Review article

Acquired hearing loss and brain plasticity

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Abstract

Acquired hearing loss results in an imbalance of the cochlear output across frequency. Central auditory system homeostatic processes responding to this result in frequency specific gain changes consequent to the emerging imbalance between excitation and inhibition. Several consequences thereof are increased spontaneous firing rates, increased neural synchrony, and (in adults) potentially restricted to the auditory thalamus and cortex a reorganization of tonotopic areas. It does not seem to matter much whether the hearing loss is acquired neonatally or in adulthood. In humans, no clear evidence of tonotopic map changes with hearing loss has so far been provided, but frequency specific gain changes are well documented. Unilateral hearing loss in addition makes brain activity across hemispheres more symmetrical and more synchronous. Molecular studies indicate that in the brainstem, after 2–5 days post trauma, the glutamatergic activity is reduced, whereas glycinergic and GABAergic activity is largely unchanged. At 2 months post trauma, excitatory activity remains decreased but the inhibitory one is significantly increased. In contrast protein assays related to inhibitory transmission are all decreased or unchanged in the brainstem, midbrain and auditory cortex. Comparison of neurophysiological data with the molecular findings during a time-line of changes following noise trauma suggests that increases in spontaneous firing rates are related to decreases in inhibition, and not to increases in excitation. Because noise-induced hearing loss in cats resulted in a loss of cortical temporal processing capabilities, this may also underlie speech understanding in humans.

Keywords: Noise trauma, Human, Animal, Spontaneous firing rates, Tonotopic maps, Molecular changes

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1. Introduction

Acquired hearing loss can result from noise trauma, ototoxic drugs, head trauma, asphyxia, long-term otitis media in infancy, aging, and progressive hearing loss of genetic origin. Cross-modal changes induced by hearing loss will not be covered. This review is limited to the effects of noise trauma and ototoxic drugs causing permanent threshold shifts as these have been studied extensively in animals. To start this review, some of the brain changes occurring in humans with either bilateral or unilateral hearing loss, as measured with auditory evoked responses and brain-imaging techniques will be illustrated. The review of the animal studies will first cover structural changes in the brainstem, followed by tonotopic map changes in midbrain and auditory cortex resulting from neonatally and adult induced deafness. This will be supplemented by reviewing available data on changes in spontaneous firing rates and neural synchrony, which have implications for mechanisms underlying tinnitus. Then some pertinent molecular studies showing effects of noise trauma on the balance between excitation and inhibition will be introduced. The review will finish with drawing a timeline for the molecular and electrophysiological changes following noise trauma in adults.

2. Human studies

The human studies that are reviewed here describe cortical changes resulting from acquired hearing loss as measured by electroencephalography (EEG), magnetoencephalography (MEG), and structural and functional neural imaging.

2.1. Bilateral hearing loss

Dietrich et al. (2001) examined the plasticity of the human auditory cortex by means of MEG measurements in patients with steep high-frequency hearing loss. They found that high-frequency cortical neurons deprived of their usual most sensitive afferent input now responded to tone frequencies adjacent to the frequency range of the partial hearing loss. This suggests a reorganization of the tonotopic map and/or loss of lateral inhibition. Dietrich et al. (2001) illustrated this (Fig. 1b) by averaged auditory evoked fields (AEFs) from the left supratemporal cortex of a patient to the stimulated right ear at the lesion edge frequency of 7000 Hz (audiogram in Fig. 1c). The results for 4000 Hz, which is in the normal hearing range, are displayed for comparison in Fig. 1a. The maxima and minima of the wave N1m (see inset Fig. 2) distributions are marked by gray circles, and reveals higher field amplitudes for auditory stimulation at the lesion edge frequency (Fig. 1b) as compared to the frequency in the normal hearing range. This is likely due to the loss of lateral inhibition normally provided by frequencies in the hearing loss range. Dietrich et al. (2001) noted that for 12 normal hearing subjects the equivalent current dipoles (ECDs) of the N1m were not located significantly different across the investigated frequencies compared to those for the eight patients with high-frequency hearing loss. This would argue against a reorganization of the cortical tonotopic map.

Neuroanatomical alterations associated with hearing loss were investigated by Husain et al. (2011) in three groups of subjects: those with hearing loss and tinnitus, those with hearing loss without tinnitus, and normal hearing controls without tinnitus. Voxel-based morphometry (VBM) analysis of structural magnetic resonance imaging (MRI) results showed a decrease in gray matter in superior and medial frontal gyri in participants with hearing loss compared to normal hearing controls. In addition, diffusion tensor imaging “showed decreases in fractional anisotropy values in the right superior and inferior longitudinal fasciculi, corticospinal tract, inferior fronto-occipital tract, superior occipital fasciculus, and anterior thalamic radiation for the hearing loss group relative to normal hearing controls.” This suggests white matter loss in these areas. Husain et al. (2011) also found that hearing loss rather than tinnitus had the greatest influence on gray and white matter changes. Melcher et al. (2013) also used VBM to compare structural MRIs of tinnitus subjects and non-tinnitus controls with very precisely matched, clinically normal audiograms, i.e., ≤20 dB HL for frequencies ≤8 kHz. There were no definitive differences between tinnitus and control groups in GM volume and concentration. However, thresholds at supra-clinical frequencies (≥8 kHz) were negatively correlated with GM volume in ventral posterior cingulate cortex, dorsomedial prefrontal cortex, and a subcallosal region that included ventromedial prefrontal cortex. Melcher et al. (2013) concluded that non-clinical hearing loss, i.e., for frequencies >8 kHz, regardless of tinnitus presence, induces structural brain changes. Boyen et al. (2013) also applied VBM analyses to MRIs of normal-hearing control subjects, hearing-impaired subjects without tinnitus and hearing-impaired subjects with tinnitus. The two hearing impaired groups had well matched audiograms for frequencies ≤8 kHz. VBM analyses revealed that both hearing impaired groups, relative to the controls, and regardless of tinnitus had GM volume increases in the superior and middle temporal gyri, and decreases in the superior frontal gyrus, occipital lobe and hypothalamus. Region-of-interest (ROI) analyses showed a GM volume increase in the left primary auditory cortex of the tinnitus patients compared to the HI and control groups. Moreover, GM decreases were observed in frontal areas and mainly GM increases in limbic areas, both of which occurred for hearing loss irrespective of tinnitus, relative to the controls.

Summarizing, the reviewed studies indicate evidence for structural and electrophysiological changes in human auditory cortex and non-auditory areas following high-frequency hearing loss, regardless of the presence of tinnitus.

