I have referred throughout this book to tinnitus that often co-occurs with NIHL and ARHI, and more unexpectedly also with nontraumatic noise exposure. Tinnitus, as we will see, has besides psychoacoustic properties—i.e., quantifiable aspects such as pitch and loudness—also nonauditory side effects such as annoyance, stress and problems sleeping. These nonauditory effects are very similar to those for environmental noise, as described in Chapter 10. We know more about the locations in the brain where the nonauditory effects of tinnitus reside compared to those resulting from environmental noise. The simple reason is that chronic tinnitus is constantly present and is correlated with potentially permanent changes in brain activity and connectivity. Therefore I will present here an overview of those aspects of tinnitus (noise in the brain) that are relevant for the interpretation of effects of external noise on the brain. I will, when possible, refer to very recent publications (i.e., those that did not make it into my The Neuroscience of Tinnitus book\textsuperscript{1}) to illustrate this.

### 11.1 PHANTOM SOUNDS

Tinnitus is the conscious perception of sound heard in the absence of physical sound sources external or internal to the body. Sound perceived from physical sound sources inside the body such as blood flow and middle ear muscle twitching is generally called “objective tinnitus”; I will not deal with those here. About 10–15\% of adults experience tinnitus. Tinnitus is generally ignited by hearing loss, and very often by NIHL, but most chronic tinnitus is of central origin; that is, it is in the brain and not generated in the ear. A conclusive example is found in patients with one-sided deafness, who often experience tinnitus referred
to that ear, yet the tinnitus subsides when that ear is stimulated via a cochlear implant (Chapter 5). The localization of tinnitus to one or both ears is thus likely attributable to a phantom sensation and is not unlike that related to sensations or pain experienced after losing a digit or, more severely, a limb. Itch or pain in a no-longer-existing part of the body is truly annoying and so is tinnitus. The pitch of tinnitus corresponds, when there is a hearing loss, to the frequency region of that hearing loss. In case of low-frequency hearing loss the tinnitus is low pitched (“roaring”), but in high-frequency NIHL the tinnitus has a high-pitched ringing or hissing sound. In 1890, MacNaughton Jones who studied 260 cases of tinnitus described the sounds of tinnitus as follows:

“The following were the noises I have recorded as complained of by patients. The sound resembling buzzing; sea roaring; trees agitated; singing of kettle; bellows; bee humming; noise of shell; horse out of breath, puffing; thumping noise; continual beating; crackling sounds in the head; train; vibration of a metal; whistle of an engine; steam engine puffing; furnace blowing; constant hammering; rushing water; sea waves; drumming; rain falling; booming; railway whistling; distant thunder; chirping of birds; kettle boiling; waterfall; mill wheel; music; bells.”

As in a true phantom sensation, the brain “hears” the sound of the missing frequencies in one ear, both ears, or inside the head, but describing how it sounds appears to be very personal and typically referred to with known external sounds. Electrophysiological and functional imaging measurements in humans and animals suggest that neural synchrony changes, tonotopic map changes, and increased spontaneous firing rates in the auditory system are potential neural correlates of tinnitus in humans. Tinnitus is likely the result of maladaptive plasticity of the central nervous system. The central nervous system wants to restore its evoked neural activity levels that had been lowered by the hearing loss. This is done by increasing the efficacy (or gain) of its synapses. But this gain also affects the SFR, which occurs in the absence of a physical sound source, and will then generally increase. This is interpreted as sound and called tinnitus. A puzzling aspect is that only 30% of people with hearing loss experience tinnitus, so there must be other purely central nervous system aspects that promote or allow the perception of tinnitus.

### 11.2 RELATIONSHIP TO NIHL AND ARHI

Tinnitus occurs in children as well as in the elderly, in war veterans and factory workers, and in classical musicians, rock stars and disc jockeys. The prevalence of significant tinnitus across the adult lifespan
is illustrated in Figure 11.1. Significant tinnitus has to be longer than 5 minutes in duration and not immediately (and transiently) following exposure to loud noise.\(^4\) Sometimes, even more stringent definitions, such as that tinnitus has to be bothersome, are used. This typically lowers the prevalence a few percentage points. This bifurcation can be seen in Figure 11.1. A recent survey from Fujii et al.\(^5\) from the Takayama Study in Japan found essentially the same prevalence.

For normal hearing children, tinnitus prevalence is typically based on large surveys conducted at schools. Brunnberg et al.\(^6\) in a survey at mainstream schools in the Swedish county of Örebro, found the prevalence in normal hearing children (\(N = 2730\)) to be 6% (similar to that for the 20- to 30-year-olds in Figure 11.1) and that for hearing impaired children (\(N = 148\)) at 39%, which is significantly larger than in adults, but close to the values for occasional tinnitus.\(^7\) In another large study of 1100 children, normal hearing as well as hearing impaired, between 6 and 16 years (mean age 11.9 years) 374 children reported tinnitus when asked and 71 spontaneously complained about it.\(^8,9\) A Brazilian study of 506 children between 5 and 12 years of age\(^10\) found that tinnitus was experienced in 37% and that 19% suffered from their tinnitus; the prevalence of mild and profound hearing loss was 18%. The first number corresponds with the average of many other studies in children,\(^11\) but the 19% of children who suffer from tinnitus is about twice as high as the average from these other studies in children and in young adults with significant tinnitus. Juul et al.\(^12\) screened 756 children aged 7 years

FIGURE 11.1 Mean prevalence of significant tinnitus for adults. The UK(NHS) data are from\(^93\), the US(NHIS) data are from\(^94\) and\(^15\), the Swedish data are from\(^95\), and the Norway study was by\(^96\).
and found that 41% had experienced tinnitus on several occasions. The probability of spontaneous tinnitus was 27% for children without hearing loss or previous TTS but if they exhibited both hearing impairment and or previous TTS tinnitus occurred in 63%. Bartnik et al.\textsuperscript{13} reported similar numbers and found that, from 143 children who consulted their tinnitus clinic, 41% suffered from bothersome tinnitus, and nearly half of them had normal hearing. The percentage of children that experience tinnitus may include the occasional type (information not available in these references). Still the average prevalence in children with hearing impairment (39%) appears extremely high and likely includes a particular clinical subgroup looking for help.

