7th Quarterly Progress Report

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Protective and Plastic Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

In this Quarterly Progress Report we present initial results from a new study designed to define the frequency map of the human cochlear spiral ganglion. Currently, Greenwood's frequency-position function (Greenwood, 1990) for the organ of Corti (OC) is used to estimate the frequency of cochlear implant (CI) electrode arrays, both in temporal bone studies and in imaging studies of living CI recipients. However, most contemporary CIs are designed to position stimulating electrodes near the modiolus and to directly stimulate the spiral ganglion (SG) neurons within Rosenthal's canal. At the extreme base and throughout the apical cochlear turn, the OC is not adjacent to any SG neurons, and the frequencies represented are compressed into a different portion of the SG (i.e., into a more apical or basal sector, respectively). The relationship between OC and SG frequency maps also must change in different coils due to the change in relative radii of curvature. Further, critical band widths along the SG have never been systematically examined. Current CI designs space electrodes evenly, based on the assumption of constant OC critical band widths. Thus, better knowledge of the human SG "neural frequency map" may help to refine electrode design and to provide a basis for more accurately mapping CI channel filter bands to the place code of the SG. This may lead to future improvements in CI performance, especially for sophisticated CI functions such as music appreciation.

The specific goals of this study were to derive a mathematical function that would correlate represented frequency along the human OC to position along the SG, to calculate an "average" SG frequency map, to estimate the range of individual variability in represented frequency, and to examine critical band distance within the SG as a function of position along the cochlear spiral. Frequency-matched points on the OC and SG (determined by tracing the trajectories of radial nerve fibers) were expressed as percentage of total SG vs. OC length. These data demonstrated a consistent intersubject correlation that was best fit by a cubic function. This function permits derivation of SG frequency by direct substitution into Greenwood's equation. Moreover, the data demonstrated that in contrast to the critical band distance along the OC, which remains constant at about 1 mm throughout the cochlea, the critical band distance in the SG changes significantly along the cochlear spiral and is substantially compressed in the upper middle and apical cochlear coils.

In addition, during this past quarter we submitted 5 abstracts to the 2005 Conference on Implantable Auditory Prostheses (appended). Finally, we are also submitting with this Report the reprints of 3 new papers which appeared in publications during this past quarter:

1. Wardrop PJ, Whinney D, Rebscher SJ, Roland JT Jr, Luxford W, Leake PA. (2005) A Temporal bone study of insertion trauma and intracochlear position of cochlear implant electrodes. I: Comparison of Nucleus Banded and Nucleus Contour™ electrodes. Hearing Res. 203: 54-67.

2. Wardrop PJ, Whinney D, Rebscher SJ, Luxford W and Leake PA (2005) A Temporal bone study of insertion trauma and intracochlear position of cochlear implant electrodes. II: Comparison of Spiral Clarion™ and HiFocus™ electrodes. Hearing Res. 203: 68-79.

3. Vollmer, M., P.A. Leake, R. Beitel, S.J. Rebscher and R. Snyder (2005) Degradation in temporal resolution in the auditory midbrain after prolonged deafness is reversed by electrical stimulation of the cochlea. J. Neurophysiol. 93: 3339-3355.

INTRODUCTION

Greenwood's frequency-position function (Greenwood, 1990) for the organ of Corti (OC) is widely used to estimate represented frequencies for cochlear implant (CI) stimulation sites both in temporal bone studies (Kawano et al., 1996; Wardrop et al, a,b, 2005) and in imaging studies of living CI recipients (Ketten et al., 1998; Skinner et al.,2002). However, contemporary CIs marketed in the United States, including the Contour electrode marketed by Cochlear Corporation and the HiFocus and new Helix electrodes from Advanced Bionics Incorporated, position the stimulating contacts along the inner radius of the electrode carrier n the modiolus and directed toward the spiral ganglion (SG). Thus, it is noteworthy that the SG frequency map may be significantly different from that of the OC, especially in the apical cochlea where the radial nerve fibers take a tangential course into the modiolus, resulting in a significant offset between the SG somata and the region of the OC they innervate. The main goal of this study was to develop a more accurate map of estimated represented frequencies in the human SG, that ultimately can be applied in both temporal bone and imaging studies.

METHODS

Temporal bones were harvested from fresh cadaver specimens within <24 hours after death (n=7) and fixed by immersion in phosphate-buffered formalin. The tympanic membrane was opened as soon as possible after acquisition of each temporal bone to facilitate access of fixative to the middle ear and labyrinth. As shown in Figure 1, the specimens were dissected to isolate the petrous temporal bone, and the otic capsule was drilled out to orient the cochlea and to "blue line" the basal cochlear turn (Fig. 1a). The scala vestibuli was opened with a diamond dental burr and the cochlea was post-fixed in osmium tetroxide for 4 hours to stain the radial nerve fibers (Fig. 1b). Next the otic capsule was further microdissected and the cochlea was decalcified for 24-36 hours in order to fully visualize the radial nerve fibers (Fig. 1c).

