THE RESPONSE OF THE AUDITORY NERVE TO ELECTRICAL STIMULATION FOLLOWING DEAFNESS

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INTRODUCTION

At lower stimulus levels electrical stimulation of the auditory nerve produces probabilistic discharge responses in individual auditory neurons. It has recently been shown that loudness perception in cochlear implant patients can be predicted from stimulus-response models incorporating probabilistic responses of the auditory nerve (Bruce et al., 1999, 2000).

The primary aim of this study was to investigate the probabilistic firing of the auditory nerve, in both deafened and undeafened animals in the hope that this knowledge may improve our understanding of loudness perception with the cochlear implant and its relation to deafness.

We therefore examined how sensorineural hearing loss (SNHL) affects the response of single auditory nerve fibres (ANFs) to acute electrical stimulation of the cochlea.

METHODS

Treatment Groups

ANF responses were compared across groups of adult guinea pigs with either normal hearing (prior to implantation), or guinea pigs that had been deafened, either 5 weeks or six months previously, via a single dose of kanamycin (400 mg/kg s.c.) and frusemide (100 mg/kg i.v.).

Electrical Stimuli

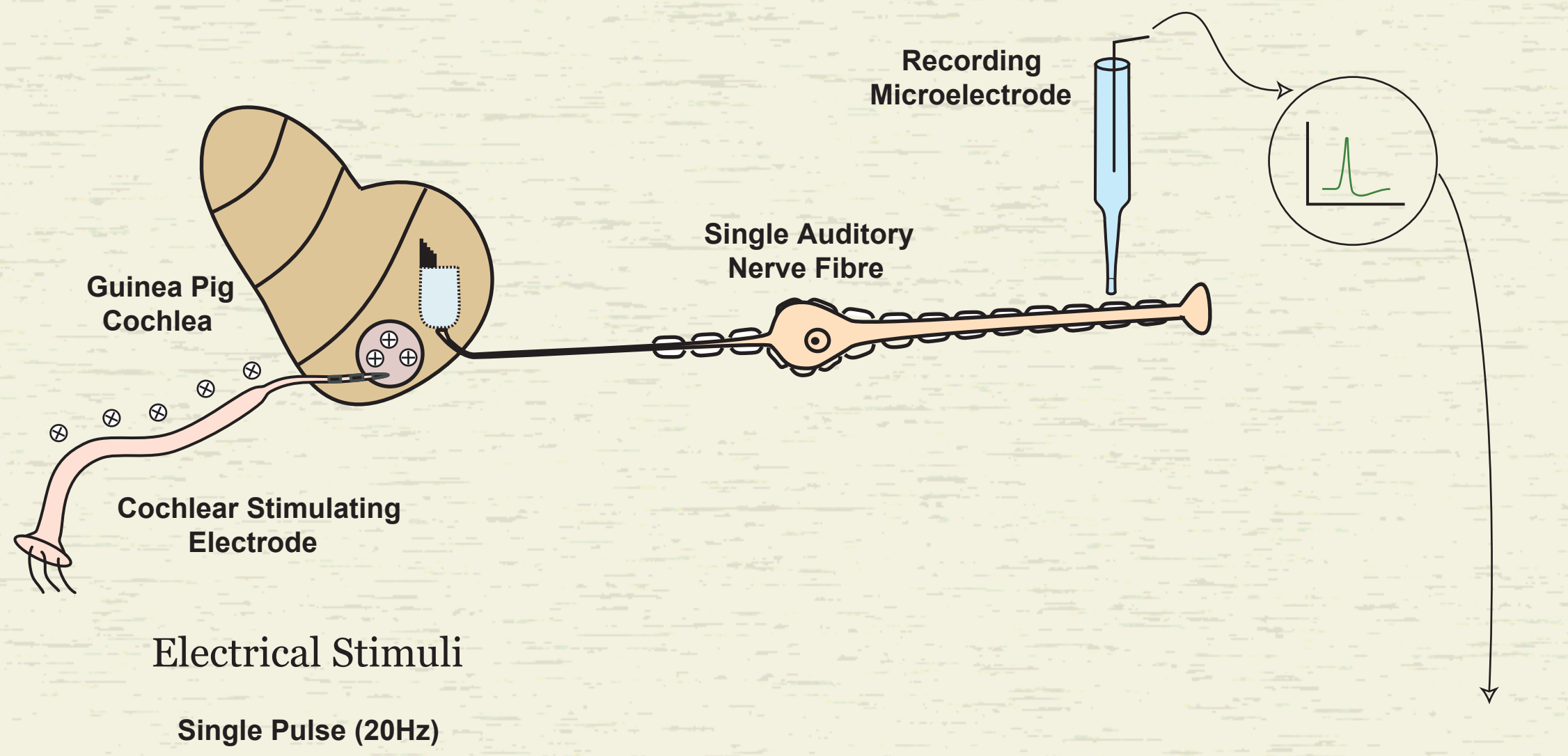
We have studied responses of ANFs to two types of monopolar, biphasic stimuli: [1] "single" pulses (repetition interval of 50 ms, presented 50 times) and [2] pulse trains at either 200 pps or 800 pps presented for 100ms for 50 trials (see diagram below). For each 200 pps burst 20 pulses were delivered to the electrode. Likewise, 80 pulses were delivered for each 800 pps burst. The stimulus was optically isolated and the electrodes were shorted between pulses in order to minimize DC production (Huang et al. 1999). Capacitors were not put in series with the electrode leads.

