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Review

Tinnitus-related neural activity: Theories of generation, propagation, and centralization

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ABSTRACT

The neuroscience of tinnitus represents an ideal model to explore central issues in brain functioning such as the formation of auditory percepts, in addition to opening up new treatment avenues for the condition in the long-term. The present review discusses the origin and nature of tinnitus-related neural activity. First, we review evidence for the hypothesis that tinnitus is caused by the central nervous system changes induced by sensory deprivation, even when hearing loss is not visible in the audiogram. Second, we suggest that changes in neural activity in individual central structures may not be sufficient to underlie the tinnitus percept. Instead, we propose that tinnitus may arise from functional alterations at multiple levels which promote abnormal propagation of neural activity throughout the network involved in auditory perception. In this context, functional coupling within and between central auditory structures may be especially important to consider. Investigating how sensory deprivation affects functional coupling between areas, which might be reflected in changes in temporal coherence of intrinsic ongoing activity patterns, may give critical insights into the mechanisms of tinnitus.

1. From peripheral to central models: the "classical" arguments and recent developments

We first review the major lines of evidence for why the field has shifted from a peripheral to a central nervous system model of tinnitus. Second, we discuss the question of why a peripheral trigger may drive central nervous system changes, and the underlying neurobiological mechanisms. Third, we consider the observation that some tinnitus subjects have a normal audiogram, and whether this is consistent with the hypothesis of a peripheral trigger for tinnitus.

1.1. The classical arguments

More than 20 years ago, tinnitus was thought to result from aberrant neural activity generated in the periphery of the auditory system. An almost exhaustive list of putative peripheral mechanisms has been reviewed (Jastreboff, 1990). In summary, tinnitus was proposed to result from increased activity in the cochlear nerve. The auditory centers, which were in charge of detecting and interpreting the tinnitus-related activity so as to ultimately produce an auditory percept, were thought to play only a minor role in the generation of tinnitus-related activity (Noreña, 2012).

More recently, however, the tinnitus field has undergone a major paradigm shift, as a central origin of tinnitus-related activity seems to have replaced the former peripheral hypothesis. Developments in basic neuroscience, in particular studies reporting central plasticity after cochlear lesions (Sasaki et al., 1980; Robertson and Irvine, 1989a; Rajan et al., 1993), have been instrumental in generating this shift. Three main arguments, that we call "classical", corroborate a central nervous system origin for the aberrant neural activity underlying the tinnitus percept.

First, while the peripheral models predicted that an increase of spontaneous firing rate (SFR) would be present in the cochlear nerve following tinnitus-inducing manipulations, only a few studies, which used salicylate to induce tinnitus, corroborated this hypothesis (Evans and Borerwe, 1982; Salvi and Ahroon, 1983). On the contrary, more recent studies have converged to suggest that cochlear damage is often accompanied by a large decrease of spontaneous firing-rate and stimulus-induced activity in the cochlear nerve (Liberman and Dodds, 1984; Wang et al., 1997; Heinz and Young, 2004). Second, surgical sectioning of the cochlear nerve, which would suppress tinnitus if the activity driving the percept originated in the cochlear nerve, does not always have this intended effect (House and Brackmann, 1981; Barrs and Brackmann, 1984; Silverstein et al., 1986; Pulec, 1995; Baguley

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et al., 2002). Third, numerous studies have shown that cochlear lesions are followed by central nervous system hyperactivity, and that noise-induced hearing loss can produce neural hypersynchrony (see Section 2). Together, these lines of evidence converged to indicate that the auditory centers themselves likely play a major role in the generation of tinnitus-related activity.

1.2. Why and how do peripheral insults lead to central changes

1.2.1. Tinnitus as the price to pay for preserving neural activity and coding efficiency

A key component of the working model of tinnitus presented above is that a decrease in peripheral drive associated with cochlear lesions eventually leads to hyperactivity in the auditory central nervous system. To understand tinnitus, it is useful to consider why these central changes may occur. One proposal is that they might serve to maintain mean neural activity at a set value and to preserve neural coding efficiency when the central auditory system faces a sensory deprivation (Schaette and Kempter, 2006; Watt and Desai, 2010, 2010; Norena, 2011; Turrigiano, 2011). In brief, homeostatic mechanisms, controlling a "central gain", could regulate the sensitivity of central neurons in order to adapt their input–output functions to the distribution of sensory inputs (Cai et al., 2009). Following sensory deprivation such as hearing loss, spontaneous activity levels and the gain of cochlear fiber input–output functions decrease, and cochlear fiber output saturation is less frequently observed (Liberman and Dodds, 1984; Heinz and Young, 2004). In other words, cochlear fibers provide the central auditory system with reduced activity. In particular, the pre-deprivation maximum firing rate of moderate-to-high threshold cochlear fibers may only rarely be reached. To date, there is no evidence for a compensatory mechanism at the interface between the cochlea and the cochlear nerve, which could preserve cochlear nerve activity following hearing loss (Liberman and Dodds, 1984; Heinz and Young, 2004; Kujawa and Liberman, 2009). As a result, the pre-trauma maximum firing rate of ventral cochlear nucleus (VCN) neurons, which are a direct target of moderate-to-high threshold cochlear fibers, would also be rarely reached. In this context, the adaptive role of a compensatory central gain is two-fold: to maintain mean central nervous system (e.g., VCN) activity at a set-point and to ensure that the dynamic range of VCN neuron firing-rates is efficiently reallocated to fit the modified range of cochlear inputs. However, these putatively adaptive central changes may come at a price: tinnitus could result from a corresponding increase in the spontaneous firing rate of central neurons, or from other byproducts of the central gain increase (e.g., changes in temporal coherence). This central gain increase may also be at the origin of hyperacusis, another condition resulting from hearing loss, which is characterized by an over-sensitivity to sound. A common origin of these conditions is consistent with the observation that tinnitus and hyperacusis are often present together (Dauman and Bouscau-Faure, 2005) and with the idea that hyperacusis may represent a "pre-tinnitus" state (Jastreboff and Hazell, 1993). Besides tinnitus resulting from noise-induced hearing loss, this central gain model could also account for tinnitus induced by conductive hearing loss or prolonged sound deprivation (Midani et al., 2006; Del Bo et al., 2008; Knobel and Sanchez, 2008; Kim et al., 2011).

