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Predicting the Perceptual Consequences of Hidden Hearing Loss

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Abstract

Recent physiological studies in several rodent species have revealed that permanent damage can occur to the auditory system after exposure to a noise that produces only a temporary shift in absolute thresholds. The damage has been found to occur in the synapses between the cochlea's inner hair cells and the auditory nerve, effectively severing part of the connection between the ear and the brain. This synaptopathy has been termed *hidden hearing loss* because its effects are not thought to be revealed in standard clinical, behavioral, or physiological measures of absolute threshold. It is currently unknown whether humans suffer from similar deficits after noise exposure. Even if synaptopathy occurs in humans, it remains unclear what the perceptual consequences might be or how they should best be measured. Here, we apply a simple theoretical model, taken from signal detection theory, to provide some predictions for what perceptual effects could be expected for a given loss of synapses. Predictions are made for a number of basic perceptual tasks, including tone detection in quiet and in noise, frequency discrimination, level discrimination, and binaural lateralization. The model's predictions are in line with the empirical observations that a 50% loss of synapses leads to changes in threshold that are too small to be reliably measured. Overall, the model provides a simple initial quantitative framework for understanding and predicting the perceptual effects of synaptopathy in humans.

Keywords

synaptopathy, auditory perception, signal detection theory

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Introduction

Since the influential article of Kujawa and Liberman (2009), physiological studies in several rodent species have shown that noise exposure can lead to dramatic and permanent physiological damage to the synapses connecting inner hair cells to auditory nerve fibers, causing them to swell and die (e.g., Fernandez, Jeffers, Lall, Liberman, & Kujawa, 2015; Furman, Kujawa, & Liberman, 2013; Liberman, Suzuki, & Liberman, 2015; Sergeyenko, Lall, Liberman, & Kujawa, 2013). This synaptopathy occurs despite no visible damage to other structures, such as the inner hair cells themselves, and no change in physiological or behavioral thresholds. A noise exposure that is severe enough to produce a temporary shift in thresholds, but not so severe as to cause a permanent threshold shift, can lead to a loss of around 50% of the synapses (Kujawa & Liberman, 2009).

Pressing questions at the moment include whether this form of synaptopathy occurs in humans, whether it is prevalent in the population, what perceptual consequences it might have, and how best to measure it. Although direct physiological measures cannot be made in living humans, a recent study by Viana et al. (2015) studied whole mounts of the sensory epithelium and osseous spiral lamina in postmortem human temporal bones with no reported otologic disease. Their findings suggest that a loss of the inner hair cell ribbon synapses may be common in the aging human cochlea, despite having a near-normal hair cell count, and so may be an important factor in presbyacusis.

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Because synaptopathy does not seem to cause any measurable elevation in absolute thresholds—the standard for clinical hearing screening—it has been termed *hidden hearing loss* (Liberman, 2015; Schaette & McAlpine, 2011). A number of recent studies have investigated potential perceptual and neural correlates of hidden hearing loss in humans (e.g., Bharadwaj, Masud, Mehraei, Verhulst, & Shinn-Cunningham, 2015; Liberman, Epstein, Cleveland, Wang, & Maison, 2016; Mehraei et al., 2016; Plack, Barker, & Prendergast, 2014; Plack et al., 2016; Prendergast et al., 2016; Ruggles, Bharadwaj, & Shinn-Cunningham, 2011; Stamper & Johnson, 2015a, 2015b). These have for the most part concentrated on perceptual tasks and neural responses that emphasize temporal coding, with the implicit or explicit assumption that temporal coding may be particularly susceptible to a loss of synaptic connections, and hence a loss of functional auditory nerve fibers. Another reason to use tasks more complex than tone detection in quiet is that it may be the high-threshold, low-spontaneous-rate fibers that are most susceptible to synaptopathy (Furman et al., 2013), which would imply the need to use suprathreshold stimuli at higher sound levels to reveal its effects.

