Auditory Cortical Responses to Electrical Stimulation of the Inferior Colliculus: Implications for an Auditory Midbrain Implant

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Lim, Hubert H. and David J. Anderson. Auditory cortical responses to electrical stimulation of the inferior colliculus: implications for an auditory midbrain implant. *J Neurophysiol* 96: 975–988, 2006. First published May 24, 2006; doi:10.1152/jn.01112.2005. The success and limitations of cochlear implants (CIs) along with recent advances in deep brain stimulation and neural engineering have motivated the development of a central auditory prosthesis. In this study, we investigated the effects of electrical stimulation of the inferior colliculus central nucleus (ICC) on primary auditory cortex (A1) activity to determine the potential benefits of an auditory midbrain implant (AMI). We recorded multiunit activity in A1 of ketamine-anesthetized guinea pigs in response to single-pulse (200 μs/phase) monopolar stimulation of the ICC using multisite silicon-substrate probes. We then compared measures of threshold, dynamic range, and tonotopic spread of activation for ICC stimulation with that of published data for CI stimulation. Our results showed that compared with cochlear stimulation, ICC stimulation achieved: 1) thresholds about 8 dB lower; 2) dynamic ranges ≥4 dB greater; and 3) more localized, frequency-specific activation, even though frequency specificity was partially lost at higher stimulus levels for low-frequency ICC regions. Our results also showed that stimulation of rostral ICC regions elicited lower thresholds but with greater activation spread along the tonotopic gradient of A1 than did stimulation of more caudal regions. These results suggest that an AMI may improve frequency and level coding with lower energy requirements compared with CIs. However, a trade-off between lower perceptual thresholds and better frequency discrimination may exist that depends on location of stimulation along the caudorostral dimension of the ICC. Overall, this study provides the foundation for future AMI research and development.

**INTRODUCTION**

Many patients suffering from sensorineural hearing loss achieve intelligible speech perception using a cochlear implant (CI) (Rauschecker and Shannon 2002; Skinner et al. 2002; Spelman 1999). However, CIs are ineffective for patients without functioning auditory nerves or implantable cochleae. This includes patients with neurofibromatosis type II (NF2), which is a genetic disease that occurs in about one in 40,000 births (Evans et al. 1992). NF2 patients usually develop bilateral vestibular schwannomas where removal almost always necessitates transection of each auditory nerve. To restore some auditory function, these patients can be implanted with an auditory brain stem implant (ABI), which consists of an electrode array placed on the surface of the cochlear nucleus. The motivation for selecting the cochlear nucleus evolved from the necessity for tumor removal at that site. However, tumor distortions complicate surgical placement of the ABI and it is not uncommon for the electrode array to move after implantation, thus compromising its functionality (Brackmann et al. 1993; Otto et al. 2002; Schwartz et al. 2003; Shannon et al. 1993). Generally these patients achieve performance comparable only to that using single-channel CIs with considerable variability in performance across patients. A penetrating ABI that allows for better alignment along the tonotopic gradient of the cochlear nucleus is currently being investigated. It may provide some improvements in performance, but surgical placement is still complicated by tumor distortions and the inability to directly expose the target site. In addition to NF2 patients, there are also nontumor patients (such as those with auditory nerve avulsion/aplasia, basal skull fracture, cochlear ossification, etc.) who cannot benefit from CIs. Surprisingly, for some nontumor patients, the ABI has been successful in restoring hearing performance levels comparable to the top CI performers (Colletti and Shannon 2005). Colletti and Shannon (2005) proposed that the dramatic difference in performance between NF2 and nontumor ABI patients may be attributed to a tumor-related disruption of neural pathways in the cochlear nucleus that are essential for speech perception. This supports the need for an alternative implantation site that bypasses the cochlear nucleus in NF2 patients. Furthermore, a new implantation site may allow for improvements in hearing performance compared with the ABI (and even the CI) that would justify its use in nontumor deaf patients. Therefore we propose the inferior colliculus central nucleus (ICC) as an alternative site for an auditory prosthesis.

The ICC serves as a critical converging station for virtually every kind of preprocessed auditory information ascending from the brain stem (Aitkin and Phillips 1984; Casseday et al. 2002; Ehret 1997). Thus the ICC should provide access to neural circuits essential for hearing restoration by an auditory prosthesis. The ICC has a highly organized tonotopic structure (Geniec and Moster 1971; Malmierca et al. 1995; Merzenich 1992).
and Reid 1974; Rose et al. 1963; Schreiner and Langner 1997; Serviere et al. 1984; Stiebler and Ehret 1985), which should allow for systematic access to different frequency regions using a penetrating electrode array auditory midbrain implant (AMI). In fact, the AMI should be able to access low-frequency regions (<1 kHz) in the ICC, which is usually not achievable in the cochlea with current CIs. Because the AMI will be in direct contact with ICC neurons, low-stimulation thresholds and localized neural activation should be achievable (Bagshaw and Evans 1976; Jolly et al. 1996; Kral et al. 1998; McIntyre and Grill 2001; Ranck 1975; Ronner et al. 1981). In humans, the inferior colliculus is surgically accessible (Kaku et al. 1999; Simmons et al. 1964). Similar to the ABI surgery in NF2 patients, AMI implantation can be performed after tumor removal with minimal added risk using a lateral supracerebellar infratentorial approach performed through a lateral suboccipital craniotomy (Lenarz et al. 2003, 2004). Using this approach, an AMI array can be inserted along the tonotopic gradient of the ICC. Details and risks associated with this approach will be presented in a future publication. One of the main advantages of AMI over ABI implantation in NF2 patients is that the inferior colliculus and its surrounding structures are relatively undisturbed by the tumors, making it better identified during surgery (T Lenarz and M Lenarz, personal communication) and possibly less affected (functionally) by the tumors (Colletti and Shannon 2005) than the cochlear nucleus. Furthermore, successful stereotactic techniques and implants that have already been developed and safely implemented for deep brain stimulation for tremor and pain suppression could be applied to the AMI (Benabid et al. 2000; Boockvar et al. 2000).

As for the auditory cortex (particularly the primary auditory field within the lateral fissure on the Heschl gyrus) and medial geniculate body (particularly the ventral division associated with the thalamocortical pathway), they may also serve as alternative sites for an auditory prosthesis (Dobelle et al. 1973; Howard et al. 2000; Otto et al. 2005a,b; Penfield and Perot 1963; Rousche et al. 2003; Winer 1984). However, they are located higher along the auditory pathway, resulting in more complex processing and exhibit less-defined tonotopic organizations than the ICC. It is also not yet clear how an electrode array can be positioned along the tonotopic gradient of those regions (e.g., the primary auditory field is deep within the lateral fissure, making access difficult).

To evaluate the ICC as a site for an auditory prosthesis, we assessed the effects of electrical stimulation of the ICC on auditory cortical activity. The concept of an ICC-based auditory prosthesis along with some of our methods and preliminary results was first reported in 2003 in a conference proceeding (Lim and Anderson 2003). As a consequence of the extensive research performed on CIs, we were particularly interested in comparing auditory cortical activity in response to ICC stimulation with that of cochlear stimulation to assess what potential improvements can be achieved by an AMI. Based on the highly tonotopic organization of the ICC and the ability to achieve close contact neural stimulation in the ICC, which is not possible for CIs, we hypothesized that ICC stimulation would achieve lower thresholds, greater dynamic ranges, and more localized, frequency-specific activation than cochlear stimulation. CI studies have shown that speech recognition performance, especially in noisy environments, is correlated with the ability to stimulate a greater number of discriminable frequency channels (Friesen et al. 2001; Shannon et al. 2004) and achieve greater dynamic ranges (Loizou et al. 2000; Zeng and Galvin 1999). Thus the ability of an AMI to achieve more localized, frequency-specific stimulation across a greater range of levels may result in improved performance over CIs.

