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Cochlear implant use following neonatal deafness influences the cochleotopic organization of the primary auditory cortex in cats

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Abstract

Electrical stimulation of spiral ganglion neurons in deafened cochlea, via a cochlear implant, provides a means of investigating the effects of the removal and subsequent restoration of afferent input on the functional organization of the primary auditory cortex (AI). We neonatally deafened seventeen cats before the onset of hearing, thereby abolishing virtually all afferent input from the auditory periphery. In seven animals, the auditory pathway was chronically reactivated with environmentally-derived electrical stimuli presented via a multi-channel intracochlear electrode array implanted at eight weeks of age. Electrical stimulation was provided by a clinical cochlear implant that was used continuously for periods of up to seven months. In ten long-term deafened cats and three age-matched normal hearing controls, an intracochlear electrode array was implanted immediately prior to cortical recording. We recorded from a total of 812 single unit and multi-unit clusters in AI of all cats as adults, using a combination of single tungsten and multi-channel silicon electrode arrays. The absence of afferent activity in the long-term deafened animals had little effect on the basic response properties of AI neurons but resulted in complete loss of the normal cochleotopic organization of AI. This effect was almost completely reversed by chronic reactivation of the auditory pathway via the cochlear implant. We hypothesize that maintenance or re-establishment of a cochleotopically organized AI by activation of a restricted sector of the cochlea – as demonstrated in the present study – contributes to the remarkable clinical performance observed among human patients implanted at a young age.

Keywords

cortical plasticity; electrical stimulation; neural prosthesis; sensorineural hearing loss

Introduction

Cochlear implants have provided over 110,000 individuals with a severe-profound sensorineural hearing loss (SNHL) with auditory input via direct intracochlear electrical stimulation (ES) of the auditory nerve. A broad range of factors affect the clinical performance of implant recipients, resulting in a wide range of speech perception skills (Blamey et al., 1996). Auditory experience, both prior to an acquired hearing loss and with the use of the implant, is strongly positively correlated with clinical performance (Blamey et al., 1996; Gantz et al., 1993; Govaerts et al., 2002; Kirk et al., 2002; Rubinstein, 2002; Rubinstein et al., 1999; Sarant et al., 2001). In particular, the central auditory pathway in children appears maximally plastic during the first 3.5 years of age (Eggermont and Ponton, 2003; Ponton et al., 1996; Ponton and Eggermont, 2001; Sharma et al., 2002) and if congenitally deaf children

are implanted early in life, a majority achieve speech perception comparable to that of postlingually deaf adults (Dowell, 2002). A factor contributing to the effects of auditory experience on performance is the effect on the central auditory pathway of the loss of afferent input associated with a profound SNHL. Although the most pertinent change is probably the ongoing shrinkage and/or loss of spiral ganglion neurons (the target of cochlea implants), a neonatal SNHL also results in a generally less well developed auditory pathway (for review see Shepherd et al., 2006). Recently, some of the cellular and molecular changes associated with changes in afferent input to the auditory cortex have been reported (Tan et al., 2007); however, the electrophysiological correlates of such changes are less clear.

Woolsey and Walzl (1942) were the first to describe auditory cortical responses to of the auditory nerve, using normal hearing cats. By recording the distribution of cortical potentials evoked by ES of neurons at discrete loci within the cochlea they established the basic cochleotopic organization of the primary auditory cortex (AI). Subsequent ES studies have shown that individual neurons within layer III/IV of the AI have well characterized input-output functions to ES : single and multi-unit recordings in acutely deafened animals exhibit either monotonic (~55%) or non-monotonic input-output functions, with dynamic ranges of approximately 10 dB (Hartmann et al., 1997; Raggio and Schreiner, 1994, 1999). In response to stimulation of fibers innervating restricted regions of the cochlea, each cortical location is preferentially activated by stimulation in a particular region. This feature of the cortical response is analogous to the preferential activation of different cortical locations by different frequencies of acoustic stimulation, and will therefore be referred to as 'local tuning'. Electrically-stimulated normal hearing cats exhibit a functional cochleotopic organization of AI along a predominantly caudal-rostral axis, which is the analogue of the well-studied tonotopic organization to acoustic stimulation (for review see Clarey et al., 1992). There are two key features of this cochleotopic organization. First, a 1-mm shift in the site of ES along the basilar membrane corresponds to an approximately 1.82-mm shift in the location of the lowest-threshold cortical activity along the caudal-rostral axis of AI (Raggio and Schreiner, 1999); this feature will be referred to as cochlea-to-cortex mapping. Secondly, using bipolar ES, a single biphasic stimulus delivered 6 dB above threshold recruits an approximately 2-mm wide dorso-ventral strip (Raggio and Schreiner, 1999); this feature will be referred to as 'cortical spread'

It is well known that the tonotopic organization of AI can be altered by changes in the animal's auditory experience during development (Zhang et al., 2001) or in output from the cochlea, such as that produced by restricted cochlea lesions (either neonatally or in adults) which result in a partial SNHL (for review see Irvine and Wright, 2005). However, the effects of a complete withdrawal of afferent drive (i.e. a severe-profound SNHL) are less clear (for review see Fallon et al., 2008). Specifically, short periods (~2 weeks) of profound SNHL, induced by ototoxic drugs, in adult cats with normal AI development, do not alter the basic characteristics of AI unit responses to cochlear ES, other than producing a decrease in threshold (Raggio and Schreiner, 1999). However, there is a degradation of the cochleotopic organization, evident as a more diffuse activation of AI (i.e. an increase in cortical spread). The effects of longer periods of SNHL, including the early developmental period, appear to be dependent on etiology. Deafening of neonatal animals with ototoxic drugs results not only in an increase in cortical spread, but also in a complete or near-complete loss of cochlea-to-cortex mapping (Dinse et al., 1997, 2003; Raggio and Schreiner, 1999). In contrast, congenitally deaf white cats appear to maintain a rudimentary cochlea-to-cortex mapping (Hartmann et al., 1997; Klinke et al., 1999; Kral et al., 2001, 2002).