Single pulse stimuli were chosen to essentially eliminate any possible inter-pulse interactions. It is anticipated that the responses to these stimuli reflect properties of the neural membrane at the site of spike initiation, such as membrane noise (Verveen, 1963). The 200 pps pulse train stimulus was chosen so that a comparison could be made with previous data collected by Shepherd and Javel (1997) in the cat. Responses to pulse train stimuli are influenced by membrane noise as well. In addition, responses can also be influenced by other neural properties, such as refraction, adaptation and sub-threshold responses to previous pulses (e.g. accomodation-like suppression of excitation). The response to the first pulse of the pulse train was also examined, as it is not expected to be influenced by refraction, but would be sensitive to membrane noise and adaptation. Through examination of the first-pulse response we could determine whether adaptation was essentially complete between successive presentations of the pulse-train.

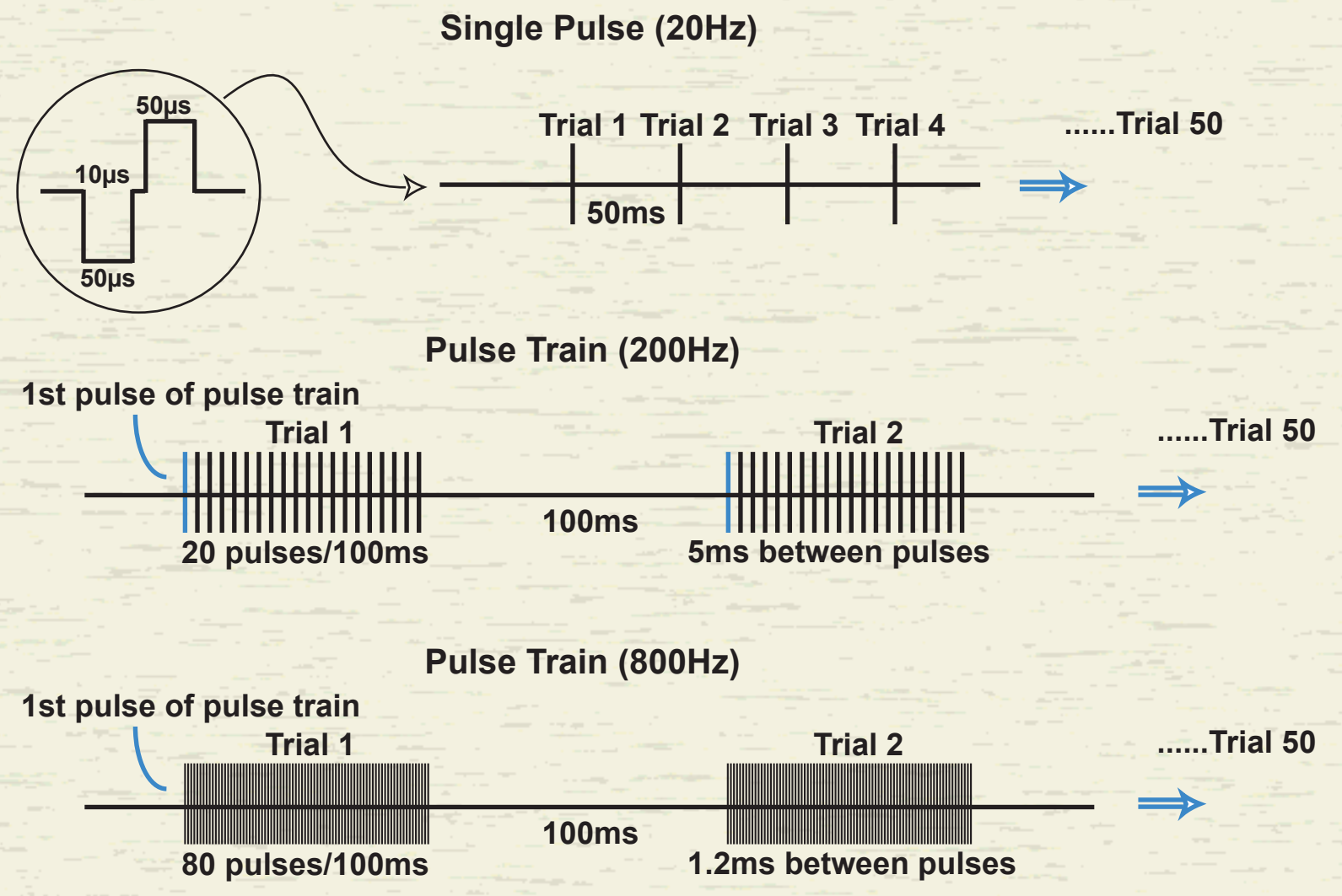
Auditory Nerve Fibre Recordings

Extracellular recordings from individual ANFs of the auditory nerve were made via a dorsal approach using glass micropipettes filled with 3M KCl.

