suppressors depending on the cancer type (Cortez et al., 2011). In particular, miR-126 is known to increase the vulnerability to toxic insults, such as 6-hydroxy dopamine, staurosporine, and amyloid-β in neurons, by regulating the insulin/IGF-1/PI3K pathway (Kim et al., 2014, 2016). These findings demonstrate that it is critical to investigate miRNA function while considering cellular context and target specificity under physiological or pathological conditions. Most importantly, Li et al. (2021) provided further support for the intercellular miRNA transport and its functional significance. Vickers et al. previously demonstrated that HDL-miRNA profiles in patients with familial hypercholesterolemia are vastly different from healthy controls (Vickers et al., 2011). It will be interesting to determine whether the ApoE-miRNA profile is significantly altered in response to pathological states. It also warrants further studies on how only certain miRNAs are selected for secretion in ApoE lipoprotein particles, are taken up by specific cells, and regulate different genes depending on the cellular context.

Taken together, Li et al. (2021) demonstrated an intriguing mechanism by which miRNAs in astrocyte-derived ApoE lipoprotein particles can impact neuronal functions by regulating lipid metabolism and epigenetics. This study is an important first step to identify miRNAs and their downstream effectors as therapeutic targets for AD.

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What's been hidden in hidden hearing loss

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Human studies of potential effects of cochlear neurodegeneration on perception have focused on impoverished input coding as the driver, with mixed results. A new study instead points to altered brain dynamics in noise as the proximal cause of hearing difficulties.

A little over a decade ago, seminal work by Kujawa and Liberman upended the belief that sensory hair cells are the most vulnerable structures in the inner ear. Instead, their work, and subsequent findings in a range of animal models, revealed that acoustic overexposure and aging can damage afferent cochlear neurons even when cochlear hair cells remain intact (Liberman and Kujawa, 2017). However, despite intense investigation, debate rages over whether cochlear neuropathy substantially affects human hearing. Specifically, while evidence that cochlear neuropathy *occurs* in humans has accumulated from both analyses of post-mortem temporal bones (e.g., Wu et al., 2019) and suprathreshold physiological measures in at-risk groups (Mai et al., 2019), whether such damage has *measurable perceptual consequences* remains an open question.

Investigations into the perceptual consequences of cochlear neuropathy generally assume that peripheral damage to

cochlear synapses degrades the representation of suprathreshold sound features in the ascending auditory pathway, which disrupts hearing in challenging listening scenarios, such as understanding speech in background noise (Bharadwaj et al., 2014). Most such studies have focused on individuals without any observable, audiometric hearing loss (that is, who don't have elevated hearing detection thresholds, as might result from damage to sensory hair cells), but who differ in their acoustic exposure history or age. If sensory deficits from cochlear synaptopathy explain differences in hearing abilities, physiological responses from the early portions of the auditory pathway should correlate with listening performance and participant history. Yet, results of such studies are inconsistent. To explain conflicting results, researchers have pointed to a lack of reliability and sensitivity in each of these measures, as each suffers from extraneous sources of variability (Bharadwaj et al., 2019). Inconsistencies across past studies hint that we've been missing a piece of the puzzle: a hidden aspect of hidden hearing loss.

The new study by Resnik and Polley (2021) may have the answer. While impaired suprathreshold coding of sensory information likely contributes to perceptual deficits, it is *not* the primary determinant of perceptual deficits in mice detecting a signal in noise. Instead, cochlear neuropathy initiates central changes that affect the balance of intracortical inhibition and excitation. Although the relative reduction in inhibition triggered by peripheral synaptopathy compensates for the reduced strength of sensory inputs presented in quiet, it also leads to nonlinear network-level effects. The resulting instabilities in cortical dynamics may be the missing puzzle piece: a key proximal mechanism explaining why some listeners have trouble hearing in background noise but not in quiet.

Cochlear hair-cell loss has long been known to spark compensatory downregulation of inhibitory processing, leading to a so-called "central gain" in the driven firing rates of central auditory neurons (Salvi et al., 2000). Cochlear neuropathy without hair-cell loss has also been shown to precipitate similar central gain not only in the mouse brainstem but also in cortex (Chambers et al., 2016). Direct measures of such effects require invasive physiology, impossible to perform in humans. However, compensatory gain helps explain why the magnitude of wave V in human evoked auditory brainstem potentials, generated by the upper brainstem, is relatively consistent, even if wave I, from the auditory nerve fibers, is weaker than normal. Crucially, while this central gain can restore detection of sounds in quiet (e.g., as often tested in clinical audiometric screenings), it cannot recover the processing of temporal detail (Chambers et al., 2016), which depends upon combining responses of many independent nerve fibers to achieve precision.

If peripheral loss resulted only in a change in a static "central gain"—a form of compensation to increase the signal reaching higher stages of the auditory system—the effects would be a simple increase in central responses. However, previous studies have already shown that the consequences go beyond simply "turning up the volume." For instance, peripheral neuropathy can interfere with the ability of neural circuits to adapt their operating points to match the fluctuations in the intensity statistics of the input stimulus (Bakay et al., 2018). Pathological forms of central gain may also contribute to tinnitus and/or hyperacusis. While these studies highlight that sensory deficits have complex effects that go beyond a central gain, until now no clear mechanistic links had emerged to describe how central gain affects target sound processing in background noise.