2.2. Unilateral hearing loss

Scheffler et al. (1998), in one of the first functional magnetic resonance imaging (fMRI) studies to compare normal hearing and unilateral deaf subjects, found that in normal hearing subjects the lateralization ratios between left and right hemispheric response areas were 3.4–5.2 for monaural stimulation and nearly balanced (ratio 1.3) for binaural stimulation. For unilateral deaf subjects the lateralization ratio between left to right response was just 1.3 towards the contralateral hemisphere of the healthy ear, which is the same as for binaural responses of normal-hearing subjects. Ponton et al. (2001) recorded long-latency cortical auditory evoked potentials (CAEPs; Fig. 2) from teens and adults with post-childhood onset profound unilateral hearing loss. Compared to monaurally stimulated normal-hearing subjects, the CAEPs recorded from central electrode sites located over auditory cortical areas
showed significant increases in inter-hemispheric waveform cross-correlation coefficients, and in inter-hemispheric CAEP peak-amplitude correlations. These increases suggest substantial changes from the normal pattern of asymmetrical (contralateral > ipsilateral amplitude) and asynchronous (contralateral earlier than ipsilateral) central auditory system activation in the normal hearing population to a much more symmetrical and synchronous activation in the unilaterally deaf. Cross-sectional analyses of CAEP data from the unilaterally deaf group also suggested that the changes in cortical activity occurred gradually and continued for at least 2 years after the onset of hearing loss. Ponton et al. (2001) concluded that these use-dependent-related changes in CAEP activity following late-onset profound unilateral deafness provided evidence of the presence and the time course of auditory system plasticity in the adult brain. Plasticity is defined as the capacity for change in the structure and/or function of the nervous system, as a result of sensory experience in auditory cortex following exposure to tonal or noise stimuli, and as resulting from sensory deprivation due to hearing loss. The same group (Khosla et al., 2003) then investigated the effects of profound acquired unilateral deafness on the adult human central auditory system by analyzing long-latency CAEPs using dipole source modeling. They recorded CAEPs elicited by clicks presented to 10 unilateral deaf and 8 control subjects. The responses in the 70–210 ms time window, including the N1–P2 and Ta-Tb components of the CAEPs, were modeled by a vertically and a laterally oriented dipole source in each hemisphere. No significant differences in dipole locations were found between groups or between sides of stimulation. The normal-hearing subjects showed significant ipsilateral–contralateral latency and amplitude differences, with contralateral source activities that were typically larger and peaked earlier than the ipsilateral activities (Fig. 3). The previously reported reduction in ipsilateral–contralateral amplitude differences based on scalp waveforms was also observed in the dipole source waveforms but only for left ear unilateral deafness. This suggests an asymmetry in the normal excitatory-inhibitory balance between hemispheres.

Maslin et al. (2013) investigated the time course of plasticity following initially gradual and then abrupt profound unilateral deafness in adult humans using CAEPs. Baseline data from the intact ear were measured in six adults with unilateral hearing loss due to a vestibular schwannoma and compared with data from six controls. Further measurements were made post tumor surgery that resulted in profound unilateral deafness at 1-, 3- and 6-months. Baseline data showed statistically higher amplitudes in the better ear of unilaterally hearing loss participants but with normal hemispheric asymmetry. Longitudinal data for the better hearing ear showed further increases in P1 amplitudes by 1-month post-surgery, and in N1 and P2 (see inset Fig. 2) amplitudes by 6-months post-surgery, with statistically different scalp field topographies indicating reduced hemispheric asymmetries. Plasticity occurred both relatively rapidly and more gradually over at least 6-months post-surgery. Pross et al. (2015) conducted a cross-sectional study on 12 subjects with long-term, adult-onset, non-traumatic unilateral hearing loss and 12 normal-hearing controls.
using MEG. Pure-tone stimuli at five frequencies were presented to each hearing ear individually. Controls showed an inter-hemispheric mean latency difference for N1m of 6.6 ms. In contrast, the unilateral hearing loss subjects showed a mean latency difference of only 1.7 ms. This loss of inter-hemispheric latency difference was statistically significant.

Summarizing, these human studies all agree on a more symmetrical and synchronous activation in the unilaterally deaf cortex. This activation was measured as AEF or CAEP amplitude, and gray matter volume. The synchrony measure was based on differences in the N1(m), P2(m) or Ta-Tb component latency in both hemispheres.

3. Animal studies

3.1. Neonatal induced hearing loss

In adult cats reared with a unilateral neonatal cochlear ablation, the primary auditory cortex (A1) contralateral to the operated ear showed a normal tonotopic map derived from both single neurons and multi-unit clusters. The thresholds were similar to those observed in the A1 ipsilateral to the operated ear (Reale et al., 1987). In contrast, recordings in normal adult cats typically showed only ~65% of A1 neurons excited by sound delivered to the ipsilateral ear, and thresholds to ipsilateral ear stimulation were significantly higher than thresholds to contralateral ear stimulation (as reviewed by Syka, 2002). Compare this to the human findings in Section 2.2.

The tonotopic map in A1 was extensively reorganized in cats with neonatal, bilateral high-frequency hearing loss induced by the ototoxic drug amikacin (Harrison et al., 1991). Anterior areas of A1, normally tuned to high frequencies, now were comprised of neurons that were almost all tuned to a single lower frequency. This edge frequency in the audiogram corresponded, at the level of the cochlea, to the border between normal and damaged hair cell regions. At stimulus frequencies corresponding to the high frequency cut-off of the cats’ audiograms enhanced amplitudes of the auditory brainstem responses (ABR) were found. This was considered evidence of a larger than normal population of neurons tuned to this frequency region (Harrison et al., 1993a) although increased neural synchrony could also have contributed. In a parallel study (Harrison et al., 1993b) newborn chinchillas and kittens were treated with amikacin to induce basal lesions in the cochlea. At maturity these animals were used in single unit electrophysiological mapping studies. Both in the central nucleus of the inferior colliculus (ICC) in the chinchilla and A1 in the cat, massive reorganization of the tonotopic maps were found. Harrison et al. (1998) found that neurons in the reorganized regions in ICC had similar thresholds and were tuned with a common characteristic frequency (CF), which corresponded to the high-frequency border of the cochlear lesion.

Rajan and Irvine (2010) recorded from A1 neurons in adult cats that were partially deafened by ototoxic drugs 2–8 days after birth. This resulted in extensive A1 topographic map reorganization. They also found that in the majority of cats, the tonotopic map reorganization segregated into two areas that had the same novel frequency inputs but differed in neuronal threshold levels and responsiveness. Immediately adjacent to normal A1 they found a ~1-mm-wide area in which thresholds and responsiveness to sound were similar to that in normal A1. Extending a larger distance from the edge of normal A1, a more extensive area of reorganization was found where neurons had poorer thresholds and responsiveness to the reorganized inputs. The two reorganized A1 areas did
not differ in frequency-tuning-curve bandwidth and response latency. Rajan and Irvine (2010) speculated: “that the two areas of A1 reorganization may reflect differences in the transcortical spatial distribution of thalamo-cortical and horizontal intracortical connections.”

Eggermont and Komiya (2000) demonstrated that exposure of 5-week-old kittens to a loud 6 kHz tone presented at 126 dB SPL for 1 h, and repeated 1 week later, produced a mild to moderate high-frequency hearing loss, and induced a profound reorganization of the tonotopic map in A1 (Fig. 4). In the reorganized cortical region, the frequency-tuning curves were of normal sharpness with near normal thresholds. Inhibitory tuning curve bandwidths were also similar to those in control animals. Spontaneous activity in the reorganized part of the cortex was significantly increased compared to the non-reorganized part. From Khosla et al. (2003).

