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Research article

Multitarget surgical neuromodulation: Combined C2 and auditory cortex implantation for tinnitus

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HIGHLIGHTS

- The data support the idea that tinnitus loudness might be controlled by 2 mechanisms.
- The 2 mechanisms are the auditory cortex mechanism and a noise-canceling mechanism.
- Combining multi-target neuromodulation influence these pathophysiological mechanisms.

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ABSTRACT

Tinnitus, as a phantom sound can express itself as a pure tone and as a noise-like sound. It is notoriously difficult to treat, and in medically, psychologically and audiologically intractable tinnitus patients sometimes intracranial electrodes overlying the auditory cortex are implanted. In this case report, we describe a patient who had a complete resolution of the pure tone component of his tinnitus by an auditory cortex implant, without any beneficial effect on the noise-like aspect of his tinnitus, even after changing the stimulation design to burst stimulation, which is known to treat noise-like tinnitus better than tonic stimulation. After an initial successful treatment of his noise-like component with transcutaneus electrical nerve stimulation, a wire electrode is inserted subcutaneously and connected to his internal pulse generator. With the dual stimulation his pure tone tinnitus remains abolished after 5 years of stimulation and his noise-like tinnitus is improved by 50%, from 8/10 to 4/10. This case report suggests that multi-target stimulation might be better than single target implantation in selected cases.

1. Introduction

Non-pulsatile tinnitus is the perception of a sound in the absence of a corresponding external sound source, and is therefore, often considered a phantom sound [35]. It is related to abnormal activity in auditory and non-auditory brain areas [58], which can be altered by neuromodulation techniques [43].

As tinnitus is most commonly related to auditory deafferentation [35] with [48,49] or without [64] audiometrical hearing loss tinnitus has been regarded as a consequence of maladaptive auditory memory traces [13], in an attempt to reduce the inherent auditory uncertainty associated with auditory deafferentation [19]. Apart from abnormal activity also pathological functional connectivity is associated with the presence of tinnitus as demonstrated by EEG [61] MEG [51,52] and fMRI [45,46]. As such it has been proposed that the phenomenologically unified percept of tinnitus can be considered an emergent property of multiple, parallel, dynamically changing and partially overlapping subnetworks, each with a specific spontaneous oscillatory pattern and functional connectivity signature [23]. Communication between these different subnetworks is proposed to occur at hubs, brain areas that are involved in multiple subnetworks simultaneously. These hubs can take part in each separable subnetwork at different frequencies [23]. Communication between the subnetworks is proposed to occur at discrete oscillatory frequencies [57]. As such, it has been proposed that the brain uses multiple nonspecific networks in parallel, each with their own oscillatory signature, that adapt to the context to construct a unified percept possibly by synchronized activation integrated at hubs at discrete oscillatory frequencies [23].

Auditory deafferentation induces compensatory increases of somatosensory influences on the auditory pathways at the level of the dorsal cochlear nucleus (DCN) [24,25,55]. The DCN receives

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auditory input from the VIIIth nerve and somatosenory input, directly from the ipsilateral dorsal column and spinal trigeminal nuclei [34,63,65] or indirectly via the dorsal raphe and locus coeruleus [67]. The pinna and the neck are innervated by the upper cervical nerves (C1–C3), which project to spinal trigeminal nuclei [1,2,30]. C2 electrical stimulation produces a pattern of inhibition and excitation, of the principal cells [37] in the ventral and dorsal division of the cochlear nucleus [53,54,66], and can hereby suppress or enhance responses to sound [53,54]. For C2 electrical stimulation, non-invasive electrical stimulations using TENS have shown that it is possible to change the tinnitus percept [33,60], as have subcutaneous electrode implants in the C2 dermatoma [21].

