

Residual inhibition

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Abstract: Following offset of an appropriate masking stimulus, tinnitus may remain suppressed for a period, typically less than a minute. This phenomenon is known as “residual inhibition” (RI). This chapter reviews the psychoacoustic properties of RI and their relation to hearing impairment, tinnitus spectra, and the spectra of masking stimuli. RI is also contrasted with tinnitus suppression produced by repetitive transcranial magnetic stimulation (rTMS) the cortical effects of which do not require the ear to reach the brain. Although the two procedures act in different ways, both may reduce tinnitus by interrupting abnormal synchronous activity among networks of neurons that generate tinnitus. Therapies that induce tinnitus suppression by these methods have been reported to reduce tinnitus distress by processes that are not well understood.

Keywords: tinnitus; residual inhibition; masking; transcranial magnetic stimulation; neural synchrony

Introduction

One of the fundamental properties of tinnitus is that it can be masked by external sounds. In his classic studies of tinnitus masking, Feldman (1971) observed that a substantial number of participants experienced a brief reduction in their tinnitus following the cessation of the masker. This phenomenon has come to be known as “residual inhibition” (RI), although the term “residual suppression” is more neutral with regard to its possible underlying mechanisms (Terry et al., 1983). Because RI is one of the few procedures that may reduce or eliminate tinnitus for brief periods, it is surprising that except for foundation studies now more than 20-years-old, few studies on RI have been published (Henry and Meikle, 2000). It is possible (although by no means certain) that the

mechanisms that are involved in RI are similar to (or overlap with) those that cause the generation of tinnitus. If this working hypothesis is accepted, efforts to understand RI should take guidance from advances in our knowledge of the mechanisms underlying tinnitus.

In this chapter I review early and recent research on the psychoacoustic properties of RI and their relationship to properties of tinnitus. An attempt is made to understand these phenomena in terms of common underlying neurophysiological mechanisms. Evidence from many different studies (Chapter 2) suggests that most forms of tinnitus result from a loss of inhibition in central auditory structures consequent on hearing impairment or the aging process. When inhibitory deficits occur, synchronous neural activity that is normally constrained by feedforward inhibition to acoustic features in the stimulus (normal auditory perception) may develop spontaneously among networks of neurons in the affected auditory

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cortical regions, giving rise to the sensation of tinnitus (Eggermont and Roberts, 2004; Weisz et al., 2007) (see Chapters 2 and 6). Synchronous activity in the auditory cortex appears to recruit via intracortical or corticothalamic pathways a distributed network involving other brain regions (Schlee et al., 2007), some of which have been identified by anatomical (Muhlau et al., 2006) and functional brain imaging studies (Melcher et al., 2000; Lockwood et al., 2001; Wienbruch et al., 2006; Plewnia et al., 2007). This general view of the pathophysiology of tinnitus has implications for the psychoacoustic properties of tinnitus, for tinnitus masking, and for understanding RI, which are discussed in this chapter. Tinnitus suppression induced by repetitive transcranial magnetic stimulation (rTMS) (Chapters 34 and 35) is also mentioned, because it may achieve some of its effects by processes overlapping those of RI. Study of the clinical benefits of RI and from treatment with rTMS is an emerging area of investigation (Vernon and Meikle, 2003; see Chapter 49).

Psychoacoustic properties of tinnitus, masking, and RI

Feldman categorized masking effects into three main categories according to whether auditory thresholds and tinnitus masking curves converged only at some frequencies ("convergence," 34% of patients with chronic tinnitus), at most frequencies ("congruence" type, 32% of patients), or showed only a weak trend ("distance" type, 22% of patients). The existence of these patterns was confirmed by subsequent studies using pure tones or narrow band noise as masking stimuli (Mitchell, 1983; Tyler and Conrad-Ames, 1984), with convergence tending to be the most common form (53% in the study of Mitchell). However, when masker intensity is calculated as sensation level (SL) in each of these studies, it appears that for each pattern the sound intensity needed to mask tinnitus is lowest when masker frequency is in the frequency region where impairments of auditory function are present. Almost all participants in these studies report masking when presented with

sounds in this region (94% in the study of Mitchell, 1983).

