Which types of hearing loss can be reversed, and how can these be identified?

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Progressive hearing loss is common in the human population but its aetiology is heterogeneous, hampering efforts to develop ways of stopping its progression. Three main sites can be affected within the cochlea: sensory hair cells (sensory); neural or synaptic defects (neural); and/or stria vascularis dysfunction affecting the fluids bathing hair cells (strial). Treatments aimed at the initial site-of-lesion may be useful.

We used hearing-impaired mouse mutants as examples of each site-of-lesion to ask if the hearing loss can be reversed after it has already developed, as a proof-of-concept. The mutations carry a large insertion in an intron designed to disrupt transcription. We removed the mutagenic insertion to activate gene function at selected ages using a tamoxifen-inducible Flp recombinase. Hearing was assessed using Auditory Brainstem Responses (ABRs) before tamoxifen injection and at intervals afterwards. We found that the severe hearing loss due to strial defects in *Spns2*^{tm1a} mutants could be partially reversed following excision of the mutagenic insertion, and the earlier the tamoxifen injection, the better the reversal of hearing loss (Martelletti *et al.* 2023, PMID:37552762). Deafness due to a primary synaptic defect (*Otof*^{tm1a}) was also reversed. However, in three examples of primary hair cell defects (*Whrn*^{tm1a}; *Myo7a*^{tm1a}; *Cdh23*^{tm2a}) and two other examples of neural defects (*Pex3*^{tm1a}; *Wbp2*^{tm2a}) there was minimal or no reversal of hearing loss.

As certain types of progressive hearing loss appear to be good candidates for treatments to improve hearing and other types not, it would be useful to develop diagnostic tools to distinguish the primary site. To do this, we used a panel of mouse mutants with strial, sensory or neural sites-of-lesion combined with non-invasive physiological tests. One test that was useful in separating strial dysfunction from sensory or neural defects was inter-trial phase coherence (ITC), a measure of the phase coherence of the individual trial-level ABR responses.

These findings provide a proof-of-concept that will give a foundation for future development and application of therapies for progressive hearing loss in humans.