

First Quarterly Progress Report

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Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

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1. Introduction

The objective of this research is to evaluate the feasibility of intra-neural stimulation as a means of auditory prosthesis. Conventional cochlear implants, consisting of an array of electrodes in the scala tympani of the cochlea, have proven to be a successful means of stimulating the auditory nerve. Nevertheless, the position of a scala-tympani electrode array, in a volume of electrically conductive perilymph, located at a variable distance from the osseous spiral lamina, and separated from auditory nerve fibers by a bony wall, results in multiple indirect, attenuated current paths from stimulated electrodes to nerve fibers. The lack of direct access to auditory nerve fibers imposes the following limitations that, in principle, might be reduced or eliminated by stimulation with *intra-neural* electrodes positioned directly in the modiolus or auditory nerve trunk:

- Thresholds for stimulation with scala-tympani electrodes are relatively high. In contrast, preliminary tests of intra-neural electrodes demonstrate thresholds that are lower by 20 dB or more.
- The tonotopic spread of activation by a scala-tympani electrode is broad, often broader than the response to a one-octave noise band. Intra-neural electrodes might produce more restricted activation, at least at near-threshold current levels.
- Broad spread of activation by scala-tympani electrodes results in interactions among activated neural populations, thereby limiting the number of independent information channels. The direct access of intra-neural electrodes to more-restricted neural populations should result in reduced channel interactions and a larger number of effectively independent information channels.
- Scala-tympani electrodes can produce ectopic activation of auditory nerve fibers, i.e., activation of non-contiguous, tonotopically inappropriate cochlear locations. In animal models, for instance, monopolar stimulation of basal cochlear sites activates intra-modiolar fibers passing from the cochlear apex. Since intra-modiolar fibers travel in fascicles grouped by cochlear region, intra-neural electrodes might produce less ectopic activation, at least at low-to-moderate current levels.
- Present-day scala-tympani arrays reach only to the middle of the second cochlear turn, well short of the apical regions representing frequencies less than ~1 kHz. Intra-neural electrode arrays should have direct access to fibers originating from throughout the spiral ganglion.
- In cases of meningitis, bacterial labyrinthitis, and otosclerosis, the scala tympani of the basal turn may be occluded, rendering placement of scala-tympani electrode arrays difficult or impossible. Intra-neural electrode arrays could be used in such occlusion cases.

In contrast to those potential benefits of intra-neural stimulation, there are several potential liabilities that must be evaluated:

- The sequence of frequency sensations evoked by an intra-neural array may be variable and idiosyncratic. Scala-tympani arrays conform to the cochlear spiral, and their stimulation sites are distributed in a basal-to-apical sequence. Therefore, at least in principle, they activate an orderly sequence of auditory nerve sectors, which results in a more-or-less orderly high-to-low sequence of frequency sensations. In contrast, the complex spiral frequency organization of cochlear nerves within the modiolus will cause an intra-neural array to activate

idiosyncratic sectors of the auditory nerve and will require development of procedures to map particular electrodes onto the continuum of sound frequencies.

- Ectopic activation of auditory nerve fibers might also be a problem for intra-neural stimulation. A stimulus intended to activate fibers from basal-turn might, at high levels, spread to nearby fibers from the apical turn, resulting in activation at two or more discontinuous loci along the tonotopic axis. In contrast, higher current levels delivered to a scala-tympani electrode generally results in recruitment of fibers from contiguous and tonotopically appropriate cochlear regions. Experiments are needed to determine whether an adequate dynamic range of stimulation is available at current levels below those that elicit discontinuous activation patterns.

We are evaluating these potential benefits and liabilities of intra-neural auditory-nerve stimulation using the cat as an experimental model. We evaluate the spread of auditory-nerve activation by recording from the central nucleus of the inferior colliculus (ICC), using 32-site recording probes positioned along the tonotopic axis. In the course of this study, we plan to test several stimulating electrode arrays, including 16-site single-shank Michigan silicon-substrate thin-film arrays, four-shank Michigan silicon arrays, and 12-or-16 prong Utah Arrays. We will test two approaches, (1) a lateral approach to the nerve through the round window (the “trans-bulla” approach) and (2) an intra-cranial approach to the nerve in the internal meatus. Initial experiments will be conducted in acute anesthetized preparations, but eventually will move to a chronic preparation. These experiments will be conducted in John Middlebrooks’s lab at the University of Michigan with a subcontract with Russell Snyder at Utah State University.

2. Summary of activities for the quarter

Administrative:

- Established sub-contract with Utah State University for 25% FTE participation of Dr. Russell Snyder.
- Hired research assistant James Wiler.
- Prepared, submitted, and received approval of animal use form.