Observations in other sensory modalities support the idea that a central gain may compensate for sensory deprivation by altering neuronal sensitivity. In vision, for example, transcranial magnetic stimulation (TMS) applied to the occipital cortex can produce the perception of "phosphenes" (flashes of light). The minimum TMS intensity required to evoke phosphenes is interpreted as reflecting visual cortex excitability. Interestingly, this threshold is reduced in blind subjects (Gothe et al., 2002) or 45 min after the onset of light deprivation in normal subjects (Boroojerdi et al., 2000).

1.2.2. Relationship between type of hearing loss and tinnitus

While the central gain model can account for tinnitus induced by a decrease in sensory inputs, a complete model should also account for the observation that subjects with hearing loss do not always present tinnitus (Roberts et al., 2008). Approaching this question will eventually rely on measurements that relate particular pathologies or patterns of hearing loss to tinnitus. However, the model that we have presented makes a number of predictions. Critically, the model suggests that tinnitus relies not only on (1) an increased central gain, but also on (2) a sufficient level of spontaneous activity in the system which is abnormally amplified by this central gain (Norena, 2011). The latter half of the statement may seem counter-intuitive, given that tinnitus is accompanied by reductions in peripheral spontaneous activity (see Section 1.1). However, the normal level of cochlear nerve spontaneous activity is very high (Liberman and Dodds, 1984). Thus, even when reduced it is plausible that cochlear nerve spontaneous activity represents a main source of spontaneous input to the auditory centers. We propose that the balance between changes in central gain and peripheral spontaneous activity levels may influence the probability of developing tinnitus.

In particular, patterns of sensory deprivation which result in an increased central gain, but a relatively preserved spontaneous firing rate in the cochlear nerve, might be most likely to induce tinnitus. This is consistent with the observation that tinnitus can result from reduced sensory input due to outer hair cell loss (Ozimek et al., 2006), conductive hearing loss (Lima et al., 2007), ear wax in the ear canal (Midani et al., 2006), silence (Knobel and Sanchez, 2008) or earplugs (Schaette et al., 2012). Each of these changes is expected to reduce the level and range of input into the system, and thus to increase the central gain. However, this group of manipulations is expected to leave spontaneous firing rates relatively intact, given that the latter property is most sensitive to the functional state of inner hair cells. On the other hand, hearing loss without tinnitus may arise when the balance is shifted, such that increases in central gain are accompanied by stronger reductions in spontaneous firing rates. This may be expected, for example, when hearing loss is primarily driven by damage to inner hair cells.

An additional factor at play might be the degree of cross-modal plasticity accompanying hearing loss, namely enhanced enervation of the cochlear nucleus by somatosensory inputs following hearing loss (Shore et al., 2007; Dehmel et al., 2008). This cross-modal plasticity is expected to change the nature of input to the system, and thus to influence residual levels of spontaneous activity in the auditory pathway. Despite these lines of reasoning, it must be noted that attempts so far to link patterns of pathology (e.g., inner versus outer hair cell loss) to development of tinnitus remain not fully conclusive (Kaltenbach et al., 2002; Bauer et al., 2008).

1.2.3. Mechanisms of central gain change following sensory deprivation

As developed in the previous section, a central gain is thought to adapt the sensitivity of central auditory neurons to the sound level statistics in order to maintain a constant mean activity level and preserve neural coding efficiency. While synaptic depression may be involved in fast adaptive changes during a continuous and fluctuating acoustic stimulation (Wu et al., 2004; Dean et al., 2008), it seems more likely that other mechanisms, related to homeostatic plasticity (Turrigiano, 2011) are involved in mediating the central changes following prolonged sensory deprivation. Homeostatic plasticity mechanisms can be divided into two general categories:

homeostasis of synaptic efficacy and homeostasis of intrinsic excitability (Fig. 1).

Within the first category, synaptic scaling is a mechanism which regulates global synaptic efficacy (i.e., acting on all synapses of a neuron, rather than on a small group of synapses). It has been shown that prolonged reduction of cortical neuronal firing is accompanied by a multiplicative increase of miniature excitatory postsynaptic currents (mEPSPs), while the reverse is observed following prolonged increases in firing (Turrigiano et al., 1998). These effects on mEPSPs are mediated by expression levels of AMPA-type glutamate receptors, which are in turn regulated by calcium influx levels associated with neural activity. Activity deprivation has also been found to decrease miniature inhibitory postsynaptic currents in cortical neurons, due to a reduction of GABA receptor expression (Kilman et al., 2002). Homeostatic regulation of synaptic transmission may also involve presynaptic changes. Indeed, a chronic suppression of neural activity is accompanied by an increase of the number of docked vesicles and the total number of vesicles per synapse. Moreover, neurotransmitter release probability is increased (Murthy et al., 2001).

Results consistent with homeostatic plasticity mechanisms have been observed at various levels of the central auditory pathway. For example, excitatory synapses in the cochlear nucleus are modified following acoustic sensory deprivation (Whiting et al., 2009; Wang et al., 2011). In the inferior colliculus, sensory deprivation has been found to reduce markers of GABAergic inhibition (Milbrandt et al., 2000; Mossop et al., 2000; Argence et al., 2006). Hearing loss also results in homeostatic changes in synaptic strength in the auditory cortex (Sanes and Kotak, 2011).

The homeostasis of neural activity is also mediated by changes in the intrinsic excitability of neurons. Intrinsic excitability is modulated by the activity-dependent regulation of ionic conductances, which are in turn controlled by the expression level and properties of ion channels. For example, preventing cortical pyramidal neurons from firing for two days alters the expression of ion channels, resulting in increased sodium current and decreased potassium current. Ultimately, these changes result in increased firing rates of the deprived neurons (Desai et al., 1999). Recently, the properties of the axon initial segment (site where action potentials are induced and where voltage-gated sodium channels are densely expressed) of auditory brainstem neurons were investigated following auditory deprivation. The length of the axon initial segment increased following sensory deprivation. This was accompanied by an increase in the whole-cell sodium current, membrane excitability and spontaneous firing rates (Kuba et al., 2010). Changes in intrinsic excitability are particularly important as they are central to the process transforming synaptic inputs into spike trains. In particular, they contribute to the adjustment of the input–output function of neurons to the distribution of synaptic inputs. In this context, a downward shift of the distribution of sensory inputs produces an increase of the slope (i.e., gain) and a decrease of the threshold of the input–output function (Watt and Desai, 2010) (Fig. 1).