Ten to 15% of the population perceives tinnitus chronically and about 2.4% of the population reports severe interference with their daily living [6]. Tinnitus can cause a considerable amount of distress [32], involving sleep deprivation [4,8], depression [26], annoyance [5], cognitive problems [29], and work impairment [7,8,27,31,41]. Tinnitus is usually evaluated for its perceived loudness by audiological tinnitus matching and/or visual analog scales or numeric rating scales. Tinnitus related annoyance or distress is commonly evaluated using validated tinnitus questionnaires [42]. One of the surprising findings in tinnitus research is that the perceived tinnitus loudness as determined by tinnitus matching correlates poorly with the associated distress [5,47], suggesting that neuronal correlates of tinnitus loudness can be separated from the neuronal correlates of tinnitus distress [13,18,59]. There is a correlation however between the tinnitus related distress and the subjectively perceived loudness, as rated by a numeric rating scale or visual analog scale [62], which suggests that the neural correlates might partially overlap.

Based on a better albeit incomplete pathophysiological knowledge of tinnitus some surgical neuromodulation techniques have been described, targeting different areas of the tinnitus-related neural networks in the brain and peripheral nervous system [21].

The procedures are based on a pathophysiological model for tinnitus and follows a four-step rationale [12,20,21]:

(1) Tinnitus is related to increased activity in the auditory and frontal cortex.
(2) The anatomical location of the tinnitus generator can be determined by fMRI [17].
(3) The abnormal neuronal activity can be modulated by neuronavigated TMS resulting in transient tinnitus reduction [12].
(4) If TMS can transiently suppress the tinnitus, electrical stimulation through an electrode implanted on the same area can provide permanent tinnitus suppression [10–12,20].

The concept behind this approach is that the auditory cortex is involved in a pathologically functioning neuronal network which includes the frontal cortex, but also the parahippocampal area and insula [12,54], that generates tinnitus and that interference with this network activity by auditory cortex stimulation can alleviate tinnitus [17].

1. The same approach can be used for subcutaneous implantations in the C2 dermatoma.
2. Somatosensory tinnitus is associated with increased activity in the dorsal cochlear nucleus [36,44,55].
3. This activity can be modulated by non-invasive neuromodulation techniques such as TENS [60].
4. If beneficial a subcutaneous electrode can be implanted in the C2 dermatoma [21].

In this case report, the authors describe that the combination of 2 targets yields better results than modulating one area in the neuromodulation of tinnitus related pathological activity.

3. Case report

A 54 year old man presents at the multidisciplinary Tinnitus Research Initiative clinic at the BRAI^{2}N neuromodulation center at Antwerp University, Belgium. He suffers from posttraumatic unilateral right-sided tinnitus since 1.5 years. He was involved in a collision with a bus as a pedestrian when the side mirror of a bus hit the back of his head. The tinnitus is perceived predominantly as a high pitched pure tone component with some associated narrow band noise. The tinnitus scores 8.5/10 for loudness on a numeric rating scale and increases on fatigue and stress as well as in noise exposure. It is associated with high frequency hearing loss. The patient denies headaches, and has no neck pain that modulates the tinnitus. There are no other signs of somatosensory modulation of his tinnitus. His tinnitus does not worsen on Valsalva manoeuvers. He experiences no overt nor covert hemifacial spasms nor geniculate neuralgia. He has some intermittent balance disorders.

Tinnitus matching demonstrates the tinnitus is centered at 6000 Hz, 7 dB above hearing threshold and is associated with a hearing loss presenting as an audiometrical dip at 6000 Hz. His tinnitus questionnaire [28] demonstrates he has a grade III tinnitus, i.e., severe tinnitus.

Because the patient is intractable to audiological and drug treatments, neuromodulation tests are proposed, consisting of transcranial magnetic stimulation of the auditory cortex. He responds to TMS both on the left and right posterior part of the superior temporal gyrus, with each time a transient tinnitus suppression of 90% in a placebo-controlled fashion. This can be repeated three times with similar results. The 3 TMS sessions were performed at one week intervals.

