Neuronal Activity Evoked in the Inferior Colliculus of the Cat by Surface Macroelectrodes and Penetrating Microelectrodes Implanted in the Cochlear Nucleus

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Abstract—Persons lacking functional auditory nerves cannot benefit from cochlear implants, but an auditory brainstem implant (ABI) utilizing stimulating electrodes adjacent to or on their cochlear nucleus (CN) can restore some hearing. We are investigating the feasibility of supplementing these surface electrodes with penetrating microstimulating electrodes within the ventral CN (VCN), and how the two types of electrodes can be used synergistically. Multunit neuronal responses evoked by VCN electrical stimulation with surface electrodes and microelectrodes were recorded in the inferior colliculus (ICC) of five cats. The findings are consistent with those from patients with type II neurofibromatosis who received ABIs with both surface and microelectrodes. The patients described percepts from their microelectrodes as more similar to pure tones than those from their surface electrodes, consistent with the greater tonotopic selectivity of microelectrodes in the cats' VCN. Also, the patients describe percepts from their surface electrodes as louder than those from the microelectrodes, while in the cat, the neuronal activity evoked in the ICC by the surface electrodes tended to be greater. This concordance helps to validate our cat model as a means of investigating the synergistic use of surface and penetrating electrodes in a clinical ABI.

Index Terms—Auditory brainstem implant (ABI), auditory prostheses, cats, cochlear nucleus (CN), electrical stimulation, neural prostheses, silicon microprobes.

I. INTRODUCTION

COCHLEAR implants have restored hearing to many tens of thousands of persons with severe hearing loss, but patients lacking a functional auditory nerve cannot benefit from these devices. However, a prosthesis that includes an electrode array implanted in or on the surface of the cochlear nucleus (CN) has restored some hearing to these people. Worldwide, about 700 persons afflicted with type II neurofibromatosis (NF2) have received these auditory brainstem implants (ABIs), as have a smaller number of patients afflicted with severe hearing loss of other etiologies that preclude use of a cochlear implant [1]–[6]. NF2 occurs in about one in 40,000 live births, and these persons typically develop life-threatening vestibular schwannomas on both eighth nerves. Surgical removal of the tumors typically results in total loss of the auditory and vestibular divisions of the eighth nerves. After the tumor has been removed, an array of stimulating electrodes is placed within the lateral recess of the fourth ventricle. While nearly of these people do derive real benefits from their device, there is need for much improvement, particularly for the patients afflicted with NF2, who constitute the largest group of candidates for ABIs and whose perception of speech tends to be significantly poorer that that of users of multichannel cochlear implants. Also, while many patients whose deafness is of etiologies other than NF2 do acquire better speech perception than the NF2 patients, their performance spans a wide range, and typically they require many months or even years for their performance to approach that of users of multichannel cochlear implants [7], [8].

We would expect that the stimulus current from these relatively large surface electrodes would spread quite broadly through the CN, and thus, provide only limited access to the functional topology of the nucleus, including its tonotopic organization. In contrast, penetrating microelectrodes placed within the CN can deliver localized stimulation, and in principle, should allow for more precise and orderly access to the tonotopic organization of the CN [9], [10]. Thus, a neural prosthesis that employs microelectrodes, or a mixture of micro- and macroelectrodes, might provide ABI users with improved hearing. Several groups have investigated microstimulation within the CN in animal models [9]–[19]. In our laboratory, arrays of single iridium microelectrodes have been implanted into the VCN of cats for up to 7 years [15]. Ten persons with NF2 have received implants that include a surface array and an array of microwire penetrating microelectrodes. Their speech perception is not significantly better than that of the NF2 patients who have received only the surface arrays [20]. However, the thresholds of the auditory percepts induced by the penetrating microelectrodes were very stable during the entire postimplant interval (up to 4 years) and the patients did perceive distinct pitch percepts from each microelectrode, so the findings do validate the feasibility of intranuclear microstimulation in humans. However, the experience with these patients has demonstrated the difficulty of accurately inserting a small array of penetrating electrodes into the small human CN, which must be located using often ambiguous landmarks on the surface of the brainstem, whose topology may be distorted after removal of the eighth nerve tumor. Thus, only 14 of 72 penetrating microelectrodes produced auditory percepts, and only two patients had more than two active penetrating microelectrodes (five and four microelectrodes, respectively). This problem might be resolved by employing an
array of many penetrating microelectrodes distributed over a much larger footprint, to ensure that a sufficient number of electrode sites are placed within the central nucleus of the VCN. This strategy could best be implemented using arrays of multisite microelectrodes, which offer the advantage of placing the maximum number of independent stimulating sites into the target nucleus with the minimum number of electrode shanks and thus the minimum risk of tissue injury. Arrays of silicon probes with 16 stimulating sites have been implanted into the VCN of adult cats, for up to 314 days [10]. The thresholds and growth of the compound responses from most of the stimulating sites were very stable over time, and comparable to those of chronically implanted single-site iridium microelectrodes. If penetrating microelectrodes, and specifically multisite silicon-substrate microprobes, are to be used in conjunction with surface electrodes in future ABIs, it is important to better understand how the neurons of the CN are activated by stimulating with these two types of electrodes, and how the two types can be used synergistically.