As these prevalence studies across the lifespan (Figure 11.1) show, tinnitus is about twice as frequent in the elderly as in young adults. This increase may be related to the prevalence of hearing loss and other age-related diseases.\textsuperscript{14} Hearing loss, resulting for instance from exposure to loud noise, is considered an important risk factor for developing tinnitus. Consequently, a history of recreational, occupational, and firearm noise exposure may all be associated with increased likelihood of acquiring tinnitus. The relation between noise exposure and significant tinnitus, however, differs depending on the presence or absence of hearing impairment. Occupational noise exposure was more likely to correlate with significant tinnitus in participants with hearing impairment, while leisure-time noise exposure was more associated with increased occurrence of significant tinnitus in participants without hearing impairment.\textsuperscript{15} Engdahl et al.\textsuperscript{16} confirmed that occupation had a marked effect on tinnitus prevalence. In men, age-adjusted prevalence ratios of tinnitus (in relation to a reference population of teachers) ranged from 1.5 (workshop mechanics) to 2.1 (crane and hoist operators) in the 10 occupations with the highest tinnitus prevalence. In women, the most important contribution to the tinnitus prevalence was from the large group of occupationally inactive persons, with a prevalence ratio of 1.5. Using data from the Epidemiology of Hearing Loss Study (1993–1995, 1998–2000, 2003–2005, and 2009–2010) and the Beaver Dam Offspring Study (2005–2008) in the USA, Nondahl et al.\textsuperscript{17} examined birth cohort patterns in the report of tinnitus for adults aged 45 years and older (n = 12,689 observations from 5764 participants). They found that tinnitus tended to increase in more recent birth cohorts compared to earlier birth cohorts (Figure 11.2). On average, participants in a given generation were significantly more likely to report tinnitus than participants from a generation 20 years earlier (OR = 1.78, 95% CI = 1.44–2.21). This also may underlie the leveling off of tinnitus prevalence in Figure 11.1 for the age group above 65 years, and may thus refer back to the much lower prevalence in cohorts born before 1940.

In the context of this book it is important to know whether exposure to noise or music comprises a primary cause of tinnitus. Classical
musicians are often exposed to sound levels greater than 85 dBA for long periods of time (Chapters 2 and 9), both during practice and performance, resulting in a high prevalence (51%) of tinnitus and temporary threshold shifts in this group. A total number of 245 musicians (490 ears) of five symphony orchestras in the Netherlands participated in this study on a voluntary basis. Most musicians could be considered as normal hearing, but their audiograms showed notches at 6 kHz, a frequency that is associated with NIHL (Chapter 9). Tinnitus occurred in 17% of the participants and was most often localized in the left ear and this could not be related to the type of instrument they played. It was usually perceived as high pitched, and thus likely associated with NIHL. Hyperacusis often co-occurs with tinnitus and is found in 43% of musicians. Hyperacusis, an increased sensitivity to sound at levels that would normally not be of discomfort to an individual, has been associated with exposure to sound and is often reported in people with a known hearing loss.

Rubak et al. investigated the relationship between noise exposure and tinnitus among workers with normal hearing and hearing loss, respectively. They conducted a cross-sectional survey of 752 workers employed at 91 workplaces in Aarhus County, Denmark. In this group, tinnitus was not associated with the workers’ current occupational
noise level, with the duration of occupational noise exposure, or with the cumulative occupational noise exposure if participants had normal hearing. As expected, tinnitus was correlated with these noise exposure aspects if participants had a hearing handicap, suggesting that they had been exposed to occupational noise for a long time. These data suggest that there is no risk of noise-induced tinnitus at exposure levels where no hearing loss would be expected, e.g., as usually encountered in non-industrial workplaces. One note of caution: noise exposure with currently normal audiograms (likely excluding the frequencies above 8 kHz) can later in life cause tinnitus even in cases where the audiogram remains normal at standard frequencies (according to the author’s own experience). Corroborating this, in animals noise exposure without permanent threshold shift\textsuperscript{21} may over time cause patchy degeneration of ganglion cells and this could be causal to a later-onset tinnitus in the presence of a normal audiogram.

11.3 WHERE IN THE BRAIN IS TINNITUS?

I will first review some of the changes that, not surprisingly, occur in auditory brain areas in people with tinnitus, and then discuss the large number of other brain regions involved in bothersome tinnitus.

