Supplement

Role of Auditory Cortex in Noise- and Drug-Induced Tinnitus

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Purpose: To elucidate the role of auditory cortex in tinnitus.
Method: Neurophysiological findings in cat auditory cortex following noise trauma or the application of salicylate and quinine, all expected to induce tinnitus, were reviewed. Those findings were interpreted in the context of what is expected from studies in humans, specifically in the brains of people with tinnitus.
Results: Tinnitus is an auditory percept to which several central structures in the auditory system may contribute. Because the central auditory system has both feed-forward connections and feedback connections, it can be described as a set of nested loops. Once these loops become activated in a pathological fashion, as they may be in tinnitus, it becomes hard to assign importance to each contributing structure. Strongly interconnected networks, that is, neural assemblies, may be determining the quality of the tinnitus percept.
Conclusion: It is unlikely that tinnitus is the expression of a set of independently firing neurons, and more likely that it is the result of a pathologically increased synchrony between sets of neurons. There is clear evidence for this from both evoked potentials and from neuron-pair synchrony measures.

Key Words: tinnitus, cortex, animal model

Typically, tinnitus is quantified through questionnaires (Newman & Sandridge, 2004). Assessing a tinnitus patient in this way allows tracking treatment effects and is a strong basis for correlating the annoyance factor with psychoacoustic aspects of tinnitus. Psychoacoustic measurements can provide important properties of tinnitus such as its spectrum and loudness and what sounds can suppress it, even after it is turned off (at least for a short period; residual inhibition). One of the interesting aspects is that the tinnitus spectrum reflects the frequency region and the amount of hearing loss (Noreña, Micheyl, Chéry-Croze, & Collet, 2002). In addition, the best sound to provide residual inhibition also has these spectral properties (Eggermont & Roberts, 2004). In cases where tinnitus is present and no hearing loss is measured in the audiometric frequencies, there likely is a loss above 8 kHz, or there could be dead regions not detected by standard audiometry (Weisz, Hartmann, Dohrmann, Schlee, & Norena, 2006), or the tinnitus may be caused by somatic trauma.

However, the basis for a further understanding of tinnitus has to be objective measurements in humans experiencing it. These objective measurements should in principle suggest well-designed animal experiments to extract the neural basis of tinnitus by providing indications about what to look for. Candidate objective measurements in humans are provided by various imaging techniques such as structural magnetic resonance imaging (MRI), functional MRI (fMRI), and positron-emission tomography (PET). Structural MRI is able to detect abnormal ratios of gray matter (mostly dendrites of neurons) and white matter (mostly nerve fiber tracts) that may underlie tinnitus. In fact, a study by Mühlau et al. (2006) showed increased amounts of gray matter in the auditory thalamus of people with tinnitus, suggesting increased dendritic arborization and a potentially increased number of synapses.

Functional MRI and PET both indirectly provide a *measure of the number of neurons that are active and the degree to which they are.* They do this by measuring the energy consumption of the neurons reflected in the increased blood flow to active regions (PET) or by the relative amount of oxygen containing blood (fMRI) in a given cortical region (Logothetis, 2002). PET has a poor spatial resolution and requires averaging over long times (up to 30 min). PET data are typically also averaged over groups. However, PET has the enormous advantage that it is a silent technique, whereas the fMRI scanner noise in itself may affect (mask) the tinnitus. Functional MRI has a good spatial resolution and a better time resolution than PET (but still in the order of seconds) and also allows analysis of individual recordings. PET has been used effectively in people with gaze-induced tinnitus (Giraud et al., 1999; Lockwood et al., 2001) whereby each subject can be his own control. These researchers found increased activation during the perception of tinnitus in

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auditory association cortex but not in primary auditory cortex. Oral facial movements that increased tinnitus loudness also showed enhanced activation in auditory cortex (Lockwood et al., 1998). This suggests that there was no increased neural activity (number of neurons and/or their firing rates) in primary auditory cortex. However, the results do not exclude increased neural synchrony. Functional MRI has only recently begun to be used in the study of tinnitus (Smits et al., 2007).

