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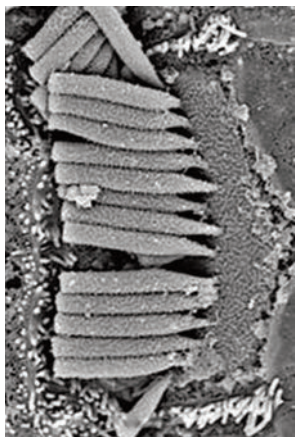
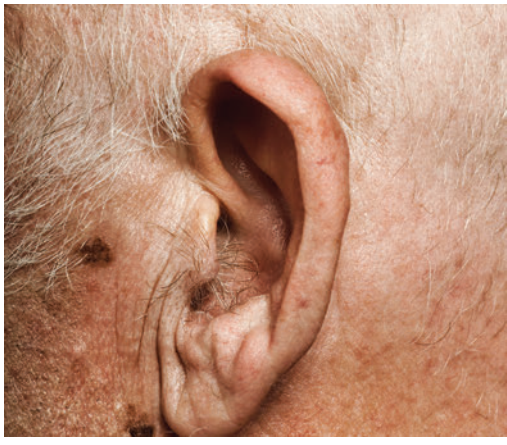
Hearing loss

and its associated conditions





Further Reading

- ▷ Hearing Loss and Healthy Aging – Workshop Summary
- ▷ Targeting challenges of active ageing
- ▷ National Institute on Deafness and Other Communication Disorders
- ▷ Action on Hearing Loss

Hearing loss and falling:
challenges of ageing societies

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Imagine that the sounds you hear become progressively attenuated every day and eventually you are cut off from music, laughter, and any other communication you enjoyed throughout your life. Words you hear may become ambiguous (for example, 'someday' and 'Sunday' may sound alike) and this word confusion confounds further your understanding of the little you are still able to hear. This will negatively impact the quality of life as we age and when proper communication with our carergivers becomes most essential to meet our increasing physical and mental needs associated with ageing. If unlucky, hearing loss might be combined with phantom sound or tinnitus, also bound to increase.

Age related sensory problems of the ear include vestibular function that also relates to an increased propensity to stumble and fall. As one ages, bones become more likely to break and less likely to heal. The declining bone health, combined with more frequent falling due to an ailing sense of balance, generates a vicious cycle that combines continued sensory decline with decreased motor function. Much of this will be an unfortunate reality for many past their 70s.

Why are those ailments that were marginal in the past playing such a dominant role in the near future? WHO demographics suggest a dramatic increase in 'seniors' in the next 25 years and nearly a 10-fold increase in centenarians, the so-called 'silver tsunami'. Ageing societies face unresolved economic sustainability issues, but also face a global pandemic of around 900 million hearing impaired people by 2050, matching the increase in life expectancy baby-boomers will otherwise enjoy. It is expected that 60% of people aged 70 or older will have some hearing impairment with a doubling of hearing impaired people every 10 years of age [1]. Hearing loss is already among the top 10 disabilities and is associated with secondary effects, including depression that is closely related to disruptions of communications and the concomitant reduction of emotionally rewarding social interactions. There are two forms of hearing loss, external or middle ear-related (conductive) hearing loss and inner ear related (neurosensory) hearing loss. Conductive hearing loss often benefits from surgical treatment such as replacement of middle ear ossicles, but help for neurosensory hearing loss is currently beyond direct therapeutic intervention. Three logical approaches exist to deal with neurosensory hearing loss:

1) ***restore hearing with cochlear implants***;

2) ***regenerate lost hair cells and neurons*** with cell or gene therapy to restore hearing;

3) ***delay the onset of hearing loss***.

Similar to hearing, age related vestibular dysfunction that is not caused by obvious pathologies such as Meniere's disease, is mostly a consequence of progressive loss of neurosensory elements of the vestibular part of the ear, such as lost hair cells and lost sensory neurons [2]. Transient dizziness may occur in up to 50% of the elderly and correlates with the reduction in numbers of vestibular hair cells. Comparable to the middle ear functional decline for hearing, there is vestibular decline in the function of otoconia with age, altering sensitivity to gravity [3]. An increasingly dysfunctional sense of balance will increase the risks of falling, resulting in rising budgets needed to heal fall-related injuries. People over 75 who fall are about five times more likely to be admitted to a long-term

