Spatial Selectivity to Intracochlear Electrical Stimulation in the Inferior Colliculus is Degraded After Long-Term Deafness in Cats

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In contemporary multichannel cochlear implants (CIs), the functional independence of stimulation sites or channels is dependent on the selective activation of neural populations in the auditory pathway. Psychophysical studies in human CI users have demonstrated that greater channel interaction is negatively correlated with the ability to rank the pitch of individual CI channels (Townsend et al. 1987) and with speech discrimination performance (Chatterjee and Shannon 1998; Henry et al. 2000; Throckmorton and Collins 1999; Zwolan et al. 1997).

Particularly poor speech discrimination performance is observed in congenitally and prelingually deaf CI users who are implanted as adults and in individuals who are implanted after long durations of deafness (Bushy et al. 1991; Dawson et al. 1992; Ruben 1986). However, it is unclear at present to what extent these observations are due to peripheral pathology or to functional changes in the central auditory system. Although congenitally deafened individuals are likely to have relatively severe cochlear pathology after long periods of deafness, their speech discrimination performance shows some improvement with increasing auditory experience (Busby et al. 1991). These observations suggest that chronic electrical stimulation of the cochlea leads to functional alterations in the central auditory system even after long-term deafness.

Animal studies have shown that hearing loss induced during the early postnatal period results in progressive and more profound anatomical degeneration in the central auditory system (e.g., Lustig et al. 1994; Moore 1990; Nishiyama et al. 2000; Nordeen et al. 1983) and functional degradation or reorganization as compared with changes observed following auditory deprivation later in life (e.g., Hardie et al. 1998; Moore et al. 2002; Raggio and Schreiner 1999; Shepherd and Javel 1997; Shepherd et al. 1999; Silverman and Clopton 1977; Trune 1982). At the University of California San Francisco (UCSF), we have developed an animal model of neonatal or very early acquired profound hearing loss to evaluate the effects of early auditory deprivation and duration of deafness on signal processing in the central auditory system. Prior studies have demonstrated that neonatally induced long-term deafness in cats results in severe peripheral pathology with survival of <10% of spiral ganglion neurons (Rebscher et al. 2001; Vollmer et al. 2000, 2005). In addition, such long-term deafness results in degraded spatial selectivity of sinusoidal electrical stimulation (Rebscher et al. 2001; Vollmer et al. 2000) and in degraded temporal resolution of neurons in the auditory midbrain, specifically in the central nucleus of the inferior colliculus (Vollmer et al. 2005).

The objective of the present study was to assess in more detail the functional consequences of early-acquired bilateral auditory deprivation and duration of deafness on the processing and representation of electrical stimuli in the auditory system. Central neuronal responses to intracochlear electrical stimulation (ICES) were evaluated in neonatally deafened cats after different durations of deafness. Because the nature of the experiments does not allow a parametric series of experiments to study the effects of deafness duration, we selected two groups of animals to represent an intermediate and a prolonged duration of deafness with clearly different extents of spiral
ganglion cell (SGC) degeneration. One group of animals (short-deafened unstimulated animals, SDU group) was studied after <1.5 yr of deafness (range: 6–14 mo; mean SGC survival ~45% of normal); the second experimental group (long-deafened animals, LD group) was studied after prolonged durations of deafness of >2.5 yr (range: 30–86 mo; mean SGC survival <7% of normal). The deafness histories of the experimental animals are summarized in Table 1.

The following auditory response parameters were evaluated in the present study: electrically evoked auditory brain stem response (EABR) thresholds and single- and multi-neuronal response thresholds in the inferior colliculus (IC), the cochleotopic organization of the IC, and the spatial selectivity, i.e., the spread of excitation/spatial tuning and dynamic range of ICES in cat IC.