In addition, electroencephalography (EEG) and magnetoencephalography (MEG), recorded by pasting multiple electrodes on the scalp or by surrounding the head with magnetic field sensors (MEG), may be able to detect differences in the strength of brain rhythms in people with tinnitus compared to those without. Studies by Weisz and colleagues (Weisz, Moratti, Meinzer, Dohrmann, & Elbert, 2005; Weisz et al., 2007) strongly suggest that in tinnitus patients the strength of oscillations in the delta frequency range (2–4 Hz) was increased, that in the alpha range (8–14 Hz) it was decreased, and that in the gamma frequency range (especially 50–60 Hz) it was also increased. As gamma band activity is typically associated with sensations, this is an important correlate. Thus, neural synchrony in certain frequency bands is increased and in others decreased.

Using the same recording techniques, one can measure auditory evoked potentials (AEPs) or auditory evoked magnetic fields (AEFs). What determines both the strength of brain rhythms and the amplitude of AEPs (AEFs) is *the amount of synchronization of the neuronal activity.* Here the findings are somewhat more at variance; both decreases in AEP amplitude (Attias, Urbach, Gold, & Shemesh, 1993; Jacobson & McCaslin, 2003) and increases (Hoke, Feldmann, Pantev, Lütkenhöner, & Lehnertz, 1989; Weisz, Wienbruch, Dohrmann, & Elbert, 2005) have been reported. It is interesting that the increased AEFs were found in the normal part of the audiogram (about one octave below the edge-frequency), suggesting that here the inhibition provided by neurons in the hearing loss region was substantially reduced, leading to both increased evoked activity and potentially also increased synchrony (Weisz, Wienbruch, et al., 2005).

High-resolution fMRI and AEP/AEF measurements can detect potential changes in the way frequencies are represented over the cortex, that is, tonotopic maps. High-resolution fMRI depends largely on the strength of the magnetic field, and field strengths $\geq$ 3T should be sufficient to see changes in the various coexisting tonotopic maps in different auditory cortical areas (Formisano et al., 2003; Scarff, Dort, Eggermont, & Goodyear, 2004). However, this has not yet been applied to tinnitus patients. Doing the same with AEPs/AEFs, especially using the N100 component, is impossible, as the spatial resolution is insufficient and the various components tend to be generated by several areas (Lütkenhöner, Krumbholz, & Seither-Preisler, 2003). Somewhat better results are expected based on middle latency responses or auditory steady state responses (ASSRs; Lütkenhöner, Krumbholz, Lammertmann, et al., 2003; Wienbruch, Paul, Weisz, Elbert, & Roberts, 2006). Despite these technical problems, AEP/AEF measurements have detected clear deviations from normality in tinnitus patients (Mühlnickel, Elbert, Taub, & Flor, 1998; Weisz, Wienbruch, et al., 2005; Wienbruch et al., 2006). As the ASSR is generated in primary auditory cortex and the N100 in secondary cortical areas, these results point to tonotopic map changes in those cortical areas in people with tinnitus.

To summarize, these findings in humans suggest at least three potential neural correlates of tinnitus: increased spontaneous firing rates (SFR), increased neural synchrony, and potential changes in the cortical tonotopic maps.

Animal Models and Tonotopic Maps

Behavioral techniques have shown that animals can experience tinnitus (Moody, 2004) following the application of the same agents that can cause tinnitus in humans. The agents explored are mostly noise trauma and ototoxic drugs including salicylates. Besides applying noninvasive imaging techniques, animal models also allow the recording of single-unit SFRs, local field potentials (these are in fact AEPs recorded intracranially), and measurement of the synchrony between single-unit activity. The main advantage of these invasive techniques is that one knows exactly where the activity originates. In addition, the high spatial accuracy (single-cell resolution) also allows the construction of cortical tonotopic maps for different areas. Furthermore, one can record from the same neurons before and after the application of drugs or exposure to noise.

