Tinnitus: maladaptive plasticity?

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Tinnitus is a symptom, not a disease. Tinnitus is often accompanied by hyperacusis as well as hearing loss. Tinnitus is foremost not an auditory disorder but a particular consequence of hearing loss, and then only in about 1/3 of the cases. Tinnitus can also result from insults such as whiplash, via somatic-auditory interaction in the dorsal cochlear nucleus. These are examples of bottom-up mechanisms that may underlie tinnitus. Much is known about necessary neural substrates of tinnitus, but much less about the sufficient ones. I will review proposals from animal research for these neural correlates, i.e., increased spontaneous firing rates, increased neural synchrony and reorganized cortical tonotopic maps. These can occur following noise trauma, but also following long-term exposure to non-traumatic (< 70 dBA) sounds. Homeostatic plasticity may play a role. I will compare these findings with what is known from human imaging and electrophysiology in tinnitus patients, and suggest that animal studies and human findings related to tinnitus are so far not fully compatible.

INTRODUCTION

Tinnitus, defined as the percept of sound in the absence of external sounds, is common. Its average prevalence ranges from about 7% in adolescents to about 17% in the elderly. The most common cause is hearing loss, in particular noise-induced hearing loss. However, head and neck injuries also constitute a large percentage, presumably through the interaction of somatosensory and auditory inputs in the dorsal cochlear nucleus (DCN). Ototoxic drugs that do not cause permanent hearing loss such as salicylates present only a small fraction of the etiology. Furthermore, stopping their use typically ends the tinnitus. One of the conundrums is that only 30% of people with hearing loss develop tinnitus, whereas in those that develop it, at most half find the tinnitus bothersome. This suggests that top-down influences, such as attention, effects of stress, and potentially central gating mechanisms play a role in the tinnitus percept (Roberts *et al.*, 2010; 2013).

Tinnitus is a conscious percept, namely, people who have tinnitus are aware of it and can express to others how it sounds. Consciousness most likely has a solid neural correlate (De Ridder *et al.*, 2011). One of the burning questions facing animal research into tinnitus must thus be: Are animals conscious of their tinnitus? According to Ward (2011) conscious percepts are thalamocortical based, thereby putting mammals firmly in possession of the putative neural substrate. But can they express the presence of their tinnitus? Behavioral tests in animals generally do not

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rely heavily on thalamocortical activity; however, they may reflect subthalamic changes in spontaneous activity or in synaptic gain, or both. For instance, cortical ablation generally allows relearning of conditioned response and hardly affects pre-pulse (or gap) startle reflexes (Eggermont, 2013). Understandably, tests that can unambiguously indicate whether an animal perceives tinnitus are essential to advance tinnitus research.

ANIMAL MODELS OF TINNITUS

Laboratory studies have shown that tinnitus may develop in humans almost immediately after exposure to loud traumatic sounds. Animal studies can be used to discover the neural substrates related to such early-onset, and often transient, tinnitus. After traumatic noise, prolonged exposure to occupational or recreational noise, or following slowly acquired losses during aging, tinnitus may over time develop from an intermittent presence to a chronic status, and likely acquire a dominant central contribution.

So far, animal models of tinnitus have concentrated on acute or chronic application of salicylate and on acute and chronic exposure to traumatic noise. Neural correlates of these applications form presumed substrates for tinnitus. Currently, most animal research is combined with behavioral tests. As I have outlined elsewhere (Eggermont, 2013), the results of these tests are not straightforward for the determination of the presence of tinnitus.

Spontaneous activity

Let us focus on the neurobiological correlates of noise-induced hearing loss, in particular those that relate to spontaneous activity, as this most likely relates to tinnitus. A potential neural correlate of tinnitus is increased spontaneous firing rate (SFR). Typically, SFR does not change in animals with aging, neither in dorsal cochlear nucleus (Caspary *et al.*, 2005) nor in auditory cortex (Turner *et al.*, 2005). Thus, aging in itself is unlikely to be a tinnitus-inducing factor, albeit that it may enhance pre-existing tinnitus given the increased incidence of tinnitus with age.