A missing component so far, however, is a theoretical understanding of what the perceptual consequences of synaptopathy should be. Although tasks involving the processing of temporal envelope and temporal fine structure have been hypothesized to be sensitive to synaptopathy (e.g., Bharadwaj et al., 2015; Ruggles et al., 2011), no clear explanation has been provided for why tasks involving temporal coding (as opposed to, say, intensity coding) should be particularly sensitive to its effects. One approach has been to attempt to produce acoustic simulations of the hypothesized deficits. In one case that explicitly simulates deficits in temporal coding (Pichora-Fuller, Schneider, Macdonald, Pass, & Brown, 2007), the time waveform is temporally jittered to produce temporal distortions, which in turn lead to poorer performance in some perceptual tasks, such as speech perception in noise. However, the jittering leads to a severe distortion of both the temporal and spectral aspects of the stimulus. Even though the authors attempted to control for the spectral distortions, in practice, it is difficult to tease apart the different contributions, as it requires numerous assumptions regarding how the information in processed in the peripheral auditory system. In another case (Lopez-Poveda & Barrios, 2013), synaptopathy was simulated using digital audio by simply omitting a certain proportion of audio samples from the sampled waveform, in a process termed *stochastic undersampling*. Although these types of manipulations are inspired by biological processes, it is far from clear that they in fact create similar physiological representations or perceptions once the manipulated waveforms are processed by the auditory system. In the case of stochastic undersampling, there are many effects of this processing that affect speech perception, but in ways that seem unlikely to reflect the underlying physiology of synaptopathy. For instance, the omission of samples leads to spectral distortions of the stimulus, the extent of which is determined by the choice of reconstruction filters, unrelated to the auditory system. In addition, waveform normalization after processing ensures that absolute thresholds are unaffected by the processing (because the root mean square of the waveform remains the same by definition) but in ways that seem unlikely to reflect perception following synaptopathy. For instance, in the extreme case of undersampling, a pure tone would be represented by a single remaining sample that would be scaled to have the same rms as the entire pure tone, and so would be heard as a loud click or bang, rather than a tone. Thus, although the processing (by design) produces the desired effect of leaving absolute thresholds intact, it does so at a cost of seemingly unrealistic consequences for perception.

In the current article, a different approach is taken. Using the well-established framework of signal detection theory (Green & Swets, 1966), the information present in the auditory nerve is used to predict the perceptual effects of losing the information from a certain proportion of the auditory nerve fibers. The results of these simple simulations show that a surprisingly large proportion of synapses would need to be lost in order for the effects to be perceptually measurable, regardless of whether the task involves sound detection or more complex processes, such as temporal discrimination. The model provides an initial and simplistic framework that can be compared with perceptual data and be extended to more realistic situations and conditions.

Predicting Effects of Synaptopathy Using Signal Detection Theory

Model Assumptions

The analyses given here follow in the tradition of Viemeister (1988), who calculated the number of auditory nerve fibers required to achieve human levels of intensity discrimination, based on the response properties of single neurons. As an example along the same lines, consider the case where an increment in the intensity of a stimulus (or the addition of a tone to background noise) is to be detected via an increase in firing rate within a population of auditory neurons. The sensitivity of a single neuron is given by difference in mean or expected firing rates in response to the baseline and the incremented stimuli $\left(\overline{R_2} - \overline{R_1}\right)$, divided by the standard deviation (σ, i.e., the trial-to-trial variability of the neural response).

This provides a measure of sensitivity, d', for each individual neuron

$$d' = \frac{\overline{R_2} - \overline{R_1}}{\sigma} \quad (1)$$

Assuming independence between all neurons, the optimal decision rule is to combine the information from across all N neurons (e.g., Green, McKey, & Licklider, 1959):

$$d'_{TOT} = \sqrt{\sum_{n=1}^{N} d_n'^2} \quad (2)$$

If we assume that all the neurons carry equal information, then doubling the number of independent neurons leads to an increase in d' by a factor of $\sqrt{2}$, or about 1.4. However, if the neurons are all completely correlated, then no benefit is derived from combining the information from multiple neurons, as the total information is the same as the information from just a single neuron. Therefore, as the degree of correlation increases from 0 to 1, the increase in sensitivity as a function of N decreases from a factor of $\sqrt{N}$ to a factor of 1 (no change).

In estimating the effect of losing synapses (and hence functionally losing auditory nerve fibers), the simplest assumptions are that (a) the response of each auditory nerve fiber is independent from the responses of the others and (b) the information from all the auditory nerve fibers is optimally combined. In this case, the sensitivity of the system is described by the d'_{TOT} shown in Equation (2), where d'_n is the sensitivity of an individual auditory nerve fiber, n. For this initial analysis, a further simplifying assumption is that all auditory nerve fibers carry equal information, so that a given loss of functional auditory nerve fibers is not dependent on exactly which nerve fibers are lost.

