15 Tinnitus

In this chapter, we will focus on cortical stimulation (CS) for the management of subjective tinnitus (see [Box 15.1](#) for an overview).

Tinnitus (Moller et al 2011, Langguth et al 2013) is classified according to whether the perceived noise has its source within the patient's body known as objective tinnitus or *somatosounds* (for example, myoclonic contractions of the tensor tympani muscle or blood vessels) or if it is only perceivable to the patient and lacks a specific sound source, namely subjective tinnitus. Subjective tinnitus is by far the most common form. As the most common cause for tinnitus is hearing loss, subjective or non-pulsatile tinnitus is often considered as an auditory phantom phenomenon, analogous to phantom pain. There are most likely different forms of tinnitus, each with a different pathophysiological mechanism. For example tinnitus resulting from a microvascular compression of the vestibulocochlear nerve is related to ephaptic transmission between different fibers that make up the nerve, and responds to carbamazepine, in contrast to other forms of tinnitus. Some forms of cervicogenic tinnitus respond to C2 modulation by TENS or occipital nerve stimulation via implanted electrodes. Tinnitus can take the form of continuous buzzing, hissing or ringing, or a combination of these or other characteristics. It can be heard in one or both ears, but it can also be perceived holocranially. Tinnitus can occur intermittently or have a pulsatile character. The intensity of the phantom sound can vary from a subtle noise to high intensity sounds which cannot be masked by any external noise. Many patients with tinnitus also report symptoms such as frustration, annoyance, insomnia, hyperacusis, anxiety, depression, irritability and concentration difficulties and these symptoms are highly relevant for determining tinnitus severity. Thus, tinnitus represents a highly prevalent and potentially distressing condition with a wide range of symptoms that are likely to place a huge burden on patients and significantly impair their quality of life. Its socioeconomic relevance is illustrated by the dramatically increased risk for disability pension among tinnitus patients. In epidemiological surveys around the globe (Europe, USA, Japan, Africa and China), roughly one fifth of men and one sixth of women reported to perceive tinnitus, with 4.4% and 2.1%, respectively, reporting high tinnitus intensity. Tinnitus is most commonly associated with hearing loss, which explains why its prevalence increases with age, i.e. due to age-related presbycusis, but it is on the rise in young people as good. About 90% of high school students report tinnitus after leisure-induced noise exposure and about 15% have permanent tinnitus, but in most of them it is not perceived as intrusive. In addition, tinnitus is a common disability in young people resulting from warfare and was the first-most prevalent handicap for US veterans receiving compensation in 2011.

Box 15.1: TINNITUS

The concept behind the CS approach is that the areas involved in a pathologically functioning neuronal network that generates tinnitus can be visualized and that interference with this tinnitus network activity by cortical stimulation can alleviate tinnitus. The procedure follows a four-step rationale ([Fig.15.1](#)):

1. Tinnitus is thought to be related to altered activity in the auditory and frontal cortices, as well as in the amygdalo-(para)hippocampal area, anterior and posterior cingulate cortex, and insula ([Fig.15.2-3](#)).

2. The anatomical location of the tinnitus generator can be determined by functional imaging techniques (e.g. fMRI).
3. The abnormal neuronal activity can be transiently modulated by neuronavigated TMS and other non-invasive CS techniques (Vanneste et al 2011, Vanneste and DeRidder 2012, Song et al 2013)
4. If the patient responds to step 3, electrical stimulation through an electrode implanted on the same area (ICS) can provide permanent tinnitus suppression.

Fig. 15.1: ladder approach to auditory cortex implantation

Fig. 15.2: different clinical aspects of tinnitus (e.g. loudness, distress, location, mood) are represented by different oscillatory networks which communicate at different frequencies and mutually interact in specific brain structures (hubs). AC: auditory cortex, OFC: orbitofrontal cortex, PHC: parahippocampal area, sgACC: subgenual anterior cingulate cortex

	Phase 1	Phase 2	Phase 3	Phase 4
Deafferentation	Very small bandwidth	Small bandwidth	Large bandwidth	Very large bandwidth
Audiometry	Normal to minimal hearing loss (< 20 dB)	Normal to minimal hearing loss (< 20 dB)	Normal to minimal hearing loss (< 20 dB)	Severe hearing loss (> 20 dB)
Compensation mechanism	Decrease lateral inhibition (Rajan 1998)	Receptive field widening (Chen 1996)	Dendritic and axonal sprouting (Hoy 1985, Hsieh 2007)	Retrieval from memory (De Ridder 2012)
Location of compensation	Auditory cortex	Auditory cortex	Auditory cortex	{para}hippocampus

Fig. 15.3: plastic changes in tinnitus related to deafferentation. Depending on the bandwidth of the deafferentation different plastic changes might occur, starting with changes in lateral inhibition, followed by widening of the receptive fields, and sprouting. These changes occur in the auditory cortex. If deafferentation occurs in a large bandwidth, compensatory changes in the auditory cortex might not be sufficient to fill in the deafferentation gap, and parahippocampal mechanisms might be required. Thus in tinnitus associated with no or little hearing loss the auditory cortex might be the ideal neuromodulation target, in tinnitus with hearing loss the parahippocampus might be the ideal target for neuromodulation.

