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IMPORTANCE OF COCHLEAR HEALTH FOR IMPLANT FUNCTION

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Abstract

Amazing progress has been made in providing useful hearing to hearing-impaired individuals using cochlear implants, but challenges remain. One such challenge is understanding the effects of partial degeneration of the auditory nerve, the target of cochlear implant stimulation. Here we review studies from our human and animal laboratories aimed at characterizing the health of the implanted cochlea and the auditory nerve. We use the data on cochlear and neural health to guide rehabilitation strategies. The data also motivate the development of tissue-engineering procedures to preserve or build a healthy cochlea and improve performance obtained by cochlear implant recipients or eventually replace the need for a cochlear implant.

Keywords

Auditory prosthesis; multichannel cochlear implant; cochlear health; temporal integration; ECAP; neurotrophin

1. Introduction

The pioneers of the multichannel cochlear implant have created a wonderful tool that has enabled thousands of hearing impaired individuals to function almost normally in a hearing world (Clark et al., 1979, 1987; Hochmair-Desoyer et al., 1981, Hochmair et al., 2006; Schindler and Merzenich, 1985; Wilson et al., 1991; Wilson and Dorman, 2008). At the same time, the cochlear implant has presented the research community with many

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interesting challenges, one of the most significant of which is dealing with a partially degraded auditory nerve, the target of cochlear implant stimulation. One of the first challenges we face is understanding how the condition of the nerve affects cochlear implant function and how we might use that understanding to improve the quality of perception that patients experience using the implant. These studies also motivate efforts to improve the health of the cochlea and the target neural population. Here we review approaches that our laboratories have used to address this challenge, aided by a rich base of research from other laboratories.

Results from early work relating neural status to performance with the implant have challenged the basic assumption that the condition of the auditory nerve is important for speech recognition with cochlear implants. Studies of the number of remaining spiral ganglion neurons (SGNs) in cadaveric temporal bones from deceased patients showed little relationship to cochlear-implant function in life (Khan et al., 2005a). In fact in some cases, negative correlations between speech recognition and SGN counts have been found (Nadol et al., 2001; Fayad and Linthicum, 2006). However, interpretation of these results is difficult because there are confounding variables, such as cognitive ability, that can contribute strongly to speech recognition using the degraded signals delivered by cochlear implants (Heydebrand et al., 2007). In addition, the condition of the auditory nerve at the time of death might be different from the condition when the subject's ability to use the implant was assessed. In any case, the anatomical status of the auditory nerve (e.g., spiral ganglion cell counts and other anatomical features observable under the light microscope) might not be sufficient to characterize the health of the neural population since they might not reveal changes in the sensitivity or conductive properties of the nerves in a pathological state.

In the following sections, we review two approaches that we have taken to evaluate the importance of cochlear health for cochlear-implant function. The first approach (reviewed in Section 2) looks at variation in implant function across stimulation sites in a multichannel implant consistent with the assumption that the health of the cochlea and auditory nerve varies along the length of the cochlea. These studies use within-subject designs, reducing complications from confounding across-subject variables such as response criteria and cognitive ability. The second approach (reviewed in Section 3) is to directly compare cochlear implant function to observed anatomy across animals with a range of cochlear pathology. We then use functional measures that are correlated with cochlear pathology in animals to noninvasively estimate the health of the cochlea in humans who have various degrees of speech recognition performance. In Section 4, we review experiments designed to test the translation of our experimental results to the clinical practice of programming cochlear implant sound-processors, and in Section 5, we discuss biological approaches to improving cochlear health and cochlear implant function. Research protocols from our human and animal laboratories have been reviewed and approved by the University of Michigan Medical School Institutional Review Board (IRBMED) and the University of Michigan Committee on the Use and Care of Animals (UCUCA) respectively.

2. Across-site patterns of implant function in humans

It is clear from post-mortem studies of temporal bones in people who would have been candidates for cochlear implants, as well as those who had cochlear implants, that pathology along the length of the cochlea in the deaf or deaf-implanted ear is not uniform and that the pattern of pathology along the length of the cochlea differs across individuals (Hinojosa and Marion, 1983; Khan et al., 2005b). If the pathology has a significant influence on implant function, it follows that functional responses to cochlear implant stimulation should differ across stimulation sites along the electrode array in individual users and across users. The functional response to stimulation of individual electrodes in the cochlear implant can be assessed using psychophysical or electrophysiological measures. For speech signals, which require stimulation of multiple electrodes, we can assess the importance of individual stimulation sites by selecting specific sites for the processor map. These approaches are detailed below.

There are now a relatively large number of studies that have assessed cochlear implant function for each individual electrode along the length of the cochlear implant electrode array (Zwolan et al., 1997; Donaldson and Nelson, 2000; Pfingst and Xu, 2004; Bierer and Faulkner, 2010; Pfingst et al., 2008; Garadat et al., 2012). These studies reveal several important characteristics: (1) the functional response to electrical stimulation varies appreciably from one stimulation site to the next along the electrode array; (2) the across-site patterns of implant function are different for each subject; (3) for a given subject, the across-site patterns are stable over time in most of the cases that have been tested to date; and (4) the across-site pattern in a given subject is not the same for all measures.

Examples of patterns of across-site variation in modulation detection thresholds for 12 different subjects are shown in Figure 1. The variation from one stimulation site to the next is consistent with the idea that implant function depends on conditions near the stimulating electrodes. Contributions of more central processes, such as the ability of the subject to interpret signals coming from the periphery, would be expected to be more uniform across stimulation sites compared to contributions of conditions near the stimulation sites. The long term stability of the across-site patterns (Figure 2) suggests that they are rooted in physical conditions in the cochlea and are not due to random trial-to-trial variations such as variation in the subject’s attentional state. If the functional measures are dependent on conditions near the implanted electrodes, it is reasonable to expect occasional changes at some sites due to changing conditions in the cochlea (neural degeneration, tissue growth, etc.) and we do occasionally see such changes. However, for most of the cases in Figure 2, the patterns were unchanged from the first test to when a second test was done 1.3 to 3.0 years later. It is important to note that the initial data in this test for stability were obtained in subjects who had been using their implants for a long time. The first data were obtained an average of 4.6 years (range of 1.6 to 8.5 years) after implantation. Conditions might have been less stable immediately after implantation.

The fact that the across-site patterns of MDTs and masked MDTs are different for each subject (Figure 1) suggests that the pattern is due to pathology or other conditions near the electrodes and not due to the normal variation in anatomy or physiology as a function of

apical-basal position in the cochlea. We cannot say, based on these data, what conditions near the implant are affecting the functional measures. However, we have found that for any given subject, the across site patterns for various measures of implant function are not the same for all measures, suggesting that the underlying mechanisms differ across measures. Examples of across-site patterns for six different measures are shown for two subjects in Figure 3. Performance that is relatively good at one site on one measure might be relatively poor at the same site for another measure. For example, Subject 60's right ear (S60R), modulation detection thresholds (MDTs) are high (poor) at the most basal stimulation sites (especially site 1), lowest (best) around stimulation site 7, and highest (poorest) around stimulation site 13. For the same ear, gap-detection thresholds (GDTs) are also high (poor) at site 1 and low (good) around site 8 but they remain low at the more apical sites where the MDTs are poor. Thus, the simple notion that one functional measure can be used to identify all aspects of cochlear pathology is not valid. Reductions in the number of stimulable neurons might affect one functional measure while another functional measure might be dependent on temporal properties of the surviving neurons and be unaffected by fiber density.

Differences in the probable mechanisms underlying various functional measures of implant function can be illustrated by comparing across-site patterns of response to electrical stimulation using absolute detection thresholds versus modulation-detection thresholds. Variables that result in an increase in absolute detection thresholds do not necessarily cause an increase in modulation-detection thresholds. We examined the relationship between across-site patterns of detection threshold levels (T levels) and modulation-detection thresholds (MDTs) in 12 ears with cochlear implants. In 8 of the 12 cases, the across-site correlations between T levels and MDTs were not statistically significant ($p > 0.05$) suggesting that T levels are not a reliable predictor of MDTs. This suggests that the mechanisms underlying high T levels and high MDT levels are not the same.

At least two variables are thought to affect the levels of current required for absolute stimulus detection: distance of the electrodes from the neurons (Shepherd et al., 1993) and a second variable such as the condition of the stimulated population of neurons (Long et al., 2014). The second variable, i.e., what remains after accounting for the distance of the electrodes from the modiolus, has been shown to be important for speech recognition (Long et al., 2014). In a multi-electrode implant it is likely, for example, that elevations in detection thresholds at some of the sites along the length of the cochlea are due primarily to distance from the electrodes to the nerves and elevations at other sites are most influenced by neural pathology. The latter mechanism might also affect modulation detection, resulting in high correlations between the two measures, but the former, not so much.

The magnitude of across-site variation in absolute detection thresholds is strongly influenced by the electrode configuration (Pfingst and Xu, 2004; Bierer, 2007). The across-site variation is much smaller for monopolar than for bipolar or tripolar configurations, suggesting that the degree of current spread near the stimulation site affects the magnitude of threshold variation. In contrast, the across-site variation in modulation-detection thresholds for bipolar stimulation is similar to that for monopolar stimulation (Pfingst, 2011). This suggests that the MDTs might be less dependent on the number of surviving

SGNs close to the stimulation site and more dependent on temporal- or intensity-encoding properties of those neurons.

We use site-selection strategies to determine the effects of cochlear health on speech recognition. Most users of cochlear implants require multiple stimulation sites with frequency-specific channels of information distributed along the tonotopic axis of the cochlea in order to achieve reasonable speech perception. However, it is not always advantageous to use all of the available sites. Speech recognition scores typically increase as a function of the number of channels up to at least 8 channels (Friesen et al., 2001) and we have found that some subjects can benefit from many more channels. We can test the effects of estimated cochlear pathology on speech recognition performance using multichannel speech processors by selecting sites for the speech processor map that we estimate to be good or poor based on a psychophysical or electrophysiological measure of performance for stimulation of the individual stimulation sites. An example of such an experiment is illustrated schematically in Figure 4 and in detail in the paper by Garadat and colleagues (2012). In this case, the stimulation sites were selected based on masked modulation detection thresholds (i.e., MDTs measured in the presence of an unmodulated masker on an adjacent stimulation site). Electrodes 1 and 22 in the 22-electrode array were excluded and the remaining 20 electrodes were divided into 5 four-electrode segments. The two sites from each segment that had the lowest (best) MDTs were selected for one processor map and the two sites per segment that had the highest (worst) MDTs were selected for the other map. Dividing the electrode array into 5 segments allowed us to maintain stimulation along the whole tonotopic axis when selecting high-MDT or low-MDT stimulation sites. Testing the high-MDT and low-MDT maps in the same subject allowed us to avoid complications by other subject-specific variables that could make interpretation of across-subject comparisons difficult. Twelve subjects were tested in this experiment and all 12 showed better speech recognition in noise with the low-MDT map (better modulation detection) than with the high-MDT map (poorer MDT detection). This suggests that the conditions near the stimulating electrodes that yielded high or low MDTs were important for recognition of speech signals, particularly sentences in noisy backgrounds.

