Selective Fiber Losses in the Auditory Nerve as Neural Correlates of Tinnitus

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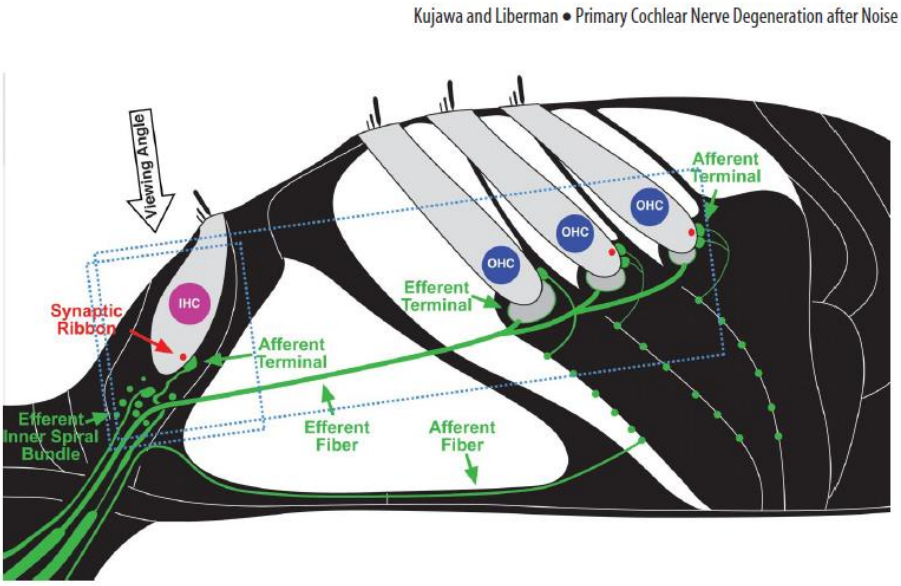
Introduction

This final project investigated the impact of selective damage to low spontaneous rate auditory nerve fibers in the development of an AN population output characteristic of tinnitus in individuals with normal audiograms, which is theorized to be the result of a maladaptive plasticity. An auditory nerve model was identified that allowed selective damage to low SR fibers, its output was used to generate a population response of fibers evenly spaced at the center frequencies of a 1/3 octave frequency band, and the effects of selective deafferentiation was quantified. Individual fiber responses were shown to be significantly different between damage conditions, with varied effect as a function of spontaneous rate. This result is consistent with other current work.

Background and Literature Review

The physiology of the cochlea is well documented. In this figure included in (Lin, Furman, Kujawa, & Liberman, 2011), the Organ of Corti is shown with a cartoon representation of afferent and efferent AN fiber attachments to outer and inner hair cells.



Recently, it has been shown in a variety of animal models that exposure to very loud sounds is not necessary to induce selective loss of fibers in the AN that have low spontaneous rates; indeed, that these fibers can be damaged without loss of IHC/OHCs. Critically, these fibers are responsible for carrying timing information for complex sounds, thus they directly impact real-world listening situations without affecting standard threshold audiometric testing (Kujawa & Liberman, 2009; Lin et al., 2011; Maison, Usubuchi, & Liberman, 2013). This ``hidden'' form of hearing loss has recently been shown to occur as a result of age in the absence of any NIHL (Sergeyenko, Lall, Liberman, & Kujawa, 2013).