15.1 Surgical Approach and Targeting

15.1.1 Auditory Cortex

15.1.1.1 Rationale

Auditory cortex stimulation may interfere with persistent gamma band activity, which is thought to code tinnitus intensity. In a study using MEG during electrical stimulation of the auditory cortex, the stimulation increased spectral correlation across low and high gamma band activity, between alpha and beta activity, whereas delta/theta activity decreased (Ramirez et al 2009). This has been confirmed by recordings from electrodes overlying the secondary auditory cortex: maximal tinnitus suppression was obtained by current delivery exactly at the BOLD spot, elicited by tinnitus-matched sound presentation in the MRI machine (DeRidder et al 2009, 2011). The BOLD spot co-localizes with increased and coupled gamma and theta (a supposed carrier wave required for co-activation of the tinnitus network) activity, as opposed to the other electrode poles which show normal alpha peaks. These spectral changes normalize when stimulation induces tinnitus suppression, both on electrode and in source localized EEG recordings (DeRidder et al 2009, 2011). Thus, theta-gamma might be causally related to a conscious auditory phantom percept (VanDerLoo et al 2009, DeRidder et al 2009, 2011) and electrical stimulation via implanted electrodes reduces tinnitus perception by interfering with this anomalous activity embedded in a larger tinnitus network.

15.1.1.2 Target Identification

Both MSI (Magnetic Source Imaging = MEG fused with MRI) (Seidman et al 2008) and fMRI have been used for exactly localizing the auditory cortical hyperactivity. The cerebral activation induced by an external sound, that matches the tinnitus sound in frequency and presented via earphones, can be detected by fMRI. S-LORETA (Standardized low-resolution brain electromagnetic tomography) is another technique useful to capture anomalous tinnitus-related activity, but has low spatial resolution and as such cannot be employed for surgical planning. However, it may have an impact on patient selection: when comparing 5 patients who responded to auditory cortex implants with five patients who did not, sLORETA analysis demonstrated that whether or not someone is going to respond has nothing to do with differences in auditory cortex activity (De Ridder, under revision): in contrast to what was expected, differences between responders and non-responders were demonstrated in left and right parahippocampal areas for gamma, and in the left amygdala-hippocampal-parahippocampal area extending into the left insula for beta3. Variability in PET scan activation before and after rTMS failed to support the hypothesis that low-frequency rTMS improves tinnitus by reducing cortical activation at the stimulation site, questioning the utility of PET for targeting (Mannemeier et al 2011).

15.1.1.3 Modulation of Auditory Activity with rTMS

Subsequently, the exact area of the auditory cortex that is processing the tinnitus tone is stimulated by TMS. A neuronavigation system is useful for exactly localizing the target area for TMS on the patient's head. If tinnitus can be transiently suppressed by TMS of this area, an electrode is surgically placed extradurally, overlying the secondary auditory cortex exactly at the site where fMRI demonstrated hyperactivity and where TMS was successful (DeRidder et al 2009, 2011, Langguth et al 2009, Song et al 2013).