Therefore, the patient is considered a candidate for an implant of an epidural auditory cortex implant [12,20]. Following a previously described protocol he undergoes a fMRI followed by an extradural electrode implant overlying the left posterior part of the superior temporal gyrus, i.e., the secondary auditory cortex [10–12,20]. The reason to select the left side for the implant is that it is in agreement with both sides of an ongoing debate in the tinnitus field on whether tinnitus patients should be implanted on the contralateral side of the perceived tinnitus, or always on the left side, irrespective of the tinnitus side [9]. This results in a complete suppression of the pure tone component of the tinnitus, but the noise-like component is less successfully suppressed. Whereas initially his noise-like tinnitus is reduced from 8 to 4/10, the noise-like phantom sound remains and worsens again to 6/10 both for loudness and distress, even after changing the stimulation design to burst stimulation, which is better in suppressing noise-like tinnitus than tonic stimulation [20,22].

Reprogramming the electrode does not yield a better suppression of the noise-like sound and the patients still feels distressed by the sound (7/10), even though the pure tone component is abolished. He notes that on maximal rotation of his neck to the left his tinnitus improves by 50%. Therefore, further investigations are performed to evaluate whether his noise-like component can be further suppressed by modulating the somatosensory influences on the auditory system. A trial test with a transcutaneous electrical nerve stimulation (TENS) at C2, according to a previously described method [60], can maximally reduce the noise from 7/10 to 1–2/10, in a placebo controlled way, and is consistent in 4 sessions, each with a week interval. Therefore, the patient starts using the TENS on a daily basis with good result. After 3 months the beneficial effect of the TENS wears off.

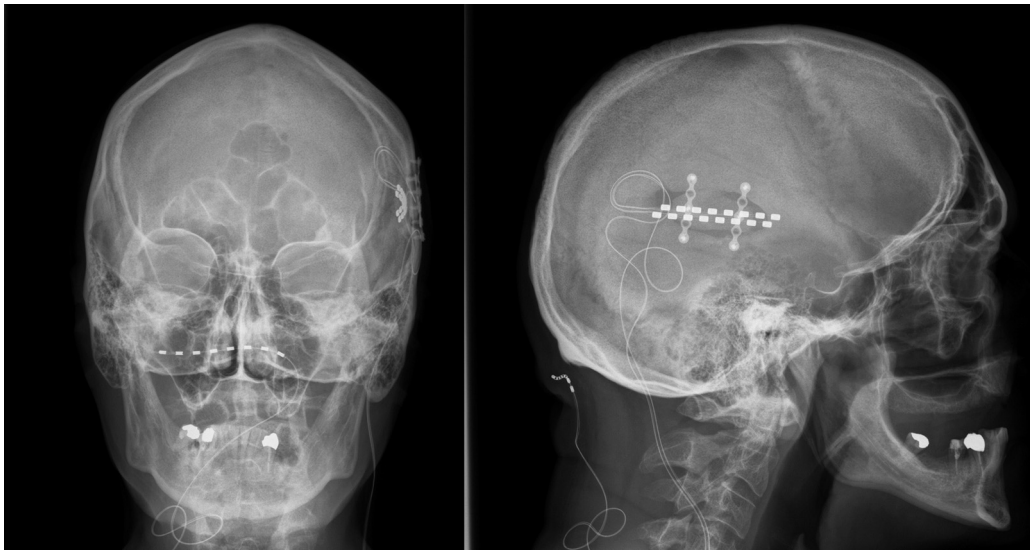

Fig. 1. the extradural electrode overlying the posterior part of the superior temporal gurus (=auditory cortex) (right figure) completely reduces the pure tone component. It is supplemented by a C2 nerve field stimulation (left figure) that can reduce the noise-like component by 50%, from 8/10 to 4/10.

In view of the earlier beneficial effect of the TENS a trial is proposed with peripheral nerve field stimulation of the C2 dermatoma via the percutaneous insertion of a wire electrode (Octrode®, SJMedical, Plano, Tx, USA) according to a technique previously described [14,50]. This technique has been successfully used in a small group of patients for somatosensory tinnitus [21].

