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The Yin and Yang of Auditory Nerve Damage

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Chambers et al. investigate consequences in the central auditory system after profound cochlear denervation. They observed gains in firing rate in auditory cortex despite nearly absent auditorynerve and brainstem responses, suggesting an important role of central plasticity and its clinical implications.

In Chinese philosophy, the terms "yin" (dark) and "yang" (bright) are used to describe the opposite aspects of natural forces or phenomena that, while appearing contradictory on the surface, are intrinsically complementary and interconnected to each other. In many ways, this is how the properties of the nervous system are often presented to us. In this issue of *Neuron*, Chambers et al. (2016) describe a surprising finding on how auditory cortex recovers from devastating peripheral nerve damage. As we know, the auditory system has a long pathway leading from the cochlea to cortex, much longer than all other sensory systems. What we eventually hear depends on neural activities at the highest level (cortex), but all information has to go through the front door (cochlea). Damages to this front door often lead to permanent loss of hearing. The examples are plentiful, from genetically inherited abnormality of the inner ear to drug- or noise-induced hair cell losses. Sometimes even seemingly mild acoustic trauma to the peripheral organ can result in lasting damage in neural structures downstream. Such examples can be readily found in our daily hearing experience (for example, when attending a thundering rock concert or constantly listening to loud music from an earbud).

Acoustic trauma could cause long-lasting and irreversible damage to the hair cells connecting the auditory nerve. Several years ago, a landmark study showed that in noise-induced hearing loss, exposures causing only reversible behavioral threshold shifts (and no hair cell loss) nevertheless cause permanent loss of > 50% of auditory nerve/hair-cell synapses and delayed degeneration of the auditory nerve (Kujawa and Liberman, 2009). Our ears seem to be quite susceptible to noises in the hearing environment. However, how such perturbations to our peripheral auditory organ affect functions of the central auditory system remains largely unclear. Given what we have known of the mechanisms of the auditory periphery and brainstem, it has long been assumed that damage to the cochlear machinery would result in unrecoverable losses of function in neural structures beyond. On the other hand, in all sensory systems, damage to the peripheral organs often leads to compensatory reorganizations at cortical levels. For example, losing one's limb in an accident will eventually cause a shift in cortical representation of the limbs and surrounding body surfaces in the somatosensory cortex (Merzenich et al., 1984). Such reorganization can lead to sensation of the lost limb, the so-called "phantom limb" phenomenon (Flor et al., 1995). The underlying mechanism behind these changes is neural plasticity, in particular at the cortical level. However, besides topographic reorganizations in cortical maps, we know relatively little of what central plasticity could do in helping restore the information lost at the receptor level. In subjects with sensorineural hearing loss, commonly observed symptoms such as elevated hearing threshold, reduced frequency resolution, and increased difficulties in hearing in noisy backgrounds have traditionally been attributed to alterations in cochlear mechanics or the loss of particular cell types in the cochlea or auditory nerve (Moore, 2007). There has been a paucity of data on contributions from central auditory system to these behavioral symptoms.

Sensorineural hearing loss in human populations can be caused by environmental exposures or diseases and usually involves complicated changes that affect the cochlear transduction and amplification machinery. The mammalian cochlea is innervated by two types of afferent

fibers as well as efferent fibers. In order to isolate the deficits due to periphery damage and contributions of central processing, the investigators in the Chambers et al. (2016) study used a method to selectively eliminate afferent fibers from Type-I spiral ganglion neurons without damaging other types of afferent fibers, efferent fibers, or sensory and non-sensory cells in the organ of Corti. They did so by injecting ouabain, a Na^{2+}/K^{+} ATPase pump inhibitor, into the round window of one ear, and left the other ear intact. Ouabain has been shown to specifically lesion Type-I spiral ganglion neurons in mice (Lang et al., 2005). The mice with periphery damage caused by ouabain injection have been used to model auditory neuropathy spectrum disorder in which sound enters the inner ear normally but the transmission of signals from the inner ear to the brain is impaired (Yuan et al., 2014).