15.1.1.4 Implantation of Electrodes Over the Auditory Cortex: Technical Aspects.

Surgically implanting an extradural electrode carries a minimal risk of complications. An incision is made 5 to 6 cm above the external ear canal, based on the fMRI data: the location of the auditory cortex and the placement of the surgical incision vary among different individuals and between the left and right side in the same patient. The location of the incision in the skin is therefore guided by the fMRI. The skin incision is about 5 cm long and followed by a split of the temporal muscle. A small 1x5cm hole is made in the skull and the dura is coagulated with bipolar forceps to disconnect small sensory fibers that innervate the dura, lest the electrical stimulation cause pain by activation thereof. Thereafter, the stimulating strip –which carries 4 to 16 contacts- is placed on the exact spot with 1-2 mm accuracy based on the fMRI data and sutured onto the dura. The bone flap is placed back and secured with titanium screws and plates. After that, the lead to the stimulating electrode is tunneled to the chest where it is connected to an extension lead, and further tunneled to the abdomen where it is passed through the skin to the outside of the body. The electrode leads that exit the abdomen are connected to a stimulator, usually after 3 days, as, during the first days postoperatively, the tinnitus is often markedly decreased from intraoperative stimulation or anesthesia. During the external trial stimulation, the different electrode contacts are activated, one by one - or more than one at a time, depending on what gives the best suppression. The trial sessions are limited to one hour because it is difficult for the patient to concentrate for longer times, and a good suppressive effect can take anywhere from one day to weeks or even months. A programmable internal pulse generator (IPG) is then implanted in the abdomen or the gluteal region and the electrode is connected with a new extension lead to the IPG. The stimulation parameters (frequency, amplitude, and pulse width) can be changed postoperatively to find the best parameters for maximal tinnitus control. Stimulation is not performed continuously: switching the stimulator 5 seconds ON and 5 seconds OFF is usually sufficient. As the patient does not feel the electrical impulses, he or she does not know whether the stimulator is ON or OFF. With a given stimulation program the tinnitus reoccurs after a certain amount of time in most cases. Tinnitus recurrence can be prevented by running alternately several different stimulation programs using different electrode contacts. During the first period after

the implantation, the tinnitus returns very quickly when the stimulator is turned off. However, as in another ICS protocols (see [chapters 8, 10](#)), after years of stimulation, it may take weeks before the tinnitus fully relapses when the stimulator is switched off or the battery has become drained.

Intradural (DeRidder et al 2009) and intracerebral (Seidman et al 2008) electrode placement onto and into the primary auditory cortex have been performed. However, complication risks are much higher and treatment results are not superior to the epidural approach (DeRidder et al 2009).

15.1.1.5 Outcome

Multiple small and one larger series of patients with auditory cortex electrodes have been published. 43 patients with severe treatment-resistant tinnitus (Goebel and Hiller's Scale grade 3 and 4) were implanted with a cortical electrode overlying the secondary auditory cortex. Before implantation, all patients underwent TMS test sessions on separate dates by a third party. A >20% improvement on the VAS scale on two separate occasions makes the patients eligible for implantation. Although all patients responded to TMS, 1 out of 3 patients did not respond to ICS. Among responders, perceived tinnitus loudness decreased on average by 51.3%. There was a significant, but weak, positive correlation ($r = .34, p < .05$) between the magnitude of relief from the TMS tests and ICS (DeRidder et al 2011).

Burst stimulation (5 stimuli of 1 ms pulse width, 1ms interpulse interval delivered at 500 Hz, 40 times a second) is more efficient than tonic stimulation: with tonic stimulation only 1 in 3 patients responded to stimulation, while with burst stimulation, half of the non-responding patients did benefit, resulting in a total response rate of 2 out of 3 patients ([Fig.15.4](#)). *Burst stimulation was specifically superior to tonic stimulation for suppressing noise-like tinnitus* (DeRidder et al 2011), analogous to what has been described for TMS. In contrast to TMS, where the suppression effect decreases with longer tinnitus duration, no correlation was found between the effect of electrical cortical stimulation and tinnitus duration for the same study population, suggesting that *ICS acts on tinnitus by a different mechanism than TMS*. Furthermore, all patients responded to TMS, as this was an inclusion criterion for implantation, and not all patients responded to the implant. Treatment effects also depended on tinnitus type. *Pure tone tinnitus* can be suppressed better than narrow band noise or the combination of pure tone and narrow band noise, and *unilateral tinnitus* better than bilateral tinnitus. This approach has been replicated by other centers with similar or different results. A French study obtained persisting 65% tinnitus reduction in a woman using an fMRI based extradural auditory cortex implant (Litre et al 2009, 2010). Another study of eight patients using a similar technique but different hardware found no permanent tinnitus suppression (Friedland et al 2007). In six out of the eight patients, temporary effects on tinnitus perception were observed. However, tinnitus distress decreased slowly over time, even without suppression of tinnitus intensity.