To test our hypothesis, we placed one multisite silicon-substrate probe along the tonotopic axis of the ICC and another along the tonotopic gradient of the primary auditory cortex (A1) in guinea pigs. We then recorded cortical activity in response to electrical stimulation of different regions within the ICC and compared these results to those of CI stimulation presented by Bierer and Middlebrooks (2002), who used a similar animal model and stimulus parameters (200 μs/phase, single monopolar pulses). Cortical activation patterns in response to CI stimulation were previously characterized by other researchers (Beitel et al. 2000; Raggio and Schreiner 1994, 1999; Vollmer et al. 2001). However, these studies were performed in deafened cats and usually used bipolar stimulation. Therefore we were unable to directly compare our results with the findings presented in those studies. Based on Bierer and Middlebrooks (2002), our results showed that ICC stimulation, as hypothesized, elicits lower thresholds, greater dynamic ranges, and more localized, frequency-specific activation in A1 compared with cochlear stimulation. However, threshold levels and the extent of localized activation may depend on the caudorostral location of stimulation within the ICC.

METHODES

Anesthesia and surgery

Experiments were performed on young pigmented guinea pigs (246–588 g; Elm Hill Breeding Labs, Chelmsford, MA) in accordance with policies of the University of Michigan Committee on the Care and Use of Laboratory Animals. The animals were initially anesthe- sized with an intramuscular injection of ketamine hydrochloride (40 mg/kg) and xylazine (5 mg/kg) with additional supplements to maintain an areflexive state. Atropine sulfate (0.05 mg/kg) was administered periodically to reduce mucus secretions in the airway. Hair was removed from the incision area using animal clippers and each animal was placed into a stereotaxic device (David Kopf Instruments, Tujunga, CA). The animals were covered with a warm-water heating blanket to maintain their rectal temperature at 38.0 ± 0.5°C.

The skull was opened on the right side to expose the auditory cortex and occipital lobe and the dura was removed. Using hydraulic manipulators, silicon-substrate Michigan probes with 16 sputter-deposited iridium sites (Center for Neural Communication Technology, University of Michigan, Ann Arbor, MI (Anderson et al. 1989; Drake et al. 1988; Najafi et al. 1985) were inserted into the ICC and A1 (Fig. 1). The ICC probe had two shanks separated by 500 μm (all distances are center to center) and each shank had eight electrode sites linearly spaced at intervals of 200 μm. Each shank was 15 μm thick, 8 mm long, and tapered in width from 400 μm to a few microns at the tip. Each site had an area of about 400 μm² and an activated impedance of <100 kΩ (at 1 kHz). Activating the ICC sites from iridium to iridium oxide (by cyclic voltammetry) enabled us to use them for both recording and stimulation (Anderson et al. 1989). However, based on the electrochemical charge injection limit for iridium oxide (about 3 mC/cm²) (Beebe and Rose 1988; Weiland and Anderson 2000), we limited stimulation to a maximum current level of 56.2 μA (200 μs/phase pulses). We presented stimulus levels in logarithmic (dB)
steps relative to 1 µA. Thus 56.2 µA corresponded to the maximum stimulus level (35 dB) still within the charge injection limit of 60 µA. The ICC probe was inserted 45° off the sagittal plane through the occipital cortex (not shown in Fig.1A) into the inferior colliculus where one shank was placed rostral to the other. Both shanks were aligned along the tonotopic axis of the ICC (Merzenich and Reid 1974; Schreiner and Langner 1997; Snyder et al. 2004). The A1 probe had eight shanks each separated by 200 µm and each shank had two electrode sites separated by 50 µm. Each shank was 15 µm thick, 1.6 mm long, and tapered in width from 50 µm to a few microns at the tip. Each site had an area of about 400 µm² and an impedance of 1–2 MΩ (at 1 kHz). The A1 probe was inserted approximately perpendicular to the cortical surface where each shank was positioned into a different frequency region in A1 (Redies et al. 1989b; Wallace et al. 2000). The sites were inserted to a depth of about 700–900 µm, which corresponded approximately to layer IV (Wallace et al. 2000) and where we observed the strongest acoustic-driven activity. Because both sites on each shank were located in a similar frequency region, we used the site eliciting greater acoustic-driven activity for data analysis, resulting in a total of eight A1 sites for each animal. For a given experiment, the ICC and A1 probes usually recorded from neurons sensitive to frequencies across a similar 3- to 4-octave range between about 2 and 30 kHz. We were unable to access the entire frequency range in guinea pigs (about 0.05–45 kHz, roughly spanning 3 mm in ICC based on Fig.1E in Malmierca et al. 1995 and 3–4 mm in A1 based on Fig. 3 in Wallace et al. 2000) because of the limited distance spanned by our probe sites (1.4 mm). Thus we spanned a frequency range that allowed us to simultaneously sample reasonably low and high frequencies. After placement of each probe, the brain was covered with agarose to reduce swelling, pulsations, and drying.

Stimulation and recording setup

Experiments were conducted in a sound-attenuating chamber and controlled by a computer interfaced with TDT hardware (Tucker-Davis Technology, Alachua, FL) using custom software written in MATLAB script (The MathWorks, Natick, MA). The TDT-MATLAB system digitally generated both the acoustic and electrical stimuli at a 100-kHz D/A sampling rate (24-bit). For recording, all neural signals were digitized at a sampling rate of 25 kHz (16-bit) and band-pass filtered between 0.3 and 3 kHz.

For acoustic stimulation, sound was presented by a speaker coupled to the left ear through a hollow ear bar. The speaker-ear bar system was calibrated using a 0.25-in. Brüel & Kjaer condenser microphone (Nærum, Denmark) where the tip of the ear bar was inserted into a short plastic tube with the microphone inserted into the other end. The tube represented the ear canal. To aid in the positioning of the probes, varying levels of pure tones and broadband noise that were 50 ms in duration with 5- and 0.5-ms rise/fall ramp times, respectively, were presented to elicit acoustic-driven activity in the contralateral ICC and A1. Poststimulus time histograms (PSTHs) and frequency response maps (FRMs) were then plotted to confirm probe placement in the ICC and A1 (for details, see Data analysis below). Figure 2 shows
leading) from 1 to 56.2.

Antidromic spike activity in layers III and IV of A1. Figure 4 et al. 1987). Thus it is possible that we may have also recorded V can elicit spike activity in layers III and IV of the cortex (Schofield dendritic processes extending from corticotectal cells located in layer visual cortex to the superior colliculus, that antidromically activated responses were contaminated with antidromic spike activity recorded (Mitani and Shimokouchi 1985). Although we attempted to position antidromically activate cortical neurons originating from layer V exist from A1 to ICC and that electrical stimulation within ICC can decreasing in first spike latency as the stimulus level was increased. In spikes between 0 and 2 ms except at very high stimulus recorded on each A1 site, which resulted in the elimination of all electrical stimulation in the ICC, we removed the stimulus artifact (timestamp) of the largest peak (positive or negative) of that spike. We a spike and an algorithm was used to determine the time of occurrence SD of the background (without spikes) neural signal was detected as acoustic or electrical stimulation. Any value exceeding 3.5 times the detected as a spike and an algorithm was used to determine the time of occurrence (timestamp) of the largest peak (positive or negative) of that spike. We then displayed these spike timestamps as PSTHs across 40 trials. For electrical stimulation in the ICC, we removed the stimulus artifact recorded on each A1 site, which resulted in the elimination of all spikes between 0 and 2 ms from stimulus onset. Based on visual inspection of the PSTHs, we did not observe stimulus-driven spike activity with latencies as short as 2 ms except at very high stimulus levels where spike latencies began to approach 2 ms.