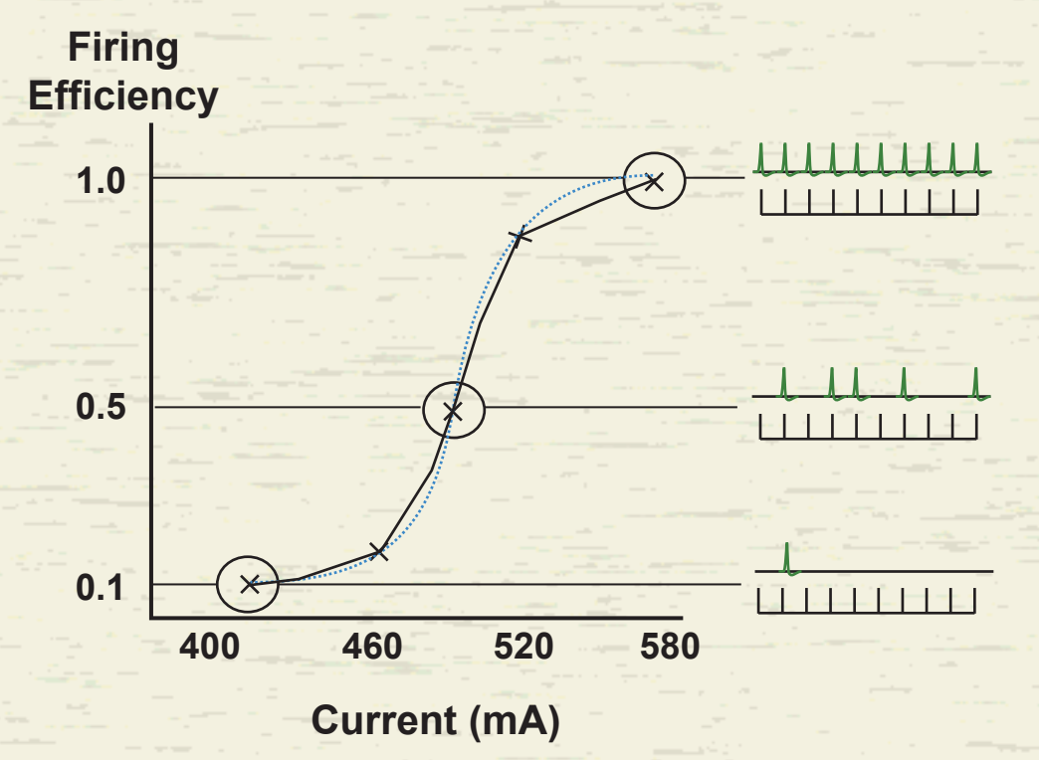
Experimental Setup



Electrical Stimuli



Input-Output Function



Data Handling

Discharge-rate level (input-output; IO) functions to electrical stimuli were generated for each neuron by plotting the firing efficiency against stimulus amplitude (see diagram above). It should be noted that with our current spike detection method, it is possible that *some* stimulus artifacts may have been incorrectly classified as spikes for the 800 pps stimuli – particularly at higher amplitudes.

For the data in section 1. of the results:
From the IO curves, the dynamic range for each ANF was calculated as the range of stimulus intensities occurring between firing efficiencies of 0.1 and 0.9. The latency was defined as the time between a spike reaching 2/3 maximum amplitude and the onset of the preceding stimulus pulse. Latencies were calculated at firing efficiencies of 0.1, 0.5 and 0.9.

For the pulse-train data is illustrated in the last plot of section 1 and the plots in section 3:
PST Histograms are used to illustrate how ANF excitability varies across pulse number. Because the observed responses to pulse trains are highly dependent on stimulus level and discharge probability, a significant number of PST histograms are required to illustrate the range of temporal responses observed. For the first 5 graphs in section 3, each curve represents a separate PST histogram. Each PST was calculated using data only from a narrow range of estimated discharge probabilities (i.e., firing efficiencies - FE). To further simplify the graphs, each PST was normalized such that the FE to the first pulse was set to 1.0 and the remaining FEs in the PST were scaled proportionately.

Data Pool

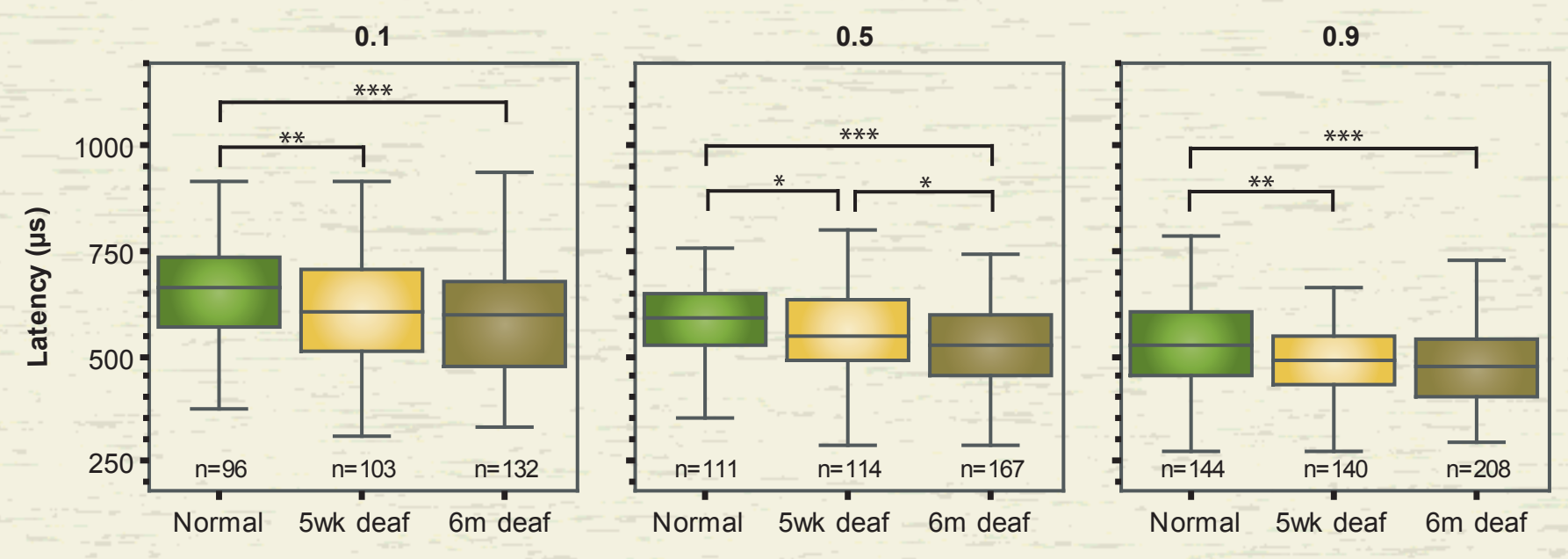
	Normal Hearing	5 weeks Deafened	6 months Deafened
Number of Animals	18	11	12
Number of Neurons	157	157	225
Number of IOs			
Single Pulse	175	156	241
200pps	67	66	73
800pps	11	17	8

Neurons exhibiting oscillatory or electrophonic behavior were excluded from the present analyses. Statistical comparisons were made between deafened and undeafened animals using a Mann-Whitney *U* test on ranks.