This may be related to the fact that an electrode with only two contacts was used which limits the way the electrodes can be programmed. The finding of decreased tinnitus distress with unchanged tinnitus intensity could possibly be explained by disruption of the phase synchronization between the ‘general distress network’ and the tinnitus related activity in the auditory cortex (DeRidder et al 2011b). TMS of the auditory cortex not only disrupts local ongoing activity but also long-range connections in a larger network. In some patients tinnitus suppression can be obtained, but only for short times (1 to 3 days) after which the effect wears off, even after extensive reprogramming. Perhaps, the lemniscal thalamocortical system predominantly connecting to the primary auditory cortex is less plastic than the extralemniscal system, predominantly connecting to the secondary auditory cortex (DeRidder et al 2009). In four patients an intradural electrode on the primary auditory cortex was inserted in the Sylvian fissure, stimulating gray matter of the primary auditory cortex (DeRidder et al 2009). In two patients the goal was to obtain stabilization of tinnitus suppression, because the stimulus parameters had to be reprogrammed every 2 to 3 days. In both patients the intradural positioning resulted in stabilization of tinnitus suppression. Another approach has been proposed, inserting a wire electrode in the white matter beneath layer 6 of the primary auditory cortex. This has been performed successfully, using Magnetic Source Imaging for target localization, resulting in tinnitus suppression (Seidman et al 2008).

Fig. 15.4: response rate to auditory cortex stimulation: burst stimulation can rescue 50% of stimulation failures and can further improve 50% of responders to tonic stimulation.

15.1.2 Frontal Cortex

Tinnitus was among the many indications for which frontal lobotomy has been performed. In Elithorn (1953)’s study, 13 of 17 patients improved, 3 were unchanged and 1 patient’s tinnitus worsened. In Beard (1965)’s series of 20 patients selected for surgery he states that “*In fact, of the 19 patients who survived the operation, 11 felt that their head noises were just the same but bothered them less and 8 felt that they had*

improved". This suggests that disconnecting the frontal lobe from the rest of the brain has a particular impact on the affective component of the tinnitus. Indeed functional imaging studies using source localized EEG and MEG have shown that tinnitus distress is related to a network involving the anterior cingulate cortex (ACC), anterior insula and frontal cortex, whereas the auditory cortex is involved in the perceived tinnitus intensity (DeRidder et al 2011b, Vanneste and DeRidder 2012, Vanneste et al 2013). Other imaging studies showed that the primary hubs in tinnitus consist of the PCC, dACC, and subgenual ACC (sgACC), extending into the orbitofrontal cortex (OFC) and parahippocampal area (Schlee et al 2009, Husain and Schmidt 2014). Disconnecting frontal and auditory cortex by frontal lobotomy likely dissociated the affective component from the perceived loudness. More specifically, tinnitus distress is related to insufficient inhibition from the dorsolateral prefrontal cortex (DLPFC) and activation by the posterior cingulate cortex (PCC) (Joos et al 2012, Silchenko et al 2013). Non-invasive stimulation targeting the frontal cortex by means of tDCS can modulate tinnitus (e.g. Faber et al 2011). The tinnitus suppressing effect of stimulating the frontal cortex is mediated via the ACC and parahippocampal area, decreasing the increased gamma band activity in the auditory cortex (Vanneste and DeRidder 2011). Based on these results, a translation to invasive permanent neuromodulation was initiated, surgically targeting the DLPFC to treat tinnitus (DeRidder et al 2011).

In a patient refractory to conservative medical management and resistant to TMS of the auditory cortex, a neuronavigation-based auditory fMRI-guided frontal cortex TMS session was performed in a placebo-controlled way. A maximal tinnitus suppression of 50% was obtained reliably after stimulation of the right DLPFC. This TMS result was used as a prognostic indicator and two extradural electrodes (Lamitrode 44, SJMedical Neurodivision, Plano Tx, USA) were implanted over the spot in the DLPFC, where tinnitus frequency-matched tones induced BOLD activation in the fMRI. The tinnitus immediately improved postoperatively from VAS 7/10 to 4/10 and has progressively improved for more than one year. The initial VAS of 7/10 has decreased after 1 year to 2/10. This suggests that, in selected patients, focal extradural electrical stimulation of the DLPFC at the area of tinnitus-matched-sound elicited BOLD activation is capable of partially suppressing contralateral tinnitus. Electrophysiological data demonstrate that DLPFC stimulation by both epidural electrodes and tDCS reduces gamma band activity in the auditory cortex (Vanneste and DeRidder 2011, DeRidder et al 2011, 2013) which is abnormally increased in tinnitus ([Fig.15.5](#)).

Fig. 15.5: frontal (left) and hippocampal cortical (right) stimulation for tinnitus suppression, based on tinnitus sound evoked BOLD activation.