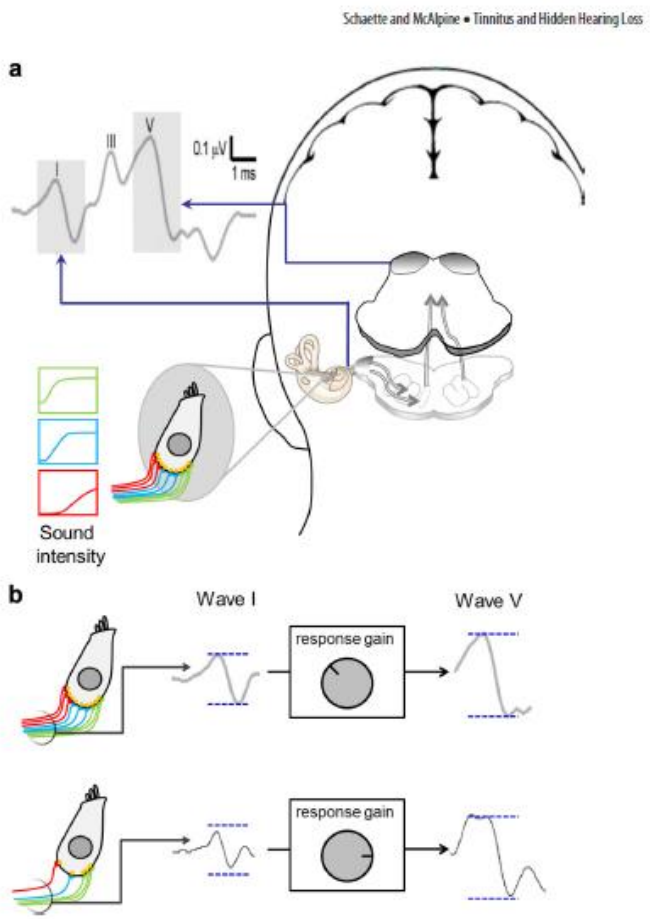
Tinnitus is the transient or persistent auditory percept of a sound in the absence of an external stimulus. It usually takes the form of a ringing or buzzing noise across narrow or wide frequency bands. Persistent tinnitus has several potential causes: it may occur as a side-effect of certain medications (ototoxic tinnitus); muscular disorders of the middle ear or chronic hypertension (pulsatile tinnitus); or a wide range of noise-induced hearing loss (NIHL) phenomena. In the first several cases, it is generally possible to record the perceived sound from the ear; thus these are usually referred to as objective tinnitus. In the final case, however, it is usually only the patient who can perceive the sound; thus this is usually referred to as subjective tinnitus.

While the phenomenon of subjective tinnitus (hereafter, tinnitus) is well-known, its pathologies are generally poorly understood and its mechanisms are debatable in many cases. It is well known that NIHL and tinnitus are often seen together, and it has been suspected for some time that NIHL contributes to development of tinnitus in many patients. However, it has also been recently shown that tinnitus can commonly occur in patients who have normal audiograms – and thus, as currently assessed in a clinical setting, no NIHL.

A very plausible model of tinnitus is that, as a result of under-stimulation due to damaged afferent fibers, areas in the auditory cortex that are highly innervated by the auditory nerve (AN) exhibit a pathological plasticity, and create phantom sound percepts in the absence of normal stimulus (Schaette & Kempter, 2006; Wang, Brozoski, & Caspary, 2011).

The standard model for mechanisms of NIHL relies on the notion that NIHL is primarily the result of inner and outer hair cell (IHC/OHC) damage in the cochlea as a result of exposure to very loud sound.

Here, we reexamine these proposed mechanisms for NIHL-induced subjective tinnitus that currently enjoy wide support in light of recently published data (Furman, Kujawa, & Liberman, 2013) suggesting previously unconsidered mechanisms of lower auditory system damage. Suggestively, development of subjective tinnitus is also more common in older adults, even those who have normal audiograms. Schaette et. al propose a schematic cartoon of this effect, in which increased gain as a plastic compensatory effect to loss of low-spont fibers effects systematic instability and hypersensitivity in the auditory cortex (Schaette & McAlpine, 2011)



Specific Aims

The goal of this final project was to model a population of auditory nerve fibers and demonstrate that selective damage to low spontaneous rate fibers produces a deficit characteristic of a “hidden hearing loss” tinnitus.