Previous studies have reported conflicting results with respect to changes in IC response thresholds following long-term deafness. Two studies observed increased thresholds in the IC of long-deafened animals (pulses: Shepherd and Javel 1997; sinusoids: Vollmer et al. 2000). In contrast, a third study reported that deafness duration and the degree of peripheral pathology had no effect on IC thresholds to sinusoidal stimulation (Rebscher et al. 2001). To clarify the conflicting results, the present study reports IC thresholds for both pulsatile and sinusoidal stimuli in a larger number of long-deafened animals, including animals reported previously by our lab (Rebscher et al. 2001; Vollmer et al. 2000).

Whether the normal cochleotopic organization of ICES is maintained after long durations of neonatal deafness is likewise disputed in the literature. Previous studies in normal hearing cats (e.g., Brown et al. 1997; Merzenich and Reid 1974; Oliver 1987; Oliver and Morest 1984; Rose et al. 1966), in neonatally deafened, unstimulated cats with deafness durations pooled over 0.5–2.6 yr, and in neonatally deafened, early stimulated cats (age at initial stimulation 7.5–18 wk, stimulation period 4–30 wk) (Snyder et al. 1990, 1991) demonstrated a cochleotopic frequency gradient that was systematically related to IC depth. In contrast, Shepherd and colleagues (1999) described only a rudimentary cochleotopic organization in neonatally deafened animals (duration of deafness: ~12 mo) and in one animal that was deafened as a juvenile and studied after a long duration of deafness (7.8 yr). None of these earlier studies specifically explored the effect of long-term auditory deprivation on the cochleotopic organization of the IC in more than one long-deafened animal. To resolve this conflict, a principle focus of the present study is to identify and compare the cochleotopic organization of ICES in both the external (ICX) and the central nucleus (ICC) of the IC in a larger number of short- and long-deafened animals.

We previously reported spatial tuning width data of IC neurons in response to sinusoidal stimulation in several LD animals (Rebscher et al. 2001; Vollmer et al. 2000). The present study extends our previous work by examining a larger cohort of long-deafened animals, including a group examined after undergoing chronic electrical stimulation, by determining the spread of excitation in response to both sinusoidal and pulsatile electrical stimulation, and by examining the dynamic ranges of single neurons and multineuron clusters. The rationale for evaluating the responses to pulses was to examine the spatial selectivity of neurons in response to the pulsatile waveform that was used to evaluate temporal resolution in the same long-deafened animals reported in a previous study (Vollmer et al. 2005) and to investigate waveform-specific differences in thresholds and spatial distributions of responses in the IC for sinusoidal and pulsatile cochlear stimulation. Because pulsatile signals are used in most contemporary CI speech processing strategies, it is also of interest to evaluate spatial selectivity of neuronal responses to pulsatile signals.

**TABLE 1. Summary data for neonatally deafened animals**

<table>
<thead>
<tr>
<th>Animal ID</th>
<th>Age at Initial Stimulation, mo</th>
<th>Duration of Chronic Stimulation, wks</th>
<th>Age at Study, mo</th>
<th>Spiral Ganglion Survival, % normal</th>
<th>Stimulation Characteristics</th>
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<td>68.8</td>
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Summary of onset and duration of deafness, chronic stimulation history and behavioral training for the neonatally deafened animals included in this report. SP, speech processor; Beh, behavioral training.
A final goal of the current study was to study the effects of chronic electrical stimulation on threshold distributions and spatial selectivity in the adult auditory system following long-term congenital deafness. The LD animals in the present study were divided into two subgroups. The first group was studied acutely after prolonged deafness (long-deafened, unstimulated animals, LDU group), and the second group received a unilateral CI as adults and several weeks to months of electrical stimulation (long-deafened stimulated animals, LDS group) (Table 1). With the exception of one additional animal in the LDU group (K03), the individual animals in the subgroups and the electrical signals used for chronic stimulation of the LDS animals are identical to those reported in our previous study on temporal resolution in LD animals (Vollmer et al. 2005). The earlier study indicated that chronic ICES reversed the degradation in temporal resolution of electrical stimulation observed in unstimulated long-deafened animals. The findings from the prior study demonstrated that auditory experience can profoundly alter the functional status of the long-deafened, adult auditory system despite the extremely severe cochlear pathology observed in these animals and emphasized the potential of brain plasticity in the modulation of temporal resolution and coding of electrical signals in the central auditory system. The evaluation of both temporal and spatial data from the same animals provides a valuable basis to assess the potential and the limitations for modulatory effects elicited by chronic ICES on different signal processing strategies in the long-deafened central auditory system.