In general, as shown in Fig. 3, ICC stimulation elicited an onset response in A1 that increased in spike rate and duration while decreasing in first spike latency as the stimulus level was increased. In some of the responses, antidromic spike activity was also observed. Anatomical studies (Feliciano and Potashner 1995; Winer 2005; Winer et al. 1998) showed that monosynaptic corticofugal projections exist from A1 to ICC and that electrical stimulation within ICC can antidromically activate cortical neurons originating from layer V (Mitani and Shimokouchi 1985). Although we attempted to position our recording sites in layer IV of A1, it is possible that some of our responses were contaminated with antidromic spike activity recorded from layer V. There is also evidence, at least for projections from the visual cortex to the superior colliculus, that antidromically activated dendritic processes extending from corticocortical cells located in layer V can elicit spike activity in layers III and IV of the cortex (Schofield et al. 1987). Thus it is possible that we may have also recorded antidromic spike activity in layers III and IV of A1. Figure 4A shows an example of an orthodromic A1 response preceded by an antidromic PSTH peak with a more magnified view in Fig. 4B. The short latency and precisely stimulus locked nature of the antidromic PSTH peak is characteristic of antidromic activity. Furthermore, previous studies showed that orthodromic activity from the ICC to A1 (through the thalamus) cannot follow pulse rates >100 pulses/s, whereas antidromic activity can follow pulse rates significantly >100 pulses/s (Mitani and Shimokouchi 1985; Rose and Metherate 2001). Figure 4C presents an example where the orthodromic onset response was rapidly diminished by the third pulse, whereas the antidromic spike activity robustly followed a pulse train of 120 pulses/s. All the short-latency, robustly timed PSTH peaks we tested could follow pulse rates >100 pulses/s. Thus we eliminated these antidromic spikes from our data set before performing further analysis. If there are A1 output neurons that project to both the ICC and other A1 regions, then it is possible that indirect antidromic spikes resulting from antidromically stimulated axon collaterals activating other A1 neurons were present in our recordings. We were unable to distinguish the indirect antidromic spikes (if they existed) from the orthodromic spikes. Refractory effects elicited in antidromically activated cortical neurons that could alter orthodromic activation in these same neurons may also have been present. We did not attempt to eliminate these indirect and refractory antidromic effects because they will contribute to the overall percept elicited by ICC stimulation and should be included in our analysis to more accurately assess the potential effects of an AMI.

Below, we present our methods for calculating the various parameters used in this paper. For analysis, we used a total of eight A1 sites (one site from each shank) aligned along the tonotopic gradient of A1 for each animal. Because the ICC probe had two shanks each with eight sites aligned along the tonotopic axis of the ICC, a maximum of two separate ICC tonotopic placements were available for analysis in each animal. Initially, we recorded and characterized the acoustically driven response patterns for each site. We then recorded the neural activity on all eight A1 sites in response to electrical stimulation (single pulses) of each site along a given ICC shank.

**Data analysis**

All analysis was performed on multiunit activity in response to acoustic or electrical stimulation. Any value exceeding 3.5 times the SD of the background (without spikes) neural signal was detected as a spike and an algorithm was used to determine the time of occurrence (timestamp) of the largest peak (positive or negative) of that spike. We then displayed these spike timestamps as PSTHs across 40 trials. For electrical stimulation in the ICC, we removed the stimulus artifact recorded on each A1 site, which resulted in the elimination of all spikes between 0 and 2 ms from stimulus onset. Based on visual inspection of the PSTHs, we did not observe stimulus-driven spike activity with latencies as short as 2 ms except at very high stimulus levels where spike latencies began to approach 2 ms.

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**DRIVEN SPIKE RATE.** The driven spike rate was taken as the total spike rate minus the spontaneous spike rate and was calculated from the PSTHs for a set time window. This window was selected based on visual assessment of all the PSTHs (compared with the spontaneous PSTHs where no stimulus was presented) and what has been used for other ICC (Snyder et al. 2004; Syka et al. 2000) and A1 (Arenberg et al. 2000; Bierer and Middlebrooks 2002) recording studies. For acoustic stimulation where the stimulus duration was 50 ms, we used 100 pulses/s. Thus we eliminated these antidromic spikes from our data set before performing further analysis. If there are A1 output neurons that project to both the ICC and other A1 regions, then it is possible that indirect antidromic spikes resulting from antidromically stimulated axon collaterals activating other A1 neurons were present in our recordings. We were unable to distinguish the indirect antidromic spikes (if they existed) from the orthodromic spikes. Refractory effects elicited in antidromically activated cortical neurons that could alter orthodromic activation in these same neurons may also have been present. We did not attempt to eliminate these indirect and refractory antidromic effects because they will contribute to the overall percept elicited by ICC stimulation and should be included in our analysis to more accurately assess the potential effects of an AMI.
ELECTRICAL THRESHOLD. The threshold was calculated from the BEST FREQUENCY (BF). Pure tones varying in frequency (2–30 kHz, onset activity (Figs. 3 and 4) and is consistent with what Bierer and Middlebrooks (2002) used for their CI-stimulated A1 responses.

BEST FREQUENCY (BF). Pure tones varying in frequency (2–30 kHz, 8 steps/octave) and level (0–70 dB SPL, 10 dB steps) were each presented for four trials all in a randomized sequence at 1/s. For each recording site, we calculated the normalized driven spike rate in response to each stimulus and plotted an appropriate FRM (Fig. 2). Figure 5 displays an example of a denoised FRM where any value <3.1 times the SD of the spontaneous spike rate was set to zero. From this denoised FRM, we visually obtained the threshold and bandwidth at 10 dB above threshold (BW10). We then calculated the BF by taking the centroid of activity across BW10. Because the aim of this study was to assess the tonotopic mappings from ICC to A1, it was important to ensure that the BF of each site did not significantly shift over time. Thus we obtained a BF for each site at the beginning and at the end of each experiment. Only animals with BF shifts <1/8-octave (the FRM frequency bin resolution) for all sites were used for data analysis. All results presented in this paper use the average of the two BFs obtained for each site.