Cortical tonotopic maps (Merzenich, Knight, & Roth, 1975) are typically constructed by estimating at densely spaced recording sites the characteristic frequency (CF) of the neuron. This is that frequency that activates the neuron at the lowest sound level. There is an orderly representation of CFs along the cortical surface (the tonotopic axis), whereas perpendicular to it the CFs tend to be the same (iso-frequency strips). An example of the tonotopic organization in the auditory cortex of normal hearing cats (Noreña & Eggermont, 2005) is shown in Figure 1a.

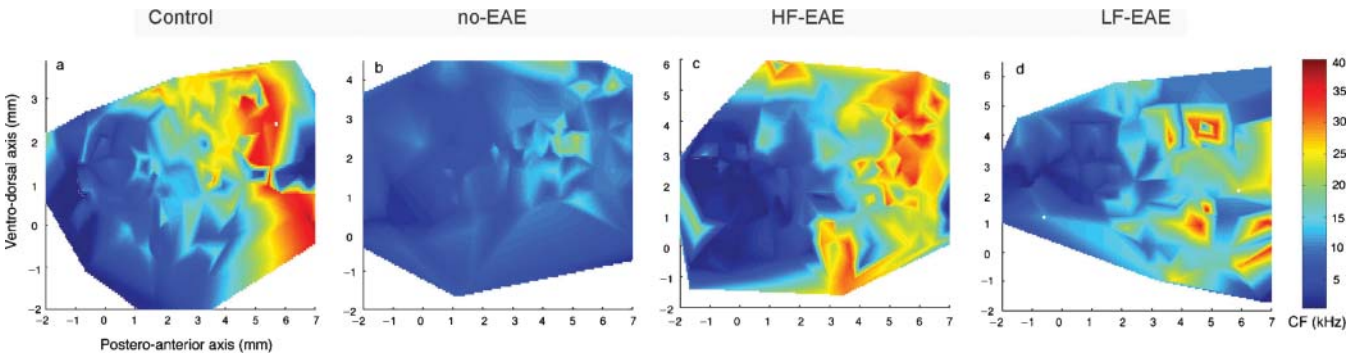
Noise Trauma: Effects on Auditory Periphery

Besides causing loss of outer hair cells and potentially inner hair cells (Liberman & Kiang, 1978), noise exposure also causes neurotoxic effects as a result of the excessive glutamate release by the surviving inner hair cells onto the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Puel, Ruel, Gervais d'Aldin, & Pujol, 1998). This causes the neurites to detach from the inner hair cells and thereby produces a temporary high-frequency hearing loss. The synapses may reestablish over a time period of a few days (Puel, d'Aldin, Ruel, Ladrech, & Pujol, 1997). Spontaneous and driven firing rates in auditory nerve fibers are reduced in the cochlear regions where inner hair cell stereocillia are affected, and may be enhanced for regions where there is only outer hair cell loss (Liberman & Dodds, 1987). In general, the SFRs following noise trauma are reduced compared to control (Liberman & Kiang, 1978).

Acute Effects of Noise Trauma on Auditory Cortex

The best way to study this is to record simultaneously from a large number of neurons and establish a solid baseline of

Figure 1. Group tonotopic maps for control cats (a), cats exposed to 5 kHz, 120 dB SPL for 2 hr and kept in a quiet room (b), cats exposed to 5 kHz, 120 dB SPL for 4 hr and kept in a high-frequency enriched acoustic environment (c), and cats exposed to 5 kHz, 120 dB SPL for 4 hr and kept in a low-frequency enriched acoustic environment (d). EAE = enriched acoustic environment; HF = high-frequency; LF = low-frequency.