Modern cochlear implants provide chronic ES that not only reactivates the auditory pathway, providing patients with auditory information, but that may also provide trophic support to spiral ganglion neurons and facilitate the normal development of the auditory pathway (for review

see Shepherd et al., 2006). Chronic ES can lead to changes in the cochleotopic organization of the inferior colliculus, including an expanded representation of a stimulated region in both immature (Snyder et al., 1990) and mature (Moore et al., 2002) animals, or even the fusing of two simultaneously stimulated regions (Leake et al., 2000). In the auditory cortex, environmentally-derived chronic ES in congenitally deaf cats has been reported to result in an increase in long-latency (>150 ms) field potentials, larger current source densities (particularly in layers II & III), and more sustained single- and multi-unit activity (Klinke et al., 1999). However, there has been no systematic investigation of stimulation-induced changes in single- or multi-unit threshold or dynamic range. In studies using either optical imaging (Dinse et al., 1997, 2003) or field potential recordings (Klinke et al., 1999; Kral and Tillein, 2006), environmentally-derived chronic ES has also been reported to cause an additional increase in cortical spread over that associated with deafness alone. However, the effects of environmental derived chronic stimulation on the cochleotopic organization of single- or multi-unit activity in AI in long-term deafened animals are not clear. We have therefore investigated the effects of environmentally-derived chronic ES delivered during early developmental periods on both the basic response properties of AI units and the cochleotopic organization of AI. Preliminary findings have been presented in abstract form (Fallon et al., 2007a, 2007b, 2007c).

Materials and Methods

Deafening procedure

Twenty healthy cats with otoscopically normal tympanic membranes were used in the present study. Three served as normal hearing controls; the other seventeen were administered a daily subcutaneous (s.c.) injection of neomycin sulfate (60 mg/kg) from one day after birth for seventeen days (Leake et al., 1991). Hearing status was then measured, and if the animal was not profoundly deaf neomycin injections were continued in three-day increments until the animal was profoundly deaf. The criterion of profound deafness was the absence of a monaural click-evoked auditory brainstem response (ABR) at 93 dB peak equivalent (p.e.) sound pressure level (SPL) in either ear. ABRs were recorded in an electrically isolated, sound-attenuated Faraday room using standard electrophysiological techniques (Coco et al., 2007). Briefly, the animals were premedicated with xylazine (4 mg/kg; s.c.), and sedated with ketamine (20 mg/kg; intra-muscular [i.m.]); the animal's temperature was maintained at $37 \pm 1^\circ \text{C}$. Computer-generated 100- μs rarefaction clicks were presented from a loudspeaker placed 10 cm from the pinna, with the contralateral external ear canal plugged with an ear mould compound (Otoplastik®). ABRs were recorded differentially using subcutaneous stainless steel electrodes (vertex positive; neck negative and thorax ground) with responses amplified by a factor of 10^5 and filtered (high pass: 150 Hz, 24 dB/octave; low pass: 3 kHz, 6 dB/octave). Five hundred responses were averaged, and threshold was defined as the minimum stimulus intensity producing a response amplitude of at least 0.2 μV for wave IV (a latency window of 4.0–4.5 ms following stimulus onset) in 2 repeated recordings.

Cochlear implantation and chronic stimulation

At eight weeks of age, seven randomly selected deafened animals were unilaterally implanted (left cochlea) with an eight-ring scala tympani electrode array and lead-wire assembly (Figure 1A), using previously published techniques (Coco et al., 2007). Briefly, surgery was performed under aseptic conditions, with each animal premedicated using acepromazine maleate/atropine sulphate (0.05 ml/kg s.c.) and maintained at a surgical level of anesthesia using a closed circuit anesthetic machine delivering a mixture of halothane and oxygen. The bulla cavity was opened and flushed with amoxicillin (10 mg/ml), and the round window membrane was incised. The array was inserted 8 mm into the scala tympani, placing the most apical electrode (E1) at the ~10-kHz place and the most basal electrode (E8) at the ~26-kHz place (Brown et al., 1992), and the round window was sealed with crushed muscle. The leadwire was fixed at the bulla

and on the dorso-lateral part of the skull, before passing subcutaneously to exit the body through an incision at the nape of the neck. Three deafened animals also received an extra-cochlear ball electrode placed in the temporalis muscle to allow for monopolar stimulation (see below and Table 1).

Fourteen days after surgery, and every month thereafter during the chronic stimulation program (see below and Table 1), an electrically evoked ABR (EABR) was recorded for each stimulating electrode using standard electrophysiological techniques. Optically isolated biphasic current pulses were generated under computer control and delivered to the intracochlear electrode array. Responses were recorded differentially using the same techniques as described for the ABR, except for the inclusion of a sample-and-hold circuit to remove electrical artifact (Black et al., 1983). Two recordings were made at each current level and current amplitude was reduced to levels below threshold, defined as the current level required to evoke a peak-trough response amplitude of at least 0.2 μ V for wave IV of the EABR (a latency window of 2.4–2.9 ms following stimulus onset) for both responses.

After the first EABR recordings (i.e. at two months of age), the chronic stimulation program was initiated. To reflect the temporal distribution of normal clinical usage, animals received stimulation for at least 16h/day, 7 days/week. Each animal received unilateral stimulation at multiple sites within the lower basal turn from a Nucleus® CI24 cochlear implant and Nucleus® ESPrit 3G speech processor (Table 1). The speech processors were programmed to deliver stimulation at 500 pulses per second (pps) per electrode at stimulus levels from 3 dB below to 6 dB above the EABR threshold, using either monopolar ($n = 3$) or common ground ($n = 4$) electrode configurations (see Figure 1). For monopolar stimulation, each biphasic current pulse had a 25- μ s phase interval and an 8- μ s inter-phase gap, while for common ground stimulation each biphasic current pulse had a 100- μ s phase interval and a 50- μ s inter-phase gap. The different pulse durations reflect the greater efficacy of monopolar stimulation, although both configurations are used clinically (Seligman and Shepherd, 2004). These stimulus levels were assessed by monitoring behavioral characteristics (orienting responses including head and pinna movements) for each animal and were confirmed to be perceivable and to cause no discomfort. Both self vocalizations and vocalizations by other animals housed in the facility produced changes in the stimulus levels that were within the perceivable range for each animal. Similarly, other environmental sounds associated with the normal running of such a facility would be expected to have also been perceivable, and this was confirmed by observation of orienting responses to environmental events. The stimulator package was carried in a harness worn by the animal which did not restrict movement. Animals were chronically stimulated for periods up to 7 months (Table 1), with stimulation continuing until the commencement of the acute electrophysiological experiments.