11.3.1 The Auditory System

Two recent comprehensive studies by Melcher and colleagues did set the tone for a positive identification of the auditory brain areas involved in generating tinnitus. Gu et al.\textsuperscript{22} reported physiological correlates of two perceptual abnormalities in the auditory domain that very frequently co-occur: tinnitus and hyperacusis. Patients with and without tinnitus, all with clinically normal hearing thresholds, underwent both behavioral testing to assess their sound-level tolerance (i.e., the presence or absence of hyperacusis) and fMRI to measure sound-evoked activation of central auditory centers. Despite receiving identical sound stimulation levels, subjects with hyperacusis showed elevated evoked activity in the auditory midbrain, thalamus, and primary auditory cortex compared with subjects with normal sound tolerance. This reflects the increased gain for processing external auditory stimuli. Primary auditory cortex, but not subcortical centers, showed elevated activation specifically related to tinnitus, i.e., in the absence of hyperacusis. The results directly link both hyperacusis and tinnitus to hyperactivity within the central auditory system. The authors hypothesized that the tinnitus-related elevations in cortical activation could reflect undue attention drawn to the auditory domain. This is consistent with the lack
of tinnitus-related effects subcortically where activation is typically less modulated by attentional state. Melcher et al. tested for differences in brain structure between tinnitus and control subjects. Voxel-based morphometry (VBM) was used to compare structural MRIs of tinnitus subjects and nontinnitus controls, all with normal or near-normal thresholds at standard clinical frequencies (≤8 kHz). Mean hearing threshold through 14 kHz, age, sex and handedness were extremely well matched between groups. There were no significant differences in gray matter (GM) volume and concentration between tinnitus and nontinnitus subjects. However, the modulated gray matter (scaling the images by the amount of local volumetric contraction or expansion in order to preserve the total designated amount of GM in the normalized images), probability in ventral posterior cingulate cortex, dorsomedial prefrontal cortex, and a subcallosal region that included ventromedial prefrontal cortex were negatively correlated with hearing thresholds at frequencies above 8 kHz (Figure 11.3). Strong, significant correlations with anxiety were seen in the cerebellum, and hearing threshold at frequencies above 8 kHz with several midline regions: ventral posterior cingulate cortex (vPCC), dorsomedial prefrontal cortex (dmPFC), and ventromedial prefrontal cortex (vmPFC). The observed correlation between brain structure in regions engaged in cognitive and attentional processes, and hearing sensitivity at frequencies (>8 kHz) needs more research as it could be a priming process for tinnitus. See also Figure 8.6.

Boyen et al. using voxel-based morphometry, showed that both hearing impaired people without and with tinnitus, relative to the controls, had GM increases in the superior and middle temporal gyri, and decreases in the superior frontal gyrus, occipital lobe and hypothalamus. In agreement with Melcher et al. no significant GM differences were found between both patient groups. Subsequent region-of-interest (ROI) analyses of all cortical areas, the cerebellum and the subcortical auditory nuclei showed a GM increase in the left primary auditory cortex of the tinnitus patients compared to the hearing impaired people without tinnitus and control groups. These results suggest a specific role of the left primary auditory cortex and the additional involvement of various nonauditory brain structures in tinnitus. Boyen et al. found it impossible to draw conclusions on the causal relation between GM differences, hearing loss and tinnitus. In the case of hearing loss, it was considered unlikely that abnormalities in the brain cause peripheral sensorineural hearing loss. However, the GM increase in the left primary auditory cortex of tinnitus subjects could represent a pre-existing vulnerability to develop tinnitus in response to sensory neural hearing loss. Alternatively, the GM increase could be a consequence of increased ongoing neural activity presumed to underlie tinnitus.
Langers et al. investigated tonotopic maps in primary auditory cortex of 20 healthy controls and 20 chronic subjective tinnitus patients. The goal was to test the hypothesis, proposed on basis of animal and previous human studies that tinnitus results, among others, from an abnormal tonotopic organization of the auditory cortex. Subjects were recruited from the hospital’s tinnitus outpatient clinic (for the patient group) as well as from advertisements in various media (for the control and patient groups). The patients reported no history of neurological or psychiatric disorders, and were not undergoing tinnitus treatment at the time of the study. All subjects were selected to have normal or near-normal hearing up to 8 kHz. Tonotopic representations in the bilateral
human auditory cortices were obtained in a paradigm that was identical to that in a previous publication, which showed in more detail for the current control group that tonotopic maps could be robustly extracted. The study found no evidence for a reorganization of cortical tonotopic maps (Figure 11.4). This is perhaps not surprising since there was no appreciable hearing loss. It had been previously shown that in animals there is no reorganization of the cortical tonotopic map for hearing losses \( \leq 25 \text{ dB} \). However, the study clearly did demonstrate that reorganized tonotopic maps in auditory cortex are not a requirement for tinnitus to occur.

11.3.2 Tinnitus and Nonauditory Brain Regions

Nonauditory areas are heavily involved in tinnitus, especially in cases of bothersome tinnitus. Largely due to the extensive analyses of resting brain EEG in tinnitus patients by De Ridder’s group in Antwerp, Belgium and Weisz and colleagues in Konstanz, Germany, it has become clear that a large diversity of brain areas is involved in the perceptual and emotional aspects of tinnitus (Figure 11.5).

Rauschecker et al. proposed the first consistent model that incorporates the interaction between the limbic and auditory system, amplifying on the earlier prescient model of Jastreboff. They proposed that:

“(1) In most, if not all, cases, the process leading to tinnitus is triggered by a lesion to the auditory periphery, e.g., a loss of hair cells in the inner ear resulting from acoustic trauma or aging. (2) Loss of input in the lesioned frequency range leads to an overrepresentation of lesion-edge frequencies, which causes hyperactivity and possible burst-firing in central auditory pathways, constituting the initial tinnitus signal. (3) Under normal circumstances, the tinnitus signal is cancelled out at the level of the thalamus by an inhibitory feedback loop originating in paralimbic structures: activity from these structures reaches the TRN, which in turn inhibits the MGN. If, however, paralimbic regions are compromised, inhibition of the tinnitus signal at the thalamic gate is lost, and the signal is relayed all the way to the auditory cortex, where it leads to permanent reorganization and chronic tinnitus.”