15.1.3 Hippocampal Stimulation

The amygdala, hippocampus and parahippocampus have been implicated in tinnitus. The auditory cortices are densely connected to the posterior parahippocampal area in a reciprocal way: this latter acts as a gatekeeper to the hippocampus and hence to the medial temporal lobe memory system, where salient information is encoded into long-term memory: a dysfunction in this mechanism is posited as an explanation for complex auditory phantom percepts such as auditory hallucinations (Diederer et al 2010) and speculatively also tinnitus: the para-hippocampus might be related to the constant updating of the tinnitus percept from memory, thereby preventing habituation. The most robust functional connectivity in resting state EEG and fMRI studies is the sgACC - parahippocampal – auditory cortex connection, which is critical in tinnitus (Maudoux et al 2012), both for distress (sgACC-parahippocampal) and loudness perception (Vanneste, under revision). Thus targeting this parahippocampal central hub should theoretically dissociate the loudness from the distress, and could thereby induce habituation to the sound, resulting in silencing the tinnitus percept.

CLINICAL CASE: a 59 year old patient has been implanted with an electrode in the amygdalohippocampal region. He presented with 5-year intractable right-sided pure tone tinnitus at 8000 Hz 10 dB SL present. He was neither responsive to medication nor to TMS. An fMRI elicited BOLD activation at the amygdalohippocampal junction only at the tinnitus matched frequency (8000 Hz), not at a control frequency (4000 Hz), suggesting a tinnitus-frequency-specific activation of this area. The technique used was the same as the one used for auditory cortex and DLPFC stimulation, i.e. an fMRI was performed with tinnitus-matched sounds and the BOLD activation in the amygdalohippocampal area was used as a target for stimulation. However, as no TMS can be performed to transiently suppress these targets, supraselective injection of amytal was performed in the anterior choroidal artery, demonstrating a transient (10 minutes) improvement in the pure tone component of the tinnitus using a technique previously described (DeRidder et al 2006). The patient experienced a transient tinnitus reduction of 30% by ipsilateral amytal injection, and by 60% on contralateral amytal injection. After contralateral injection, he also described a heavenly feeling and a disinterest in his tinnitus. A wire electrode was inserted via a posterior parietal entry under fMRI guided stereotactic conditions and inserted till the BOLD activated area in the amygdala was reached. The day after the surgery, the electrode was activated. During the first week, the tinnitus remained unchanged, but it was not perceived as annoying anymore. During the second week, its intensity decreased, but recurred in the third postoperative week, and could no longer be quelled even by intensive reprogramming. A placebo effect could not be excluded, since a blinded test had not yet been performed. On the other hand, habituation might explain the loss of effect, as also seen after auditory cortex stimulation in the Friedland et al (2007)'s study. A wire electrode limits the programming strategies, which are essential for long-lasting therapeutic success. A theoretically better option would be to insert a paddle electrode with many contacts (8 or 16) subdurally via a subtemporal approach, at the inferior part of the medial temporal lobe, covering the amygdaloparahippocampal area, thus turning deep brain stimulation into cortical stimulation (Fig.5).

15.2 Methodological Aspects

15.2.1 Non-invasive Stimulation as a Prognostic Test for Surgical Neuromodulation

TMS has been used for screening patients who might benefit from chronically implanted electrodes. However, available data question this approach. It was found that TMS is not a good predictor for deciding who is going to benefit from an implant (DeRidder et al 2011). Only patients who responded twice in a placebo controlled fashion to TMS on two separate days were implanted, but only a subgroup responded to the implant. However, TMS has some prognostic value if the patient is a responder to the implant, as a small but significant correlation was found between the amount

of tinnitus suppression obtained by TMS and the amount obtained by the implant ($r = .38, p < .05$).

15.2.2 Neurostimulation Designs: burst & tonic

The stimulation design (burst versus tonic stimulation) significantly influences outcome. Tonic stimulation is not capable of suppressing noise-like tinnitus, but only pure tone tinnitus (DeRidder et al 2007, 2010). However, based on data from burst TMS (DeRidder et al 2007, 2010), changing the electrical stimulation design to burst stimulation benefited patients presenting with noise-like tinnitus (DeRidder et al 2007, 2009, 2010). Furthermore, if a patient presented with both a pure tone and a noise-like component, both components had to be relieved to yield a substantial decrease in tinnitus-related distress (DeRidder et al 2009, Langguth et al 2009): only suppressing the pure tone component, even if completely, did not benefit the patients. Indeed, burst stimulation allays almost half (13/27 or 48%) of initially unresponsive patients to tonic stimulation. Furthermore, 50% of patients who respond to tonic stimulation benefit more from burst than tonic stimulation: tinnitus suppression was 24% with tonic, versus 53% with burst stimulation. In sum, adding burst stimulation switches the outcome from poor response to an acceptable, even though far from ideal, suppression rate. A total of 2 out of 3 (29/43 or 67%) participants responded to stimulation via the implanted electrodes with an average tinnitus reduction of 53% (DeRidder et al 2011). Some participants in the study only responded to tonic stimulation. This subgroup of patients has a 52% suppression effect. So both burst and tonic stimulation have the same amount of suppression in individual patients, yet more patients benefit from burst stimulation than from tonic stimulation. Thus the question arises when to apply burst or tonic stimulation. Tinnitus duration, age, and gender were not predictive, whereas the tinnitus character was, i.e. noise-like tinnitus responds better to burst stimulation, pure tones respond equally well to burst and tonic stimulation, confirming our previously published data (DeRidder et al 2009). A previous burst TMS study demonstrated that women seem to respond better to burst TMS than men (DeRidder et al 2007), but this seems not to hold for ICS. Also, pure tone tinnitus was suppressed to a greater extent (70% tinnitus reduction) than noise-like tinnitus (40 % reduction). The worst results (only 29% reduction) were obtained in individuals who had a combination of pure tone and noise-like tinnitus.