The magnitude of across-site variation in functional measures might be another indication of cochlear pathology. If cochlear pathology is minimal, the conditions along the length of the cochlea are more likely to be uniform. Consistent with this idea, the magnitude of across-site variation in detection thresholds has been found to be correlated with speech recognition (Pfingst et al., 2004). This measure is strengthened by correcting for across-site variation in distance of the electrodes from the modiolus (Long et al., 2014). However, the correlation could be weakened in across-subject comparisons due to confounding across-subject variables.

The data on across-site patterns of implant function in humans described in this section provided indirect evidence that conditions in the cochlea near the individual sites of stimulation affect implant function, including recognition of speech signals. The data also suggest that the conditions affecting function are not the same for all measures of function. However these data do not tell us the specific conditions that affect each measure. Additional insight into the relationship between cochlear conditions and implant function

can be gained from direct comparison of anatomy and cochlear implant function in animal models.

3. Relation of cochlear health to implant function in animals

One of the advantages of using experimental animal models is that these experiments provide better control over events occurring between the functional assessments and harvesting of the temporal bones for histological analysis. By better understanding the relationship between simple functional measures and neural anatomy near the implant, one can develop non-invasive measures that can be used to estimate nerve survival in humans at the time when more complex functions such as speech recognition are assessed.

In studying cochlear implant function in animal models, as in humans, it is important to consider the time course of events after implantation. We have consistently found that implant function assessed at the behavioral and electrophysiological levels is unstable during the first weeks after implantation (Pfingst, 1990; Su et al., 2008; Watts et al., 2014). Typically, psychophysical and electrophysiological thresholds rise, sometimes dramatically, during the first few days after implantation and then slowly recover to reach a relatively stable lower level. A probable contributor to this initial fluctuation is an inflammatory response to the implantation and/or to any deafening treatment that preceded implantation. It can occur following implantation in a hearing ear. Since SGN cell bodies do not regenerate once they are lost, this rise and recovery of thresholds is not due to changes in SGN density, though it might be due to a temporary loss of function or reduction of sensitivity of SGN cells. In humans these changes are not often seen because the patients are typically not tested until the prosthesis is activated several weeks after implantation. In any case, it is clearly important to follow implant function over time until stable before obtaining data to relate function to SGN survival.

Our research in guinea pigs has focused on two closely-related psychophysical measures (temporal integration; TI and multipulse integration; MPI) and two closely-related electrophysiological measures (ECAP growth functions and EABR growth functions) that are correlated with SGN density (Kang et al., 2010; Pfingst et al., 2011, 2014). These measures are based on commonly used clinical measures so they would involve tasks that require little or no training of the patients. This is in contrast to previously used measures such as MDTs which are too time consuming to use for analysis of the implant in a busy cochlear implant clinic. In our guinea pig subjects, the functional measures were assessed in long-term implanted animals after psychophysical and electrophysiological responses had stabilized. In these studies various levels of nerve survival across animals were created using a variety of procedures and the functional data were collected for electrodes located in the lower half of the basal turn. To create a wide range of nerve survival across animals in this region, a variety of treatments were used. Some animals were implanted in a hearing ear. The implant insertion created various amounts of damage, but typically some IHCs were preserved and SGN preservation ranged from moderate to very good. Other animals were deafened by cochlear infusion with neomycin prior to implantation. This typically destroyed all hair cells and most supporting cells and resulted in SGN degeneration to low levels within a month after injection. A third group was deafened with neomycin but then

inoculated with a viral vector containing a neurotrophin gene insert. The vector transfected the mesothelial cells in the scala tympani and upregulated production of neurotrophins, which resulted in greater SGN preservation than in animals receiving neomycin alone. Additional details regarding the neurotrophin gene therapy procedures are reviewed in Section 5.

3.1. Psychophysical temporal integration and multipulse integration functions

Examples of temporal integration (TI) functions (detection threshold versus pulse-train duration for fixed-rate pulse trains) are shown in Figure 5 and quantified in Table 1. As the pulse-train duration increased up to about 300 ms, thresholds decreased, as is typical in classic temporal-integration experiments (Gerken et al., 1990; Shannon, 1989). In a healthy cochlea that had surviving IHCs and high SGN densities (>70% of normal) near the cochlear implant electrodes, we found that thresholds decreased as a function of stimulus duration more rapidly than in cases with poorer nerve survival (Figure 5 and Table 1).

Multipulse integration (MPI) functions (detection threshold versus pulse rate functions for fixed-duration pulse trains) show similar characteristics to the TI functions, particularly below 300 pps. In both cases, thresholds decrease as the number of pulses in the stimulus increase, although the underlying mechanisms vary across pulse rates (Viemeister and Wakefield, 1991; McKay et al., 2013; Zhou and Pfingst, 2013). The best correlations with measures of cochlear health were for pulse rates below 1000 pps (Pfingst et al., 2011). In most ears with preserved hearing, surviving IHCs, and SGN densities greater than 70% of normal, thresholds decreased as a function of pulse rate with slopes of 1 to 3 dB per doubling of pulse rate. However, in ears without IHCs and with SGN densities less than 70% of normal, we found that the MPI functions were very shallow with slopes less than 1 dB per doubling of pulse rate. These conclusions are based on data from 50 animals with a large range of SGN and IHC survival (Pfingst et al., 2014). It is not clear from the data we have to date if it is the IHCs or the high SGN densities (or some other variable that we have not yet assessed) that is responsible for the steep MPI and TI slopes. To date, we have achieved SGN preservation at greater than 70% of normal in guinea pigs only when IHCs are present. However, in human subjects who have no measurable hearing and thus probably have poor IHC survival, we find that some stimulation sites do have steep MPI functions (Zhou et al., 2012; Zhou and Pfingst, 2014a). Also, from published reports we know that human subjects can maintain SGN densities at high levels for long periods of time in the absence of IHCs (e.g., Hinojosa and Marion, 1983). Thus, we believe that IHCs are not necessary to achieve steep MPI functions but that other aspects of cochlear health, such as SGN density, that are supported in the guinea pig animal model by the presence of IHCs, are the underlying variables necessary for multipulse integration and temporal integration. It is important to note however that, in the studies conducted to date, the anatomical and electrophysiological measures used to assess cochlear health account for only about 50% of the variance across animals in MPI slopes (Pfingst et al., 2011, 2014). Thus it seems that multiple measures of cochlear health, in addition to SGN density, will be needed to fully understand the mechanisms underlying this measure of cochlear implant function.

To determine the relationship between the level of cochlear health as assessed by MPI function slopes and cochlear implant function as assessed by speech recognition in humans, we used a within-subject design in people with bilateral cochlear implants. Specifically we tested the hypothesis that the ear differences in speech recognition in subjects with bilateral cochlear implants could be predicted by ear differences in the slopes of MPI functions. This design allowed us to estimate cochlear-neural health in the same test session where speech recognition was measured. By using a within-subjects design, we reduced confounding effects of across-subject variables.

We hypothesized that the effects of sparse neural survival on speech recognition would include reduced resolution of spectral information. With sparse neural survival, stimulation of the individual electrodes would not be as effective at targeting independent populations of neurons, and this could result in a reduced number of effective spectral channels and smeared neural representation of spectral envelopes. The reduced spectral resolution would make listening in fluctuating noises particularly challenging because the implant users would be less able to segregate the target speech signals from the background noise. The smeared neural representation of spectral information would lead to difficulties with perceiving speech features that depend on spectral acoustic cues.

In 8 bilaterally implanted listeners with different degrees of ear asymmetry, we found that the ears with better cochlear health as estimated by the slopes of the MPI functions were also those that performed better in sentence recognition in an amplitude-modulated noise background and phoneme recognition at challenging signal to noise ratios (SNRs) (Zhou and Pfingst, 2014a). The magnitude of ear differences in the MPI slopes also proportionally predicted the magnitude of the subjects' ear differences in speech reception thresholds (signal to noise ratios required for 50% correct recognition of CUNY sentences), consonant recognition at 0 dB SNR, and perception of the place of articulation feature of consonants. More interestingly, perception of various consonant sounds that have distinct spectral correlates was correlated with estimated neural survival in the corresponding frequency regions accessed by the implant. It should be noted that these ear differences did not seem to be related to the subjects' duration of experience with the device. These findings were consistent with our hypotheses that cochlear health is important for speech recognition in fluctuating noises and perception of spectral cues.

3.2. Objective electrophysiological measures

Several electrophysiological measures of implant function have been shown to correlate with nerve survival in animal models. These include electrically-evoked auditory brainstem response (EABR) input-output (growth) functions (Smith and Simmons, 1983; Hall, 1990) and various derivatives of electrically-evoked compound action potential (ECAP) growth functions (Prado-Guttierrez et al., 2006; Ramekers et al., 2014). Figure 6 shows examples of ECAP growth functions for guinea pigs with various levels of SGN density in the region of the implant as detailed in Table 1. In contrast to the psychophysical TI and MPI functions, which were most effective at distinguishing between very high levels of cochlear health and all lower levels of health, the ECAP growth function slopes are reasonably good at reflecting cochlear health throughout a large range of SGN densities in the absence of hair cells

(Pfingst et al., 2014). However, the spiral ganglion cell densities account for only about 50% of the variance in the ECAP growth function slopes. Note that positions of the curves along the abscissa, as reflected in the current required to evoke a 100 μV ECAP response (Table 1, column 7), are not predictive of nerve survival, but the slopes (rate of growth as a function of input level; Table 1, column 6) are. We found similar results for electrically-evoked auditory brainstem (EABR) amplitude-growth functions (Pfingst et al., 2014).

We are currently examining ECAP growth functions in humans. Preliminary results indicate that (1) the slopes vary from one stimulation site to the next across the electrode array and (2) the across-site patterns of these slopes are stable over time. Future work will examine their relationship to various features of speech recognition. Clinically, ECAP measures are currently used primarily to estimate appropriate stimulation levels. This is done using ECAP thresholds, which typically correspond roughly to comfortable listening levels. However the correlations between ECAP thresholds and behavioral measures of comfortable loudness are variable and this has limited their clinical utility (Miller et al., 2008). Further work is needed to study the implementation of advanced ECAP measures such as amplitude-growth functions or spread-of-excitation measures as these could serve as an efficient, objective means to improve programming if efforts are successful.

4. Potential clinical applications

The current knowledge of how pathology affects cochlear implant function has motivated studies aimed at improving speech recognition by using data on the across-site patterns of cochlear health in the implanted ear to guide processor fitting. The idea is to use stimulation sites that are in healthier regions of the cochlea and to avoid or rehabilitate sites that are near poorer conditions. We refer to these approaches as “site selection” and “site rehabilitation” strategies.