Chambers et al. (2016) showed that ouabain decimated synaptic innervation of inner hair cells without affecting cochlear amplification, which was also observed in human patients (Starr et al., 1996). The selective and specific damage to only one type of afferent fiber is an elegant and clever experimental design by these investigators. As expected from human patients with auditory neuropathy spectrum disorder (Zeng et al., 2005), when the mice were tested through their ouabain-treated ear, the investigators found that the treatment virtually eliminated tone-evoked acoustic startle response and grounded auditory nerve response to nearly zero even at loud sound levels (Figure 1, bottom). However, to their surprise, the mice behaved almost normally in tone detection tasks using their ouabain-treated ear. This was really puzzling. How could these animals hear sounds with little information passing through the front door of their auditory system? The answer to this question is what makes this study fascinating.

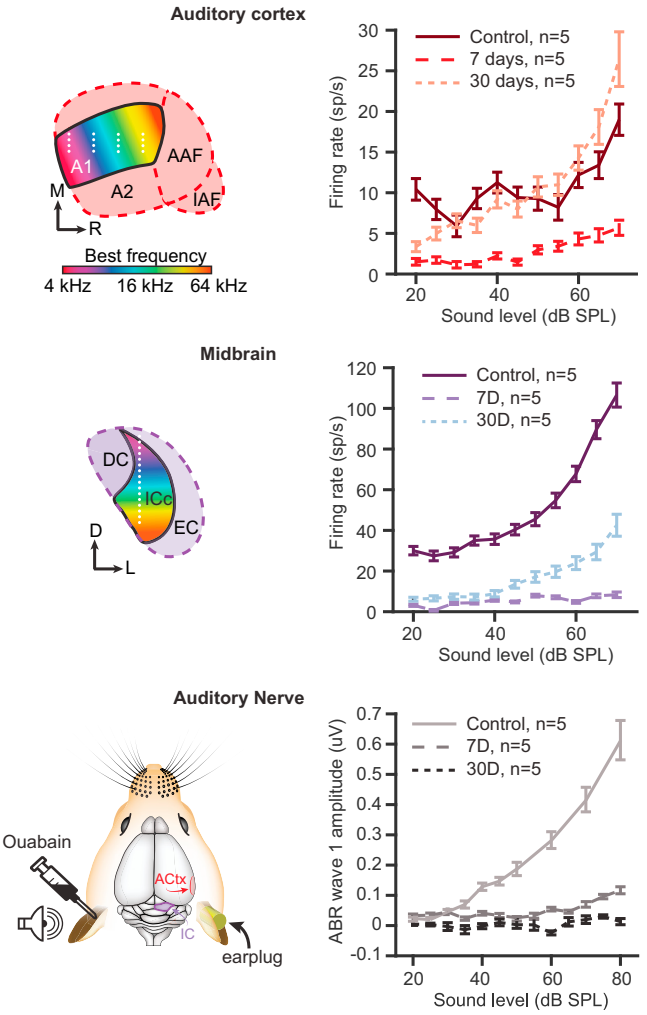

Figure 1. Neural Responses to Monaural Sound Stimulation along Ascending Auditory Pathway in a Mouse Model of Auditory Neuropathy Spectrum Disorder

Illustration of neural responses to tones across sound level recorded from mice with ouabain-mediated denervation of the contralateral ear from auditory nerve, measured by auditory-brainstem response (ABR) wave 1 component (bottom row), the central nucleus of the inferior colliculus in the midbrain (middle row), and the primary auditory cortex, A1 (top row). In each structure, comparisons are made between three conditions: control (intact ear) and 7 and 30 days after ouabain treatment (adopted from Chambers et al., 2016).

These investigators traced neural responses to sound stimulation from the auditory nerve to the inferior colliculus in the midbrain, an obligatory station of ascending auditory pathway, and all the way to the primary auditory cortex. All examined neural structures were silent after the ouabain treatment. But, slowly, the investigators began to observe the emergence of neural responses, first at the midbrain and then at the auditory cortex. The recovery progressed further and further as the time passed. In the midbrain, the neural responses of the inferior colliculus reappeared but never restored to the control condition (response to the intact ear) even after 30 days, a long time in a mouse's life (Figure 1, middle). Surprisingly, responses of auditory cortex neurons to the ouabain-treated ear eventually caught up with those of the intact ear (Figure 1, top). This explains why the animal can still detect tones after the damage to their ouabain-treated ear. A plausible explanation for why this happened is the neural plasticity that appeared to become increasingly more potent along the ascending pathway. There has been a long line of rich literature on cortical plasticity in the adult brain since the classic experiments conducted in the somatosensory cortex in the 1980s. Those experiments showed that the injury to the peripheral nerve or skin receptors resulted in massive cortical reorganization even in adult animals (Merzenich et al., 1984). There was also evidence that the neural plasticity was not present in the same form and magnitude in the thalamus (Wang et al., 1995). Presumably, the processing stations along the ascending auditory pathway were less susceptible to the neural plasticity than auditory cortex.