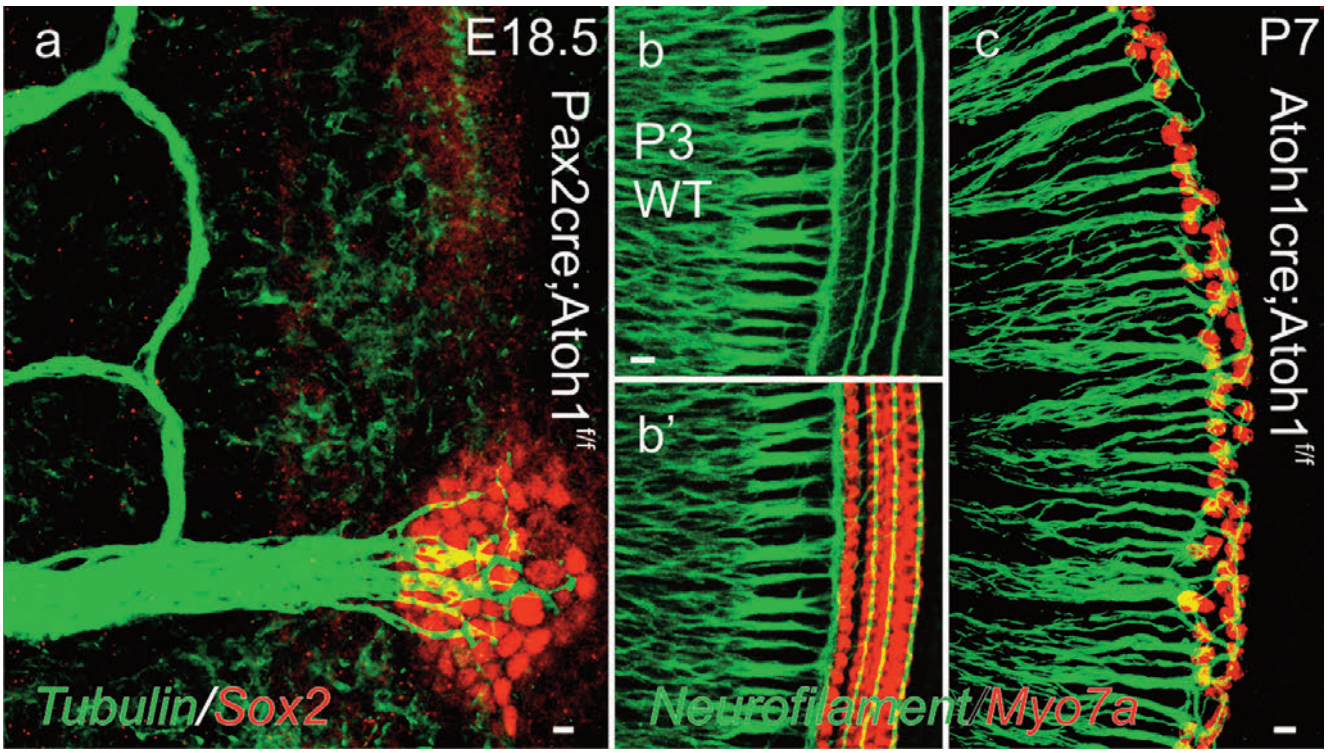

Fig. 1 Innervation remains in genetically engineered mice even after early and profound loss of all (a) or most (c) hair cells have been eliminated using the conditional deletion of the important transcription factor Atoh1 that is essential for hair cell differentiation. Please note that even complete loss of any differentiation is compatible with some residual innervation in areas of incomplete differentiation. Even after a targeted deletion of this transcription factor there is a slow decline in hair cell number over time associated with a very profound retention of innervation density (compare b,c). Myo7a indicates hair cells, Sox2 indicates undifferentiated precursors, tubulin and neurofilament labels fibers. Data are from Pan et al., 2010, 2011).

care facility for a year or longer with an estimated cost of $60 billion by 2025 in the US alone. As with neurosensory hearing loss, three approaches are currently pursued to restore vestibular function:

1) ***restore vestibular function with vestibular implants***;

2) ***regenerate lost hair cells and neurons*** with cell or gene therapy to restore hearing;

3) ***delay the onset of vestibular loss***.

Below I will explore the state of the art of each of these approaches for the ear and discuss the strength, weakness and risks associated with each approach.