Equipment acquisition:

- Tucker-Davis Technologies RX8-5 DSP Processor with 24 channels of D/A conversion: This will serve as a signal source for the electrical stimulation. Sixteen channels will be used for the intra-neural electrodes and 8 for a conventional scala-tympani implant
- A beam splitter and digital camera for the operating microscope: These devices will permit continuous viewing of microsurgical procedures allowing collaborative modification and development of these procedures, training of personnel in the microsurgery, and documentation of the intra-neural location of electrodes.
- Pulse oximeter: for monitoring the animal’s heart rate, oxygen saturation, and core temperature
- Stereotaxic frame: to ensure consistent orientation of ICC recording probes
- Personal computer with high-capacity SCSI hard drives: needed to accommodate the high data rate associated with simultaneous data acquisition on 32 recording channels

Technical activities:

- Design of a 16-channel optically isolated current source for use with relatively high-impedance intra-neural electrodes. Design of this device is complete and fabrication is under way. Prior to completion of the 16-channel device, experiments this quarter have used an 8-channel current source modified from cochlear implant experiments.
- Modification of the stereotaxic frame: The frame was adapted to coordinate with existing magnet-base instruments and to facilitate orientation adjustments of the entire frame.
- Design and construction of a 32-channel headstage for the Michigan recording probes: This device serves as the input to 2 Tucker-Davis PA16 amplifiers.
- Modification and enhancement of existing software to expand from 16 to 32 recording channels: This involved changes in software for data acquisition, on-line graphical display, off-line graphical analysis, and off-line spike sorting.

Scientific activities:

- Dissection of four cat cadaver heads: Two heads were studied prior to any *in vivo* studies to explore possible trans-bulla approaches to the auditory nerve. Two other heads were dissected after *in vivo* experiments to document actual electrode placements.
- Physiological experiments in three cats: These acute experiments involved recording from the ICC and cochlear stimulation with sounds (in normal-hearing conditions) and with electrical pulses through both scala-tympani and intra-neural electrode arrays. The first of those experiments yielded only marginally useful data due to technical difficulties. The second two experiments yielded useful data pertinent to the tonotopic spread of activation. Initial data will be summarized in the next section.

3. Initial Results: Spread of tonotopic activation in the ICC in response to acoustic, scala-tympani, and intra-neural stimulation of the cochlea

Russell Snyder visited the PI's lab at the University of Michigan where we conducted physiological experiments in three cats. These initial experiments focused on intra-neural stimulation using a 16-site single-shank Michigan array, which was positioned in the modiolar portion of the auditory nerve using a trans-bulla approach. We recorded the ICC responses evoked by this intra-neural array using 32-channel probes. We presented single electrical pulses, and quantified the tonotopic spread of activation in the form of spatial tuning curves.

Summary of Methods: Experiments were conducted in barbiturate-anesthetized cats. The right ear was deafened by disarticulation of the ossicles. The right inferior colliculus was visualized by aspiration of overlying occipital cortex. A multi-channel recording silicon recording probe was inserted through the ICC oriented in the coronal plane and angled from dorsolateral to ventromedial at an angle of 45° from the mid-sagittal plane. The probe had 32 recording sites (400 μm^2 in area) positioned on a single shank at 100 μm intervals. Neural waveforms were recorded simultaneously from all 32 sites and saved to computer disk. On-line peak picking and graphic display permitted continuous monitoring of responses. Off-line spike sorting allowed examination of isolated single unit and multi-unit cluster activity.

Each experiment began with testing of responses to acoustic stimulation in normal-hearing conditions. Calibrated noise- and tone-burst stimuli were presented through a hollow ear bar to

the left ear. The position of the recording probe was adjusted based on responses to sounds, then the brain surface was covered with agarose and the probe was fixed in place with acrylic cement. Measurements of frequency tuning provided a functional measure of the location of each recording site along the tonotopic axis.

After completion of tests with acoustic stimuli, the left cochlea was deafened by intra-scalar injection of neomycin sulfate and a banded electrode array was implanted in the scala tympani. This scala-tympani array was a 6-electrode animal version of the Nucleus24 device from Cochlear Corp. The dimensions were identical to the distal 6 electrodes of the human device: platinum band electrodes, 400 μm in diameter, centered at 750 μm intervals along a silastic carrier. Electrical stimuli through the cochlear implant consisted of single biphasic pulses, 40 or 200 μs per phase, initially cathodic. Stimuli were presented in monopolar (MP) and bipolar (BP) electrode configurations.

Testing of the scala-tympani electrode was followed by testing of intra-neural stimulation. The stimulating array was a 16-site thin-film silicon-substrate Michigan probe. The sites were positioned at 100- μm intervals along a single shank. In these initial experiments, we were equipped with only 6-channel stimulation electronics, so those channels were directed either to the 6 most distal sites (i.e., in 100- μm intervals) or to every third site (i.e., in 300- μm intervals). Stimuli were biphasic pulses, 40 or 200 μs per phase, initially cathodic, presented in a MP configuration.

The intra-neural electrode array was positioned as follows. The left bulla was opened to expose the cochlea. The round-window membrane was excised and the rim of the round-window was enlarged with a diamond burr. The beveled tip of a 26-gauge needle was used to make an opening in the osseous spiral lamina below the spiral ganglion. The hole was enlarged with a fine reamer. The probe was inserted under visual control using a micromanipulator. We tested several orientations of the stimulating array. The most successful in these initial experiments was oriented approximately in the horizontal plane, from rostralateral to caudomedial, approximately 25° from the coronal plane. Figure 1 shows the probe insertion point in a cadaver dissection. The white and blue arrows indicate the basilar membrane and spiral ganglion, respectively, and the blue circle indicates the location of the opening for insertion of the stimulating array.