As the trial is deemed successful a permanent subcutaneous electrode is inserted and attached to the IPG (EON®, SJMedical, Plano, Tx, USA) which activates his auditory cortex electrode. His noise-like tinnitus after the activation of the subcutaneous electrode is reduced to 4/10 and has remained so for 5 years. His pure tone tinnitus has remained absent, i.e., 0–1/10 Fig. 1.

4. Discussion

This case report describes the successful treatment of tinnitus by combining auditory cortex stimulation with C2 nerve field stimulation via implanted electrodes overlying the auditory cortex and subcutaneous electrodes modulating the C2 dermatoma.

The clinical picture the patient presents with suggests that the tinnitus is related to the trauma induced auditory deafferentation as the tinnitus pitch matches the hearing loss, analogous to an amputee feeling phantom pain in the missing limb [13]. And in limited auditory deafferentation, the auditory cortex is involved in encoding tinnitus loudness [19,56], and is therefore, targeted first in an attempt to treat the patient's intractable tinnitus, using methods that have shown some success previously [12,20]. As correctly proposed by a reviewer it would also be possible that the deafferentation (hearing loss) existed already before the trauma and that the trauma to the head and neck triggered the tinnitus on the basis of the preexisting hearing loss. Both mechanisms are compatible with what has been suggested before on the relationship between trauma and tinnitus [63].

However, it has been shown that noise-like tinnitus is resistant to auditory cortex stimulation with tonic stimuli, both in transcranial magnetic stimulation [15,16] and with implanted electrodes [11]. His tinnitus cannot be suppressed, even by burst stimulation, which has been developed to specifically treat noise-like tinnitus [20,22].

It has been shown by non-invasive brain stimulation (rTMS) that targeting more than one area of the networks involved in tinnitus is more successful than using a single target [38,40]. The underlying idea is that targeting just one area might result in compensatory mechanisms that might reduce the benefit of the applied stimulation, as suggested by the principles of network science [3]. Therefore, we attempted to deliberately target one of the described compensatory mechanisms in deafferentation, in this case, the somatosensory compensation [25], by a non-invasive trial stimulation to verify whether this does indeed result in better tinnitus suppression. This was motivated by the fact that extreme neck rotation, which is signaled through the C2 nerve [66], clinically altered the patient's tinnitus loudness, likely mediated through somatosensory-auditory interactions mediated via the C2 nerve influencing DCN activity [24,25].

The fact that the tinnitus improvement is longstanding suggests that this strategy might be worthwhile of further studies. The exact mechanism involved in the C2 nerve field stimulation is unknown yet, but it has been shown that it can reduce tinnitus loudness in a small pilot study of highly selected patients [21], and that there is a frequency-specific and tonic/burst-specific modulating effect on the auditory pathways, as demonstrated by an fMRI study [39].

As common to all case reports, $n = 1$ is no proof of the concept proposed in this case report. Furthermore only the preoperative TMS and TENS tests are performed in a placebo controlled way, but not the results of the implanted electrodes. The results of the electrodes could therefore, be due to non-specific effects, albeit less likely because of the presurgical placebo-controlled tests. One reason for not performing placebo stimulations is that the auditory cortex electrode was implanted 3.5 years before the subcutaneous electrode, and it is known that after long-term auditory cortex stimulation for tinnitus suppression the residual inhibition can be weeks to months [50], making it virtually impossible to perform a placebo stimulation of the auditory cortex while stimulation continues via the C2 electrode. Furthermore, the amplitude required for highest efficacy in the C2 dermatoma is suprathreshold for paresthesias, precluding correct placebo stimulation of the C2 electrode.

It is also unknown whether this would have a similar effect in other patients, or whether this might only be beneficial for clinical somatosensory tinnitus, or tinnitus modulated by the somatosensory system (subclinical).

