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An Auditory Phantom Percept That Does Not Impair External Sound Perception

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Review of Zeng et al.

To accurately represent the world, the brain must distinguish between internally generated activity and activity evoked by external stimuli. When internal brain dynamics mimic stimulus-evoked activity patterns, phantom perception may occur (Kenet et al., 2003). One common form of phantom perception is tinnitus, the perception of sound in the absence of an external acoustic source. Generally, tinnitus emerges as a sequela of damage to the auditory periphery. In response to decreased peripheral input, neurons throughout the central auditory pathway increase their spontaneous firing rates and sensory response gain (Eggermont and Roberts, 2004). However, tinnitus develops in only approximately half of individuals with hearing loss, and, conversely, tinnitus can emerge after only subtle damage to the inner ear (Schaette and McAlpine, 2011). Thus, while hyperactivity and hyperexcitability throughout the central auditory pathway are associated with tinnitus generation, the precise neurobiological basis of tinnitus remains unknown.

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A stumbling block in understanding the neural basis of tinnitus is a methodological mismatch between human and animal studies. While it is straightforward for humans to report their subjective experience, techniques for recording from the human brain lack sufficient resolution to identify the neural circuits responsible for tinnitus. Conversely, in animals where it is possible to record neural activity with cellular resolution and cell-type specificity, it is difficult to devise behavioral tasks that unambiguously indicate animals are experiencing tinnitus-like percepts. One potentially powerful way to bridge the gap between human and animal studies is to test whether tinnitus percepts interfere with auditory perception, because perceptual abilities are measurable in both humans and animals. Because tinnitus percepts can be modulated by the presence of external sound (Feldmann, 1971), it is plausible that tinnitus percepts might also interfere with the processing of external sounds.

One important aspect of sound processing is gap detection. Brief silent gaps in sounds are critical cues for auditory scene analysis and speech perception. Gaps in ongoing sound can also attenuate the acoustic startle reflex induced by intense sounds. Tinnitus might fill in these silent gaps, thus rendering them inaudible. If this occurs, tinnitus might blunt gap-induced attenuation of the startle reflex. Therefore, previous studies have attempted to use the acoustic startle reflex to diagnose the presence of tinnitus in animals. Indeed, gap-based prepulse inhibition of the acoustic startle reflex is impaired after peripheral damage to the auditory system across multiple animal models (Longenecker et al., 2018). However, evidence of impaired gap detection in humans is lacking (Boyen et al., 2015).

A recent study by Zeng et al. (2020) systematically tested whether tinnitus interfered with gap detection and other aspects of auditory perception across many behavioral tasks and stimulus parameters in human listeners. To optimize interference between tinnitus and external stimuli, the authors first had to quantify what each individual's tinnitus sounded like. To identify individual tinnitus percepts, subjects matched an external tone to their tinnitus in both frequency and level. Consistent with previous work, tinnitus percepts were most commonly matched to high-frequency (~4 kHz), low-level tones (~10 dB above hearing thresholds; Moore, 2012).

To address whether tinnitus fills in gaps in sound for human listeners, Zeng et al. (2020) used an adaptive procedure to estimate gap detection thresholds across a range of sound frequencies. Gap detection thresholds in tinnitus subjects were comparable to those in control subjects, even for tones matched to individual tinnitus frequencies and levels. Not only does the absence of impairment in tinnitus subjects cast doubt on behavioral approaches based on gap detection in animal models, it also suggests that the neural generator of tinnitus is independent from pathways for the perception of external sounds.

Given that gap detection was not impaired, the authors asked whether other facets of auditory perception would reveal interactions between internal tinnitus percepts and the perception of external stimuli. Even near their individual tinnitus frequencies, tinnitus patients were as adept as control subjects at discriminating tiny differences in sound frequency. Further, across multiple sound levels, tinnitus subjects were equal or better than control subjects in sound intensity discrimination. More perceptually demanding tasks, including tone in noise detection, temporal modulation detection, and speech in noise recognition, also failed to reveal a deficit in tinnitus subjects. The lack of differences across all tested tasks and stimuli is striking, leading the authors to suggest that tinnitus and external sound have an asymmetrical relationship: while in most cases tinnitus can be masked by external sounds, tinnitus does not seem to interfere with perception of external sound.

To explain the asymmetry in how externally and internally generated percepts interact, Zeng et al. (2020) propose a simple attention normalization model with two channels, one representing the "top-down" tinnitus signal and the other representing a physical stimulus, inspired by models of visual attention (Reynolds and Heeger, 2009). In the model, the total percept of the observer is the weighted sum of attention to tinnitus and attention to the stimulus. In the absence of external stimuli, the total percept is dominated by tinnitus, as all attention is allocated to the phantom percept. The primary insight of the model is that while keeping attention to tinnitus fixed, increasing attention to the external stimulus can attenuate the perceived tinnitus loudness by up to a factor of five. The model suggests that engaging in near-threshold perceptual tasks could direct attention away from the tinnitus percept, possibly accounting for the lack of differences between tinnitus subjects and controls across many measures of auditory perception.