RESULTS

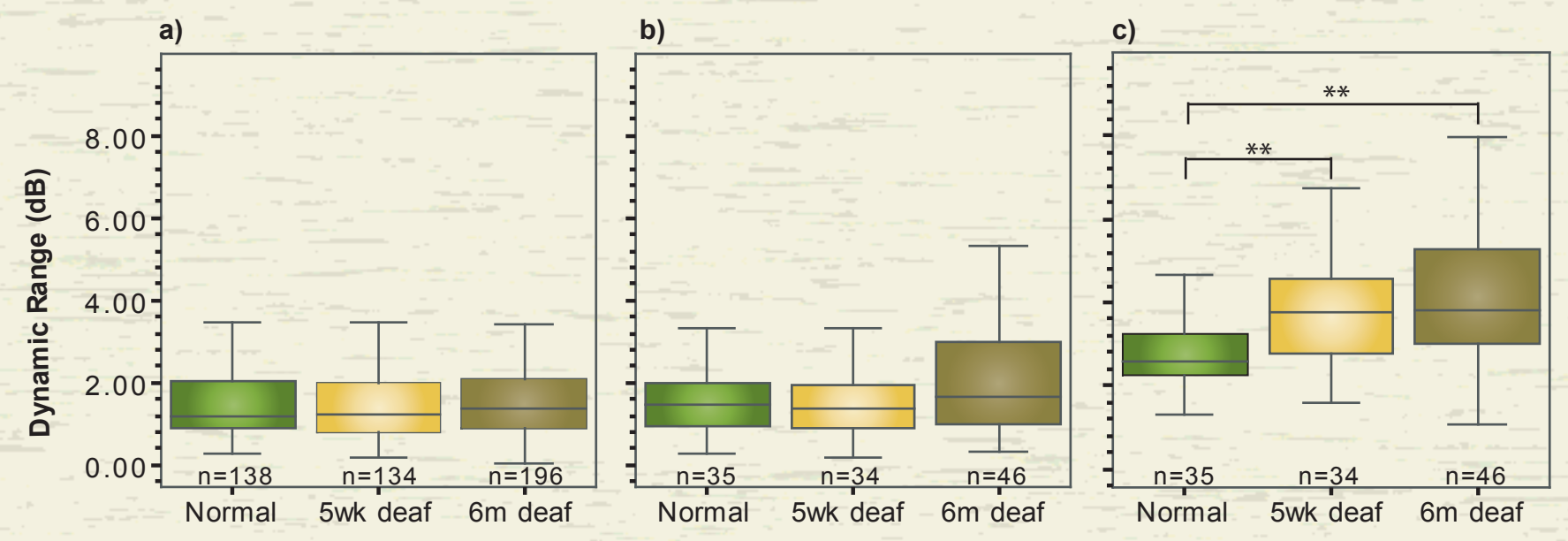
1. Effects of Duration of Deafness on ANF Firing

For both single pulse (below) and 200pps pulse train data (not shown) there was a decrease in latency observed with deafness. This effect was similar regardless of the level of probabilistic firing. This data is consistent with Shepherd and Javel's (1997) findings in the cat and with their observations of a correlation between retraction of the peripheral dendrites of ANFs with increasing SNHL, and their hypothesis of a resultant central migration of the initiation site.



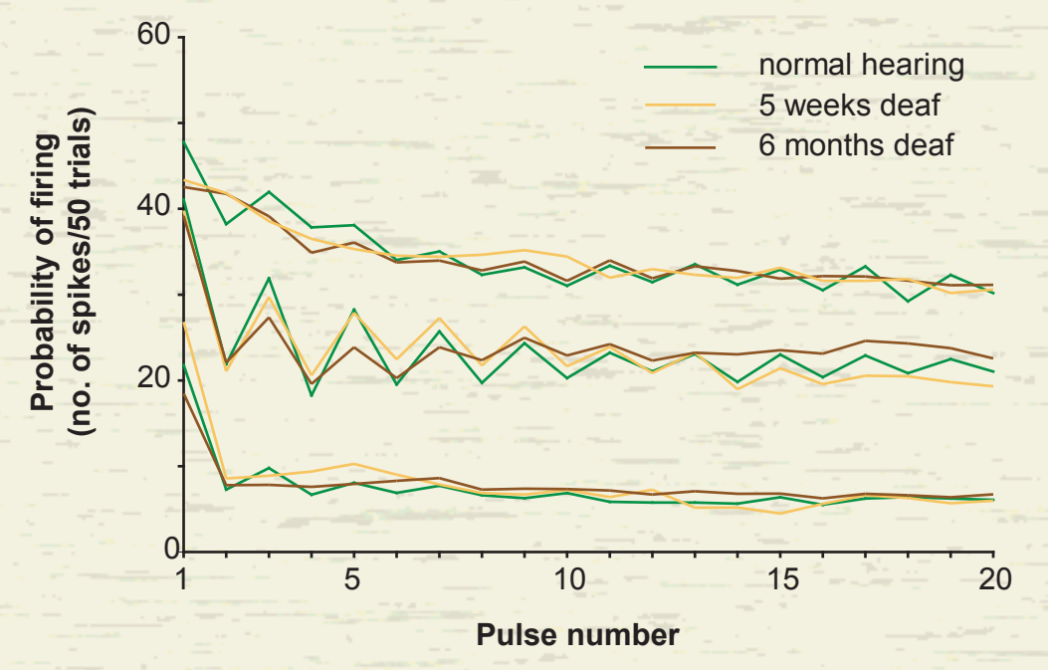
ANF latencies calculated at 0.1, 0.5 and 0.9 firing efficiencies during single pulse stimulation.
Each box plot represents pooled data from the number of neurons indicated. The upper and lower limits of each box indicate the 25th-75th percentiles respectively, with the median indicated inside each box. The lower and upper range bars outside each box indicate the 5th-95th percentiles respectively. The effect of hearing status is compared within each panel. *p<0.05, **p<0.01, ***p<0.001, *U*.