15.3 Complications

Side effects are limited and do not occur at stimulation parameters required for tinnitus suppression. Side effects may occur when high frequency, high intensity stimulation is used. Different kinds of side effects have occurred during parameters

search: a feeling of intoxication, altered spatial localization of external sounds, difficulty finding appropriate words, dizziness, vertigo and hearing perception changes (hearing perceived as being clearer - related to even their own voice), as well as out of body experiences (DeRidder et al 2009, Langguth and DeRidder 2013). Some patients with tinnitus have an associated feeling of aural pressure, the feeling as if there is water inside the ear. In all patients with successful tinnitus suppression, these associated pressure feelings decreased, however the stimulation design that best suppressed tinnitus and best suppressed pressure feelings were not always identical. Complications specific for the extradural implantation of electrodes overlying the auditory cortex are limited. Epileptic seizures occurred in 3 of the 43 patients (DeRidder et al 2011). In two patients, the fits occurred while patients were still having an external stimulator, possibly due to prolonged stimulation without enough OFF intervals: the patients are now only using programmable IPGs during the period of externalized stimulation. In a third patient, the epileptic seizure occurred during in-hospital programming. Patients with a history of epilepsy are thus best excluded from this procedure. Two major complications occurred with intradural implants. One of the 4 patients who was implanted with the electrode directly on the surface of the primary auditory cortex (DeRidder et al 2009) developed a postoperative intracranial bleeding in the superior temporal sulcus, at a distance from the Sylvian fissure, in which the electrode was inserted, with speech disturbances as a result. Moreover, the tinnitus decreased as a result of the bleeding. Another developed an intracranial abscess that required surgical evacuation, with removal of the electrode, with good outcome but worsening of the tinnitus. Thus, *this treatment should be preferentially performed extradurally, as with the extradural technique in the last 30 patients no serious complications were encountered*.

15.4 Failures

In responders vs non-responders, differences were demonstrated not in the auditory cortex, but in left and right parahippocampal areas for gamma frequency band, and in the left amygdala-hippocampal-parahippocampal area extending into the left insula for beta3 band. However, the electrodes were implanted extradurally overlying the secondary auditory cortex. Therefore we analyzed the functional connectivity between auditory cortex and hippocampal/parahippocampal area and established a difference in the functional connectivity with increased lag-phase synchronization for the delta, theta2, beta2 for responders between the auditory cortex and the hippocampus, but especially the beta3 band between the auditory cortex and parahippocampal area (De Ridder, under revision). This suggests that the mechanism of action is not via suppression of increased synchronized gamma band activity in the auditory cortex, which is hypothesized to be the final common pathway for tinnitus, but via an indirect modulation of high frequency activity (beta3 and gamma) in the parahippocampus.

Only patients who have good functional connectivity between the stimulated auditory cortex and the parahippocampal area benefit from the stimulation. Thus, combined activity (beta3 and gamma in parahippocampus) and functional connectivity (beta3 between auditory cortex and parahippocampus) measurements could be investigated in the future as response predictors to an auditory cortex implant.

15.5 Conclusion

How can results be improved?