To that end, three specific aims were selected:

1. Evaluation and selection of an auditory nerve model suited to exploring deaffentation effects.
2. Comparison of the effects of deafferentation on low and high spontaneous rate populations of AN neurons.
3. Demonstration that population AN fiber response reflects characteristic features of relevant models of tinnitus

Methods

There are many models of the auditory nerve that are published and available. Many of them are heavily focused on specific areas of research. Extensive work by Carney et. al. have produced a large array of derived models, each of which focuses on specific types of AN behavior (M G Heinz, Colburn, & Carney, 2001a, 2001b; Michael G. Heinz, Colburn, & Carney, 2001).

McAlpine and Schaette have also proposed an AN model focused on tinnitus research (Schaette & McAlpine, 2011), but their model was described but not currently available to the broader research community.

For this work, the model developed by Ian Bruce was selected (M. S. a. Zilany & Bruce, 2006; M. S. A. Zilany & Bruce, 2007) specifically for its availability, and for its ease of configuration. The model, a schematic of which is presented below, allows the weighting factors of OHC and IHC contributions to be changed on a fiber by fiber basis, independently of other parameters. The model is written in MATLAB, and named 'zbcat', as it was derived in part from experimental data recorded in the cat AN.

The model takes a sound stimulus of arbitrary intensity and form, passes it through a middle ear response filter, and then creates modeled spike trains as a combination of three control filters governing relative contributions of the OHC and IHC.

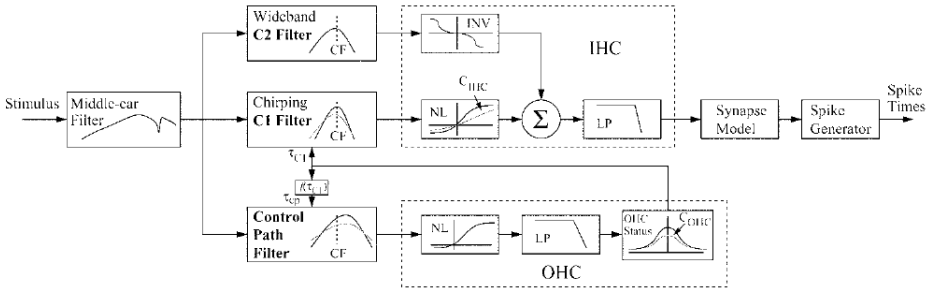


FIG. 1. Schematic diagram of the auditory-periphery model. The input to the model is an instantaneous pressure waveform of the stimulus in Pa and the output is the AN spike times in response to that input. The model includes a middle-ear filter, a feed-forward control path, a signal-path C1 filter, and a parallel-path C2 filter, the inner hair-cell (IHC) section followed by the synapse model and the discharge generator. Abbreviations: outer hair cell (OHC), low-pass (LP) filter, static nonlinearity (NL), characteristic frequency (CF), inverting nonlinearity (INV). C_{OHC} and C_{IHC} are scaling constants that control OHC and IHC status, respectively.

A model auditory nerve was constructed. Each fiber was specified by a collection of parameters. Across a range of 80 – 20 kHz, 24 nerve fibers were created. Each fiber had a center frequency (CF) corresponding to the peak 1/3 octave frequency across that range. In every case, the fibers had unmodified full OHC participation in the model, reflecting the case in which tinnitus may be present without NIHL.

Two sub-populations were created with different spontaneous rates. The low spontaneous rate fibers had a spike rate of 10 spikes/s, and the high spontaneous rate fibers had a spike rate of 80 spikes/s.

