Chapter 13
Neural Synchrony and Neural Plasticity in Tinnitus

Larry E. Roberts

Keypoints

1. Most individuals with chronic tinnitus have high-frequency hearing loss, induced by noise exposure, otological disease, or the aging process. Physiological evidence suggests that in such individuals, tinnitus is likely caused not by irritative processes that persist in the ear after cochlear injury, but by changes that occur in central auditory pathways when the ear is partly disconnected from the brain.
2. In animals, hearing loss induced by experimental noise trauma leads to a reorganization of tonotopic maps in the primary auditory cortex, such that frequencies near the edge of normal hearing come to be overrepresented at the expense of frequencies in the hearing loss region. Neurons show increased spontaneous firing rates in cortical and subcortical auditory structures, and in the auditory cortex, increased synchronous activity in the region of hearing impairment.
3. Evidence from physiological, psychoacoustic, and human brain imaging studies suggests that increased neural synchrony (temporally coupled neural activity) in the hearing loss region may be an important mechanism contributing to tinnitus. Tinnitus spectra and residual inhibition functions overlap the region of auditory threshold shift, consistent with this hypothesis.
4. Several forms of neural plasticity may contribute to changes in spontaneous firing rates and neural synchrony that develop after hearing loss. Because the tuning of auditory neurons can be modified by acoustic training procedures throughout the lifespan, it may be possible to reverse some of the neural changes underlying tinnitus.
5. For this goal to be achieved, it must be possible to modify auditory representations by acoustic training in individuals with tinnitus, and the neural modifications induced by training must intersect with the underlying tinnitus mechanisms. Auditory plasticity in normal hearing individuals and people with tinnitus requires further study.

Keywords Mechanism of tinnitus • Neural synchrony Cortical reorganization • Neural plasticity • Tinnitus spectrum • Residual inhibition

Abbreviations

HL	Hearing level
CF	Center frequency
RI	Residual inhibition
ASSR	Auditory steady-state response
AM	Amplitude modulation
EEG	Electroencephalogram
MEG	Magnetoencephalography

Introduction

Although our understanding of the mechanisms of tinnitus comes from many sources, two recent lines of research, in particular, have provided insight into the question of how the sensation of tinnitus is generated. The first line of research has shown that hearing loss induced by noise exposure in animal models leads to a reorganization of tonotopic maps in the primary auditory cortex, such that frequencies near the edge of nor-

L.E. Roberts (✉)
Department of Psychology, Neuroscience, and Behavior, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada L8S 4K1
e-mail: roberts@mcmaster.ca

A.R. Møller et al. (eds.), *Textbook of Tinnitus*,
DOI 10.1007/978-1-60761-145-5_13,

mal hearing come to be overrepresented at the expense of frequencies in the hearing loss region [1–3]. Because hearing loss is a putative cause of tinnitus, it was suggested that this overrepresentation, or changes in neuron response properties associated with it, may underlie tinnitus percepts [4, 5]. The second line of research demonstrated that neural representations for sound in the primary auditory cortex are not fixed after early development but can be modified over the lifespan by procedures such as deafferentation or auditory training that alter the organism's experience with sound [6, 7]. This phenomenon is called "neural plasticity" (see Chap. 12). These two lines of research have converged to ask whether neural plasticity may be involved in the generation of tinnitus, and if so, whether acoustic training procedures might be designed to reduce tinnitus or prevent its development when hearing loss occurs.

This chapter reviews evidence from animal models of hearing loss, human psychoacoustic studies, and brain imaging experiments that suggests that tinnitus is generated by abnormal synchronous (temporally coupled) neural activity that develops in the auditory cortex when central auditory structures are deafferented by cochlear pathology. It is useful to formulate a perspective on the neural basis of tinnitus, because treatment procedures designed to reduce tinnitus must interact with this mechanism if tinnitus is to be altered. I also briefly review evidence for neural plasticity in the auditory system and ask whether the rules that describe auditory plasticity in normal hearing individuals apply as well to individuals with tinnitus. This cannot be assumed, because people with tinnitus experience not only some degree of hearing loss but also an auditory sensation that may interfere with the remodeling process. In a later chapter (Chap. 72), we discuss current approaches to sensory training from the perspective of research on these two questions.

The Neural Synchrony Model of Tinnitus

It is widely recognized that most individuals who have tinnitus also have sensorineural hearing loss caused by injury, otological disease, noise exposure, or the aging process. Even when auditory thresholds are in the normal range (≤25 dB HL), tinnitus sufferers often have evidence for restricted cochlear dead regions [8] or show threshold elevations in the audiogram on the order of 10 dB in the tinnitus frequency range compared to age-matched controls [9] suggesting that some degree of hearing impairment is present. In most cases, however, it is doubtful that chronic tinnitus is generated by irritative processes that persist in the cochlea damaged by hearing loss. Damage to the cochlea caused by lesioning or noise exposure typically leads not to an increase in spontaneous activity in auditory nerve fibers, which might be expected from such processes, but rather to a decrease in auditory nerve activity, pointing to a reduction of input to central auditory structures [5]. These observations suggest that the sensation of tinnitus in the majority of individuals is generated not in the ear but by changes that have occurred in central auditory pathways when the brain has been partly disconnected from the ear by hearing loss (deprivation of input, see Chap. 11). Consistent with this understanding, most individuals who had tinnitus before removal of a vestibular schwannoma with sectioning of the auditory nerve also had tinnitus after the operation. Tinnitus is also a predictable outcome after sectioning of the auditory nerve in individuals who did not have tinnitus before their operations for vestibular schwannomas or other conditions [10] (see Chap. 39).