Results: Responses to acoustical tones were used to identify the positions of recording sites relative to the tonotopic axis. The frequency tuning of responses to tones was similar to those commonly reported in the ICC. The tonotopic progression of characteristic frequencies (CFs) as a function of the relative depth in the IC (distance along the shank of the recording probe) was consistent with the commonly reported tonotopic organization of the ICC. Figure 2 shows frequency response areas recorded in one animal under normal-hearing conditions. Each panel represents responses at one recording site, with the most superficial site represented at the upper left, progressing column-wise to the deepest site represented at the lower right. Within each panel, the horizontal axis represents tone frequency and the vertical axis represents sound level. Characteristic frequencies in these recordings progressed sequentially and ranged from about 1 to 32 kHz, a range of five octaves.

Following recordings in normal-hearing conditions, the left cochlea was deafened, a scala-tympani electrode array was implanted, and ICC responses to scala-tympani stimulation were recorded. Scala-tympani stimulation in the MP configuration produced broad activation of recording sites spanning the tonotopic axis. In Fig. 3 and subsequent figures, spread of activation

is represented by spatial tuning curves. The spatial tuning curve in each panel represents the activation pattern evoked by one banded electrode (for the scala-tympani array) or one stimulation site (for the intra-neural array). The contours represent cumulative discrimination index (d') for discrimination of one current level from the next higher level based on the trial-by-trial distribution of spike counts. The left-most contour in each panel represents threshold at $d'=1$, and contours increase to the right in increments of $\frac{1}{2} d'$ unit. Monopolar stimulation at the

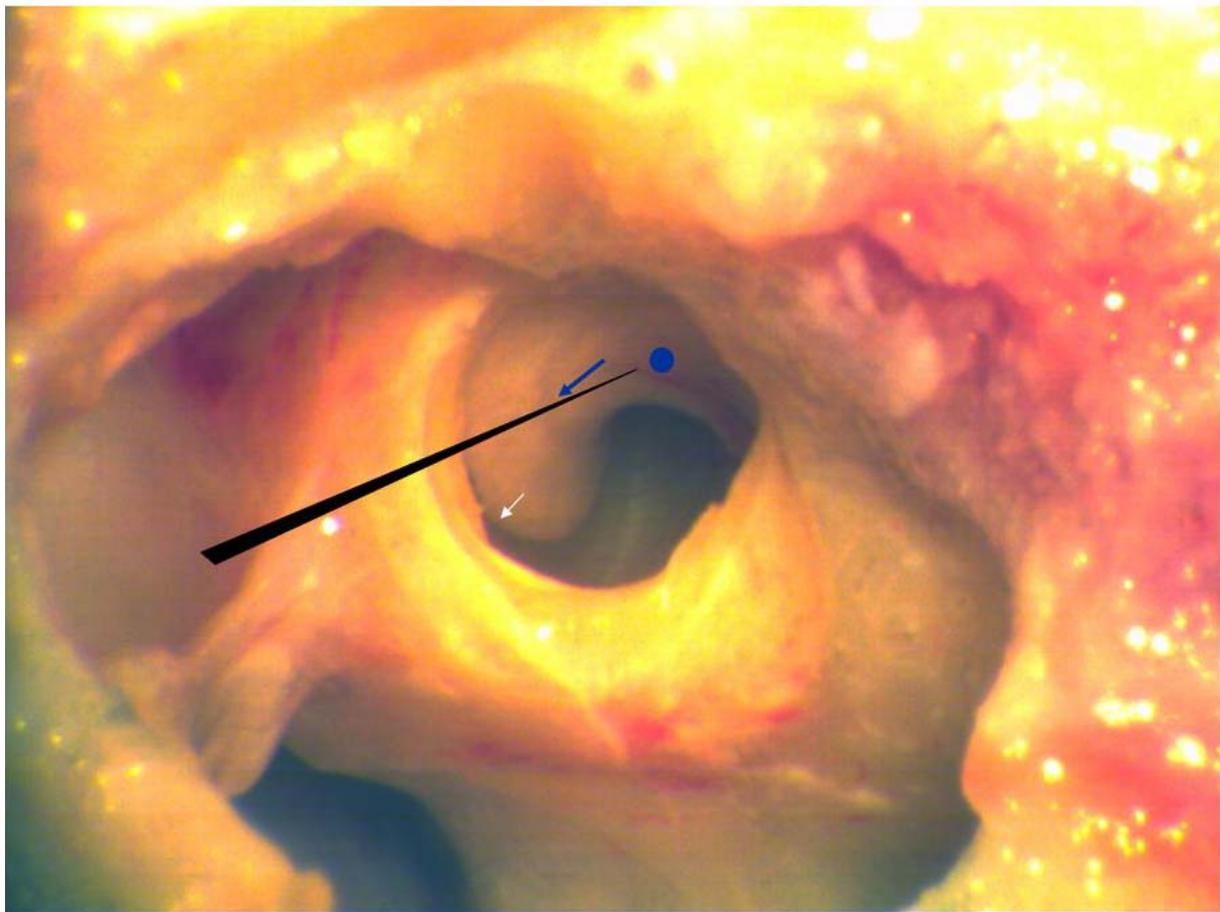


Figure 1. The approach used to insert the intra-neural stimulating array. This view is roughly orthogonal to the round window (center), which was exposed by making a hole in the lateral wall of the bulla. The round window membrane has been removed from the round window, but the round window is otherwise intact. The basilar membrane of the basal half of basal turn can be seen at the white arrow as a dark crescent. The parallel arc of the spiral ganglion can be seen as a dark line in the osseous spiral lamina (blue arrow). The blue circle indicates the location of the hole in the bone of the modiolus through which the intraneural silicon array was inserted. The trajectory of the insertion (black taper) began from slightly below and to the left and proceeded to slightly above to the right of this view.