tuning curves, SFRs, and the amount of neural synchrony between these simultaneously recorded neurons. Then, with the recording electrodes in place, expose the animal to loud sound (e.g., 5 kHz, 120 dB SPL) for 1 hr, and then record the activity from the same recording sites again and as a function of time after the trauma (Noreña, Tomita, & Eggermont, 2003). The findings showed, as expected, an initial loss of sensitivity, with the highest increase in threshold around 8 kHz (about one half an octave above 5 kHz); these thresholds improved over the following 6 hr of recording from the same sites. On average, 40-dB hearing loss remained 6 hr after the exposure. It was interesting that neurons with a pretrauma CF around 10 kHz had a CF close to 5 kHz after the trauma, a frequency that they did not respond to before the trauma. This effect was immediate and must be attributed to the loss of activity in the 10-kHz region, activity that normally would inhibit thalamic inputs to the 5-kHz area. This disinhibition unmasks previously silent excitatory inputs and shifts the tuning curve dramatically to lower CFs. This is likely a precursor to subsequent changes in the tonotopic map that take place only after several weeks (Eggermont, 2006). Immediately after the trauma (Noreña & Eggermont, 2003), there was a slight decrease in SFR, regardless of the CF of the neuron. It took 2 hr at least before the SFR had increased (on average twofold) in neurons with CFs below the trauma tone frequency and those with CFs more than one octave above the trauma tone frequency. Surprisingly, the one-octave-wide region above the trauma tone frequency did not show a change in SFR compared to pretrauma conditions. One could interpret the increases at lower and higher CFs again to a loss of inhibition from the one-octave-wide CF region above the trauma tone frequency. The fact that the SFR change was not instantaneous suggests that other factors likely play a role. In stark contrast, the neural synchrony was significantly increased immediately after the trauma. Because tinnitus tends to develop immediately after a noise trauma (but may reside again later), this suggests that the neural correlate, at least for transient tinnitus, is not increased SFR but increased neural synchrony.

Chronic Effects of Noise Trauma

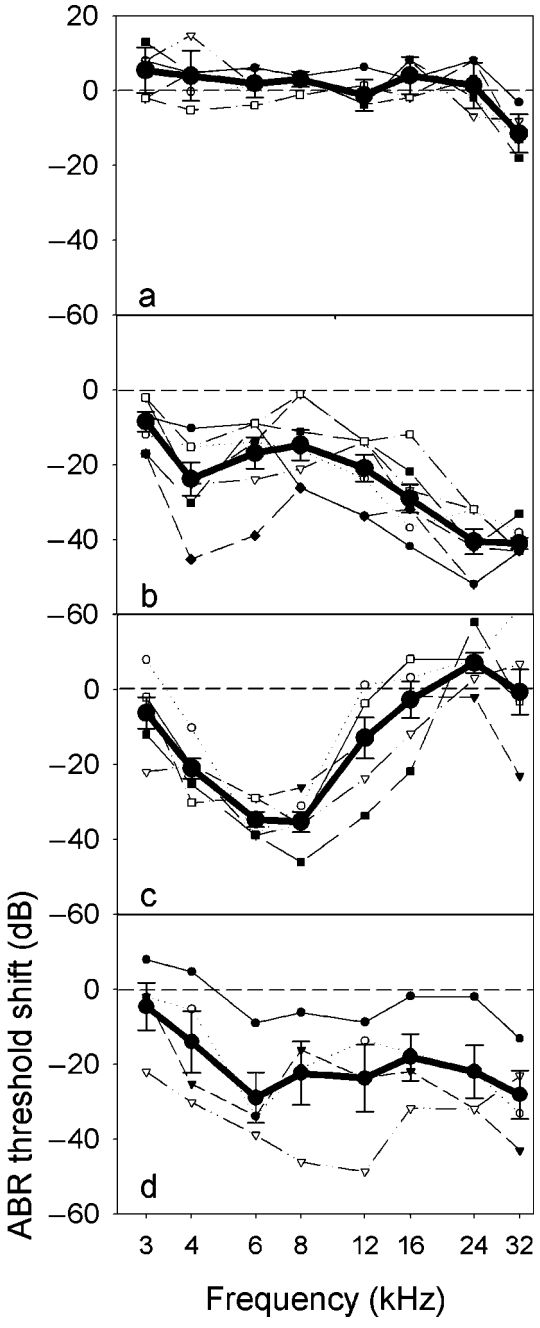
The 1-hr exposure presented in the previous section would hardly result in a permanent hearing loss when measured after at least 3 weeks postexposure. For this reason, we exposed for 2 hr at the same level, and later even for 4 hr. After the exposure, the cats with their littermates were placed into a quiet room (only cat vocalizations and cat-made toy noises). The audiograms for individual animals and the average are shown in Figure 2b. One notices a two-part hearing loss: a 10–45-dB (mean 25) dip around 4 kHz and a sloping loss for higher frequencies.