Three previous studies have compared electrical stimulation of the CN by surface electrodes and multisite silicon-substrate microelectrodes. el-Kashlan et al. [11] used electrophysiological and autoradiographic procedures to investigate the relative effectiveness of stimulation of the VCN by surface and penetrating microelectrodes implanted acutely into the cochlea nucleus of pigmented guinea pigs. They found that the penetrating microelectrodes were able to activate the auditory system at a lower threshold and with a relatively wider dynamic range than the surface electrodes. Liu et al. [17] evaluated surface and penetrating microelectrodes implanted acutely on or within the CN of cats and guinea pigs. For the guinea pigs, their findings were similar to those of el-Kashlan et al. [11]. However, in the cat, the dynamic range of the surface electrodes was slightly greater, although the difference between the two electrode types was not statistically significant. Rosahl et al. [21] compared the thresholds and dynamic ranges of very small (4400 \( \mu \text{m}^2 \)) stimulating electrodes implanted acutely within and on the surface of the cat CN. They found that the threshold of the electrically evoked auditory brainstem response was somewhat higher for the surface electrodes, while the dynamic range of the two types was essentially identical. They suggested that in a clinical ABI, insertion of penetrating CN electrodes can be guided and monitored using some of the same procedures developed for implantation of the surface electrodes.

The purpose of our study was to compare, in the same animals, the neuronal responses evoked in the cat inferior colliculus (ICC) by electrical stimulation with penetrating microelectrodes and surface macroelectrodes implanted chronically in and on the VCN and to determine if the findings are consistent with the percepts reported by the human patients who have received the arrays of surface and penetrating electrodes. The surface electrodes had the same surface areas as those in the clinical ABI. Our broad objective is to develop an animal model that will inform how surface and penetrating electrode can best be used synergistically in an ABI. A specific objective of the present study was to compare the ability of the surface and penetrating microelectrodes to selectively access the tonotopic organization of the VCN. This strategy could best be implemented using arrays of multisite silicon-substrate microelectrodes designed and fabricated by our personnel, using deep reactive-ion etching, which yields thick (75 \( \mu \text{m} \)) mechanically sturdy probes that should be suitable for eventual clinical use [22]. Both array types have 16 microstimulating sites distributed over four penetrating shanks, and the geometric surface area of each site is 2000 \( \mu \text{m}^2 \). For both types of probes, the four electrode sites on each shank are 0.8–1.7 mm below the probe’s transverse spine. To form an array, the spines of two probes are encapsulated in EpoTek 301 epoxy to form the button superstructure. Fig. 1(A) shows a complete array of two probes (4 shanks and 16 electrode sites) extending from the epoxy button superstructure. The arrays also contained two rectangular platinum macroelectrodes with geometric surface areas of approximately 0.4 mm\(^2\) [see Fig. 1(B)], as on the surface array used in the clinical ABI. In our arrays, the macroelectrodes are set between the silicon shanks, which in Fig. 1(B) are oriented toward the camera.