There was no effect of single-pulse stimulation or the first pulse of the pulse train on dynamic range following SNHL. However there was a large increase in dynamic range in animals deafened for both five weeks and six months. The increase in dynamic range with pulse trains, but *not* with single-pules, suggests that deafness has a substantial impact on the interactions between pulses in a pulse-train.



The dynamic range responses of auditory nerve fibres in each treatment group during a) single-pulse, b) first-pulse of the 200pps pulse train and c) 200pps pulse train stimulation. **p<0.01, *U*.

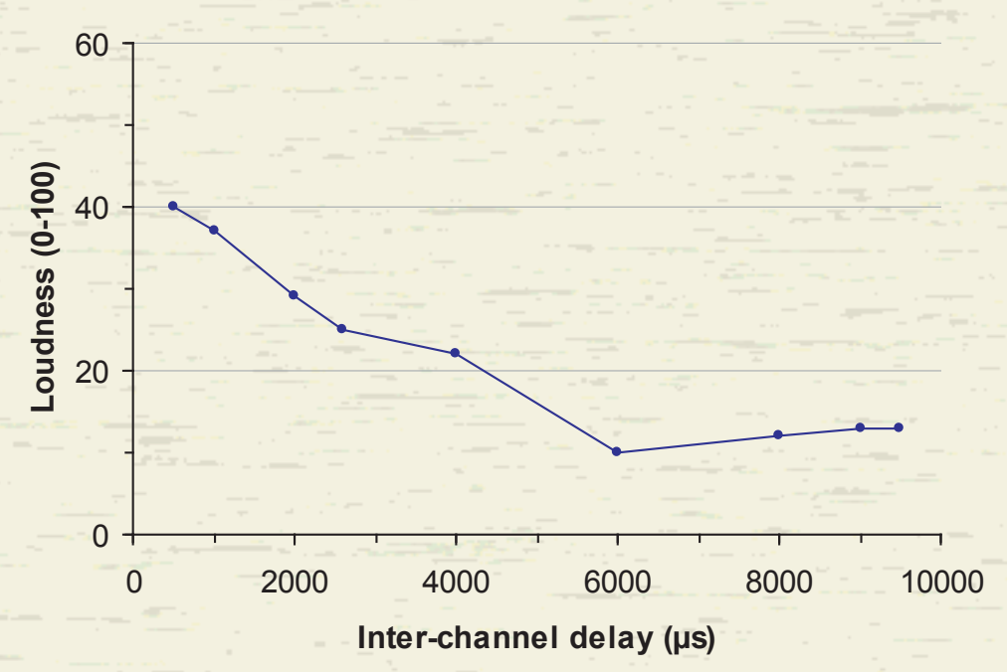
To determine if the change in dynamic range with deafness was due to differences in the effects of interactions between pulses within the pulse train, we examined how the firing efficiency changed within the pulse-train. We also wanted to determine if such changes were a function of duration of deafness. Although there was a decrease in neural excitability across the pulse train (see section 3 for further details), our preliminary analyses indicate there were no differences in these patterns between deafened and undeafened animals.



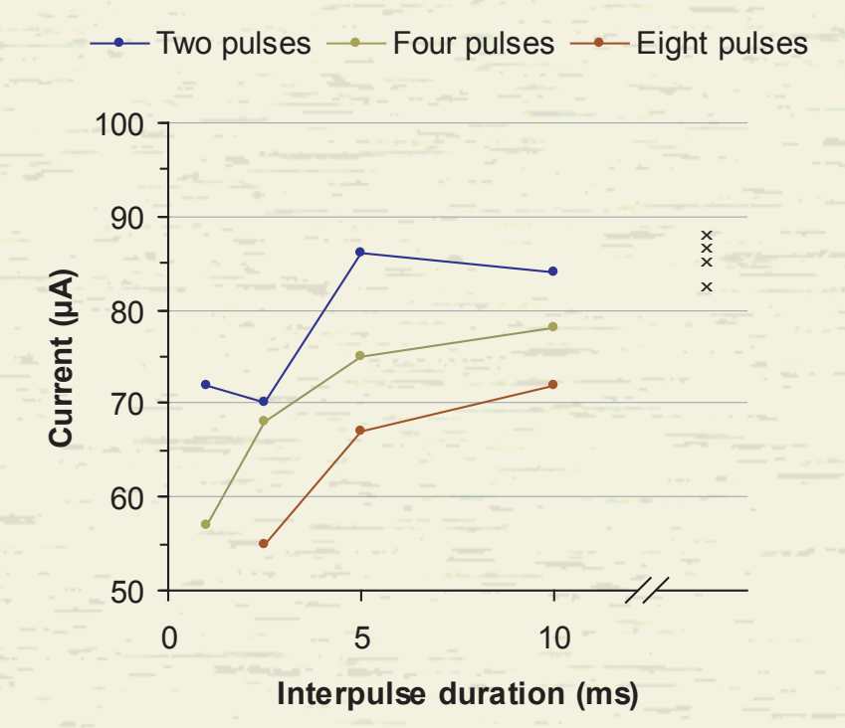
The change probability of firing across pulse number. The data is for 200pps stimulation. At all firing efficiencies there was a general reduction in the probability of firing during the first half of the pulse-train. At firing efficiencies less than 0.4 the probability of firing was approximately three-four times greater on the first than subsequent pulses. This effect was similar across treatment groups. Second, between firing efficiencies of 0.2-0.7 a serrate ("saw-tooth") pattern was apparent with a periodicity of every second pulse (i.e. every 10 ms).