4.1. Site-selection strategies

One approach for applying functional data to processor fitting is to simply turn off a few sites that have been judged to have poor function based on psychophysical or electrophysiological data. To test the clinical feasibility of this approach, we turned off selected sites in the processor maps of long-time stable users of cochlear implants. We compared speech recognition results obtained with these experimental maps to results obtained with the subjects’ everyday-use maps. In one of the first experiments with this approach, Zwolan and colleagues created experimental processor maps that contained only stimulation sites that were discriminable from neighboring sites. With these maps, 7 of the 9 subjects obtained better speech recognition scores on at least one of a variety of speech recognition tests relative to performance with all stimulation sites. In a later experiment (Garadat et al., 2013), we used masked modulation detection thresholds (masked MDTs) as the functional measure for site selection. To avoid creating large gaps in the tonotopic map, we divided the electrode array into 5 segments and turned off only one site in each segment. In this strategy, the bandwidths of the remaining stimulation sites were broadened after site removal in order to transmit the complete speech spectrum. This resulted in better mean performance across all sites in MDTs but by broadening the frequency allocation to each of the remaining channels we slightly reduced the spectral resolution of the processor map. We

found better speech recognition in noise (correct performance at more challenging signal to noise ratios) in all 12 of the tested subjects compared to performance with their everyday speech processor map, consistent with the better mean modulation detection ability. However, we found some negative effects on vowel recognition, consistent with the reduced spectral resolution.

The problem of reduced spectral resolution can be avoided in patients who have bilateral implants. With bilateral implants, frequency reallocation might not be necessary because the missing frequencies at the removal sites in one ear can be represented at the corresponding stimulation sites in the contra lateral ear. Given that the spectral information across the two ears is cohesively fused centrally, a complete spectrum can be transmitted without having to compromise spectral resolution, and the overall psychophysical acuity can be improved at the same time. This dichotic site selection strategy was tested in 8 subjects with bilateral implants. The strategy effectively improved the subjects' recognition of sentences and consonants in noise, as well as vowels, relative to the subjects' performance using their everyday map (Zhou and Pfingst, 2012). Despite the fact that the subjects might have different insertion depths for the two implants, they all demonstrated cohesive spectral fusion of the dichotic signals by reporting hearing one sound from the two implants.

4.2. Site rehabilitation

Instead of removing poorly performing sites, an alternative to improving overall modulation sensitivity is to improve performance at the sub-optimal sites by adjusting their stimulation parameters. This site rehabilitation strategy is based on the fact that modulation sensitivity improves as a function of stimulation level (Pfingst et al., 2007). In a recent experiment (Zhou and Pfingst, 2014b), we increased the stimulation levels at poorly performing sites. The manipulation was hypothesized to improve modulation detection at the poorly performing sites, which in turn would improve speech recognition. Results from 9 subjects showed significantly improved speech reception thresholds using the site-specific level-adjusted maps (Zhou and Pfingst, 2014b). Interestingly, increasing the stimulation levels at all sites by the same amount did not improve speech reception thresholds. Modulation sensitivity at the adjusted levels at the sub-optimal sites was improved relative to that prior to level adjustment, suggesting that the improvement in speech reception thresholds following site-specific level adjustments was a result of increased acuity for detecting envelope modulation.

4.3 Future Directions

The effects of these optimization strategies have only been tested acutely. The results were promising since long term training might further enhance these benefits. Preliminary results with a limited number of subjects have shown that although speech recognition performance fluctuates over time, the relative differences between the optimized map and the subject's everyday map remains. Studies designed for systematic long term training are warranted to examine whether these benefits could be further increased. Subjective reports from patients reveal that these optimized processor maps provide a perceptual clarity and are helpful in their daily communications.

Many of the site selection and site-rehabilitation strategies tested to date are too time consuming for everyday use in the clinic. A goal for future studies is to identify simpler and more efficient measures for identifying the better and weaker sites in the cochlear implant electrode array so that the clinician can quickly determine which sites to choose for the processor map and/or for parameter adjustment.

5. Improving Cochlear Health

The ultimate goal for tissue engineering approaches addressing cochlear pathology is to bring the cochlea to a normal healthy state, at which point the cochlear implant will be obsolete. While achieving that goal seems distant, many partial successes in preserving and/or regenerating the biology of the cochlea can be applied today and in the near future to enhance the function of the cochlear implant. From the studies reviewed in Sections 2 and 3, it is evident that conditions near individual electrodes in the cochlear implant are important for various features of implant function, including speech recognition in background noise. While the specifics of which conditions are important for implant function are not known, strong candidates include the number of surviving spiral ganglion cell bodies and central processes, the presence or absence of auditory nerve peripheral processes, and the health of the surviving neurons, which is likely influenced by the presence of inner hair cells and supporting cells. Surgical and tissue engineering techniques are being developed that can support the survival, and in some cases regeneration or replacement, of these basic elements. These will be reviewed in subsections 5.2 and 5.3 below.

5.1. Hearing preservation

Cochlear implant functionality has improved dramatically since the original single-channel implants. As the quality of speech recognition achieved with cochlear implants increases, the implants are becoming the therapy of choice for people who have some residual hearing but are achieving inadequate benefit from acoustic hearing aids. Thus, many patients are being implanted in ears that still have some acoustic hearing. A number of studies in humans and animals have shown that at least some residual acoustic hearing can be preserved by using less traumatic implant designs, careful surgical technique (often referred to as “soft surgery”) and pharmacological agents such as steroids (e.g., Turner et al., 2008; Kang et al., 2010; Pfingst et al., 2011; von Ilberg et al., 2011). Such residual hearing in implanted ears can supplement electrical hearing by providing temporal fine structure and low-frequency hearing that is usually not adequately provided by the implant. Importantly however, these procedures also serve to preserve the health of the implanted cochlea and auditory nerve, providing functional benefits for electrical hearing per se as detailed in Section 3 above.

5.2. Neural preservation

One of the benefits of preservation of IHCs, as noted above, is that they support the preservation and health of the auditory nerve. Supporting cells in the organ of Corti can serve a similar function (Sugawara et al, 2005). In cochleae where IHCs and supporting cells are absent or nonfunctional, auditory-neuron preservation can be enhanced by delivering one or more therapeutic reagents. The most common molecules used in laboratory animal experiments to maintain the neural substrate in deaf ears are neurotrophins (Budenz et al.,

2012; Ramekers et al., 2012). Neurotrophins are soluble molecules that are secreted by cells and act by binding to cell surface receptors (von Bartheld and Fritzsch, 2006). Once binding occurs, the receptors undergo dimerization and autophosphorylation. This leads to activation of downstream signaling pathways, resulting in a diverse range of cellular responses including survival, growth, proliferation and more, depending on the stage of development and type of cell. NT-3 and BDNF have been the most commonly used neurotrophins for preserving auditory neurons. Nerve preservation with neurotrophins has been demonstrated in several animal models for human disease, including ototoxicity (Shibata et al., 2011; Wise et al., 2005) and hereditary-based deafness (Fukui et al., 2012; Takada et al., 2014; Yu et al, 2014).

To be clinically applicable, the delivery of neurotrophins will need to be accomplished by a delivery method that can maintain long term presence of neurotrophins in the cochlear fluids. Although there is currently no perfect delivery vehicle, several methods are showing progress and promise. Delivery via viral vectors, especially adeno-associated viral vectors (AAVs), may lead to long term gene expression with little or no side effects (Lalwani et al., 1998; Sapieha et al., 2006). Long-term survival of the mesothelial cells that are transfected when the AAVs are injected into the scala tympani is prerequisite for sustained neurotrophin secretion. The extent of turnover in this tissue needs to be better characterized. Co chlear implants with drug-eluting capability offer another method for secretion of neurotrophins (or other reagents) into the cochlea (Jolly et al., 2010). The advantage of the latter method is the lack of any risks associated with viral vectors and the ability to control the concentration and rate of delivery. Other methods such as mini-osmotic pumps or electroporation of naked DNA may be used for short term delivery of neurotrophins (the former) or the genes encoding them (the latter) (Hendricks et al., 2008; Pinyon et al., 2014).

5.3. Preserving fluid spaces

The presence of fibrous tissue in the scala tympani is a common finding in animal and human ears that receive cochlear implants. Because the fibrous tissue is in close proximity to the implant electrodes, it can lead to increased impedance and might have a negative impact on hearing with the prosthesis. Models to address the effects of fibrous tissue on current spread (Hanekom, 2005) may be helpful for further elucidating the interaction between the electrode and the cochlear fluid space. Adverse effects, including uncontrolled ossification of the cochlea leading to resorption of all neural substrate, suggest the need to better understand the causes for connective tissue growth and means to prevent or reverse it.

One commonly discussed cause for connective tissue growth is an inflammatory response. An attempt to reduce inflammatory tissue response with intraoperative intracochlear steroid deposition has shown lower postoperative impedances (e.g., Paasche et al., 2009). Advances in elucidating the signals that mediate the immune response in the cochlea were recently accomplished by challenging the ear with an immunogenic reagent lipopolysaccharide (LPS) and then assessing levels of micro-RNAs. The study has identified three different micro-RNAs that were elevated (Rudnicki et al., 2014). These molecules can serve as targets that may be blocked for preventing inflammatory reaction thereby reducing the connective tissue growth.

5.4. Regeneration

5.4.1. Auditory nerve peripheral processes—In the deaf cochlea, peripheral processes of the auditory nerve which once innervated the inner hair cells tend to die back, leaving the cell body and central axon intact and available for activation by electrical stimulation. It is generally believed, but not yet proven, that if the peripheral processes can be induced to grow toward the implanted electrode array, cochlear implant function will be improved. Hypothesized benefits of regrowing the peripheral processes include reduced thresholds and improved spatial resolution (reduced channel interaction).

Experiments using BDNF or NT-3 have shown that elevated levels of the neurotrophins in the cochlear fluids attract sprouting of auditory nerve fibers toward the source of the neurotrophins (Glueckert et al., 2008; Shibata et al., 2010; Wise et al., 2010). We have used adeno-associated viral vectors (AAVs) with neurotrophin gene inserts to upregulate production of neurotrophins in the deaf ears. When introduced into the scala tympani of ears with no hair cells or supporting cells, these vectors can transfect cells in the mesothelial layer lining the scala tympani and secrete the neurotrophin which can then attract neurites to grow toward the source of the neurotrophin in the area where the cochlear implant electrodes would reside (Figure 7).