ELECTRICAL THRESHOLD. The threshold was calculated from the neural response recorded on each A1 site in response to stimulation of an ICC site using a mathematical framework based on signal detection theory (SDT) (Britten et al. 1992; Green and Swets 1966). In particular, we used a method similar to that described by Britten et al. (1992) to plot receiver operating characteristic (ROC) curves from trial-by-trial spike rates for the “stimulus” and the “no-stimulus” case for different stimulation levels. By adjusting a criterion spike rate level, we were able to obtain the percentage of “stimulus” trials exceeding that criterion (correct hits) and that of “no-stimulus” trials (false alarms) and plotted these values for varying criterion levels to obtain an ROC curve. Spike rates were computed within a window 2 to 30 ms from stimulus onset or, in the case of no stimulus, a 28-ms window from the spontaneous data. Based on this framework, the area under the ROC curve corresponded to the performance level (or percentage correct, PC) of an ideal observer detecting a stimulus based on the measured spike rates in a two-alternative-force-choice paradigm. After computing the area of each ROC curve, we were able to plot PC as a function of stimulus level (neurometric curve), which ranged from 0.5 (chance) to 1 (perfect detection). These curves were interpolated for analysis. For our method, we defined electrical threshold as the stimulus level corresponding to a PC equal to 0.76. This value was selected because it corresponds to a discrimination index (d') equal to 1 if we assume that the trial-by-trial spike rates for the “stimulus” and “no-stimulus” case follow equal-variance normal distributions. This SDT procedure gives a conservative estimate of threshold in that it estimates the level at which a stimulus-driven response can be detected on single trials. Often, an increase in across-trial mean spike rate could be observed at current levels a few decibels lower than the SDT-derived threshold, as shown in Fig. 3.

DYNAMIC RANGE. To compare our dynamic ranges with those of cochlear stimulation, we used a method similar to that presented by Bierer and Middlebrooks (2002). Dynamic range was calculated in that study by taking the difference between the stimulus levels corresponding to 0.75 and 0.25 of the saturated (maximum) spike rate recorded on the lowest-threshold A1 site in response to a stimulated cochlear site. For our study, we were unable to achieve saturated spike rates in A1 with most of our stimulated ICC sites because we could not stimulate at >56.2 μA. Thus we used the maximum unsaturated spike rate to calculate the dynamic range. As a result, our dynamic ranges represented lower estimates because the dynamic range actually increases as the maximum spike rate increases (up to saturation).

IMAGE WIDTH. The method for computing the extent of activation spread along the tonotopic gradient of A1 in response to ICC stimulation was also taken from Bierer and Middlebrooks (2002) to allow for comparison with cochlear stimulation results. We computed rate-level functions for all eight A1 recording sites in response to stimulation of a given ICC site. These eight sites were linearly spaced (0.2-mm intervals) along the tonotopic gradient of A1. For each A1 site, we normalized the rate-level function by the maximum driven spike rate obtained for that A1 site across all ICC stimulation sites and current levels to emphasize stimulus-driven activity relative to the maximum amount of activity that could be elicited on that A1 site. From the eight normalized rate-level functions that each corresponded to a different cortical place, we calculated the area under the plot of normalized spike rate versus cortical place (in mm) for a given stimulus level. We then divided this area by the maximum normalized spike rate for that stimulus level. The result was the width of a rectangle of unit height with area equal to the area under the normalized spike rate versus cortical place curve. We plotted these image widths versus stimulus level relative to the lowest threshold observed across all eight A1 sites (see Fig. 9 for examples). These curves were interpolated for further analysis. A1 image widths provided a consistent measure for activation spread along the tonotopic gradient of A1 in response to ICC stimulation. For some cases, the activation spread extended beyond the length of our recording probe, causing an underestimation of the true image width. However, these truncated image width curves still showed characteristics similar to those of the normal curves.

RESULTS

All analyses are based on data obtained from six animals. In five of the six animals, we recorded cortical activity in response to electrical stimulation of sites along both ICC shanks. For one animal, we had valid data for only one of the ICC shanks. Thus cortical recordings in response to stimulation of 88 different ICC sites (11 total ICC shank placements, eight sites per shank) were available for data analysis. For each stimulated ICC site, we recorded the corresponding neural activity on eight sites aligned along the tonotopic gradient of A1.

Stimulation thresholds

Thresholds were calculated from the responses recorded on the A1 sites with the closest BF to the stimulated ICC sites and are presented in Fig. 6A. The mean threshold for this BF-aligned analysis was 34.1 μA (SD 17.4). This was based on 79 ICC sites. Stimulation of the remaining nine sites, even at the
The lowest threshold site was 31.2 dB. Some A1 sites with BF different from the BF closest to the stimulated ICC site should have the lowest threshold. Howev-
er, this was not always the case (see Tonotopic mapping below). Some A1 sites with BF different from the closest BF value exhibited the lowest threshold. The mean threshold for these lowest threshold sites was 31.2 μA (SD 17.3) (Fig. 6B). This was based on 80 ICC sites where the remaining eight sites had thresholds 2 dB above 56.2 μA. Even if all nine sites had thresholds 2 dB above 56.2 μA, the mean threshold including these sites would still only be about 38 μA.

Ideally if a perfect point-to-point tonotopic mapping between ICC to A1 exists, the A1 site with the BF closest to the stimulated ICC site should have the lowest threshold. However, this was not always the case (see Tonotopic mapping below). Some A1 sites with BF different from the closest BF value exhibited the lowest threshold. The mean threshold for these lowest threshold sites was 31.2 μA (SD 17.3) (Fig. 6B). This was based on 80 ICC sites where the remaining eight sites had thresholds slightly >56.2 μA.

We compared our ICC stimulation thresholds to those obtained for cochlear stimulation to demonstrate that ICC stimulation achieves lower thresholds. Using similar stimulation parameters (200 μS/phase single pulses) and A1 recordings in a guinea pig model, Bierer and Middlebrooks (2002) obtained a median threshold for cochlear stimulation of 67.2 μA (5th percentile: 37.8 μA, 25th: 53.3, 75th: 75.4, 95th: 119.4). Their thresholds were calculated by taking the stimulus level corresponding to 0.25 of the saturated (maximum) driven spike rate for their lowest threshold A1 sites. We were not able to use this method for comparison because 91% of the rate-level functions corresponding to our lowest threshold A1 sites were nonsaturating. Nevertheless, we were still able to compare our ICC stimulation thresholds with their cochlear stimulation thresholds. Bierer and Middlebrooks (2002) showed that cochlear stimulation exhibited very steep rate-level functions with dynamic ranges usually <2 dB. As a result, using our threshold calculation method for their cochlear data would not have caused significant deviations from their median value of 67.2 μA. For the lowest threshold A1 sites, the median threshold for ICC stimulation was 26.2 μA (5th percentile: 12.0 μA, 25th: 18.8, 75th: 32.0, 95th: 47.7), which was even less than the lower 5th percentile threshold for cochlear stimulation. Discrepancies caused by using different threshold calculation methods or not including some slightly higher threshold sites are minor compared with this 8-dB decrease in median threshold.

Dynamic ranges

We calculated the dynamic range from the neural activity recorded on the lowest threshold A1 site for each stimulated ICC site and obtained a mean dynamic range of 5.2 dB (SD 2.3). This was based on 80 ICC sites where the remaining eight sites did not have sufficiently low stimulation thresholds to perform this analysis. The mean dynamic range for cochlear stimulation was 1.1 dB (SD 0.6). As explained in Methods, our dynamic ranges for ICC stimulation were lower estimates. Thus ICC stimulation achieved a mean dynamic range that was ≈4 dB greater than that achieved by cochlear stimulation.

Tonotopic mapping

As shown in Fig. 7, frequency-specific stimulation was achievable in the ICC. Electrical stimulation of a low BF region in ICC elicited activity in a similar low BF region within A1, whereas stimulation of a higher BF region in ICC elicited activity in a higher BF region within A1. As the stimulus level decreased by 10.2 dB, mean rate across 40 trials where any values less than or equal to 3 means any values less than or equal to 3 were set to white and any values greater than or equal to 30 were set to black to allow for better visualization of the responses.