The relation of masker frequency and intensity (SL) to hearing impairment implies that the frequency spectrum of tinnitus overlaps the frequency range where hearing loss is present. This is because it is in this frequency range that tinnitus sounds would be most confusable with the maskers. Evidence on this question is clouded to some degree by the fact that many studies measuring tinnitus frequencies have not measured the hearing threshold above 8 kHz. Another factor is that the frequency of tinnitus has often been measured by matching the tinnitus to pure tones that may not cover the bandwidth of the tinnitus. Fowler (1944) stated that even tinnitus that sounds like a pure tone is in fact always a narrow band of frequencies; Reed (1960) found that only ~1/4 of the participants in their studies were able to select a pure tone to match their sensation. Despite limitations such as these, Vernon and Meikle (2003) found that 75% of the participants in their studies reported tinnitus pitch matches above 3 kHz, which is the region where hearing impairments are most common. Noreña et al. (2002) measured tinnitus frequencies in participants with tonal tinnitus by presenting, one at a time, pure tones spanning the frequencies of the audiogram, including the region of hearing impairment up to 14 kHz. The participants in these studies were asked to state whether each pure tone corresponded to a component of their tinnitus, and if it did, to rate on a 10-point scale (10 = tinnitus) the extent to which the frequency was part of their tinnitus sensation. Results from four representative participants are reproduced in Fig. 1. In each of the 10 individuals tested (all reporting a tonal sound to their tinnitus), several frequencies were judged to resemble the tinnitus sensation, and these frequencies spanned the region of hearing impairment.

Psychoacoustic measurements presented by Noreña et al. suggest that even in tonal tinnitus it may be more appropriate to speak of the tinnitus "spectrum" than of the tinnitus "pitch." The findings also imply a relation between the tinnitus spectrum, masking efficiency, and elevation of the hearing threshold. A relationship among these variables is expected if neural hypersynchrony in

