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Effect of the stimulation level on the refractory behavior of the electrically stimulated auditory nerve

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Abstract: The refractory behavior of the electrically stimulated auditory nerve can be described by the recovery function, which plots the ECAP amplitude in response to a masker/probe stimulus pair as a function of the time interval (Masker Probe Interval, MPI) between the two stimuli. The recovery function is characterized by two time intervals or periods: In the first interval (the Absolute Refractory Period, ARP), typically lasting for 300 to 400us, the neurons stimulated by the masker are in absolute refractory and unable to respond to the probe stimulus. As the MPI is gradually increased beyond the ARP, the stimulated neural population is increasingly able to respond to the probe stimulus (i.e. relative refractory) as the inhibitory effects of the masker diminishes. This second interval (the Relative Refractory Period, RRP) can be characterized by the time constant of an asymptotically increasing exponential function (Morsnowski et al. 2006). This recovery time constant provides an indication of the neurons' temporal characteristics. Previous reports (e.g. Battmer et al. 2004) suggest that this time constant is affected by the stimulation level used to determine the recovery function. Such a dependency would make it difficult to characterize the refractory behavior of the stimulated neurons using the recovery function. In this study, the refractory behavior of the electrically stimulated auditory nerve with respect to stimulation level was examined retrospectively. It was expected that increasing the stimulation level would result in more deterministic behavior.

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Effect of the stimulation level on the refractory behavior of the electrically stimulated auditory nerve

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Introduction

The refractory behavior of the electrically stimulated auditory nerve can be described by the recovery function, which plots the ECAP amplitude in response to a masker/probe stimulus pair as a function of the time interval (Masker Probe Interval, MPI) between the two stimuli. The recovery function is characterized by two time intervals or periods: In the first interval (the Absolute Refractory Period, ARP), typically lasting for 300 to 400 μ s, the neurons stimulated by the masker are in absolute refractory and unable to respond to the probe stimulus. As the MPI is gradually increased beyond the ARP, the stimulated neural population is increasingly able to respond to the probe stimulus (i.e. relative refractory) as the inhibitory effects of the masker diminishes. This second interval (the Relative Refractory Period, RRP) can be characterized by the time constant of an asymptotically increasing exponential function (Morsnowski et al. 2006). This recovery time constant provides an indication of the neurons' temporal characteristics.

Previous reports (e.g. Battmer et al. 2004) suggest that this time constant is affected by the stimulation level used to determine the recovery function. Such a dependency would make it difficult to characterize the refractory behavior of the stimulated neurons using the recovery function.

In this study, the refractory behavior of the electrically stimulated auditory nerve with respect to stimulation level was examined retrospectively. It was expected that increasing the stimulation level would result in more deterministic behavior.

Method

The ECAP recovery function's time constant estimates how fast the stimulated neurons are able to recover from a given single stimulus. In order to examine the effect of the stimulation level, recovery functions measured intraoperatively or postoperatively for 36 Nucleus Freedom cochlear implant (CI) recipients on a total of 59 intracochlear stimulation sites at more than one stimulation level were evaluated. Postoperative measurements were made at the CI recipients' subjectively determined Loudest Acceptable Presentation Level (LAPL).

The standard configuration for the measurements used a recording site located 2 electrodes remotely from the stimulation site. Each measurement involved 50 averages presented at a rate of 80pps, and the modified forward-masking paradigm from Miller et al. (2000) was used for the artefact reduction.

Results

Figure 1a shows how the recovery time constants varied with the corresponding nominal (unmasked) response amplitude, which is directly related to the stimulation level. Intraoperative and postoperative results were very similar. Postoperative stimulation levels were generally slightly lower, being limited by the highest acceptable stimulation level (LAPL).

The slope of the line segments between each adjacent pair of points indicates the sensitivity of the recovery time constant to changes in the response amplitude, and these are summarized in Figure 1b. At low nominal response amplitudes, variations in the recovery time are larger, becoming less with increasing nominal response amplitude, particularly for response amplitudes above 100 μ V. Also, the majority of the changes are reduced time constants (negative values in Figure 1b). Increased time constants are generally seen only at lower response amplitudes.