After noise trauma, the SFR in cat auditory nerve fibers was significantly reduced (Liberman and Kiang, 1978). *In vivo* experiments in hamster dorsal cochlear nucleus indicated massive increases in SFR 5-180 days after noise exposure (Kaltenbach *et al.*, 2000). Complete or nearly complete section after 4 weeks of ascending (Zacharek *et al*., 2002) or descending inputs (Zhang *et al.*, 2006) did not significantly affect the magnitude of SFR in the dorsal cochlear nucleus, suggesting that increased SFR is either a self-contained neural network phenomenon or reflects intrinsic cell changes. The increase in SFR in hamster dorsal cochlear nucleus correlated with the strength of the behavioral index of tinnitus (Kaltenbach *et al.*, 2004). Vogler *et al.* (2011) investigated SFRs in the ventral cochlear nucleus (VCN) of guinea pigs exposed for 2 h to a 10-kHz tone presented at 124 dB SPL. After a 2-week recovery period, the mean SFR in noise-exposed ears was significantly

elevated (by a factor of about two) compared to sham controls. This was more evident in primary-like and onset categories of neurons.

The independence of SFR from cochlear input demonstrated in the DCN (see above) could not be replicated for recordings in the central nucleus of the inferior colliculus (ICC) in noise-exposed (10-kHz tone at 124 dB SPL for 1 h) guinea pigs. The increase in SFR ceased after cochlear ablation, cochlear cooling, or perfusion with a pre-synaptic transmitter release inhibitor, or after destroying the post-synaptic receptors with kainic acid (Mulders and Robertson, 2009).

The time of onset of increased SFR in ICC was present by 12 h post acoustic trauma, whereas data obtained within approximately 4 h of the cessation of acoustic trauma showed no evidence of hyperactivity. These data suggest that hyperactivity in the inferior colliculus (IC) is a relatively rapid plastic event beginning within hours rather than days post cochlear trauma. Hyperactivity did not show any further systematic increase between 12 h and up to 2 weeks post acoustic trauma. At recovery times of 12 and 24 h, hyperactivity was widespread across most regions of the IC, but at longer recovery times it became progressively more restricted to ventral regions corresponding to the regions of the cochlea where there was persistent damage (Mulders and Robertson, 2013).

Recovery after acoustic trauma resulted in more neurons with high SFR compared to control animals, resulting in an increase in the average SFR. At recovery times up to 4 weeks after the exposure, the increased SFR disappeared when cochlear input to the ICC was destroyed. Thus, the hyperactivity in the ICC after acoustic trauma is dependent on activity in the contralateral cochlea. How this could happen, with the persisting hyperactivity in the DCN after cochlear ablation at about the same post-recovery time, is unclear. However, the VCN may provide the dominant input to the ICC and determine the SFR. This is likely, as we have seen that after chronic trauma SFRs are increased in the VCN (Vogler *et al.*, 2011). When the recovery time after acoustic trauma is extended to 8 and 12 weeks, cochlear ablation does not significantly decrease the increased spontaneous activity measured in the IC. This demonstrates that central hyperactivity that develops after acoustic trauma evolves from an early stage, when it is dependent on continued peripheral afferent input, to a later stage in which the hyperactivity is intrinsically generated within the central nervous system (Mulders and Robertson, 2011).

In cat primary auditory cortex (AI), a significant increase in SFR occurred at least 2 hours after the trauma, but not immediately (< 15 min) following it (Noreña and Eggermont, 2003). At least 3 weeks after the trauma, the SFR was significantly higher than in controls at all characteristic frequencies (CFs) tested, so increased SFR in AI is not restricted to the region of the hearing loss, although that region showed a more pronounced increase (Noreña and Eggermont, 2006).

The degree to which spike firing from two different, simultaneously recorded, neurons is time-locked or synchronized can be quantified by the cross-correlogram (Eggermont, 1992). Effects of acute noise trauma on neural synchrony were studied by Noreña and Eggermont (2003) in AI. A significant increase in peak cross-

correlation coefficients was apparent within 15 minutes of the trauma, and increased by a further 50% at 2 h after the trauma (Fig. 1). This suggests an important role for neural synchrony in the generation of tinnitus, potentially eclipsing that of increased SFR. Several weeks to months after the trauma, all neuron pairs in the reorganized region of auditory cortex showed significant neural correlations (Noreña and Eggermont, 2005). Weisz *et al.* (2007) proposed that gamma band activity, which is increased in tinnitus patients, may reflect the synchronous firing of neurons within the auditory cortex and constitute the neural code of tinnitus.