Cortical recording and data analysis

At five to thirteen months of age, acute electrophysiological experiments were performed to record the basic response properties of AI neurons, and to map the cochleotopic organization of AI. Anesthesia was induced with ketamine and xylazine (20 mg/kg i.m., 2 mg/kg s.c.) and a tracheal cannula was inserted. Sodium pentobarbitone (intravenous) via a slow-infusion pump was used to maintain a steady light level of surgical anesthesia throughout the recording period. Heart rate, respiration rate, end-tidal CO₂, and core body temperature were maintained within normal levels. Just prior to the experiment, normal hearing controls ($n = 3$; referred to as “normal hearing”) were unilaterally deafened by perfusion of neomycin sulfate (10% w/v solution) through the cochlea (Hardie and Shepherd, 1999). These animals and the long-term deaf controls ($n = 10$) were implanted unilaterally with an electrode array and an extra-cochlear ball electrode using the same surgical techniques to those used for the chronically implanted animals. Animals were placed in a stereotaxic apparatus in a sound-attenuated Faraday room,

and a craniotomy performed to expose the auditory cortex contralateral to the implanted cochlea. The dura mater was removed, and a calibrated photograph was taken of AI and surrounding cortex. Single- and multi-unit recordings were made from AI using a combination of single tungsten micro-electrodes (WPI; Sarasota, Florida), and linear (NeuroNexus Technologies; Ann Arbor, Michigan) and planar (Cyberkinetics; Foxborough, Massachusetts) silicon arrays. In most cats, an attempt was made to record from the low-frequency region of AI in the rostral bank of the posterior ectosylvian sulcus (PES) by making recordings at a range of depths in long penetrations down the sulcal bank. Recording locations were marked on the photograph relative to the vascular landmarks. Multi-unit recordings from the tungsten micro-electrodes were amplified by a factor of 10^4 , filtered (high pass: 300 Hz, 24 dB/octave; low pass: 3 kHz, 6 dB/octave), and displayed on an oscilloscope. The oscilloscope trigger level was set to discriminate action potentials clearly above the noise level, and the trigger pulses were sampled at 20 kHz. Single- and multi-unit recordings from the silicon arrays were captured at a sample rate of 30 kHz using the Cerebus system (Cyberkinetics; Foxborough, Massachusetts) and single- or multi-unit recordings were identified off-line using standard spike discrimination techniques in IgorPro (Wavemetrics; Lake Oswego, Oregon).

In normal-hearing controls, a frequency – intensity response area was determined at each cortical recording site at which single- or multi-unit responses to ipsilateral acoustic stimulation could be recorded. Acoustic stimuli consisted of 50-ms tone bursts with 5-ms linear rise/falls, and were presented at a range of frequencies (0.1 – 40 kHz) and intensities (0 – 80 dB SPL) via a calibrated speaker coupled to speculum inserted in the ipsilateral auditory meatus. Characteristic frequency (CF) was defined as the frequency at which the minimum SPL was required to elicit a response greater than twice the spontaneous activity.

To characterize the basic response properties of AI neurons to ES, a range of stimulus currents, on a range of intracochlear electrodes, was utilized. Input-output functions for each stimulating electrode were determined with a randomized stimulus matrix that consisted of currents from 0 to up to 2 mA on all stimulating electrodes, presented at a rate of up to 1.5 stimuli per second. Each input-output function was fitted with a saturating Gaussian function (Sachs and Abbas, 1974), from which the threshold (defined as the current required to achieve a half maximal response), an estimate of the error in determining the threshold, and dynamic range (defined as the current range required to achieve an increase in response from 10% to 90% of maximal) for each stimulating electrode could be determined (see Figure 2E). For each recording site, the ‘best electrode’ (BE, the analogue of CF) was defined as the stimulating electrode with the lowest normalized threshold. It was necessary to normalize cortical thresholds to EABR threshold for that electrode configuration, as stimulation mode, hearing status and stimulating electrode location can all alter threshold (see Results). If the thresholds on two adjacent stimulating electrodes were not significantly different, the average of the two electrodes was assigned as BE. If the thresholds of three or more adjacent stimulating electrodes, or two non-adjacent stimulating electrodes, did not differ, the site was defined as being ‘broadly tuned’ and was excluded from subsequent analysis. The ‘depth of tuning’ (an analogue of acoustic band-width) at each site was defined as the difference in threshold, expressed in dB, between BE and the two adjacent electrode thresholds (see Figure 3). The effects of mode of stimulation, hearing status, and chronic ES on the basic response properties of AI units were assessed with one-, two- or three-way ANOVAs with Bonferroni corrections of post-hoc t-test analysis where appropriate. A large number of long-term deaf animals was used to ensure sufficient statistical power to examine the potentially complex interactions between experimental treatments.