FIG. 6. A: electrical thresholds for neural activation on A1 sites with the closest BF to the stimulated ICC sites (n = 79). B: electrical thresholds for neural activation on A1 sites with the lowest threshold for the stimulated ICC sites (n = 80). Stimulation of some sites had thresholds greater than our maximum level of 56.2 μA.

FIG. 7. Interpolated multisite poststimulus time histograms (M-PSTHs) for 2 different stimulus levels (in decibels) above threshold. For each stimulus level, 8 M-PSTHs are presented. Each M-PSTH represents one ICC site located along a single shank and is labeled on top with the site number and BF as well as the stimulation threshold for that ICC site. Site number corresponds to location along an ICC shank where site #1 (lowest BF site) is furthest from the shank tip. For a given M-PSTH, ordinate corresponds to the recording location (in millimeters) in A1. Each labeled location corresponds to a recording site in A1 (and BF) and is the distance from the lowest BF site. Abscissa corresponds to the time from stimulus onset that spike activity occurs on each A1 site. Color scale corresponds to total spike rate across 40 trials where <3 means any values less than or equal to 3 were set to white and >30 means any values greater than or equal to 30 were set to black to allow for better visualization of the responses.
increased, the total spike rate and extent of activation spread in A1 gradually increased. Even at 5 dB above threshold (Fig. 7B), cortical activity usually did not spread across the entire electrode array as was observed for cochlear stimulation for stimulus levels just a few decibels above threshold (see next section). One interesting observation from Fig. 7 is that for stimulation of the low BF ICC sites (particularly #1–3), neural activity extended from a low BF region into higher BF regions in A1 somewhat in a discontinuous pattern as the stimulus level was increased above threshold. This pattern of activity for low BF ICC sites was observed in some of the other animals.

To provide a more quantitative assessment of the tonotopic mapping between the ICC and A1, we plotted the BF of the A1 site with the lowest threshold for a stimulated ICC site against the BF of that ICC site (Fig. 8A). Only 80 ICC sites are shown because stimulation of the remaining eight sites did not have valid thresholds. Perfect mapping is depicted by the diagonal line in which stimulation of an ICC site causes activity with the lowest threshold on an A1 site with the same BF. However, because perfect BF alignment between the ICC and A1 sites was not always possible because of the set geometry of the electrode sites, we represented the closest possible BF alignment with dots. Stimulation of 45% (dots) of the ICC sites elicited spike activity with the lowest threshold on A1 sites with the closest BF. Stimulation of 42.5% (circles) of the ICC sites elicited the lowest thresholds on A1 sites with BFs that were still only one or two sites away from the closest BF site. The fact that almost 90% of all the stimulated ICC sites elicited the lowest threshold on an A1 site with an approximately similar BF demonstrates the frequency-specific nature of ICC stimulation. In some cases (12.5%; triangles and pluses), ICC stimulation caused the lowest threshold of activation on an A1 site that had a BF quite different from that of the stimulated ICC site. Possible explanations include the activation of passing fibers or the existence of some neural connections across frequency layers (see DISCUSSION). For the edge BFs (approaching 2 or 32 kHz along the abscissa), the points began to plateau and deviate from the diagonal line. This is explained by the fact that the BF range for a given ICC shank usually spanned a greater frequency range than the A1 sites. Therefore in a given animal, the A1 site with lowest or highest BF value tended to be mapped to all the ICC sites that had lower or higher BF values, respectively.

Although frequency-specific ICC stimulation was achievable at threshold levels, we were also interested in determining whether this specificity was maintained for higher stimulus levels. For Fig. 8B, we took each of the eight A1 sites for a given ICC shank placement and determined the BF of the ICC site that elicited the maximum driven activity on that A1 site. Because there were 11 ICC shank placements, we had a total of 88 A1 sites. We then plotted the BF of the stimulated ICC site that caused the maximum driven activity on an A1 recording site against the BF of that A1 site. Maximum driven activity corresponded to the largest driven spike rate value recorded on a given A1 site across all stimulated sites and current levels. Note that the axes are reversed compared with Fig. 8A to emphasize that for a given A1 site, we selected one ICC site across eight total stimulated ICC sites. About 44% (dots) of the A1 sites reached their maximum driven activity in response to stimulation of the ICC site with the closest BF and about 24% (circles) of the A1 sites reached maximum driven activity in response to stimulation of the ICC site that was still only one or two sites away from the closest BF site. Thus ICC stimulation at higher levels achieved frequency-specific activation, although less robustly than stimulation at lower levels. About 32% (vs. the 12.5% for thresholds in Fig. 8A, triangles and pluses) of the A1 sites reached maximum driven activity in response to stimulation of the ICC site that was more than two sites away. It is possible that stimulation with higher levels may cause inhomogeneous spread of current and activation throughout the ICC that may activate passing fibers as well as distant neurons in a more complicated pattern. One interesting observation is that most of the points in Fig. 8B representing distant BF sites are located in the bottom right corner of the plot corresponding to a low BF ICC site-high BF A1 site region. Possible explanations for this result are presented in the DISCUSSION. Overall, Fig. 8 demonstrates that frequency-specific mapping, for the most part, is achievable in the ICC at threshold levels as well as higher stimulus levels.

Cortical spread of activation

We calculated A1 image width to quantify the extent of activation spread along the tonotopic gradient of A1 in response to ICC stimulation and compared these results to that of cochlear stimulation. Figure 9 presents several image width curves as a function of stimulus level relative to threshold for cochlear stimulation. For Fig. 9, we used the method of Oden (1976) to estimate the BF ICC site was observed in some of the other animals.

To provide a more quantitative assessment of the tonotopic mapping between the ICC and A1, we plotted the BF of the A1 site with the lowest threshold for a stimulated ICC site against the BF of that ICC site (Fig. 8A). Only 80 ICC sites are shown because stimulation of the remaining eight sites did not have valid thresholds. Perfect mapping is depicted by the diagonal line in which stimulation of an ICC site causes activity with the lowest threshold on an A1 site with the same BF. However, because perfect BF alignment between the ICC and A1 sites was not always possible because of the set geometry of the electrode sites, we represented the closest possible BF alignment with dots. Stimulation of 45% (dots) of the ICC sites elicited spike activity with the lowest threshold on A1 sites with the closest BF. Stimulation of 42.5% (circles) of the ICC sites elicited the lowest thresholds on A1 sites with BFs that were still only one or two sites away from the closest BF site. The fact that almost 90% of all the stimulated ICC sites elicited the lowest threshold on an A1 site with an approximately similar BF demonstrates the frequency-specific nature of ICC stimulation. In some cases (12.5%; triangles and pluses), ICC stimulation caused the lowest threshold of activation on an A1 site that had a BF quite different from that of the stimulated ICC site. Possible explanations include the activation of passing fibers or the existence of some neural connections across frequency layers (see DISCUSSION). For the edge BFs (approaching 2 or 32 kHz along the abscissa), the points began to plateau and deviate from the diagonal line. This is explained by the fact that the BF range for a given ICC shank usually spanned a greater frequency range than the A1 sites. Therefore in a given animal, the A1 site with lowest or highest BF value tended to be mapped to all the ICC sites that had lower or higher BF values, respectively.