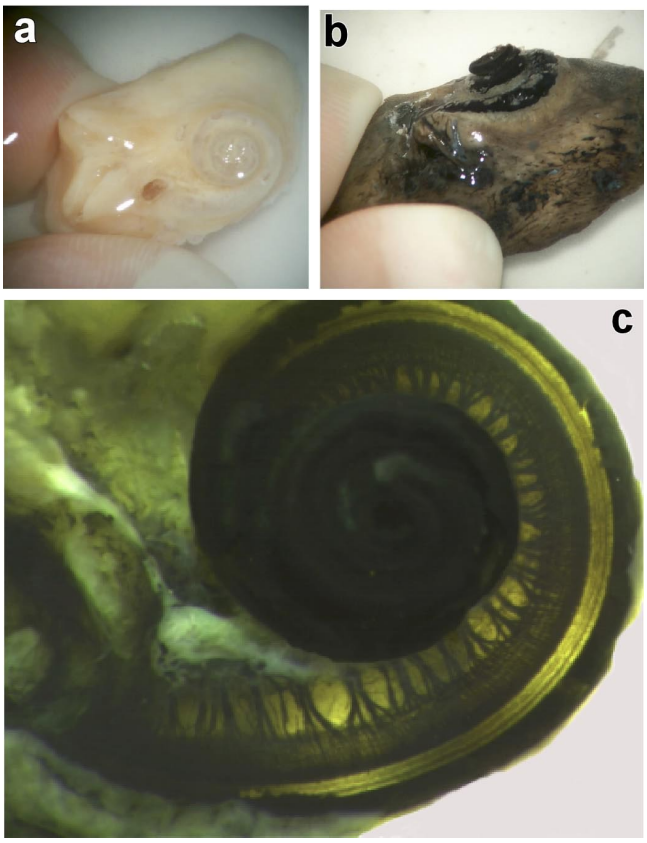

Figure 1. Human temporal bone specimens were fixed in formalin within <24 hrs after death, the petrous temporal bone was isolated and the otic capsule thinned (a). The scala vestibuli was opened and the cochlea was stained with osmium tetroxide (b), further microdissected, and then decalcified for 24-36 hours to visualize the radial nerve fibers (c).

After dissection, each cochlea was embedded in epoxy resin and then bisected through the middle of the modiolus, in a plane that was as parallel as possible to the radial nerve fibers on each side of the basal turn. Then each half-coil of the cochlea was isolated from the two larger blocks using razor blades and remounted on a glass slide in a classic surface preparation. However, because the OC and SG of the human cochlea are vertically offset from one another, the OC was positioned upside down on the slide (with the reticular lamina closer to the slide and the basilar membrane facing upward) so that the OC was flat and parallel to the slide, with the adjacent spiral ganglion offset above the OC.

Digital images of the surface preparations were captured and calibrated, and the OC was measured in each half-coil piece and in the 2-3 pieces of the remounted hook at the base of the cochlea (Fig.2). Next, radial sections were cut at selected locations to examine SG morphology, to determine the precise points where the SG terminated at the base and apex, and also to make measurements of the distance from the OC to the center of the SG at regular intervals (Fig. 3) These measurements were plotted on the digital images of the surface preparations, and the SG perimeter was drawn on the images and measured directly. Next the radial nerve fiber trajectories were traced to define a series of frequency-matched points along the OC and SG.

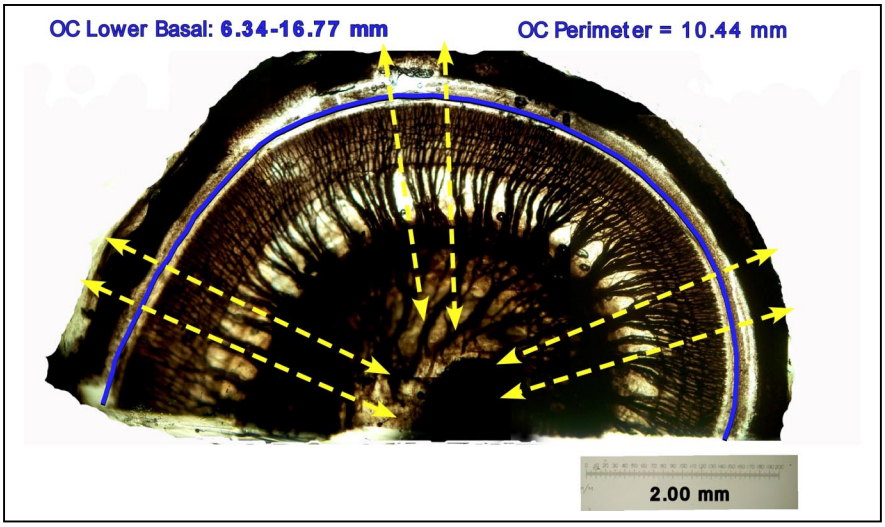

Figure 2. Digital image of the lower basal turn specimen taken from a surface preparation of an epoxy-embedded human cochlea. The blue line defines the OC length. The yellow dashed lines indicate where radial sections were prepared (Fig. 3) to examine the SG and to measure the distance from the OC to the SG (see Fig. 4).

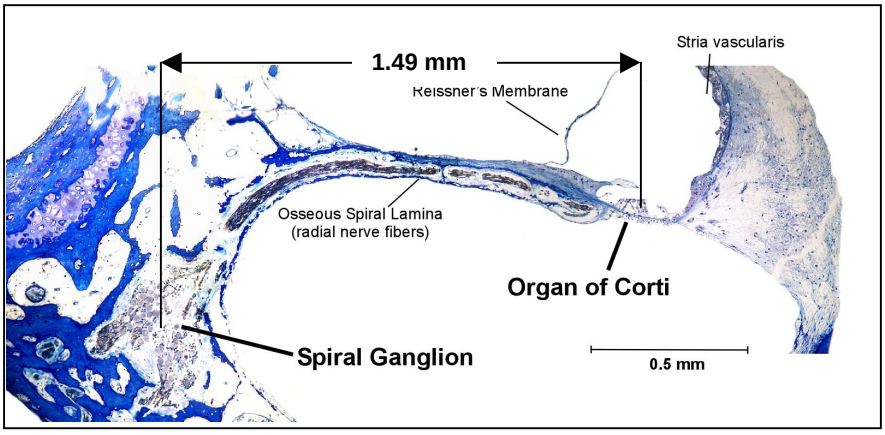

Figure 3. Digital image of a radial section of the OC and SG taken from from the lower basal turn 20% from the basal end of the OC.

The distance from the OC to the SG was 1.49 mm in this example. These measurements were used to define the SG center as shown in Figure. 4.