As developed in this section, the central nervous system has a vast repertoire of mechanisms controlling the mean activity levels and the shape of the input–output function of central neurons. This redundancy may be required to provide the system with the

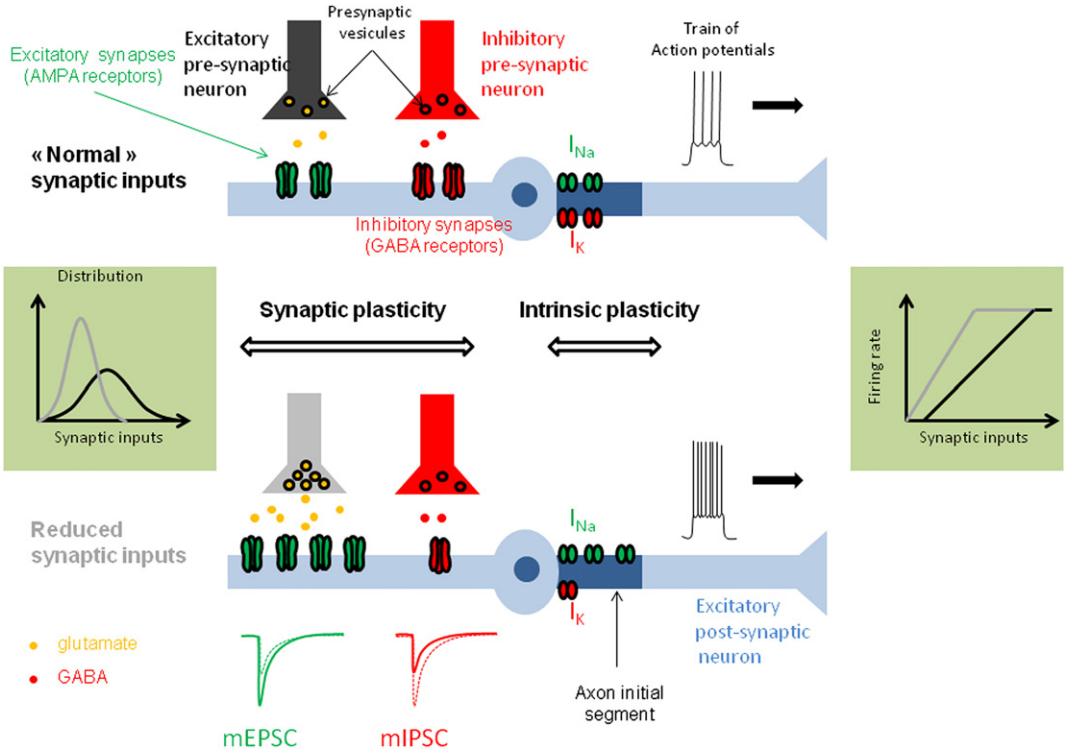

Fig. 1. Basic scheme of homeostatic plasticity following activity deprivation. On the left, the mechanisms related to pre- and post-synaptic homeostasis are illustrated. Activity blockade has been shown to increase AMPA channel expression and decrease GABA channel expression on postsynaptic neurons. These changes result in increased miniature excitatory postsynaptic currents (mEPSCs, before and after activity blockade, dotted and continuous line, respectively) and decreased miniature inhibitory postsynaptic currents (mIPSCs). At the presynaptic level, chronic suppression of neural activity is accompanied by an enlargement of the synapse size and an increase of the neurotransmitter release probability. On the right, homeostasis of intrinsic excitability is shown. I_{Na}: voltage-dependent sodium channels; I_K: voltage-dependent potassium channels. Activity blockade increases I_{Na} and decreases I_K. The distribution of synaptic inputs and the input–output function of the post-synaptic neuron are shown at the extreme left and right, respectively. At the extreme left, the distribution of synaptic inputs are represented (black line: before activity deprivation, gray line: after activity deprivation). At the extreme right, the firing rate of the post-synaptic neuron as a function of the synaptic inputs is represented. Overall, these changes combine to preserve mean neural activity around a set point. As a side effect, such changes may also result in increased spontaneous activity.

necessary flexibility to adapt neural properties to an ever-changing pattern of sensory inputs.

1.3. Evidence for cochlear damage in tinnitus subjects with normal audiograms

While influential, the proposition that tinnitus results from central changes induced by cochlear lesions does not, at first sight, account for tinnitus in subjects with a normal audiogram. However, several recent studies suggest that cochlear lesions can be present even when an audiogram is normal, and are thus consistent with the idea that central changes and tinnitus may be initially triggered by peripheral auditory system deficits. In one recent study, a moderate noise trauma induced reversible hearing loss in mice, as assessed by compound action potentials, auditory brainstem responses and acoustic distortion products. However, while the hearing thresholds (analogous to the audiogram) recovered to normal values after several days or weeks, nearly 50% of the high-frequency region cochlear fibers were degenerated, and the number of synaptic ribbons (structure involved in vesicle delivery to the active zone) of inner hair cells was correspondingly reduced (Kujawa and Liberman, 2009). One interpretation of these results is that the normal hearing thresholds following recovery resulted from intact low-threshold cochlear fibers, while the high-threshold fibers underwent long-term damage.

A recent study carried out on subjects with normal audiograms, and either with or without tinnitus, investigated whether more sensitive measures of sensory-transduction were impaired in the tinnitus subjects (Schaette and McAlpine, 2011). Auditory brainstem responses were obtained in both groups from clicks presented at high levels (90 and 100 dB SPL). The high levels of stimulation used in this study "saturated" the (potentially intact) low-threshold cochlear fibers, allowing assessment of high-threshold fiber functioning. The amplitude of wave I of the auditory brainstem response was reduced in tinnitus subjects compared to non-tinnitus subjects, suggesting the presence of cochlear lesions (of high-threshold cochlear fibers) in the tinnitus group. In contrast, the amplitude of centrally-generated wave V was similar in the two groups, arguing for a central gain mechanism compensating for the reduced sensory inputs in the tinnitus group. These results suggest that cochlear damage, particularly affecting high-threshold cochlear fibers, may be present in tinnitus subjects with normal audiograms.

In another study, psychophysical tuning curves were used to assess whether cochlear dead regions (cochlear regions that function poorly, if at all) were present following noise trauma (Etchelecou et al., 2011). Cochlear dead regions were found in 70% of the subjects, while 88% of the subjects reported tinnitus. Interestingly, the extent of dead regions diminished over time in approximately 50% of the subjects. The psychophysical tuning curves measured from two subjects, each at two different time points, are shown in Fig. 2. The data highlight the ability of the auditory system to recover from noise-induced hearing loss, as the subjects presented dead regions during the first measurement session but not during the second session. Further, this recovery was accompanied by only a slight change in hearing thresholds, suggesting an additional dissociation between hearing thresholds and other metrics of cochlear function.