Animal models of hearing loss have begun to give a picture of the changes that occur in central auditory pathways following auditory deafferentation. The understanding supported by these studies is summarized in Fig. 13.1a (from [5]), which depicts the primary auditory cortex of a cat that has sustained a high-frequency hearing loss induced by noise trauma. The left side of the figure shows the undamaged region, including thalamocortical afferents synapsing on input neurons followed by feed-forward (i) and lateral (ii) inhibition after one synaptic delay. Feed-forward inhibition is functionally dissociable from lateral inhibition [11] and quenches target neurons after their depolarization, which may protect thalamocortical synapses from down-regulation (and preserve their cochleotopic tuning) when the neurons are driven by uncorrelated input from horizontal fibers in the tonotopic map. Animal studies have shown that when a region of the tonotopic map is disconnected from the ear by cochlear damage (right side of Fig. 13.1a), auditory neurons in the affected region begin to respond preferentially to input conveyed by horizontal fibers as their thalamocortical input is impaired or lost. As a consequence, the cortical tonotopic map "reorganizes" when the affected neurons begin to express the tuning preference of their neighbors, leading to an overrepresentation of edge frequencies in the tonotopic gradient

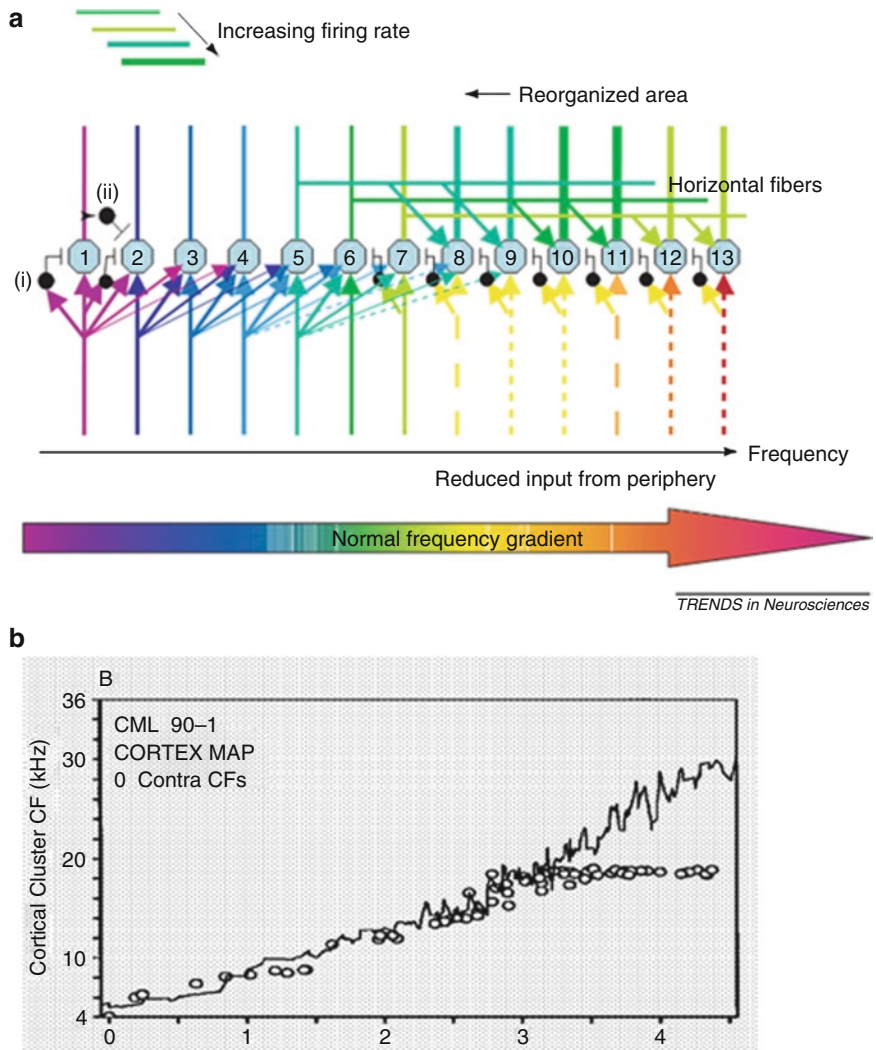

Fig. 13.1 Central effects of hearing loss in the cat. (**a**) Tonotopic map of primary auditory cortex depicting intact thalamocortical input to neurons in a low-frequency region (*left*) and diminished thalamocortical input to a high-frequency region affected by hearing loss (*right*). Neurons in the damaged region begin to express the tuning of their unaffected neighbors via horizontal fibers when their thalamocortical input is lost. Feed-forward (i) and lateral (ii) inhibition is depicted in the intact low-frequency region. Graphic from Eggermont and Roberts [5] (with permission). (**b**) Tonotopic representation in a normal cat (*solid line*) and in a cat with high-frequency hearing loss induced by noise trauma (*open circles*). The abscissa is transcortical distance from a reference point near the apex of the basilar membrane. An overrepresentation of edge frequencies is seen in the hearing impaired cat. Data from Rajan and Irvine [2] (with permission)

(an example is shown in Fig. 13.1b, from [2]). It has been proposed that this overrepresentation of edge frequencies may correspond to the tinnitus percept, which was thought to be confined to the edge of normal hearing. However, this is doubtful not only because of evidence to be presented below but also because it is not obvious how the activity of the affected neurons would be heard in terms other than their original cochleotopic tuning.