Predictions for Detecting a Signal in Quiet or in Noise

Many studies have shown that the sensitivity to a signal in noise or quiet is proportional to the signal intensity, for a given signal duration and frequency (e.g., Green et al., 1959; Hicks & Buus, 2000). For instance, a 3-dB increase in level leads to a doubling in d' with all else remaining equal. Taking our simplified assumptions along with Equation (2), we can see that a decrease in the number of functional auditory nerve fibers by a factor F will lead to a decrease in the overall d'_{TOT} by a factor $\sqrt{F}$. In other words, a 50% (factor of 2) loss in auditory nerve fibers will lead to a reduction in sensitivity by a factor of $\sqrt{2}$. Because d' and intensity are proportional, a $\sqrt{2}$ *decrease* in d' implies a $\sqrt{2}$ *increase* in the intensity required to maintain threshold. This translates into a 1.5-dB increase in threshold. In other words, the model predicts that a 50% loss of fibers leads to only a 1.5-dB change in threshold—one that is not measurable with standard audiometric equipment. Similarly, a dramatic 90% loss of fibers would still only predict a 5-dB increase in thresholds in quiet or in noise. Indeed, even a 99% loss of fibers would only lead to a 10-dB increase in threshold, which is still within the range of normal hearing (i.e., up to 20 dB HL). The relationship between predicted threshold change (where a negative number implies a loss of sensitivity or increase in threshold) and proportional loss of synapses is shown in Figure 1 for losses between 0% and 99% of synapses. The relatively small changes in predicted threshold for large losses of synapses may help explain why only small changes were observed in chinchilla audiometric thresholds, even in the presence of an 80% loss of inner hair cells (Lobarinas, Ding & Salvi, 2013).

Predictions for Auditory Discrimination of Intensity, Frequency, and Interaural Time Differences

Similar predictions can be derived for any auditory task where the simplifying assumptions are reasonable and where the relationship between d' and the relevant stimulus parameter is known. For frequency discrimination, d' is generally proportional to the difference in frequency, Δf (e.g., Dai & Micheyl, 2011). Thus, by the same logic as outlined earlier, any decrease in d' due to loss of fibers would result in a proportional increase in the Δf to maintain a given level of performance at threshold. For instance, a 50% loss of synapses would result in a predicted decrease in d' of $\sqrt{2}$, and so frequency-discrimination thresholds should increase by the same amount. Although a change in threshold from, say, 1% to 1.4% might be measurable within an individual subject, the large individual differences observed in normal-hearing listeners would make it difficult to distinguish from other factors in the general population, especially given the very large range of performance that can reach an order of magnitude, even among young normal-hearing listeners (e.g., Whiteford & Oxenham, 2015).

For the discrimination of intensity differences, d' has been found to be roughly proportional to the change in level (in dB), ΔL (Buus & Florentine, 1991; Buus, Florentine, & Zwicker, 1995). Thus, according to our simplified model, a 50% loss of functional fibers would be predicted to produce a factor of $\sqrt{2}$ increase in the just-noticeable difference (JND). For instance, a JND of 1 dB would increase to 1.4 dB, which again would be barely measurable. It would take a more dramatic loss of 75% of synapses even to double the JND to 2 dB.

The detection of interaural time differences (ITDs) is one psychoacoustic measure that almost certainly

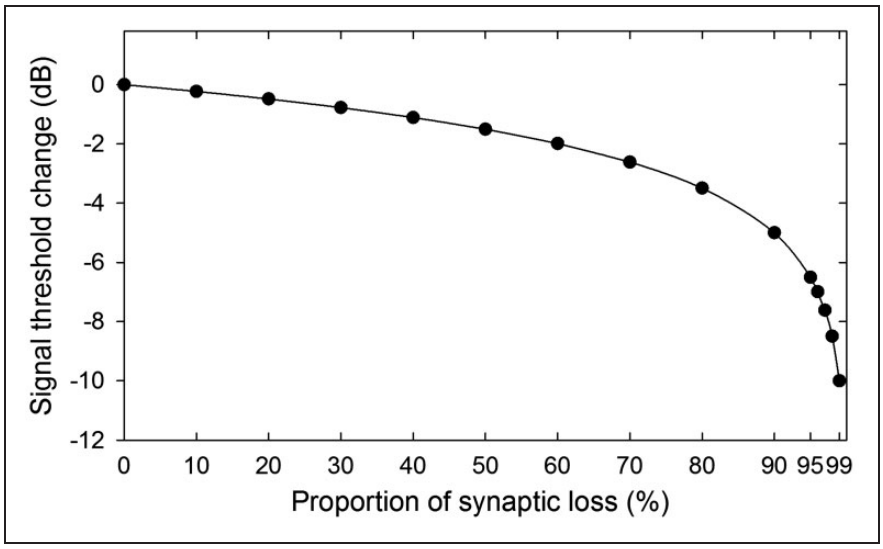

Figure 1. Illustration of the predicted change in absolute or masked threshold, as a function of the proportion of lost synapses. As shown, even a 99% loss of synapses results in only a 10-dB change in threshold.