**II. METHODS**

**A. Electrode Arrays**

We implanted arrays of either of two types of multisite silicon-substrate microstimulating electrodes into the cats’ VCN. One type was a modification of the arrays constructed from thin-film “Michigan” probes [10] fabricated at the University of Michigan under the direction of Design Engineer Jamille Hetke, and supplied through NeuroNexus, Inc. The second array type [see Fig. 1(A)] employs multisite silicon-substrate microstimulating microelectrodes designed and fabricated by our personnel, using deep reactive-ion etching, which yields thick (75 \( \mu \text{m} \)) mechanically sturdy probes that should be suitable for eventual clinical use [22]. Both array types have 16 microstimulating sites distributed over four penetrating shanks, and the geometric surface area of each site is 2000 \( \mu \text{m}^2 \). For both types of probes, the four electrode sites on each shank are 0.8–1.7 mm below the probe’s transverse spine. To form an array, the spines of two probes are encapsulated in EpoTek 301 epoxy to form the button superstructure. Fig. 1(A) shows a complete array of two probes (4 shanks and 16 electrode sites) extending from the epoxy button superstructure. The arrays also contained two rectangular platinum macroelectrodes with geometric surface areas of approximately 0.4 mm\(^2\) [see Fig. 1(B)], as on the surface array used in the clinical ABI. In our arrays, the macroelectrodes are set between the silicon shanks, which in Fig. 1(B) are oriented toward the camera.

**B. Surgical Procedures**

The procedure for implanting the array of stimulating electrodes was as described previously [10]. In the modified array used in the present study, one surface electrode rests on the dorsomedial surface of the CN, directly over the dorsal CN and the second surface electrode residing ventral and lateral of the first. The silicon shanks penetrate into the VCN. This is intended to model a clinical ABI in which an array of surface electrodes is placed within the lateral recess of the fourth ventricle, and thus, primarily over the dorsal nucleus, and an array of penetrating electrodes inserted into the ventral nucleus [20].

**C. Recording of Neuronal Responses and Data Analysis**

Recordings from the central nucleus of the ICC were obtained in nonrecovery experiments, conducted in a double-wall
sound isolation booth (Audiometrics 120 A-SP), at 24–136 days after implantation of the stimulating arrays. The cats were anesthetized with isoflurane and oxygen, and their heads fixed in a stereotaxic frame. To facilitate delivery of acoustic stimuli, a hollow ear bar was used in the ear ipsilateral of the chronically implanted stimulating array and contralateral of the ICC from which recordings were made. The other ear bar was solid in order to attenuate acoustic stimuli. The tonotopic organization of the anteroventral and posteroverntal CN is retained in the ICC, wherein the isofrequency laminae are oriented approximately perpendicular to its dorsilateral–ventromedial (DLVM) axis, with low acoustic frequencies represented dorsally and laterally and high frequencies represented ventrally and medi ally [23]–[26]. Shivdasani et al. [19] found in the rat that there was generally good correlation between the electrical and acoust ic mapping of the VCN into the contralateral ICC. We recorded multiunit neuronal activity at 16 recording sites separated by 200 µm and spanning 3 mm along the DLVM axis of ICC, using a multisite silicon-substrate probe fabricated by NeuroNexus, Inc. In each cat, data were collected with the recording array entering the IC from 3 to 5 locations on its dorsal surface. The data presented here are from penetrations entering the dorsolateral surface of the colliculus. At least in the gerbil, this lateral region of the ICC receives tonotopically organized inputs from most of the rostrally projecting brainstem auditory nuclei, including the contralateral ventral and dorsal cochlear nuclei and the lateral and medial superior olives [27], [28]. For each insertion of the recording probe, the representation of acoustic frequencies in the ICC was mapped using acoustic tone bursts of 75 dB sound pressure level, 0.5–35 kHz, and 40 ms in duration with a rise and fall time of 10 ms. These were delivered through a broadband loudspeaker (~±5 dB, 200 Hz–5 kHz). The depth of the recording array was adjusted so that a strong neuronal response to a tone of approximately 5 kHz was maximum at the tenth deepest recording site.