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Cortical spread of activation

We calculated A1 image width to quantify the extent of activation spread along the tonotopic gradient of A1 in response to ICC stimulation and compared these results to that of cochlear stimulation. Figure 9 presents several image width curves as a function of stimulus level relative to threshold for ICC stimulation and a typical cochlear image width curve that was presented by Bierer and Middlebrooks (2002). ICC stimulation usually elicited spread of activation along the tonotopic
Cortical Spread of Activation

FIG. 9. A1 image width curves plotted as a function of stimulus level relative to threshold (in decibels). A typical cochlear image width curve was obtained from Bierer and Middlebrooks (2002), scaled appropriately to match the ordinate and abscissa scales presented in this figure, and plotted for direct comparison with several ICC image width curves.

gradient of A1 that gradually increased with stimulus level. However, cochlear stimulation elicited activity that spread across the entire electrode array within a few decibels above threshold. About 91% of our ICC image width curves exhibited less activation spread than achieved by cochlear stimulation. This is based on 78 ICC sites where the remaining 10 sites had thresholds that were too high to provide enough data points above threshold for accurate comparisons. All ICC image width curves in Fig. 9, except for “ICC Ex1,” are examples of curves that showed less activation spread compared with cochlear stimulation.

One issue with analyzing all of our ICC sites is that stimulation of some of the outer sites (with respect to their location along a shank) exhibited truncated image width curves arising from the finite length of our A1 recording probe. As shown in Fig. 7, activity extended beyond the length of our A1 probe for some of the outer ICC sites (sites #1–3, 7–8). This results in slopes for their image width curves that tend to be artificially shallow. Therefore we reanalyzed our data using only the two center sites along our ICC shanks to minimize this truncation effect. Out of 18 ICC sites that had sufficiently low thresholds to perform this analysis, about 83% still exhibited less activation spread than cochlear stimulation.

Caudorostral ICC effects

In each animal, two separate shanks were inserted along the tonotopic axis of the ICC but in different isofrequency locations with one shank 500 μm rostral to the other. As a result, we were able to compare thresholds and activation spread in A1 for stimulation of a caudal versus a rostral ICC region.

To compare thresholds for a given animal, we averaged the ICC stimulation thresholds (in μA) across all eight sites along the rostral shank and along the caudal shank. Threshold corresponded to the A1 site with the lowest threshold for a stimulated ICC site. We then divided the average rostral threshold by the average caudal threshold to obtain an average threshold ratio. A ratio >1 indicated higher thresholds for more rostral ICC regions, whereas a ratio <1 indicated lower thresholds for more rostral regions. Figure 10 plots this ratio for five of our six animals. For the remaining animal, data were available for only one of the shanks. Threshold data from all five animals exhibited ratios <1, indicating that, on average, stimulation of more rostral regions elicited lower thresholds of activation in A1. Ideally we would have liked to compare the caudorostral effects along a given isofrequency lamina within the ICC. However, the set geometry of the ICC probe caused the electrode sites to be located within slightly different BF regions. Therefore we compared average thresholds across shanks instead.

In a similar manner, we compared activation spread across A1 in response to rostral versus caudal locations of stimulation within the ICC by calculating an average spreading ratio for each stimulus level. This spreading ratio was calculated by averaging the A1 image widths (in mm) for all eight sites along the rostral shank and along the caudal shank for a given stimulus level, and then dividing the average rostral image width by the average caudal image width. A ratio >1 indicated that greater activation spread was observed in A1 for stimulation of more rostral ICC regions, whereas a ratio <1 indicated less activation spread. To ensure that equivalent stimulus levels were used across all our ICC sites, we applied the SDT framework used for threshold calculation. For equivalent thresholds, we selected the stimulus level that corresponded to a PC of 0.76 for each ICC site. Similarly, we can select equivalent stimulus levels by selecting the stimulus level that corresponds to a specific PC value for each ICC site and determine the average spreading ratio for that PC value. Assuming our per trial spike rates for the “stimulus” and “no-stimulus” cases follow equal-variance normal distributions, these levels can also be represented in terms of d’ (relative to spontaneous activity). For example, a PC equal to 0.86 corresponds to a d’ equal to 1.5 and a PC equal to 0.92 corresponds to a d’ equal to 2. Figure 11 plots the average spreading ratio for five of our six animals and for different PC values, where a larger PC value corresponds to a higher stimulus level. Not all the animals had points for the higher PC values because we did not have enough data at these stimulus levels to accurately calculate the average spreading ratio. We also did not compare PC values >0.92 because of this issue. As shown in Fig. 11, all the ratios across different stimulus levels were >1 except for one point for animal number five. This suggests that, on average, stimulation of more rostral ICC regions generally elicited greater spread of activation along the tonotopic gradient of A1.

FIG. 10. Ratio plot for comparing stimulation thresholds between rostral and caudal ICC regions. Ratio for each animal was taken as the average threshold across the rostral shank sites divided by the average threshold across the caudal shank sites. A ratio value <1 indicated lower thresholds for more rostral ICC regions, and vice versa.
The goal of this study was to test the hypothesis that ICC stimulation achieves lower thresholds, greater dynamic ranges, and more localized, frequency-specific activation in A1 than cochlear stimulation. To achieve this goal, we recorded multiunit activity along the tonotopic gradient of A1 in response to electrical stimulation of different sites along the tonotopic axis of the ICC using multisite probes. Our results show that compared with cochlear stimulation, ICC stimulation achieves thresholds that are about 8 dB lower and dynamic ranges that are $\geq$4 dB greater. ICC stimulation also results in more localized, frequency-specific activation in A1 than is observed for cochlear stimulation. These findings suggest that an AMI may outperform current CIs. Studies on CI patients have shown that speech perception performance, particularly in noisy environments, is correlated with greater dynamic ranges (Loizou et al. 2000; Zeng and Galvin 1999). Thus an AMI may achieve better level coding and performance compared with CIs. Speech perception performance, especially in noisy environments, has also been correlated with the number of discriminable frequency channels of information available to a CI patient (Friesen et al. 2001; Shannon et al. 2004). More localized, frequency-specific activation achieved by AMIs may also translate into enhanced performance for deaf patients. Furthermore, AMIs may have reduced energy requirements as a result of lower thresholds and thus longer battery life compared with CIs. Overall, these findings support the argument that the ICC has potential as a site for an auditory prosthesis, and that an AMI may provide enhanced level and frequency discrimination with lower energy requirements compared with a CI. However, there are a few caveats to these claims.