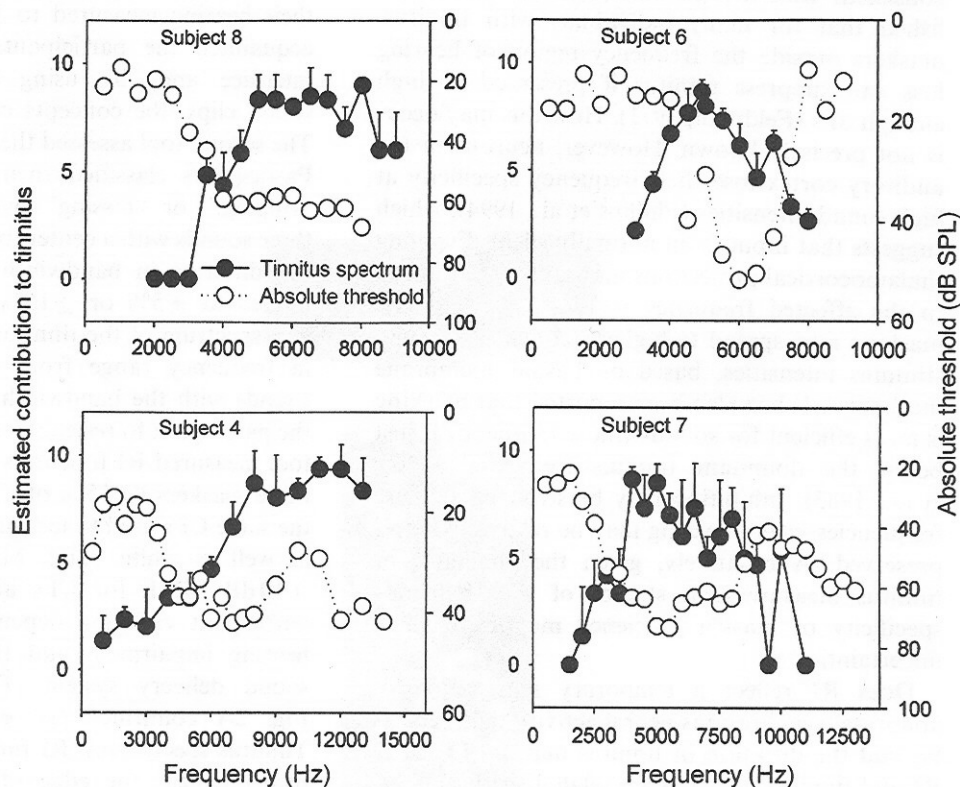


Fig. 1. Estimated tinnitus spectrum in relation to hearing loss in four individuals with tinnitus (adapted with permission from Noreña et al., 2002). The results are representative of 10 participants tested, all reporting tonal tinnitus. Etiology was auditory trauma (Participants 6 and 7), sudden hearing loss (Participant 4, tinnitus 1 year duration), or unknown (Participant 8, tinnitus 3 years duration). Hearing thresholds were measured in 500 Hz steps from 0.5 to 8 kHz (up to 14 kHz when hearing loss at 8 kHz did not exceed 70 dB HL) using a staircase method. After threshold determination, participants adjusted the intensity of tones within the studied frequency range (one randomly selected tone at a time) to match the loudness of their tinnitus. Participants then stated whether the frequency corresponded to one of the components of their tinnitus spectrum, and if it did, gave a rating on a 10-point scale (10 = tinnitus) of the extent to which the frequency was part of their tinnitus sensation. Tones were presented monaurally either to the tinnitus ear (Participants 4, 6, and 7, unilateral cases) or to the ear where tinnitus was most pronounced (Participant 8, bilateral case). In each of the 10 cases tested, the rated tinnitus spectrum spanned the region of hearing loss.

cortical regions affected by hearing impairment is the basis of tinnitus. Maskers are effective only when presented above individual sound thresholds (Vernon and Meikle, 2003). When a masker of sufficient intensity is presented in the region of hearing impairment, excitation is injected via thalamocortical pathways into the affected frequency region followed by comparatively stronger feedforward inhibition after one synaptic delay (Douglas and Martin, 1990; Cruikshank et al., 2007). Inhibition may serve to restrict synchronous activity induced by the masker to neurons that code for acoustic properties contained in the

sound, leading to its normal perception, which interferes with the perception of tinnitus. Concurrently, inhibition would be expected to disrupt the abnormal synchronous neural activity that is believed to underlie tinnitus, diminishing its perceptual salience (Eggermont and Roberts, 2004). By comparison, masking sounds presented at other frequencies (i.e., at frequencies outside of the cortical region affected by hearing loss) may leave the tinnitus relatively intact, because tinnitus is not generated in these frequency regions.

A challenge for this hypothesis is to explain properties of masking that do not appear to be

consistent with it. For example, it is well established that for many individuals with tinnitus, maskers outside the frequency region of hearing loss can suppress tinnitus if presented at high enough SLs (Feldman, 1971). How this may occur is not precisely known. However, neurons in the auditory cortex lose their frequency specificity at high sound intensities (Phillips et al., 1994), which suggests that input from normally silent diverging thalamocortical projections may convey inhibition to the affected frequency regions. Alternatively, masking may spread to higher frequencies at high stimulus intensities, based on basilar membrane mechanics. It has also been reported that masking is most efficient for sounds whose frequency is just below the dominant tinnitus frequency (Terry et al., 1983). Inhibition may be stronger at these frequencies where hearing may be relatively better preserved. Alternatively, given the challenge of tinnitus measurement, studies of the frequency specificity of masker efficiency may have some uncertainties.

Does RI reflect a temporary segregation of abnormal synchronous neural activity that persists beyond the duration of tinnitus masking? Clearly RI and tinnitus masking are related. Although estimates vary, the proportion of individuals with tinnitus who report some degree of RI is in excess of 75% (Vernon and Meikle, 2003; Roberts et al., 2006), which is in the same range as those reporting masking. RI requires the use of masking sounds that exceed the minimum masking level (MML; Terry et al., 1983); cases of RI without some degree of prior masking, while logically possible, have not been reported in the literature. RI depth and duration increase as masker intensity is raised to +20 dB MML (Terry et al., 1983; Tyler et al., 1984), revealing a dose-response relationship that is consistent with disruption of synchronous neural activity in auditory structures as its basis.