5.4.2. Inner hair cells—An additional way to enhance the cochlear substrate is by generating new inner hair cells. These may help sustain the neurons and may also contribute to the acoustic hearing in treated ears. Early demonstration of hair cell regeneration in explants of mature mammalian ears has been accomplished using over-expression of developmental genes (Shou et al., 2003). This was followed by demonstration of new ectopic hair cells in mature guinea pig ears (Kawamoto et al., 2003). Once a substantial number of new IHCs can be reliably grown in deaf ears, their contribution would be to significantly enhance the outcome of the prosthesis and possibly to replace it. It is therefore imperative that implanted ears retain as much as possible of the original auditory epithelium, which can serve as a substrate for hair-cell regeneration.

5.4.3. Spiral ganglion cells—In addition to replacement of hair cells, placing new neurons in the cochlea is being experimentally pursued for treating ears with a severe or complete loss of auditory neurons. The use of stem cells is the most feasible approach for introducing new neurons into the cochlea. Several groups have been able to accomplish this goal (Bas et al, 2014; Shi and Edge, 2013) and improvement in auditory brainstem response (ABR) thresholds in an animal model of auditory neuropathy has been demonstrated (Chen et al., 2012).

6. Conclusions

Several lines of evidence strongly suggest that conditions in the cochlea and the auditory nerve in localized areas near the cochlear-implant electrode array play an important role in implant function. Psychophysical and electrophysiological studies in human subjects demonstrating subject-specific patterns of implant function that vary considerably from one stimulation site to the next are most easily explained in terms of variation in conditions near the individual electrodes in the scala tympani. These conditions could include proximity of

neurons to the electrodes, the health of those neurons and the presence of bone or fibrous tissue in the current paths from the electrodes to the neurons. The functional measures have been used successfully to guide processor fitting, resulting in improved speech recognition in human cochlear implant users. Psychophysical and electrophysiological studies in animals show across-ear differences that are correlated with anatomical measures of cochlear conditions and neural health. However, the anatomical measures examined to date generally account for only about 50% of variance in the psychophysical or electrophysiological measures of implant function (e.g., Pfingst et al., 2011; 2014). Additional research is needed to understand the relationship between cochlear structure and implant function. For clinical application it is critical to understand the relationship between psychophysical and electrophysiological measures of implant function, cochlear health, and speech recognition. The literature documents a wide range of successes and failures from attempts to predict speech recognition based on psychophysical and electrophysiological measures and to apply these measures in clinical practice (e.g. Fu, 2002; Miller et al., 2008; Hughes and Stille, 2008; McKay et al., 2013), so much work remains to be done. Overall, the studies described in this paper demonstrate the importance of cochlear health for cochlear implant function and support ongoing tissue engineering experiments in animals that are designed to improve the conditions in the cochlea and improve the function of the cochlear implant, or in the long run possibly enable normal hearing.

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Abbreviations

AAV	adeno-associated viral vector
Ad	adenovirus
ASM	across-site mean
BDNF	brain-derived neurotrophic factor
C level	maximum comfortable level
CUNY sentences	a sentence test developed at the City University of New York
DPI	days post implantation
EABR	electrically-evoked auditory brainstem response
ECAP	electrically-evoked compound action potential
GDT	gap-detection threshold
IHC	inner hair cell
MDT	modulation detection threshold

MPI	multipulse integration
N1	first negative potential
NT-3	neurotrophin-3 protein
NTF-3	neurotrophic factor-3 gene
P2	second positive potential
SGN	spiral ganglion neuron
SNR	signal to noise ratio
TI	temporal integration
T level	detection threshold level

References

Bas E, Van De Water TR, Lumbreras V, Rajguru S, Goss G, Hare JM, Goldstein BJ. Adult human nasal mesenchymal-like stem cells restore cochlear spiral ganglion neurons after experimental lesion. Stem Cells Devel. 2014; 23:502–514. [PubMed: 24172073]

Bierer JA. Threshold and channel interaction in cochlear implant users: Evaluation of the tripolar electrode configuration. J. Acoust. Soc. Am. 2007; 121:1642–1653. [PubMed: 17407901]

Bierer JA, Faulkner KF. Identifying cochlear implant channels with poor electrode-neuron interface: Partial tripolar, single-channel thresholds and psychophysical tuning curves. Ear Hear. 2010; 31:247–258. [PubMed: 20090533]

Budenz CL, Pfingst BE, Raphael Y. The use of neurotrophin therapy in the inner ear to augment cochlear implantation outcomes. Anat. Rec. 2012; 295:1896–1908.

Chen W, Jongkamonwiwat N, Abbas L, Eshtan SJ, Johnson SL, Kuhn S, Milo M, Thurlow JK, Andrews PW, Marcotti W, Moore HD, Rivolta MN. Restoration of auditory evoked responses by human ES-cell-derived otic progenitors. Nature. 2012; 490:278–282. [PubMed: 22972191]

Clark GM, Blamey PJ, Brown AM, Gusby PA, Dowell RC, Franz BK, Pyman BC, Shepherd RK, Tong YC, Webb RL, Hirshorn MS, Kuzma J, Mecklenburg MJ, Money DK, Patrick JF, Seligman PM. The University of Melbourne - Nucleus multi-electrode cochlear implant. Adv. Otorhinolaryngol. 1987; 38:1–181.

Clark GM, Pyman BC, Bailey QR. The surgery for multiple-electrode cochlear implantations. J. Laryngol. Otol. 1979; 93:215–223. [PubMed: 429901]

Donaldson GS, Nelson DA. Place-pitch sensitivity and its relation to consonant recognition by cochlear implant listeners using the MPEAK and SPEAK speech processing strategies. J. Acoust. Soc. Am. 2000; 107:1645–1658. [PubMed: 10738818]

Fayad JN, Linthicum FH Jr. Multichannel cochlear implants: relation of histopathology to performance. Laryngoscope. 2006; 116:1310–1320. [PubMed: 16885730]

Friesen LM, Shannon RV, Baskent D, Wang X. Speech recognition in noise as a function of the number of spectral channels: Comparison of acoustic hearing and cochlear implants. J. Acoust. Soc. Am. 2001; 110:1150–1163. [PubMed: 11519582]

Fu Q-J. Temporal processing and speech recognition in cochlear implant users. Neuroreport. 2002; 13:1635–1639. [PubMed: 12352617]

Fukui H, Wong HT, Beyer LA, Case BG, Swiderski DL, Di Polo A, Ryan AF, Raphael Y. BDNF gene therapy induces auditory nerve survival and fiber sprouting in deaf Pou4f3 mutant mice. Sci. Rep. 2012; 2:838. [PubMed: 23150788]

Garadat SN, Pfingst BE. Relationship between gap detection thresholds and loudness in cochlear-implant users. Hear. Res. 2011; 275:130–138. [PubMed: 21168479]

Garadat SN, Zwolan TA, Pfingst BE. Across-site patterns of modulation detection: relation to speech recognition. J. Acoust. Soc. Am. 2012; 131:4030–4041. Erratum: J. Acoust. Soc. Am. 134, 715. [PubMed: 22559376]

Garadat SN, Zwolan TA, Pfingst BE. Using temporal modulation sensitivity to select stimulation sites for processor maps in cochlear implant listeners. Audiol. Neurotol. 2013; 18:247–260.

Gerken GM, Bhat VKH, Hutchison-Clutter M. Auditory temporal integration and the power function model. J. Acoust. Soc. Am. 1990; 88:767–778. [PubMed: 2212302]

Glueckert R, Bitsche M, Miller JM, Zhu Y, Prieskorn DM, Altschuler RA, Schrott-Fischer A. Deafferentation-associated changes in afferent and efferent processes in the guinea pig cochlea and afferent regeneration with chronic intrascalar brain-derived neurotrophic factor and acidic fibroblast growth factor. J. Comp. Neurol. 2008; 507:1602–1621. [PubMed: 18220258]

Hall RD. Estimation of surviving spiral ganglion cells in the deaf rat using the electrically evoked auditory brainstem response. Hear. Res. 1990; 49:155–168. [PubMed: 2292495]

Hanekom T. Modelling encapsulation tissue around cochlear implant electrodes. Med. Biol. Eng. Comput. 2005; 43:47–55. [PubMed: 15742719]

Hendricks JL, Chikar JA, Crumling MA, Raphael Y, Martin DC. Localized cell and drug delivery for auditory prostheses. Hear. Res. 2008; 242:117–131. [PubMed: 18573323]

Heydebrand G, Hale S, Potts L, Gotter B, Skinner M. Cognitive predictors of improvements in adults' spoken word recognition six months after cochlear implant activation. Audiol. Neurotol. 2007; 12:254–264.

Hinojosa R, Marion M. Histopathology of profound sensorineural deafness. Ann. N. Y. Acad. Sci. 1983; 405:459–484. [PubMed: 6575668]

Hochmair I, Nopp P, Jolly C, Schmidt M, Schosser H, Garnham C, Anderson I. MED-EL Cochlear implants: State of the art and a glimpse into the future. Trends Amplif. 2006; 10:201–219. [PubMed: 17172548]

Hochmair-Desoyer IJ, Hochmair ES, Burian K, Fischer RE. Four years of experience with cochlear prostheses. Med. Prog. Technol. 1981; 8:107–119. [PubMed: 6895542]

Hughes ML, Stille LJ. Psychophysical versus physiological spatial forward masking and the relation to speech perception in cochlear implants. Ear Hear. 2008; 29:435–452. [PubMed: 18344869]

Jolly C, Garnham C, Mirzadeh H, Truy E, Martini A, Kiefer J, Braun S. Electrode features for hearing preservation and drug delivery strategies. Adv. Otorhinolaryngol. 2010; 67:28–42. [PubMed: 19955719]

Kang SY, Colesa DJ, Swiderski DL, Su GL, Raphael Y, Pfingst BE. Effects of hearing preservation on psychophysical responses to cochlear implant stimulation. J. Assoc. Res. Otolaryngol. 2010; 11:245–265. [PubMed: 19902297]

Kawamoto K, Ishimoto S, Minoda R, Brough DE, Raphael Y. Math1 gene transfer generates new cochlear hair cells in mature guinea pigs in vivo. J. Neurosci. 2003; 23:4395–4400. [PubMed: 12805278]

Khan AM, Handzel O, Burgess BJ, Damian D, Eddington DK, Nadol JB Jr. Is word recognition correlated with the number of surviving spiral ganglion cells and electrode insertion depth in human subjects with cochlear implants? Laryngoscope. 2005a; 115:672–677. [PubMed: 15805879]

Khan AM, Whiten DM, Nadol JB Jr, Eddington DK. Histopathology of human cochlear implants: Correlation of psychophysical and anatomical measures. Hear. Res. 2005b; 205:83–93. [PubMed: 15953517]

Lalwani AK, Walsh BJ, Carvalho GJ, Muzyczka N, Mhatre AN. Expression of adeno-associated virus (AAV) integrated transgene within the mammalian vestibular organs. Am. J. Otol. 1998; 19:390–395. [PubMed: 9596192]