After the acoustic mapping, 1500 controlled-current, biph asic stimulus pulses (150 µs/phase in duration, at 50 pps) were delivered through each of the stimulating microelectrode sites and surface electrodes. For the activated iridium penetrating microelectrodes, the stimulus amplitude ranged from 10 to 30 µA (1.5 to 4.5 nC/phase, and approximately, 75–225 µC/cm²). The stimulus amplitude was limited to 30 µA and 4.5 nC/phase because continuous stimulation in the cat CN for 7 h at a higher amplitude produces significant tissue damage surrounding the microelectrode tips [16]. For the surface electrodes, the range of stimulus amplitudes was 160 to 1200 µA (24–180 nC/phase, and approximately, 6–45 µC/cm²). In some cases, the medial surface electrode induced strong contraction of the cat’s facial musculature even at relatively low amplitudes (<600 µA), and these data were not used. For the platinum surface electrodes, the maximum charge density and charge per phase was within the recommended range for fully reversible charge injection by platinum and well below the threshold for stimulation-induced neural damage in cat cerebral cortex [29], [30]. After completing the data acquisition for all stimulating electrode sites, the recording array in the ICC was retracted by 12 mm. The amount of retraction was adjusted precisely by centering the acoustic response around 5 kHz on the fourth deepest site, and the data acquisition was repeated. Neuronal action potentials were detected offline as events whose amplitude exceeded 2.5 times the rms value of the filtered signal [10]. They were allotted into bins 100 µs in width, yielding 16 poststimulus time (PST) histograms, one for each recording site along the DLVM axis of the ICC. The 16 histograms represent, in PST and depth in the ICC, the MUA evoked by the electrical stimulation in the VCN. Response maps of the MUA in poststimulus time and depth in the ICC were generated from the 16 PST histograms. These maps are analogous to those generated from MUA recorded in the cerebral cortex of the guinea pig by other investigators [31], [32]. Separate maps were generated for the deeper and shallower and shallower positions of the recording array. The time and depth coordinates of the activity centroids were computed as the means, in depth in the ICC and in PST, of the counts of the MUA in the bins comprising the maps. Computation of the centroid can be seriously skewed by low-level MUA that is far removed in depth and time from the maxima of the neuronal response evoked by the stimulus in the VCN. This background activity contributes only a few counts to each histogram bin and thus the centroids were generated only from histograms bins in which the spike count was at least 50% of the “averaged maximum count” (AMC) [31]. The PST histograms’ maxima is well defined by the average of the counts in the four bins (the 400 µs time window) around the bin with the highest count, so we computed this average for each of the 16 histograms and selected the largest of these as the AMC [10].

The amount of neuronal activity induced in the ICC by each of the stimulating electrodes in the contralateral CN was quantified as the number of extracellular spikes from all 16 PST histograms, during 1500 successive presentations of the stimulus pulses (“Total neuronal activity”). As noted previously, separate response maps were generated for deeper and shallower positions of the recording array. In a few instances, the activity evoked from an electrode site in the CN was distributed over both maps, and the total neuronal activity was computed from a contiguous but nonoverlapping set of histograms (maps) from the deeper and shallower acquisitions. This metric for total neuronal activity recognizes that loudness is not well encoded by the activity of individual neurons in the IC [33]. There is evidence that, at least to a first approximation, the percept of loudness is proportional to the total neuronal activity evoked by an acoustic stimulus [34]–[36]. Fig. 2 shows plots of total neuronal activity evoked in the ICC by 40 ms acoustic tone bursts of different frequencies. The data were acquired during 60 successive presentations of the acoustic stimulus at 1 s⁻¹, but in Fig. 2 are rescaled to 1500 presentations, to aid comparison with the data from the electrical stimulation. The sound pressure level was measured using a Bruel & Kjaer 2239 A sound level meter placed at the aperture into the hollow ear bar of the stereotaxic frame, which is certainly somewhat greater than the SPL at the cat’s eardrum. The total neuronal activity recorded in the ICC increases in an approximately linear manner with the decibel SPL, which supports the premise that it represents a neural code for loudness. The low-frequency tone pulses (0.6 kHz) evoked activity that was distributed over a greater range of depth in the
Fig. 2. Total neuronal activity evoked by 40 ms tone bursts of different frequencies, plotted against the total multiunit neuronal activity recorded in the central nucleus of the contralateral ICC. The data were acquired during 60 successive presentations of the acoustic stimulus at 1 s⁻¹, but here are rescaled to 1500 presentations, to aid comparison with the data from the electrical stimulation. The right-hand ordinate scale is for the large response evoked at 0.6 kHz. All data were acquired from a single animal. The sound pressure level was recorded at the aperture of the hollow stereotaxic ear bar. The broad, gray trace is fourth-order regression for all of the data, indicating an overall response threshold of approximately 65 dB.