The effects of a long-term SNHL, with or without chronic ES, on the cochleotopic organization of AI were quantified in two ways. First, a cortical map of the variation in BE across AI was constructed. The BE maps were analyzed for a correlation between BE and rostro-caudal location in AI (approximately parallel to the main tonotopic axis in normal hearing animals)

to assess changes in the cochlea-to-cortex mapping. Detailed analysis of BE maps was limited to the region of AI between the lip of rostral bank of PES and a point on the gyrus 2 mm caudal to the anterior ectosylvian sulcus (AES; see Figure 5). In a normal hearing cat this region typically spans a CF range from 5 – 10 kHz near the lip of PES to the high-frequency edge of AI near AES (Reale and Imig, 1980), matching the frequency range/place of our intracochlear stimulating electrode array. Finally, cochleotopic organization of AI was also assessed by measuring the cortical spread of activation – defined as the area of cortex that was activated by a stimulus 2 dB above the minimum cortical threshold for a particular intracochlear electrode. To calculate the cortical areas activated, Voroni tessellation was used to create tessellated polygons, with electrode penetration sites at their centers (Bao et al., 2003). In this way, every point in the region of cortex enclosed within our region of interest (dashed rectangles in Figure 5A, C & E) could be assigned a threshold derived from a sampled cortical site that was closest to this point.

Results

Electrically evoked auditory brainstem responses

EABR thresholds exhibited a complex dependence on stimulation mode and stimulating electrode position (Figure 1). As expected, common-ground stimulation required significantly more charge per phase to elicit a response than monopolar stimulation (one-way ANOVA; $p < 0.001$). For both modes of stimulation, EABR thresholds recorded during the acute electrophysiological experiments were not significantly different between groups (two-way ANOVA; $p > 0.05$ in each case), but varied systemically with stimulating electrode (two-way ANOVA; $p < 0.001$ in each case). For common-ground stimulation, Bonferroni adjusted post-hoc analysis indicated that thresholds for electrodes in the middle of the electrode array (viz., electrodes 4–7 (E4 – E7)) were significantly higher than that for electrode 1 (E1, Figure 1B). For monopolar stimulation, such analysis indicated that thresholds for electrodes at the basal end of the electrode array (viz., E6 and E7) were significantly higher than that for E1 (Figure 1C).

Cortical recordings

Recordings were made from a total of 812 multi-unit clusters in AI (79 normal hearing; 398 long-term deaf; 207 chronic common-ground stimulation; 128 chronic monopolar stimulation), from which a total of 28 single-unit recordings were identified. Figure 2A illustrates a multi-unit recording from a silicon array in AI of a long-term deaf animal (D10). From this recording it was possible to isolate a single unit, indicated by the asterisk in Figure 2A, the waveform of which is shown in the spike overlay inset in Figure 2B. The post-stimulus time histograms of both the single- and multi-unit recording (minus the single unit's response) made at this location exhibited stereotypical responses to ES (Figure 2B & C, respectively). All recorded units, regardless of experimental group, displayed this 'onset only response', with decreasing mean first spike latency and jitter with increasing stimulus current. The input-output functions (Figure 2D & E) of both were monotonic functions that were well approximated by a saturating Gaussian function, as were the ES input-output functions from all recordings in all animals, i.e. there were no responses to ES that exhibited a non-monotonic response with increasing stimulus current. In contrast, approximately 40% of the units in normal hearing animals that were responsive to ipsilateral acoustic stimulation exhibited non-monotonic acoustic rate – level functions at CF. Figure 3 illustrates the seven ES input-output functions recorded from a multi-unit cluster in AI of a long-term deaf animal (D10), along with a plot of the normalized thresholds (see Materials and Methods). From this plot it is apparent that BE for this recording site is E2; the depth of tuning is 4.6 dB. At all recording sites at which it was possible to determine a BE for both a single-unit and a multi-unit cluster ($n = 11$) there was agreement

between the two determinations. The following analysis will therefore focus on results from multi-unit clusters.

As summarized in Table 2, a long-term SNHL resulted in a small but significant decrease in normalized cortical threshold compared to normal hearing controls, using either common-ground or monopolar stimulation of the BE for that cortical location, although the magnitude of the decrease was greater for common-ground stimulation. The effects of chronic ES on the decrease in threshold were dependent on the mode of stimulation. Common-ground stimulation partially reversed the decrease, whereas monopolar stimulation resulted in thresholds that were not significantly different to those in long-term deaf animals. As expected, common-ground stimulation resulted in a greater dynamic range than monopolar stimulation, but a long-term SNHL, with or without chronic ES, did not result in a significant change in dynamic range for either mode of stimulation.

Local Tuning

It was possible to determine a best electrode for 90% or more of the multi-unit clusters recorded across all groups (see Table 2). There was no significant difference in the percentage of tuned cortical locations for normal hearing, long-term deaf, and chronically stimulated animals, nor was there a difference with the mode of stimulation (Two-Way ANOVA; P 's > 0.05). As illustrated in Figure 4, common-ground stimulation resulted in significantly deeper tuning than monopolar stimulation (Two-Way ANOVA; $p < 0.01$). A long-term SNHL did not result in a significant change in the depth of tuning for either stimulation mode. However, the effects of chronic ES were dependent on the mode of stimulation: monopolar stimulation resulted in significantly deeper tuning than was observed in the long-term deaf group (Two-way ANOVA; Bonferroni post-hoc; $p < 0.001$); while common-ground stimulation did not ($p > 0.05$).