First, ICC stimulation exhibited a wide range of thresholds for neural activation in A1. Considering that the stimulation sites were in direct contact with their neural targets, this observation raises some questions as to why thresholds would be $>56 \mu$A for some sites but are as low as 10 $\mu$A for other sites. For cochlear stimulation, Bierer and Middlebrooks (2002) were able to achieve thresholds of activation in A1 as low as 38 $\mu$A, which corresponded to the lower 5th percentile across all their stimulation sites. Thus some cochlear stimulation thresholds were actually lower than some of our higher ICC stimulation thresholds. As will be discussed in the next section, this variation in thresholds may be dependent on location of stimulation within the ICC. Yet the question remains as to what would cause such variations in thresholds. There is evidence supporting the existence of spatially distinct, functional regions within the ICC (Bruno-Bechtold et al. 1981; Cant and Benson 2006; Loftus et al. 2004; Oliver et al. 1997; Ramachandran and May 2002; Roth et al. 1978; Semple and Aitkin 1979; Schneiderman and Henkel 1987). This functional segregation of information originates as parallel projections from the brain stem to the ICC (Cant and Benson 2003) and appears to maintain some segregation up to A1, at least in association with different binaural features of sound (Andersen et al. 1980; Calford and Aitkin 1983; Middlebrooks and Zook 1983; Middlebrooks et al. 1980; Redies et al. 1989a; Rodrigues-Dagaeff et al. 1989; Rutkowski et al. 2000; Velievsky et al. 2003). Therefore, it is possible that stimulation of certain regions within the ICC elicits activity only within certain regions of A1. If our A1 sites were not recording from a cortical region correctly aligned with the stimulated ICC site, higher stimulus levels may have been required to activate neighboring ICC neurons that then projected to the cortical regions where our A1 sites were located. Based on this explanation, ICC stimulation thresholds may be even lower than those presented in this paper. There is also evidence that the ICC consists of a complex network of excitatory and inhibitory neural connections (Kelly and Caspary 2005). Thus it is possible that single-pulse stimulation of certain ICC regions may predominantly activate inhibitory neurons or may not properly activate these complex circuits, and only with higher stimulus levels is activity finally elicited in A1. If this is true, then it may become necessary to avoid stimulating these regions or to determine better stimulation strategies that can more effectively activate these regions.

Second, ICC stimulation achieves greater dynamic ranges than cochlear stimulation based on multiunit activity and on a logarithmic scale. Although this suggests that ICC stimulation may improve level coding compared with cochlear stimulation because of the enhanced dynamic range, it is still unclear as to how these electrophysiological results will translate into perceptual effects. Level discrimination may involve coding consisting of a large population of neurons and the fact that we were sampling only a small number of neurons could obscure the real mechanism for level coding. For example, we showed that based on multiunit activity ICC stimulation achieves greater dynamic ranges than cochlear stimulation. However, perceptually, cochlear stimulation may still achieve equivalent (or greater) dynamic ranges if higher level percepts are elicited by recruiting a greater number of neurons. It is also possible that perceptual thresholds for ICC stimulation may require activation of a larger population of neurons, as occurs with cochlear stimulation. This would in turn increase thresholds and possibly reduce the dynamic range for ICC stimulation. Another question is whether discriminable level steps follow a logarithmic scale. CI studies have shown that Weber fractions tend to decrease with stimulus level and absolute thresholds (Drennan and Pfingst 2005; Nelson et al. 1996; Pfingst et al. 1983). It is possible that the Weber fractions for cochlear
stimulation may be smaller than those for ICC stimulation because of their higher thresholds. As a result, cochlear stimulation may still achieve an equivalent number of discriminable level steps as ICC stimulation even with smaller dynamic ranges (in dB). It will be necessary to perform behavioral studies in animals and eventually in humans to determine how our neural data relate to behavioral performance, and to compare discriminable level steps as a function of stimulus level and threshold between ICC and cochlear stimulation.

Third, we demonstrated that frequency-specific ICC stimulation was achievable at both threshold and higher stimulus levels. However, we did observe cases where stimulation of some ICC sites elicited spike activity in an A1 region with a different BF. Previous anatomical studies showed that the ICC consists of stellate (less flat) cells that span across multiple layers and can project to the medial geniculate body (Oliver 2005). Thus it is possible that activation of these neurons within a specific BF region may have activated neurons within other ICC laminae and/or different BF regions within the medial geniculate body (and A1). The ICC also consists of a complicated network of incoming and outgoing projections that can traverse across multiple frequency laminae (Oliver 2005). Thus it is also possible that stimulation of a certain BF region may have activated passing fibers that elicited spike activity in cortical regions with different BFs. This would further explain why we observed tonotopically scattered (to- ward higher BFs) activation patterns by stimulating in low BF regions. Nevertheless, we did observe cases where stimulation of some ICC sites elicited spike activity in an A1 region with a lower BF (Fig. 7 and 8B). Malmierca et al. (1995) showed in guinea pig ICC that the low-frequency region of the ICC is close to the external nucleus of the inferior colliculus, which is known to receive a large number of corticofugal projections (Bajo and Moore 2005; Faye-Lund 1985; Herbert et al. 1991; Huffman and Henson 1990; Winer et al. 1998). This is also possible that high current stimulation of low BF ICC regions antidromically activated cortical neurons that then activated other BF cortical regions by axon collaterals. This is assuming that the same A1 neurons projecting to the external nucleus of the inferior colliculus also project to other A1 regions. As to whether the extent of BF-misaligned cortical activation by ICC stimulation presented in this study will limit hearing performance needs to be investigated in future AMI patients. Of significant importance is what perceptual effects will result from BF-misaligned cortical activation by stimulation of low BF regions, especially at higher levels. If low-frequency percepts and pitch information are compromised as a result of losses in level coding, then speech perception and hearing performance may be limited. There are several techniques that may reduce BF-misaligned activation if it proves to be a limiting factor. A simple solution, particularly for low BF-misaligned activation, would be to shift-transform the incoming sound to higher frequencies or, in general, to pitch-rank the stimulation sites to improve frequency coding. This would require that frequency specificity does not significantly change with level. If BF-misaligned activation is predominantly caused by stimulation of passing fibers, then specific stimuli designed to activate cells (more than fibers) could improve frequency-specific stimulation.

McIntyre and Grill (2000) showed that different electrical waveform parameters (i.e., polarity, biphasic asymmetry) can be used to activate cells more effectively than fibers, and may be effective for AMI stimulation. Considering that the ICC consists of two-dimensional, inhomogeneous isofrequency laminae (Bruno-Bechold et al. 1981; Cant and Benson 2006; Loftus et al. 2004; Oliver et al. 1997; Ramachandran and May 2002; Roth et al. 1978; Shneiderman and Henkel 1987), there may exist regions that offer better frequency coding characteristics (such as less passing fibers or stellate cells). Those regions can be identified across AMI patients (based on CT/MRI of the implanted array and correlated performance) and serve as target locations for future implantees. Different electrode configurations (i.e., bipolar, quadrupolar) may also be effective in steering current to activate those ICC regions (Jolly et al. 1996; Kral et al. 1998). These questions and issues must be investigated and will require studies in the first implanted AMI patients where we can assess the effects of location and types of stimulation on different percepts and hearing performance.

Fourth, to demonstrate that ICC stimulation elicited more localized activation patterns within A1 compared with cochlear stimulation, we compared A1 image width curves on a logarithmic scale. As mentioned above with respect to the issues associated with discriminable level steps, it is unclear whether comparing activation spread on a logarithmic scale is perceptually accurate. To partially address this issue in comparing activation spread between caudal and rostral ICC regions, we used the SDT framework to select equivalent level steps based on spike rate. Ultimately, we will need to perform experiments in behaving animals and humans to confirm whether our electrophysiological results translate into perceptually consistent effects.