Considering the evidence that peripheral (cochlear) damage may be present in tinnitus subjects with a normal audiogram, an easily-administered psychoacoustic task designed to detect this damage could prove useful in clinical settings. The "threshold equalizing noise" (TEN) test is one candidate (Moore et al., 2000; Moore, 2004). In contrast with the traditional audiogram, which is thought to be sensitive to the functional state of low-threshold fibers, the TEN test measures thresholds in noise and thus probes the state of high-threshold fibers. The TEN test is currently used for revealing the presence of cochlear dead regions (a kind of "all-or-none" test, where dead regions are defined as frequency regions where thresholds in noise are at least 10 dB greater than normal). A slight modification could allow this test to be more widely employed for diagnostic purposes, as a kind of screening for impaired functioning of high-threshold fibers. More specifically, hearing thresholds in noise are expected to be slightly above the noise level (1–2 dB) in normal hearing subjects, but more elevated in subjects with cochlear dysfunction. In a previous study, this approach was used to investigate the possible presence of abnormal cochlear functioning in tinnitus subjects with a normal audiogram (Weisz et al., 2006). The average hearing thresholds obtained in noise (presented at 80 dB) were elevated in tinnitus subjects (by 8 dB) compared to those measured in control subjects. The elevations in threshold were observed at frequencies close to the dominant pitch of tinnitus. The results of this study suggest that tinnitus subjects with a normal audiogram may have cochlear lesions within the frequency range of the tinnitus percept.

In conclusion, studies to date support a model whereby tinnitus results from central nervous system changes which are triggered by peripheral lesions. Specifically, homeostatic plasticity mechanisms may regulate a central gain mechanism, and tinnitus might be a side-effect of these changes. More recent studies suggest that even in tinnitus patients with normal audiograms, peripheral lesions can be present. Further studies are required to test and

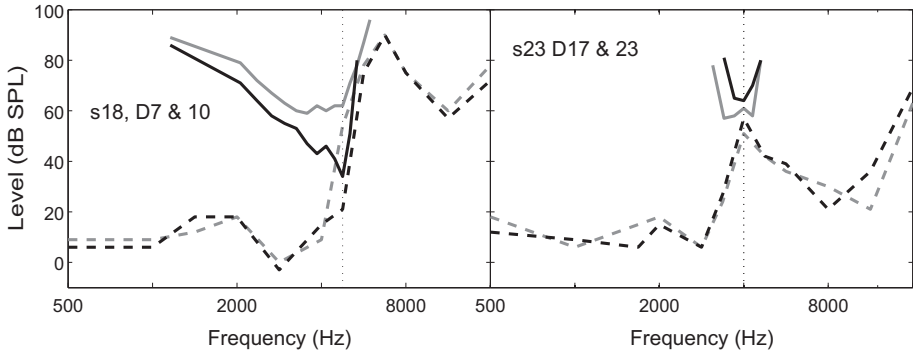

Fig. 2. Psychophysical tuning curves (continuous lines) and absolute thresholds (dotted lines) obtained from two subjects following noise trauma. Left panel: tests were carried out 7 days (gray lines) and 10 days (black lines) after trauma. Right panel: tests were carried out 17 days (gray lines) and 23 days (black lines) after trauma. The vertical line in each panel indicates the frequency of the target tone. One notes a shift in the tip(s) of the PTCs for the first session of tests (suggesting the presence of dead regions), and the V-shape pattern of the PTC for the second session of tests. In the right panel, one observes a recovery of the PTC. On the other hand, absolute thresholds were almost identical between the two test sessions. From Etchelecou et al. (2011).

develop methods aimed at detecting cochlear damage that cannot be measured by the audiogram, and determine whether this damage may account for tinnitus in subjects with normal audiograms.

2. The central neurophysiological changes that may induce tinnitus

2.1. The basic requirements for producing a (phantom) perception

Similar to an auditory percept induced by acoustic stimulation, tinnitus is thought to result from a distributed pattern of neural activity, extending to the areas involved in conscious perception. Beyond this broad description, however, the precise mechanisms underlying the conscious perception of sound are not fully understood. This question has recently been addressed in human subjects using fMRI, EEG/MEG and other electrophysiological techniques (Boly et al., 2007; Gaillard et al., 2009; Sadaghiani et al., 2009; Dehaene and Changeux, 2011). These studies indicate that while subconscious stimulation produces only weak neural activation in primary sensory cortical areas, stimulation that is accompanied by conscious perception results in increased activation within primary areas and the recruitment of a distributed network of non-primary cortical areas including the inferior parietal, frontal and cingulate areas, as well as changes in long-distance temporal coherence between specific brain regions. Based on these studies one can reason that tinnitus, initially triggered by sensory deprivation, may also be accompanied by changes throughout a similar network of brain areas within and beyond the central auditory pathway. Thus, it may be useful to interpret tinnitus-related changes in terms of their likelihood to impact on neural activity propagation up to and throughout this network.

2.2. Changes in spontaneous firing rate in tinnitus

The most straightforward change in neural activity which could underlie tinnitus would be an increase of spontaneous activity levels. Even if tinnitus-related activity originated in sub-cortical structures, an increase of spontaneous firing rate above a certain threshold could propagate through the system and impact on the key areas involved in conscious perception. Therefore, it seems plausible that increases in spontaneous firing rate could result in tinnitus.

Indeed, spontaneous firing rates are known to be increased at virtually all levels of the central auditory system following noise trauma or hearing loss (Kaltenbach and Afman, 2000; Sumner et al., 2005; Noreña and Eggermont, 2006; Bledsoe et al., 2009; Mulders and Robertson, 2009; Vogler et al., 2011). However, the time course of these changes diverges from that of tinnitus. Specifically, it seems that the mechanisms producing an increase of firing rate require between a few hours and a few days to occur (Kaltenbach and Afman, 2000; Noreña and Eggermont, 2003; Bauer et al., 2008; Mulders and Robertson, 2009). On the other hand, many studies have reported that tinnitus is experienced immediately following noise trauma (Loeb and Smith, 1967; Mcfeely et al., 1999; Mrena et al., 2004; Schreiber et al., 2010). These observations together suggest that the acute stages of noise-induced tinnitus may not result from increased spontaneous activity. Rather, elevated spontaneous firing rates may represent a more slowly emerging by-product of another network-level change which occurs earlier in time. Recent studies also question the link between increased spontaneous activity and chronic tinnitus. The effects of acoustic trauma and two ototoxic drugs (cisplatin and carboplatine) on the neural activity in the inferior colliculus were investigated on animals tested behaviorally for tinnitus (Bauer et al., 2008). While behavioral evidence for tinnitus was observed after all treatments, spontaneous firing rates were significantly increased after acoustic trauma and cisplatin treatment but not after carboplatine treatment.