depends on auditory-nerve phase locking. Here again, however, d' is proportional to the ITD (e.g., Hafter & Carrier, 1972), so that a 50% reduction in fibers is predicted to lead to an increase in the threshold ITD by a factor of only $\sqrt{2}$, so from 50 to about 71 μs—again well within the range of variability within the young normal-hearing population, which can also exceed an order of magnitude (e.g., Spencer, Hawley, & Colburn, 2016).

Predicting the effects of synaptopathy on more complex tasks, such as speech understanding in noise, will take a more detailed approach. However, signal detection-based approaches have been applied to the problem of speech understanding (e.g., Micheyl & Oxenham, 2012; Müsch & Buus, 2001a, 2001b), so such approaches could likely be used to predict how speech intelligibility would change in the face of cochlear synaptopathy.

Model Limitations

The predictions of the perceptual consequences of synaptopathy are, of course, dependent on the model assumptions. All assumptions are highly simplified, and some are more justifiable than others, as follows:

The first assumption is that the responses from individual auditory-nerve fibers are independent. Based on available data, this assumption seems reasonable (in contrast to auditory cortical responses; see Micheyl, Schrater, & Oxenham, 2013). However, as mentioned earlier, if some correlation is assumed between neurons, then the predicted effect of a loss of fibers becomes even smaller: As the assumed correlation increases from 0 to 1, the predicted change in d' decreases from a factor of $\sqrt{F}$ to no change at all.

The second assumption is that all fibers carry equal information. This is clearly not the case: For instance, at low intensities, most coding will be done by high-spontaneous-rate fibers with low thresholds; similarly, fibers with low characteristic frequencies will have little influence on the coding of high-frequency sounds. In terms of high- versus low-spontaneous-rate fibers, if synaptopathy does selectively affect low-spontaneous-rate fibers (Furman et al., 2013), then it may selectively and disproportionately impair processing at higher sound levels, so that an overall loss of 50% of synapses may include almost all low-spontaneous-rate fibers, which in turn could produce measurable perceptual effects.

The third assumption is that perceptual performance is limited by the variability in the responses of auditory nerve fibers. If performance is limited both by a more central source of neural noise or variability that occurs after information from the auditory-nerve fibers has been combined (σ_C), as well as by the auditory nerve itself (σ_{AN}), and if all fibers carry equal information, then the relation between the overall sensitivity and the sensitivity of each auditory nerve fiber expands to (White & Plack, 1998):

$$d'_{TOT} = \frac{N\left(\overline{R_2} - \overline{R_1}\right)}{\sqrt{N\sigma_{AN}^2 + \sigma_C^2}} \tag{3}$$

When $\sigma_{AN}^2 \gg \sigma_C^2$, then Equation (3) becomes equivalent to Equation (2), and overall sensitivity is proportional to $\sqrt{N}$. However, when $\sigma_C^2 \gg \sigma_{AN}^2$, then overall sensitivity will be proportional to N. Thus, for our example involving a 50% loss of fibers, thresholds will

increase by between 1.5 dB and 3 dB, depending on the extent to which performance is limited more peripherally or centrally, respectively. In our extreme example of a 99% loss of fibers, even if performance limitations are dominated by central noise, then the predicted increase in thresholds is still only 20 dB.

The fourth assumption is that the statistical distributions can be considered Gaussian and continuous. This assumption may fail in the cases where small numbers of neurons are involved or where the responses are more discrete in nature. For instance, if a brainstem neuron requires coincident input from two auditory-nerve fibers to respond, then it will fail completely if one of the fibers is no longer active.

Overall, the model should be treated as a very rough first approximation, but it nonetheless provides some insights into why a dramatic loss of synapses may result in behavioral changes that are barely measurable. More sophisticated and realistic models will likely provide an important tool in our quest to better understand the nature and perceptual consequences of different forms of damage to the human auditory system.

Conclusions

This article outlines predictions of a highly simplified model based on signal detection theory and shows how a dramatic loss of auditory nerve fibers may result in only small, and in some cases unmeasurable, decreases in behavioral performance. Such modeling can be used as a baseline with which to make specific predictions regarding the perceptual consequences of hidden hearing loss.

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