Furthermore, this patient responded well to auditory cortex stimulation, which is definitely not always the case [11,12,68,69], and it has been shown that responsiveness to auditory cortex stimulation predicts the efficacy of C2 stimulation but less so vice versa

[70]. So it is unknown whether people who respond partially but insufficiently to subcutaneous C2 nerve field stimulation might also benefit from associated auditory cortex stimulation.

In summary, based on the principles of network science [3] this multitarget strategy attacks a central area involved in tinnitus generation (auditory cortex) as well as a well-known compensation mechanism (C2-cochlear nucleus interactions) in an attempt to better suppress this enigmatic symptom.

References

[1] V.C. Abrahams, B. Lynn, F.J. Richmond, Organization and sensory properties of small myelinated fibres in the dorsal cervical rami of the cat, J. Physiol. 347 (1984) 177–187.
[2] V.C. Abrahams, F.J. Richmond, J. Keane, Projections from C2 and C3 nerves supplying muscles and skin of the cat neck: a study using transganglionic transport of horseradish peroxidase, J. Comp. Neurol. 230 (1984) 142–154.
[3] R. Albert, H. Jeong, A.L. Barabasi, Error and attack tolerance of complex networks, Nature 406 (2000) 378–382.
[4] J. Alster, Z. Shemesh, M. Ornan, J. Attias, Sleep disturbance associated with chronic tinnitus, Biol. Psychiatry 34 (1993) 84–90.
[5] G. Andersson, Tinnitus loudness matchings in relation to annoyance and grading of severity, Auris Nasus Larynx 30 (2003) 129–133.
[6] A. Axelsson, A. Ringdahl, Tinnitus – a study of its prevalence and characteristics, Br. J. Audiol. 23 (1989) 53–62.
[7] D.M. Baguley, Mechanisms of tinnitus, Br. Med. Bull. 63 (2002) 195–212.
[8] T. Cronlein, B. Langguth, P. Geisler, G. Hajak, Tinnitus and insomnia, Prog. Brain. Res. 166 (2007) 227–233.
[9] D. De Ridder, Should rTMS for tinnitus be performed left-sided, ipsilaterally or contralaterally, and is it a treatment or merely investigational? Eur. J. Neurol. 17 (2010) 891–892.
[10] D. De Ridder, G. De Mulder, T. Menovsky, S. Sunaert, S. Kovacs, Electrical stimulation of auditory and somatosensory cortices for treatment of tinnitus and pain, Prog. Brain. Res. 166 (2007) 377–388.
[11] D. De Ridder, G. De Mulder, E. Verstraeten, K. Van der Kelen, S. Sunaert, M. Smits, S. Kovacs, J. Verlooy, P. Van de Heyning, A.R. Moller, Primary and secondary auditory cortex stimulation for intractable tinnitus, ORL J. Otorhinolaryngol. Relat. Spec. 68 (2006) 48–54, discussion 54–45.
[12] D. De Ridder, G. De Mulder, V. Walsh, N. Muggleton, S. Sunaert, A. Moller, Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus. Case report, J. Neurosurg. 100 (2004) 560–564.
[13] D. De Ridder, A.B. Elgoyhen, R. Romo, B. Langguth, Phantom percepts: tinnitus and pain as persisting aversive memory networks, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 8075–8080.
[14] D. De Ridder, M. Plazier, T. Menovsky, N. Kamerling, S. Vanneste, C2 subcutaneous stimulation for failed back surgery syndrome: a case report, Neuromodulation 16 (2013) 610–613.
[15] D. De Ridder, E. van der Loo, K. Van der Kelen, T. Menovsky, P. van de Heyning, A. Moller, Do tonic and burst TMS modulate the lemniscal and extralemniscal system differentially? Int. J. Med. Sci. 4 (2007) 242–246.
[16] D. De Ridder, E. van der Loo, K. Van der Kelen, T. Menovsky, P. van de Heyning, A. Moller, Theta, alpha and beta burst transcranial magnetic stimulation: brain modulation in tinnitus, Int. J. Med. Sci. 4 (2007) 237–241.