Limbic and auditory brain areas are thought to interact at the thalamic level. While a tinnitus signal originates from lesion-induced plasticity of the auditory pathways, it can be tuned out by feedback connections from limbic regions, which block the tinnitus signal from reaching auditory cortex. If the limbic regions are not functioning properly, this “noise-cancellation” mechanism breaks down, and chronic tinnitus results. Although increased neural synchrony or increased SFR in auditory cortex in response to hearing loss may be necessary for the tinnitus perception to arise, it is likely not sufficient.
Again note that only 30% of people with NIHL suffer from tinnitus. Various findings suggest that the subcallosal area links limbic-affective systems with thalamo-cortical perceptual systems. In addition the subcallosal area in its posterior portion overlaps with the nucleus accumbens (NAc). The NAc (and its associated network in the medial prefrontal cortex) contains dopaminergic and serotonergic neurons.
among other types. The dopaminergic system within the NAc is well known for its involvement in reward behavior and avoidance learning, and the serotonergic neurons play a modulatory role in various emotion-related systems. The NAc receives glutamatergic input from the amygdala, as well as projections from the hippocampus and the raphe nuclei (Figure 11.6). The latter are the major origin of the serotonergic system and are responsible for the regulation of sleep of the ventral striatum (cf. Figure 10.9). Serotonin excites the GABAergic neurons of the thalamic reticular nucleus, which in turn exert a powerful inhibitory influence on sensory thalamic relay cells. TRN-mediated inhibition can also cause thalamic relay neurons to shift between tonic and burst-firing modes, the latter of which requires cells to be in a hyperpolarized state. Cochlear lesions as we have seen (Chapter 3) typically result in cortical tonotopic map changes, and increased SFR and neural synchrony (and thus an initial tinnitus signal) in the ascending auditory pathways. Rauschecker et al.\textsuperscript{31} proposed that normally, the unwanted SFR (noise signal) is identified by the limbic system and eliminated from perception by feeding it back to the

FIGURE 11.5 Overview of the different brain areas involved in tinnitus based on resting state EEG in tinnitus patients. From\textsuperscript{97}, with permission from the authors.
(inhibitory) TRN, which subtracts it from the afferent auditory signal. This mechanism would then fail in about 30% of people with NIHL, but why it would do so is unknown.

The ventromedial prefrontal cortex (vmPFC) and NAc are part of a canonical cortico-striatal-thalamic circuit, in which vmPFC exerts excitatory influence on the NAc, among other structures (Figure 11.6). Regardless of its origin, NAc hyperactivity may indicate the perceptual relevance of the tinnitus sensation (and/or perhaps the aversiveness of stimuli matched to the tinnitus-frequency), with the ultimate objective of affecting perception. VmPFC also projects to the TRN, which is in a position to inhibit (or modulate) communication between auditory cortex and the auditory thalamus (Figure 11.6). Thus, inefficient vmPFC output could prevent inhibition of the tinnitus signal at the thalamic level. The study of Melcher et al.23 linked gray matter in the vmPFC specifically to hearing loss at frequencies >8 kHz, i.e., outside the range normally tested in clinical audiometry. However, correlations were also present in the 2–8 kHz frequency range. It may thus well be that the suggestions made by Rauschecker et al.31 for the changes in the vmPFC

FIGURE 11.6 Schematic of proposed auditory-limbic interactions in tinnitus. Sensory input originates subcortically and enters both auditory and limbic circuits via the medial geniculate nucleus (MGN). Under normal circumstances, the limbic system may identify a sensory signal as perceptually irrelevant (e.g., transient tinnitus following loud noise exposure) and inhibit the unwanted signal at the MGN via projections from the ventromedial prefrontal cortex (vmPFC) to the auditory thalamic reticular nucleus (TRN, red pathway). Thus, propagation of the unwanted signal (e.g., transient tinnitus) is reduced in both circuits. In chronic tinnitus, inefficient vmPFC output prevents inhibition of the tinnitus signal, resulting in continued thalamocortical activity and the constant perceptual presence of the tinnitus signal. Cortical structures are noted in gray, thalamus is noted in blue, basal ganglia in green, and amygdala in lavender. Abbreviations: medial dorsal nucleus (MDN), ventral pallidum (VP), amygdala (amyg), auditory cortex (AC). Reprinted from 33, copyright 2011, with permission from Elsevier.
are due to hearing loss. Thus, hearing losses in the high frequencies (>8 kHz) may prime the system for tinnitus perception. Whether this includes the 70% of people with hearing loss and no tinnitus remains unclear.

In support of the above model, Leaver et al.\textsuperscript{33} reported both functional and structural correlates of chronic tinnitus in limbic and auditory regions of the human brain. In tinnitus patients, the NAc exhibited hyperactivity specifically for stimuli matched to each patient’s tinnitus frequency. Corresponding anatomical differences were identified in the vmPFC, later corroborated by Melcher et al.\textsuperscript{23} which is strongly connected to the ventral striatum. Indeed, the magnitude of these effects in NAc and vmPFC were related, suggesting that these regions play a similar role in tinnitus pathology. Within auditory cortex, Leaver et al.\textsuperscript{33} noted hyperactivity in mHG, the likely location of primary auditory cortex and posterior superior temporal gyrus (pSTG), a secondary auditory region. This increased activity in tinnitus patients was present for all stimuli in pSTG; however, hyperactivity in mHG was restricted to tinnitus-frequency matched stimuli and was positively correlated with tinnitus-related limbic abnormalities as well.

The observation that spontaneous fMRI activity is not random noise, but is specifically organized in the resting human brain\textsuperscript{34} has boosted a new approach to tinnitus research. This so-called resting-state functional connectivity reflects correlations in slow (<0.1 Hz) spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal. A potentially related electrophysiological correlate of spontaneous BOLD fluctuations is the slow (<0.1 Hz) voltage fluctuation that has been observed with EEG recording.\textsuperscript{35} Brain rhythms with higher frequencies\textsuperscript{36} that can be more easily recorded by EEG and MEG are phase-locked to these very low-frequency oscillations.\textsuperscript{37} If spontaneous neural activity reflects ordered brain states it should show highly specific patterns, and these should reflect the functional architecture of the networks.