Long-term exposure to different types of non-traumatic acoustic environments also results in changes in SFR activity in the cat AI (Munguia *et al.*, 2013). Four different groups of adult cats were exposed to moderate-level (~70 dB SPL) behaviorally irrelevant sounds for several weeks to months, and their SFRs were compared with those in control cats. The sounds consisted of random multi-frequency tone pip ensembles with various bandwidths (2-4 kHz, 4-20 kHz, and a pair of third-octave bands centered at 4 and 16 kHz), as well as a "factory noise". Auditory brainstem response (ABR) thresholds, ABR wave-3 amplitudes at ~55 and 75 dB SPL, and distortion product otoacoustic emission (DPOAE) amplitudes were unaffected by the exposure. However, we found that the SFR decreased within the exposure frequency range and increased outside the exposure range. This increased SFR for units with characteristic frequencies outside the exposure frequency range, which was slow to reverse after the exposure offset, suggests a mechanism for tinnitus in the absence of hearing loss.

Stimulus evoked activity

Stimulus-induced neural responses are also altered following noise-induced hearing loss (NIHL). Significant effects reflecting central gain changes have been found. Despite a reduction in the compound action potential amplitude of the auditory nerve and in the local field potential of the cochlear nucleus following noise trauma in the rat, the local field potential amplitude in the IC was typically enhanced at higher intensity levels (Wang *et al*., 2002), and so was the local field potential in auditory cortex (Yang *et al.*, 2007).

Tonotopic maps are representations of the distribution of CF as a function of spatial coordinates in an auditory nucleus or cortex. Local mechanical damage to the cochlea, ototoxic-drug damage to the cochlea, and NIHL all cause tonotopic map changes in AI (Eggermont and Roberts, 2004). The map changes are not causally related to the hearing loss (Noreña and Eggermont, 2005), but are always accompanied by increased SFR and increased neural synchrony, pointing to their correlative rather than causal nature. We suggested that this prolonged synchronization would induce the perception of tinnitus (Noreña and Eggermont, 2003; Seki and Eggermont, 2003).

Several stages of cortical reorganization can be differentiated. The first relates to the unmasking of normally inhibited connections (Calford, 2002). This unmasked excitatory activation could be the result of loss of GABA-mediated inhibition (Wang

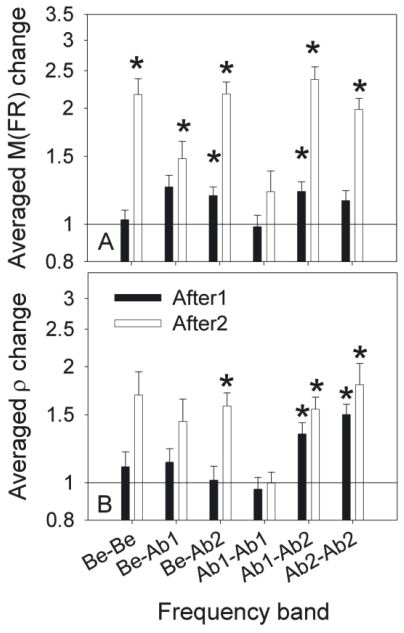

Fig. 1: Effect of the acoustic trauma on cross-correlation coefficient (ρ). (A) Change in M(FR) averaged (geometric mean) into six frequency bands. (B) Change in ρ averaged (geometric mean) into six frequency bands, immediately (After1) and a few hours (After2) after the acoustic trauma (± S.E.M., * $p < 0.0083$). Immediately after the acoustic trauma (black bars), one notes that ρ is significantly increased in the Ab2-Ab2 group whereas M(FR) is not. Be: below the trauma-tone frequency (TTF). Ab1: within 1 octave of the TTF. Ab2: 1-2 octaves above TTF. From Noreña and Eggermont (2003).

et al., 2011). A second stage involves structural changes such as axonal sprouting, as well as alterations in synaptic strength. Finally, use-dependent plasticity might lead to additional changes based on Hebbian learning and long-term potentiation. Tonotopic map changes do not occur if, immediately after noise trauma, a compensatory complex sound that mimics the frequency range of the hearing loss in bandwidth and level is presented for several weeks (Noreña and Eggermont, 2005). It is assumed that during the presentation of this compensatory sound the down regulation of inhibition that usually follows NIHL (Milbrandt *et al.*, 2000) does not occur, and that the unmasking of new excitatory inputs (Noreña and Eggermont, 2003) does not happen or is reversed. When this 'unmasking' trigger for tonotopic map reorganization is absent, map changes do not occur, despite a remaining hearing loss. Furthermore, no increases in SFR and neural synchrony were seen (Noreña and Eggermont, 2006).