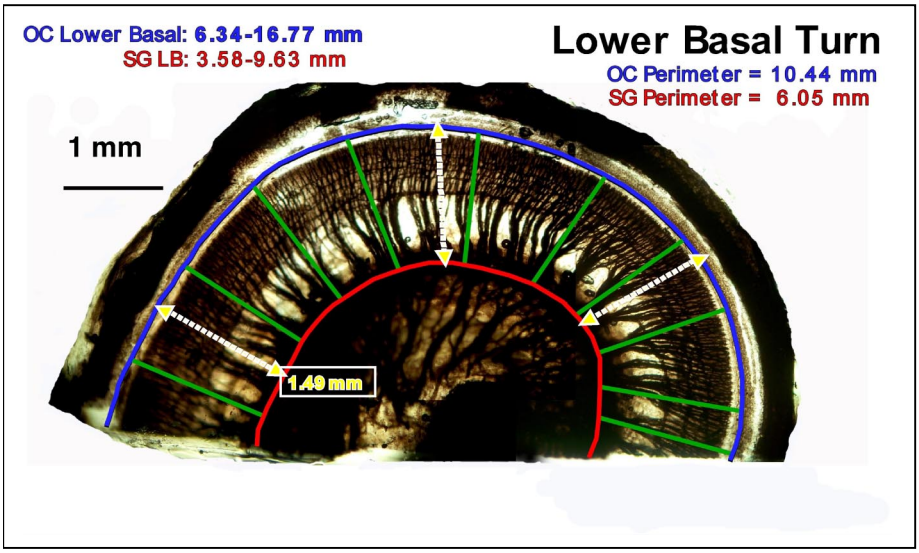

Figure 4. Blue line indicates the OC which measured 10.44 mm in this example (6.34 - 16.77 mm from the base). Red line is the SG, which measured 6.05 mm at its approximate center as delineated in the radial sections. For example, for the section shown in Figure 3 the distance from the OC to the SG was 1.49 mm, as plotted at the left of the image here. Green lines show radial nerve fiber trajectories defining the frequency-matched points on the OC and SG.

RESULTS

a. Measurements.

Table 1 presents measurements obtained for the 7 cochlear specimens studied to date. The mean OC length was 33.31 mm, whereas the SG length averaged 13.96 mm (n=6). Direct morphometric analysis showed that no spiral ganglion cell bodies are adjacent to the basal 2% and apical 11.14% of the organ of Corti. The ratio of SG to OC length was fairly similar in different-sized cochleae, with a range of 0.40 to 0.43.

Table 1. Summary of Measurements in 7 Cochleae

Specimen #:	7R	4R	5R	8R	15L	14R	6R	Mean
OC length (mm):	30.5	32.31	33.44	36.16	32.45	36.87	31.41	**33.31**
SG length (mm):	12.54	14	14.2	14.58	13.44	14.62	n/a	**13.90**
SG length /OC length:	0.41	0.43	0.42	0.4	0.41	0.4	n/a	**0.41**
% OC basal without SG:	1.31	1.98	3.47	1.38	2.13	1.84	n/a	**2.02**
% OC apical without SG:	11.64	9.22	11.33	10.26	11.37	12.99	n/a	**11.14**
% OC length at V:	59.08	59.36	64.74	55.56	61.14	n/a	60.01	**59.98**
Frequency at V (Hz):	1051	1035	764	1273	937	n/a	998	**1000**

b. The Spiral Ganglion Frequency-Position Function.

Frequency-matched coordinates on the OC and SG were determined by tracing the trajectories of radial nerve fibers at numerous points along the cochlear spiral. These data are presented in Figure 5. Percentage length along the SG was found to relate consistently and predictably to percentage length along the organ of Corti, with minimal intrasubject and intersubject variability. The data were best-fit by the cubic function: $y = -8E\text{-}5x^3 + 0.005x^2 + 1.3245x$. Since Greenwood's function calculates frequency for the organ of Corti, the represented frequency for the SG (i.e., % distance from base) is then easily calculated using the new SG frequency-position function.