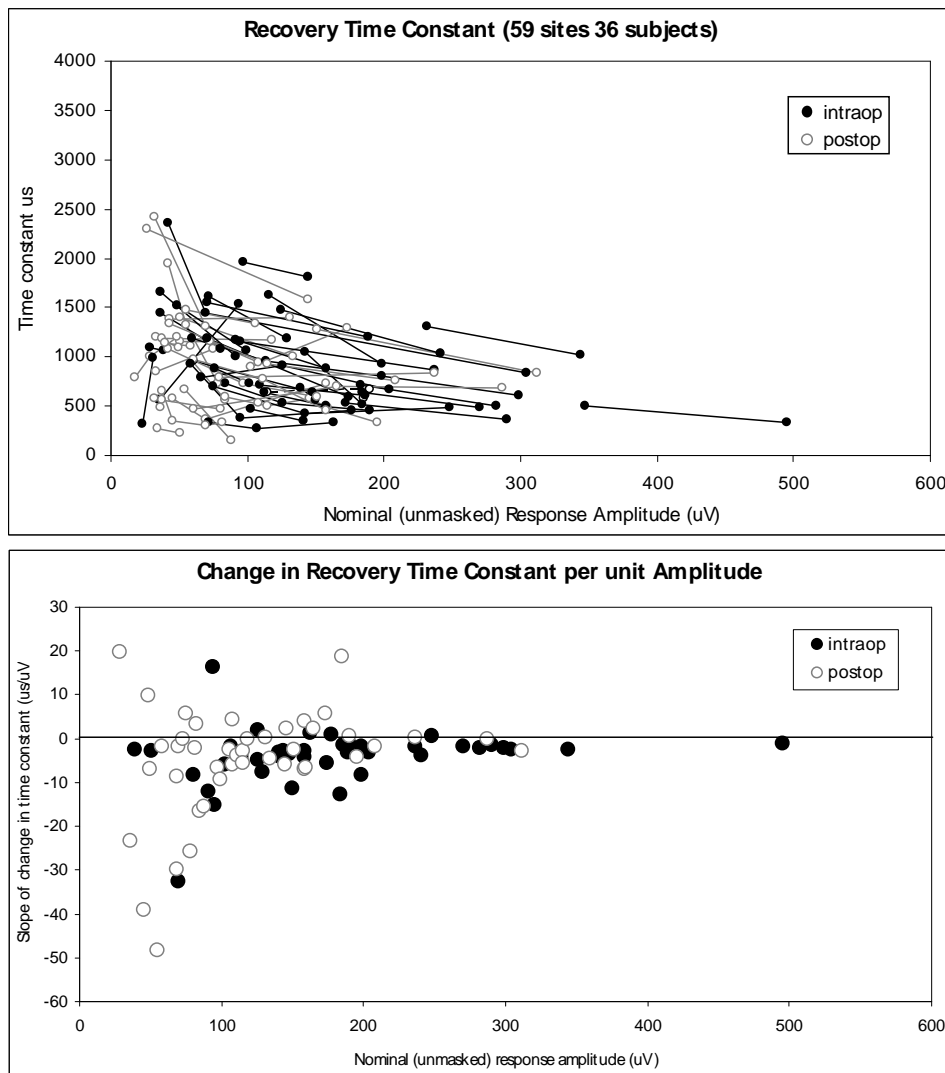


Figure 1: Top (Fig. 1a): Recovery time constants measured at minimally 2 stimulation levels for 59 sites from 36 CI recipients. Each line segment corresponds to measurements made at a single site. The x-axis corresponds to the final response amplitude of the recovery function where the masker no longer has any effect on the probe. Bottom (Fig. 1b): The rate of change in the recovery time constant (with respect to the response amplitude) between adjacent points of each line segment in Fig. 1a (as given by its corresponding slope) is plotted here against the larger x-axis value of each line segment pair. Large variations in the time constant become less frequent (approach zero) with increasing nominal (unmasked) response amplitude. Above 100uV, the changes in the recovery time constant are of the same order of magnitude as the measurement noise (around 20uV).

Discussion

From the above results, the recovery time constant appears to be independent of the stimulation level, provided that the corresponding nominal (unmasked) response amplitude were sufficiently large (>100uV). At lower response amplitudes, the results exhibit larger and seemingly stochastic variations in the behavior of the time constant.

One possible explanation for the larger variations in the time constant observed at lower response amplitudes could be the susceptibility of the recovery time constant estimates to noise in the ECAP measurements. However, given that the noise levels in ECAP measurements are generally lower (around 20uV) with the Nucleus Freedom CI, such an explanation is not very likely. An alternative explanation could be that larger response amplitudes are more likely to be associated with more deterministic behavior from the responding neurons, whereas smaller response amplitudes are more likely to incorporate activity that is less deterministic (and hence more stochastic) in nature. The estimates of the recovery time constant are then affected accordingly.

The ability to obtain clear ECAP measurements is highly related to the synchrony of activity in the responding neural population. Highly synchronized activity yields also larger response amplitudes, again suggesting more deterministic behavior from the responding neurons. An additional factor to consider is that larger response

amplitudes also often involve larger responding neural populations. However, the size of the responding neural population is not expected to contribute to stochastic variations in the corresponding neural response amplitude.