WHERE IN THE BRAIN IS TINNITUS?

Auditory system

A recent study by Gu *et al.* (2010) allowed an identification of the auditory brain areas involved in generating tinnitus. They reported physiological correlates of two perceptual abnormalities in the auditory domain that very frequently co-occur: tinnitus and hyperacusis. Despite receiving identical sound stimulation levels, subjects with hyperacusis showed elevated evoked activity in the auditory midbrain, thalamus, and primary auditory cortex compared with subjects with normal sound tolerance. This reflects the increased gain for processing external auditory stimuli. Primary auditory cortex, but not subcortical centers, showed elevated activation specifically related to tinnitus, i.e., in the absence of hyperacusis. The results directly link both hyperacusis and tinnitus to hyperactivity within the central auditory system.

Langers *et al.* (2012) investigated tonotopic maps in primary auditory cortex of 20 healthy controls and 20 chronic subjective tinnitus patients. The goal was to test the hypothesis, proposed on basis of animal and previous human studies (Eggermont and Roberts, 2004) that tinnitus results, among others, from an abnormal tonotopic organization of the auditory cortex. All participants had normal or near-normal hearing up to 8 kHz. The study found no evidence for a reorganization of cortical tonotopic maps in these tinnitus patients. This is perhaps not surprising since there was no appreciable hearing loss. It had been previously shown (Fig. 2) that in animals there is no reorganization of the cortical tonotopic map for hearing losses $\leq$ 25 dB (Rajan, 1998; Seki and Eggermont, 2002). However, Langers *et al.* (2012) clearly did demonstrate that reorganized tonotopic maps in auditory cortex are not a requirement for tinnitus to occur.

Although tinnitus is a percept of sound in the absence of external stimulation, whereas hyperacusis is an increased response to external stimulation, they are often co-occurring. The prevalence of hyperacusis in tinnitus patients can be as high as 79% (Dauman and Bouscau-Faure, 2005). Jastreboff and Hazell (1993) described hyperacusis as a 'manifestation of increased central gain', which may cause enhanced perception of peripheral signals. Threshold measures are not sensitive indicators, as Kujawa and Liberman (2009) demonstrated that cochlear (inner hair cell ribbon synapses) and nervous damages (high-threshold auditory nerve fibers) can occur in the presence of normal audiometric thresholds.

Non-auditory brain regions

Amplifying on a prescient model of Jastreboff (1990), Rauschecker *et al.* (2010) proposed the first consistent model that incorporates the interaction between the limbic and auditory system: "(1) In most, if not all, cases, the process leading to tinnitus is triggered by a lesion to the auditory periphery, e.g., a loss of hair cells in the inner ear resulting from acoustic trauma or aging. (2) Loss of input in the lesioned frequency range leads to an overrepresentation of lesion-edge frequencies, which causes hyperactivity and possible burst-firing in central auditory pathways,

constituting the initial tinnitus signal. (3) Under normal circumstances, the tinnitus signal is cancelled out at the level of the thalamus by an inhibitory feedback loop originating in paralimbic structures: activity from these structures reaches the thalamic reticular nucleus, which in turn inhibits the medial geniculate nucleus. If, however, paralimbic regions are compromised, inhibition of the tinnitus signal at the thalamic gate is lost, and the signal is relayed all the way to the auditory cortex, where it leads to permanent reorganization and chronic tinnitus." In essence, Rauschecker *et al.* (2010) proposed that normally, the unwanted SFR (noise signal) is identified by the limbic system and eliminated from perception by feeding it back to the (inhibitory) thalamic reticular nucleus, which subtracts it from the afferent auditory signal. This mechanism would then fail in about 30% of people with NIHL, but why it would do so is unknown.