Other changes in the response properties of auditory neurons documented by animal studies of hearing loss are more likely to contribute to the tinnitus percept. One such change is that neurons in cortical and subcortical auditory structures (but not auditory nerve fibers) increase their spontaneous firing rates as input from the ear is diminished. This effect could reflect an adaptive rescaling of neuron input/output functions by homeostatic plasticity [12] when afferent input to central auditory structures is impaired, or inhibitory deficits consequent on deafferentation, or most probably both factors. At the level of the cortex, increased spontaneous firing has been observed to occur across the tonotopic map, including tonotopic regions that are affected by hearing loss (typically high-frequency regions) as well as regions that are less affected (typically low-frequency regions). Increased spontaneous neural activity is likely to be an important factor in the development of tinnitus, although it has been suggested by several investigators that uncorrelated neural activity may not be sufficient to generate a coherent sound percept. A second change that may occur is an increase in the *temporally synchronous activity* of a population of

neurons, which is expressed as an increase in cross-correlated neural firing when compared to control animals [13]. This change is more closely confined to the hearing loss region and appears to reflect synchronous network activity that is forged over lateral connections by neuroplastic mechanisms operating in this region [14], possibly because the quenching effect of feed-forward inhibition is lost. It should be noted that although thalamocortical input to the affected tonotopic region is affected by cochlear injury, the output of the synchronously active neurons remains intact. The neural synchrony model of tinnitus suggests that this output (which is conveyed to the thalamus by nerve fibers more numerous than the forward path) is processed by other brain regions and generates the tinnitus percept (see Chap. 12).

This picture of the neural mechanism of tinnitus has implications for the psychoacoustic properties of tinnitus. One implication is that when participants in a study are asked to rate sounds of different frequencies for similarly to their tinnitus, ratings should not be restricted to the region of the audiometric edge (although contrast enhancement at the edge may contribute [15]), but should instead span the region of hearing loss, increasing in proportion to the depth of hearing impairment. This result should be obtained for individuals with tonal tinnitus as well as tinnitus with wider bandwidths because audiometric function is similar among these tinnitus types [16]. Independent studies by laboratories in France [17], Canada [9], and New Zealand [18] have confirmed this prediction (see Fig. 13.2). A further implication is that post-masking suppression of tinnitus by band-limited noise maskers (called "residual inhibition," or RI, in the tinnitus literature) should increase proportionately as the center frequency (CF) of the masking sound enters the tinnitus frequency region. This is because these masking sounds (which are presented at intensity levels exceeding the hearing threshold and the tinnitus sound) should reinject feed-forward inhibition into the affected regions of the cortical tonotopic map, temporarily disrupting the synchronous activity underlying tinnitus and weakening the tinnitus percept. This prediction has also been confirmed (Fig. 13.2; from [9]). It should be noted that RI does not appear to be caused by habituation of the affected neurons to frequencies contained in the masker. On the contrary, these neurons are actually more easily driven by amplitude-modulated sounds presented to the tinnitus frequency region during RI than during tinnitus (see Fig. 13.3, from [19, 20]),

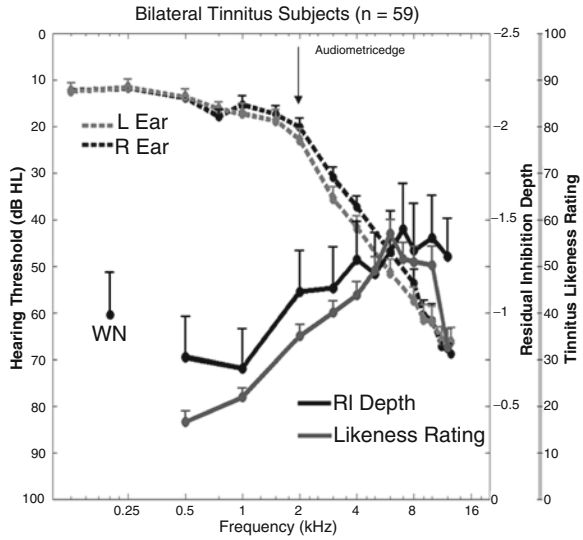

Fig. 13.2 Relation of the tinnitus spectrum (likeness rating) and the residual inhibition function (RI depth) to hearing loss in bilateral tinnitus ($n = 59$ cases). To obtain the tinnitus spectrum, the participants rated the pitch of each of 11 sounds for its likeness to their tinnitus. A rating exceeding 40 corresponded to a sound that was beginning to resemble the tinnitus. Likeness ratings diminished at 12 kHz, probably because these sounds were not well matched for loudness owing to the depth of hearing loss at this frequency. RI was measured following presentation of band-limited noise maskers differing in center frequency (CF) (band pass ±15% of CF). A rating of −5 corresponded to "tinnitus gone." From Roberts et al. [9]

possibly because their capture by synchronous network activity underlying tinnitus has been disrupted. Rapid rescaling of subcortical auditory input to the frequencies contained in the masker could also contribute to this effect [21]. Other brain imaging results that support the neural synchrony model include evidence for (1) a degraded frequency (tonotopic) representation above ~2 kHz in the region of primary auditory cortex in individuals with tinnitus compared to controls [22] (this reorganization resembling that seen in animal models of hearing loss) and (2) increased spontaneous oscillatory brain activity in individuals with tinnitus [23]. The latter effect tracks the laterality of the tinnitus percept and may reflect augmented network underlying this condition.