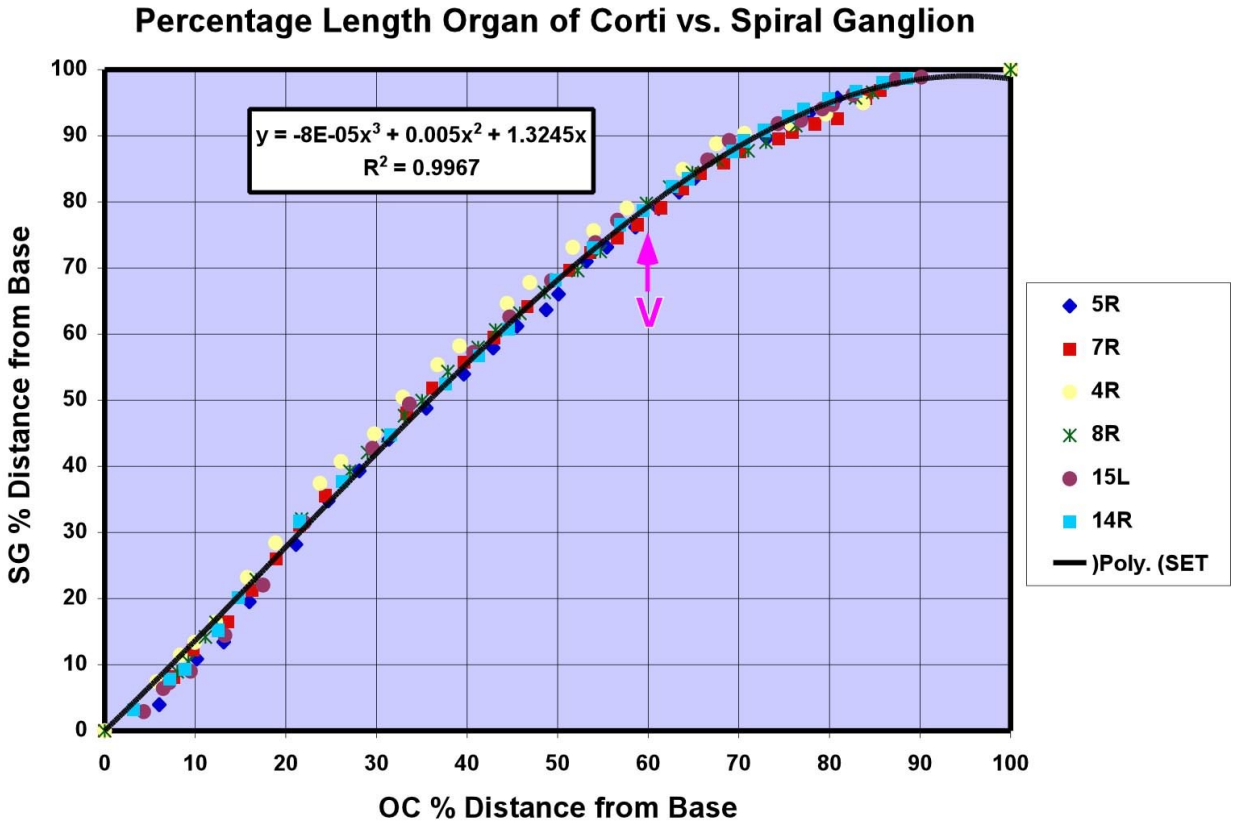

Figure 5. Frequency-matched points along the OC and SG were determined by tracing the trajectories of radial nerve fibers. These data are plotted here for the 6 cochleae in our data. A good correlation between percentage length along the organ of Corti and percentage length along the SG was demonstrated (r^2>0.99). The data were best-fit by the cubic function shown in the graph. Mean location for the anatomical reference point V is indicated by arrow (see below).

As anticipated, the frequency-position function for the spiral ganglion is quite different from that of the basilar membrane for a considerable proportion of the cochlea, and particularly for the most apical third of the cochlea. During cochlear dissections, an anatomical reference point was created by marking the site on the upper basal coil judged to be closest to the vestibule. This marker, which was termed V, was maintained throughout subsequent processing and embedding of the cochlea. The mean location of V in our study group was 60% from the basal end of the OC (Table 1), but on average this point would be located 78% from the base of the SG, as indicated by the arrow in Figure 5.

c. An Anatomical Reference Point for Relating the SG Frequency Map to Living CI Subjects Via Imaging Studies

Ultimately, the goal of this work is to allow the estimation of represented frequency based on cochlear place for CI electrodes in living subjects utilizing advanced imaging methods. This would be valuable for: 1) defining the optimum insertion distances for CI electrode arrays; 2) developing an empirical method for matching the assigned frequency bands in a speech processor to represented frequency based on cochlear place of stimulation - this may improve clinical results particularly in infants and congenitally deaf subjects; and 3) elucidating which specific neural structure(s) are the target(s) for electrical stimulation. Calculated using the Greenwood function, the mean frequency at our anatomical reference point V was 1000 Hz, but the represented frequency at V varied from 1275 to 760 Hz (a range of ~ 0.75 octaves) for the specimens in our study. This landmark (center of the vestibule) can be imaged in living subjects and the CI electrode closest to V can be defined. However, given the variability in frequency at V in this pilot study (presumably due to individual variability in cochlear size) it seems likely that accurate estimates of frequency for individual CI electrodes in living subjects will require a method of estimating OC (or SG) length. We hypothesize that a measure of overall cochlear size (specifically, the maximum diameter of the basal turn measured at the round window) as defined in pre-operative images will correlate with OC length. Additional temporal bone studies are required to develop and validate this measure.

Insertion depths of various CI electrode arrays have been reported in several previous studies, such as in Wardrop et al. 2005a,b. Contemporary CIs including the Cochlear Contour™ shown in Figure 6 and the Advanced Bionics Hi Focus™ and Helix™ electrode arrays, all position stimulating sites facing the modiolus and as close as possible to the SG. Such designs assume that the SG is the target of CI stimulation.

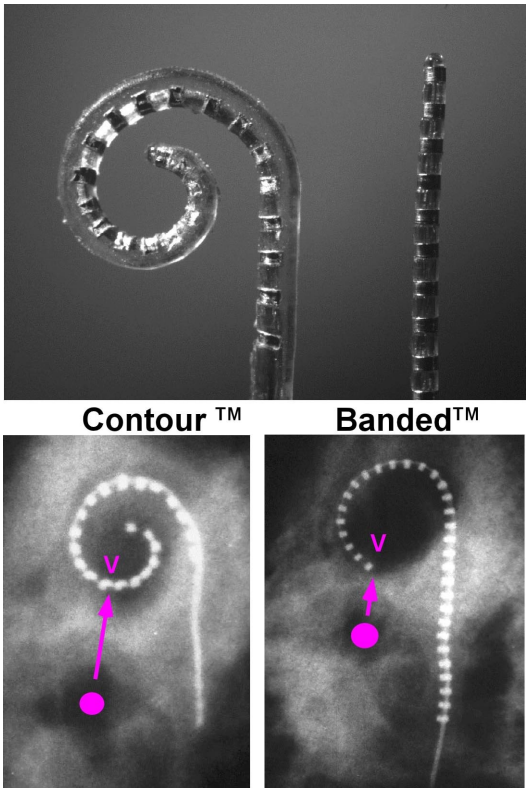

Figure 6. In contrast to older designs (e.g., Banded array at right), many contemporary CI electrodes such as the Contour electrode (left) from Cochlear Corporation have stimulating contacts arrayed along the inner radius of the carrier, as close as possible to the SG cells. For our pilot study attempting to relate our anatomical data to imaging studies, an anatomical landmark V was defined as the point on the upper basal turn closest to the center of the vestibule. X-ray images show implanted CIs with the electrode nearest V indicated. Our anatomical data provide a means of estimating insertion distances and represented frequencies for V and determining the extent of individual variability. Ultimately, if a metric can be developed that will allow us to predict OC length from imaging studies, our data should allow accurate estimation of cochlear place frequencies for CI electrodes in living subjects.