lowest current levels (as in Fig. 3) activated the recording probe sites located in the deepest half of the ICC, representing the high frequency basal cochlea. At stimulation levels only about 2 dB higher, neural activation spread to encompass the entire tonotopic axis of the ICC, including the representation of apical cochlear sites well away from any of the scala-tympani electrodes. The activation of the apical representation presumably indicates spread of excitation to intra-modiolar

apical fibers passing the basal scala-tympani electrodes. Stimulation of successively more apical scala-tympani electrodes produced only a weak tonotopic trend. Spread of activation was more restricted for BP scala-tympani stimulation (Fig. 4). One can see a tonotopic trend of the most basal electrode activating deepest ICC sites (upper left panel) to more apical electrodes activating sites nearer the center of the ICC (lower left panel). The dynamic range for saturation of firing rates of most neurons in MP and BP scala-tympani stimulation was less than 10 dB.

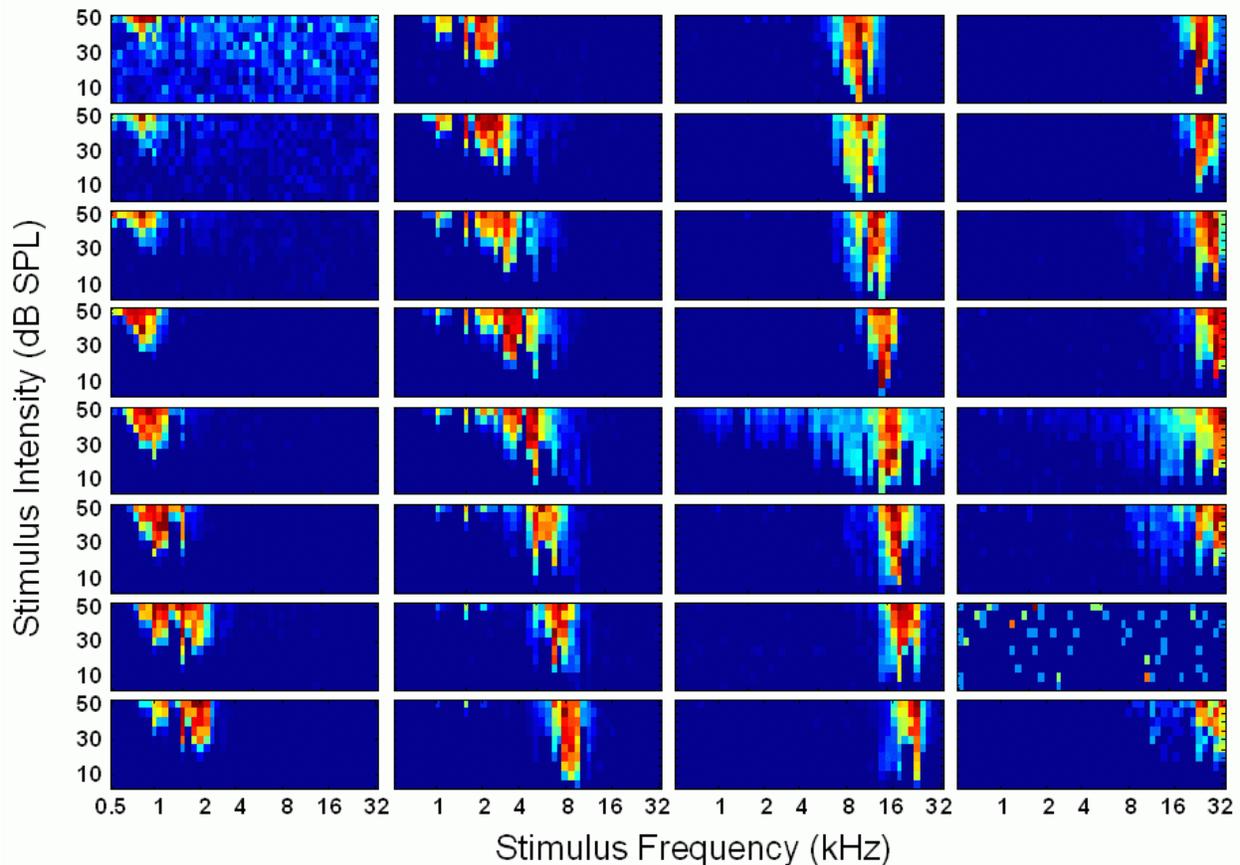


Figure 2. Frequency response maps evoked by tones in normal hearing animals, recorded simultaneously using a 32 channel, single shank recording probe. The maps are arranged column-wise with those recorded from more superficial sites located at the upper left and those from deeper sites on the lower right. Note the progressive shift in the magnitude and threshold of the responses to higher frequencies as sites shift from superficial to deep (down the columns, and across the rows).