Long CJ, Holden TA, McClelland GH, Parkinson WS, Shelton C, Kelsall DC, Smith ZM. Examining the electro-neural interface of cochlear implant users using psychophysics, CT scans, and speech understanding. J. Assoc. Res. Otolaryngol. 2014; 15:293–304. [PubMed: 24477546]

McKay CM, Chandan K, Akhoun I, Siciliano C, Kluk K. Can ECAP measures be used for totally objective programming of cochlear implants? J. Assoc. Res. Otolaryngol. 2013; 14:879–890. [PubMed: 24048907]

McKay CM, Lim HH, Lenarz T. Temporal processing in the auditory system: insights from cochlear and auditory midbrain implantees. J. Assoc. Res. Otolaryngol. 2013; 14:103–124. [PubMed: 23073669]

Miller CA, Brown CJ, Abbas PJ, Chi S-L. The clinical application of potentials evoked from the peripheral auditory system. Hear. Res. 2008; 242:184–197. [PubMed: 18515023]

Nadol JB Jr, Shiao JY, Burgess BJ, Ketten DR, Eddington DK, Gantz BJ, Kos I, Montandon P, Coker NJ, Roland JT Jr, Shallop JK. Histopathology of cochlear implants in humans. Ann. Otol. Rhinol. Laryngol. 2001; 110:883–891. [PubMed: 11558767]

Paasche G, Tasche C, Stover T, Lesinski-Schiedat A, Lenarz T. The long-term effects of modified electrode surfaces and intracochlear corticosteroids on postoperative impedances in cochlear implant patients. Otol. Neurotol. 2009; 30:592–598. [PubMed: 19546829]

Pfingst BE. Changes over time in thresholds for electrical stimulation of the cochlea. Hear. Res. 1990; 50:225–236. [PubMed: 2076974]

Pfingst BE. Effects of electrode configuration on cochlear implant modulation detection thresholds. J. Acoust. Soc. Am. 2011; 129:3908–3915. [PubMed: 21682413]

Pfingst BE, Burkholder-Juhasz RA, Xu L, Thompson CS. Across-site patterns of modulation detection in listeners with cochlear implants. J. Acoust. Soc. Am. 2008; 123:1054–1062. [PubMed: 18247907]

Pfingst BE, Colesa DJ, He mbrador S, Kang SY, Middlebrooks JC, Raphael Y, Su GL. Detection of pulse trains in the electrically stimulated cochlea: Effects of cochlear health. J. Acoust. Soc. Am. 2011; 130:3954–3968. [PubMed: 22225050]

Pfingst BE, Colesa DJ, Watts MM, Su GL, Budenz CL, Raphael Y. Neurotrophin gene therapy in deafened ears with cochlear implants: Long-term effects on nerve survival and functional measures. Assoc. Res. Otolaryngol. Abst. 2014; 37:174.

Pfingst BE, Xu L. Across-site variation in detection thresholds and maximum comfortable loudness levels for cochlear implants. J. Assoc. Res. Otolaryngol. 2004; 5:11–24. [PubMed: 14605920]

Pfingst BE, Xu L, Thompson CS. Across-site threshold variation in cochlear implants: Relation to speech recognition. Audiol. Neurotol. 2004; 9:341–352.

Pfingst BE, Xu L, Thompson CS. Effects of carrier pulse rate and stimulation site on modulation detection by subjects with cochlear implants. J. Acoust. Soc. Am. 2007; 121:2236–2246. [PubMed: 17471737]

Pinyon JL, Tadros SF, Froud KE, AC YW, Tompson IT, Crawford EN, Ko M, Morris R, Klugmann M, Housley GD. Close-field electroporation gene delivery using the cochlear implant electrode array enhances the bionic ear. Sci. Transl. Med. 2014; 6:233ra54.

Prado-Guitierrez P, Fewster LM, Heasman JM, McKay CM, Shepherd RK. Effect of interphase gap and pulse duration on electrically evoked potentials is correlated with auditory nerve survival. Hear. Res. 2006; 215:47–55. [PubMed: 16644157]

Ramekers D, Versnel H, Grolman W, Klis SF. Neurotrophins and their role in the cochlea. Hear. Res. 2012; 288:19–33. [PubMed: 22465680]

Ramekers D, Versnel H, Strahl SB, Smeets EM, Klis SF, Grolman W. Auditory-nerve responses to varied inter-phase gap and phase duration of the electric pulse stimulus as predictors for neuronal degeneration. J. Assoc. Res. Otolaryngol. 2014; 15:187–202. [PubMed: 24469861]

Rudnicki A, Shivatzki S, Beyer LA, Takada Y, Raphael Y, Avraham KB. microRNA-224 regulates Pentraxin 3, a component of the humoral arm of innate immunity, in inner ear inflammation. Hum. Mol. Genet. 2014; 23:3138–3146. [PubMed: 24470395]

Sapieha PS, Hauswirth WW, Di Polo A. Extracellular signal-regulated kinases 1/2 are required for adult retinal ganglion cell axon regeneration induced by fibroblast growth factor-2. J. Neurosci. Res. 2006; 83:985–995. [PubMed: 16493686]

Schindler, RA.; Merzenich, MM. New York: Cochlear Implants Raven Press; 1985.

Shannon, RV. A model of temporal integration and forward masking for electrical stimulation of the auditory nerve. In: Miller, JM.; Spelman, FA., editors. Cochlear Implants. Models of the Electrically Stimulated Ear. New York: Springer-Verlag; 1989. p. 187-203.

Shepherd RK, Hatsushika S, Clark GM. Electrical stimulation of the auditory nerve: the effect of electrode position on neural excitation. Hear. Res. 1993; 66:108–120. [PubMed: 8473242]

Shi F, Edge AS. Prospects for replacement of auditory neurons by stem cells. Hear. Res. 2013; 297:106–112. [PubMed: 23370457]

Shibata SB, Budenz CL, Bowling SA, Pfingst BE, Raphael Y. Nerve maintenance and regeneration in the damaged cochlea. Hear. Res. 2011; 281:56–64. [PubMed: 21596129]

Shibata SB, Cortez SR, Beyer LA, Wiler JA, Di Polo A, Pfingst BE, Raphael Y. Transgenic BDNF induces nerve fiber regrowth into the auditory epithelium in deaf cochleae. Exp. Neurol. 2010; 223:464–472. [PubMed: 20109446]

Shou J, Zheng JL, Gao WQ. Robust generation of new hair cells in the mature mammalian inner ear by adenoviral expression of Hath1. Molec. Cell. Neurosci. 2003; 23:169–179. [PubMed: 12812751]

Smith L, Simmons FB. Estimating eighth nerve survival by electrical stimulation. Ann. Otol. Rhinol. Laryngol. 1983; 92:19–23. [PubMed: 6824273]

Su GL, Colesa DJ, Pfingst BE. Effects of deafening and cochlear implantation procedures on postimplantation psychophysical electrical detection thresholds. Hear. Res. 2008; 241:64–72. [PubMed: 18558467]

Sugawara M, Corfas G, Liberman MC. Influence of supporting cells on neuronal degeneration after hair cell loss. J. Assoc. Res. Otolaryngol. 2005; 6:136–147. [PubMed: 15952050]

Takada Y, Beyer LA, Swiderski DL, O'Neal AL, Prieskorn DM, Shivatzki S, Avraham KB, Raphael Y. Connexin 26 null mice exhibit spiral ganglion degeneration that can be blocked by BDNF gene therapy. Hear. Res. 2014; 309:124–135. [PubMed: 24333301]

Turner CW, Reiss LA, Gantz BJ. Combined acoustic and electric hearing: preserving residual acoustic hearing. Hear. Res. 2008; 242:164–171. [PubMed: 18164883]

Viemeister NF, Wakefield GH. Temporal integration and multiple looks. J. Acoust. Soc. Am. 1991; 90:858–865. [PubMed: 1939890]

von Bartheld CS, Fritzsch B. Comparative analysis of neurotrophin receptors and ligands in vertebrate neurons: Tools for evolutionary stability or changes in neural circuits? Brain Behav. Evol. 2006; 68:157–172. [PubMed: 16912469]

von Ilberg CA, Baumann U, Kiefer J, Tillein J, Adunka OF. Electric-acoustic stimulation of the auditory system: a review of the first decade. Audiol. Neurotol. 2011; 16(Suppl 2):1–30.

Watts MM, Pfingst BE, Colesa DJ, Raphael Y, Kabara LL, Budenz CL. Functional changes over time after deafening, post-deafening treatments, and cochlear implantation. Assoc. Res. Otolaryngol. Abst. 2014; 37:315–316.

Wilson BS, Dorman MF. Cochlear implants: A remarkable past and a brilliant future. Hear. Res. 2008; 242:3–21. [PubMed: 18616994]

Wilson BS, Finley CC, Lawson DT, Wolford RD, Eddington DK, Rabinowitz WM. Better speech recognition with cochlear implants. Nature. 1991; 352:236–238. [PubMed: 1857418]

Wise AK, Hume CR, Flynn BO, Jeelall YS, Suhr CL, Sgro BE, O'Leary SJ, Shepherd RK, Richardson RT. Effects of localized neurotrophin gene expression on spiral ganglion neuron resprouting in the deafened cochlea. Mol. Ther. 2010; 18:1111–1122. [PubMed: 20216530]

Wise AK, Richardson R, Hardman J, Clark G, O'Leary S. Resprouting and survival of guinea pig cochlear neurons in response to the administration of the neurotrophins brain-derived neurotrophic factor and neurotrophin-3. J. Comp. Neurol. 2005; 487:147–165. [PubMed: 15880560]

Yu Q, Wang Y, Chang Q, Wang J, Gong S, Li H, Lin X. Virally expressed connexin26 restores gap junction function in the cochlea of conditional Gjb2 knockout mice. Gene Ther. 2014; 21:71–80. [PubMed: 24225640]

Zhou N, Pfingst BE. Psychophysically-based site selection coupled with dichotic stimulation improves speech recognition in noise with bilateral cochlear implants. J. Acoust. Soc. Am. 2012; 132:994–1008. [PubMed: 22894220]

Zhou, N.; Pfingst, BE. Comparison of temporal integration and multipulse integration functions in humans with cochlear implants; Conference on Implantable Auditory Prosthesis Program Book; 2013. p. 194

Zhou N, Pfingst BE. Relationship between multipulse integration and speech recognition with cochlear implants. J. Acoust. Soc. Am. 2014a in press.