Aizawa and Eggermont (2006, 2007) exposed 6–7 week old kittens to a 1/3rd octave band noise centered at 5 kHz for 2 h at 120 dB SPL, and measured the effects when they were adult. The resulting ABR threshold shift was about 20–40 dB from 1 to 32 kHz. The mild chronic noise-induced hearing loss increased the minimum detectable VOT and gap duration by 10 ms. (Aizawa and Eggermont, 2006). In noise-exposed cats, temporal modulation-transfer functions (tMTFs) to amplitude-modulated (AM) noise, showed a marked increase for low modulation frequencies (Aizawa and Eggermont, 2007). In contrast, for click trains the magnitude of the tMTF was generally decreased. Thus, a mild hearing loss induced by noise exposure in early age causes a decrease in cortical neural temporal resolution when measured in adulthood.

3.2. Adult-induced hearing loss

I will focus here on changes in spontaneous firing rate (SFR), changes in neural synchrony (as measured by the peak value of the cross-correlogram for spike pairs), and again on changes in frequency-tuning and in tonotopic maps. Not always all these measures were done in the studies mentioned. To set the stage, I first review some structural and functional changes in the brainstem following unilateral cochlear ablation and noise trauma respectively.

3.2.1. Unilateral hearing loss

3.2.1.1. Auditory brainstem. Unilateral cochlear lesions resulting from noise trauma or cochlear ablation cause structural damage in the brainstem. Suneja et al. (1998a) reported increasing area loss in ipsilateral ventral cochlear nucleus (VCN) of the guinea pig after unilateral cochlear ablation. The damage for the ipsilateral antero-VCN (AVCN) and postero-VCN (PVVN) was not yet visible at 7 days post trauma, but showed clearly at ~1 month, and kept increasing with longer survival times. In the ipsilateral lateral superior olive (LSO), the reduction in area was only significant at 147 days post trauma. No significant effect was found in the contralateral
After exposing chinchillas (with one ear occluded) to a 4-kHz octave-band noise at 108 dB SPL for 3 h, Kim et al. (2004a) found that freshly occurring synaptic degeneration appeared in each period from 1 to 16 weeks. During the initial period of presumed relative inactivity, the calyx of Held endings in the trapezoid nucleus lost nearly all of their synaptic vesicles. After several months recovery all these changes reversed and the endings ultimately recovered their normal appearance. Their sources in the VCN, the globular bushy cells, however, were atrophied, presumably as a consequence of a reduction in normal activity. Kim et al. (2004b) used the same exposure paradigm but allowed periods of 6 and 8 months after a single exposure. They found a chronic, continuing process of neurodegeneration involving excitatory and inhibitory synaptic endings. Electron microscopic observations demonstrated freshly occurring degeneration even as late as 8 months. Degeneration was widespread in the neureil and included the synapses on the globular bushy cells, which form part of the main ascending auditory pathway. Kim et al. (2004b) suggested that: “Noise-induced hearing loss thus may progress as a neurodegenerative disease with the capacity for synaptic reorganization within the cochlear nucleus.” Kim et al. (2004c) allowed the animals to survive for periods up to 32 weeks. The losses of axons and synaptic terminals were significant after 1 week’s survival and progressed for 16–24 weeks after exposure. Cell bodies in the VCN lost both excitatory and inhibitory endings at first and later recovered a full complement of excitatory but not inhibitory terminals. These findings are consistent with a loss and regrowth of synaptic endings and with a reorganization of synaptic connections that favors excitation. This pattern of change may provide a structural basis for the enhanced excitability of CN neurons, and the elevation of SFRs after noise-induced cochlear damage.

### 3.2.1.2. Auditory midbrain

Experiments in the ferret (Moore and Kowalchuk, 1988) showed that after unilateral cochlear ablation in adult animals, the proportion of neurons excited from the intact ear in the ipsilateral inferior colliculus (IC), normally driven by the now-ablated ear, was unusually high. Mossop et al. (2000) explained this by finding that unilateral deafening causes a reduction in inhibition in the adult gerbil IC contralateral to the ablated ear. Within minutes after the ablation, multiple-unit recordings showed up to 60% increases in the proportion of responsive recording sites to stimulation of the hearing ear. At 24 h and 7 days survival after the ablation, glutamic acid decarboxylase (GAD) protein levels showed significant decreases in the IC contralateral to the ablated cochlea, relative to those in the ipsilateral IC. GAD is an enzyme that catalyzes the decarboxylation of glutamate to γ-amino butyric acid (GABA). At 1 yr survival no significant difference compared to the control group remained. This suggested to Mossop et al. (2000) the presence of at least two short-term mechanisms involved in the central response to cochlear ablation. One is a very rapid, stimulus-related, functional unmasking, as a result of decreased inhibition. The other is a more delayed reduction in the capacity of GABA synthesis in the IC.

Snyder and Sinex (2002) recorded frequency-response areas of ICC neurons to contralateral and ipsilateral tones after inserting and fixing-in-place tungsten microelectrodes. Response areas were recorded from most electrodes before, immediately after, and several hours after restricted mechanical lesions of the spiral ganglion. These lesions produced a “notch” in the tone-evoked compound action potential (CAP) audiogram, i.e., a narrow range of lesion frequencies with elevated thresholds. Responses of contralateral ICC neurons, which responded to these lesion frequencies, showed threshold elevations to the lesion frequencies with either no change in sensitivity to other frequencies or with dramatic decreases in threshold to lesion-edge frequencies. These changes in sensitivity produced shifts in CF that could be more than an octave. Thresholds for neurons with new CFs matched the prelesion thresholds of neurons tuned to the lesion-edge frequencies. These results indicated that responses of ICC neurons were produced by convergence of auditory information across a wide range of ANFs and that the acute “plastic” changes occurred within 1 h of an ANF lesion.

However, after making similar mechanical cochlear lesions, and allowing recovery for up to 18 months, Irvine et al. (2003) found that the frequency organization of ICC contralateral to the lesioned cochlea was explicable as the residue of prelesion responses. This was based on the finding of elevated thresholds in this region. Irvine et al. (2003) observed onset response changes not attributable to residual responses in about 40% of penetrations, but in only some cases was this associated with the appearance of low-frequency response fringes. This suggests that onset “plasticity,” i.e., unmasking (as seen by Snyder and Sinex, 2002), is vastly different from tonotopic map reorganization after a long recovery time, as observed in auditory thalamus and cortex.

Coomber et al. (2014) exposed the left ear of guinea pigs to noise bursts with a duration of 500 ms and ISI of 200 ms; having a center frequency of 10 kHz with a bandwidth of 1 kHz, and presented at 120 dB SPL for 1 h. They used the Preyer reflex (Berger et al., 2013) to assign guinea pigs to a tinnitus or non-tinnitus group. They found that 7–8 weeks post-exposure both SFRs and spontaneous bursting in the ICC were elevated after noise exposure. However, they found no significant differences between the tinnitus and non-tinnitus animals. Coomber et al. (2014) concluded that elevated IC neuronal firing may not be a unique indicator of tinnitus, but reflect changes that occur with a mild-to-moderate hearing loss, independent of the development of tinnitus.