1. Tinnitus-related plasticity changes in the inferior colliculus are mediated by BDNF (brain-derived neurotrophic factor) (Tan et al 2007). At the same time, the same Val66Met polymorphism in the BDNF gene determines whether one responds to TMS or tDCS (Cheeran et al 2008). Thus it could be of interest in the future to determine BDNF polymorphisms in patients and correlate them to the response rate to ICS.
2. Future targets to assess on the basis of neuroimaging evidence include the PCC and ACC. The ACC is involved in the salience attached to the tinnitus as well as the distress. Whereas the dorsal ACC is activated in distress in general, the subgenual ACC is related to the amount of tinnitus distress, and indirectly related to the loudness perception, via a putative noise-canceling mechanism. This noise canceling mechanism could involve the pregenual ACC, analogous to what has been described for pain: depending on the clinical picture, the sgACC, dACC or pregenual ACC could then be targeted. The PCC acts as a switch between memory encoding and memory retrieval and co-processes tinnitus-related distress. The effective connectivity from the PCC to the auditory cortex might thereby also influence the perceived loudness indirectly.
3. Burst stimulation consisting of closely spaced high frequency (500 Hz) spikes (n=5) delivered 40 times a second (40 Hz burst mode) can better suppress noise-like tinnitus than currently used tonic stimulation and can further improve the amount of tinnitus loudness suppression (DeRidder et al 2010). This bursting can lead to rerouting and multiplexing, resulting in activation of functionally connected networks, with attendant clinical benefit. Coordinated reset stimulation and pink and brown noise stimulation are other stimulation protocols worth pursuing: pink noise, for instance, mimics the frequency spectrum of normal physiological ongoing resting state activity at the level of the cortex (De Ridder, unpublished results).
4. For tinnitus too (see [Chapter 17](#)), the future rests with closed-loop stimulation. A tinnitus detector has recently been developed (Hiseni et al 2009). In tinnitus, the predominant alpha activity is replaced by theta and beta/gamma activity and the real-time detection of this electrophysiological signature in the individual brain can be exploited to stimulate only when this becomes chronic.

References

General Reviews

- DeRidder D, Langguth B, Plazier M, et al. Auditory cortex stimulation for intractable tinnitus. In: Canavero S (ed) Textbook of therapeutic cortical stimulation. New York: Nova Sci., 2009, 353-361
- Langguth B, DeRidder R, Eichhammer P, Hajak G. TMS for refractory tinnitus. In: Canavero S (ed) Textbook of therapeutic cortical stimulation. New York: Nova Sci., 2009, 337-352
- Langguth, B., et al., Tinnitus: causes and clinical management. *Lancet Neurol*, 2013; 12: 920-30.
- Langguth, B. and D. De Ridder, Tinnitus: therapeutic use of superficial brain stimulation. *Handb Clin Neurol*, 2013. 116: p. 441-67.
- Moller A et al (eds) Textbook of Tinnitus. New York: Springer, 2011; 753-762.24.

Specific Studies

- Beard, A.W., Results of leucotomy operations for tinnitus. *J Psychosom Res*, 1965. 9(1): p. 29-32
- Cheeran, B., et al., A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *J Physiol*, 2008. 586(Pt 23): p. 5717-25.
- De Ridder, D., S. Vanneste, and M. Congedo, The distressed brain: a group blind source separation analysis on tinnitus. *PLoS One*, 2011b. 6(10): p. e24273.
- De Ridder, D., et al., Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression. *J Neurosurg*, 2011. 114(4): p. 903-11 (also 912-921 for part B)
- De Ridder, D., et al., Dorsolateral Prefrontal Cortex Transcranial Magnetic Stimulation and Electrode Implant for Intractable Tinnitus. *World Neurosurg*, 2011.
- De Ridder, D., et al., Remote tentorium meningioma causing sudden sensorineural deafness. *Surg Neurol*, 2008. 70(3): p. 312-7; discussion 318.
- De Ridder, D., et al., Amygdalohippocampal involvement in tinnitus and auditory memory. *Acta Otolaryngol Suppl*, 2006(556): p. 50-3.
- De Ridder, D., et al., Do tonic and burst TMS modulate the lemniscal and extralemniscal system differentially? *Int J Med Sci*, 2007. 4(5): p. 242-6.
- De Ridder, D., et al., Theta, alpha and beta burst transcranial magnetic stimulation: brain modulation in tinnitus. *Int J Med Sci*, 2007. 4(5): p. 237-41.
- De Ridder, D., et al., Burst stimulation of the auditory cortex: a new form of neurostimulation for noise-like tinnitus suppression. *J Neurosurg*, 2010. 112(6): p. 1289-94.
- De Ridder D, Song JJ, Vanneste S. Frontal cortex TMS for tinnitus. *Brain Stimul*. 2013 May;6(3):355-62.
- Diederen, K.M., et al., Deactivation of the Parahippocampal Gyrus Preceding Auditory Hallucinations in Schizophrenia. *Am J Psychiatry*, 2010. 167(4): p. 427-35.
- Elithorn, A., Prefrontal leucotomy in the treatment of tinnitus. *Proc R Soc Med*, 1953. 46(10): p. 832-3.
- Faber, M., et al., Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex. *Brain Stimul*, 2011.
- Friedland, D.R., et al., Feasibility of Auditory Cortical Stimulation for the Treatment of Tinnitus. *Otol Neurotol*, 2007. 28(8): p. 1005-1012.
- Hiseni, S., et al., A Nano Power CMOS Tinnitus Detector for a Fully Implantable Closed-Loop Neurodevice. *IEEE xplore*, 2011. Conference Proceedings, BIOCAS 2009: p. 33-36.
- Husain, F.T. and S.A. Schmidt, Using resting state functional connectivity to unravel networks of tinnitus. *Hear Res*, 2014. 307: p. 153-62.
- Joos, K., S. Vanneste, and D. De Ridder, Disentangling depression and distress networks in the tinnitus brain. *PLoS One*, 2012. 7(7): p. e40544.