2. Psychophysical Measures of Loudness and Probabilistic Firing of ANFs

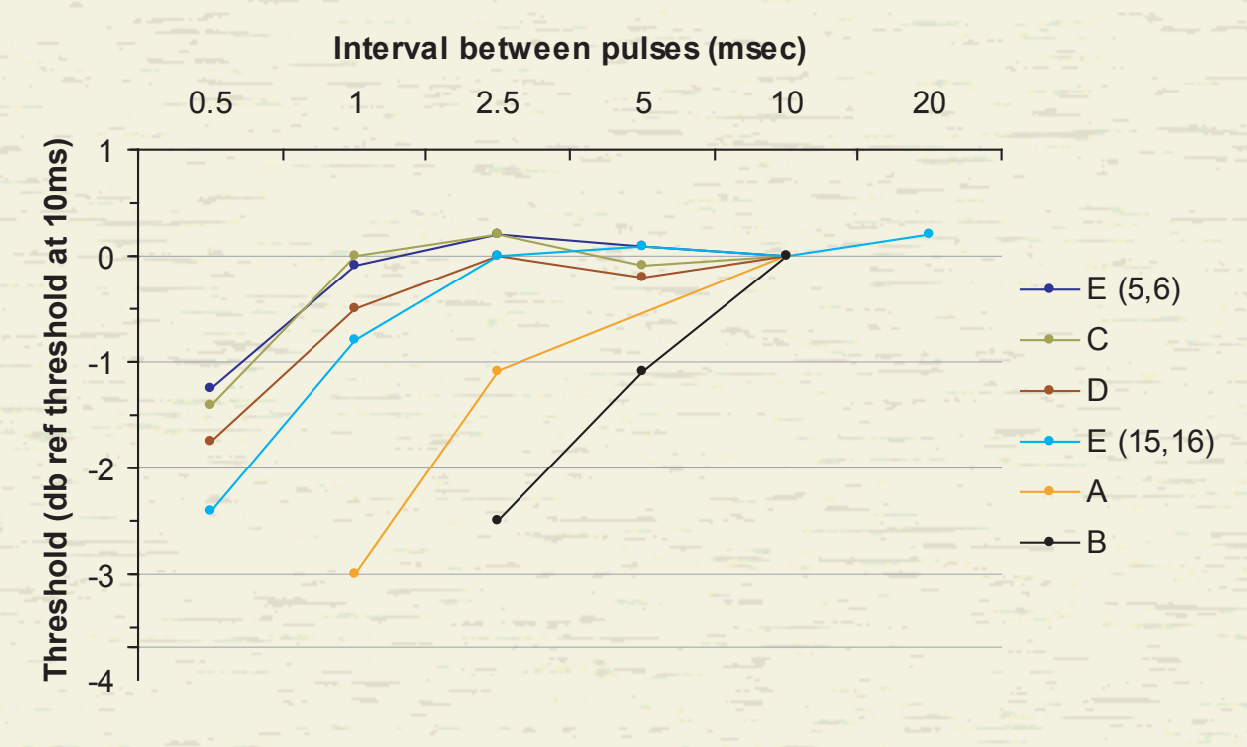
As outlined in the introduction, loudness perception in cochlear implant patients can be better predicted from stimulus-response models incorporating probabilistic responses of the auditory nerve (Bruce et at., 1999, 2000). In light of this, we sought to examine whether existing psychophysical data on the effect on interpulse interval on loudness and perceptual threshold (White, 1984a,b), could be explained by our data.
Data from White (1984a,b) showed that as the time interval between pulses is decreased, threshold current decreases and loudness increases. Paradoxically, existing neurophysiological data would likely predict that as the interpulse interval is decreased, the likelihood of neural firing would *decrease* due to the effects of refraction. However, our data in the next section suggest an alternative neurophysiological phenomenon may underlie these effects.



Loudness as a function of the delay between the initiation of single 200 µsec biphasic pulses on two channels. The first channel was monopolar electrode (1) and the second channel was monopolar electrode (7). Subject A made 9 loudness estimates for each of the interchannel delays. Loudness was determined via a slider used by subjects to indicate how loud the sound was. The slider was divided into 100 linear units. Adapted from White (1984).