Overall, these results suggest that changes in spontaneous firing rates may not underlie the tinnitus percept, at least at an acute stage. In the next paragraphs, we discuss other properties of neural activity which impact on its propagation, and evidence for changes in these properties in tinnitus.

2.3. Changes in the temporal coherence of neural activity

2.3.1. Temporal coherence in spiking activity

Neural activity can be characterized not only by the rate of discharge of neurons, but by the pattern of discharge within and across areas. Temporal coherence is one descriptor of firing patterns, and relates to the relative timing of the activity between two measurement sites within the same structure or between different structures. Temporal coherence is thought to have important consequences for the propagation of neural activity, and thus may be important in the context of tinnitus.

For example, temporal coherence between two nearby or distant pre-synaptic areas can enhance the probability that those areas will excite a common target post-synaptic structure. Namely, synchronized pre-synaptic spikes arriving at a target neuron are thought to be more efficient in driving that neuron, than are non-synchronized spikes (Abeles, 1991; Diesmann et al., 1999; Siegel et al., 2012). Abeles (1991) proposed a feed-forward neural arrangement, called the synfire chain (synchronous firing chain), emphasizing the impact of neural synchrony on the propagation of neural activity (see Fig. 3).

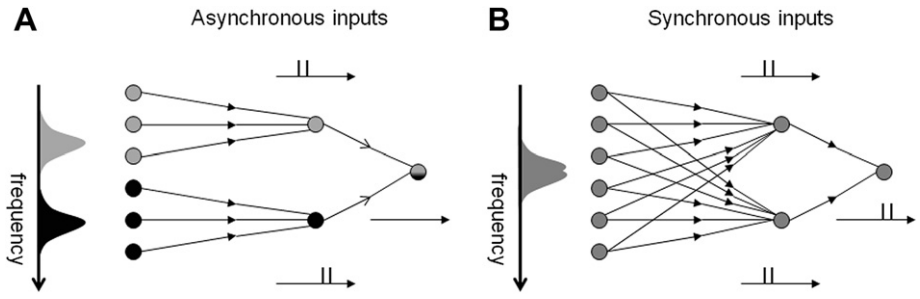

Fig. 3. Effect of presynaptic spike synchrony on the propagation of neural activity. (**A**) Post-synaptic neurons receiving inputs from two different neural populations, presenting different frequency tuning for example, tend to spike asynchronously. If the inputs of these neurons converge on another neuron, they may fail to activate it. (**B**) Post-synaptic neurons receiving inputs from a single neural population, sharing the same frequency tuning for example, tend to spike synchronously. If the inputs of these neurons converge on another neuron, they are more likely to activate it.

Interestingly, acute and chronic hearing loss produce a functional reconfiguration within the auditory cortex that, based on similar reasoning to the synfire chain model, may impact on neural synchrony within this structure (Fig. 4). A cochlear lesion or noise trauma, restricted to a portion of the sensory epithelium (high frequencies, for example) induces a shift in the frequency tuning of cortical neurons. Neurons initially responsive to the affected frequency region now become tuned to nearby frequencies, corresponding to the edge frequency of hearing loss (Robertson and Irvine, 1989b; Rajan et al., 1993; Noreña et al., 2003; Noreña and Eggermont, 2005). Given the normal role for lateral inhibition in sharpening frequency tuning (Suga et al., 1997; LeBeau et al., 2001; Wang et al., 2002), one may reason that such functional changes during acute stages could result from "unmasked" excitatory responses due to a decrease of lateral inhibition. Evidence from other systems would suggest that molecular (homeostatic plasticity), and at later stages, structural changes may further consolidate these functional changes (Darian-Smith and Gilbert, 1994; Buonomano and Merzenich, 1998; Clem and Barth, 2006; Keck et al., 2008; Watt and Desai, 2010).

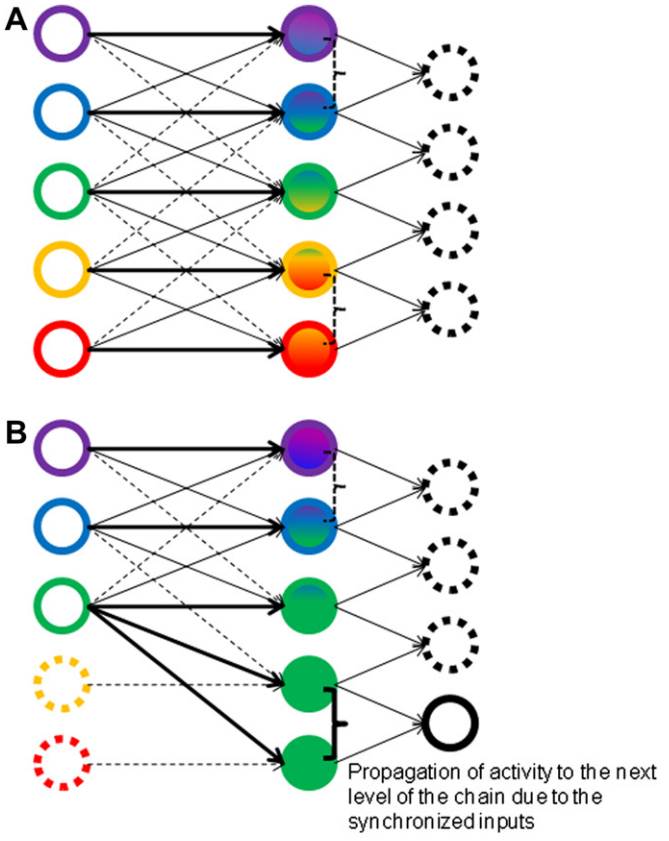

Fig. 4. The schematic illustrates the changes in functional connectivity after hearing loss that lead to tonotopic map reorganization and increased synchrony. (**A**) Colored rings represent thalamic neurons (color corresponding to the characteristic frequency). These neurons provide input to cortical neurons. The connections are divergent. Neurons at the next level (auditory cortex) are filled with colors representing the weight of their thalamic inputs (in terms of frequency), whereas the color of their contour represents their characteristic frequency. As the cortical neurons receive inputs from different sources, the synchrony between them during ongoing activity may be relatively low (dotted brackets). As a result, their combined input may fail to activate neurons at subsequent levels (dotted black circles). (**B**) Dotted circles represent the projection region of a sensory deafferentation. The connectivity between these neurons and the next level is reduced. On the other hand, the connectivity between "green frequency" (edge frequency of the sensory deafferentation) neurons at thalamic level and neurons at cortical level representing the deafferented region is enhanced. As a result, the cortical neurons become more sensitive to the green frequency. The neurons within the reorganized cortical region (newly sensitive to the "green frequency") receive common inputs from the green neurons at the lower level. This might increase synchrony between neurons within the reorganized area (and to a less extent, between this region and the edge region). This population of neurons might be more effective in activating neurons at subsequent stages.