Tinnitus may be related to changes in the resting-state neural networks of the brain. Maudoux and colleagues\textsuperscript{38,39} tested 13 chronic tinnitus patients and 15 age-matched healthy controls with a 3T MRI scanner during resting condition (i.e., eyes closed, no task performance). Connectivity was investigated using independent component analysis. Tinnitus and control groups showed different graph-connectivity patterns (Figure 11.7). In the control group (left panel), the connectivity graph could be divided into two distinct anti-correlated networks. The first one encompassed the auditory cortices and the insula (red nodes). The second one comprised frontoparietal and anterior cingulate cortices, brainstem, amygdala, basal ganglia/nucleus accumbens and parahippocampal regions (blue nodes). In the tinnitus group (middle panel), only the auditory cortex-insula network was present. Direct
group comparison (Figure 11.7, right panel) showed in the tinnitus group an increased functional connectivity between auditory cortical areas and the left parahippocampal region, being part of the second network in controls. Connectivity in extraauditory regions such as brainstem, basal ganglia/NAc, cerebellum, parahippocampal, right prefrontal, parietal, and sensorimotor areas was increased in tinnitus subjects. Thus, there was a modification of cortical and subcortical functional network connectivity in tinnitus patients that serves attention, memory, and emotion.

These findings corroborate the implication of nonauditory regions in tinnitus physiopathology and suggest that various regions of the brain seem involved in the persistent awareness of the phenomenon as well as in the development of the associated distress leading to disabling chronic tinnitus. This increase in functional connectivity between auditory and parahippocampal regions in tinnitus agrees with findings of Vanneste et al. who used resting-state EEG measurements. Comparing resting-state electrical brain activity of tinnitus patients and
controls, they reported an increased activity in the gamma-frequency band in the parahippocampal area. They also found an increase in connectivity between parahippocampal regions and auditory cortical areas in tinnitus patients compared to control subjects. Highly and low distressed tinnitus patients differed in terms of activation of the left middle frontal gyrus, supporting the idea of a fronto-parietal-cingulate network, which seems to be more active in highly distressed tinnitus patients. Since Golm et al. compared highly and low distressed tinnitus patients, matched for tinnitus loudness, this emphasized the role of the prefrontal cortex in the emotional processing of tinnitus. The middle frontal gyrus had been linked to the perception of tinnitus and recently also to tinnitus distress. Two decades ago, Jastreboff had already suggested that the prefrontal cortex was a region for integrating sensory and emotional characteristics of tinnitus.

11.4 LISTENING TO TINNITUS

Listening to your own tinnitus and matching it to externally generated sounds allows a quantification of the tinnitus percept. This area of research uses psychoacoustic methods that can assess tinnitus pitch and loudness, and measure the effects of masking sounds on the tinnitus percept.

11.4.1 Tinnitus Pitch

Pitch matches occur often in the frequency region of maximum hearing loss or occasionally at the edge frequency of the hearing loss. The tinnitus percept can often be synthesized by combining pure tones into a tinnitus spectrum (Figure 11.8). Pitch-matching reliability varies widely across patients. Pitch matches can also vary from day-to-day or within a day. This may represent subtle shifts in the dominant frequencies in the tinnitus spectrum. Moore and Vinay examined the relationship between tinnitus pitch and the edge frequency of the hearing loss using 11 participants selected to have mild-to-moderate sloping hearing loss (greater loss at high frequencies than at low frequencies) and tonal tinnitus. Prior to testing in the main experiment, subjects were given specific training to help them to avoid octave errors in their pitch matches. Pitch matches made after this training were generally lower in frequency than matches made before such training, often by one or two octaves. A clear relationship was found between the values of the edge frequency of the hearing loss and the mean pitch matches following training; the correlation was 0.94. Generally, the pitch matches were
They suggested that the reason that they found a clear relationship between the values of the edge frequency of the hearing loss and the mean pitch matches while other researchers mostly have not found a clear relationship was the training that they gave to reduce octave errors. This is consistent with an early report of Graham and Newby showing that training to reduce octave errors reduced the variability of pitch matches to tinnitus, although Penner argued that “the variability in matches to the tinnitus is not due to octave confusion.” In summary, the tinnitus percept is usually complex in quality. Although tinnitus can sometimes be matched by adjusting the frequency of a pure tone, the matches are often unreliable across sessions. The matching frequencies tend to fall in regions where the hearing loss is greatest. In cases where the tinnitus is described as tonal, and for people with sloping audiograms, the frequency that matches the tinnitus may correspond to an edge in the audiogram, where the hearing loss increases relatively abruptly. Again, more research is needed to confirm this finding. For temporary tinnitus produced by exposure to intense sounds, the

FIGURE 11.8 (A) Hearing thresholds were measured at frequencies from 0.25 to 16.00 kHz. Results were averaged over both ears, and shown by means of boxplots (showing inter-quartile ranges). Stimuli were presented at all octave frequencies from 0.25 to 8.00 kHz at two different intensity levels that differed by 20 dB. The light gray bars indicate the approximate presentation levels. In the analysis, the sound-evoked activation levels were interpolated to a uniform intensity level of 40 dB HL, indicated by the dark gray line (B) Patients performed a tinnitus spectrum test in which they indicated the subjective “likeness” to their tinnitus percept of a range of sound stimuli with varying center frequencies. The majority of subjects showed high-frequency tinnitus (solid; likeness increasing with frequency); one subject showed a low-frequency tinnitus (dashed; likeness decreasing with frequency); two subjects showed a spectrum that could not be classified as high- or low-frequency (dotted; with a peak or a dip at intermediate frequencies). From With permission from the authors.
frequency that matches the tinnitus may correspond to the upper edge of the region over which maximum TTS occurs.