Cochlear implants are a well established prosthetics that can partially restore hearing [4]. In most people suffering from loss of hair cells, apparently enough sensory neurons are spared to allow such cochlear implants to function effectively. Some animal models with genetically induced hair cell loss (Fig. 1) mimic human deafness gene mutations and result in long term retention of many neurons [5-7], resembling more closely the human condition with little loss of spiral ganglion neurons upon loss of hair cells [8,9]. Such genetically engineered mice with a closer resemblance to human ears with hair cell loss need to be explored to further improve the usefulness of cochlear implants. Ultimately, cochlear implants will benefit only those that can afford them. Without a major change in overall cost, cochlear implants will financially burden ageing societies with limited benefits to the many deaf people unable to pay for them.

Vestibular implants are the logical extension of cochlear implants to serve the vestibular impaired that have lost hair cells and sensory neurons with age [2], diminishing sensory function proportionally to the neurosensory loss. As with the auditory system, nerve fibers appear to remain long-term and could be used to implant electrodes which, if connected to a gyroscope, could provide information about position and movement of the head in space. Some vestibular implants have been tested for

semicircular replacement in humans and seem to provide useful information [10]. However, it currently appears unlikely that vestibular implants will function in the very near future (next 15 years) at the level of cochlear implants (in use for 30 years) to combat effectively the predicted vestibular impairment in a large number of elderly. Like cochlear implants, vestibular implants need to solve the cost issues to be useful for the many elderly in need of such prostheses. Genuine to vestibular implants, people will need to learn to work with the reduced vestibular information provided by the implant, a challenge for those elderly with reduced motor skills.

Neurosensory regeneration has made great strides in the last few years to generate an increasing number of hair cells *in vitro* using various sources of stem cells [11,12]. Justifiably, this success in generating differentiated and functional hair cells sparked an increasing interest in private and public sponsors to support such research. Combined with progress in the generation of induced pluripotent stem cells out of one's own cells through the Yamanaka factors, this approach may seem like the miracle cure ready to be explored to combat hearing or vestibular dysfunction of the elderly in the very near future. However, upon closer examination, a number of unresolved problems abound for each of the various approaches pursued by different groups [13]. Pending unforeseeable advances in the next few years, these techniques may not be ready to help restore hearing or balance in a cost-effective way within the next 15 years to stem the tide of the hearing and vestibular impairment pandemic of the rapidly ageing societies.

Cell based therapy: At the core of the problem of any cell based approach towards reconstitution of lost hair cells lies the inner ear hearing (Fig.2) and vestibular sensory epithelia, a cellular mosaic of unprecedented, functionally relevant microarchitecture [14]. Undoubtedly, generating a hair cell in the dish from various cellular sources is an astounding and worthwhile scientific endeavour [11,12,15]. But turning those hair cells into the right kind of cell, inserted in the right place, with the right orientation to restore function, requires additional information. The limited data on how this is achieved during development [16] do not provide the information needed to help differentiate such *in vitro* generated hair cells into the right kind of cell after implantation. Moreover, *in vitro* hair cell generation has not produced cochlear hair cells, generating only vestibular hair cells. How to regulate different cell types, such as inner and outer hair cells of the organ of Corti *in vivo* during development is now moving into focus [16], but we do not know enough about this process to differentiate the right hair cell at the right place deliberately. For example, hair cell polarity is extremely complicated at a molecular level [17]. Combined with the fact that ageing ears are unlikely to retain the necessary molecular topologic information to guide without help the correct differentiation, substantial additional work is needed to turn the obvious gain obtained with this cell based approach over the last few years into an affordable therapy for the many. It seems more likely in the near future this approach will be applied to restore limited and fairly recent dysfunction caused by loss of comparatively few hair cells, relying on residual landmarks to allow those implanted cells to integrate properly using existing cells as a scaffold for regeneration.