Cochlea-to-cortex mapping

Representative cochleotopic maps of AI recorded in normal hearing, long-term deaf and chronically stimulated animals for common-ground and monopolar stimulation are illustrated in Figure 5 and 6, respectively. In Figure 5B and 6B, the normal tonotopic organization of AI (determined using ipsilateral acoustic stimulation) is apparent (black triangles). Analysis of the cortical maps for acoustic stimulation and for all of the mapped area (i.e., including the rostral bank of PES) in the three normal hearing animals resulted in correlations between CF and caudo-rostral position that ranged from 0.85 to 0.95 and were significant in each case (Pearson correlation; P 's < 0.05). The average frequency-to-cortex mapping factor was 5.3 ± 0.3 kHz/mm (mean $\pm$ SEM). In each of these animals, intracochlear ES was able to elicit responses over a similar cortical extent as acoustic stimulation. As demonstrated in Figure 5B and 6B, there was a clear cochleotopic organization for ES, but this organization was primarily in the area of cortex responsive to acoustic stimulation from 5 – 30 kHz (i.e. corresponding to activation of spiral ganglion neurons located adjacent to the intracochlear electrode array), which is located on the gyral surface between PES and AES. As noted in the Methods section, analysis of the BE maps was therefore limited to the region of AI between a point on the gyrus just rostral to PES and a point on the gyrus 2 mm caudal to AES. In each of the normal hearing controls, there was a clear cochlea-to-cortex mapping for ES, as reflected in a significant positive correlation between BE and caudo-rostral position. For the normal hearing control animal for which data are presented in Figure 5B (N1, common-ground stimulation) the correlation was 0.80, while for N3 (monopolar stimulation), shown in Figure 6B, the correlation was 0.62. The mean correlations (Figure 7A) were 0.64 and 0.62 for common-ground and monopolar stimulation, respectively. The average cochlea-to-cortex mapping factors in the normal hearing animals (Figure 7B) were 1.5 ± 0.2 mm/mm (mean $\pm$ SEM) for common-ground stimulation ($n = 3$) and 1.2 for monopolar stimulation ($n = 1$), i.e. a 1-mm shift along the basilar membrane corresponds to 1.5-mm and 1.2-mm shifts across the cortex for common-ground

and monopolar stimulation, respectively. As illustrated by the analysis presented below and in Figure 7, it is likely that this small difference reflects inter-individual differences rather than a difference between the different modes of stimulation.

Figure 5C and figure 5D and D and figure 6C and D illustrate that a long-term neonatal SNHL resulted in a complete loss of cochlea-to-cortex mapping regardless of stimulation mode; the cochlea-to-cortex mapping correlations in the two cases illustrated were -0.68 for common-ground stimulation and -0.10 for monopolar stimulation. Across all 10 cases there was no significant positive correlation (Pearson correlation; P 's > 0.05 ; Figure 7A). In contrast, and as illustrated by the cases in Figure 5E and F (correlation 0.62) and 6E and F (correlation 0.76), all chronically stimulated animals (common-ground: $n = 4$; monopolar: $n = 3$) exhibited significant positive cochlea-to-cortex mapping: correlations, and the mean correlations (0.5 ± 0.1 and 0.5 ± 0.1 , respectively; Figure 7A), were significant. The mean cochlea-to-cortex mapping factors were 1.4 ± 0.4 mm/mm and 0.9 ± 0.2 mm/mm for common-ground and monopolar stimulation, respectively (Figure 7B). Neither cochlea-to-cortex mapping correlations nor mapping factors differed significantly between the two groups of chronically stimulated animals, nor did they differ significantly from those in normal animals (Two-Way ANOVA; P 's > 0.05 ; Figure 7).

Cortical spread

As illustrated by data from an individual normal hearing animal (N1) in Figure 8A, only a small area of AI responded to near-threshold stimulation of a single intracochlear electrode. As the stimulus current was increased above threshold, the area of AI activated by the stimulus increased monotonically. The activated area reached a plateau of approximately 13 mm^2 for stimulation more than 7 dB above the minimum cortical threshold. A similar pattern of monotonic increase in activated area with increasing stimulus intensity was observed for all combinations of stimulus electrode, stimulation mode, and experimental group. However, as illustrated by the data from a long-term deaf animal (D5) and a common-ground chronically stimulated animal (CG2) in Figure 8B & C, the shape of the activated area vs. stimulus level curve varied, and the maximum area of activation was substantially greater in the deafened animals (approximately 24 mm^2 in Figure 8B and 23 mm^2 in Figure 8C). All animals exhibited a near-linear increase in activated area with stimulus intensities up to 2 dB above the minimum cortical threshold, and this intensity was therefore used to compare the extent of the spread of activation under different conditions. Using this criterion, the functions illustrated in Figure 8A – C result in a cortical spread of activation of 6.7, 12.6 and 11.8 mm^2 for the normal hearing, long-term deaf and chronically stimulated animals, respectively. Cortical spread was not dependent on the stimulating electrode or mode of stimulation used (three-way ANOVA; P 's > 0.3), and the data presented in Figure 8D are therefore pooled across these variables. In both the long-term deaf and chronically stimulated groups there was an approximately three-fold increase in the cortical spread of activation for stimulation on a single intracochlear electrode compared to the normal animals (three-way ANOVA; $p < 0.001$; Bonferroni Post-Hoc; $p < 0.001$).

Discussion

We have provided evidence on the effects of a long-term neonatal SNHL, with or without chronic ES via a clinically available multichannel cochlear implant, on both the basic response properties (viz., threshold, dynamic range, input-output functions, and local tuning) and the cochleotopic organization of single- and multi-unit activity in AI. We addressed cochleotopic organization at two levels: i) cochlea-to-cortex mapping (i.e. the relative shift along the caudal-rostral axis of AI for a given shift along the basilar membrane) and ii) 'cortical spread' of activation (i.e. the extent of cortical activation at 2 dB above the minimum cortical threshold).

It is clear that an extended period of profound deafness that includes the early developmental period, results in a complete loss of the normal cochleotopic organization of AI. Importantly, these deafness induced changes can be reversed by providing afferent input to AI via environmentally-derived chronic intracochlear ES.

Electrically evoked auditory brainstem responses

There was a systematic variation in EABR threshold with stimulating electrode number, which is likely due to the location of the stimulating electrodes within the scala tympani affecting both the current paths and the distance between the electrodes and their target neural elements. The cat cochlea – like all mammalian cochleae – is tapered (Hatsushika et al., 1990), and the more basal electrodes will therefore lie at a greater distance from the spiral ganglion neurons, leading to an increase in EABR threshold (Shepherd et al., 1993). Additionally, the more basal electrodes lie closest to the round window, and monopolar stimulation using these electrodes would therefore be expected to result in a greater proportion of the stimulating current exiting the scala tympani via the round window and not activating neural elements. However, in contrast to previous reports from our laboratory using bipolar stimulation (chronic ES: Coco et al., 2007; acute ES: Hardie and Shepherd, 1999), EABR thresholds for long-term deaf animals in the present study, with or without chronic ES, were not significantly different to those of acutely deafened controls. This is likely due to the large inter-animal variability seen in EABR threshold measurements, and is consistent with a recent report from Vollmer et al. (2007).