11.4.2 Tinnitus Loudness

Tinnitus loudness is usually measured by a rating procedure, or by matching it to the level of external sounds. The loudness of tinnitus is typically matched to sound levels that are only a few dB above the hearing threshold at the tinnitus frequency. However, because of the recruitment type of hearing loss that frequently underlies tinnitus, these few dBs could still represent a fairly loud sound. The loudness level of tinnitus fluctuates and this could be due to test–retest variability, actual fluctuation of the tinnitus loudness, and changes in tinnitus pitch or loudness produced by the measurement stimulus if presented to the tinnitus ear. Presenting a matching stimulus to the contralateral ear might reduce potential interference with tinnitus loudness, but because of central interactions might not completely eliminate them. One way to avoid this sound–tinnitus interaction is to use cross-modal loudness matching, or using constraint psychophysical scaling. The constrained scaling procedure trains subjects in loudness estimation on a standard response scale that closely resembles the Sone scale created by Stevens.

11.4.3 Tinnitus Masking and Residual Inhibition

Masking is based on two mechanisms: 1) a so-called “line-busy” effect where the masking sound activates the neurons and prevents them from firing to a probe sound (e.g., tinnitus), and 2) a suppression effect where the masker interferes with the mechanical activity pattern of the probe sound in the cochlea. Although pure tones can mask tinnitus completely in the majority of patients, masking of tinnitus does not follow the standard effects that a masker has on an external probe sound. It appears that the cochlear suppression mechanism is impaired in tinnitus patients likely because of the hearing loss (based on a comparison of simultaneous masking or forward masking measurements of psychoacoustic frequency tuning). If the changes induced by the masker, and the generation site of tinnitus, were at the cochlear level, the masking of an external pure tone would be similar to the masking of tinnitus. This finding again points to central mechanisms of tinnitus.

Residual inhibition is a post-masking effect that, because of its long duration (usually seconds, but can last for minutes to hours), is a central effect. The residual inhibition is generally largest when using masking sounds in the hearing loss range and that resembled the tinnitus
The results suggest that cortical map reorganization induced by noise-induced hearing loss, which results in an overrepresentation of the edge frequency in the audiogram, is not the principal source of the tinnitus sensation. Because in that case one would expect the tinnitus pitch to match the edge frequency and that edge-frequency sounds would result in the largest residual inhibition. The duration of the residual inhibition is likely related to recovery from the habituation induced by the masker (Chapter 7).

11.5 NONAUDITORY EFFECTS OF TINNITUS

11.5.1 Is Tinnitus a Form of Pain?

In some ways tinnitus resembles neuropathic pain. Pain and tinnitus both may cause emotional and psychological distress out of proportion to the magnitude of the injury. Moreover, both pain and tinnitus are often associated with dysfunctional, inappropriate coping strategies. Early studies had already pointed to the similarity of severe tinnitus and central neuropathic pain that occurs without stimulation of pain receptors. For instance, perception of auditory stimuli is often abnormal in tinnitus patients, and perception of nociceptive stimuli is often abnormal in people with central pain. Many individuals with severe tinnitus often have hyperacusis and individuals with central pain often have hyperalgesia. The similarity between these two forms of enhanced sensitivity and excessive reaction to normal sound (hyperacusis) and normal touch (hyperalgesia) is striking. Hyperalgesia is dependent on NMDA receptor mediated activity and the loss of inhibitory control. It is likely, but so far not demonstrated, that hyperacusis has the same neural correlates. Chronic pain is in part an emotion and tinnitus is also, in part, an emotion.

Neuropathic pain likely arises as a result of changes in the properties of neurons in the CNS, called central sensitization (Chapter 7). Several mechanisms that may cause the central sensitization of pain have been described. The best-characterized mechanism involves a change in the function of NMDA receptors in the spinal cord dorsal horn neurons. Activation of sensory neurons by painful stimuli leads to activation of pain-projection neurons in the spinal cord. During strong and/or persistent nociceptive stimulation sufficient amounts of substance P and glutamate are released to sustain the depolarization of the spinal cord neurons. When this happens, Mg$^{2+}$ ions that normally block the NMDA channel are removed, allowing Ca$^{2+}$ to flow through the channel into the neuron. This results in the amplification of pain messages being relayed to higher brain centers. Similar changes in NMDA
activation in the cochlea following salicylate application and noise trauma have been described and suggest another aspect in the analogy between tinnitus and pain.

11.5.2 Tinnitus as a Conscious Percept

Tinnitus, just as pain, is a conscious percept, which requires attention to be perceived, does not wake you up, and can often be inaudible when attention is directed to other aspects of conscious processing. The starting point for understanding what makes tinnitus audible and often annoying is identifying the neural correlates of awareness. Laureys and Schiff have reviewed imaging studies showing that patients in a persistent vegetative state show a reduced blood flow in the anterior and posterior cingulate, in the precuneus, and in fronto-parietal-temporal areas. In these patients sound activates the primary auditory cortex on both sides, but no activity is observed in the inferoparietal cortex, in the hippocampus or in the anterior cingulate cortex (ACC). These areas are coactivated with primary auditory cortex in normal controls, suggesting that activity in primary auditory cortex is insufficient to produce a conscious percept of sound. This may also apply to tinnitus. This is also illustrated in the differences in brain activation for near threshold sounds, which are sometimes perceived and sometimes not. When such sounds are perceived the dorsal ACC and the anterior insula are activated, and when they are not consciously perceived there is only activation in auditory cortex.