Given that neurons across the reorganized area (those formerly representing the region of hearing loss, and those formerly representing the edge region) now receive the same "copy" of sensory inputs (originating from the edge-frequency of hearing loss), the synchrony of spiking activity among these neurons is expected to increase (Fig. 4B). Indeed, several studies have reported significant changes in neural synchrony in auditory cortex following noise trauma (Komiya and Eggermont, 2000; Seki and Eggermont, 2003; Noreña and Eggermont, 2006; Engineer et al., 2011). Interestingly, one of these studies reported increased neural synchrony immediately after noise trauma, at times before changes in spontaneous firing rate emerged (Noreña and Eggermont, 2003). At these early time points, the increase in synchrony was limited to neurons with a pre-trauma characteristic frequency above the trauma frequency.

These increases in neural synchrony within the auditory cortex are expected to favor the propagation of spontaneous activity through the corresponding regions, i.e. the trauma-frequency representation region. The rapid time course of such changes implies that the propagation of activity could be enhanced before spontaneous firing rates are increased (see previous section). The altered flow of activity that results, if it affects the network involved in auditory perception, may contribute to the acute tinnitus percept.

2.3.2. Changes in the temporal coherence of sub-threshold ongoing activity

An additional factor which impacts on neural activity propagation is the temporal coherence within sub-threshold "ongoing" (i.e., intrinsic or spontaneous) brain activity. Since Hans Berger and his discovery of the alpha rhythm, it is well known that ongoing activity measured from populations of neurons is modulated most prominently at certain frequencies. This rhythmic behavior might reflect the existence of intrinsic neural oscillations, sometimes related to internal motor or sensory sampling routines (Buzsáki, 2006; Schroeder et al., 2010). Alternatively, this behavior may be driven by a combination of the dynamics of neuronal networks (which function at preferred timescales) and/or rhythmic stimulus properties. Regardless of the origin of rhythmic ongoing activity, its presence implies that neuronal ensembles can shift in a coherent manner between states of low or high excitability. The degree of temporal coherence in ongoing brain activity, whether spontaneous or stimulus-induced, has been proposed to play critical roles in various cognitive processes such as perception, attention, and even consciousness (Crick and Koch, 2003; Lakatos et al., 2005; Fries et al., 2007; Busch et al., 2009; Uhlhaas et al., 2009; Wyart and Sergent, 2009; Panzeri et al., 2010; Schroeder et al., 2010).

Ongoing rhythmic changes in excitability are not necessarily accompanied by perception (but see the model of Llinás below), even though their amplitude can be as large as that of sensory-evoked responses (Makeig et al., 2002). However, the state of ongoing activity will affect the likelihood that incoming activity will excite a structure and be propagated (VanRullen and Koch, 2003; Busch et al., 2009; Mathewson et al., 2009; Vanrullen et al., 2011; Siegel et al., 2012). In a recent study which illustrates the impact of ongoing rhythms on neural propagation and perception, the visual cortex was activated through transcranial magnetic stimulation so as to induce phosphenes, while cortical activity was simultaneously recorded with EEG (Dugué et al., 2011). Interestingly, it was found that the probability of perceiving phosphenes varied (by about 15%) with the phase of ongoing alpha oscillations. Thus, the state of temporally coherent fluctuations in excitability can affect perceptual detectability of sensory stimuli.

Additionally, the temporal coherence in the ongoing activity between two brain areas affects neural activity propagation between them. For example, if the sending and receiving areas oscillate at the same frequency, with an "optimal" phase difference (pre-synaptic inputs arriving at the "preferred" phase of post-synaptic neurons), the probability for the neural activity to be successfully transmitted will be enhanced (Womelsdorf et al., 2007; Siegel et al., 2012). More generally, temporal coherence (not necessarily rhythmic) between pre- and post-synaptic areas critically affects the fidelity of information transfer between them.

We next separately consider evidence in tinnitus for changes in brain rhythms within single regions, or for changes in the temporal coherence of brain rhythms between regions, and their possible significance.

2.3.2.1. Temporal coherence of ongoing activity within single brain regions. Changes in brain rhythms within a single area may reflect the degree of temporal coherence within that area. This interpretation comes from considering the mechanistic origin of brain rhythms. The rhythms observed with macroscopic recording techniques typically employed in human studies, such as EEG and MEG, as well as local field potential measurements in animals, reflect the degree of synchronous activity in geometrically organized local neuronal ensembles (Mitzdorf, 1985). Thus, one interpretation is that changes in the strength of macroscopic activity fluctuations reflect changes in the degree of synchrony or temporal coherence of the local neuronal ensembles being sampling from.

Rodolfo Llinas developed a model suggesting that tinnitus may be caused by altered brain rhythms, based primarily on considering how sensory deafferentation was expected to alter physiological properties of the thalamocortical system (Llinás et al., 1999, 2005). In brief, an oscillation at around the theta (4–8 Hz) frequency was proposed to emerge in thalamic neurons representing the deafferented region, due to the reduced sensory input and the resulting thalamic cell hyperpolarization (Llinás and Jahnsen, 1982; Tsien et al., 1988). In turn, this oscillation would entrain the non-specific (nonlemniscal) thalamocortical system, thus promoting large scale oscillatory thalamocortical coherence at this low frequency. At the cortical level, the slow and coherent oscillation would reduce the amount of lateral inhibition reaching an adjacent area (edge region of hearing loss), leading to the emergence of gamma activity in this region. This gamma activity was proposed to underlie the tinnitus percept. This model does not appear sufficient to account for the perceptual characteristics of tinnitus, because it predicts a tinnitus pitch at the edge frequency of hearing loss, while tinnitus has been shown to be above that frequency (Norena et al., 2002; Roberts et al., 2006; Sereda et al., 2011). However, based on cellular and anatomical considerations, it made predictions that were influential regarding the oscillating behavior of cortical neurons following sensory deprivation.