As described here, the neural synchrony model accords an important role to the primary auditory cortex in the generation of tinnitus percepts. However, neuron response properties, including increased spontaneous activity and map reorganization, are also altered by hearing loss in subcortical auditory structures [24, 25], although neural synchrony in these regions has not yet

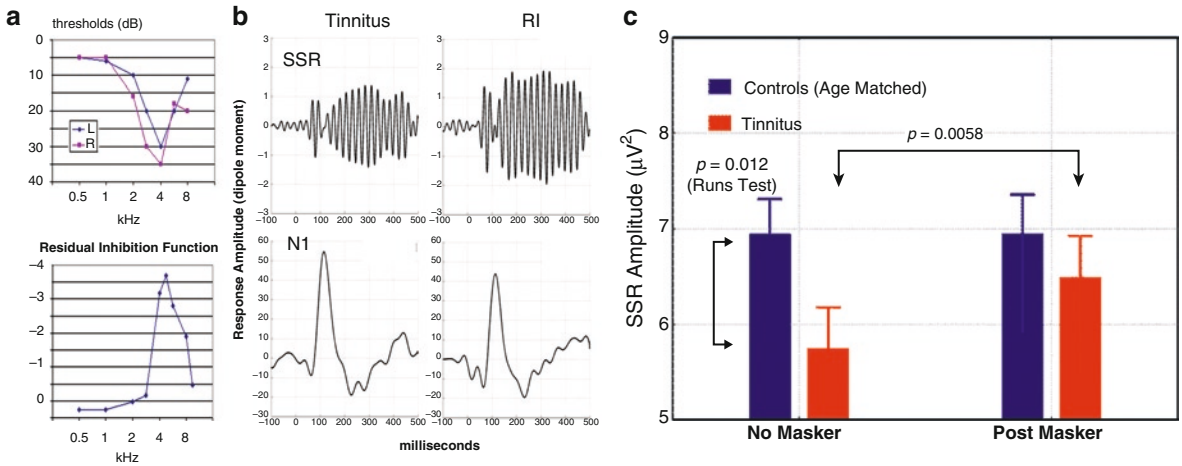

Fig. 13.3 Electromagnetic correlates of residual inhibition (RI). (**a**) Audiogram and corresponding RI function for a single individual with hearing loss around 4 kHz. A band-limited masker (±15% of CF) centered at 4 kHz in the notch region corresponded to the tinnitus sensation and gave good RI. This masker was used to induce RI in this individual in (**b**). (**b**) The brain response evoked by 4 kHz 40-Hz AM probe tones (duration 0.5 s) delivered after 30 s of masking when the person was experiencing RI (*top right* panel) or tinnitus (*top left* panel, no preceding masker). This brain response (called the 40-Hz auditory steady-state response or ASSR, measured here by magnetoencephaolography [MEG]) localizes tonotopically to the region of the primary auditory cortex (see Fig. 13.4a) and gives a picture of neural activity occurring in this region (the 4-kHz region in this recording). The ASSR is larger in RI compared to tinnitus (Roberts, Weisz, Wienbruch and Bosnyak, 2001, unpublished data). Unlike the ASSR, the N1-evoked response (localizing to secondary auditory cortex) adapted after masking (*lower* panel). (**c**) Subsequent research using electroencephalographic (EEG) recordings [19] found that enhancement of the ASSR after masking is specific to individuals with tinnitus ($n=14$, $p=0.0058$) and is not seen in age-matched controls ($n=14$, $p=0.99$). Without masking ASSR amplitude is reduced in tinnitus ($p=0.012$) returning toward normal levels after masking. Unlike the ASSR, the N1 adapted after masking ($p=0.007$, results not shown; cf. (**b**) *lower*). It should be noted that in (**c**), the probe stimulus (5 kHz) was matched for intensity to a 1-kHz 65-dB SL tone in the region of normal hearing (a procedure that controls for loudness recruitment in individuals with tinnitus)

been studied. Changes occurring in subcortical structures could be projected to the primary cortex and determine some of the effects seen there, as well as some distinct properties of tinnitus including its modulation by somatosensory inputs in many patients [26, 27]. Alternatively, the changes seen in subcortical nuclei could be sculpted by returning output from the auditory cortex, which may recruit a brain network supporting tinnitus percepts. Functional brain imaging studies have implicated several brain areas in tinnitus [28–31], including frontal and limbic areas that may subserve, respectively, the attentional and emotional aspects of tinnitus described by Jastreboff [32] in a comprehensive model of tinnitus published more than a decade ago.

These lines of evidence pointing to a role for neural synchrony in tinnitus have implications for how sensory training might best be conducted (see Chap. 72). The neural synchrony hypothesis implies that the goal of training should be to disrupt the synchronous neural activity believed to underlie tinnitus percepts. When significant residual hearing is present (delivered by surviving on-target thalamocortical projections or thalamocortical radiations), this goal could be attempted by training suprathreshold sounds in the tinnitus frequency region. These sounds may reinject feed-forward inhibition into the tonotopic map and/or rescale neuron transfer functions in subcortical structures to represent the trained frequencies, thereby disrupting neural synchrony and strengthening thalamocortical synapses previously down-regulated by abnormal synchronous network behavior. Maskers that induce RI may operate in a similar fashion, although repeated induction of RI does not appear to convey a lasting benefit [33], at least in the absence of active auditory training. Alternatively, acoustic training in the region of normal hearing could convey uncorrelated inputs into the affected map region via lateral connections, disrupting neural synchrony or suppressing it by lateral inhibition. Before considering research on various approaches (see Chap. 72), it is

useful to briefly consider what is known about how auditory remodeling works in individuals with normal hearing, and how it may contribute to the development of tinnitus.