[17] D. De Ridder, E. van der Loo, S. Vanneste, S. Gais, M. Plazier, S. Kovacs, S. Sunaert, T. Menovsky, P. van de Heyning, Theta-gamma dysrhythmia and auditory phantom perception, J. Neurosurg. 114 (2011) 912–921.
[18] D. De Ridder, S. Vanneste, M. Congedo, The distressed brain: a group blind source separation analysis on tinnitus, PLoS One 6 (2011) e24273.
[19] D. De Ridder, S. Vanneste, W. Freeman, The Bayesian brain: phantom percepts resolve sensory uncertainty, Neurosci. Biobehav. Rev. 44 (2014) 4–15.
[20] D. De Ridder, S. Vanneste, S. Kovacs, S. Sunaert, T. Menovsky, P. van de Heyning, A. Moller, Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression, J. Neurosurg. 114 (2011) 903–911.
[21] D. De Ridder, S. Vanneste, T. Menovsky, B. Langguth, Surgical brain modulation for tinnitus: the past, present and future, J. Neurosurg. Sci. 56 (2012) 323–340.
[22] D. De Ridder, S. Vanneste, E. van der Loo, M. Plazier, T. Menovsky, P. van de Heyning, Burst stimulation of the auditory cortex: a new form of neurostimulation for noise-like tinnitus suppression, J. Neurosurg. 112 (2010) 1289–1294.
[23] D. De Ridder, S. Vanneste, N. Weisz, A. Londero, W. Schlee, A.B. Elgoyhen, B. Langguth, An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks, Neurosci. Biobehav. Rev. 44 (2014) 16–32.
[24] S. Dehmel, Y.L. Cui, S.E. Shore, Cross-modal interactions of auditory and somatic inputs in the brainstem and midbrain and their imbalance in tinnitus and deafness, Am. J. Audiol. 17 (2008) S193–209.
[25] S. Dehmel, S. Pradhan, S. Koehler, S. Bledsoe, S. Shore, Noise overexposure alters long-term somatosensory-auditory processing in the dorsal cochlear nucleus – possible basis for tinnitus-related hyperactivity? J. Neurosci. 32 (2012) 1660–1671.
[26] R.A. Dobie, Depression and tinnitus, Otolaryngol. Clin. North Am. 36 (2003) 383–388.
[27] J.J. Eggermont, L.E. Roberts, The neuroscience of tinnitus, Trends Neurosci. 27 (2004) 676–682.
[28] G. Goebel, W. Hiller, [The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire], Hno 42 (1994) 166–172.
[29] R.S. Hallam, L. McKenna, L. Shurlock, Tinnitus impairs cognitive efficiency, Int. J. Audiol. 43 (2004) 218–226.
[30] J. Hekmatpanah, Organization of tactile dermatomes, C1 through L4, in cat, J. Neurophysiol. 24 (1961) 129–140.
[31] A.J. Heller, Classification and epidemiology of tinnitus, Otolaryngol. Clin. North Am. 36 (2003) 239–248.
[32] J.L. Henry, P.H. Wilson, Coping with tinnitus: two studies of psychological and audiological characteristics of patients with high and low tinnitus-related distress, Int. Tinnitus. J. 1 (1995) 85–92.
[33] C. Herraiz, A. Toledano, I. Diges, Trans-electrical nerve stimulation (TENS) for somatic tinnitus, Prog. Brain Res. 166 (2007) 389–394.
[34] K. Itoh, H. Kamiya, A. Mitani, Y. Yasui, M. Takada, N. Mizuno, Direct projections from the dorsal column nuclei and the spinal trigeminal nuclei to the cochlear nuclei in the cat, Brain Res. 400 (1987) 145–150.
[35] P.J. Jastreboff, Phantom auditory perception (tinnitus): mechanisms of generation and perception, Neurosci. Res. 8 (1990) 221–254.
[36] J.A. Kaltenbach, The dorsal cochlear nucleus as a contributor to tinnitus: mechanisms underlying the induction of hyperactivity, Prog. Brain Res. 166 (2007) 89–106.
[37] P.O. Kanold, E.D. Young, Proprioceptive information from the pinna provides somatosensory input to cat dorsal cochlear nucleus, J. Neurosci. 21 (2001) 7848–7858.
[38] T. Kleinjung, P. Eichhammer, M. Landgrebe, P. Sand, G. Hajak, T. Steffens, J. Strutz, B. Langguth, Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study, Otolaryngol. Head Neck Surg. 138 (2008) 497–501.