IHC participation, a proxy measure of selective deafferentation, was varied between 0-100% in 25% steps to model an increasingly severe progression of AN damage. Though published results discussed

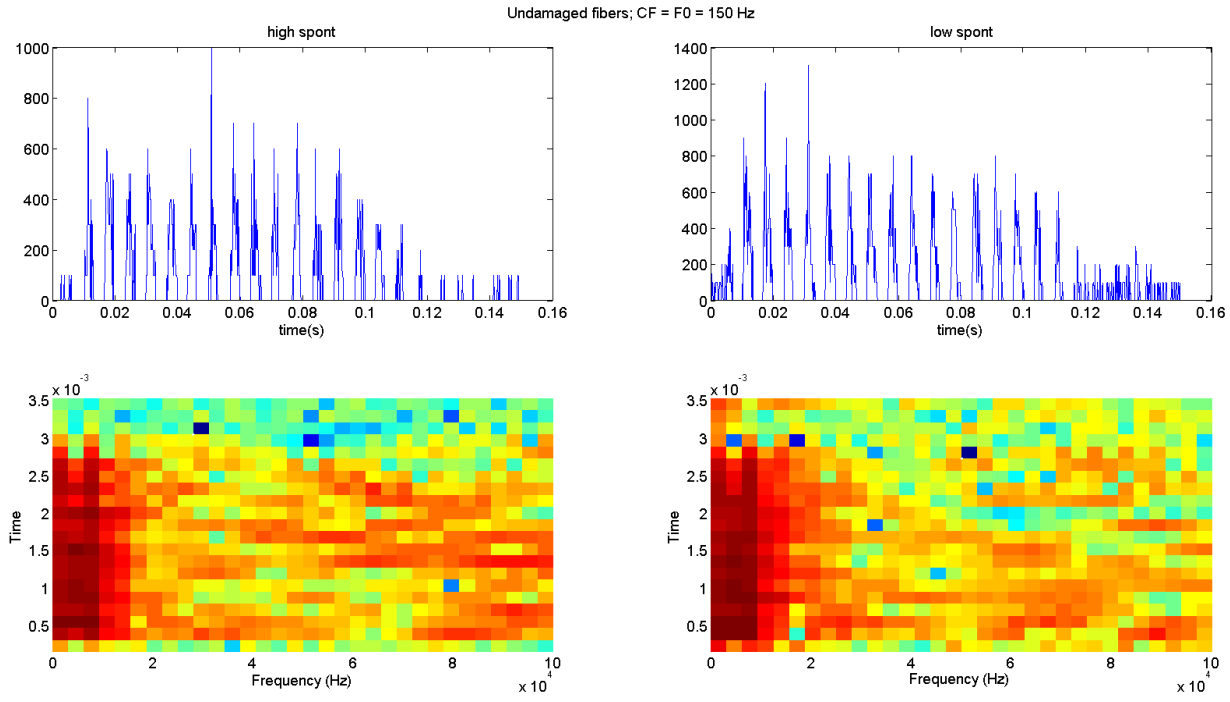
above (Furman et al., 2013) implicate IHC impairment only in the low-spont population, IHC impairment was applied to both low and high spont populations to assess the relative impact on their output, with the hypothesis that high spont populations would be less affected.

The stimulus presented to all fibers was a 50dB SPL (re 20 muPa) pure tone of 100ms duration, with a ramp time of 5ms. Stimulus frequencies equaled the CFs of each fiber; in this way, each fiber was exposed to its CF as well as a sample of relative off-tones spaced in third octaves.