The reason for the differences at lower and higher response amplitudes (stimulation levels) is unclear at present. One could hypothesize that the deterministic activity arises from stimulation of the ganglion cell body (axons) which is expected to result in neural responses with a smaller latency. In contrast, the less deterministic activity may arise from more peripheral stimulation (i.e. dendritic processes) which requires more time to integrate before forming a measurable compound action potential. However, no correlation was found between the time constant changes and either the site of stimulation nor age, assuming that the loss of the more peripheral processes are greater towards the more basal regions of the cochlea or with time respectively. This hypothesis will be investigated further.

For comparison, routine clinical recovery function data from 105 CI recipients on 393 stimulation sites were also analyzed. This data involved only a single stimulation level at each site, and is shown in Figure 2 together with the multiple stimulation level data from Figure 1. The single stimulation level data shows very similar characteristics as the multiple stimulation level data above.

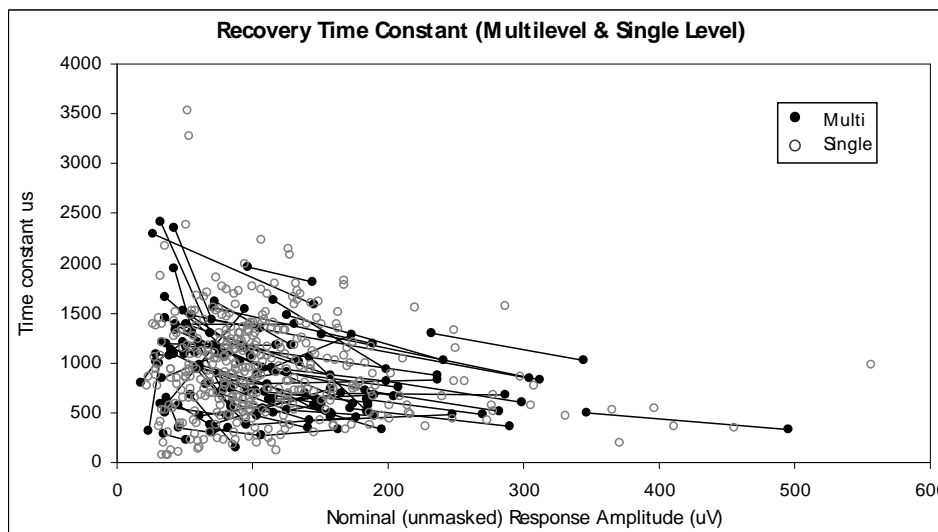


Figure 2: Recovery time constants from recovery functions made at a single stimulation level from 393 sites in 105 CI recipients, displayed here together with the (multiple level) data from Fig 1a, show very similar characteristics. The recovery time constants cover a wide range of values, from around 100us to over 2000us.

Even at the higher nominal (unmasked) response amplitudes (and assuming that they no longer vary depending on the stimulation level), the recovery time constants were found to range from as little as 100us to as much as 2000us. These differences in the recovery time constants were also not found to correlate with the site of stimulation nor age. The implications of these differences in time constants are not clear at present and will be the subject of future investigations.

There is little comparative human recovery function data available with normal hearing listeners. Ohashi et al. (2005) measured the CAP response to acoustic click pairs intratympanically from the promontory using a needle electrode, producing better results than previous attempts using extratympanic recordings (eg. Coats & Dickey 1972, Spoor et al 1976, Murnane et al. 1998). They used inter-click intervals of 3ms to 300ms, with the click pairs being presented at a rate of up to 4000Hz, compared with NRT recovery functions which involve masker/probe intervals of 0.1ms to 10ms, and the masker/probe pairs presented at much lower rates of 80Hz. Ohashi et al (2005) reported full recovery of the CAP between 118 and 278ms depending on the click intensity, attributing the recovery process to a combination of relative refractory effects and short term adaptation effects. The NRT recovery functions are typically fully recovered by 5 to 10ms. It would therefore appear that the recovery time constants under electrical stimulation are somewhat shorter compared to acoustic stimulation. It is difficult to conclude from here whether this is due to the state (healthy versus pathological) of the auditory neurons or not.

Conclusions

The overall results confirm the dependence of the refractory behavior on the stimulation level. Stimulation levels that produced response amplitudes below 100uV showed significantly more variations in the time constants. With response amplitudes above 100uV, the refractory behavior is presumably more deterministic. An examination of existing literature suggests that recovery from electrical stimulation is much shorter than from acoustic stimulation. Additionally, there was little correlation found between the site of stimulation and age in the present data. However, these factors need to be more systematically investigated in future prospectively designed studies.

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