In patients with tinnitus, PET imaging has shown that frontal and parietal areas are coactivated with auditory cortex. Reorganization of tonotopic maps in auditory cortex correlate most of the time with phantom sound percepts but is insufficient to make tinnitus distressing. This also requires activation of the ACC. Imaging studies of psychological stress further suggest that bothersome tinnitus is correlated with a functional coupling of amygdala, dorsal ACC, insula, and locus coeruleus that occurs after stress. Such stress can lead to sustained salience of the stressor and an aversive memory thereof. De Ridder et al. suggested that a deficient thalamic gating function can emerge as a consequence of an aversive tinnitus memory together with chronic stress and represents an additional factor contributing to the perpetuation of the phantom percept. They suggested that both tinnitus and phantom pain are perceptual states of continuous learning, where—in the absence of an external input—the phantom percept is reinforced and the connection with aversive emotional associations is continuously updated.
11.5.3 Annoyance and Stress

Tinnitus causes annoyance and stress. Results of psychoacoustic loudness estimates of tinnitus have shown repeatedly to have little if any correlation with the degree of tinnitus severity or annoyance. The annoyance of tinnitus appears to be determined more by the level of hearing loss, and the presence of hyperacusis. A person with severe hyperacusis has difficulty tolerating everyday sounds, some of which may seem unpleasantly loud to that person but not to others, and often show signs of depression. Chronic tinnitus affects approximately 15% of the population (Figure 11.1). Severe distress due to the phantom noise is experienced by 20% of the tinnitus patients. This distress cannot be predicted by psychoacoustic features of the tinnitus. It is commonly assumed that negative cognitive emotional evaluation of the tinnitus and its expected consequences is a major factor that determines the impact of tinnitus-related distress. The latter is generally assessed using tinnitus questionnaires. There are at least a dozen published outcome instruments that are used to obtain tinnitus severity ratings, however, there is no consensus regarding their use across tinnitus treatment centers. Recently, Meikle et al. designed and tested a new questionnaire, the Tinnitus Functional Index, incorporating the best of nine widely used questionnaires.

11.5.4 Tinnitus and Sleep

Individuals with tinnitus have often sleep problems but it is not known if they are a result of the acoustic percept of tinnitus disturbing normal sleep, or if there are common causes underlying tinnitus and sleep problems. Sleep problems impair the quality of life of individuals with tinnitus and the impairment correlates with the severity of the tinnitus. However, the nature of the relationship between tinnitus and disturbed sleep in individuals with tinnitus is not clearly understood. In the following the available reports are reviewed. Previous theories of tinnitus have assumed a largely “reactive” role for limbic structures that reflects a mostly learned distress response.

In their landmark study of tinnitus severity in 1,800 patients who attended the Tinnitus Clinic at Oregon Health Sciences University, Meikle et al. found that tinnitus severity ratings were highly correlated with sleep disturbance. Alster et al. assessed the reported prevalence and severity of sleep disturbance in chronic tinnitus in military personnel associated with noise-induced permanent hearing loss. Mini Sleep Questionnaire (MSQ) scores for sleep disturbance were found to be higher than those of normal controls in 77% of the patients. The self-rated severity of the tinnitus was greater in subjects with higher sleep
disturbance scores. Asplund\textsuperscript{71} evaluated the relation of tinnitus to sleep in a group of 10,216 elderly men and women in northern Sweden. Tinnitus was reported by 14.9% of the men and 12.0% of the women. Poor sleep was reported by 14.4% of the men and 27.9% of the women. Among subjects with tinnitus poor sleep and frequent waking were more common in both sexes, while difficulties in falling asleep after awakening at night were reported more often by women.

Hébert and Carrier\textsuperscript{72} reported on 102 participants (51 with and 51 without tinnitus), assessed with the Pittsburgh Sleep Quality Index, the Beck-II depression inventory, a hyperacusis questionnaire, and a tinnitus-reaction questionnaire (tinnitus group only). Participants were matched for health and relevant socioeconomic factors. Tinnitus patients had greater self-reported sleep difficulties compared with control subjects, specifically sleep efficiency and sleep quality. High tinnitus-related distress was associated with greater sleep disturbance. Sleep complaints in this population were mainly explained by hyperacusis, a hallmark of severe tinnitus, and to a lesser extent by subclinical depressive symptoms. A second important finding was that hearing loss, even at the high frequencies that characterize tinnitus, could be ruled out as a significant contributor to sleep difficulties. The increased sensitivity to external noise (hyperacusis) is thus the most likely cause of sleep problems.

Test et al.\textsuperscript{73} studied 298 male volunteers that were occupationally exposed to harmful industrial noise, and their sleep quality as measured by MSQ. Participants with average hearing loss greater than 25 dB in the range of 1000–4000 Hz were defined as the research group (n = 99) and were compared to those with no hearing impairment (n = 199). Sleeping disorders were age related (30% higher MSQ score among workers above 50 years). Tinnitus was the highest sleep-disturbing factor, with 75% higher score among those affected. Tinnitus was the leading insomnia factor (OR = 11.91; CI 95% = 1.56–91.2), followed by hearing impairment (OR = 3.051; CI 95% = 1.18–7.86). Although tinnitus was the main sleep-disrupting factor, hearing impairment among workers occupationally exposed to harmful noise independently contributed to sleep impairment, especially to insomnia, regardless of age and years of exposure. Tinnitus and insomnia tended to intensify one another, and successful tinnitus therapies often improve insomnia complaints.

A study in 4705 persons with tinnitus who were all members of the German Tinnitus Association suggested that severe tinnitus-related distress as well as severe depressive and anxious mood, somatic symptom severity and hyperacusis are often associated with sleep disturbances, whereas factors related to tinnitus perception play a minor role.\textsuperscript{74}
11.6 SIMILARITIES OF TINNITUS AND ENVIRONMENTAL SOUND EFFECTS ON THE BRAIN

Recent reviews by Kraus and Canlon\textsuperscript{75} and Wallhäusser-Franke et al.\textsuperscript{67,74} respectively connected nonauditory effects of noise and tinnitus to activity in the limbic system. The sensation of sound and noise, or the absence of sound, not only induces structural or functional changes in the central auditory system but can also affect limbic regions such as the amygdala and hippocampus (Figure 11.9). The amygdala is particularly sensitive to meaningful sound, such as animal vocalizations or speech, crying or music. As we have seen in the previous chapter, the amygdala plays a central role in auditory fear conditioning, regulation of the acoustic startle response and can modulate auditory cortex plasticity. A stressful acoustic stimulus, such as noise, causes amygdala-mediated release of stress hormones via the HPA-axis, which may have negative effects on health, as well as on the central nervous system (Chapter 10). In contrast, short-term exposure to stress hormones elicits positive effects such as hearing protection (Chapter 12). Noise exposure affects hippocampal neurogenesis and LTP in a manner that affects structural plasticity, learning and memory. Tinnitus, typically induced by NIHL, is associated with emotional stress, depression and anatomical changes of the hippocampus.\textsuperscript{76} In turn, the limbic system may play a role in the generation as well as the suppression of tinnitus indicating that the limbic system may be an essential target for tinnitus treatment.