Gene based approaches: While research over the last few years has concentrated on approaches of cellular interactions sufficient in simpler systems with a regular mosaic of hair cells and supporting cells [18] also found in the vestibular sensory epithelia, such interactions cannot restore the sophisticated cellular patterns needed to fully restore hearing in the mammalian organ of Corti (Fig. 2). For example, attempts to use the ubiquitous Delta-Notch system are well understood in their ability to generate a regular mosaic of hair cells and supporting cells [19]. However, it has not even theoretically been solved how the linear arrangement of inner hair cells of the human organ of Corti with the broad cellular contacts between hair cells facing the continued row of Inner Pillar cells can be generated in the right position. It appears that the mammalian hearing organ has

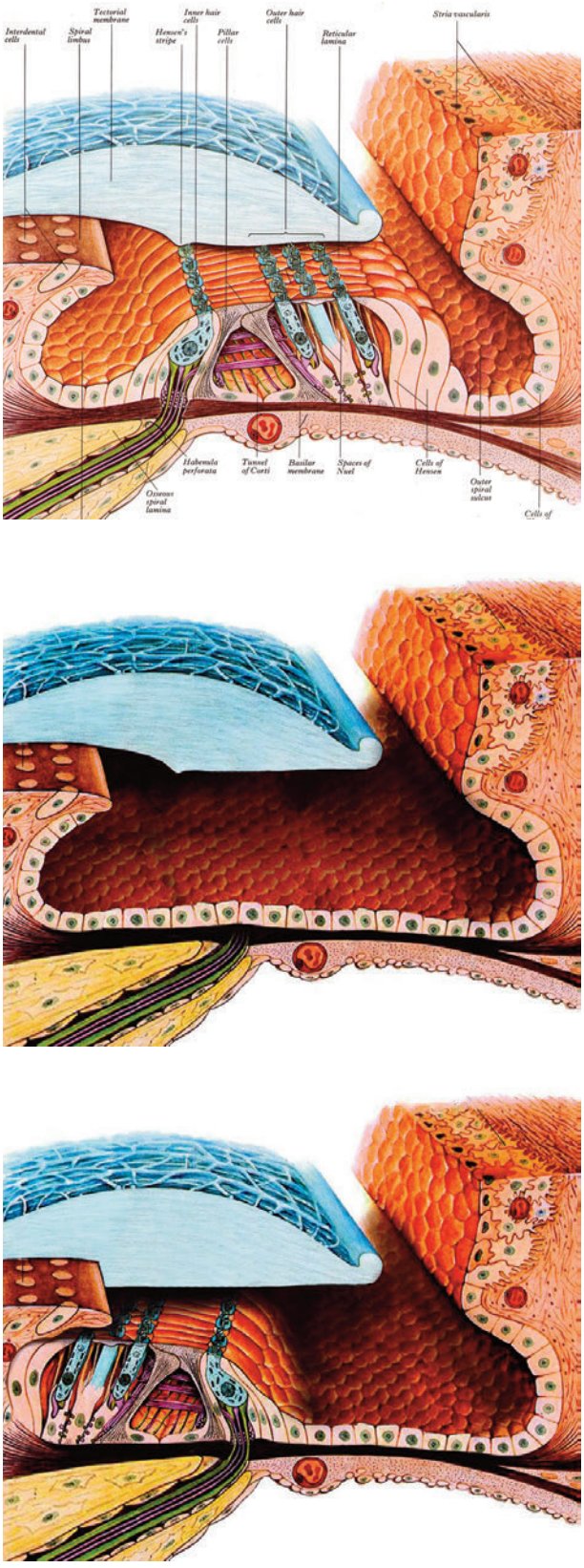

Fig. 2 Top shows the normal organisation of the organ of Corti, courtesy of Grant's Anatomy. Note the distinct distribution of different cell types each with a specific function in the hearing process. The middle shows the extreme form of a 'flat epithelium', a nearly featureless distribution of cells. This condition is found after long term hair cell loss. Bottom shows a hypothetical perfectly regenerated organ of Corti that is, however, in the wrong position overlying bone and has the wrong overall polarity. Such a perfectly regenerated organ of Corti will most likely be unresponsive to sound and thus of no benefit in terms of restoring hearing.

evolved the sophisticated cellular mosaic starting from simpler sensory epithelia comparable to the vestibular parts of the mammalian ear [20] where some limited regeneration is possible in newborns [18]. As with cell based therapy, a gene therapy approach using random viral transfection [21,22] has not begun to address the topological expression problem to restore a fully functional hearing organ. Moreover, in systems where success in transforming adult cells by viral delivery has been accomplished years ago [23], there is still no success in sight to restore functionally single cells [24]. Restoring hearing with either gene or cell therapy has at the moment not yet found a way to replace or regenerate mechanosensory hair cells precisely over the bony lip of Rosenthal's canal to ensure proper function of the restored mammalian hearing organ. To boot, treatments based either on gene or cell therapy will likely be as expensive and for the immediate near future less effective than cochlear implants. Therefore, like cochlear implants, gene and cell therapy for hearing loss require major progress to adjust the overall cost into a range that enables the high-throughput approach needed to correct hearing and vestibular impairment in hundreds of thousands of elderly needing them in the next 25 years.