Returning again to our anatomical landmark V, a CI electrode carrier that takes a trajectory under the OC would need to insert a stimulating contact to a point 20 mm from the extreme base of the OC, (i.e., 60% of 33.31 mm), to stimulate at V (1000 Hz) in the average cochlea. (This might even be a maximum estimate of insertion length, because surgeons generally insert the CI electrodes through a cochleostomy anterior to the round window and therefore several mm from the basal end of the OC.) In contrast, if a CI electrode carrier were ideally positioned around the cochlear modiolus directly adjacent to the SG, the approximate insertion depth required to reach V would be 78% of 13.9 mm or about 10.84 mm in the average cochlea, or 11.4 mm for the longest SG in our group. Since our anatomical measurements define the length of the SG at its approximate midpoint, one would have to add a small increment to account for the slightly longer trajectory along the inner wall of the modiolus. Thus, if the target for CI electrodes is in reality the SG, then our data suggest that an insertion depth of 16-17 mm should be about optimal. (Given that the entire length of the SG was never longer than 14.7 mm, and adding 1-2 mm to account for the slight increase in length from the middle of the SG to the modiolar wall.)

d. Estimates of Critical Band Distance in the Human Spiral Ganglion.

The frequency-position function for the SG derived as described previously (Fig. 5) allows us to provide the first estimates of critical band distance in the human spiral ganglion. Unlike critical band width for the OC, which remains constant from base to apex, the critical band distance estimated along the SG varies as a function of position, and becomes progressively narrower from base to apex as illustrated in Figure 7.

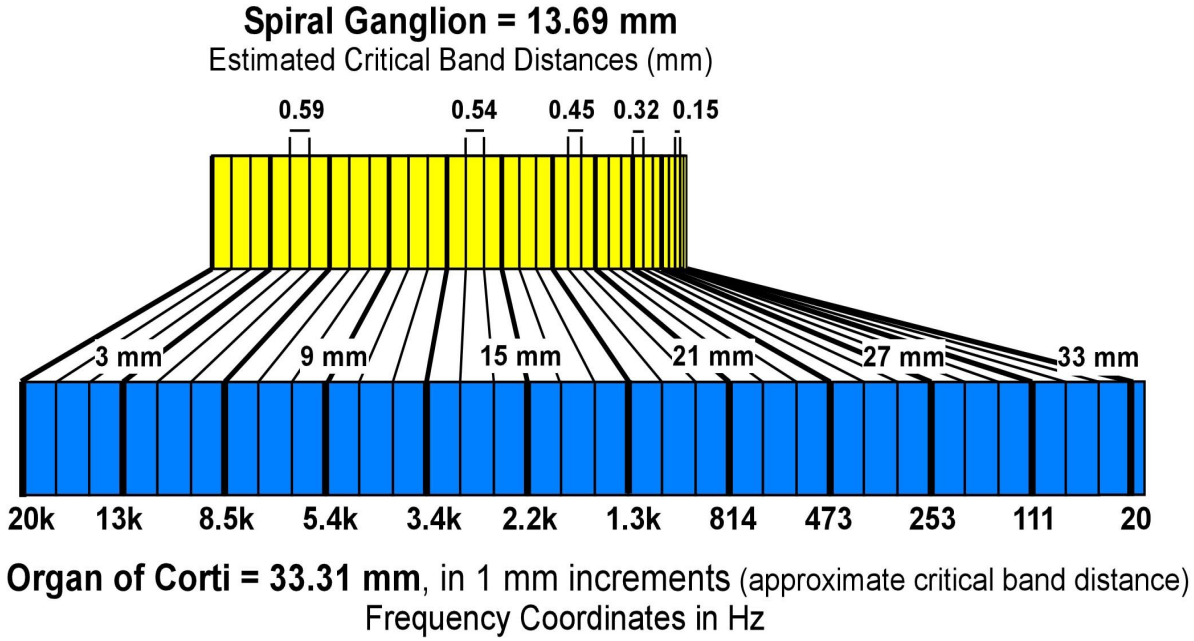

Figure 7. Approximate critical band distances in the OC (blue bands) and SG (gold bands) for the "average" cochlea based on our data set. A critical band distance on the OC is equal to 1/35 the basilar membrane length or 0.95 mm for our mean cochlea and is constant throughout the cochlea. In contrast, the SG critical band distance varies and becomes progressively shorter from base to apex as illustrated.

Figure 7 illustrates this finding by plotting data for the "average" cochlea, based on the mean values from our temporal bone series. A critical band distance for the OC is equal to 1/35 the basilar membrane length and is constant throughout the cochlea (Greenwood, 1990). For our average cochlea, the organ of Corti was 33.31 mm long and the precise critical band distance would be 0.95 mm (1/35th of 33.31). For simplicity in Figure 7, the organ of Corti is illustrated as 33 mm long, comprising 33 critical bands of approximately 1 mm. Spiral ganglion critical band widths were estimated throughout the cochlea by using the function derived in Figure 5 to estimate the length of ganglion associated with each millimeter of organ of Corti, as calculated for our mean SG length of 13.9 mm. The compression of critical band distance within the SG is particularly pronounced in the apical 35% percent of the cochlea (frequencies of 750 Hz and lower), where the radial nerve fibers take an increasingly tangential course from the OC into the SG. Specifically, SG critical band distance is about 0.6 mm near the base, diminishes to about 0.45 mm in the upper basal turn (21 mm), and is only about 0.32 mm in the lower middle turn (24 mm) in the region representing frequencies around 500 Hz.

One intriguing implication of these calculations is that if the goal is to provide equal frequency resolution along CI electrode arrays, then individual electrodes should not be spaced at uniform intervals - as is the case in all contemporary CI designs. Rather, apical electrodes should be more closely spaced and more basal electrodes should be more widely separated.