Zhou N, Pfingst BE. Effects of site-specific level adjustments on speech recognition with cochlear implants. Ear Hear. 2014b; 35:30–34. [PubMed: 24225651]

Zhou N, Xu L, Pfingst BE. Characteristics of detection thresholds and maximum comfortable loudness levels as a function of pulse rate in human cochlear implant users. Hear. Res. 2012; 284:25–32. [PubMed: 22245714]

Zwolan TA, Collins LM, Wakefield GH. Electrode discrimination and speech recognition in postlingually deafened adult cochlear implant subjects. J. Acoust. Soc. Am. 1997; 102:3673–3685. [PubMed: 9407659]

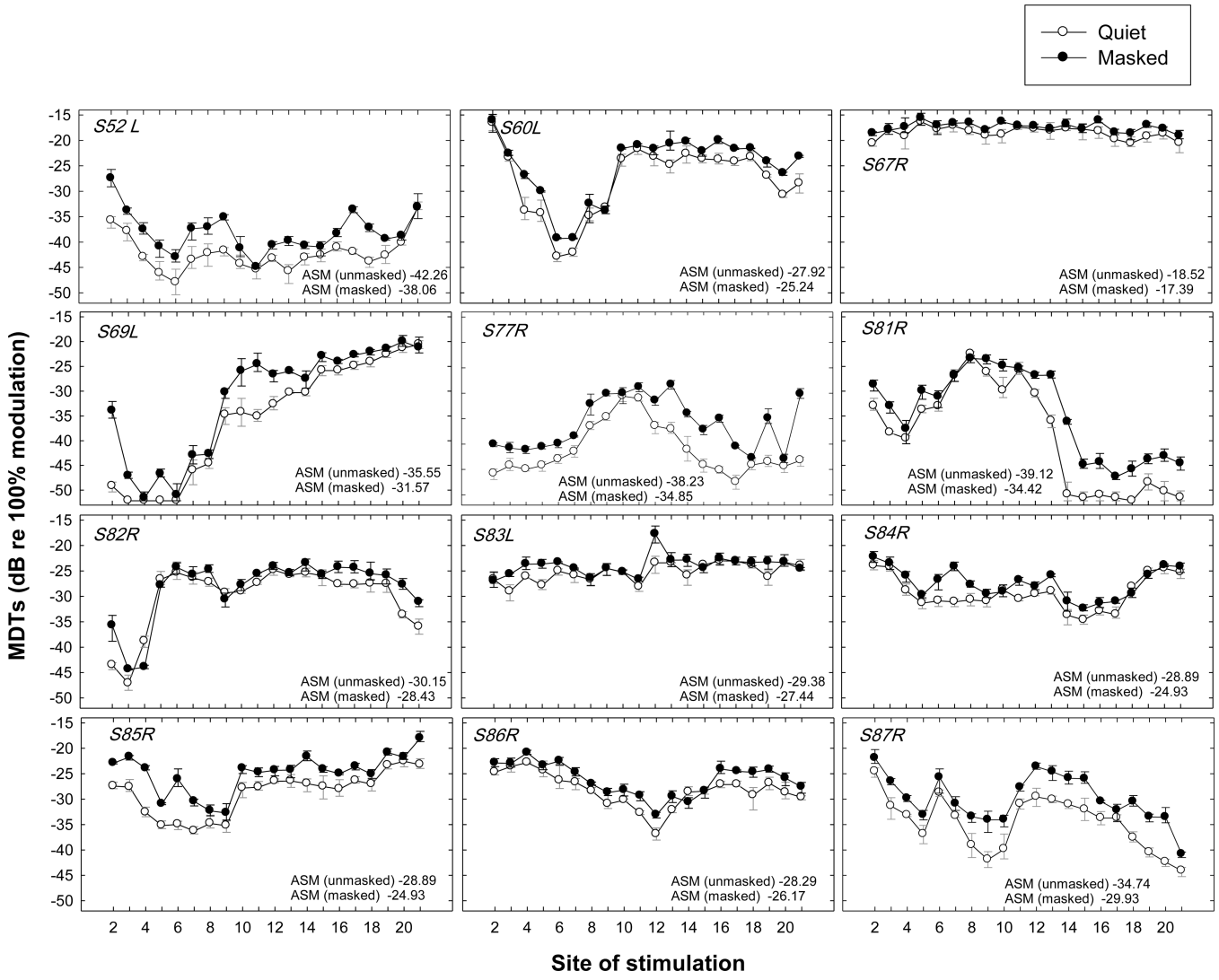

Figure 1.

Modulation detection thresholds (MDTs) as a function of stimulation site for 12 human subjects with 22-electrode cochlear implants. Stimulation sites (electrodes) are numbered 1 to 22 from the basal end to the apical end of the cochlear implant electrode array. MDTs represent the minimum modulation depth at which a subject can discriminate an amplitude-modulated pulse train from a non-modulated pulse train. Functions for MDTs in quiet (open circles) and in the presence of non-modulated masker on an adjacent, more apical, electrode (filled circles) are shown. Larger negative values indicate better performance. Across-site mean (ASM) MDTs are shown in the lower right corner of each panel. Error bars show ranges of values from three estimates at each site. Data are from Garadat et al., 2012.

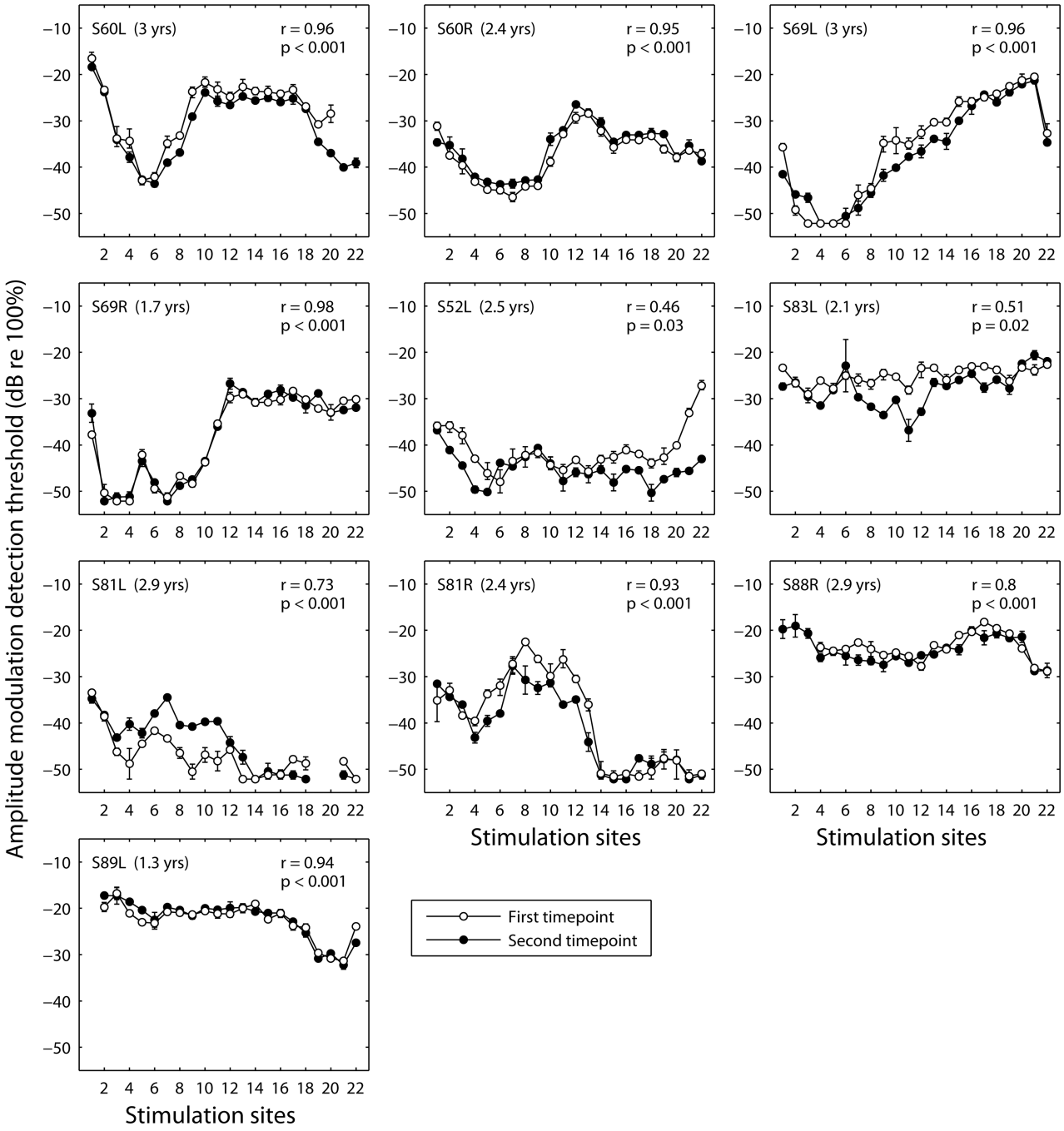

Figure 2.

Stability of modulation detection thresholds over time. Data for 10 ears are shown with the subject and ear designation given in the upper left corner of each panel. Modulation detection thresholds were measured at all available stimulation sites at two timepoints with the time elapsed between the two timepoints (in years) shown in each panel. The first and second sets of data are shown in different symbols: open symbols for the first timepoint and filled symbols for the second timepoint. Each data point represents the mean of two measurements at a given timepoint with error bars representing the range of the data.

Statistics for correlation across the electrode array between the data at the first and second timepoints are shown in the upper–right corner of each panel. For these correlations the means of the two measurements at each site at the first timepoint were correlated with the means of the two measurements at each site at the second timepoint.