If segregation of synchronous activity in regions of hearing impairment is responsible for RI, functions relating the depth of RI to masker characteristics should asymptote in the region of hearing loss, as tinnitus spectra appear to do. Roberts et al. (2006, 2007) devised three computerized tools controlled by the participant to assess this prediction

for 59 individuals with bilateral tinnitus who had their hearing measured to 16 kHz. The first tool acquainted the participants with the computer interface and, by using participant-controlled sound clips, the concepts of loudness and pitch. The second tool assessed the properties of tinnitus. Participants classified their tinnitus as "tonal," "ringing," or "hissing" by selecting one of the three sounds with a center frequency (CF) of 5 kHz but differing in bandwidth (pure tone, or noise limited to $\pm 5\%$ or $\pm 15\%$ of CF, respectively). The spectrum of the tinnitus was then determined in frequency range from 0.5 to 12 kHz, using sounds with the bandwidth previously chosen by the participant to resemble their tinnitus. The third tool measured RI functions using 11 band-limited noise maskers ($\pm 15\%$ of CF, 30 s duration) with the same CFs used to measure the tinnitus spectra, as well as white noise. Masking level averaged +10 dB MML for CFs above 5 kHz; between-participant variation depended on the extent of hearing impairment and the capabilities of the sound delivery system. The results shown in Fig. 2A confirmed the expected relationships. Tinnitus spectra and RI functions increased commencing near the edge of normal hearing and spanned the region of hearing impairment, with some diminution at 12 kHz where masker intensity (SL) was attenuated owing to the depth of hearing loss. Band-limited maskers with CFs in the tinnitus region also induced significantly greater RI than did white noise. The dependence of RI on CF and hearing function is especially striking in cases of notched hearing impairment. One early such case assessed by the procedure of Roberts et al. is shown in Fig. 2B (Roberts and Platt, 1998 unpublished). This participant reported elimination of tinnitus for ~ 30 s for narrow band maskers with CFs near 5 kHz, which also corresponded the region of hearing impairment and the tinnitus sensation. Maskers with CFs outside the region of hearing impairment were not effective. Although participants of this kind are not common, they do exist (Bailey, 1979) and set the frequency dependence of RI and its relation to hearing impairment into sharp relief. Interestingly, Kitajima et al. (1987) reported that maskers with frequencies in the tinnitus spectrum notched out can produce