### 3.2.1.3. Auditory cortex

Within hours of making mechanical unilateral damage to the organ of Corti shifts in CF toward frequencies spared by the lesions occasionally occurred, but thresholds were greatly elevated compared to normal (mean difference was 31.7 dB in five animals). Thirty-five to 81 days after such damage, the area of contralateral auditory cortex in which the lesioned frequency range would normally have been represented was now occupied by an expanded representation of sound frequencies adjacent to the frequency range damaged by the lesion (Robertson and Irvine, 1989). Rajan et al. (1993) made similar mechanical lesions unilaterally in adult cats, and found that 2–11 months after the unilateral cochlear lesion the tonotopic map in the contralateral A1 was altered. Along the tonotopic axis of A1 the total representation of lesion-edge frequencies could extend up to ~2.6 mm rostral to the area of normal representation of these frequencies. There was no topographic order within this enlarged representation. In the lesioned animals ipsilateral and contralateral maps differed in the region of A1 in which there had been a reorganization of the map of the lesioned cochlea. Comparable changes were found in the auditory thalamus (Kamke et al., 2003).

Following a 2-h unilateral noise exposure (97-dB noise with one-fourth octave band centered at 7 kHz) to the left ears, Basura et al. (2015) tested guinea pigs semiweekly before and after noise exposure using gap–prepulse inhibition of acoustic startle measures to test for tinnitus (Turner et al., 2006). Spontaneous neural activity was recorded, and only those animals with behavioral evidence of tinnitus showed increased spontaneous firing rates in primary auditory cortex, suggested as a purported neurophysiological correlate of tinnitus (Eggermont and Roberts, 2004).

### 3.2.2. Bilateral hearing loss

In this section, I review effects of hearing loss on cortical brainstem.
tonotopic maps but also changes in spontaneous firing rates and spontaneous neural synchrony. Changes in spontaneous firing activity in the auditory system as a result of bilateral hearing loss were recently reviewed in Eggermont (2015b).

3.2.2.1. Auditory nerve. The effects of noise-induced hearing loss (NIHL) on spontaneous firing rates in auditory nerve fibers were early on investigated by Liberman and Kiang (1978). They exposed cats for 1–4 h to narrow band or broadband noise with levels between 100 and 117 dB SPL, and recorded ANF activity at 15–305 days after the trauma. They found that frequency regions without threshold increase showed the normal bimodal distribution of SFRs. For ANFs in the hearing loss region, the SFR distribution had lost its normal bimodal appearance. Now one found mostly SFRs between 10 and 40 sp/s. ANFs that had become unresponsive to sound generally showed spontaneous bursting or no spontaneous activity at all. It was noted that SFRs were hardly ever increased after noise trauma (Liberman and Kiang, 1978).

3.2.2.2. Auditory brainstem. Superficial multi-unit recordings, likely from fusiform cells, in the dorsal cochlear nucleus (DCN) of hamsters after noise trauma induced by a 4 h exposure to a 10 kHz tone at 125 dB SPL showed strongly increased SFR (Kaltenbach et al., 1998, 2000). There was no correlation between SFR increase and the amount of threshold increase. In these hamsters, mean SFRs increased from below normal levels at day 2 post-exposure to higher than normal levels at day 5. The mean SFR continued to increase gradually over the next 6 months. Using the same exposure paradigm and recording from single fusiform cells of the DCN in hamsters, Finlayson and Kaltenbach (2009) showed average SFRs of 8.7 sp/s in controls and 15.9 sp/s after exposure.

Completely contrasting results were reported by Ma and Young (2006). They exposed cats to a 250 Hz band of noise centered at 10 kHz for 1 h. After a one-month recovery period, neural activity was recorded in the DCN of a decerebrated preparation, which also eliminates corticofugal activity towards the DCN among other effects. The threshold shift, determined from compound action potential (CAP) audiograms, showed a sharp threshold elevation of about 60 dB for neurons with CFs above the 5–10 kHz lower-edge frequency of the hearing loss. In contrast to the above-described results in hamsters that were subjected to a similar exposure level and duration, SFRs in fusiform cells with elevated thresholds were not increased over those in unexposed animals. A notable difference that may bear on this is that in decerebrated cats the corticofugal effects on the DCN (Luo et al., 2008) are absent. It is possible that the hyperactivity in the DCN normally arises from auditory cortex as significant increases in SFR occur much earlier in A1 than in DCN or ICC (Noreña and Eggermont, 2003, Table 1).

Vogler et al. (2011) exposed guinea pigs for 2 h to a 10 kHz tone presented at 124 dB SPL. After a 2-week recovery period, the mean SFR in the VCN of noise-exposed ears was significantly elevated (by about a factor two) compared to sham controls. This was more evident in primary-like and onset types of neurons.

3.2.2.3. Auditory midbrain. Vogler et al. (2014), using the same exposure as in the VCN (Vogler et al., 2011), also showed increased SFR in the ICC in regions corresponding to the frequencies at which there was peripheral hearing loss (12–20 kHz). Most unit types, with the exception of onset cells, showed a significantly increased mean SFR. Thus, in contrast to findings in the VCN, hyperactivity in the ICC was not confined to a particular cell type. This was confirmed by Ropp et al. (2014) in Sprague-Dawley rats that showed in ICC a median pre-trauma SFR = 10.4 sp/s and a post-trauma one of 14.1 sp/s. They found that abnormal SFRs were restricted to target neurons of the VCN. Nearly identical patterns of hyperactivity were observed in the contralateral and ipsilateral ICC. The elevation in SFR was found for frequencies well below and above the region of maximum hearing loss. Mulders and Robertson (2013) showed, as in the DCN, that acoustic trauma (10 kHz tone at 124 dB SPL for 1 h) in guinea pigs showed SFR increases at 12 h post-trauma, but not at 4 h post trauma, suggesting an earlier plastic change in ICC compared to the DCN (see above).

Manzoor et al. (2012) investigated whether IC hyperactivity is dependent on input from the contralateral DCN by comparing recordings of spontaneous activity in the ICC of noise-exposed and control hamsters before and after ablation of the contralateral DCN. One group of animals was binaurally exposed to intense sound (10 kHz, 115 dB SPL, 4 h), whereas the control group was not. Both groups were studied 2–3 wk later by recording SFRs over two 30-min periods. Ablation of the DCN resulted in major reductions in SFR in the ICC to levels similar to those in control animals. The results suggest that hyperactivity in the IC is dependent on support from the DCN. Because the VCN also becomes hyperactive following noise exposure (Vogler et al., 2011), and there are both direct and indirect inputs to the IC from the VCN, increased SFR in the IC may be dependent on inputs from VCN as well as DCN. Manzoor et al. (2013) then recorded SFRs in both DCN and IC between 1 and 6 weeks after exposure. For each of the three recording times, multiunit SFR was mapped as a function of CF in the DCN and IC. Similarities in these SFR-CF profiles suggest that the shape of the activity profile in ICC results from a passive relay from the DCN. However, the SFR levels were generally much lower in the IC than in the DCN. Mulders and Robertson (2011) had earlier shown that increased SFR in the ICC induced by noise trauma was abolished by ablation of the cochlea up to 6 weeks after noise trauma but not if cochlear ablation was performed later. So it is likely that this should result in decreased SFR in the DCN, however, Koerber et al. (1966) had shown that cochlear destruction did not change the SFR in the DCN, whereas it did in the VCN.