Finally, it is important to consider the effects of anesthesia on our cortical recordings. Ketamine, which was used to anesthetize the animals in our experiments, has been shown to alter the spontaneous firing rate and stimulus-driven activity (rate and temporal pattern) in the auditory cortex (Syka et al. 2005; Zurita et al. 1994). Changes in frequency coding properties have also been observed under anesthesia (Gaese and Ostwald 2001, 2003). Although ketamine generally decreases the overall spontaneous neural activity, it is evident from these findings that the effects of anesthesia are complex and may involve changes in synaptic activity within cortical and subcortical regions. Therefore it is difficult to predict how cortical activity in response to ICC stimulation might change when recording from an awake preparation. Importantly for this study, it is not clear whether ketamine affects cortical activity to a similar extent when electrically stimulating the ICC versus the cochlea. It is possible that regions below the ICC, such as the cochlear nucleus (Anderson and Young 2004; Evans and Nelson 1973; Ritz and Brownell 1982), that are also affected by anesthesia can indirectly alter the cortical activity elicited by cochlear stimulation in a way that would not occur for ICC stimulation. Future studies aimed at recording cortical activity in awake and behaving animals can begin to address these anesthesia effects.

Caudorostral organization within the ICC?

Stimulation of more rostral ICC regions elicited lower thresholds and greater spread of activation in A1. This was

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consistently observed in all five animals that were analyzed. These results suggest that neural elements organized along the caudorostral extent of the ICC may process ascending sound information in different ways. There is anatomical evidence supporting the hypothesis that spatially distinct, functional regions exist and may be spatially organized across and within different frequency layers of the ICC (Bruno-Bechtold et al. 1981; Cant and Benson 2006; Loftus et al. 2004; Oliver et al. 1997; Ramachandran and May 2002; Roth et al. 1978; Shneiderman and Henkel 1987). In particular, Loftus et al. (2004) showed that at least in cat and for lower BF regions (<5 kHz), there was some caudorostral organization of synaptic inputs originating from different brain stem nuclei. However, it is still not clear whether a caudorostral organization exists for higher BF regions and, importantly for an AMI, whether such an organization exists with respect to ICC neurons projecting to higher auditory centers. In addition to a spatial organization of projections ascending into and originating from the ICC, there is also the possibility that descending projections from higher auditory centers may project to and modulate the ICC in a spatially organized manner. Studies have shown that the cortex (Feliciano and Potashner 1995; Mitani et al. 1983; Suga et al. 2000; Torterolo et al. 1998; Winer et al. 1998; Yan and Ehret 2002) as well as other brain regions (Winer 2005; Winer et al. 2002) have monosynaptic and polysynaptic descending projections into the ICC. As shown in Fig. 4, it was possible to activate some of the monosynaptic corticofugal projections antidromically, which may have affected cortical activity by axon collaterals. It is also possible to orthodromically activate descending fibers projecting to the ICC that can directly affect the ICC neurons simultaneously being activated by the same electrical stimulus. Thus activation of these descending projections that may be spatially organized could also be responsible for some of the differences we observed when stimulating along the caudorostral dimension of the ICC.

Implications for an AMI

An important advantage that an AMI would have over CIs (and surface ABIs) is the ability to achieve low threshold and localized, frequency-specific stimulation, which may allow for a greater number of independent frequency channels. In addition, ICC stimulation provides an enhanced dynamic range, which may result in an increased number of discriminable level steps. These improvements suggest that an AMI may outperform current CIs. However, one cannot exclude the effects of temporal processing. CIs effectively transmit temporal information by using high-rate, amplitude-modulated pulses. However, unlike auditory nerve fibers, neurons located higher along the auditory pathway, such as in the ICC or A1, are less capable of phase-locking to the stimuli (Langner 1992; Langner and Schreiner 1988; Lu and Wang 2004; Lu et al. 2001). This has been attributed to the hypothesis that temporal coding becomes partially transformed into a spatial representation of sound within higher auditory centers. As a result, temporal coding in AMI patients not only may involve temporal patterns of activation but also may depend on spatial activation along and within different isofrequency ICC laminae. Similarly, one cannot exclude the effects caused by bypassing the auditory brain stem. The cochlear nucleus is known to reencode the rather homogeneous auditory nerve activity into a neural representation of different features of sound that are then transmitted to other auditory centers (Romand and Avan 1997). The superior olivary complex is important for processing binaural information and the nuclei of the lateral lemniscus are important for both binaural processing and temporal coding (Helfert and Aschoff 1997). Thus an AMI will need to somehow activate the ICC in a manner that restores some of these features that are essential for speech perception, sound localization, and source identification. There is anatomical evidence suggesting that certain brain stem nuclei [i.e., dorsal cochlear nucleus (DCN), medial superior olive (MSO), lateral superior olive (LSO)] project to spatially distinct functional regions within the ICC (Bruno-Bechtold et al. 1981; Cant and Benson 2006; Loftus et al. 2004; Oliver et al. 1997; Ramachandran and May 2002; Roth et al. 1978; Shneiderman and Henkel 1987). This suggests that it may be possible to stimulate distinct regions within the ICC to restore some essential features of sound specifically associated with different brain stem nuclei. For example, there are neurons clustered together within low-frequency ICC regions that are binaurally excited (EE), sensitive to interaural time differences (ITDs), and appear to receive inputs predominantly from the MSO (Loftus et al. 2004; Ramachandran and May 2002). By appropriately stimulating these ICC regions, it may be possible to elicit some binaural percepts associated with EE and ITD features normally extracted from MSO neurons. This is not to claim that all projections from the brain stem are segregated into distinct functional ICC regions that can be individually stimulated. Many ICC regions exhibit response properties that probably result from substantial convergence of information across multiple brain stem nuclei (Chase and Young 2005). Furthermore, compensating for the bypassed coding of the brain stem may require specific temporal stimulation strategies to ensure that important sound features processed in the ICC are successfully transmitted to higher centers. Understanding where and how to stimulate the ICC to restore important sound features, including those extracted at the brain stem level, will require psychophysical studies in AMI-implanted patients. By assessing how location of stimulation within the ICC (by imaging the AMI array using CT and MRI) and different stimulation strategies affect auditory perception, we can begin to optimize AMI placement and implementation to improve hearing performance.

Based on our results, a trade-off may exist between frequency specificity and threshold. Electrical stimulation of more rostral ICC regions elicited lower thresholds of neural activation in A1, which may correlate with lower perceptual thresholds. However, stimulation of rostral ICC regions also elicited greater spread of activation along the tonotopic gradient of A1, which may correlate with a reduced number of discriminable frequency channels available for an AMI. Psychophysical experiments need to be performed to assess whether this trade-off observed for cortical activity correlates with perceptual effects associated with frequency discrimination and thresholds. If so, it will be important to determine whether an optimal location exists within the ICC to maximize the benefit of both features.

If pathways from the ICC to the auditory cortex are segregated according to function, sufficient cortical coverage may require a more extensive coverage of the ICC rather than one optimal location. Achievement of a broader distribution of
stimulation sites with perhaps finer resolution would require an electrode array with a higher shank count or more than one device with the associated signal processing and switching electronics. Because site count is a critical resource allocation and has an impact on the overall complexity of the implant, continued research in this area is needed.

Even with the improvements in threshold, dynamic range, and frequency specificity that ICC stimulation achieves over cochlear stimulation, more complicated temporal and spatial patterns of stimulation throughout the ICC may be required to effectively implement an AMI. The fact that we observed antidromic activation by ICC stimulation suggests that descending coding features as well as compensation for artificial antidromic effects may also need to be incorporated for successful AMI implementation, and will be investigated in future studies. On the other hand, simple stimulation strategies combined with the brain’s potential for plasticity and learning may be sufficient for achieving intelligible speech perception using an AMI. Ultimately, the hope is that the AMI will serve as a successful alternative to the ABI for NF2 patients and eventually provide another option for patients generally unable to benefit from a CI.

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