[39] S. Kovacs, R. Peeters, D. De Ridder, M. Plazier, T. Menovsky, S. Sunaert, Central effects of occipital nerve electrical stimulation studied by functional magnetic resonance imaging, Neuromodulation 14 (2011) 46–55, discussion 56–47.
[40] P.M. Kreuzer, M. Landgrebe, M. Schecklmann, T.B. Poeppl, V. Vielsmeier, G. Hajak, T. Kleinjung, B. Langguth, Can temporal repetitive transcranial magnetic stimulation be enhanced by targeting affective components of tinnitus with frontal rTMS? A randomized controlled pilot trial, Front Syst. Neurosci. 5 (2011) 88.
[41] B. Langguth, T. Kleinjung, B. Fischer, G. Hajak, P. Eichhammer, P.G. Sand, Tinnitus severity, depression, and the big five personality traits, Prog. Brain Res. 166 (2007) 221–225.
[42] B. Langguth, P.M. Kreuzer, T. Kleinjung, D. De Ridder, Tinnitus: causes and clinical management, Lancet. Neurol. 12 (2013) 920–930.
[43] B. Langguth, M. Schecklmann, A. Lehner, M. Landgrebe, T.B. Poeppl, P.M. Kreuzer, W. Schlee, N. Weisz, S. Vanneste, D. De Ridder, Neuroimaging and neuromodulation: complementary approaches for identifying the neuronal correlates of tinnitus, Front Syst. Neurosci. 6 (2012) 15.
[44] R.A. Levine, Somatic (craniocervical) tinnitus and the dorsal cochlear nucleus hypothesis, Am. J. Otolaryngol. 20 (1999) 351–362.
[45] A. Maudoux, P. Lefebvre, J.E. Cabay, A. Demertzi, A. Vanhaudenhuyse, S. Laureys, A. Soddu, Auditory resting-state network connectivity in tinnitus: a functional MRI study, PLoS One 7 (2012) e36222.
[46] A. Maudoux, P. Lefebvre, J.E. Cabay, A. Demertzi, A. Vanhaudenhuyse, S. Laureys, A. Soddu, Connectivity graph analysis of the auditory resting state network in tinnitus, Brain Res. 1485 (2012) 10–21.
[47] A. Moller, Tinnitus, in: R. Jackler, D. Brackmann (Eds.), Neurotology, Mosby, St. Louis, 1994, pp. 153–166.
[48] A. Norena, C. Micheyl, S. Chery-Croze, L. Collet, Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus, Audiol. Neurootol. 7 (2002) 358–369.
[49] A.J. Norena, J.J. Eggermont, Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus, Neuroreport 17 (2006) 559–563.
[50] M. Plazier, I. Dekelver, S. Vanneste, G. Stassijns, T. Menovsky, M. Thimineur, D. De Ridder, Occipital nerve stimulation in fibromyalgia: a double-blind placebo-controlled pilot study with a six-month follow-up, Neuromodulation 17 (2014) 256–264.
[51] W. Schlee, T. Hartmann, B. Langguth, N. Weisz, Abnormal resting-state cortical coupling in chronic tinnitus, BMC Neurosci. 10 (2009) 11.
[52] W. Schlee, N. Weisz, O. Bertrand, T. Hartmann, T. Elbert, Using auditory steady state responses to outline the functional connectivity in the tinnitus brain, PLoS One 3 (2008) e3720.
[53] S.E. Shore, Multisensory integration in the dorsal cochlear nucleus: unit responses to acoustic and trigeminal ganglion stimulation, Eur. J. Neurosci. 21 (2005) 3334–3348.
[54] S.E. Shore, H. El Kashlan, J. Lu, Effects of trigeminal ganglion stimulation on unit activity of ventral cochlear nucleus neurons, Neuroscience 119 (2003) 1085–1101.
[55] S.E. Shore, J. Zhou, Somatosensory influence on the cochlear nucleus and beyond, Hear Res. 216–217 (2006) 90–99.
[56] E. van der Loo, S. Gais, M. Congedo, S. Vanneste, M. Plazier, T. Menovsky, P. Van de Heyning, D. De Ridder, Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex, PLoS One 4 (2009) e7396, 7391–7395.
[57] S. Vanneste, M. Congedo, D. De Ridder, Pinpointing a highly specific pathological functional connection that turns phantom sound into distress, Cereb. Cortex. 24 (9) (2013) 2268–2282.