Results of stimulation with the intra-neural electrode array reflected the spiral geometry of auditory nerve fibers within the modiolus. Low frequency fibers from the apical turn (which are mapped superficially in the ICC) are found in the center of the intra-modiolar nerve trunk, overlaid first by middle-turn fibers, and then, most peripherally, by high frequency fibers from the cochlear base (mapped to the deep ICC). Examples of spatial tuning curves from MP stimulation of intra-neural arrays are shown in Fig. 5. An intra-neural electrode placement that penetrated little more than 600 μm into the nerve (Fig. 5A, B) resulted in ICC activation

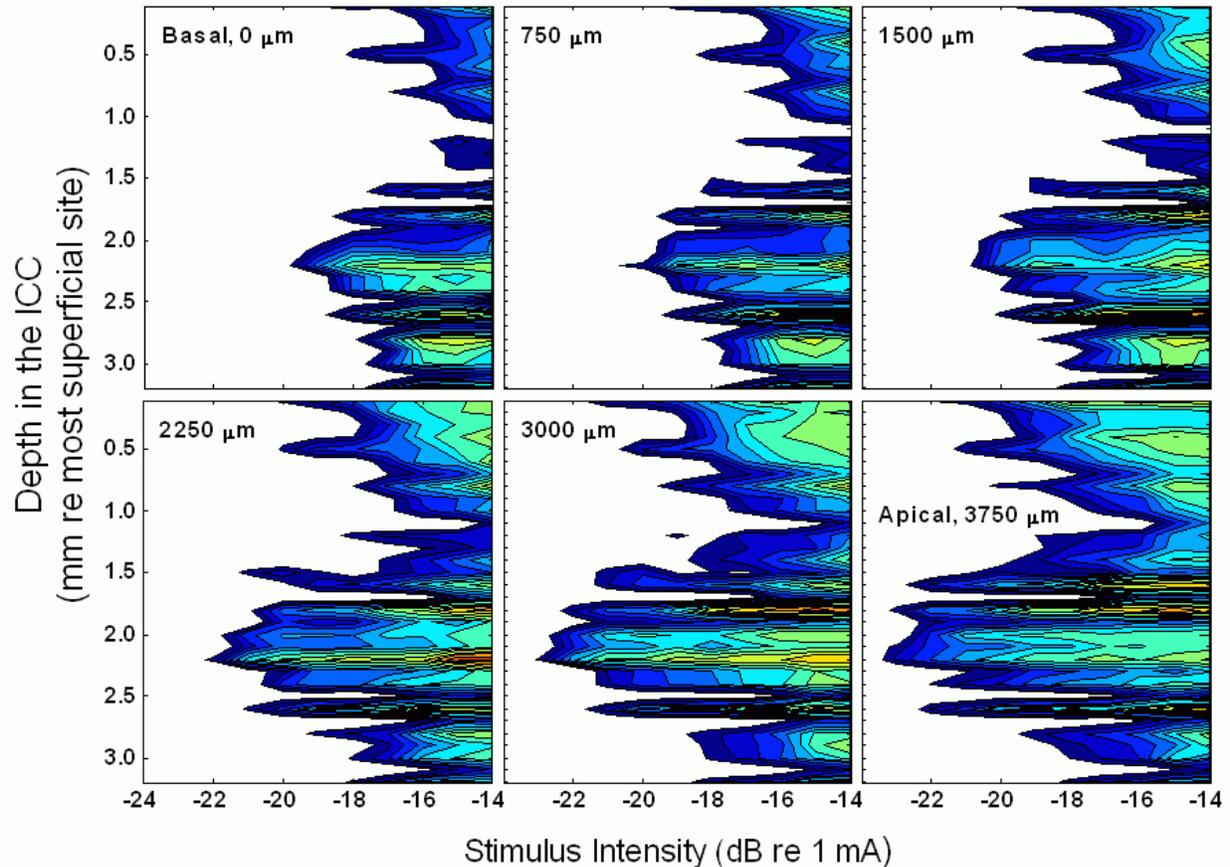


Figure 3. Spatial tuning curves (STCs) evoked by monopolar stimulation using a banded intra-scalar electrode array. In this and subsequent STCs, cumulative d' for activity evoked at progressively deeper ICC recording sites (0= site 1; 3.1 mm= site 32) are plotted on the ordinate and stimulation intensity is plotted on the abscissa. Each panel represents the distribution of activity evoked in the ICC by monopolar stimulation using a progressively more apically located band on the intra-scalar array. Note the broad activation across the tonotopic axis (ordinate) of the activity in each panel. Note also the weak tonotopic progression across the panels from progressively more apically located stimulation bands. Finally, note the progressive shift in threshold for STCs evoked by the basal bands (located in the relatively larger cavity of the basal scala tympani) to those evoked by the apical bands (located in the relatively smaller apical scala).

restricted to the basal (high-frequency) representation. Stimulation at the deepest site in that penetration (Fig. 5A) activated a fairly broad band of the high-frequency representation in the ICC (corresponding to CFs ranging from about 8 to 32 kHz), but that band was constant in width across a nearly 15-dB range of current levels. A stimulation site 200 μm more superficial along the stimulating array (Fig. 5B) produced activation restricted to sites in the ICC with CF sites restricted to around 20-22 kHz. Increasing the current by 7 dB at that site resulted in a spread of activation to the ~8-to-32-kHz band. Based on the high-frequency activation and on *post-mortem* dissection, we infer that this first placement of the stimulating array lay in a branch of the modiolar nerve originating in the most basal portion of the hook region of the cochlea. When the

stimulating array was advanced deeper into the nerve trunk, the most distal stimulating site activated the representation of lowest frequencies in the most superficial ICC sites (Fig. 5C). Stimulation at this location in the auditory nerve across a dynamic range of >12 dB produced activation restricted to the most dorsal ICC recording sites, representing CFs <1 kHz. At the highest current levels in this example, activation eventually spread to the ICC representation of middle-to-basal turn fibers.