Some studies have reported physiological results in line with this model (Weisz et al., 2005; van der Loo et al., 2009). In one MEG study, the amplitude of brain rhythms recorded during silence were compared between controls and tinnitus subjects. The authors reported enhanced activity in the delta frequency range, and decreased activity in the alpha range, in tinnitus subjects (Weisz et al., 2005). A later study showed that enhanced delta band activity in tinnitus subjects was reduced following residual inhibition, a manipulation which transiently reduces the tinnitus percept (Kahlbrock and Weisz, 2008). This corroborated a potential role for enhanced delta activity in the tinnitus percept. Increase amplitude of gamma band activity has also been reported in tinnitus subjects (Weisz et al., 2007). In a separate study, a significant positive correlation was reported between gamma band activity in the auditory cortex contralateral to the tinnitus ear and tinnitus loudness, as assessed from a visual analog scale (van der Loo et al., 2009). In contrast, a different pattern of results was reported more recently on subjects experiencing acute tinnitus. MEG recordings were carried out on musicians following band practice, when temporary hearing loss and tinnitus were experienced (Ortmann et al., 2011). As tinnitus was transient following the noise exposure, ongoing activity could be compared between times when tinnitus was present or absent. In 13 out of 14 cases, transient tinnitus was accompanied by increased gamma activity, but only in the right auditory cortex. If such increased gamma was related to the percept, it would predict that tinnitus would be perceived only in the left ear. However, the tinnitus was perceived either bilaterally or in the right ear in 11 out 14 subjects. Tinnitus was not accompanied by altered delta or alpha band activity, as reported in earlier studies. Finally, the results of another MEG study do not corroborate the hypothesis suggesting that gamma activity constitutes the neural correlates of tinnitus loudness. Intriguingly, while the correlation was positive between gamma power and tinnitus loudness in residual inhibition, the correlation was the opposite in residual excitation (Sedley et al., 2012).

The discrepancies between these studies could relate to the acute versus chronic nature of tinnitus being studied in different cases. Additionally, it is unknown whether the changes reported in these studies relate to the tinnitus percept itself, versus other accompanying changes such as the extent of hearing loss (Adjamian et al., 2012), or due to the effects of attention or distress (Joos et al., 2012).

Much less is known about whether brain rhythms are altered in animal models of hearing loss and tinnitus. In a recent study, we explored whether tinnitus inducers alter the pattern of ongoing activity in the auditory cortex of awake rodents. We did not observe increased activity in the delta band following noise trauma or salicylate administration. On the other hand, a reduction of cortical activity in frequency bands above 10 Hz was observed (Noreña et al., 2010). However, this study used electrodes with relatively low impedance that sample from a large cortical volume. This may have prevented revealing the putative fine-scale neural changes related to noise trauma and salicylate administration, which could be restricted to the deafferented region of the auditory cortex.

The studies above indicate that a consistent picture has not emerged, regarding alterations in brain rhythms within single regions in humans or animal models following tinnitus induction. Additionally, the impact of such changes on sensory processing is not yet fully understood, although we proposed that increased oscillation amplitudes within single regions may reflect increased synchrony of local neuronal ensembles.

2.3.2.2. Temporal coherence of ongoing activity between brain regions. A putative neural correlate of tinnitus may relate to altered temporal coherence of ongoing neuronal activity between brain areas. As mentioned previously, an auditory percept is likely to arise through a distributed network mechanism. Thus, tinnitus is expected to be accompanied by changes to the configuration of this network, which may be visible as changes in temporal coherence across brain areas.

Large-scale changes involving remote brain areas have recently been explored with MEG recordings in tinnitus subjects (Schlee et al., 2008, 2009). In particular, using phase locking measures (Lachaux et al., 1999), it was shown that the degree of coupling in ongoing neuronal activity between remote areas (left and right frontal cortices, anterior cingulate cortex, left and right temporal cortices, left and right parietal cortices, posterior cingulate cortex) was altered in tinnitus subjects. Namely, the coupling was significantly reduced in the alpha frequency band, but increased within the gamma frequency band (Schlee et al., 2009). The majority of

significant coupling involved the left temporal cortex in subjects with short tinnitus duration. On the other hand, in subjects with a long history of tinnitus, the increased coupling was less pronounced within left temporal cortex, but other regions such as the anterior cingulate cortex and the left parietal cortex became integrated into the network. These studies point towards changes between auditory and nearby cortical areas in the initial stages of tinnitus, which may relate to the emergence of the tinnitus percept. It is possible that more widespread changes at later stages could be involved in other dimensions of the condition (see below).

Overall, studies addressing altered temporal coherence in tinnitus seem a promising avenue of future research, given the distributed nature of the network involved in auditory perception. However, in interpreting such changes it will be important to consider which aspect of the condition they might relate to. For example, altered auditory-limbic interactions have been proposed in tinnitus, which may relate to changes in the perceived importance of the tinnitus percept or its emotional salience (Rauschecker et al., 2010; Kraus and Canlon, 2012). Some researchers have recently focused on neural changes relating to the affective dimensions of the condition (De Ridder et al., 2011). At a more fundamental level, given the potential significance of altered somatosensory-auditory multisensory interactions in the generation of tinnitus (Shore et al., 2007), one may expect to observe altered connectivity between these modalities. Changes in these separate aspects or components of the tinnitus condition likely involve separate brain networks, which may overlap to varying extents with the network involved in auditory perception itself. Intriguingly, to our knowledge no animal studies have yet addressed whether changes in temporal coherence between brain areas occur following tinnitus induction. Such studies may be particularly informative in revealing network-level changes associated with tinnitus. In addition, measurements of temporal coherence have the distinct advantage of being "translational". In other words, related measurements (e.g., MEG, EEG, and local field potential) can be performed in both humans and in animals. This allows animal studies to be guided by observations in human subjects, and in turn for mechanistic insights gained from animal studies be used to interpret and direct future measurements made in human subjects.

3. The centralization of tinnitus

We and others have emphasized the idea that tinnitus likely involves a distributed network, involving areas in addition to the peripheral and central auditory pathways themselves (Schlee et al., 2009; Rauschecker et al., 2010; De Ridder et al., 2011). Recent studies also provide evidence that the neural changes associated with tinnitus may become progressively "centralized" over time, i.e. less dependent on the auditory periphery or low-level auditory structures (see below). However, while structures outside of the auditory pathway may play an increasingly important role in mediating the salience- and distress-related components of tinnitus, several pieces of evidence argue for a key persistent role for the central and even peripheral auditory pathway in driving the tinnitus percept.