PRELIMINARY CONCLUSIONS

1) Substantial intersubject variability was observed in both basilar membrane and spiral ganglion lengths across the limited number of cochlear specimens included in our study to date. Basilar membrane (Organ of Corti) length ranged from 30.5 mm to 36.87 mm (mean, 33.31 mm) and the SG was 40-45% as long, ranging from 12.54 mm to 14.62 mm (mean, 13.9 mm). These findings are consistent with numerous prior reports indicating a large degree of variation in human organ of Corti length (Bredberg, 1968; Ulehlova et al. '87; Hardy, 1988; Kawano et al., 1996; Ketten et al., 1998: Skinner et al., 2002). Direct morphometric analysis showed that no spiral ganglion cell bodies are adjacent to the basal 2% and apical 11% of the organ of Corti; a previous report of 5% and 15%, respectively, was based on lower-resolution 3-D reconstructions (Kawano et al., 1996).

2) Current CI are designed to position stimulation sites facing the modiolus and as close as possible to the SG. The implicit assumption is that the SG is the target for electrical stimulation. If so, then the optimum insertion depth for a perimodiolar CI may be about 16-17 mm (slightly longer than the maximum length of the SG observed). This is an important issue, since shorter insertion depths may be less likely to cause trauma to the cochlea (Wardrop 2005b), thus optimizing clinical outcome.

3) A frequency-position function for the human spiral ganglion has been derived from the Greenwood function for represented frequency along the organ of Corti. Frequency-matched coordinates on the OC and SG were determined directly in temporal bone specimens by tracing the trajectories of radial nerve fibers visualized by

staining with osmium tetroxide followed by brief decalcification. Normalized length along the SG (% distance from the base) was highly correlated to normalized length along the organ of Corti, and was best described by a cubic function. Since Greenwood's function allows calculation of frequency along the organ of Corti, this new equation provides an accurate frequency-position function for the spiral ganglion.

4) The frequency-position function for the spiral ganglion differs significantly from that for the organ of Corti. There is a significant offset between represented frequency along the OC and that of the SG in the apical third of the cochlea due to the tangential trajectory of the radial nerve fibers in this region and the shorter length of the SG.

5) An anatomical reference point marked in the upper basal coil of each cochlea (V, point closest to the vestibule) was located on average 60% from the basal end of the OC. This point corresponded to 78% from the basal end of the SG. The mean represented frequency at V was 1 kHz as calculated with the Greenwood function, but the frequency at V ranged widely from 764 Hz to 1237 Hz in different individual specimens. Further investigation will be required to determine whether individual variation in represented frequency is as large if frequency is defined as a function of angular rotation around the cochlear spiral.

6) Estimated critical band distances in the spiral ganglion diminish systematically from base to apex, unlike critical bandwidths on the organ of Corti, which remain constant throughout the cochlea. It has been suggested that a critical bandwidth for the human cochlea subtends a distance of 1/35 of the OC length, or about 1 mm (Greenwood,1990). Applying the new SG frequency-position function, corresponding critical bandwidth distances in the SG decrease from about 0.6 mm in the basal cochlea to about 0.3 mm at a represented frequency of 500 Hz.

One interesting implication of this compression is that in order to provide equal frequency resolution with a CI, individual electrodes should not be spaced at uniform intervals along the array as is the case in all contemporary CI designs. Rather, apical electrodes should be progressively more closely spaced than more basal electrodes.

7) Ultimately, our goal is to provide a relatively simple and accurate method for estimating represented frequency based upon cochlear place for CI electrodes imaged in living subjects. Given the individual variability in cochlear size, and the dependence of represented frequency on OC length, accurate estimation of frequency for CI electrodes in living subjects would be greatly facilitated by development of a method for estimating OC or SG length that can be extrapolated from measurements of cochlear size that can be executed in imaging studies.

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Wardrop P, Whinney D, Rebscher SJ, Luxford W, Leake P.A. 2005b. A temporal bone study of insertion trauma and intracochlear position of cochlear implant electrodes. II: Comparison of Spiral Clarion™ and HiFocus II™ electrodes. Hear Res 203: 68-79.

WORK PLANNED FOR NEXT QUARTER

1) Ongoing data analyses of spiral ganglion survival, and morphology of the cochlear nucleus as well as electrophysiological data will continue in our new experimental group of subjects that have been deafened at 30 days rather than neonatally, to examine possible critical periods in the anatomical effects of deafness and chronic electrical stimulation on the cochlea and cochlear nucleus.

2) Two subjects currently undergoing chronic electrical stimulation will be studied in terminal acute electrophysiological studies recording from the inferior colliculus and primary auditory cortex. On of these subjects is an animal deafened at 30 days of age rather than neonatally; the second subject is a neonatally deafened, single channel stimulation subject that will be studied to provide additional data needed for a planned publication correlating IC and AI temporal following in control, chronically-stimulated, and long-deafened animals.

3) During the next quarter, two subjects will be deafened at 30 days of age (rather than neonatally) as part of our new series. During the current quarter, unfortunately, one subject that we attempted to deafen for this series failed to meet the criterion profound hearing loss after 33 days of injections and had to be eliminated from the experiment because of dehydration due to the prolonged aminoglycoside treatment. A second subject was sacrificed as a control at 9 weeks of age. One of the two new subjects will be euthanized as a control at 8-9 weeks of age during the next quarter. The other will be implanted unilaterally at the same age and will undergo chronic daily 2-channel intracochlear electrical stimulation in this new experimental series designed to evaluate the potential critical period effects of a short period of normal hearing early in life.

4) Last quarter Dr. Leake traveled to the University of Melbourne to visit the group working under Dr. Robert Shepherd's NIH Contract with the same title as this contract. The purpose of this visit was to spend several days in detailed discussions reviewing technical aspects of chronic electrical stimulation studies in cats being conducted at both sites and to examine possible factors that may underlie disparities in results obtained by our two groups. During the next quarter a summary of the discussion, conclusions and unresolved issues from that visit will be prepared for inclusion in a subsequent QPR.

5) Studies of the human cochlea will continue, with new analyses directed toward developing and validating a measure of cochlear size (e.g., mean of 2 maximum cochlear diameters, measured orthogonal to each other) that we hypothesize will be correlated with organ of Corti length and also can be replicated in conventional imaging studies, for application in living cochlear implant subjects.