dorsolateral ICC, which accounts for the greater total neuronal activity.

The spread of neuronal activity in the ICC was quantified as the standard deviation of the distribution of the activity about the centroid, and as such is a commonly used measure of the dispersion of a distribution function, which is designated as “Dispersion of neuronal activity.” Together, the “Total neuronal activity” and “Dispersion of neuronal activity” describe the relation between the neuronal activity induced in the ICC by the simulating electrodes, and the dispersion of this activity across the tonotopic gradient of the ICC. As is the case for acoustic stimuli and intracochlear stimulation, both tonotopic dispersion of neuronal activity and total induced neuronal activity vary with stimulus amplitude [37], and therefore, the dispersion of activity was calculated separately for each stimulus amplitude.

The location of a stimulating electrode’s activity centroid and the dispersion of its activity in the ICC was quite variable when a small amount of neural activity was evoked by the stimulus. Also, the dispersion and total activity metrics are vulnerable to quantization error when the actual dispersion in the ICC is on the order of the spacing of the recording sites in the ICC (200 µm). To control for artifactual expansion of the dispersion metric due to the background neural activity not evoked by the electrical stimulation, the dispersion was computed only from the PST histogram bins in which the activity was at least 20% of the AMC. Second, we accepted only those data for which the CN stimulus induced enough neuronal activity so that the depth of the centroid of the neuronal activity in the ICC did not differ by more than 100 µm from the depth of the centroid evoked by the next largest stimulus amplitude (or next lowest amplitude, in the case of the response to the largest stimulus amplitude).

III. RESULTS

Data were obtained from five cats in which the stimulating array was implanted for 24–136 days. Fig. 3 shows the response maps of the activity evoked in the ICC of cat CN173 by 3 of
the penetrating microelectrodes sites and by the lateral surface electrode of the CN stimulating array depicted in Fig. 3(1). Each map is a composite of contiguous, nonoverlapping segments of two maps acquired at different depths in the ICC, as described in Section II. Maps of the neuronal activity evoked by low amplitude (left column) and higher amplitude (right column) stimulation are shown. The foci of activity evoked by different microelectrode sites were at different depths in the ICC, corresponding to their different positions along its tonotopic gradient. In most instances, the neuronal activity evoked by the microelectrodes was restricted to a single focus or to two foci differing in post-stimulus time but at nearly the same depth in the ICC. However, as the stimulus amplitude was increased, the activity from microelectrode 16 (which was close to the dorsolateral surface of the CN) developed a second focus in the low-frequency region [see Fig. 3(E) and (F)]. In fact, the response evoked by microelectrode 16 at 30 µA resembles that evoked from the lateral surface electrode, which was directly above it.

Fig. 4 shows the dispersion of the neuronal activity evoked from the penetrating and surface electrodes along the tonotopic axis of the ICC, plotted against the total neuronal activity, for five cats. Each microelectrode or surface electrode is represented by multiple identical symbols corresponding to the responses to different stimulus amplitudes, from 10 to 30 µA for the penetrating microelectrodes, and 160 to 600–1200 µA for the surface electrodes. (In some cats, the stimulus current to the medial surface electrode was limited by the onset of strong contractions of the facial musculature.) For both the surface and penetrating electrodes, total evoked neuronal activity and dispersion of activity increased with stimulus amplitude. For three of the five cats (CN165, CN166, and CN168), the dispersion of the neuronal activity in the ICC was similar for the surface and penetrating microelectrodes, when the stimulus amplitude was low (the data points near the left edge of the plots). However, over most of their range of total neuronal activity, most of the microelectrodes produced less dispersion of neuronal activity than the surface electrodes (microelectrode 16 of CN173 being a notable exception). In contrast, the surface electrodes were, in most cases, able to induce more neuronal activity than the microelectrodes, although in cats CN166 and CN168, the medial surface electrodes did induce contractions of the facial muscles and strong electromyographic signals, probably due to current spread into the facial nucleus, which interfered with microelectrode recording in the ICC, and reduced the maximum stimulus amplitude. The human users of ABIs frequently experience “nonauditory responses” from a subset of their surface electrodes, some sufficiently strong so as to render the particular electrode unusable [3].