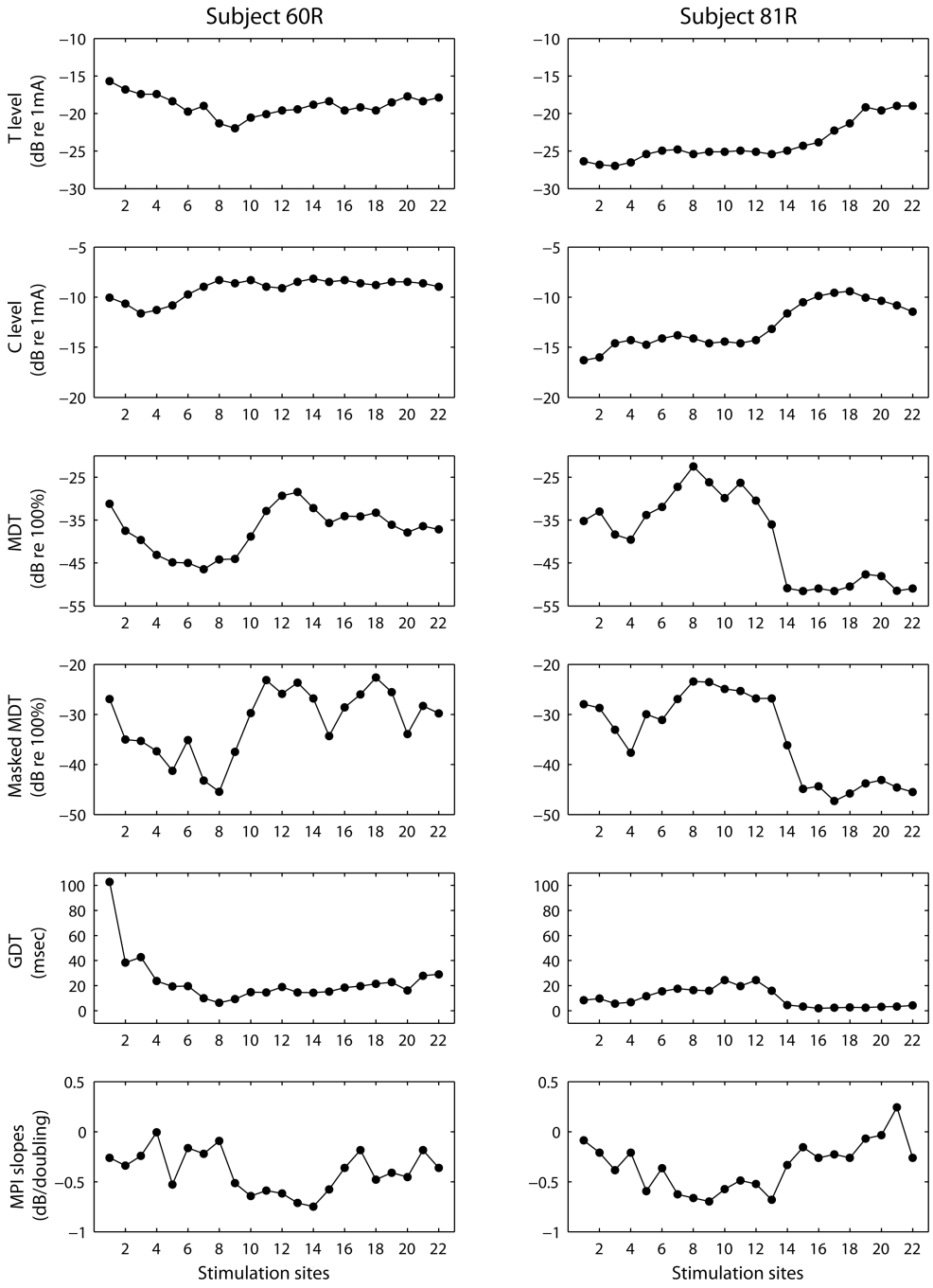

Figure 3.

Across-site patterns for six psychophysical measures in two subjects (one subject per column). The measures are from the top absolute detection threshold (T level), maximal comfortable level (C level), modulation detection threshold (MDT), modulation detection threshold in presence of a masker on the electrode immediately basal to the probe (masked MDT), gap-detection threshold (GDT), and slope of the multipulse integration function (MPI slopes). All measures were obtained using an MP 1+2 configuration. The supra-threshold functions were measured at levels corresponding to 50% of the site's dynamic

range. More information about methods used to collect these types of data can be obtained from previous publications from this laboratory. For T levels, C levels and MDTs and masked MDTs, see Garadat et al., 2012 or Zhou and Pfingst, 2012. For GDTs see Garadat and Pfingst, 2011. For MPI slopes see Zhou et al., 2012 or 2014a).

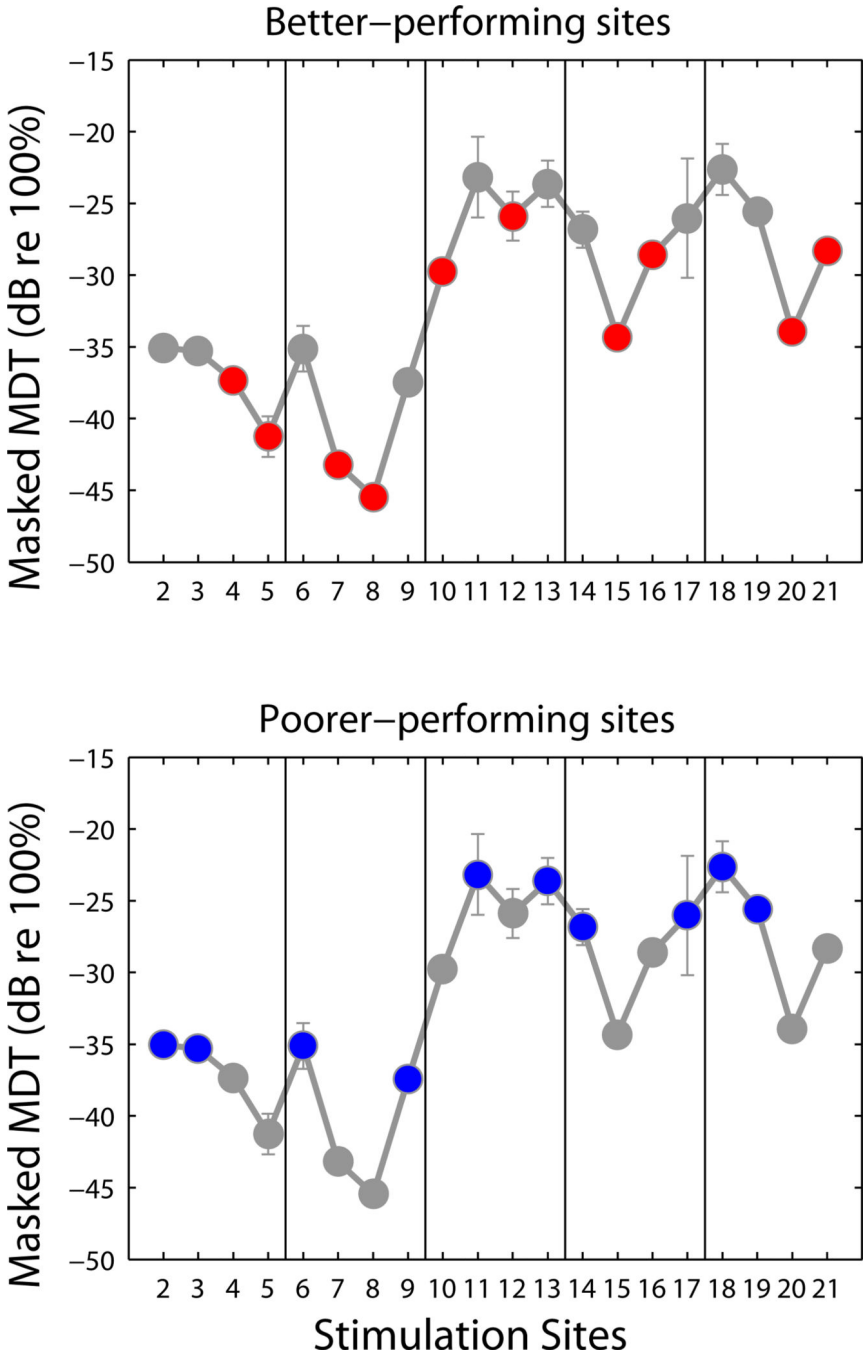

Figure 4.

Examples of a site-selection strategy to test the relevance of MDTs for speech recognition, based on the study by Garadat and colleagues (2012). Two 10-electrode processor maps were created: one with 10 of the better-performing sites (red circles in the top panel) and one with 10 poorer-performing sites (blue circles in the bottom panel). To maintain coverage of the full range of place-pitch information, the electrode array (electrodes 2 through 21) was divided into 5 segments and two sites were selected from each segment. Speech recognition,

particularly sentence recognition in noise, was better in most subjects when the map with the better-performing sites was used.

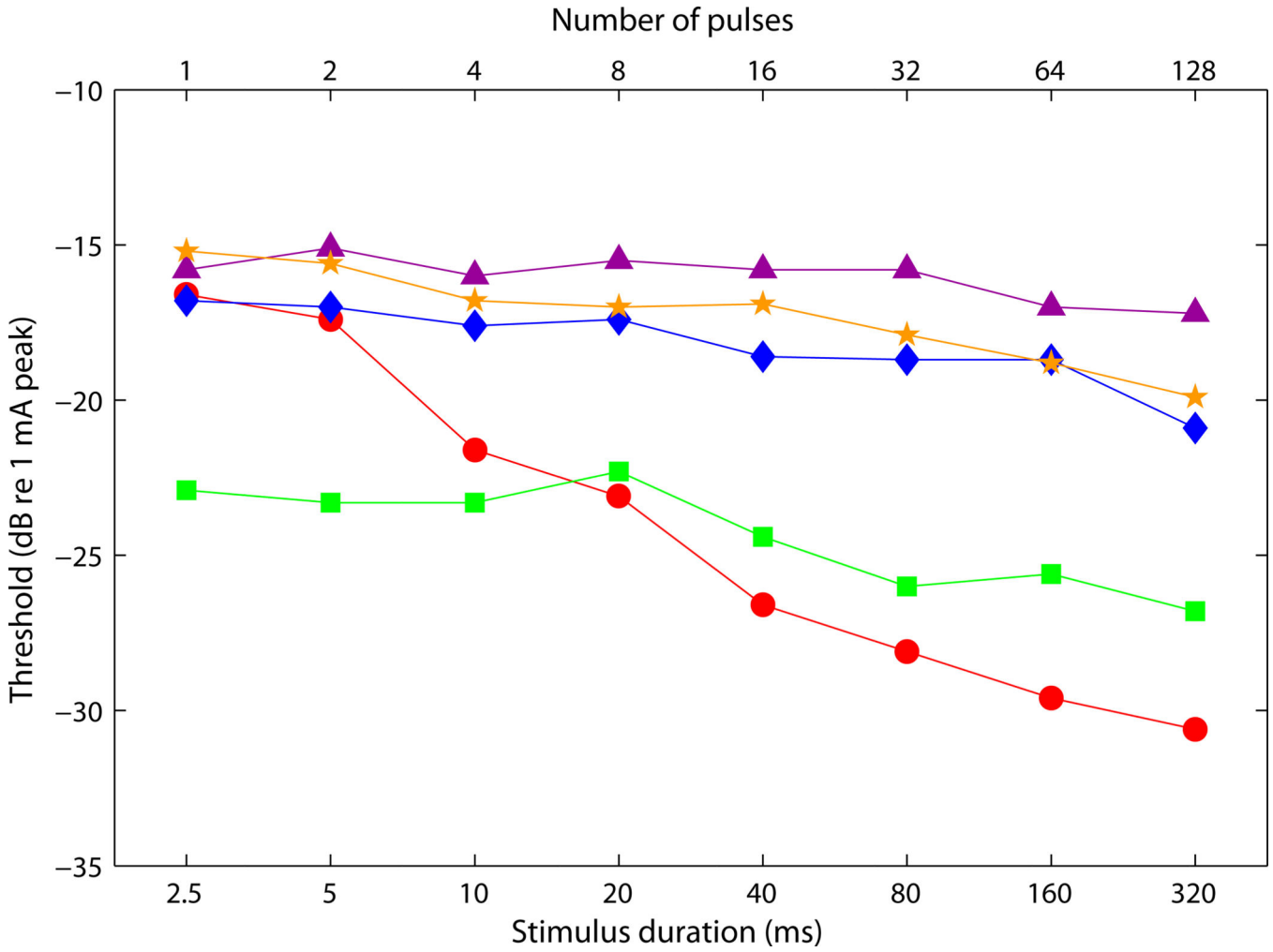

Figure 5.