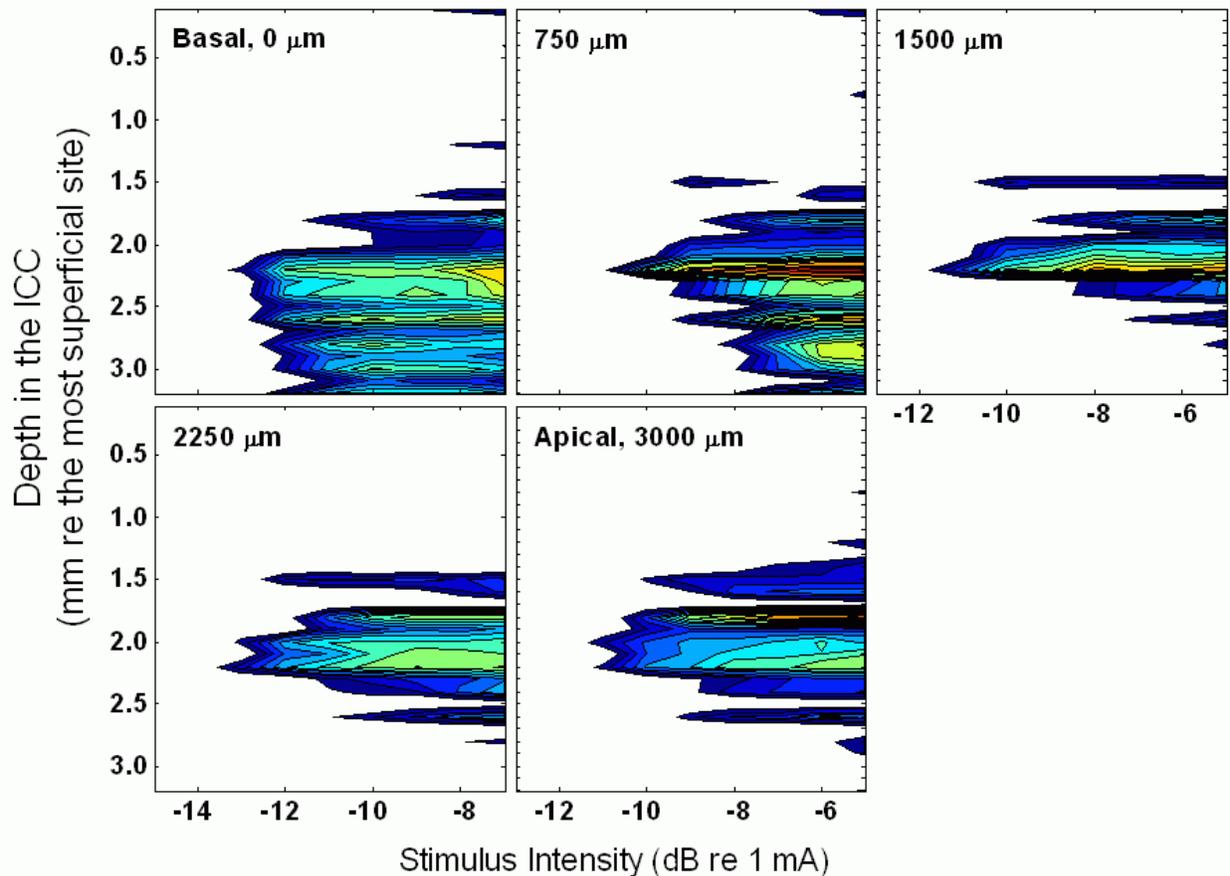


Figure 4. STCs evoked using bipolar stimulation of a banded intra-scalar electrode array. The activity evoked by this bipolar stimulation is restricted to a relatively narrow range of ICC sites arrayed along the tonotopic axis of the ICC. All these bands, which are located in the basal (high frequency) region of the cochlea, evoke activity in the deep, high frequency region of the ICC. In addition, there is a clear tonotopic progression in the ICC location of activity evoked by these bands. More apically located bands evoke activity at more superficial ICC sites tuned to lower frequencies.

Penetrations that spanned 1500 μm depth in the nerve (with stimulation sites at 300 μm intervals) showed a tonotopy that was consistent between the two animals in which useable electrical stimulation data were obtain. The tonotopic relation of intra-neural stimulation sites to locations of ICC activation in one animal is shown in Fig. 6. Stimulation of the distal-most sites in this intra-neural array (Fig. 6A and B), presumably located beyond the central axis of the modiolar nerve, activated the middle-turn (mid-frequency) representation in the ICC. Progressively more proximal sites along this same array moved closer to the central axis of the

nerve and activated more apical (lower frequency) ICC representations, resulting in a dorsal shift in the pattern of ICC activation (Fig. 6C). Eventually, the activation began to spread to basal fibers, resulting in strongly two-lobed spatial tuning curves in the ICC (Fig. 6D). Activation of the most proximal sites along this array (Fig. 6F) produced activation restricted to the basal-turn (high frequency and deepest) ICC representation.