Fig. 5 shows the total neuronal activity evoked in the ICC from the contralateral CN by 1500 successive presentations of the stimulus pulse, plotted against the dispersion of the evoked neuronal activity along the tonotopic axis of the ICC. The data are for the microelectrode sites from five cats in which neuronal activity was evoked by a stimulus current of 30 µA (4.5 nC/phase) or less. Data were acquired for each electrode site at multiple stimulus amplitudes (10–30 µA for the microelectrodes, 160 to 600–1200 µA for the surface electrodes) and so each stimulating electrode sites is represented by multiple symbols of the same type. In cats CN165 and CN168, the medial surface electrodes induced strong muscle contractions over the upper portion of the range of stimulus amplitude, which interfered with the recording of neuronal activity in the ICC.

Conversely, for the microelectrodes, the maximal charge density and charge per phase (4.5 nC/phase and approximately 225 µC/cm²) reached the threshold for stimulation-induced tissue injury during prolonged stimulation in the cat CN [16].

Fig. 6(A) shows the locations in the ICC of the centroids and the dispersion of activity evoked by the ten CN microelectrode sites that produced responses in the ICC of cat CN173 and by the two surface electrodes in the same animal. Fig. 6(B) shows the equivalent acoustic frequencies of the centroids of the response evoked in the ICC by each of 42 microelectrodes pulsed at 30 µA, and by nine surface electrodes pulsed at 600 µA, from all five cats. The centroids and the dispersions of the neuronal activity of 24 acoustic responses evoked by tone bursts of ~75 dB SPL (at the aperture of the hollow stereotaxic ear bar) are also shown. The equivalent acoustic frequencies of the centroids of the electrically induced responses were determined from the locations of the centroids of the acoustic responses. In a particular cat, these stimulus currents (30 and 600 µA for
Fig. 5. Total multiunit neuronal activity evoked in the ICC from the contralateral CN by the penetrating microelectrodes, and by the surface electrodes, plotted against the stimulus amplitude for the five cats depicted in Fig. 4. The surface electrodes required more current to evoke a comparable amount of neuronal activity but at a much smaller charge density; however, in most cats, they were able to evoke more neuronal activity at the highest stimulus amplitude. Note the different ordinate scales for different animals.