3.2.2.4. Auditory cortex. Schwaber et al. (1993) recorded tonotopic maps in macaque A1, and then deafened the high-frequency range of the cochlea by kanamycin and furosemide, and 3 months later remapped A1 in the same animals. The input deprived area of A1 underwent extensive reorganization and became responsive to the not-affected frequencies. The region of cortex that originally represented the low frequencies was not obviously affected by the cochlear hearing loss.

Seki and Eggermont (2002) presented findings in A1 of cats exposed for 2 h to a 115 dB SPL, 6 kHz tone at 36 days, 56 days or 118 days after birth. The age of exposure had no effect on any of the changes in response parameters after the trauma. They (as Rajan, 2001) found a fairly sharp demarcation in the amount of hearing loss (20–25 dB) that caused cortical tonotopic map reorganization. For cats showing reorganization of the tonotopic map, the frequency-tuning curve bandwidth at 20 dB above threshold at CF (BW20dB) increased with increasing threshold at CF. Threshold at CF and BW20dB increased with time after exposure. However, for CFs above 6 kHz, the BW20dB for cats with reorganization of the

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<th>Time-line of significant changes in spontaneous firing rate after noise trauma.</th>
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<td>≤15 min</td>
<td>&gt;2 h</td>
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<tr>
<td>ANF</td>
<td>=</td>
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<tr>
<td>VCN</td>
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† significant increase; = no significant change.
The inhibitory frequency-tuning curve bandwidths for the trauma cats did not change significantly in the 2–16 weeks after exposure (Fig. 5b). The inhibitory bandwidth was not correlated with the excitatory BW20dB. Minimum spike latency was initially increased, but subsequently decreased with time after exposure at a rate that was two times faster in cats with reorganized cortex than in cats with normal tonotopic maps, to reach the same asymptotic value (Fig. 5c). Seki and Eggermont (2003) found elevated spontaneous firing rates in regions with reorganization of the tonotopic map compared to the neurons in the non-reorganized cortical regions in the same animals. This SFR increased in the first month after trauma and then stabilized (Fig. 6). A second finding was that in these regions the peak cross-correlation coefficients were also increased relative to the non-reorganized parts.

An overview of the changes in spontaneous firing in the auditory system rates is shown in Table 1. Norena and Eggermont (2003) showed for cat A1 that the pairwise cross-correlation coefficient for spike-pair firings ($p$) was increased immediately (<15 min) after the traumatizing exposure (5 or 6 kHz and presented for 1 h at 115–120 dB SPL). The full lines in Fig. 7A,C represent the linear regression lines between the log (changes in $p$) and log (changes in geometric mean firing rate $M(FR)$). The Lowess (Locally Weighted Scatterplot Smoothing) curves for changes in $p$ as a function of log ($M(FR)$ changes) are shown in Fig. 7B,D; the full line corresponds to the ‘significant group’ (both neurons with CFs from 0 to 2 oct. above the trauma-tone frequency, TF) that showed a significant increase in $p$ after the trauma. The dotted line corresponds to the ‘non-significant group’ (one of the neuron pair with CF <$TF$) for which $p$ was not significantly changed after the trauma. Immediately after the trauma (<15 min), a linear regression on all the data showed that the changes in $p$ were not related to the changes in $M(FR)$.

Seki and Eggermont (2003) had found in exposed cats, recorded from between 2 weeks and 4 months after the exposure, a significant increase in $p$ (about a factor 1.4) in the reorganized parts of A1. These frequency-dependent changes in $p$ in long-standing tone-induced hearing loss are consistent with, and of the same size as, the acute ones seen in the Norena and Eggermont (2003) study a few hours after the trauma (Fig. 7).

Engineer et al. (2011) induced noise trauma by exposing rats to 1 h of 115-dB SPL, octave-band noise centered at 16 kHz. This resulted in about 15–20 dB permanent hearing loss at 11 weeks post trauma in the frequency region between 4 and 32 kHz. For this small permanent hearing loss one would not expect tonotopic map changes (Rajan, 2001; Seki and Eggermont, 2002). However, Engineer et al. (2011) found that the tonotopic map was reorganized. The also found that and the average multi-unit SFR, and the degree of synchronization between spontaneous multiunit firings recorded at closely spaced electrode sites, were significantly increased.

Cats exposed to a traumatizing noise (1/3rd octave band noise centered at 5 kHz at 120 dB SPL for 4 h) and immediately thereafter placed for a few weeks in an enhanced acoustic environment (EAE) presented a much-restricted hearing loss compared with similarly exposed cats that were recovering for the same time in a quiet environment (Norena and Eggermont, 2005). The EAE spectrally matched the expected hearing loss range and was ~40 dB above the
level of the expected hearing loss. The permanent hearing loss in the quiet environment-reared cats ranged from 6 to 32 kHz with the largest loss (on average, 40 dB) between 24 and 32 kHz. In contrast, the hearing loss in the EAE cats was restricted to 6–8 kHz at a level of, on average, 35 dB and with normal thresholds in the 16–32 kHz range. Despite the remaining hearing loss for the EAE cats in the 6–8 kHz range, tonotopic map changes in primary auditory cortex could no longer be demonstrated (the curves for normal hearing cats and EAE cats overlapped completely), suggesting that the recovery in an EAE prevented this reorganization (Fig. 8a).

In addition, Noreña and Eggermont (2005) compared the tonotopic organization of one EAE cat with that of a recovery-in-quiet cat having a similar hearing loss (Fig. 8b). This ‘quiet’ cat had been exposed for 2 h to a 6 kHz pure tone at 120 dB SPL and recovered in a quiet environment after the trauma. From a comparison with the control cat, the CF-distance map in the EAE cat appears normal (Fig. 8c). In contrast, the recovery-in-quiet cat presents a strongly modified, reorganized map; namely, only two CFs are represented: one at ~5 kHz and the other at ~17 kHz. This result corroborates a previous study where a mechanically-induced notched-hearing loss had been shown to induce an over-representation of the two cutoff frequencies (Robertson and Irvine, 1989). The fact that the ‘quiet-recovery’ cat presented an amount of hearing loss in the notch (similar to the averaged values in the EAE group) that was sufficient to induce cortical tonotopic reorganization suggests that it would also have been sufficient for the EAE cat. Thus, targeted acoustic stimulation following noise trauma prevented reorganization of the tonotopic map.