Results and Discussion

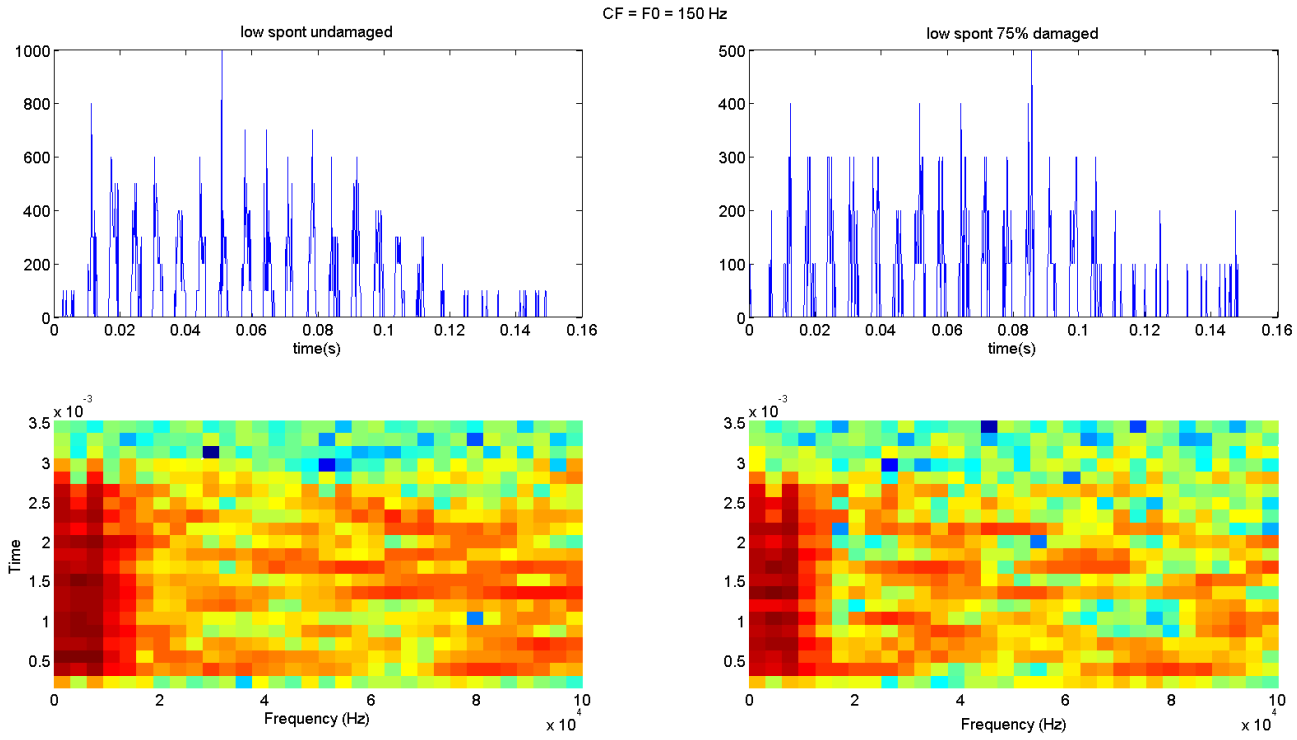
The spike train outputs of the model were used to estimate peri-stimulus time histograms (PSTHs) with a 50-repetition average response and a bin width of 0.2 ms. These were further visualized as spectrograms, created with a 64-point hamming window with 50% overlap.

A baseline model response was established for fully healthy fibers stimulated at their CF. An example of low- and high- SR fibers is shown below with a CF of 150 Hz.