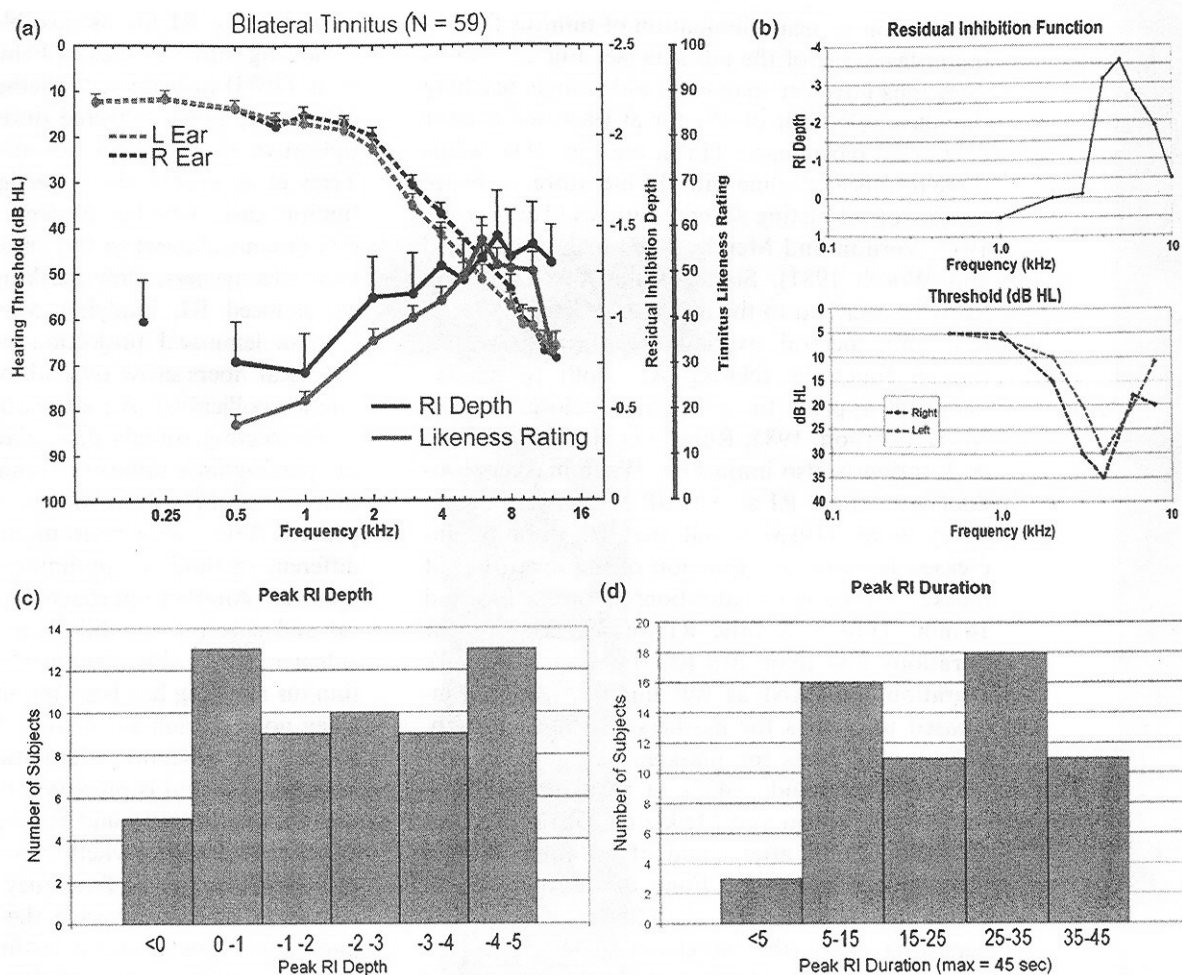


Fig. 2. Properties of residual inhibition. (a) Residual inhibition functions in relation to hearing loss and the tinnitus spectrum in bilateral tinnitus ($n = 59$ cases). RI induced by band-limited noise maskers ($\pm 15\%$ of CF) tracks the tinnitus spectrum and spans the region of hearing impairment. Each masking sound was presented for 30 s in a random order three times and followed by a rating of RI depth (-5 equals tinnitus elimination). RI depth induced by maskers with CFs above 4 kHz is greater than RI depth induced by white noise ($p < 0.028$, data point to the left). (Data from Roberts et al., 2006, 2007). (b) RI function (upper panel) in a participant with bilateral tinnitus and a well-defined notch at 4 kHz in the audiogram (lower panel). The tinnitus spectrum was described by narrow-band sounds with CFs centered at 4 kHz (data from Roberts and Platt, 1998, unpublished). (c) Frequency histogram of peak RI depth. Peak RI depth was determined as the deepest RI produced by the masking sounds used to measure the RI Function of Panel A (mean of three measurements). (d) Frequency histogram of peak RI duration (the longest duration RI at any masker, mean of three measurements). After each trial, RI testing resumed at 45 s (time-out limit) (data of C and D are from Roberts et al., 2007).

masking but induce less RI than their complements.

The RI functions shown in Figs. 2A, B are in qualitative agreement with the hypothesis that segregation of abnormal synchronous activity in a tinnitus network underlies RI. There is, however, considerable variability between participants in the

depth of RI and its duration, which, while it should not obscure significant main findings, needs to be understood. Some participants report near elimination of tinnitus for brief periods, and others only partial suppression. In the study of Roberts et al. (2007) 73% of participants reported some degree of RI, including 22% who described

elimination or near elimination of tinnitus following at least one of the maskers (see Fig. 2C). Peak durations however spanned a wide range, reaching the allowable limit of 45 s for at least one masker in 9 of 59 participants (15%, see Fig. 2D). While these results are in line with the literature, there are reports of RI lasting several minutes (Terry et al., 1983; Vernon and Meikle, 2003) or hours (Hazell and Wood, 1981). Some of this variability can likely be ascribed to the masking parameters loudness and spectral overlap described above, although functions relating RI depth to masker intensity appear to asymptote below +20 dB MML (Vernon, 1985; Roberts et al., 2007). Masker duration is also important. When maskers producing maximal RI at +10 dB MML were tested, Terry et al. (1983) found that RI duration increased linearly as a function of the logarithm of masker duration for durations between 10 s and 10 min. Thus very little RI was experienced for durations less than 10 s (cf. Tyler et al., 1984). Duration measured as full tinnitus recovery increased to ~100 s for maskers of 100 s duration, but to only 200 s for maskers ten times longer. On the other hand, ~43% of participants in the archive of Vernon and Meikle (2003) reported RI exceeding 2 min after 1 min of broadband noise (intensity unspecified). Four of 59 participants tested by Roberts et al. (2007) reported RI persisting 45 s (the maximum allowed before time-out) at all masker frequencies, suggesting that tinnitus was suppressed for the duration of RI testing (~1 h). Hazell and Wood (1981) reported that in a small percentage of their patients, 15 min of continuous masking gave RI lasting most of the day. To date, the factors that predict RI of long duration are not known. Standardization of methods would be helpful in charting tinnitus recovery functions more accurately and relating them to their determining conditions.