Preventive measures as a viable short term solution to delay or even prevent hearing loss and vestibular dysfunction. Obviously, identifying the genes that are associated with age related hearing loss could provide preventive measures for some forms of such hearing loss and such work is now underway. Clinical trials with several small molecules [Ebselen (SPI-1005), AM-111] that intervene with hair cell death induced acute sensorineural hearing loss by various mechanisms are progressing with overall positive results under defined conditions [25]. However, continuous treatment with such medication to prevent age related hair cell loss is unlikely in the near future. In fact, how the hearing organ deteriorates with age and progressive hair cell loss has only been investigated in animal models of rapid cell loss due to genetic, chemical or sound related destruction of hair cells [1,7]. How much such catastrophic

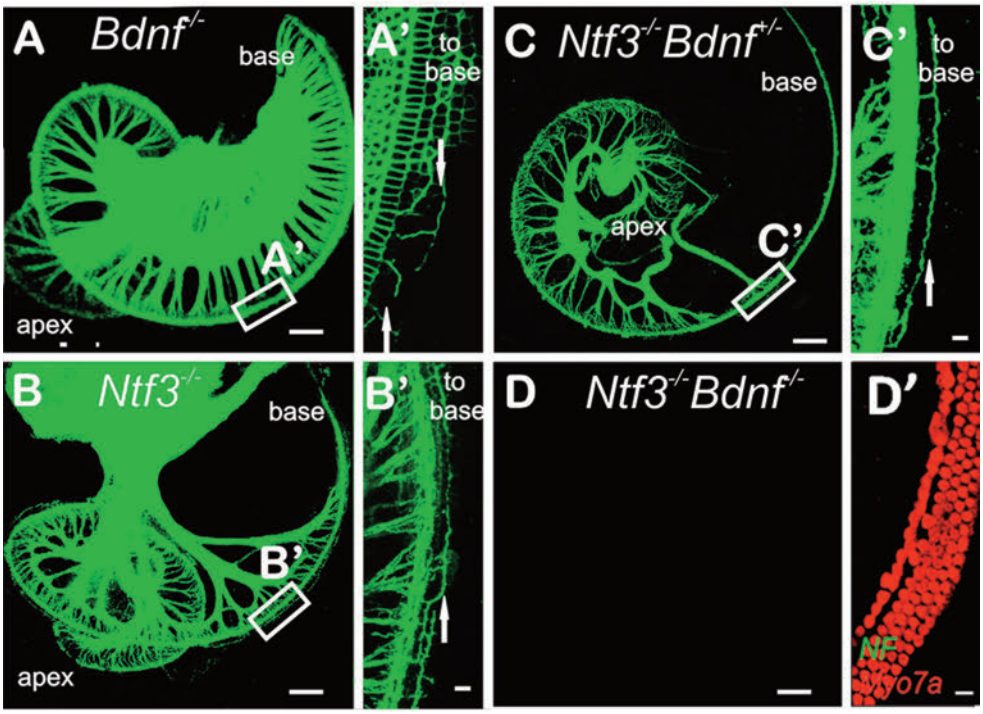

Fig. 3 Loss of neurotrophins can more effectively eliminate innervation compared to loss of hair cells using genetic engineering instead of various drugs that may also affect viability of neurons directly. Note that the severity of neuronal loss depends on the neurotrophin removed (Ntf3 is more important compared to Bdnf; A,B) and is additive (partial loss of Bdnf adds additional loss to the Ntf3 phenotype, C, eliminating both leads to complete loss of innervation (D) but retention of hair cells (D'). NF, neurofilament immunochemistry; Myo7a, Myosin 7a antibody staining. Data after Yang et al., 2011.

loss of hair cells resembles the slow deterioration with age remains unknown. Simply speaking, the approach taken for restoration will depend on the remaining cells of the hearing or vestibular organ left after slow loss of most, but not all, hair cells. Models that mimic such age related progressive hair cell loss are needed to fill that void to develop therapies more targeted to the apparently slowly progressing loss of cochlear and vestibular neurosensory cells [2,26].