6) Several members of our group will present talks or posters (see appended abstracts) and Dr. Leake will moderate one of the scientific sessions at the 2005 Conference on Implantable Auditory Prostheses, July 30 - August 4 at the Asilomar Conference Center, CA.

APPENDIX:

ABSTRACTS SUBMITTED FOR 2005 CONFERENCE ON IMPLANTABLE AUDITORY PROSTHESES

FREQUENCY MAP FOR THE HUMAN COCHLEAR SPIRAL GANGLION

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Greenwood's frequency-position function (Greenwood, 1990, JASA 87) for the organ of Corti (OC) is widely used to estimate represented frequencies for cochlear implant (CI) stimulation sites both in temporal bone studies and in imaging studies of living CI recipients. However, many contemporary CIs position the stimulating electrodes near the modiolus to target the spiral ganglion (SG), and the SG frequency map may be significantly different from that of the OC, especially in the apical cochlea. The main goal of this study was to develop a more accurate method for estimating represented frequencies in the human SG that can be applied in both temporal bone and imaging studies. Further, since OC length is a required metric for application of the frequency-position function, a specific goal was to develop a method for estimating OC length that can be applied in both temporal bone and imaging studies.

Cadaver cochleae (n=9) were fixed <24 hours postmortem, stained with osmium tetroxide, microdissected, decalcified briefly, embedded in epoxy resin and then examined in surface preparations. In digital images, the OC and SG were measured, and the radial nerve fiber trajectories were traced to define a series of frequency-matched coordinates along the two structures. These data showed that whereas the distance along the OC that corresponds to a critical bandwidth is constant throughout the cochlea, the critical bandwidth distance in the SG changes significantly along the spiral.

The mean OC length was 33.13 mm. In contrast, the mean SG length (at the center of Rosenthal's canal) was only 13.69 mm. OC length was significantly correlated with SG length (r^2=0.76; $p<0.005$). The mean length of the inner modiolar wall adjacent to the SG (closest possible position of a CI electrode) was 15.49 mm. Frequency-matched points along the SG and OC, expressed as percent of length, showed a highly consistent intersubject correlation that was best fit by a cubic function. This function allows derivation of SG frequency by substitution into Greenwood's equation. Further, OC and SG length each showed significant correlation (r^2=0.78 and 0.86 respectively; $p<0.005$) with cochlear size (average of the maximum diameter of the basal coil and the orthogonal diameter). This finding should enable us to estimate OC length in imaging studies (by measuring cochlear diameter) and thereby to infer represented frequency in living subjects.

The positions of individual CI electrodes in the cochlea can be correlated with psychophysical measures such as pitch perception, threshold and dynamic range. More accurate frequency maps for the OC and SG should permit better matching of the filter band for each CI processor channel to its stimulation site, potentially increasing clinical benefits (e.g., especially for music appreciation).

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EFFECTS OF DEAFNESS AND ELECTRICAL STIMULATION IN ANIMALS WITH EARLY-ACQUIRED HEARING LOSS

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Previous studies reported by our group have shown that electrical stimulation delivered by a cochlear implant (over periods of several months) promotes improved survival of spiral ganglion cells (SGC) in cats deafened neonatally by administration of an ototoxic drug. In the present study we explored the possible role of developmental critical periods by studying a new deaf animal model. Cats were deafened at 30 days of age (rather than immediately after birth) in order to model early acquired hearing loss. The deafening procedure was identical to that used previously for neonatal deafening. One experimental group was studied immediately after deafening at 8-9 weeks of age. A second group received a cochlear implant at 8-9 weeks of age and underwent unilateral electrical stimulation with temporally challenging signals (325 pps/60Hz AM) for periods of 18-30 weeks. Data from the 2 groups were compared to 2 groups of neonatally deafened animals that were carefully matched to the 30-day deafened groups for age and duration of stimulation.

In the 30-day deafened group studied at 8-9 weeks of age, SGC survival was already significantly reduced, despite the fact that these subjects had adult-like hearing thresholds when ototoxic drug administration was initiated, and they were studied only about 1-2 weeks after profound hearing losses occurred. There was, however, an interesting difference in the distribution of surviving SGC within the cochlea. The neonatally deafened animals exhibited a consistent pattern of higher SGC survival in the base and apex, and more marked loss in the middle of the cochlea. In contrast, the 30-day deafened group showed more variable survival throughout the cochlea.

Electrical stimulation delivered over a mean of 6.3 months significantly enhanced SGC survival in the 30-day deafened group (n=4), with maintenance of about 17% higher cell density in the stimulated ears. However, the neonatally deafened group (n=5) showed a similar increase of about 19%. Thus, there was no significant difference in SGC survival between the 30-day deafened group (modeling early acquired deafness) and the neonatally deafened group (modeling congenital deafness), at least in the limited number of subjects studied to date.

Measurements of cochlear nucleus (CN) size, however, revealed significantly higher values in the 30-day group as compared to neonatally deafened cats at 8-9 weeks of age. There was also a trend toward larger CN size in the 30-day deafened group studied after chronic electrical stimulation, as compared to the neonatally deafened, stimulated group. These preliminary findings suggest that a short period of normal auditory experience may be significant in lessening degenerative changes in the central auditory system after early-acquired deafness (as compared to the effect of congenital deafening).

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FUTURE DEVELOPMENT OF COCHLEAR IMPLANT ELECTRODES

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Optimum performance for future cochlear implant (CI) recipients will require an improved interface between sophisticated sound processors and the stimulated auditory neurons. Psychophysical studies, modeling and electrophysiological data all predict that patient performance will benefit if CI electrodes are consistently inserted without trauma and are optimally positioned. In this ongoing study we examined 64 cadaver temporal bones implanted with 5 different CI electrode arrays with the specific goal of developing strategies that will both minimize trauma and improve electrode positioning.