Hearing loss as described above results in rapid shifts in the receptive fields of auditory cortical neurons. The rapidity of these shifts has led to the suggestion that subthreshold inputs may be unmasked by a selective loss of inhibition. Scholl and Wehr (2008) confirmed that acute acoustic trauma disrupts the balance of excitation and inhibition by selectively increasing and reducing the strength of inhibition at different positions within the receptive field. To their surprise, they found that at relatively high test-tone levels the inhibition was abolished for frequencies far below the trauma-tone frequency but was markedly enhanced near the edges of the region of elevated peripheral threshold. Consequently, the expansion of these receptive fields was the result of loss of inhibition but not by a simple unmasking process but by delaying rather than abolish responses (Scholl and Wehr, 2008).

4. Molecular studies

Underlying the electrophysiological changes resulting from acquired hearing loss are molecular changes. The ones of interest here are mainly related to the balance of excitation and inhibition. This balance results from changes in receptors for excitatory and inhibitory transmission, and protein and gene expressions related to excitatory and inhibitory transmission.

4.1. Excitatory and inhibitory transmission changes

Cochlear ablation deafferents the cochlear nucleus. Potashner et al. (1997) found that this resulted in reduced glutamate release and uptake at 2 days, and abundant fiber degeneration at 7 days post ablation in the auditory brainstem in adult guinea pigs. At 145 days post ablation, excitatory glutamatergic transmission was strengthened in the cochlear nucleus, in the superior olivary complex (SOC), and in the auditory midbrain (VNLL and ICC). After cochlear ablation (Suneja et al., 1998b), also in adult guinea pigs, glycine release declined bilaterally in the DCN, and transient elevations of glycine release occurred at 59 days bilaterally in the medial superior olive. In addition, GABA release in the medial nucleus of the trapezoid body (MNTB) was elevated at 5 days, near the control at 59 days, and elevated again at 145 days. Suneja et al. (1998a) found that post-lesion binding of strychnine declined ipsilaterally in most of the ventral CN and in the lateral superior olive. Changes in strychnine binding relative to that in age-matched controls were interpreted as altered activity and/or expression of synaptic glycine receptors. Binding was down in the ipsilateral DCN and in the anterior part of the contralateral AVCN, and was elevated in the contralateral LSO. Muly et al. (2004) exposed one ear of anesthetized adult chinchillas to a 4-kHz octave-band noise at 108 dB SPL for 3 h, which damaged the cochlea and induced degeneration in auditory nerve fibers (ANFs). During the first postexposure week, before ANFs degenerated in the 2–8 kHz region, glutamatergic synaptic release in the cochlear nucleus (CN) ipsilateral to the deafened ear was elevated and uptake was depressed. By 14 days post exposure, when ANFs had degenerated,

Fig. 8. Tonotopic maps for three groups of cats (a) and comparison between two cats having similar hearing loss but different posttrauma recovery (EAE or quiet) and a control (normal hearing) cat (b,c). a. CF of AI neurons according to the location of the recording site along the anteroposterior axis relative to the CF ~ 8 kHz location in each cat. b. ABR threshold shifts. c. CF of AI neurons according to the location of the recording site along the anteroposterior axis. The EAE cats, quiet-type cats, and the control cats are represented by filled triangles, open squares, and filled gray circles, respectively. Further explanation in the text. From Noreña and Eggermont (2005).
glutamatergic synaptic release and uptake in the CN became deficient. By 90 days, an increase in transmitter release and in AMPA receptor binding suggested an upregulation of excitatory transmission.

Combining the data from this research group (Table 2) we may conclude that decreases in excitatory activity go together with increases in inhibitory activity and vice versa. Reversals in the direction of the excitatory activity changes were found in the brainstem between day 59 and 90–145 days. Such reversals did not occur for inhibitory activity.

4.2. Protein markers for excitation and inhibition

Milbrandt et al. (2000) characterized noise-induced changes in GABA markers in the IC. Four groups (unexposed control, 0 h post-exposure, 42 h post-exposure, and 30 days post-exposure) of 3-month old male Fischer 344 rats that were exposed to a high intensity sound (12 kHz, 106 dB) for 10 h. The resulting hair cell damage was primarily confined to the basal half of the cochlea. Milbrandt et al. (2000) observed a significant decrease in glutamic acid decarboxylase (GAD65) immunoreactivity in the IC membrane fraction compared to controls at 0 h and 42 h post-exposure, with complete recovery by 30 days post-exposure. GAD65 and GAD67 are enzymes that catalyze the decarboxylation of L-glutamic acid to GABA. Browne et al. (2012) tested the hypothesis that excessive noise exposure increases expression of markers of excitation and plasticity, and decreases expression of inhibitory markers over a 32-day recovery period. They monaurally exposed adult rats to a 16 kHz, 1/10th octave band of noise at 115 dB SPL for 1-h. Animals were euthanized at 0, 4, 8, 16 or 32 days following acoustic trauma. Browne et al. (2012) provided a 32-day time-course investigation of excitatory protein expression (NR2A, Calb1), inhibitory protein expression (GABA_A, GAD-67) and expression of the growth/plasticity protein GAP-43 in the contralateral and ipsilateral AC, IC and DCN. Compared to controls, noise-exposed animals had significantly lower levels of GABA_A1 in the contralateral AC at day-16 and day-32, lower levels of GAD-67 in the ipsilateral DCN at day-4, lower levels of Calb1 in the ipsilateral DCN at day-0, lower levels of GABA_A1 in the ipsilateral AC at day-4 and day-32. GAP-43 was reduced in the ipsilateral AC for the duration of the experiment. These complex fluctuations in protein expression suggested to Browne et al. (2012) that: “for at least a month following acoustic trauma the auditory system is adapting to a new pattern of sensory input.” The Milbrandt et al. (2000), and Browne et al. (2012) results are summarized in Table 3. Note that all protein expressions decreased after noise trauma for the one-month survival period studied. Browne et al. (2012) suggested: “that the characteristic decrease of inhibition that is observed after acoustic trauma, may not necessarily be due to significant increases of excitatory neurotransmission-related proteins; rather a significant decrease of inhibitory-neurotransmission related proteins which leads to an overall increase in excitation.”

5. A time line of plastic changes following noise trauma

Central tonotopic map reorganization is likely initiated by a decrease in spontaneous and driven firing rates in ANFs as a result of high-frequency hearing loss. This results in an imbalance in the firing rates across ANFs with lower and higher CFs and may induce a cascade of central changes—frequency-specific loss of inhibition and increase of central gain—leading to tonotopic map reorganization (Rajan et al., 1993). It is known that auditory cortical neurons in cats and macaques receive their excitatory inputs from a relative broad frequency band, as reflected in the broad LFP-based tuning curves (Fig. 9; Norena and Eggermont, 2002; Eggermont et al., 2011; Kajikawa and Schroeder, 2011). However, inputs at frequencies surrounding the narrower spike-based frequency-tuning curve of the neuron are usually inhibited or “masked” (Norena and Eggermont, 2003).