The study by Resnik and Polley (2021) addresses this gap. After inducing cochlear neuropathy in mice, they used chronic two-photon calcium imaging to track the ensuing changes in the activity of parvalbumin-positive inhibitory neurons and excitatory pyramidal cells in the auditory cortex over the course of many days. By analyzing the firing patterns of the cortical neuronal ensembles, they showed that cochlear neural damage set in motion different changes in inhibitory and excitatory cells in the cortex. Over the course of about two weeks, these different effects converged to produce a state of net hyperexcitability. Concomitantly, the mice exhibited impaired target tone detection in background noise but not in quiet.

Strikingly, an analysis of trial-by-trial outcomes in synaptopathic mice revealed that rather than impairing coding of the target stimulus directly, the altered excitatory-inhibitory balance affected the dynamics of the nonlinear cortical circuit. Specifically, noise sporadically drove the neural ensemble to an instability, characterized by hyper-correlated excursions in ensemble activity. Critically, this "runaway" noise response preceded the appearance of the target far more often on trials in which the mice failed to detect the target (the miss trials) than on trials with a correct detection. This pattern was not present in the normal-hearing mice, whose cortical responses maintained a typical balance of excitation and inhibition. In the normal-hearing mice, fluctuations in the target-evoked response predicted behavioral misses; in contrast, transient surges in correlated, noise-driven activity just prior to the target onset were the best predictors of the more numerous lapses in mice with cochlear neural degeneration.

The current study makes clear that peripheral neural degeneration triggers changes throughout the auditory system that can help compensate for weakened sensory inputs when listening in quiet. However, perturbing the balance of inhibition and excitation can unleash atypical neural dynamics in the local cortical microcircuit that fundamentally alter responses to sound in noise. Although "optimal detector" models of listening behavior have yielded tremendous insight into psychoacoustic phenomena, the perceptual consequences of unstable, nonlinear cortical dynamics triggered by cochlear neuropathy cannot be accounted for by simple models of degraded coding in the ascending pathway (e.g., see Oxenham, 2016). Future human studies may benefit from a more detailed analysis of the error and lapse patterns in listening behavior and associated neural activity. Psychoacoustic studies that disentangle different sources of stimulus-dependent and stimulus-independent internal noise in a signal-detection theoretic context may give insight into the previously hidden impacts of cochlear neuropathy on perception.

DECLARATION OF INTERESTS

H.B. and B.S.-C. have consulted for Otonomy, Inc.

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Timing isn't everything: opposing roles for perisomatic inhibition

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Perisomatic inhibition from parvalbumin-containing (PV) interneurons is critical for timing, but the role of cholecystokinin-containing (CCK) interneurons remains obscure. Utilizing a novel mouse model, Dudok et al. demonstrate fundamentally distinct behavioral roles for these neuronal subpopulations during behavior.

Inhibition from the diverse GABAergic neuronal population finely tunes excitatory principal cell activity through selective innervation along the somatodendritic axis. Perhaps more so than any other source, perisomatic inhibition directly onto soma and proximal dendrites has an outsized role in controlling neuronal activity. Within the hippocampus, perisomatic inhibition largely arises from parvalbumin-containing (PV) and cholecystokinin-containing (CCK) basket cells (BCs), named for the dense mesh of axonal contacts surrounding their postsynaptic targets (Pelkey et al., 2017). Extensive research has established the unique characteristics of fast-spiking PV cells. With sub-millisecond precision, PV cells are exquisitely tuned to provide reliable feedforward and feedback control, with an essential role in theta oscillations and sharp wave ripples (SWRs), thought to support memory encoding and consolidation (Hu et al., 2014). In contrast, CCK cells exhibit regular-spiking patterns and asynchronous transmitter release (Hefft and Jonas, 2005), a baffling feature for efficient information storage, as this would be predicted to result in the loss of critical temporal information. The compelling study by Dudok et al. (2021) finally suggests an intriguing potential function for this asynchronous release. In an innovative set of experiments, the authors observed opposing activity patterns between perisomatic-targeting PV and CCK cells. The novel observation that CCK cells are more active during disorganized periods of activity between running behavior and SWR replay suggests they may serve to orchestrate an important "idle state" of the hippocampus.

The wealth and dearth of knowledge concerning PV and CCK cells, respectively, can at least partially be attributed to the availability of genetic tools. With a unique expression profile of the protein parvalbumin, as well as the easily distinguishable fast-spiking pattern, PV cells have been a relatively accessible target for research. In contrast, CCK cells have long resisted investigation. Cholecystokinin is expressed by several neuronal populations, and the regular-spiking pattern is not clearly distinct. The authors overcame these obstacles by building upon recent transcriptomic observations that the *Sncg* gene (encoding gamma synuclein) preferentially labels CCK interneuron subtypes (Gouwens et al., 2020), prompting the development of a novel *Sncg* transgenic mouse. In transfecting with conditional viral reporters, the authors observed *Scng* mice labeled CCK interneurons with greater specificity than other markers and greater sensitivity