Neuroplastic Remodeling in Tinnitus

A feature common to the neural synchrony model and the wider framework of Jastreboff [32] is a role for neural plasticity in the generation of tinnitus percepts. Although direct evidence is lacking and not easily procured, there are compelling reasons to propose a role for such mechanisms in tinnitus. Spike-timing-dependent plasticity [34] appears to be general property of cortical neurons, and this mechanism, acting in concert with increased spontaneous firing rates consequent on inhibitory deficits and homeostatic plasticity [12], would be expected to facilitate the formation of synchronous networks in regions of the primary auditory cortex affected by hearing loss. Synchronous activity appears to be expressed over cortical distances that exceed those expected from thalamocortical radiations, which implicates temporal coincidence mediated by horizontal fibers as a driving mechanism [14]. From the limited data available, it appears that cross-correlated activity develops within hours of hearing loss and grows over time [13], although the limit of this growth is not known. Neural plasticity has the potential to explain the variability that is seen in tinnitus percepts among affected individuals, with the addition of no new principles.

In the last 15 years, much has been learned about how neural plasticity remodels auditory representations in normal hearing animals. Experience with sound has a profound effect on tonotopic organization and the tuning properties of auditory neurons in the developing brain [35, 36] and after maturity as well [37, 38]. Neural modeling during development appears to be driven largely by the spectrotemporal statistics of the acoustic input, such that neural representations become tuned to the sounds present in the animal's environment. After maturity, top–down mechanisms begin to play an additional role, preferentially gating neural plasticity in the auditory cortex for sounds that are important for behavioral goals [6, 39]. Several response properties are affected by acoustic training in mature organisms, including shifts in the tuning preference of auditory neurons toward the trained stimuli [6, 7], spike rates induced by these stimuli [40, 41], tuning bandwidth [42, 43], response latency in post-stimulus time histograms [41, 42], and tonotopic map expansions for the trained sounds [44]. However, passive immersion in a distinctive acoustic environment can still have profound effects on neuron response properties and neural organization in the adult brain [38], which may reflect, at least in part, changes in subcortical auditory nuclei that are driven unselectively by stimulus input. These broad principles derived from animal studies appear to be applicable to humans as well [45–48], although much remains to be discovered about the specific rules that guide remodeling in both domains and the mechanisms that underlie them.

Whether these principles apply as well to individuals with tinnitus is less well established. A brain response that is relevant to this question is the stimulus-driven "auditory steady-state response" (ASSR, shown earlier in Fig. 13.3b). This response is evoked in the electroencephalogram by sounds that are amplitude modulated (AM) near 40 Hz, localizes tonotopically to cortical sources in the region of primary auditory cortex, and gives a picture of changes occurring in or projecting to this region during auditory training (see Fig. 13.4a). In individuals with normal hearing, acoustic training to detect single pulses of enhanced amplitude in a 40-Hz AM 2 kHz sound of 1-s duration has been found to modify temporal population activity expressed in the primary auditory cortex. This effect is expressed as an advance in the phase of the ASSR, which reflects a reduction in the time delay between the 40-Hz response and stimulus waveforms (see Fig. 13.4b). The phase advance is a robust phenomenon that consolidates after 24–72 h, increases with continued training, relates perceptual performance, and does not require explicit behavioral training for its appearance [48]. ASSR amplitude is also increased by auditory training, implying more neurons depolarizing synchronously to represent the trained sound [48]. However, the training effect on ASSR amplitude lags that on phase, does not correlate well with perception, and is not observed when multiple sound frequencies are presented during training [49].

These results are from individuals with normal hearing who were studied in order to discover rules that guide remodeling in the human brain. What happens when individuals with tinnitus are trained? The answer to this question is presently not well established.