At least two different types of inhibitory mechanisms, phasic and tonic, could be involved in the tuning properties of the neurons (Calford et al., 1993; Rajan, 2001; Norena and Eggermont, 2002; Norena et al., 2003). The tonic inhibition (driven by spontaneous activity of afferent inputs) is supposed to spread widely across frequency and to be proportional to the amount of spontaneous firing rate of excitatory inputs. When, as a result of hearing loss the spontaneous firing rates in ANFs are reduced, this tonic inhibition is also reduced, with an imbalance of excitation and inhibition as the result. As a consequence, inputs that were previously inhibited are “unmasked” (Calford et al., 1993; Calford, 2002; Norena and Eggermont, 2003; Norena et al., 2003). The recent findings by Scholl and Wehr (2008) showed that inhibition is abolished for frequencies far below the trauma-tone frequency but markedly enhanced but delayed near the edges of the region of elevated peripheral threshold, thereby allowing excitation to prevail.

Below is a synopsis of the changes that occur in the molecular changes and neural response properties from minutes to several months after the end of the traumatizing sound exposure that may elucidate the differential effects of unmasking and use-dependent synaptic plasticity in producing tonotopic map reorganization.

5.1. Less than six hours after trauma

In the first hour after trauma, significant decreases occurred in the expression of Calb1 (reflecting excitatory transmission) in the ipsilateral DCN, GAD-65 in contralateral IC, GAD-67, GAP-43 and Calb1 in the ipsilateral AC (Table 3). Within hours of mechanical unilateral damage to the organ of Corti in guinea pigs, Robertson and Irving (1989) and Norena and Eggermont (2003) found that shifts in CF toward frequencies spared by the lesions could occur, but thresholds were greatly elevated compared to normal.

In the first 15 min after the trauma, changes in the surround inhibition in cat A1 were observed in spectro-temporal receptive fields (STRFs; Fig. 10) for random multi-frequency stimuli (Valentine and Eggermont, 2004). STRFs were originally described for continuous white noise stimuli in the auditory midbrain (Eggermont et al., 1983) or spectrally rippled noise stimuli in auditory cortex (Klein et al., 2000). On the left-hand side of Fig. 10 the STRF for the pre trauma recording is shown for 65 dB SPL. One notices a circumscribed region with higher than average activation (yellow-to-dark red) around the peak response at 7 kHz. This region has a 25% excitatory frequency-response width of <0.5 octave (yellow-green area). Surrounding the excitatory response area is an
inhibitory one (dark blue). Two hours following the exposure (5 kHz presented for 1 h at 115–120 dB SPL) right-hand side of Fig. 10), the excitatory frequency response area for this neuron was hardly changed (the CF of the neuron was less than 1 octave above the trauma tone frequency) but the inhibitory surround and post-activation suppression has disappeared. As a consequence, the duration of the STRF nearly doubled (Eggermont, 2006). In this example, one could not have deduced the disappearance of the surround inhibition from a broadening of the response area, as previously suggested by Rajan (1998; 2001).

Within the first 15 min after trauma the SFR in cat A1 across the entire CF range was unchanged, whereas the peak cross-correlation coefficient (r) for spike-pair timing was significantly increased (Fig. 7), but only for pairs of neurons with CFs above the trauma tone frequency. After at least 2 h post trauma, the SFR was increased for all CFs and the cross-correlation coefficient was further increased for units with CF > TF (Noreña and Eggermont, 2003). This suggests that at this time point r changes are more indicative about the frequency spectrum of the tinnitus, which is related to the hearing loss (Noreña et al., 2002; Roberts et al., 2008) than the SFR, which occurred indiscriminate of CF.

### 5.2. Within two weeks after the trauma

Two to five days after the trauma, the release of glutamate was reduced in the entire ipsilateral cochlear nucleus, the MSO and MNTB, and the uptake of glycine in the LSO as well (Table 2). Protein markers for inhibitory transmission (GABA<sub>a</sub>, GAD-65 and GAD-67) were decreased for ipsilateral DCN, ipsi and contralateral IC and ipsilateral AC. Markers for excitatory transmission (NR2A and Calb1) were not changed (Table 3).

Multi-unit recordings in the dorsal cochlear nucleus of hamsters exposed to 10 kHz at 125 dB SPL for 4 h (Kaltenbach et al., 1998, 2000) showed mean SFRs that increased from below normal levels at day 2 post-exposure to higher than normal levels at day 5. The mean SFR continued to increase gradually over the next 6 months. Acoustic trauma (10 kHz tone at 124 dB SPL for 1 h) in guinea pigs did not result in SFR changes at 4 h post-trauma but it did after 12 h in the ICC. Two weeks of recovery after acoustic trauma resulted in more neurons with significantly higher SFR compared to control animals (Mulders and Robertson, 2013).

One to three days after the trauma (5 kHz tone, 2 h with 115 dB SPL) hearing and cortical unit thresholds have typically recovered

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### Table 3

Changes in various inhibitory and excitatory related proteins compared to control.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Neurotransmitter proteins</th>
<th>0 hr</th>
<th>2–4 days</th>
<th>16 days</th>
<th>32 days</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCN ipsi</td>
<td>GAD-67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Browne</td>
</tr>
<tr>
<td>DCN ipsi</td>
<td>Calb1</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>Browne</td>
</tr>
<tr>
<td>IC contra</td>
<td>GAD-65</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
<td>Milbrandt</td>
</tr>
<tr>
<td>IC ipsi</td>
<td>GAD-67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Browne</td>
</tr>
<tr>
<td>IC contra</td>
<td>NR2A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Browne</td>
</tr>
<tr>
<td>AC contra</td>
<td>GABA&lt;sub&gt;a&lt;/sub&gt;</td>
<td></td>
<td></td>
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<tr>
<td>AC ipsi</td>
<td>GABA&lt;sub&gt;a&lt;/sub&gt;</td>
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<td>AC ipsi</td>
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<td>Browne</td>
</tr>
<tr>
<td>AC ipsi</td>
<td>GAP-43</td>
<td></td>
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<td></td>
<td>Browne</td>
</tr>
<tr>
<td>AC ipsi</td>
<td>Calb1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Browne</td>
</tr>
</tbody>
</table>

Note that none of the excitatory transmission markers (Calb1 and NR2A) showed any increase. Excitatory proteins are shown in normal font, inhibitory proteins in bold, the plasticity-related protein in italics. Data from Browne et al. (2012) and Milbrandt et al. (2000). ↓ significant decrease; = no significant change compared to controls.
beyond the level found at six hours after the trauma (Eggermont, 2006). When localized hearing losses remain, such as shown in audiograms in Fig. 11a the frequency tuning curves now show CF’s (Fig. 11c) near both edge-frequencies (5 and 12 kHz) bordering the hearing loss range. In an extensive sampling over about a 3 mm cortical area that normally would be tuned to the hearing loss range, all sites show CFs of –4 and –13 kHz (Fig. 11b), with a normal to slightly elevated range of thresholds. Frequency tuning curves are broad, approximately two to three octaves, and well above the mean found in normal cats. Plotting the BW$_{20\text{dB}}$ against distance along the tonotopic axis for three cats shows that on either side of the hearing loss range the BW$_{20\text{dB}}$ values are low whereas in between they are up to three times as high (Fig. 11d). This reflects the unmasking of excitatory regions on either side of the original range of frequency selectivity (cf. Fig. 9).