TINNITUS AS MALADAPTIVE PLASTICITY IN THE CENTRAL NERVOUS SYSTEM

A common hypothesis is that tinnitus results from an imbalance between excitation and inhibition as a result of a maladaptive down-regulation of inhibitory amino-acid neurotransmission in the central auditory pathway. This loss of inhibition may be a compensatory response to loss of afferent input such as that caused by acoustic insult and/or age-related hearing loss, the most common causes of tinnitus in people. Compensatory plastic changes may result in pathologic neural activity that underpins tinnitus (Wang *et al.*, 2011). Homeostatic mechanisms stabilize the mean firing activity of a neuron over a time period of a few days, and typically do so by scaling the efficacy of the neuron's synapses (Turrigiano, 1999). An important aspect of synaptic scaling is that the direction of change in the synaptic strength depends on both the nature of the synapse and the nature of the postsynaptic neuron. Cortical pyramidal neurons are embedded in networks with extensive recurrent excitatory and inhibitory feedback. Pyramidal-neuron firing rates reflect not only their excitatory drive, but also the balance between excitatory inputs from other pyramidal neurons and inhibitory inputs from GABAergic interneurons.

In the healthy auditory system, homeostatic plasticity could help to ensure that the working point of auditory neurons is within the right range of firing rates independent of the prevailing acoustic environment. Homeostatic plasticity in auditory neurons might also prevent us from perceiving normal spontaneous neuronal activity as sound. Schaette and Kempter (2006; 2009) modeled the effects of homeostatic plasticity by a change in a gain factor proportional to the deviation of the mean activity from a certain target rate. In their model, homeostatic plasticity restores the mean firing rate of neurons in the DCN after hearing loss. Thus, both stimulus-driven and spontaneous mean firing rates are scaled upward to the pre-noise exposure target level. This applies to all affected neurons along the auditory pathway. Restoring the mean rate therefore likely increases the spontaneous rate throughout the auditory system. Knipper et al. (2012) suggested that "two divergent kinds of hyperactivity at the level of the DCN may differently influence higher brain areas after auditory trauma. Hyperactivity in sound-driven pathways may be

regarded in the context of a rather typical compensatory response of a healthy system that, after sensory deprivation, adapts the synaptic strength toward original levels through homeostatic scaling".

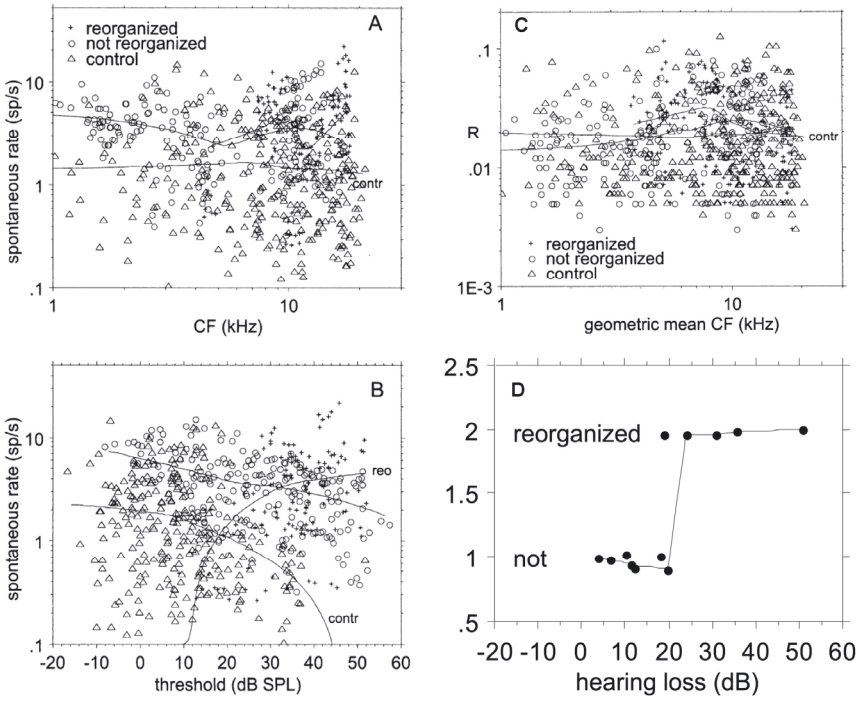

Fig. 2: Dependence of SFR (A, B) and synchrony (C) on CF and threshold is not dependent on the presence of tonotopic map reorganization. (D) Presence of map reorganization on the average hearing loss measured by ABR above 6 kHz. From Seki and Eggermont (2002; 2003).