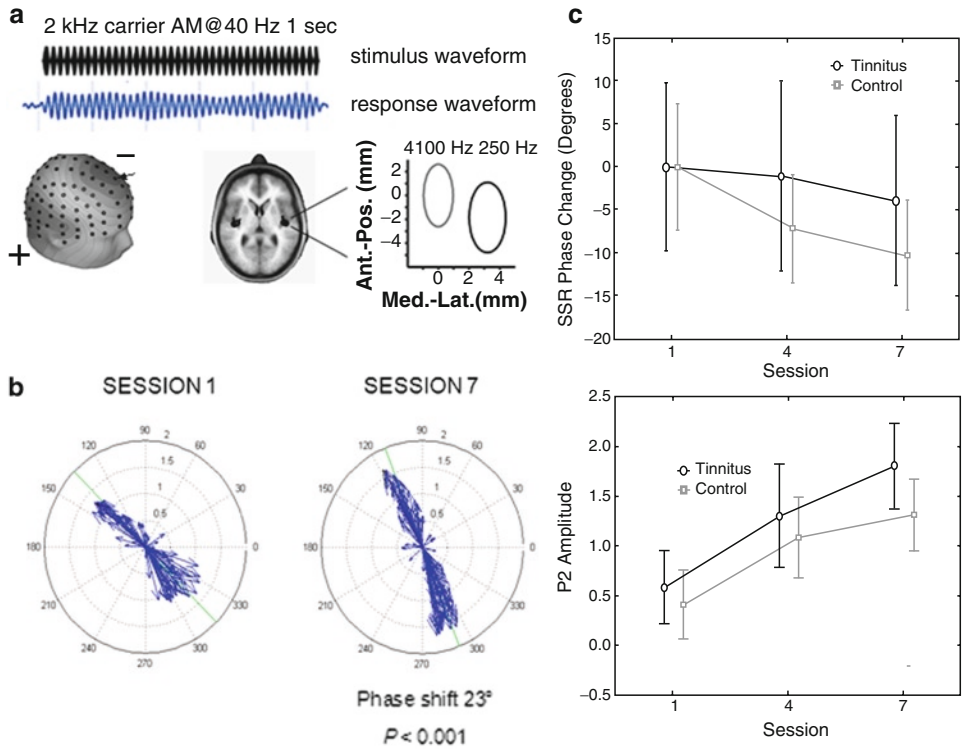

Fig. 13.4 Effects of auditory training on auditory-evoked potentials. (**a**) Response evoked by a 2-kHz tone amplitude modulated at 40 Hz (ASSR). The stimulus waveform and the response waveform recorded at electrode Cz are shown, together with the bipolar scalp topography (128 sensors). In inverse modeling, the cortical generators for an ASSR evoked by a carrier frequency of 4,100 Hz localized medial to those for an ASSR evoked by a carrier frequency of 250 Hz, in the region of primary auditory cortex. (**b**) Compass plots showing the amplitude (vector length) and phase (vector angle) of the ASSR at each of 128 sensors, before (*left* panel) and after (*right* panel) seven sessions of acoustic training. Individuals with normal hearing who did not have tinnitus ($n=9$) were trained to detect a single 40-Hz AM pulse of enhanced amplitude in a stimulus of 1-s duration (carrier frequency 2 kHz). A phase shift of 23° was observed ($p<0.001$, advance of the response waveform toward the stimulus waveform), but the amplitude enhancement did not reach significance. (**c**) *Upper* panel: The phase shift (over seven sessions of training) did not reach significance in the participants who had tinnitus ($p=0.44$) but was present in their age-matched controls ($p=0.006$). In both groups, the carrier frequency was 5 kHz (in the tinnitus frequency region of the individuals with tinnitus). Negative values indicate a shift of ASSR phase toward the stimulus waveform. *Lower* panel: The P2 transient-evoked response (latency ~180 ms) increased with training in both groups, suggesting that secondary auditory areas are remodeled normally in individuals who have tinnitus (cf. [49])

In a preliminary study [20], we found that while a group of control participants age matched to a tinnitus group showed the expected phase advance when trained on a 5-kHz 40-Hz AM sound ($n=11, p=0.006$), only two of eight participants with tinnitus did so, resulting in a nonsignificant group effect overall ($p=0.44$, see Fig. 13.4c, upper panel). It is possible that synchronous neural activity underlying tinnitus may have obstructed or reset training effects in the primary auditory cortex of the participants who had tinnitus (5 kHz was chosen for study because it is in the tinnitus frequency range). However, remodeling of secondary auditory cortical areas appeared to be normal in those who had tinnitus. The P2 (latency ~180 ms) auditory-evoked potential, which localizes to cortical sources in this region and is known to be highly plastic [49], showed a normal enhancement in both groups after auditory training (Fig. 13.4c, lower panel). Several other long latency (>100 ms) auditory evoked potentials localizing to secondary cortex or beyond are known to increase with acoustic training in the laboratory in normal hearing individuals (in order of increasing latency: N1 [50], N1c [49], Ta [51], P2 [47–49, 52], N2 [53], MMN [54]), or to be enhanced for musical sounds in trained musicians (N1c [55], P2 [55–57], anterior frontotemporal sources [58], induced frontotemporal

gamma oscillations [59]). These evoked potentials reveal a distributed neural system for auditory (and perhaps other) learning in the human brain that may overlap with neural structures involved in tinnitus. However, the behavior of the responses during acoustic training in tinnitus is unknown.

Most studies of human auditory learning have employed active training procedures in which adults attended to and processed the sound stimuli while making discriminative decisions. However, there is growing evidence that remodeling of equal magnitude occurs when the sounds are presented as background cues, even when individuals are engaged in watching a subtitled film and have no knowledge of auditory task structure [47, 48, 60]. The ASSR and P2 effects described above were remodeled equally by active training, compared to when the auditory stimuli were presented passively as background sounds to individuals with normal hearing [48]. Animals housed in distinctive sound environments with no processing demands also display significant auditory remodeling, even in adulthood [37, 38]. A working hypothesis based on animal data is that these effects are produced by a rescaling of neuron input/output transfer functions in subcortical auditory structures by fundamental mechanisms that are stimulus driven and expressed in the auditory cortex throughout the lifespan. Explicit auditory training may produce additional changes mediated by attention, but this more mature mechanism is not a prerequisite for remodeling. The fact that auditory representations are modified by passive as well as active exposure could be good news for tinnitus, to the extent that arduous training regimens may be avoided.

Overview and Conclusion

Animal research in the last two decades has established that neural plasticity is a fundamental property of neurons in the auditory system. Evidence has also accumulated that hearing loss leads to changes in central auditory pathways, including tonotopic map reorganization and increased neuron firing rates in primary auditory cortex that may be forged by neuroplastic mechanisms into abnormal synchronous network behavior that generates tinnitus. In this Chapter, I have summarized physiological, psychoacoustic, and brain imaging evidence pointing to a role for neural synchrony in tinnitus.

Also reviewed were results from animal research indicating that cortical representations for sound in the primary auditory cortex are not fixed after early development as was once believed, but can be modified by auditory training well into adulthood. The findings have spawned renewed research into the question of whether tinnitus can be reduced or eliminated by acoustic training designed to normalize aberrant auditory neural representations. For this goal to be achieved, it must be possible to modify auditory representations by acoustic training in individuals with tinnitus, and the neural modifications induced by training must intersect with tinnitus mechanisms. Preliminary research suggests that areas of secondary auditory cortex remodel normally in individuals with tinnitus compared to normal controls, although whether this is true of the primary auditory cortex requires further study.