IV. DISCUSSION

The limited, albeit very useful benefits that patients with NF2 derive from the extant ABIs demonstrates the need for improved central auditory prostheses for patients who are not candidates for cochlear implants. At least for the foreseeable future, any ABI that includes penetrating microelectrodes will also include an array of surface electrodes placed within the lateral recess; therefore, it is important to determine how the surface and penetrating electrodes can best be used in synergy. The results from our cat model are consistent with the findings from patients with NF2 who have received both the penetrating and surface electrodes (“PABI patients”), and this concordance helps to validate our cat model as a means of exploring these issues. In particular, the PABI patients tend to describe the percept for the penetrating electrodes as more similar to pure tones than those from the surface electrodes, which is consistent with the greater tonotopic specificity of the penetrating electrodes implanted in the feline CN. The patients also report a greater range of pitch percepts with the penetrating electrodes [20], and they report that the percepts from the surface electrodes tend to be louder than those from the penetrating electrodes, which also is consistent with our findings in the cat that the maximum total neuronal activity evoked in the ICC by the surface electrodes tended to be greater.
Our findings also are consistent with those of other investigators who have reported that the threshold for neuronal activation in the ICC is lower for microstimulation within the CN as compared to stimulation with macroelectrodes on the surface of the nucleus [11], [17]. Shivdasani et al. [19] found that about 20% of their electrode sites in the rat VCN did not induce detectable neuronal activity in the ICC, even in response to a high stimulus amplitude (100 µA). In our study, approximately 50% of the penetrating electrode sites did not induce detectable neuronal activity in the contralateral ICC in response to a stimulus of 30 µA (4.5 nC/phase), in spite our recording arrays having been inserted into the ICC along an axis intended to sample its full tonotopic gradient. A partial explanation for our results may lie in the tracer studies conducted by Benson and Cant (2008) showing that a particular location within the VCN does not project uniformly to all parts of an isofrequency lamina within the ICC. If indeed a penetrating electrode within the VCN produces nonhomogeneous activation of the neurons across an isofrequency stratum in the ICC, this could engender a tendency to underestimate the tonotopic selectivity of the penetrating electrodes. If our recording array does not pass through the location in the ICC at which the stimulating site induced its maximum neuronal activity, we would underestimate the total neuronal activity for that site. Then, in Fig. 4, the data points for that electrode would be shifted toward the left where the dispersion of the neuronal activity tends to be more similar for the surface and penetrating electrodes. The surface electrodes appeared to be less affected by this issue, since we were able to record neuronal activity in the ICC from nine of the ten surface electrodes.

Many of the ICC response maps contain two foci of activity, as illustrated in Fig. 3, by microelectrodes 7, 13, and 16. The simplest explanation for the multiple foci with different latencies after the stimulus pulse is that the electrode was activating more than one neuronal projection to the IC. If the two foci are at very different positions along the tonotopic gradient of the ICC, the dispersion of the activity would be calculated as being very large, as in the case of microelectrode 16 in Figs. 3 and 4. This type of unpredictable activation of the tonotopic gradient of the CN might complicate the use of microelectrodes in a clinical prosthesis. Shivdasani et al. [19] also found that with microstimulation in the VCN of the rat, a significant minority of the electrode sites in the VCN produced activity at positions along the tonotopic gradient of the ICC that did not correspond to what was predicted by acoustic stimulation. However, in our study, the two foci were nearly always the same depth in the ICC, as exemplified by electrodes 13 and 7 in Fig. 3. Microelectrode 16 in cat CN173 was the only instance in the entire study in which a microelectrode activated two foci at very different depths in the ICC.