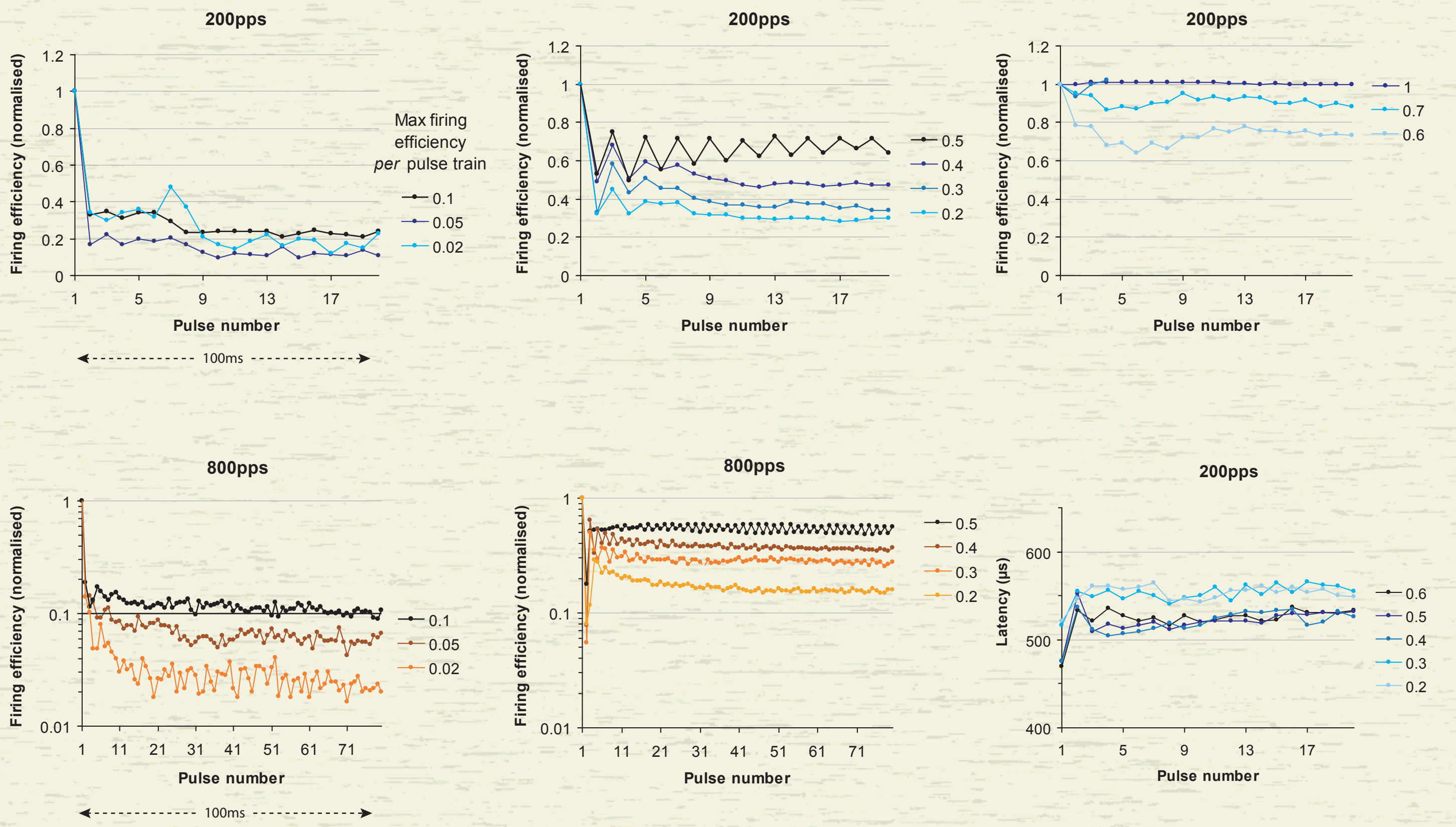
Threshold current as a function of the inter-pulse duration (i.e., inter-pulse delay) in msec. Each curve represents thresholds for a different number of pulses in the pulse-train: 2, 4, or 8 pulses. Pulses were biphasic and 200 µsec in duration. Data is from subject B with monopolar electrode (1) stimulated. Adapted from White (1984a)..



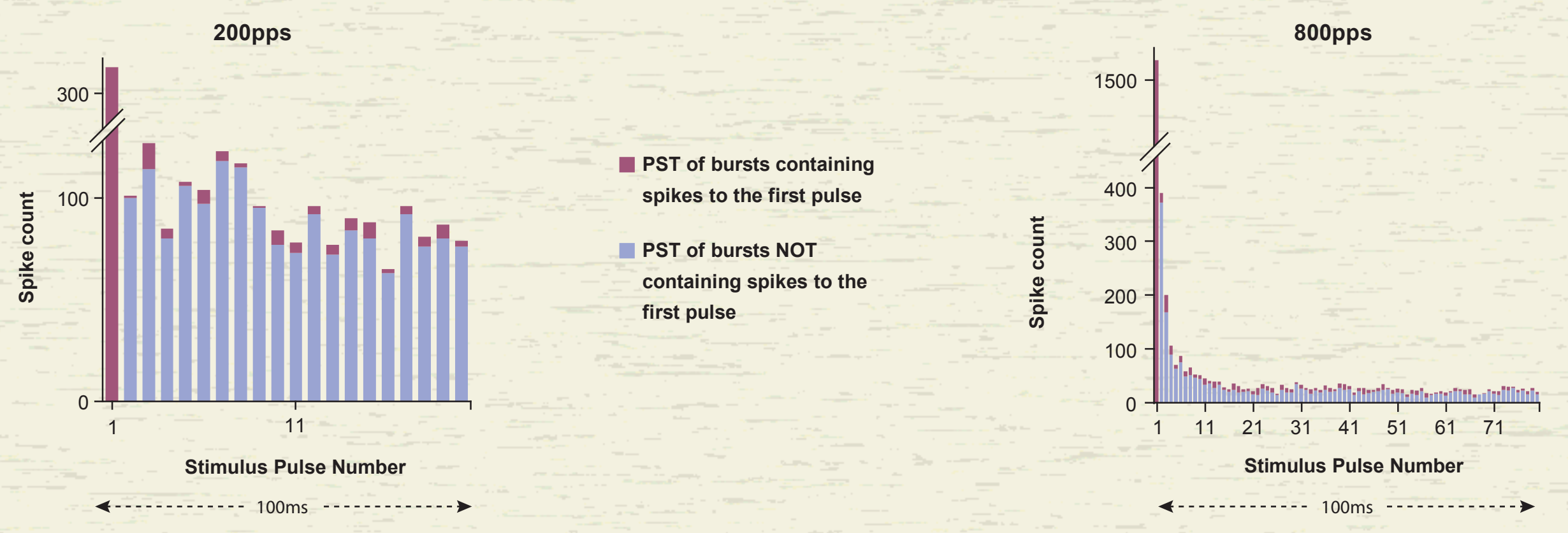
Threshold current as a function of the inter-pulse duration (i.e., inter-pulse delay) in msec for an 8-pulse pulse-train. Each curve represents thresholds for a different subject: subjects A, B, C, D, and E. In the case of subject E, two electrode configurations are illustrated. Pulses were biphasic and 200 µsec in duration. Adapted from White (1984b).