Although RI duration induced by current methods is typically brief, RI can be a source of relief for tinnitus sufferers who have experienced a sound that otherwise has known only a life of its own. Vernon and Meikle (2003) have described instances where patients broke into tears at their first experience of silent ears after years of unremitting noise. Hence there is much current interest

in optimizing RI for its possible clinical benefits. Following earlier studies by Feldman (1971), Terry et al. (1983) investigated whether refresher bursts of masking noise delivered during RI had a multiplicative effect on RI duration (they did not). Terry et al. (1983) also investigated in unilateral tinnitus cases whether maskers presented ipsilateral or contralateral to the tinnitus ear differed in their effectiveness. Only masking in the ipsilateral ear induced RI, implying convergence at some level in lemniscal projection pathways (75% of lemniscal fibers cross over above the level of the inferior colliculus). An alternative approach aims at engineering sounds that relate more closely to the participant's tinnitus. Commercial devices for tinnitus masking have begun to adopt this approach (<http://www.neuromonics.com>) although different methods of optimization are at present untested. Another approach explores how temporal and spectral variability may be exploited to enhance RI. In this respect it is noteworthy that tinnitus masking has been reported to be superior when noise stimuli are delivered independently to the two ears (dichotic stimulation) than when the same noise sound is presented to both ears (diotic stimulation; Johnson and Hughes, 1992). It is also important to assess whether continuous exposure to low intensity, high frequency background environmental sounds covering the region of hearing impairment can induce a lasting RI, particularly in new tinnitus cases. Noreña and Eggermont (2005, 2006) found that exposure to such sounds compared to low frequency sounds or to silence prevented hypersynchrony and cortical map reorganization that otherwise occurred in cats exposed to traumatic noise. This therapeutic effect appeared to be additional to changes in the auditory periphery, which partly restored normal hearing function (Noreña and Eggermont, 2005).

The duration of RI is of interest not only for clinical applications but also for understanding tinnitus. The perspective adopted for this chapter leads one to predict gradual recovery from tinnitus suppression, as synchronous networks resume their activity after masker offset. Recovery must reflect the time constants of neural processes that modulate the return of hypersynchrony (some candidates are discussed in the next section).

However, a practical limitation of RI for use in clinical applications relates to sound intensity level. For participants with deep hearing impairment, maskers presented at intensities needed to induce RI (+10 dB MML) may deliver sound pressures in excess of 100 dB to the ear. Continuous exposure to such sounds for extended lengths of time pose a risk of exacerbating peripheral hearing injury. Transcranial magnetic stimulation (TMS) may have an advantage in such cases, because its effects do not require the ear to reach the brain. TMS may induce some of its effects by mechanisms that are at work in RI. Because it can be directed to selected brain areas, TMS can also identify brain regions that form part of the tinnitus network.

Transcranial magnetic stimulation

TMS is a procedure through which a magnetic field is injected into the brain, inducing currents that cause cortical neurons within the field of rapidly changing magnetic flux to depolarize (see Chapters 34 and 35). Because this neural input occurs independently of synaptic events involved in ongoing network activity, it would be expected to disrupt the abnormal synchronous activity that is believed to underlie tinnitus, leading to its temporary suppression.