Input-output functions and other response characteristics

All neuronal clusters recorded from AI exhibited monotonic input-output functions for ES using either mode of stimulation (i.e., responses increased with increasing stimulus current to a saturated plateau). This is in contrast to the reports from Raggio and Schreiner (1994; 1999), who observed non-monotonic responses in almost half of their recordings using bipolar ES. While it is tempting to attribute the difference to the mode of stimulation, Hartmann et al. (1997) also used bipolar ES, but did not report a significant proportion of non-monotonic responses. Cortical responses exhibit a rapid accommodation to repetitive ES (Schreiner and Raggio, 1996), and the shape of the input-output functions can therefore easily be affected by the stimulus presentation order. We randomized stimulus presentation order across both stimulus intensity and stimulating electrode, and are therefore confident that our results represent the input-output characteristics independent of accommodation and other activity-dependent processes. As noted in the Results, a substantial proportion of acoustically-responsive clusters in the normal-hearing animals had non-monotonic rate – level functions at CF, in accordance with previous reports (Clarey et al., 1992).

Mean cortical thresholds were higher than EABR thresholds in normal hearing animals for both modes of stimulation, consistent with previous reports for monopolar stimulation (Beitel et al., 2000). Cortical thresholds to monopolar stimulation were significantly lower than common-ground thresholds, even after normalizing to EABR thresholds. This difference in threshold is most simply explained by central integration of the broader cochlear activation patterns observed with monopolar stimulation (see for example Arenberg et al., 2000; Bierer and Middlebrooks, 2002; Frijns et al., 1996; Snyder et al., 2008). Consistent with previous reports (Raggio and Schreiner, 1999), a long-term SNHL encompassing the early developmental period resulted in a decrease in cortical threshold relative to EABR threshold, regardless of the mode of stimulation. This change in cortical threshold relative to EABR threshold indicates an increase in the excitability of AI, as there was no effect of a long-term SNHL on EABR threshold. Tan et al. (2007) have recently described a decrease in a range of activity-dependent molecular markers within the auditory cortex of the rat following a long-term SNHL. Amongst the many changes observed was a down-regulation of voltage-gated

sodium channels throughout all cortical layers, which would be expected to lead to a decrease in the intrinsic excitability of individual neurons. It would therefore seem likely that the increase in excitability of AI in our study is the result of a reduction in inhibition, rather than an increase in excitation *per se*. Chronic ES had a relatively small and variable effect on cortical thresholds: chronic monopolar stimulation resulted in little change in thresholds, while chronic common-ground stimulation partially restored thresholds, similar to the effect seen with evoked potential recording and chronic analogue ES (Klinke et al., 2001). Monopolar stimulation consistently resulted in a significantly smaller dynamic range than common-ground stimulation, but dynamic range was unaffected by a long-term SNHL, with or without chronic ES.

Local Tuning

Although cortical responses to ES of the auditory nerve were first reported over 60 years ago (Woolsey and Walzl, 1942), to our knowledge there have been no studies that have systematically examined the effects of hearing status (particularly after neonatal deafening) with or without chronic ES on the local tuning of cortical locations to stimulation at multiple cochlear sites. We found that at least 90% of cortical locations that respond to ES exhibit a significant degree of local tuning. The proportion of multi-unit clusters exhibiting local tuning was independent of ES mode or the hearing status of the animal, and is similar to that seen for acoustic stimulation in normal hearing animals (Phillips and Irvine, 1981; Schreiner and Sutter, 1992; Sutter, 2000). It is of interest, however, that both stimulation mode and hearing status could affect the depth of tuning. Because of the relatively shallow tuning commonly observed in the auditory midbrain with pulsatile ES (e.g. Vollmer et al., 2007), we chose to express the depth of tuning as the increase in threshold for a given shift along the basilar membrane rather than using the more common metric of the bandwidth at a specified level above threshold. Using the Greenwood cochlear frequency-position function (Greenwood, 1990) and the AI data of Phillips et al. (1994) we calculate the depth of tuning for acoustic stimulation to be in the order of 40 dB/mm. Monopolar stimulation resulted in relatively shallow tuning (1.9 dB/mm), while common-ground stimulation produced deeper tuning (2.7 dB/mm). Prolonged periods of profound deafness, with or without chronic common-ground stimulation, did not produce changes in the depth of tuning relative to normal hearing animals. However, prolonged periods of profound deafness resulted in a trend towards shallower tuning for monopolar stimulation, and chronic monopolar stimulation resulted in a significant increase in the depth of tuning. These results are consistent with the general view that monopolar stimulation results in broad activation in the cochlea and throughout the auditory pathway (see for example Arenberg et al., 2000; Bierer and Middlebrooks, 2002; Frijns et al., 1996; Snyder et al., 2008). A naïve comparison of these results with those obtained with acoustic stimulation would give the impression that all modes of ES result in markedly broader tuning than acoustic stimulation. However, if the dynamic ranges of the different forms of stimulation are taken into consideration, then all modes of stimulation result in an increase in threshold of approximately 50% of the dynamic range for each millimeter shift along the basilar membrane.