The neurocognitive model of insomnia\textsuperscript{77,78} proposes that excessive arousal prevents attenuation of sensory and cognitive activity during the wake/sleep transition in insomniacs and thereby indirectly produces sleep discontinuities. It is assumed that such arousal is the result of classical conditioning. Increased arousal together with increased short-term memory formation is held responsible for the common misperception insomniacs have about their sleeping time, as they mistake actual sleep for wakefulness. Hyperarousal also plays a role in Jastreboff’s neurophysiological tinnitus model.\textsuperscript{32} Besides altered activation in auditory brain regions, there is evidence that tinnitus is associated with increased activity in regions associated with emotion processing and the control of autonomic bodily functions such as prefrontal cortex and the amygdala.\textsuperscript{33} This is thought to be a feature that is common to many disorders that are associated with unexplained functional somatic symptoms and that show high comorbidities with depressivity and anxiety such as tinnitus or sleep disorders.\textsuperscript{43}

As we have seen in Chapter 10, exposure to noise can trigger the release of glucocorticoids by activation of the HPA-axis via the
amygdala (Figure 10.7). Noise exposure activates neuroendocrine cells containing corticotropin-releasing hormone in the hypothalamic paraventricular nucleus, which stimulates release of adrenocorticotropin hormone in the pituitary gland. ACTH release and the resulting secretion of corticosterone (a major glucocorticoid in rodents) in the adrenal gland increase with noise intensity. The increased levels of ACTH as well as corticosterone remained elevated for the duration of noise presentation along with behavioral stress response. Corticosterone (rodents) or cortisol (humans) in turn activates glucocorticoid receptors (GR) which are expressed in several tissues and organs including the inner ear hair cells, spiral ganglion neurons and spiral ligament. Noise can impair both cognition and memory. Subjects performing a memory task (picture encoding) showed a decreased number of correct responses when exposed to noise during the task. fMRI revealed increased activity in the amygdala and decreased activity in the hippocampus, which may be due to suppression mediated by amygdala.
Simoens and Hébert suggest heightened glucocorticoid sensitivity in tinnitus in terms of an abnormally strong GR-mediated HPA-axis feedback (despite a normal corticoid receptor-mediated tone) and lower tolerance for sound loudness with suppressed cortisol levels. Long-term stress exposure and its deleterious effects therefore constitute an important predisposing factor for, or a significant pathological consequence of, tinnitus.

Tinnitus is strongly associated with emotional stress, anxiety and depression. Like external noise, the internally generated noise of tinnitus may cause emotional distress resulting in mood disorders like depression. In turn, stress or depression may contribute to the development of tinnitus. Reciprocal interactions of auditory areas and areas processing emotion appear essential for tinnitus generation. The phantom sound may be caused by disinhibition, increased spontaneous activity, neural synchronization, and tonotopic reorganization in the central auditory system. Furthermore, since the auditory and limbic systems are interconnected, tinnitus can affect emotional as well as cognitive properties of the limbic system. In turn, the limbic system may play a role for tinnitus generation or stabilization.

Subcortical connections from the ascending auditory system to the amygdala may also contribute to tinnitus generation. The dorsal cochlear nucleus is typically hyperactive during tinnitus and there is evidence that it may affect attention and emotion via the locus coeruleus, the reticular formation and the raphe nuclei. A final common pathway of tinnitus consisting of regions that are activated by all cases of tinnitus has been proposed, in which the amygdala and hippocampus have a fundamental function together with the parabrachial nucleus and insula (cf. Figure 11.9). De Ridder et al. proposed involvement of learning mechanisms which creates a particular awareness of the phantom sound and a role of a distress network consisting of anterior cingulate cortex, anterior insula and amygdala. Thus, many of the network components identified in highly distressed tinnitus patients appear similar to those that mediate the stress and sleep disturbances induced by environmental noise.

11.7 SUMMARY

Noise in the brain (tinnitus) associates with the same emotional/fear responses as environmental sounds do in case of annoyance, stress, sleep disturbances, etc. This underscores that a phantom percept results from the same real brain activity as that induced by environmental sounds. Tinnitus is caused by NIHL but maybe not by ARHI. This is based on the leveling off in the tinnitus prevalence around the common retirement age of 65. If this can be attributed to a lower level of noise.
exposure in older people at the time they were entering the workforce is not clear but highly likely. Where in the brain is tinnitus located? The level of activity in auditory cortex correlates with tinnitus loudness. The level of annoyance and distress, however, correlates with the modification of cortical and subcortical functional connectivity in tinnitus encompassing attention, mnemonic, and emotional networks. These areas include, among others, the parahippocampal area, the limbic system and the basal ganglia. It has been suggested that the basal ganglia may regulate the thalamic reticular nucleus that governs the thalamo-cortical neural flow, and that dysfunction therein opens the gate for perceiving phantom sounds. There is a surprising similarity between the tinnitus-annoyance-stress-sleep deprivation-cardiovascular disease networks and those for environmental sound effects on these systems.

References

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