Hearing and balance loss is a major aspect of the ageing problem but few of the nine hallmarks of ageing [27] have thus far been investigated [1,28]. Areas now viewed as most promising in terms of intervention of ageing elsewhere have been less explored in the ear such as cellular interactions that ultimately trigger the specific cellular demise. In fact, altered intercellular communication is presumed to be the leading aspect of neuronal loss in the ageing brain [27]. As with the central nervous system, the intercellular communication is an essential feature of embryonic neuronal viability with a well characterised molecular basis [29]. If, and how, neurons support hair cells in the long term, as they do in taste buds, remains to be explored. Recent data suggest that such a feedback from neurons to hair cells may exist and may provide a possible avenue for therapeutic intervention.

Three aspects should make prevention of neuronal loss the most important target for the immediate future. First, having the ageing ear connected with thousands of neurons to the brain instead of a few hundred [26] will benefit the future multichannel cochlear implants to use those additional channels. Second, should hair cell regeneration become feasible with further technical improvement [30], the nerve fibers and their connections with the brain are already in place to readily connect regenerated hair cells with the brain. Finally, while still in its infancy, it appears that proper neuronal connection may help sustain hair cells, much like taste buds require innervation for long term maintenance [31]. Neuronal retention is mediated through neurotrophic support molecules released from the ear and the brain [32]. Mutants lacking these factors (Fig. 3) have demonstrated the fast loss of neurons [33]. Small molecules have now been generated that appear to rescue the innervation in the absence of hair cells [34]. Such work needs to be built upon to evaluate if these small molecules can enhance long term viability of neurons so that they, in turn, can possibly support hair cell

survival. Minimally, this line of work will improve the survival of more neurons after hair cell loss to be used with cochlear implants or, once the problems outlined above are resolved, to connect newly generated hair cells with the cochlear nuclei.

In summary, concentrating more funded research on the long-term maintenance of neurons will have the greatest immediate benefit of retaining hearing and balance and to be used by cochlear and vestibular implants. Once restoration of hearing and vestibular hair cells is possible, remaining neurons could be used to restore hearing and balance.

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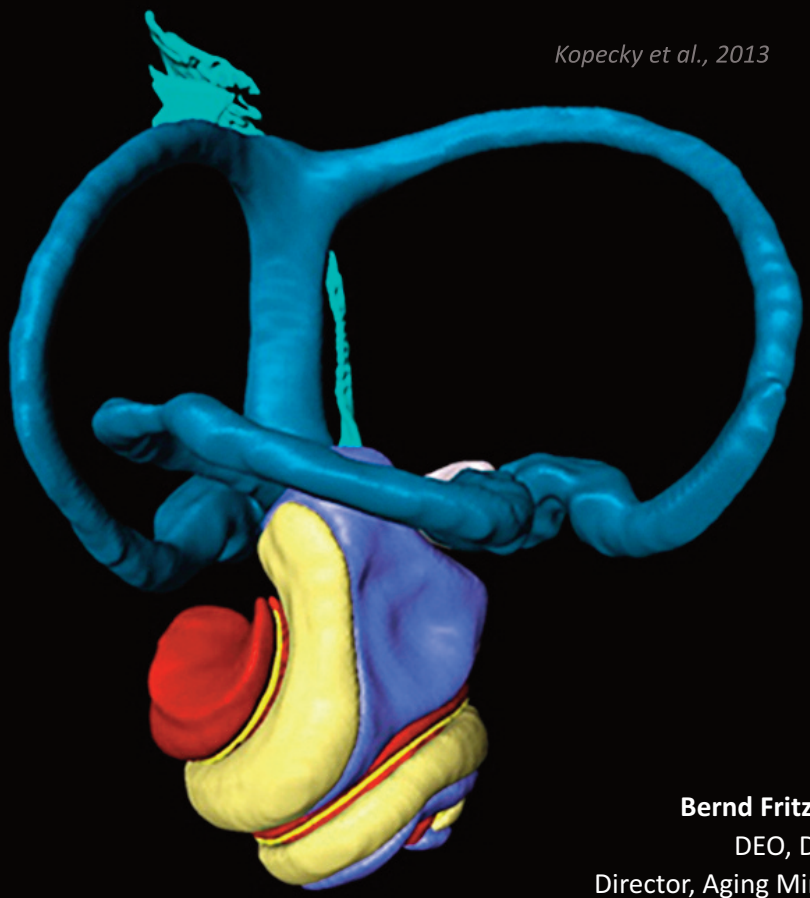

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