Fig. 6(B) illustrates the rough parity of the tonotopic specificity of a moderately strong acoustic tone (75 dB SPL at the aperture to the hollow stereotactic ear bar, and approximately 10 dB above response threshold) and that of intracochlear microstimulation at a stimulus amplitude (30 µA) at the upper end of the range used. For electrode sites in the low-frequency (ventral) region of the CN, the first-order regression lines of the microstimulation-induced and acoustically induced responses are nearly superimposed. In all of the cats, the microstimulating sites exhibited greater tonotopic selectivity than the surface electrode only when the total induced neuronal activity was relatively large (see Fig. 4). This is not what would be expected if the surface and microelectrodes were activating neurons deep in the VCN, and thus, at some distance from the surface electrode, whereby we would expect the tonotopic selectivity of the penetrating electrode to be greater than that of the surface electrodes across the entire range of stimulus amplitude. It is notable that the metrics for dispersion and total activity would be vulnerable to quantization error when the actual dispersion in the ICC is on the order of the spacing of the recording sites (200 µm), but there remains the question of how the large surface electrodes are able induce activity in the ICC that spans as little as 200 µm. It is likely that the surface electrodes and the penetrating microelectrodes activated different neuronal pathways from the CN to the IC, and the surface electrodes may have been activating efferent neurons close to the dorsolateral surface of the nucleus. For all of the penetrating and surface electrode sites, the mean latency between the onset of the stimulus pulse and the centroids of the neuronal activity in the ICC was slightly, but significantly greater for the surface electrodes (4.47 ms for the surface electrodes versus 4.08 ms for the penetrating electrodes, *P* < 0.001 in an unpaired *t*-test), suggesting that the surface and penetrating electrodes were activating at least somewhat different projections into the ICC. The dorsal and ventral cochlear nuclei each send tonotopically organized overlapping projections to the ICC [28], [38], [39]. The feline dorsal CN is organized tonotopically, with high acoustic frequencies represented dorsally and laterally, and low frequencies represented ventrally and medially [40]. Takahashi et al. [18] found that microstimulation in both the ventral and dorsal cochlear nuclei of the rat could access the tonotopic organization of the primary auditory cortex, and in fact, the dynamic range was greater for the stimulation in the dorsal nucleus. The neural substrate of this tonotopic organization of the DCN resides immediately beneath our surface electrodes and so could be accessible with reasonably good tonotopic selectivity even by the relatively large electrodes. Numerous modeling and empirical studies have shown that the current density very close to stimulating electrodes is nonuniform [41], and therefore, with a very low-amplitude stimulus for which only neurons that are very close to the electrode would be excited, the excitation might be restricted to a small and highly localized population of DCN neurons. The influence of the spatial nonuniformity of the near field would be expected to be exaggerated if the neuronal excitability is determined by a higher order function of the current density [42], [43]. At intermediate stimulus amplitudes, the spatial profile of the current distribution is proportional to the electrode areas, rendering greater spatial specificity to smaller electrodes [44]. Finally, at very high stimulus amplitudes, and thus, very far from the electrodes, both large and small monopolar electrodes resemble point sources, and thus, the current density in the tissue is determined by the stimulus charge per phase. The relation between tonotopic selectivity and neuronal activation seem in this study, especially for cats CN165, CN166, and CN168 may represent the first two stages of the progression described above. It is
quite possible, however, that the surface electrodes of a clinical prosthesis would not be capable of the relatively high tonotopic selectivity seen in our cat model, since the human CN is overlaid by a thickened glia limitans, and the neurons lie at least 0.5 mm below the surface of the brainstem [45].

In our study, most of the penetrating electrodes did afford better tonotopic selectivity over most of their range of stimulus amplitudes, while most of the surface electrodes induced more neuronal activity without exceeding a charge density that ensures fully reversible charge injection. For the surface electrode, the maximum stimulus current was limited by the onset of muscle contractions, probably due to the spread of the stimulus into the facial nerve or nucleus. Overall, the tonotopic selectivity of the penetrating electrodes was about twice as great as that of the surface electrodes, according to the metric used in this study [see Fig. 6(B)]. This suggests the possibility of developing a sound processing strategy that capitalizes on the superior tonotopic selectivity of the microelectrodes and also on the ability of the surface electrodes to induce more neuronal activity, e.g., a processor that directs the encoded representation of low-level sounds from a particular spectral band to a microelectrode, but which also directs the encoded high-level sounds to a surface electrode with approximately the same center frequency. However, in view of the uncertainties inherent in partitioning the dynamic range of the sound between the penetrating and surface electrodes, it would be advantageous to develop penetrating electrodes that can inject greater charge per phase in order to extend their dynamic range to something approaching that of the surface electrodes. This must be done in a way that does not induce neuronal injury or significant suppression of neuronal activity during prolonged stimulation [14], [16], [46], [47], while also preserving their tonotopic selectivity. It may also be possible to exploit the greater tonotopic selectivity of the penetrating electrodes in order to use compressed analog stimuli rather than pulsatile electrical stimulation. Patients with NF2 exhibit higher modulation detection thresholds (MDT) than do ABI users whose deafness is of other etiologies [7], and the elevated MDT is the only psychoacoustic variable that has been found to distinguish the NF2 ABI users. It is likely that all users of ABIs, including those with NF2, would benefit from a prosthesis that affords improved modulation detection. A pulsatile stimulus interleaved across channels does reduce channel interaction, but is not well suited to access the neural codes for amplitude modulation, which appears to be the synchrony of the action potentials generated by an ensemble of neurons [48], [49]. With relatively low-rate pulsatile stimulus, the neuron’s action potentials will tend to be synchronized with the stimulus pulses rather than with the modulation of the driving signal, a phenomenon that would not be present with analog stimulation.

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REFERENCES


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