, discussion, 93–4.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., et al., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356.

Shargorodsky, J., Curhan, G.C., Farwell, W.R., 2010. Prevalence and characteristics of tinnitus among US adults. Am. J. Med. 123, 711–718.

Shetake, J.A., Engineer, N.D., Vrana, W.A., Wolf, J.T., Kilgard, M.P., 2012. Pairing tone trains with vagus nerve stimulation induces temporal plasticity in auditory cortex. Exp. Neurol. 233, 342–349.

Song, J.J., 2015. Dysfunctional noise cancelling of the rostral anterior cingulate cortex in tinnitus patients. PLoS One 10, e0123538.

Song, J.J., De Ridder, D., Van de Heyning, P., Vanneste, S., 2012. Mapping tinnitus-related brain activation: an activation-likelihood estimation metaanalysis of PET studies. J. Nucl. Med. 53 (10), 1550–1557

Syka, J., 2002. Plastic changes in the central auditory system after hearing loss, restoration of function, and during learning. Physiol. Rev. 82, 601–636.

Theodoroff, S.M., Lewis, M.S., Folmer, R.L., Henry, J.A., Carlson, K.F., 2015. Hearing impairment and tinnitus: prevalence, risk factors, and outcomes in US service members and veterans deployed to the Iraq and Afghanistan wars. Epidemiol. Rev. 37, 71–85.

Tonndorf, J., 1987. The analogy between tinnitus and pain: a suggestion for a physiological basis of chronic tinnitus. Hear. Res. 28, 271–275.

Turner, J.G., Brozoski, T.J., Bauer, C.A., Parrish, J.L., Myers, K., Hughes, L.F., et al., 2006. Gap detection deficits in rats with tinnitus: a potential novel screening tool. Behav. Neurosci. 120, 188–195.

Tyler, R., Cacace, A., Stocking, C., Tarver, B., Engineer, N., Martin, J., et al., 2017. Vagus nerve stimulation paired with tones for the treatment of tinnitus: a prospective randomized double-blind controlled pilot study in humans. Sci. Rep. 7, 11960.

van der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., et al., 2009. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS One 4 (e7396), 1–5.

Vanneste, S., Congedo, M., De Ridder, D., 2013. Pinpointing a highly specific pathological functional connection that turns phantom sound into distress. Cereb. Cortex.

Vanneste, S., Martin, J., Rennaker 2nd, R.L., Kilgard, M.P., 2017. Pairing sound with vagus nerve stimulation modulates cortical synchrony and phase coherence in tinnitus: an exploratory retrospective study. Sci. Rep. 7, 17345.

Vanneste, S., Song, J.J., De Ridder, D., 2018. Thalamocortical dysrhythmia detected by machine learning. Nat. Commun. 9, 1103.

Vanneste, S., Alsaman, O., De Ridder, D., 2019a. Top-down and bottom-up regulated auditory phantom perception. J. Neurosci. 39 (2), 364–378.

Vanneste, S., To WT, De Ridder, D., 2019b. Tinnitus and neuropathic pain share a common neural substrate in the form of specific brain connectivity and microstate profiles. Prog. Neuropsychopharmacol. Biol. Psychiatry 88, 388–400.

Weisz, N., Hartmann, T., Dohrmann, K., Schlee, W., Norena, A., 2006. High-frequency tinnitus without hearing loss does not mean absence of deafferentation. Hear. Res. 222, 108–114.

Wichova, H., Alvi, S.A., Shew, M., Lin, J., Sale, K., Larsen, C., et al., 2018. Tinnitus perception in patients after vagal nerve stimulator implantation for epilepsy. Am. J. Otolaryngol. 39, 599–602.

Yakunina, N., Kim, S.S., Nam, E.C., 2018. BOLD fMRI effects of transcutaneous vagus nerve stimulation in patients with chronic tinnitus. PLoS One 13, e0207281.

Zeman, F., Koller, M., Figueiredo, R., Aazevedo, A., Rates, M., Coelho, C., et al., 2011. Tinnitus handicap inventory for evaluating treatment effects: which changes are clinically relevant? Otolaryngol. Head Neck Surg. 145, 282–287.