We observed moderate to severe trauma at one or more locations in 63% of the temporal bones studied. Perforation of the cochlear partition, with deviation of the electrode into the scala vestibuli (SV), occurred in 42% of the insertions with electrodes designed to have equal stiffness in the vertical and horizontal planes. Similar trauma occurred in only 14% of specimens implanted with electrodes having greater stiffness in the vertical dimension. When electrodes deviated into the SV, perforation occurred at a consistent location opposite the cochleostomy (mean = 196°). In addition to their increased vertical stiffness, electrodes that were least likely to deviate into the SV were pre-curved and were advanced off a stylet insertion tool. However, this stylet must be withdrawn at the correct insertion depth for this technique to be of greatest advantage. Direct temporal bone measurements indicate that this ideal depth is highly variable, but there is currently no method to measure or predict this distance in a CI subject.

From the standpoint of electrode performance, we found that when electrodes deviated into the SV, the distances from stimulating contacts to neurons in the spiral ganglion were significantly greater and the relationship of electrode sequence to cochleotopic organization was often distorted. Finally, deviation of electrodes into the SV resulted in decreased depth of insertion (limiting stimulation to higher frequencies).

Based on these results we have successfully tested several strategies to better control the mechanical behavior of CI electrode arrays. The advantages of vertically oriented wire and plastic rib assemblies have been reported previously. We have recently fabricated electrodes based on photolithographic metallization of flexible substrates, and we also have tested liquid crystal polymer based electrodes developed in collaboration with Advanced Cochlear Systems (Seattle, WA). The vertical stiffness (1.63 and 4.9 vertical/horizontal stiffness in these two prototypes) and spiral restoration force in each of these designs can be accurately controlled. Moreover, these electrodes can be fabricated with higher contact densities than wire-based arrays and provide additional interior volume to permit the incorporation of optical or ultrasound location sensing technology, active mechanical steering capability and/or drug delivery. We suggest that future application of these design principals will facilitate production of clinical devices with significantly improved performance.

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RESPONSES TO INTERLEAVED ELECTRICAL PULSE TRAINS

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The temporal aspects of a stimulus can greatly influence the response of neurons in the central auditory system. In the inferior colliculus (IC), for instance, a neuron's response to a brief tone can be suppressed or facilitated by the occurrence of a preceding tone. Relatively little, however, is known about interactions in the IC produced by electrical stimulation of the cochlea. Such processing may play a fundamental role in cochlear implant perception.

We evaluated temporal interactions in the IC of acutely deafened guinea pigs in response to interleaved pulse trains from one and two cochlear implant channels. Multi-unit activity in the IC's central nucleus was recorded with a 16-channel silicon-substrate electrode spanning several octaves of the tonotopic axis. The stimuli were biphasic pulses delivered via an 8-electrode implant inserted into the contralateral scala tympani. Pulses were delivered bipolarly between neighboring electrodes and presented as trains of 5 pulses at a rate of 50 Hz. Trains were temporally interleaved, with train A (the masker) occurring 2 to 10 ms earlier than train B (the probe).

With the probe stimulus fixed at a level 3-5 dB above threshold, a masker presented 10 ms earlier and of the same channel and intensity caused a reduction in response at most IC recording sites. This suppression was cumulative over the duration of the stimulus, being greatest for the last probe pulse. Facilitation occurred less commonly and affected only the first probe pulse. For some neurons, suppression was evident even with a sub-threshold masker. The degree of suppression at a given IC recording site was strongly correlated with neighboring sites. Suppression was generally greater at sites non-optimally stimulated, producing an effective narrowing of activity across the IC.

As the interval between masker and probe was shortened, the degree of suppression increased. At intervals as short as 2 ms, the total response to a super-threshold masker plus probe was not significantly different than that of the masker alone. An "off-channel" masker (delivered to a channel other than the probe channel) could also suppress the response to a probe stimulus. The degree of suppression was typically proportional to the magnitude of response produced by the masker alone, indicating that cross-channel interactions are mainly a result of an adaptive mechanism similar to that of same-channel interactions. In several cases, however, an off-channel masker was found to be a more effective suppressor than a same-channel masker.

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NEURONAL INTERACTIONS OF COMBINED ELECTRIC/ACOUSTIC STIMULATION OF THE COCHLEA IN CAT INFERIOR COLLICULUS

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Using a forward masking paradigm, the present study explores the effects of combined electric and acoustic stimulation (EAS) of the cochlea on neuronal responses in the inferior colliculus (IC).

Anesthetized normal hearing cats were implanted with scala tympani electrodes, and an earphone was sealed to the ipsilateral auditory meatus for acoustic stimulation. Neuronal responses were recorded simultaneously at 16 sites along the tonotopic gradient of the central nucleus of the contralateral IC. A 60-ms acoustic masker preceded a 20-ms electric probe. Masker and probe were systematically varied in intensity and frequency.

At low intensities, electric probe frequencies >1 kHz activated IC locations that corresponded to the probe frequency (*electrophonic* effect). At increasing intensities, there was spread of activation to neighboring recording sites. For any activated recording site, masking of the probe was greatest when the electric probe was preceded by acoustic stimulation of the same frequency. Strength of masking was generally increased by increasing masker intensity.

At higher intensities, the electric probe activated additional IC locations that corresponded to the cochlear site of the stimulating electrode(s) (*electroneural* responses). This activity was masked best by acoustic frequencies that corresponded to the same cochlear site. On neighboring activated recording sites, the characteristic frequency (CF) of the masked tuning curves corresponded to the CF at the individual recording sites.

These results indicate that EAS leads to complex response interactions in the central auditory system. The spatial extent of these interactions is dependent on the intensities and spectral characteristics of both electric and acoustic stimulus components. The results also indicate that electric stimulation of the hearing cochlea evokes both low-threshold acoustic-like *electrophonic* responses and high-threshold *electroneural* responses. It is hypothesized that complex neuronal interactions in the central auditory sytem may influence the overall effectiveness of combined EAS in human subjects.

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