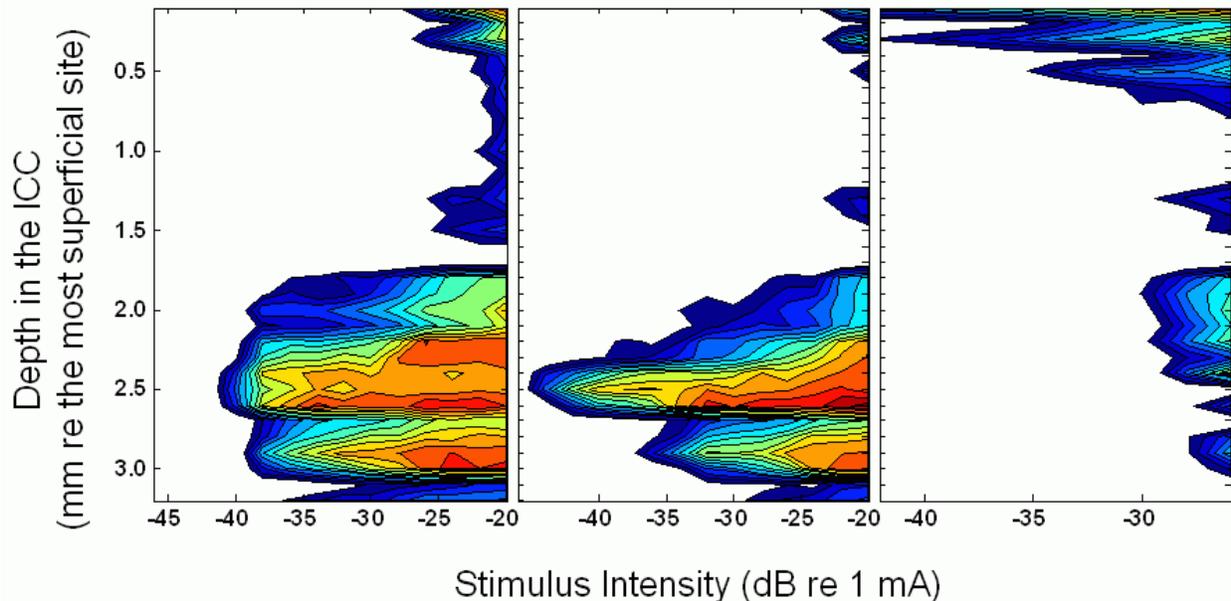


Figure 5. STCs evoked by monopolar stimulation of 3 sites of intra-neural arrays. These STCs evoked by monopolar intra-neural can be compared directly with the STCs evoked by monopolar scala-tympani stimulation, illustrated in Figure 3. The thresholds for the intra-neural STCs are lower and the activation patterns are more restricted than those seen in Fig. 3.

We note the following similarities and differences between scala-tympani and intra-neural stimulation in these early results:

- Thresholds were substantially lower for intra-neural than for scala-tympani stimulation. Monopolar intra-neural thresholds were as much as ~ 30 dB lower than for MP scala-tympani stimulation and as much as ~ 40 dB lower than for BP scala-tympani stimulation.
- Spread of activation by MP intra-neural stimulation was substantially more restricted than for MP scala-tympani stimulation but in many cases comparable to spread of activation from BP scala-tympani stimulation. More-restricted stimulus configurations for intra-neural stimulation will be explored in future experiments.
- The dynamic range from threshold to neural saturation was wider for intra-neural stimulation, roughly 20 dB for intra-neural compared to less than 10 dB for scala-tympani. Those values remain to be substantiated by additional measurements and quantified more precisely. Informally, we have the impression that scala-tympani stimulation provides a much greater dynamic range of levels between threshold and the point at which spread of activation begins to spread widely.
- The tonotopic map of site of intra-neural channel number onto tonotopic place in the ICC is non-monotonic, in keeping with the spiral organization of the auditory nerve. Nevertheless, if

one could unwrap that spiral tonotopy, the tonotopic progression of ICC activation appears more precise than that produced by the banded scala-tympani electrode array that was tested.

- Tonotopically specific stimulation with scala-tympani electrodes was limited to the basal half of the cochlea. In contrast, intra-neural stimulation could produce activation of restricted loci distributed across the entire cochlear spiral, corresponding to frequencies from below 500 Hz up to 32 kHz.