While subjects may be able to steer their attention away from tinnitus during basic perceptual tasks, the model proposed by Zeng et al. (2020) predicts that tinnitus would incur a cost in more attentionally demanding tasks. If attention is a finite resource, any attention devoted to tinnitus might limit attentional resources that could be deployed to multiple competing external stimuli. Consistent with this prediction, previous studies in humans and animals have suggested that tinnitus subjects perform worse than control subjects in auditory and nonauditory selective attention tasks (Brozoski et al., 2019). Further, human neuroimaging studies suggest that nonauditory areas involved in attentional control, such as the anterior cingulate cortex, precuneus, and hippocampus, show heightened activity in tinnitus subjects (Roberts et al., 2013). Future studies that parametrically vary attentional demands should clarify exactly how tinnitus captures attention.

Importantly, the finding that auditory perception is not impaired in tinnitus subjects also constrains theories of the neural circuits underlying tinnitus. Redundant distributed neural codes for external sound coupled with sparse local codes for internally generated tinnitus percepts could explain the perceptual asymmetry that Zeng et al. (2020) observed. External sounds recruit partially redundant ascending pathways terminating in multiple areas across both hemispheres of the cerebral cortex (Levy et al., 2019). Yet, studies in other sensory systems suggest that animals can attend to and behaviorally report artificial stimulation of single neurons or small ensembles (Houweling and Brecht, 2008; Gill et al., 2020). The percept of tinnitus might similarly emerge from hyperactivity or hypersynchrony in small ensembles of auditory neurons in the absence of external sound. Consistent with the proposal of Zeng et al. (2020), sparse codes for phantom percepts likely require attention or top-down feedback to rise to the level of conscious awareness (Van Vugt et al., 2018). At the same time, these sparse local codes for phantom percepts are unlikely to interfere with external sound perception arising through multiple parallel pathways.

As a concrete example, consider the first station of the central auditory pathway, the cochlear nucleus, which consists of a dorsal and a ventral subdivision, both of which receive input from the auditory nerve. Increased spontaneous firing and synchrony in dorsal cochlear nucleus neurons after damage to the auditory periphery is central to theories of tinnitus generation (Shore and Wu, 2019). Yet, lesions to the dorsal cochlear nucleus fail to produce deficits across numerous auditory perceptual tasks, presumably because of redundancy with the ventral nucleus (Masterton and Granger, 1988). This example illustrates a general principle: wherever in the auditory pathway the neural activity underlying tinnitus emerges, there are other parallel and redundant loci which could subserve the normal perception of external stimuli despite ongoing neural activity related to the phantom percept.

In summary, Zeng et al. (2020) present compelling behavioral evidence that auditory perception is not impaired by tinnitus. These results draw into question widely used animal behavioral models and constrain theoretical accounts of the neurobiological basis of tinnitus. Converging evidence suggests that tinnitus may be as much a disorder of attention as it is one of damage to the auditory periphery. Understanding how attention interacts with tinnitus perception will be crucial to developing effective therapies for this pervasive auditory disorder.

References

Boyen K, Başkent D, van Dijk P (2015) The gap detection test: can it be used to diagnose tinnitus? Ear Hear 36:e138–e145.

Brozoski T, Wisner K, Randall M, Caspary D (2019) Chronic sound-induced tinnitus and auditory attention in animals. Neuroscience 407:200–212.

Eggermont JJ, Roberts LE (2004) The neuroscience of tinnitus. Trends Neurosci 27:676–682.

Feldmann H (1971) Homolateral and contralateral masking of tinnitus by noise-bands and by pure tones. Audiology 10:138–144.

Gill JV, Lerman GM, Zhao H, Stetler BJ, Rinberg D, Shoham S (2020) Precise holographic manipulation of olfactory circuits reveals coding features determining perceptual detection. Neuron 108:382–393.e5.

Houweling AR, Brecht M (2008) Behavioural report of single neuron stimulation in somatosensory cortex. Nature 451:65–68.

Kenet T, Bibitchkov D, Tsodyks M, Grinvald A, Arieli A (2003) Spontaneously emerging cortical representations of visual attributes. Nature 425:954–956.

Levy RB, Marquarding T, Reid AP, Pun CM, Renier N, Oviedo HV (2019) Circuit asymmetries underlie functional lateralization in the mouse auditory cortex. Nat Commun 10:2783.

Longenecker RJ, Kristaponyte I, Nelson GL, Young JW, Galazyuk AV (2018) Addressing variability in the acoustic startle reflex for accurate gap detection assessment. Hear Res 363:119–135.

Masterton RB, Granger EM (1988) Role of the acoustic striae in hearing: contribution of dorsal and intermediate striae to detection of noises and tones. J Neurophysiol 60:1841–1860.

Moore B (2012) The psychophysics of tinnitus. In: Tinnitus (Eggermont JJ, Zeng F-G, Fay R, Popper A, eds), pp 217–253. New York: Springer.

Reynolds JH, Heeger DJ (2009) The normalization model of attention. Neuron 61:168–185.

Roberts LE, Husain FT, Eggermont JJ (2013) Role of attention in the generation and modulation of tinnitus. Neurosci Biobehav Rev 37:1754–1773.

Schaette R, McAlpine D (2011) Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. J Neurosci 31:13452–13457.

Shore SE, Wu C (2019) Mechanisms of noise-induced tinnitus: insights from cellular studies. Neuron 103:8–20.

Van Vugt B, Dagnino B, Vartak D, Safaai H, Panzeri S, Dehaene S, Roelfsema PR (2018) The threshold for conscious report: signal loss and response bias in visual and frontal cortex. Science 360:537–542.

Zeng F-G, Richardson M, Turner K (2020) Tinnitus does not interfere with auditory and speech perception. J Neurosci 40:6007–6017.