Acknowledgments The research of the author reported herein was supported by grants from the Canadian Institutes for Health Research, the Natural Sciences and Engineering Research Council of Canada, the American Tinnitus Association, and the Tinnitus Research Initiative. I thank my colleague Daniel Bosnyak for his role and Phillip Gander, Victoria Mosher, Graeme Moffat, and David Thompson for their contributions.

References

1. Robertson D, DRF Irvine (1989) Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. J. Comp. Neurol. 282:456–461.
2. Rajan R, DRF Irvine (1998) Neuronal responses across cortical field A1 in plasticity induced by peripheral auditory organ damage. Audiol. Neuro Otol. 3:123–144.
3. Noreña AJ, M Tomita, JJ Eggermont (2003) Neural changes in cat auditory cortex after a transient pure-tone trauma. J. Neurophysiol. 90:2387–2401.
4. Rauschecker JP (1999) Auditory cortical plasticity: a comparison with other sensory systems. Trends Neurosci. 22:74–80.
5. Eggermont JJ, LE Roberts (2004) The neuroscience of tinnitus. Trends Neurosci. 27:676–682.
6. Fritz J, M Elhilali, S Shamma (2005) Active listening: task-dependent plasticity of spectrotemporal receptive fields in primary auditory cortex. Hear. Res. 206:159–176.
7. Weinberger NM (2007) Auditory associative memory and representational plasticity in the primary auditory cortex. Hear. Res. 229:54–68.
8. Weisz N, T Hartmann, K Dohrmann et al (2006) High-frequency tinnitus without hearing loss does not mean absence of deafferentation. Hear. Res. 222:108–114.

9. Roberts LE, G Moffat, M Baumann et al (2008) Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. J. Assoc. Res. Otolaryngol. 9:417–435.
10. House JW, DE Brackman (1981) Tinnitus: surgical treatment. Ciba Found. Symp. 85:204–216.
11. Rajan R (2001) Plasticity of excitation and inhibition in the receptive field of primary auditory cortical neurons after limited receptor organ damage. Cereb. Cortex. 11:171–182.
12. Turrigiano GG, SB Nelson (2004) Homeostatic plasticity in the developing nervous system. Nat. Rev. Neurosci. 5:97–107.
13. Noreña AJ, JJ Eggermont (2003) Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. Hear. Res. 183:137–153.
14. Eggermont JJ (2007) Correlated neural activity as the driving force for functional changes in auditory cortex. Hear. Res. 229:69–80.
15. Llinás R, FJ Urbano, E Leznik et al (2005) Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci. 28:325–333.
16. Roberts LE, G Moffat, DJ Bosnyak (2006) Residual inhibition functions in relation to tinnitus spectra and auditory threshold shift. Acta Otolaryngol. Suppl. 556:27–33.
17. Noreña A, C Micheyl, S Chéry-Croze, L Collet (2002) Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus. Audiol. Neurootol. 7:358–369.
18. Kay F (2008) Towards improving the assessment of tinnitus pitch. Section of Audiology, Faculty of Medical and Health Sciences, University of Auckland.
19. Bosnyak DJ, PE Gander, LE Roberts (2008) The 40-Hz auditory steady-state response in tinnitus tracks age-related deficits in intracortical inhibition but does not follow the tinnitus percept. Annual Meeting of the Society for Neuroscience 2008. Washington: Society of Neuroscience 2008 Planner 850.13.
20. Roberts LE, DJ Bosnyak (2010) Neural synchrony and neural plasticity in tinnitus. In: Searchfield GD, Goodey R Editors. Proceedings of Tinnitus Discovery: Asia-Pacific Tinnitus Symposium. N Z Med J. 123:39–50.
21. Dean I, NS Harper, D McAlpine (2005) Neural population coding of sound level adapts to stimulus statistics. Nat. Neurosci. 8:1684–1689.
22. Wienbruch C, I Paul, N Weisz et al (2006) Frequency organization of the 40-Hz auditory steady-state response in normal hearing and in tinnitus. Neuroimage. 33:180–194.
23. Weisz N, S Muller, W Schlee et al (2007) The neural code of auditory phantom perception. J. Neurosci. 27:1479–1484.
24. Finlayson PG, JA Kaltenbach (2009) Alterations in the spontaneous discharge patterns of single units in the dorsal cochlear nucleus following intense sound exposure. Hear. Res. doi:10.1016.
25. Zeng C, N Nannapaneni, J Zhou et al (2009) Cochlear damage causes changes in the distribution of vesicular glutamate transporters associated with auditory and nonauditory inputs to the cochlear nucleus. J. Neurosci. 29:4210–4217.
26. Cacace AT (2003) Expanding the biological basis of tinnitus: crossmodal origins and the role of neuroplasticity. Hear. Res. 175:112–132.
27. Shore SE, S Koehler, M Oldakowski, LF Hughes, S Syed (2008) Dorsal cochlear nucleus responses to somatosensory stimulation are enhanced after noise-induced hearing loss. Eur. J. Neurosci. 27:155–168.
28. Lockwood AH, MA Wack, RF Burkard et al (2001) The functional anatomy of gaze-evoked tinnitus and sustained lateral gaze. Neurology. 56:472–480.
29. Mühlau M, JP Rauschecker, E Oestreicher et al (2006) Structural brain changes in tinnitus. Cereb. Cortex. 16:1283–1288.
30. Lanting CP, E de Kleine, P van Dijk (2009) Neural activity underlying tinnitus generation: Results from PET and fMRI. Hear. Res. 255:1–13.
31. Schlee W, T Hartmann, B Langguth et al (2009) Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neurosci. doi:10.1186/1471-2202-10-11.
32. Jastreboff PJ (1995) Tinnitus as a phantom perception: Theories and clinical applications. In: Vernon J, Moeller AR, editors. Mechanisms of Tinnitus Boston, MA: Allyn and Bacon, pp 73–94.
33. Terry AMP, DM Jones, BR Davis, R Slater (1983) Parametric studies of tinnitus masking and residual inhibition. Br. J. Audiol. 17:245–256.
34. Markram H, J Lübke, M Frotscher et al (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science. 275:213–215.
35. Zhang LI, S Bao, MM Merzenich (2001) Persistent and specific influences of early acoustic environments on primary auditory cortex. Nat. Neurosci. 4:1123–1130.
36. de Villers-Sidani E, KL Simpson, YF Lu et al (2008) Manipulating critical period closure across different sectors of the primary auditory cortex. Nat. Neurosci. 11:957–965.
37. Stanton SG, RV Harrison (1996) Abnormal cochleotopic organization in the auditory cortex of cats reared in a frequency augmented environment. Aud. Neurosci. 2:97–107.
38. Pienkowski M, JJ Eggermont (2009) Long-term, partially-reversible reorganization of frequency tuning in mature cat primary auditory cortex can be induced by passive exposure to moderate-level sounds. Hear. Res. doi:10.1026/j.hearres 2009.07.011.
39. Weinberger NM (2007) Associative representational plasticity in the auditory cortex: a synthesis of two disciplines. Learn. Mem. 14:1–16.
40. Blake DT, F Strata, AK Churchland, MM Merzenich (2002) Neural correlates of instrumental learning in primary auditory cortex. Proc. Natl. Acad. Sci. USA. 99:10114–10119.
41. Kilgard MP, MM Merzenich (2002) Order-sensitive plasticity in adult primary auditory cortex. Proc. Natl. Acad. Sci. USA. 99:3205–3209.
42. Brown M, DR Irvine, VN Park (2004) Perceptual learning on an auditory frequency discrimination task by cats: association with changes in primary auditory cortex. Cereb. Cortex. 14:952–965.
43. Kilgard MP, PK Pandya, J Vazquez, A Gehi, CE Schreiner, MM Merzenich (2001) Sensory input directs spatial and temporal plasticity in primary auditory cortex. J. Neurophysiol. 86:326–338.
44. Recanzone GH, CE Schreiner, MM Merzenich (1993) Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J. Neurosci. 13:87–103.
45. Kuhl PK (2004) Early language acquisition: cracking the speech code. Nat. Rev. 5:831–843.
46. Alain C, JS Snyder, Y He et al (2007) Changes in auditory cortex parallel rapid perceptual learning. Cereb. Cortex. 17:1074–1084.
47. Sheehan KA, GM McArthur, DV Bishop (2005) Is discrimination training necessary to cause changes in the P2 auditory