The activity of cortical neurons was recorded and compared to that of the control group presented previously. First of all, the tonotopic maps were changed dramatically (see Figure 1b) such that there were hardly any cortical sites that were sensitive to frequencies above 10–15 kHz (Noreña & Eggermont, 2005). Second, the SFR was significantly increased in those neurons that likely had preexposure CFs in the hearing loss range (as judged by their recording site and the newly acquired CF). Third, neural synchrony was increased in all neuron pairs that involved a neuron in the reorganized CF area (Noreña & Eggermont, 2006).

Hypothesis on What Underlies These Changes and How to Prevent Them

Several studies into the more molecular effects of noise trauma (Abbott, Hughes, Bauer, Salvi, & Caspary, 1999; Milbrandt, Holder, Wilson, Salvi, & Caspary, 2000; Wang, Ruan, & Wang, 2005) have found that there are changes in the effectiveness of the excitatory and inhibitory transmitter systems. These changes do occur at the brainstem, midbrain, and cortical level. Simplified, the findings are that the AMPA receptor system (that processes glutamate) is initially down-regulated (brainstem), that the gamma-aminobutyric (GABA) receptor system (inhibitory) is initially also down-regulated (midbrain), but that the other glutamate processing receptor system (NMDA) is initially up-regulated (cortex).

Figure 2. Individual (thin lines) and mean (thick lines) auditory brainstem response (ABR) audiograms for control cats (a), cats exposed to 5 kHz, 120 dB SPL for 2 hr and kept in a quiet room (b), cats exposed to 5 kHz, 120 dB SPL for 4 hr and kept in a high-frequency EAE (c), and cats exposed to 5 kHz, 120 dB SPL for 4 hr and kept in a low-frequency EAE (d).



However, within a few weeks to a month, all these changes have reverted back to (nearly) preexposure values. Thus, immediately after the noise trauma, there is now an imbalance between the excitatory and inhibitory receptor systems, particularly between the NMDA and the GABAergic systems. This imbalance may underlie the increased SFRs, and the unmasking of new excitatory inputs that we observed immediately after the trauma (see above). Continued imbalance for a few weeks may also initiate the reorganization of the tonotopic maps. Reorganization of maps and increased neural synchrony appear to be intricately linked (Bao, Chang, Davis, Gobeske, & Merzenich, 2003; Eggermont, 2007).

We reasoned that the imbalance of excitation along the tonotopic array of auditory nerve fibers (less for the hearing loss frequencies) would set up this imbalance higher up in the nervous system, as stronger excitation typically causes disproportionally stronger inhibition. By providing the animals with extra stimulation in the hearing loss range (equivalent to providing a well-fitted hearing aid), we would even out the excitation across the auditory nerve fiber array. Thus we put the next group of noise-exposed cats in the cat room with an 80-dB SPL (A-weighted) multifrequency dynamic sound environment in the frequency range of 4–20 kHz (covering the expected hearing loss range taking into account the upward spread of activity above 20 kHz).

Effect of an Enriched Acoustic Environment After Noise Trauma

We termed the posttrauma (5 kHz, 4 hr at 120 dB SPL) sound condition an enriched acoustic environment (EAE). The cats were in this sound field for 24 hr/day, 7 days/week, and for at least 3 weeks (the time expected for full cortical reorganization). The first surprise came when we measured their peripheral thresholds using auditory brainstem response. The previously pronounced hearing loss in the high frequencies encountered in the animals raised in quiet after the trauma was now completely absent (see Figure 2c); the remaining noise dip remained and was stronger than for the 2-hr-exposed cats. We interpreted this as the result of a reconnection of the neuritis to the inner hair cells, stimulated by the continued output of glutamate by those still intact inner hair cells.

The tonotopic map was normal in the EAE cats (see Figure 1c), and even detailed analysis could not detect any difference from that in the control cats (Noreña & Eggermont, 2005). We did not see any significant changes in the SFR in this group of EAE cats and no increases in neural synchrony (Noreña & Eggermont, 2006). This suggested to us that all potential neural correlates of tinnitus were completely normal and thus that tinnitus likely would be absent in cats that received the EAE treatment.