However, the nearly full recovery of auditory cortex responses, measured by firing rate, turned out to be only the bright side of the whole picture. When the investigators looked more closely at their data, they discovered that cortical responses to temporally modulated sounds were far

from being normal. In the inferior colliculus, response synchronization of the ouabain-treated ear never approached that of the intact ear even at slow repetition rates. The situation was even darker in auditory cortex, where little information on stimuli can be extracted from the temporal patterns of spiking activity. The degradation of temporal information at the cortical level does not necessarily prevent the animals from hearing tones and detecting the presence of sounds, but may impair the animals' perceptual capacities in discriminating complex sounds. After all, tones are spectrally and temporally much simpler than the complex sounds that we and mice hear in the real world, such as ultrasonic vocalizations heard by mice and, in the case of humans, speech and music in our daily life.

Chambers et al. (2016) concluded from their experiments that the increased central gains support the rudimentary sound features encoded by firing rate, but not features encoded by precise spike timing. However, the recovery of firing rate magnitude does not necessarily guarantee the restoration of all information encoded by firing rate. It has been well documented that, in auditory cortex of awake animals, firing rate can encode fine stimulus structures in time-varying signals (Lu et al., 2001; Gao and Wehr, 2015) as well as high-dimensional stimulus features such as pitch (Bendor and Wang, 2005). It is not clear whether such firing-rate-based representations could be restored after profound cochlear denervation in auditory neuropathy. Given that the ouabain-induced cochlear denervation interrupts spike timing at the midbrain, as shown by Chambers et al. (2016), the firing-rate-based transformation at the cortical level is likely distorted as well.

The important discoveries made in the study by Chambers et al. (2016) benefited from a unique feature of the auditory system. Nearly all auditory processing stations beyond the brainstem receive binaural inputs from the two ears. The investigators took this advantage in their experimental design by "deafening" one ear and leaving the other ear intact. This way, they were able to conduct side-by-side comparisons of responses between ouabain-treated ear and intact ear in single neurons or on the same recording site in the same animal. The interpretations of their neural data would have been more difficult if the ouabain-treated and control conditions were evaluated in two separate groups of animals given the amount of variability in neural responses. More importantly, the unilateral denervation experimental design lent the investigators the upper hand in revealing what neural plasticity could achieve. As their control experiments showed, when the two ears were deafened by ouabain treatment, there was a far lesser degree of recovery in auditory cortex even after 30 days. An important lesson learnt from this observation is that the signaling from an intact ear can significantly facilitate the recovery of neurons that are driven by the deafened ear. This reminds us of the debate on what to do or not do for patients with asymmetric deafness before they receive a cochlear implant in the deaf ear. It has been suggested that a good strategy for these patients is to equip the other ear with residual hearing with a hearing aid before the patient is implanted with a cochlear implant device in the deaf ear. The results from the Chambers et al. (2016) study would support such a treatment strategy.

While the study by Chambers et al. (2016) has provided interesting and important observations, many questions remain to be explored. For example, what are the cellular mechanisms that underlie the observed central response gains? What are the specific neural structures and circuits that perform the amplification between the auditory nerve and the inferior colliculus, and between the inferior colliculus and auditory cortex? To answer these questions, other experimental techniques such as intracellular recording and single-cell imaging are needed. Most importantly, one would want to know to what extent learning and practice could improve recovery at the central auditory structures after peripheral nerve damage. The animals used in the reported experiments were not subject to long-term behavioral training with challenging tasks. Researchers in this field will likely follow the path plowed by Chambers et al. (2016) to investigate strategies to restore central auditory functions in patients with auditory neuropathy spectrum disorder, now that we have seen the light at the end of the tunnel.

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