Both high frequency (10–20 Hz) and low frequency (1 Hz) magnetic stimulation delivered repetitively (rTMS) have been found to suppress tinnitus in a subset of cases, when applied to brain regions that are active in tinnitus. In a seminal study, Plewnia et al. (2003) applied trains of high-frequency rTMS (10 Hz, 3 s duration) to each of five cortical sites at 120% of motor threshold (MT, 100% equals the current intensity required to evoke finger movements). Eight of 14 (57%) tinnitus patients reported suppression of tinnitus ranging from partial to complete elimination for a period of time described as “transient” (one patient reported an increase in tinnitus). Tinnitus suppression was statistically enhanced when rTMS was delivered over left temporal and left temporal-parietal cortex compared to other regions. In a subsequent study (Plewnia et al., 2007), low

frequency rTMS (1 Hz) was navigated to a region of temporoparietal cortex that showed maximal activation determined by positron emission tomography (PET) imaging during prior lidocaine infusion for each participant, or to a control area in the lower occiput. Reduction of tinnitus was reported by six of eight participants, which lasted for 3–8 min and was larger than during sham stimulation. Tinnitus suppression was more robust for tinnitus cases of short duration (2–4 years) than for tinnitus of long standing (9–15 years), a relationship reported by De Ridder et al. (2005) as well (see Chapter 36).

Compared to RI that activates excitatory and inhibitory auditory pathways in a frequency selective fashion, the currents induced by rTMS in the targeted cortical structures are diffuse and non-specific. Nevertheless, similarities between RI and tinnitus suppression by rTMS suggest that disruption of abnormal synchronous neural activity may underlie suppression induced by both procedures. Suppression by rTMS persists for a variable range of durations, which is also true of RI. Suppression on the order of minutes found by Plewnia et al. (2007) do stand out compared to RI where reports of suppression lasting 15–45 s are more common. However, several investigators have reported RI lasting minutes and longer (Hazell and Wood, 1981; Terry et al., 1983; Vernon and Meikle, 2003). Like RI, tinnitus suppression by rTMS shows dose-dependent effects, increasing with the duration of stimulation (Plewnia et al., 2007) and with rTMS intensity (De Ridder et al., 2004). While direct comparisons between the results from RI and rTMS studies have not been published, rTMS studies concur that suppression of tinnitus by rTMS is consistently larger than suppression by sham stimulation alone (Eichhammer et al., 2003; Plewnia et al., 2003, 2007; Kleinjung et al., 2005; De Ridder et al., 2004, 2005). Thus suppression by rTMS is more than simple RI induced by sounds that are generated by the device used to generate magnetic signals. Another feature common to both types of tinnitus suppression is that in both cases tinnitus does eventually return.

Whether RI maskers can achieve suppressive effects equal to rTMS cannot be determined on the basis of published findings, but can be questioned

given the strong intracortical currents injected by rTMS. These currents may induce plastic changes in synaptic efficacy (Cooke and Bliss, 2006) that have been demonstrated for motor responses when low frequency rTMS is paired with median nerve stimulation in humans (Huang et al., 2005). However, while sham stimulation does not yield as much tinnitus suppression as rTMS, the acoustic properties of sham stimuli including their intensity and spectra are not likely to resemble the tinnitus sensation which may be required for optimal RI. It is noteworthy that suppression of tinnitus by rTMS is greater for early cases of tinnitus than for long standing ones (De Ridder et al., 2005; Plewnia et al., 2007). To be effective, therapies based on rTMS (Eichhammer et al., 2003; De Ridder et al., 2004, 2005; Kleinjung et al., 2005) or RI (Watanabe et al., 1997) may have to intervene before functional plastic changes lead to structural ones (Pons et al., 1991; Muhlau et al., 2006).

Future questions

Our understanding of the mechanisms of tinnitus and its suppression would profit greatly from the development and standardization of tools for measuring the psychoacoustic properties of tinnitus including its loudness, spectrum, and suppression by maskers (RI) or rTMS. Fortunately, one can see a degree convergence in the procedures that are being developed for assessment of tinnitus spectra and RI functions by different laboratories (Noreña et al., 2002; Henry et al., 2006; Roberts et al., 2006; Ward et al., 2007). Future studies may provide what has been lacking, which is a systematic database against which to evaluate procedures for optimizing RI and contrasting it with rTMS and other methods of intervention using common measures.

Abbreviations

CF	center frequency
MML	minimum masking level
MT	motor threshold
PET	positron emission tomography
RI	residual inhibition

rTMS	repetitive transcranial magnetic stimulation
SL	sensation level
SPL	sound pressure level
TMS	transcranial magnetic stimulation

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