Needless to say, applying a low-frequency EAE (covering the normal range of the audiogram) had no effect on SFR and neural synchrony and had only a minor effect (largely based on one animal) on the tonotopic map (Noreña & Eggermont, 2006). This low-frequency EAE obviously does not balance the excitation and inhibition deficit produced by the hearing loss (see Figures 1d and 2d).

It is important to realize that this EAE was applied immediately after the trauma. Given that the imbalance between excitation and inhibition likely only exists for up to a month (if the translation from rats to cats to humans applies) after the trauma, this suggests a relatively short window of opportunity for sound treatment that prevents tinnitus (i.e., a morning-after sound).

Effects of Salicylate and Quinine on Cortex

Although drug-induced tinnitus covers only a small percentage of human tinnitus cases (Henry, Dennis, & Schechter, 2005), the number of animal studies that used salicylate to induce it is disproportionally high (from 76 research articles on tinnitus, published between 1965 and 2007, 32 used noise trauma and 44 used salicylate to induce tinnitus). The ease of application (by injection) again allows the study of the same neurons before, during, and after the injection. The same applies to quinine, but this has been only sporadically used. Both drugs have likely direct central effects on the auditory system, in addition to causing a temporary hearing loss. Both drugs in relatively low dose do not affect, or cause a decrease in, the SFR of auditory nerve fibers (Mulheran, 1999; Stypulkowski, 1990). The few cases where very high doses of salicylate were used are suspect (especially in cats that gradually developed a fever after injection of high-dose salicylate). We used a dose of 200 mg/kg that did produce a peripheral hearing loss of about 20 dB but did not change the SFR in primary auditory cortical neurons (Ochi & Eggermont, 1996), whereas it did in secondary cortex (Eggermont & Kenmochi, 1998). Quinine at a dose of 50 mg/kg had no effect, but at 100 mg/kg it produced increased neural synchrony in primary auditory cortex without changes in SFR (Ochi & Eggermont, 1997). Again, there were clear SFR increases following quinine application in secondary auditory cortex (Eggermont & Kenmochi, 1998). Thus, the findings after presumably drug-induced tinnitus and noise-induced tinnitus may be indicative of a different pathway and comprise different changes in the central nervous system.

What Does the Auditory Cortex Do?

It is time to ask what the role of the auditory cortex is in the tinnitus percept. This section is by nature speculative and presents a very personal view of cortical function. First of all, auditory cortex is likely necessary for perceiving tinnitus; without auditory cortex, there is usually not a conscious auditory percept, and certainly not the annoyance aspect. Secondly, the auditory cortex does more than just relay information from the thalamus to cortical association areas. A case in point is that more than 99% of neural inputs to a cortical neuron are from other cortical cells; even in the input layers of auditory cortex at most 10% of the inputs are of thalamic origin (Abeles, 1991). It is thus likely that the auditory cortex works mostly on its own output. Furthermore, the output of the cortex to the thalamus likely far outweighs the input it receives from the auditory midbrain, if it parallels the visual system (Van Horn, Erisir, & Sherman, 2000), suggesting that the cortex exhibits a control function on subcortical structures.

It is likely fair to state that the cortex is more a representational system than an information processing system. The cortex has a view of the world that can be changed whenever the input from the outside world (i.e., from the thalamus) violates its expectations (as an old and trusted learning rule expresses; Rescorla & Wagner, 1972). This is also reflected in the large series of event-related potentials that are generated by such violations. One has only to think about the mismatch negativity and the P300 as odd-ball signaling components. Furthermore, in language studies there are the additional semantic (N400) and syntactic (P600) violation-indicating components (Friederici, 2002).