Cochlea-to-cortex mapping

In contrast to the local tuning of units in AI, the cochleotopic organization across AI was significantly affected by the experimental interventions (see Figure 7). Consistent with previous reports that a long-term SNHL in animals neonatally deafened with ototoxic drugs, results in weak or no signs of the normal cochlea-to-cortex mapping (Dinse et al., 1997, 2003; Raggio and Schreiner, 1999), we found no evidence of such mapping in long-term deaf cats. This is in stark contrast to the effects of a long-term SNHL in the lower auditory centers, where cochleotopic organization is well preserved at levels up to and including the central nucleus of the inferior colliculus (Leake et al., 2000; Moore et al., 2002; Shepherd et al., 1999; Snyder et al., 1990). These results suggest that the disruption in the cochlea-to-cortex

mapping must occur either in the thalamus, its projections to AI, or in AI itself. Most importantly, we found that chronic ES resulted in cochlea-to-cortex mapping that was remarkably similar to that seen in normal hearing controls, regardless of the mode of stimulation. To our knowledge, the only previous account of the effects of chronic ES is a preliminary report by Dinse et al. (2003) of a study in which optical imaging was used to assess the effects of a 3-month period of chronic stimulation in neonatally deafened cats. In contrast to our results, they reported a “profound reduction of representational selectivity” in AI of these cats. This reduction in cochleotopy reflected the fact that the region activated by a given electrode could cover nearly the entire AI. It seems likely that stimulus current in that study would have had to be well above threshold to generate a measurable reflectance signal, and that their results reflect the cortical spread of activity at supra-threshold levels that we also observed. Our results indicate that cortical cochleotopy, as conventionally defined in terms of near-threshold responses, is lost as a consequence of a profound neonatal SNHL but is normal or near-normal in animals receiving environmentally-derived chronic ES. This result suggests that cochleotopy in the thalamo-cortical system is much more dependent on (normal or near-normal) afferent activity than is cochleotopy in the IC or at lower brainstem levels. The time at which ES was introduced in this study leaves it unclear whether it prevented the loss of cochleotopy or restored cochleotopy that had been lost in the period between deafening and the initiation of stimulation.

Cortical spread

Prolonged periods of profound deafness, with or without chronic ES, resulted in a three-fold increase in the area of cortex that responded to a stimulus 2 dB above the minimum cortical threshold. This increase in cortical spread is in agreement with other studies (Dinse et al., 1997, 2003; Klinke et al., 1999; Kral and Tillein, 2006), and has been interpreted as a degradation of the cochleotopic organization of the cortex (Raggio and Schreiner, 1999). These results are in contrast to the normal spread of activation in the central nucleus of the inferior colliculus after a long-term SNHL, with or without chronic multichannel stimulation (Leake et al., 2000; Snyder et al., 1990). The present study used only chronic multichannel stimulation and therefore does not allow us to comment on the spread in activation seen in the central nucleus of the inferior colliculus with chronic single-channel stimulation (Snyder et al., 1990; Moore et al., 2002). Interestingly, for all experimental treatment groups, the cortical spread was the same for both modes of stimulation, which is contrary to the general view that monopolar stimulation results in broad activation in the cochlea and throughout the auditory pathway (see for example Arenberg et al., 2000; Bierer and Middlebrooks, 2002; Frijns et al., 1996; Snyder et al., 2008). These results suggest that the increased cortical spread does not reflect peripheral (or even lower brainstem) effects, but reflects a down regulation of inhibition in the cortex and/or changes in the efficacy of diffuse thalamo-cortical projections or of horizontal connections within AI.

When cochleotopic organization is assessed using the local tuning metric, the more commonly reported result of monopolar stimulation resulting in less selective activation is seen. However, when cochleotopic organization is assessed using either the cochlea-to-cortex mapping or cortical spread metrics, the cochleotopic selectivity of monopolar stimulation is equal to that of common-ground stimulation. This pattern of differences is of interest given that the choice of stimulation mode is of clinical relevance. Most modern cochlear implants use monopolar rather than bipolar or common-ground stimulation, as the lower thresholds with monopolar stimulation provide several engineering advantages (viz., lower power consumption, and short-duration pulse-widths leading to higher stimulation rates), albeit at the cost of broader activation in the cochlea. For a long time, it was thought that the broader activation produced by monopolar stimulation would result in poorer speech perception, but this has not proved to be the case (Mens and Berenstein, 2005). The fact that monopolar stimulation can provide

adequate spectral cues for speech perception despite resulting in broader activation in the cochlea, and poorer local tuning in AI, suggests that the other aspects of the pattern of cortical activation that are similar for the two modes of stimulation might be of greater importance than local tuning for speech perception.

Further considerations

High performing cochlear implant patients can exhibit near-normal open-set speech perception, at least in a quiet environment. Although the importance of implant experience in the clinical performance of cochlear implant users cannot be over emphasized (Blamey et al., 1996; Gantz et al., 1993; Rubinstein et al., 1999), the effects of the early reactivation of the auditory pathway via chronic ES must underlie at least part of this remarkable performance. There is growing evidence of both top-down and bottom-up influences on the plasticity of AI, with the relative contribution of the each fluctuating during development (for review see Kral and Eggermont, 2007). The present study focused on the effects of a profound neonatal SNHL, with or without chronic ES, on the cochleotopic organization of AI. Stimulation was delivered via a clinical cochlear implant and therefore contained behaviorally relevant auditory information including vocalizations (both self-generated and produced by other animals housed in the colony) and auditory stimuli related to daily feeding, grooming, and maintenance of the animal facility. Although it would be expected that environmentally-derived stimulation containing salient auditory information would have the strongest effects on cortical plasticity (see for example Bao et al., 2004), even naïve stimulation may drive cortical reorganization (Norena et al., 2006), and our results do not rule out the possibility that non environmentally-derived stimulation would not have had the same or similar effects on cochleotopy. The chronic stimulation was designed to mimic the optimal clinical conditions of early intervention and began when the animal was two months old. While there is substantial evidence of plasticity in the mature central auditory pathway (for reviews see Irvine, 2007; Weinberger, 2007), there is also evidence for ‘critical periods’ after which the effects of chronic ES are severely attenuated (Kral et al., 2006). The effect of a delay in reactivation of the auditory system on the cochleotopic organization of AI is yet to be elucidated, but the clinical evidence would suggest that a long period of delay is likely to result in a significant degradation of the cochleotopic organization.