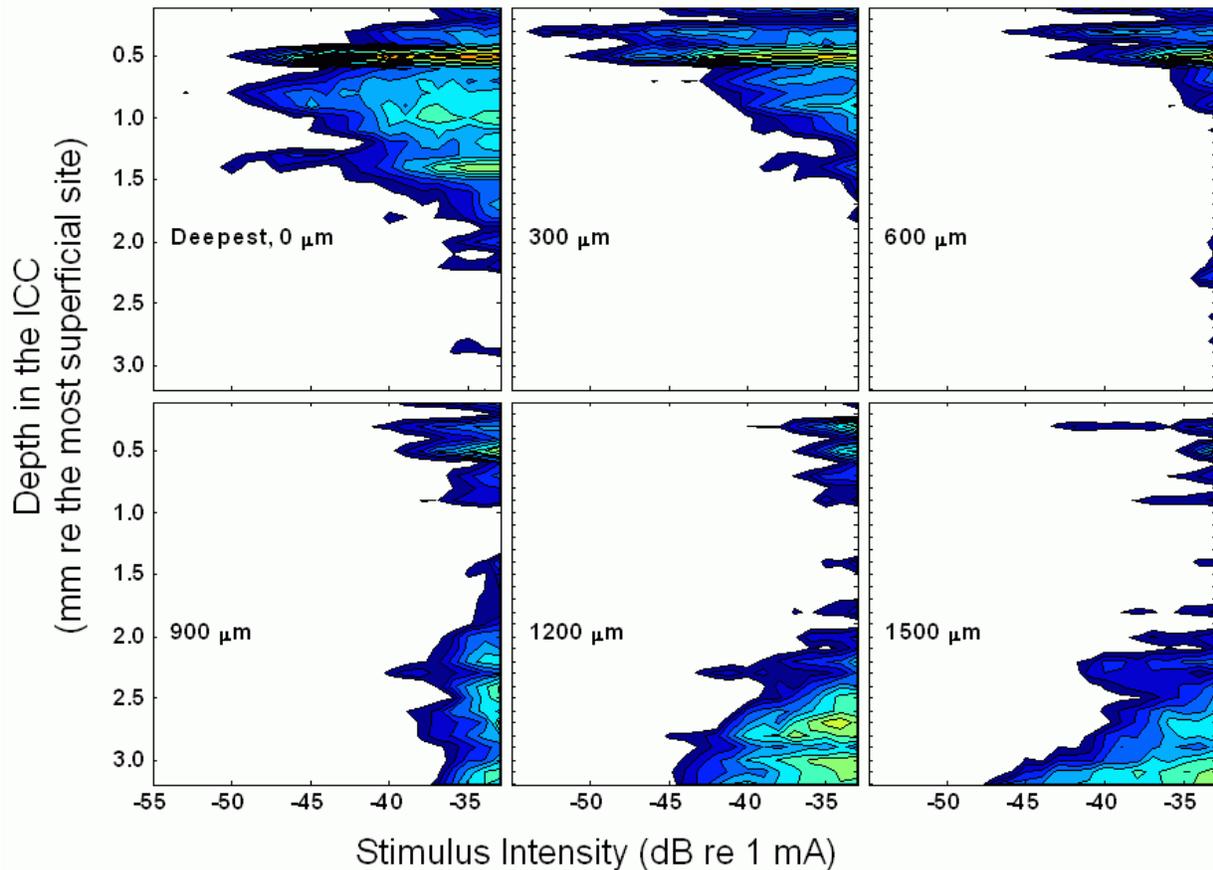


Figure 6. STCs evoked by monopolar activation of six sequential sites distributed along the shaft of a 16 site, single shaft Michigan silicon array. The upper left panel shows activity evoked by activation of the most distal site on the stimulating array and the lower right panel shows the activity evoked by the most proximal site. These six sites are separated by 300 μ . Note that the tonotopic progression of the activity evoked by successive sites is non-monotonic. The evoked activity evoked by activation of the distal-most stimulation site was centered at recording depths sites .8-1.2. Activation of the next two more proximal sites (300 μ & 600 μ) selectively activated lower-frequency (more superficial) regions of the ICC. Activation of successively more proximal sites evoked activity that abruptly shifted to higher frequency ICC (deep) regions.

Interpretation and next steps: We were encouraged by these initial results and plan soon to conduct studies with the same stimulating probe and same approach to the nerve but to extend the experiments by implementing 16-channel stimulation and evaluating more restricted electrode configurations, among other goals. One technical concern that was raised in the Request for Proposal was that electrical artifact propagating from the stimulating electrode to the

recording sites in the ICC would interfere with unit recording. We were successful in entirely rejecting that artifact through use of a fast-recovery head-stage and amplifiers (our custom head-stage and the TDT amplifiers) and use of a sample-and-hold procedure that we programmed into the digital signal processing circuit in the TDT RX5 base unit. A technical difficulty that we did not foresee, however, is that we encountered a sizeable slow-wave component that we tentatively are attributing to a waveform propagated from the auditory brainstem (i.e., like an ABR component). That component interfered with studies of responses to continuous electrical pulse trains. In the initial data set, we were able to eliminate much of that interference off line by averaging across repeated trials to form a template of the interfering wave and then subtracting that template from individual waveforms. In future experiments, we will explore details of reference electrodes, head-stage design, and recording-probe site dimensions that will reduce that slow-wave component early in the recording chain.

4. Plans for next quarter:

- Finish construction and testing of the 16-channel isolated current source and put it into service.
- Upgrade stimulation software to accommodate 16-channel stimulation.
- Enhance local-area network storage and access to large 32-channel data files to facilitate off-line data handling.
- Enhance *in situ* acoustical calibration of tonal stimuli presented through a hollow ear bar.
- Conduct physiological experiments in 2 cats. Experiments will include: (1) enhanced study of tonotopic organization using 16-channel intra-neural stimulation, included exploration of various intra-neural array trajectories; (2) comparison of spread of activation for MP, BP, and tripolar electrode configurations; and (3) evaluation of summation of activation resulting from simultaneous stimulation of two intra-neural electrodes varying in inter-electrode distance.
- Establish the position of the stimulating electrode array relative to auditory-nerve anatomy. After the completion of each of the cat experiments, position a dummy electrode at the location of the stimulating probe, and then perfuse the animal. Post-fix and stain the auditory nerve and the temporal bone with osmium and embed the tissue in plastic.

5. Personnel:

This research is being conducted by John Middlebrooks, principal investigator, with Russell Snyder, co-investigator, as a sub-contractor. James Wiler is the research associate, Chris Ellinger is the engineer, and David Rogers is the computer technician. Post-doctoral fellow Kevin Otto and MD/PhD student Alana Kirby participated in the data collection.