Analogies with phantom pain

The cause of phantom pain experience has also commonly been attributed to maladaptive plasticity: following loss of sensory input, e.g., the deprived hand area of the primary sensorimotor cortex becomes responsive to inputs from cortical neighbors (for example the face), thereby triggering pain representations relating to the hand. However, Makin *et al.* (2013) showed that, while loss of sensory input is generally characterized by structural and functional degeneration in the deprived sensorimotor cortex, the experience of persistent pain is associated with preserved structure and functional organization in the former hand area. Furthermore, phantom

pain is associated with reduced inter-regional functional connectivity in the primary sensorimotor cortex. Makin *et al.* (2013) therefore proposed that, contrary to the maladaptive model, cortical plasticity associated with phantom pain is driven by powerful and long-lasting subjective sensory experience, such as triggered by nociceptive or top-down inputs. They suggested that phantom pain be best understood in terms of experience-dependent plasticity, with chronic phantom pain providing the experience.

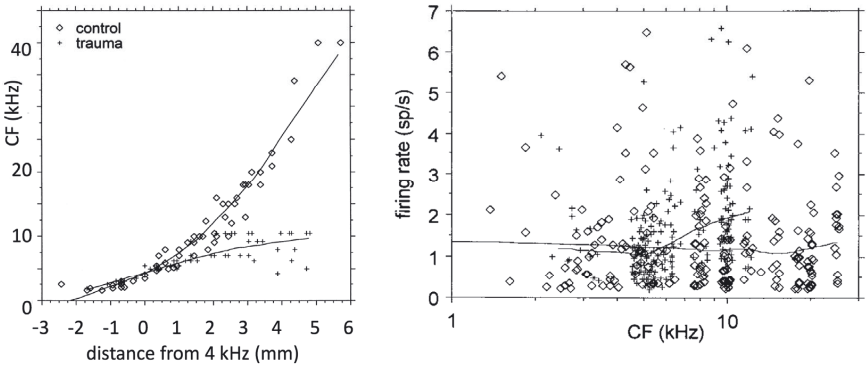

Fig. 3: Tonotopic map changes > 2 months after noise trauma (left panel). Note that in the reorganized cortex no units with CFs > 10 kHz occur, albeit that these neurons in the region with pre-trauma CFs > 10 kHz showed enhanced spontaneous activity (right panel). After Eggermont and Komiya (2000).

Makin *et al.*'s suggestion, translated to tinnitus, implies that the chronic tinnitus experience, which may be triggered either by bottom-up increased SFRs and neural synchrony or by top-down inputs from auditory-related brain areas, including limbic areas, drives plasticity because it maintains local cortical representations and disrupts inter-regional connectivity. We have seen that tinnitus does occur in the absence of tonotopic map reorganization. Local cortical representation implies a somatic memory for pitch. The missing frequencies still generate the remembered pitch as reflected in the tinnitus spectrum. This would mean that it is the continuing input to the cortex from subcortical structures that activates the auditory frequency-representation memories prior to the hearing loss, and so explains the pitch or tinnitus spectrum of tinnitus (Noreña *et al.*, 2002; Roberts *et al.*, 2008; Mulders and Robertson, 2011; Langers *et al.*, 2012). This does not violate the presence of a reorganized tonotopic map (Fig. 3), defined as the representation of CFs on the cortex, which is basically a reflection of how these neurons respond to sound just above threshold, not how their spontaneous activity is perceived. The increase in spontaneous activity in the reorganized area is referred to the reorganized CFs in

Fig. 3. The interpretation of disrupted inter-regional connectivity could then be that the connectivity between tonotopic areas and non-tonotopic areas becomes different for spontaneous activity compared to that for stimulus-induced activity.

Summarizing, homeostatic plasticity does not need to be maladaptive because the chronic tinnitus percept may either be caused by a malfunctioning gate downstream from auditory cortex, or is the result of experience-dependent plasticity with a percept engrained in memory as a result of continuous attention to it.

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