Seki and Eggermont (2003) found elevated SFRs in regions with reorganization of the tonotopic map compared to the neurons in the non-reorganized cortical regions in the same animals. In these regions the peak spike-pair cross-correlation coefficients were also increased relative to the nonreorganized parts. Furthermore, exposed animals showed higher SFRs at all CFs compared to controls regardless of the presence of cortical reorganization. SFRs were not related to the amount of hearing loss, whereas $p$ was positively correlated with the amount of PTS (Eggermont, 2015a). In addition, as in the less than 6 h after trauma condition, a change in $p$ was only found for regions (CF > TF) where the tonotopic map was reorganized, whereas SFR was increased regardless of the CF.

5.3. More than three weeks after the trauma

At 32 days post trauma, markers for inhibitory transmission were decreased in contralateral and ipsilateral AC, and so was NR2A...
a marker for excitatory transmission in contralateral IC (Table 3). At 59 days after the trauma, glutamate uptake was still decreased in AVCN, DCN, and MNTB, but increased in ICC. Uptake of glycine and GABA_A was increased in the DCN and MSO respectively. At 145 days post trauma, glutamate uptake was only decreased in DCN and increased in VCN, LSO, MSO, MNTB, and ICC. Uptake of glycine and GABA_A was increased in the entire CN, MNTB and decreased in VNLL and ICC (Table 2).

After about three weeks, and depending on the amount of hearing loss, further reorganization of the tonotopic map occurs as described above for the chronic cases (Eggermont and Komiya, 2000; Seki and Eggermont, 2002; Norena and Eggermont, 2005). There were no additional changes in average SFR and cross-correlation coefficients (Seki and Eggermont, 2003; Norena and Eggermont, 2005). Much longer survival times were used by Robertson and Irvine (1989; 35–81 days) and by Rajan et al. (1993; 2–11 months), but the effects on cortical tonotopic map reorganization did not appear to be different for their shortest and longest survival animals. This suggests that most of the electrophysiological changes in cat A1 have reached a steady-state value at ~3 weeks post trauma. Fig. 12 combines the molecular and electrophysiological (SFR) data across this timeline.

Inspecting Fig. 12 suggests that the period between 2 and 16 days is critical for setting up reorganization of the tonotopic maps. During this period inhibition is down without changes in excitation in the IC and A1. In the DCN both excitation and inhibition are down. Spontaneous firing rate in DCN, ICC and A1 is up in this period (and continues to be enhanced after that). The fact that immediately after the trauma changes in SFR do not occur (in DCN and ICC) or that SFR decreases in A1 is understandable from the reduction in excitation in DCN and A1. No changes in excitation occurred in the IC however. Full blown cortical tonotopic map reorganization in A1 after 3 weeks corresponds to the continued downregulation of inhibition in A1.

### 6. Conclusions

Whereas EEG, MEG and imaging studies have shown indications of tonotopic map changes in human auditory cortex following hearing loss, animal studies had shed some light on potential mechanisms, all purportedly related to the changing balance between excitation and inhibition. The age of induction of hearing loss, neonatal, childhood or adult does not appear to affect the final outcome; increased spontaneous firing rates, increased neural synchrony and reorganization of the cortical tonotopic map. However, neonatal induced hearing loss also results in reorganization of the tonotopic map in the inferior colliculus, which does not occur after adult acquired hearing loss. Both unilateral hearing loss and bilateral hearing loss result in the same changes, however in unilateral hearing loss the human studies strongly indicate a changed interhemispheric activation pattern with near disappearance of the contralateral dominance.

Animal studies have shown that the increases in spontaneous firing rate after noise trauma take some time to develop, at least taking a few days in the DCN and IC and then increasing till up to 6 months after the trauma. In primary auditory cortex increases in SFR take only a few hours and then no longer increase up to several months after the trauma. Up to 6 weeks post-trauma SFR increase in the ICC depends on amplification of a normal or slightly reduced SFR in ANFs. In contrast, neural synchrony in primary auditory cortex increases immediately after the trauma and continues somewhat thereafter. Whereas the changes in SFR are independent of the hearing loss, those in neural synchrony appear to be positively correlated with the amount of hearing loss. These changes can be avoided by having the animals recover in an enhanced acoustic environment, matched to the frequency range and amount of hearing loss.

Molecular studies indicate that cochlear ablation has largely the same effects as noise trauma, suggesting that only the hearing loss matters and not the way in which it is acquired. In the brainstem, after 2–5 days post trauma, the glutamatergic activity is reduced, whereas glycineric and GABAergic activity is largely unchanged. At 2 months post trauma, excitatory activity remains decreased but the inhibitory one is significantly increased. In contrast protein assays related to inhibitory transmission are all decreased or unchanged in the brainstem, midbrain and auditory cortex. This also holds for excitatory transmission related proteins immediately after trauma in brainstem and auditory cortex.

Comparison of changes in SFR with the molecular findings suggests that increases in SFR are, at least for 1 month survival, related to decreases in inhibition, and not to increases in excitation. As a final note, the plastic changes in animal auditory cortex, namely a decrease in temporal processing acuity and the reorganization of the cortical tonotopic maps, suggest that such changes, if they occur in humans with hearing loss, may be underlying the problems with understanding of speech.

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Abbreviations

A1: primary auditory cortex
ABR: auditory brainstem response
AC: auditory cortex
AEF: auditory evoked field
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANF: auditory nerve fiber
AVCN: antero-ventral cochlear nucleus
BA: Brodmann area
BDNF: brain-derived neurotrophic factor
BW: bandwidth
CAEP: cortical auditory evoked potential
CAP: compound action potential
CF: characteristic frequency
CN: cochlear nucleus
DCN: dorsal cochlear nucleus
EAE: enhanced acoustic environment
FDG: fluorodeoxyglucose
fMRI: functional magnetic resonance imaging
FRA: frequency response area
GABA: γ-aminobutyric acid
GAD: glutamic acid decarboxylase
GM: gray matter
HI: hearing impaired
IC: inferior colliculus
ICC: central nucleus of the IC
IHC: inner hair cell
LSO: lateral superior olive
MEG: magnetoencephalography
M(FR): geometric mean firing rate
MN1: medial nucleus of the trapezoid body
MU: multi-unit
NH: normal hearing
PET: positron-emission tomography
PVCN: postero-ventral cochlear nucleus
RIF: rate-intensity function
ROI: region of interest
SF: spontaneous firing rate
SEM: standard error of the mean
SG: spiral ganglion
SPL: sound pressure level
TF: trauma-tone frequency
SOC: superior olivary complex
STRF: spectro-temporal receptive field
VBM: voxelbased morphometry
VCN: ventral cochlear nucleus
VNLL: ventral nucleus of the lateral lemniscus