Examples of temporal integration (TI) functions (psychophysical detection thresholds as a function of pulse-train duration) from five animals with various levels of spiral ganglion neuron (SGN) preservation near the implant as detailed in Table 1.

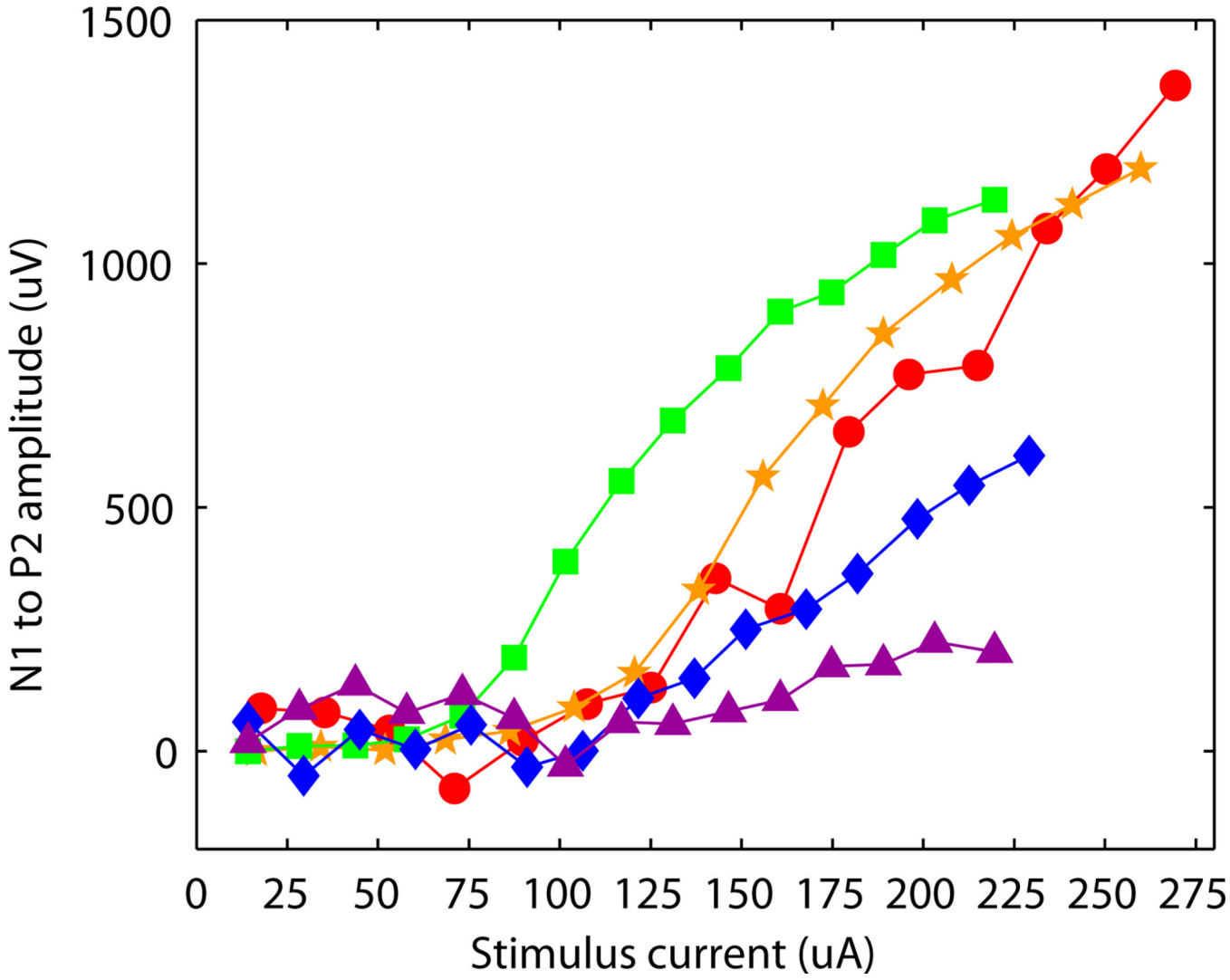

Figure 6.

Examples of ECAP amplitude-growth functions from the same five animals for which TI data are shown in Figure 5. The N1 to P2 ECAP amplitude (μV) was used because P1 was usually obscured by stimulus artifact. Growth function slopes, but not thresholds were correlated with the degree of SGN survival as detailed in Table 1.

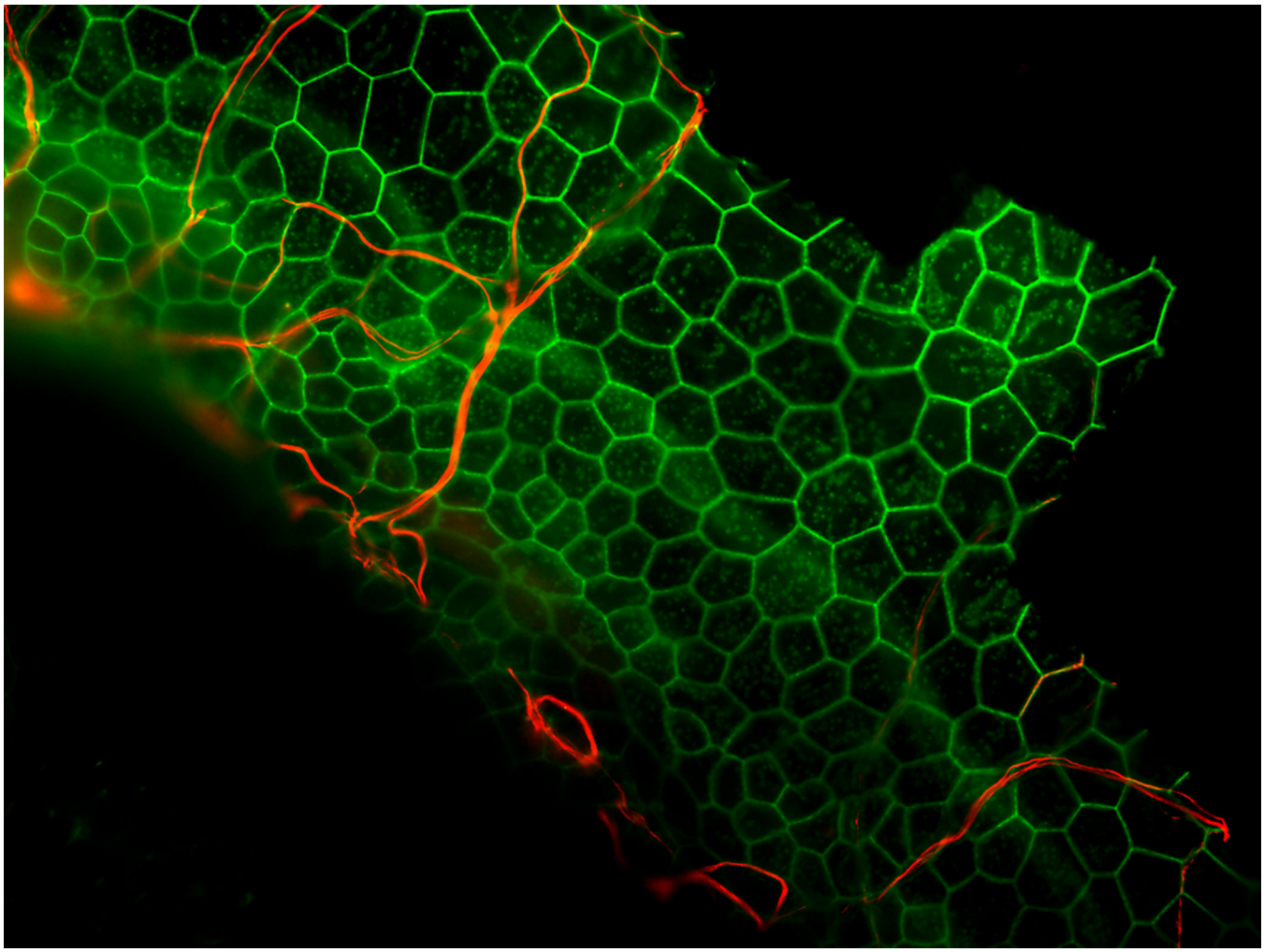

Figure 7.

Example of neurite growth toward the basilar membrane area in a deaf, neurotrophin treated ear. A whole-mount of the basal turn of the guinea pig cochlea stained for neurofilaments (red) and actin (green) and viewed with epi-fluorescence is shown. The ear was deafened with neomycin, injected with AAV. *NTF-3* a week later and obtained for histology 3 months after that. The auditory epithelium does not contain differentiated hair cells or supporting cells. Instead, it is composed of flat or cuboidal simple epithelium. Nerve fibers are seen entering the epithelium and traversing the epithelial cells. This experiment was similar to that reported by Shibata and colleagues (2010) except that AAV was used in this case instead of Ad as the vector for gene therapy.

Table 1

Relation of functional measures to anatomical measures of cochlear health for 5 guinea pig ears with various degrees of SGN density near the cochlear implant. Spiral ganglion cell densities (column 2) and inner hair cell (IHC) presence (percent of normal; column 3) were assessed in the region of the implant and just apical to the implant. Temporal integration (TI) slopes (dB / doubling of pulse-train duration; column 4) and psychophysical detection thresholds for single biphasic pulses (column 5) are based on the data shown in Figure 5. These data were obtained during a period when the psychophysical data were relatively stable. Means of three repeated threshold estimates are shown. Slopes for electrically-evoked compound action potential (ECAP) amplitude-growth functions measured (column 6) are based on best-fit linear fits to the data shown in Figure 6. Slopes were fitted to data above 100 μV to be above the noise floor. ECAP thresholds (current required to evoke a 100 μV ECAP response; column 7) were calculated from these regression lines. The ECAP data were obtained at about 150 DPI, when slopes and thresholds were relatively stable. Column 8 indicates the symbols used in Figures 5 and 6.

Subject, ear and implant	SGN Density (cells/mm^2)	IHC (%)	TI Slope (dB/doubling)	Psychophysical threshold for a single pulse (dB re 1 mA)	ECAP Slope at (μV/μA)	ECAP Thresh. (μA)	Symbols
453L1	959	87	−2.17	−16.6	8.47	122	Red circles
510L1	714	0	−0.62	−15.2	7.47	100	Orange stars
500L1	477	0	−0.58	−22.9	6.88	56	Green squares
455R1	145	0	−0.50	−16.8	4.83	123	Blue diamonds
454L1	72	0	−0.30	−15.8	1.66	143	Purple triangles