Recent MEG data obtained in tinnitus patients (reviewed above) showed that the increased coupling in the gamma band in tinnitus subjects involves a more distributed, centralized network in subjects with long tinnitus duration compared to subjects with short tinnitus duration (Schlee et al., 2009). The hypothesis that the tinnitus network could be progressively centralized over time is corroborated by studies in animals at "lower" levels of the feed-forward auditory pathway. While cochlear ablation or lesions carried out 8 weeks after noise trauma prevented the trauma-induced increase of spontaneous firing rate in the IC (Mulders and Robertson, 2009), a similar cochlear ablation carried out 12 weeks after the noise trauma was ineffective (Mulders and Robertson, 2011). Similarly, it was shown that bilateral DCN ablation performed 3–5 months after noise trauma was ineffective in abolishing behavioral evidence for tinnitus, while ablating DCN bilaterally prior to tinnitus induction (before noise trauma) prevented the development of tinnitus (Brozoski and Bauer, 2005; Brozoski et al., 2012). These studies argue for the necessity of low-level central auditory structures (cochlea and DCN) in the development of tinnitus, but suggest that chronic tinnitus can be driven independently of these structures.

On the other hand, several studies suggest that the tinnitus-related network can be persistently-influenced or modulated by activity originating in the auditory pathway, and more specifically in the peripheral auditory system. Indeed, in a large proportion of subjects, the loudness of tinnitus can be modulated by acoustic stimuli which result in masking and residual inhibition (Feldmann, 1971; Terry et al., 1983). These results suggest that tinnitus-related activity and stimulus-induced activity originating in the periphery interact in the majority of subjects (Roberts et al., 2008). Moreover, it is well-known that electric stimulation provided by cochlear implants (Quaranta et al., 2004; Baguley and Atlas, 2007) and, to a lesser extent, acoustic stimulation provided by hearing aids (Surr et al., 1985; Folmer and Carroll, 2006; Trotter and Donaldson, 2008; Schaette et al., 2010; Searchfield et al., 2010) can reduce tinnitus in some subjects. It must be acknowledged, however, that in all of these studies the acoustic or electric stimulation is accompanied by auditory perception. Therefore, these data leave open the possibility that the tinnitus-related network has become independent of spontaneous activity originating in the cochlear nerve and flowing through the auditory system.

Other findings provide evidence that the tinnitus-related network (including cortical areas) remains influenced by spontaneous activity originating in the peripheral auditory system, at least in some tinnitus patients. Cazals and collaborators made the serendipitous finding that positive current applied at the promontory or at the round window could suppress tinnitus in some subjects (Cazals et al., 1978, 1984; Portmann et al., 1979; Aran et al., 1983). Interestingly, the positive current was able to suppress tinnitus without producing an auditory percept. On the other hand, negative current was able to induce an auditory percept, but did not result in the suppression of tinnitus. The fact that negative, but not positive current, produced an auditory percept suggests that cochlear nerve activity was reduced by the positive current (Konishi et al., 1970; Teas et al., 1970; Schreiner et al., 1986). It was hypothesized that as a consequence of this neural suppression, spontaneous activity in the cochlear nerve that would normally propagate to and activate the tinnitus-related network now failed to do so. Separately, the phenomenon of residual inhibition, in which tinnitus is transiently suppressed after the offset an acoustic stimulation (Terry et al., 1983; Roberts et al., 2006, 2008), may also be consistent with the idea that tinnitus is influenced by peripheral spontaneous activity. Residual inhibition could be accounted for a persistent suppression of spontaneous neural activity, due to a neural adaptation process acting at the level of the cochlear nerve. One notes that residual inhibition could also be accounted for by neural adaptation acting at higher levels of the auditory pathway. In summary, we propose that any treatment reducing spontaneous activity in the cochlear nerve, or even at higher levels in the auditory pathways, would decrease tinnitus loudness (Norena, 2011).

Importantly, the hypothesis that spontaneous activity originating in the periphery may play a persistent role in tinnitus is not mutually exclusive with the idea that subcortical stages of the

central auditory system also play an active role in tinnitus generation. Rather, in our conception, subcortical changes may serve to "amplify" residual ongoing activity which is present in the peripheral system. While these results stand in apparent contrast to the animal lesion studies reported above, they have some support in lesion studies in tinnitus patients. The failure of cochlear nerve sectioning to abolish tinnitus in all cases is often used as evidence in support of a central model of tinnitus; however, one could rather emphasize the observation that this procedure does alleviate tinnitus in some subjects (House and Brackmann, 1981; Barrs and Brackmann, 1984; Silverstein et al., 1986; Pulec, 1995; Baguley et al., 2002). Overall, these results leave open the possibility that in some subjects, tinnitus could be driven by peripheral spontaneous activity, which may be abnormally amplified by central auditory structures and propagate throughout the cortical network involved in conscious perception.

4. Conclusion

In the present article, we review evidence for the hypothesis that tinnitus results from changes in the central nervous system, initially triggered by peripheral insults and/or sensory deprivation. Recent studies indicate that even in tinnitus subjects with normal hearing thresholds, peripheral damage can be present and thus could trigger the condition. We suggest that reduced peripheral sensory input activates homeostatic plasticity mechanisms which result in an increased central gain, and that tinnitus may result as a byproduct of this process. We next review the putative central nervous system changes that may underlie the tinnitus percept, emphasizing that a distributed network of areas underlying conscious auditory perception are likely involved. Thus, we consider how observed neural changes accompanying tinnitus might impact on the propagation of activity throughout this network. We suggest that observed increases in spontaneous activity within individual central structures may not be enough to account for tinnitus. Instead, changes in temporal coherence, a property which strongly impacts on the propagation of neural activity, may be important. We review studies suggesting that noise-induced hearing loss and the accompanying cortical reorganization alters neural synchrony within auditory cortex. Recent studies have begun to measure temporal coherence in ongoing activity between brain regions; future animal and human studies along these lines may prove to be a useful way to explore functional alterations to the network. To conclude, we discuss recent evidence for increased "centralization" of the neural correlates of tinnitus. We suggest that while the network underlying tinnitus may evolve over time, the tinnitus percept is persistently influenced by the feedforward auditory pathway and in some cases may remain dependent on the spontaneous activity flowing through the auditory pathways.

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