[58] S. Vanneste, D. De Ridder, The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks, Front Syst. Neurosci. 6 (2012) 31.
[59] S. Vanneste, M. Plazier, E. der Loo, P.V. de Heyning, M. Congedo, D. De Ridder, The neural correlates of tinnitus-related distress, Neuroimage 52 (2010) 470–480.
[60] S. Vanneste, M. Plazier, P. Van de Heyning, D. De Ridder, Transcutaneous electrical nerve stimulation (TENS) of upper cervical nerve (C2) for the treatment of somatic tinnitus, Exp. Brain Res. 204 (2010) 283–287.
[61] S. Vanneste, P. van de Heyning, D. De Ridder, The neural network of phantom sound changes over time: a comparison between recent-onset and chronic tinnitus patients, Eur. J. Neurosci. 34 (2011) 718–731.
[62] E. Wallhausser-Franke, J. Brade, T. Balkenhol, R. D'Amelio, A. Seegmuller, W. Delb, Tinnitus: distinguishing between subjectively perceived loudness and tinnitus-related distress, PLoS One 7 (2012) e34583.
[63] R.J. Weinberg, A. Rustioni, A cuneocochlear pathway in the rat, Neuroscience 20 (1987) 209–219.
[64] N. Weisz, T. Hartmann, K. Dohrmann, W. Schlee, A. Norena, High-frequency tinnitus without hearing loss does not mean absence of deafferentation, Hear Res. 222 (2006) 108–114.
[65] D.D. Wright, D.K. Ryugo, Mossy fiber projections from the cuneate nucleus to the cochlear nucleus in the rat, J. Comp. Neurol. 365 (1996) 159–172.
[66] E.D. Young, I. Nelken, R.A. Conley, Somatosensory effects on neurons in dorsal cochlear nucleus, J. Neurophysiol. 73 (1995) 743–765.
[67] J. Zhang, Z. Guan, Pathways involved in somatosensory electrical modulation of dorsal cochlear nucleus activity, Brain Res. 1184 (2007) 121–131.
[68] J. Engelhardt, R. Dauman, P. Arne, M. Allard, N. Dauman, O. Branchard, P. Perez, C. Germain, F. Caire, D. Bonnard, E. Cuny, Effect of chronic cortical stimulation on chronic severe tinnitus: a prospective randomized double-blind cross-over trial and long-term follow up, Brain Stimul. 7 (2014) 694–700.
[69] D.R. Friedland, W. Gaggl, C. Runge-Samuelson, J.L. Ulmer, B.H. Kopell, Feasibility of auditory cortical stimulation for the treatment of tinnitus, Otol. Neurotol. 28 (2007) 1005–1012.
[70] S. Vanneste, B. Langguth, D. De Ridder, Do tDCS and TMS influence tinnitus transiently via a direct cortical and indirect somatosensory modulating effect? A combined TMS-tDCS and TENS study, Brain Stimul. 4 (2011) 242–252.