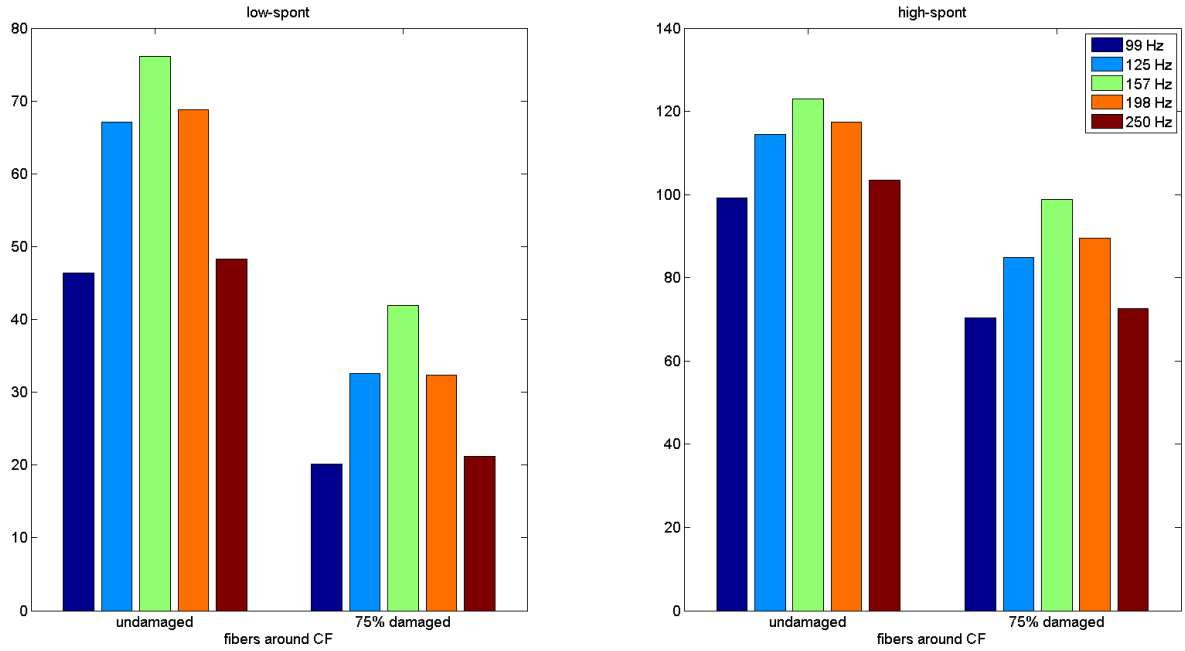
In both high and low SR cases, a strong response is shown around the target frequency in the spectrogram, and phase-locking to the stimulus is well attained. Consistent with the middle ear response time, a latency period before AN response to the tone is observed.

In contrast, low-spont fibers with 75% impairment demonstrate clear changes in behavior:



In the damaged fiber, some spectral spreading is observed, but the PSTH shows a marked change in response. While phase-locking is broadly preserved, the effective spontaneous rate rises to high-spont levels, and the phase-locked responses exhibit saturation and clipping effects at around 300 spikes/s, which impinges the envelope structure of the AN fiber response.

A further expected effect of damage is a broadening of CF tuning in affected fibers. Deafferentation of IHC contributions should result in a loss of inhibition and consequent attention to off-tones. To quantify this possible effect, the mean firing rates of modeled fibers were calculated when stimulated with their CF as well as with tones two third-octave steps away in either direction. This was performed for healthy and severely damaged (75% IHC impairement) fibers,and the results were plotted as a histogram:



In all cases, fibers reliably responded most strongly to their CFs, as expected. A one-way ANOVA was applied to determine if there was a significant broadening of the tuning curve (the relative sharpness of the differences in mean firing rates between stimulus frequency), and was shown to be significant in the low-spont case ($p = 0022$). A significant change was observed in the high spont case as well ($p = 0.0035$), but the effect is not as pronounced. Additionally, the changes in peak firing rate between damaged and undamaged low-spont fibers was significantly higher than that in the high-spont case.

Conclusions

Together, these results suggest that selective deafferentation of low-spont rate IHC contributions can show CF tuning curve broadening, decreases in sideband inhibition between adjacent fibers, evoked response saturation, and spectral smearing that are all consistent with observed changes in hidden-NIHL induced tinnitus occurrence.

Future Work

An obvious next step is to take this collected AN output and use it to generate model STRFs in the auditory cortex. This work would provide further evidence for the propagation of this maladaptive plasticity model of tinnitus into the central auditory system, where one would expect to see similar transient or permanent changes in response.

Two common packages exist to do this: STRFPak and STRFLab, both provided as matlab routines through the Theunissen lab at Berkeley (http://theunissen.berkeley.edu/Software.html). However, neither are well-suited to use of custom PSTHs without modifications that were beyond the scope of this work.

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