- Landgrebe, M., et al., Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. *Neuroimage*, 2009. 46(1): p. 213-8.
- Langguth, B., et al., Neuroimaging and neuromodulation: complementary approaches for identifying the neuronal correlates of tinnitus. *Front Syst Neurosci*, 2012. 6: p. 15.
- Langguth, B., et al., The impact of auditory cortex activity on characterizing and treating patients with chronic tinnitus--first results from a PET study. *Acta Otolaryngol Suppl*, 2006(556): p. 84-8.
- Litre, C.F., et al., [Feasibility of auditory cortical stimulation for the treatment of tinnitus. Three case reports]. *Neurochirurgie*, 2010. 56(4): p. 303-8.
- Litre, C.F., et al., Surgical treatment by electrical stimulation of the auditory cortex for intractable tinnitus. *Brain Stimul*, 2009. 2(3): p. 132-7.
- Maudoux, A., et al., Auditory resting-state network connectivity in tinnitus: a functional MRI study. *PLoS One*, 2012. 7(5): p. e36222.
- Mennemeier, M., et al., Variable changes in PET activity before and after rTMS treatment for tinnitus. *Laryngoscope*, 2011. 121(4): p. 815-22.
- Ramirez, R.R., et al., Neuromagnetic source imaging of abnormal spontaneous activity in tinnitus patient modulated by electrical cortical stimulation. *Conf Proc IEEE Eng Med Biol Soc*, 2009. 1: p. 1940-4.
- Schlee, W., et al., Mapping cortical hubs in tinnitus. *BMC Biol*, 2009. 7: p. 80.
- Silchenko, A.N., et al., Impact of acoustic coordinated reset neuromodulation on effective connectivity in a neural network of phantom sound. *Neuroimage*, 2013. 77: p. 133-47.
- Seidman, M.D., et al., Direct electrical stimulation of Heschl's gyrus for tinnitus treatment. *Laryngoscope*, 2008. 118(3): p. 491-500.
- Song JJ, Vanneste S, Van de Heyning P, De Ridder D. Transcranial direct current stimulation in tinnitus patients: a systemic review and meta-analysis. *Scientific World Journal*. 2012;2012:427941.
- Tan, J., et al., Tinnitus behavior and hearing function correlate with the reciprocal expression patterns of BDNF and Arg3.1/arc in auditory neurons following acoustic trauma. *Neuroscience*, 2007. 145(2): p. 715-26.
- Van der Loo, E., et al., Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. *PLoS ONE*, 2009. 4(10): p. e7396.
- Vanneste, S. and D. De Ridder, Differences between a single session and repeated sessions of 1 Hz TMS by double-cone coil prefrontal stimulation for the improvement of tinnitus. *Brain Stimul* 2013 Mar;6(2):155-9.
- Vanneste, S., et al., Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. *Exp Brain Res*, 2010. 202(4): p. 779-85.
- Vanneste, S. and D. De Ridder, Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. *Eur J Neurosci*, 2011. 34(4): p. 605-14.
- Vanneste, S., P. van de Heyning, and D. De Ridder, The neural network of phantom sound changes over time: a comparison between recent-onset and chronic tinnitus patients. *Eur J Neurosci*, 2011. 34(5): p. 718-31.
- Vanneste, S. and D. De Ridder, The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. *Front Syst Neurosci*, 2012. 6: p. 31.
- Vanneste, S., et al., Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression. *Exp Brain Res*, 2011. 210(2): p. 217-27.
- Vanneste S, Congedo M, De Ridder D. Pinpointing a Highly Specific Pathological Functional Connection That Turns Phantom Sound into Distress. *Cereb Cortex*. 2013 Apr 30.
- Vanneste S, De Ridder D. Noninvasive and invasive neuromodulation for the treatment of tinnitus: an overview. *Neuromodulation*. 2012 Jul;15(4):350-60.