Conclusion

Cochlear implants provide an opportunity to study the effects of elimination and restoration of afferent input on the functional organization of AI. A neonatally-induced profound SNHL results in an almost complete absence of input (both driven and spontaneous) from the peripheral auditory system to AI during the sensitive periods of early development. Under such conditions, the development of the input-output functions of neurons and local tuning in AI are largely unaffected. In contrast, the broader cochleotopic organization of AI is dependent on afferent activity: if AI develops in the absence of input from the peripheral auditory system, the normal cochleotopic organization of AI is completely lacking. Reactivation of the auditory system with behaviorally relevant ES via a cochlear implant results in a near normal cochleotopic organization of AI. The maintenance or re-establishment of a cochleotopically organized AI by activation of a restricted sector of the cochlea is likely to contribute to the improved clinical performance observed in human patients implanted at a young age.

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Figure 1. Intracochlear electrode array and EABR thresholds

A) X-ray image showing the electrode array within the basal turn of the scala tympani of a cat cochlea. Scale bar = 2 mm. RW = Round Window. Electrode numbering system: 1 = Apical; 8 = Basal; E = Extracochlear Ball. Note that electrode 8 is not used in monopolar stimulation. B & C) Mean ($\pm$ SEM) EABR thresholds varied systematically with the location of the intracochlear stimulating electrode for common-ground (B, 100 μ s per phase) and monopolar (C, 25 100 μ s per phase) stimulation. Normal hearing, long-term deaf and chronically stimulated animals have been pooled as there was no significant difference between groups (Two-way ANOVA; $p > 0.05$). * = threshold significantly greater than that for stimulation of electrode 1 (Two-way ANOVA; $p < 0.05$; Bonferroni post-hoc t-tests; $p < 0.05$). The cartoon insets at the top of B & C illustrate the current flow for the two stimulation modes.

Figure 2. Single- and multi-unit cluster response

A) Raw data recording from a multi-unit cluster response in a long-term deaf animal (D10). Activity was recorded in response to a range of stimulus currents presented to E1 (monopolar stimulation), indicated by the stimulus artifact (SA). * indicates a single unit that was isolated from the multi-unit cluster. B) Single-unit (waveform shown in inset in bottom panel) post-stimulus time histograms exhibit an increase in response with increasing current. C) Multi-unit post-stimulus time histograms (from the remaining units in the recording) also exhibit an increase in response with increasing current. Both the single- (D) and multi-unit (E) input-output functions were monotonic and were well approximated by a saturating Gaussian function.

Figure 3. Best Electrode and Depth of Tuning

A) Sample input-output functions for monopolar stimulation on different intracochlear electrodes for a multi-unit cluster response recorded from a long-term deaf animal (D10). Dashed vertical lines indicate the EABR threshold for each stimulating electrode. B) Plot of the thresholds of activation, relative EABR threshold, for each stimulating electrode (error-bars indicate the estimated error in determining the threshold). From this plot E2 was defined as best electrode and the depth of tuning was calculated to be 4.6 dB.

Figure 4. Depth of Tuning

Mean ($\pm$ SEM) depth of tuning for common ground (CG) stimulation was significantly deeper than monopolar stimulation (MP; Two-way ANOVA; $p < 0.01$) and for monopolar stimulation, chronic stimulation resulted in deeper tuning than chronic deafness. * $p < 0.01$

Figure 5. Cochleotopicity using common ground stimulation

Representative ‘Best Electrode’ maps of AI in normal hearing (N1), long-term deaf (D5) and chronically stimulated (CG2) animals using common ground stimulation. Filled symbols represent the best electrode at each recording site (see text for details). Crosses indicate locations for which it was not possible to elicit a response to electrical stimulation. Solid grey lines indicate recordings made down the rostral bank of PES. Dashed grey rectangle indicates area of interest for determination of cortical spread (see Figure 8). Black triangles in B indicate characteristic frequencies for ipsilateral acoustic stimulation. SSS = Suprasylvian Sulcus; PES = Posterior Ectosylvian Sulcus; AES = Anterior Ectosylvian Sulcus; DVCR

indicator = 2 mm bar lengths; D = Dorsal; V= Ventral; C = Caudal; R = Rostral; CR Extent = Caudo-Rostral Extent.

Figure 6. Cochleotopicity using monopolar stimulation

Representative 'Best Electrode' maps of AI in normal hearing (N3), long-term deaf (D10) and chronically stimulated (MP2) animals using monopolar stimulation. Details as in Figure 5 with the addition of grey symbols indicating 'broadly tuned' units (see text for details).

Figure 7. Cochlea-to-cortex mapping

A) There were significant (mean $\pm$ SEM) cochlea-to-cortex mapping correlations (Pearson correlations; see text for details) in normal hearing and chronically stimulated animals (CG: common-ground; MP: monopolar), but not in long-term deaf animals. B) Mean ($\pm$ SEM) cochlea-to-cortex mapping in chronically stimulated animals was not significantly different from that in normal hearing animals. There was no difference in either the cochlea-to-cortex mapping correlations or the cochlea-to-cortex mapping factors between common-ground and monopolar stimulation.

Figure 8. Extent of Cortical Activation

A) As the common ground (CG) stimulus level on a single intracochlear electrode (E1) is increased from the minimum cortical threshold to supra-threshold levels, the extent of cortical activation in a normal hearing animal (N1) monotonically increases. Insets show a 7×5 mm region of the cortex, indicated by dashed rectangle in Figure 5, activated with varying currents indicated by the arrows. B & C) A similar increase in the extent of cortical activation with increasing stimulus level is seen for stimulation in a long-term deaf animal (B, D5) and a chronically stimulated animal (C, CG2). D) Stimulation at 2 dB above minimum cortical threshold resulted in a more restricted activation in normal hearing animals than long-term deaf or chronically stimulated animals. There was no difference in the activated area between different stimulating electrodes or modes of stimulation. * $p < 0.001$