event-related brain potential to speech sounds? Brain Res. Cogn. Brain Res. 25:547–553.
48. Gander PE, DJ Bosnyak, LE Roberts (2010) Acoustic experience but not attention modifies neural population phase expressed in human primary auditory cortex. Hear. Res. do1:10.1016 (on-line ahead of print).
49. Bosnyak DJ, RA Eaton, LE Roberts (2004) Distributed auditory cortical representations are modified by training at pitch discrimination with 40-Hz amplitude modulated tones. Cereb. Cortex. 14:1088–l099.
50. Okamoto H, H Stracke, O Thiede, C Pantev (2009) Listening to tailor-made notched music reduces tinnitus loudness and tinnitus-related auditory cortex activity. Proc. Natl. Acad. Sci. USA doi:10.1073/pnas.0911268107.
51. Alain C, JS Snyder, Y He, KS Reinke (2007) Changes in auditory cortex parallel rapid perceptual learning. Cereb. Cortex. 17:1074–1084.
52. Tremblay K, N Kraus, T McGee, C Ponton, B Otis (2001) Central auditory plasticity: changes in the N1-P2 complex after speech-sound training. Ear. Hear. 22:79–90.
53. Fujioka T, B Ross, R Kakigi, C Pantev, LJ Trainor (2006) One year of musical training affects development of auditory cortical-evoked fields in young children. Brain. 129:2593–608.
54. Menning H, LE Roberts, C Pantev (2000) Plastic changes in the auditory cortex induced by intensive frequency discrimination training. Neuroreport. 11:817–822.
55. Shahin A, DJ Bosnyak, LJ Trainor, LE Roberts (2003) Enhancement of neuroplastic P2 and N1c auditory evoked potentials in musicians. J. Neurosci. 23:5545–5552.
56. Shahin A, LE Roberts, LJ Trainor (2004) Enhancement of auditory cortical development by musical experience in children. Neuroreport. 15:1917–1921.
57. Kuriki S, S Kanda, Y Hirata (2006) Effects of musical experience on different components of MEG responses elicited by sequential piano-tones and chords. J. Neurosci. 26:4046–4053.
58. Shahin AJ, LE Roberts, C Pantev, M Aziz, TW Picton (2007) Enhanced anterior-temporal processing for complex tones in musicians. Clin. Neurophysiol. 118:209–220.
59. Shahin AJ, LE Roberts, W Chau, LJ Trainor, LM Miller (2008) Music training leads to the development of timbre-specific gamma band activity. Neuroimage. 41:113–122.
60. Ross B, K Tremblay (2009) Stimulus experience modifies auditory neuromagnetic responses in young and older listeners. Hear. Res. 248:48–59.