Tinnitus, as reflected in its potential relation to changes in the cortical tonotopic maps, may be a result of maladaptive auditory plasticity. In this respect, it is useful to briefly summarize what properties remain plastic in the adult auditory system. If we start with cortical receptive fields, then we notice that these are pliable by learning (Fritz, Shamma, Elhilali, & Klein, 2003), and so are tonotopic maps (Polley, Steinberg, & Merzenich, 2006). Peripheral hearing loss also plastically changes tonotopic maps in auditory cortex (Rajan, Irvine, Wise, & Heil, 1993) and auditory thalamus (Kamke, Brown, & Irvine, 2003), but not in the auditory midbrain (Irvine, Rajan, & Smith, 2003) or cochlear nucleus (Rajan & Irvine, 1998). We have shown the intricate connection between tonotopic maps changes, increased SFR and increased neural synchrony (Noreña & Eggermont, 2005, 2006). This clearly points to an important role for thalamus and cortex in the generation of tinnitus through maladaptive plasticity, whereas other mechanisms may be responsible for the changes observed in the dorsal cochlear nucleus and auditory midbrain.

The Auditory System as a Set of Nested Feedback Loops

An aspect of the "learning by violation" rule presented above may be that the cortex tries to adjust the output of subcortical structures by its corticofugal feedback activity (Yan & Suga, 1998). In this way, increased activity at a particular cortical site can, for instance, change the representation of frequency in the auditory midbrain, and even affects the activity of hair cells in the cochlea (Suga, Gao, Zhang, Ma, & Olsen, 2000). We will explore this aspect in this last section and derive from it the potential importance of subcortical structures in the generation of tinnitus.

The auditory system is not just an afferent projection system but has a myriad of efferent connections that make it a reentrant system characterized by multiple, loosely interconnected, regional feedback loops (Spangler & Warr, 1991). The first loop is cortical and comprises both the interaction within a given cortical area and between cortical areas. A reflection of these interactive loops is found in the various oscillatory brain rhythms; for instance, the gamma band oscillation with its frequency in the 40–60 Hz range relies on connections that produce delays of 15–25 ms comprising conduction times between cells and synaptic integration times. This is a purely cortical rhythm, whereby each cortical area generates its own frequency.

The rhythms in the 8–14 Hz range (delays of about 100 ms required) likely are all dependent on the thalamus, where the interplay between the reticular nucleus and the thalamic projection cells can generate rhythmic bursting with long delays caused by the duration of inhibition or hyperpolarizations, or both. Disturbances in that rhythm have been implicated in various positive syndromes, and specifically tinnitus (Llinas, Urbano, Leznik, Ramirez, & van Marle, 2005). The cortex feeds back to the thalamus from pyramidal cells in layer VI.

The amygdala, the fear center of the brain, gets two inputs from the auditory system, a fast one via the thalamus and a slower one via the secondary auditory cortex (Farb & Ledoux, 1999; Woodson, Farb, & Ledoux, 2000). This also constitutes a loop, as the amygdala feeds back on the auditory cortex. This integration of the limbic system and the thalamo-cortical complex is involved in emotional aspects of tinnitus.

The corticofugal connections from layer V affect the auditory midbrain and have been demonstrated to affect its response properties. The midbrain is subsequently involved in a loop comprising the dorsal cochlear nucleus. The cochlear nucleus is also directly affected by corticofugal fibers (Schofield & Coomes, 2005) as is the olivary complex (Coomes & Schofield, 2004). The olivo-cochlear bundle in turn connects the hair cells with the brainstem.

Feedback loops tend to stabilize systems. It may well be that these loops in time also stabilize tinnitus that originates at more peripheral sites such as the dorsal cochlear nucleus or at more central ones such as auditory cortex. In the long run, peripheral and central activity may enhance each other, and the result is that there is no particular site in the central auditory system that can be held solely responsible for tinnitus.

Opening the loop by blocking connections—for example, by using drugs such as lidocaine (Baguley, Jones, Wilkins, Axon, & Moffat, 2005)—or by desynchronizing the activity of the nested loops—for example, by stimulation through a cochlear implant (Quaranta, Wagstaff, & Baguley, 2004) or by direct electrical (De Ridder et al., 2006) or transcranial magnetic stimulation (Plewnia, Bartels, & Gerloff, 2003) of the cortex—is likely the only way to successfully probe for a cure of tinnitus.

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