3. Changes in ANF Probabilistic Firing During Pulse Train Stimulation

We were interested in determining whether observed changes in firing efficiency across the pulse train may underlie the psychophysical data outlined in the preceding section. Please see the methods section for an explanation of the data handling for the plots below.
The PST histogram plots shown below indicate that there was a rapid drop in the likelihood of firing (normalised firing efficiency) after the initial pulse(s) of the pulse train. The majority of this drop occurs following the first pulse and within 5ms of the onset of the train. Furthermore, this suppression effect occurs not only at mid to high firing efficiencies, but also at very low firing efficiencies (eg 0.05 for 200pps, i.e. 50 spikes per 1000 pulses), suggesting the effect is unlikely to be due to refractory phenomena. Furthermore, the rapid decline in excitability appears greater during 800pps stimulation, suggesting the effect is rate dependant — and may be due to a 'build-up' of suppression due an increase in the number of stimulus pulses within a hypothetical ~5 msec integration window.
Similar plots of latency against pulse number, revealed that at low-mid range firing efficiencies the average latency was much shorter on the first pulse than subsequent pulses.



To further test the relative importance of refractory effects and hypothetical suppressive effects we plotted PST histograms similar to those shown above. Each of the PST histogram bars is divided into two segments, red and blue. These two segments are "stacked together," to form a standard histogram. The RED segment indicates the amount of neural activity that is due to bursts that DID spike to the first pulse. The BLUE segment indicates the amount of neural activity that is due to bursts that DID NOT spike to the first pulse. (A "burst" is a pulse-train of either 20 or 80 pulses.) The results indicate that a sub-threshold neural response to the first pulse significantly suppresses the discharge probability for the 2nd stimulus pulse. For the 800pps pulse-trains, the suppressive effect of the first pulse probably impacts the response probability for more than just the 2nd pulse. The histograms below also indicate refractory effects appear to have little impact at low discharge probabilities.



"Stacked" Post Stimulus Time Histograms for 200 PPS and 800 PPS pulse trains of 100 msec. Histograms are calculated from pooled data from responses with firing efficiencies between 0 and 0.02. Colored segments of the histogram bars indicate origin of neural activity as described in the paragraph above these figures.

DISCUSSION

1. These data show that several firing properties of ANFs are affected by deafness. Firstly, ANF latency is reduced. This may be due to the central migration of the action potential initiation site hypothesised to occur following dendritic retraction of ANFs with increasing SNHL. Alternatively, it may also be due to decrease in the time taken to charge the neural membrane due to effects of SNHL on the membrane. Dynamic range is increased following SNHL, however only during pulse train stimulation, and not with electrical stimulation at low rates. This suggests that neural phenomena present at low rates, such as membrane noise, appear not to be altered during pulse train stimulation.

2. Our data also provide a neurophysiological explanation of psychophysical observations of the effect of interpulse interval on loudness and perceptual threshold in cochlear implant patients. These previous observations of a decrease in threshold and increase in perceived loudness with a decrease in interpulse interval are at odds with a model of neural response assuming that refractoriness contributed substantially to the neural response. Refractoriness is expected to result in the generation of less spikes when the interpulse interval is reduced, and this should lead to an increase in threshold and a decrease in loudness. In contrast the 'suppression' we observed is expected to produce a neural response in keeping with the psychophysical data. Provided that the probability of discharge is low, a series of pulses presented rapidly, before the suppression has taken full effect, will have a greater chance of generating spikes (and therefore reducing threshold) than if the interpulse interval is lengthened and the suppression is maximal.

3. Our data also provide a strong candidate mechanism for understanding inter-channel interactions during non-simultaneous stimulation. At low, and possibly higher, discharge probabilities there is evidence for a mechanism where subthreshold neural responses suppress responses to subsequent stimuli -- on the same, or nearby, channels. This mechanism has properties similar to a simple Automatic Gain Control (AGC), where the gain of the system is reduced in accordance with the "rectified & integrated energy" within a relatively small time-window of 1-5 msec. From a membrane physiology perspective, this behavior has similarities to neural accommodation. With a better understanding of the mechanisms of these temporal interactions, it might be possible to design cochlear implants that are more effective.

Acknowledgements

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