METHODS

Deafening and implantation

This report includes results obtained from 5 neonatally short-deafened cats that were studied as adults after \( \leq 1.5 \) yr of deafness (range of deafness durations: 6–14 mo) and 12 long-deafened animals with durations of deafness exceeding 2.5 yr (range: 30–86 mo). All of these animals were deafened as newborns by systemic administration of neomycin sulfate (40–70 mg/kg im/sid) beginning on the day after birth and continuing for a total of 16–25 days (e.g., Leake et al. 1991). Neomycin injections were terminated when profound hearing loss (>105 dB) was confirmed by the absence of auditory brain stem responses to clicks (0.2 ms/ph, 20 pp). None of the animals demonstrated any residual hearing at the time of study. The animals with durations of deafness \( \leq 1.5 \) yr did not receive any electrical cochlear stimulation until the time of the final acute electrophysiological experiment and will be referred to as short-deafened unstimulated (SDU) animals.

The long-deafened animals were maintained for periods ranging from 2.5 to 7.2 yr prior to study and were divided into two groups. Seven unstimulated cats received a unilateral CI as adults after these prolonged periods of deafness and were studied acutely (long-deafened unstimulated, LDU animals). Two of these LDU animals (K16 and K24) were implanted immediately before study; the others were implanted \( \geq 1 \) wk before the electrophysiological experiment to allow thresholds to stabilize. Five additional long-deafened cats were implanted as adults after prolonged periods of deafness (range: 42–84 mo) and received several weeks to months of chronic electrical stimulation prior to study (long-deafened stimulated, LDS animals). Electrical stimulation of the auditory nerve in these animals was initiated at ages ranging from 3.5 to 7.0 yr with an average age of 5.5 yr. Table 1 summarizes the deafness and chronic stimulation histories of the individual neonatally deafened animals included in the present study.

Fourteen acutely deafened adult cats with normal auditory experience prior to the experiment served as control cats. Controls were deafened 1.5–3.5 wk before study by intravenous administration of kanamycin and ethacrylic acid (Xu et al. 1993). It should be noted that spiral ganglion survival has been shown to be virtually normal 2 wk after deafness is induced by a very similar method (administration of kanamycin and aminoxyacetic acid) (Leake et al. 1987); thus spiral ganglion survival in this control group is assumed to be normal. About half of the control animals were implanted immediately before the experiment, the others were implanted \( \sim 1–2 \) wk before study.

Prior to all surgical procedures, the animals were sedated (ketamine: 22–33 mg/kg; acepromazine maleate: 0.1 mg/kg; or inhaled isoflurane), and anesthesia was induced by pentobarbital sodium (7–10 mg/kg) delivered via an intravenous catheter. An areflexic level of anesthesia was maintained by intravenous infusion of pentobarbital sodium in Ringer solution. All procedures followed National Institutes of Health and UCSF/ACUC guidelines for the care and use of laboratory animals. Procedures of deafening, implantation, chronic stimulation, surgical preparation and recording techniques in the physiological experiment have been described in detail in previous reports (e.g., Snyder et al. 1995; Vollmer et al. 1999, 2005).

Cochlear electrodes were fabricated with two bipolar pairs of platinum-iridium ball-shaped electrodes molded into a silicone rubber carrier and were implanted into the left scala tympani under general anesthesia using aseptic surgical procedures. Because of the large round window and expanded scala tympani in the basal region of the cat cochlea, the intracochlear position of the more basal electrode pair (3,4) relative to the modiolus is more variable (Leake et al. 2000). In the present study, the thresholds of the basal electrode pair (3,4) tend to be higher, the spatial tuning curve (STC) widths tend to be broader, and the dynamic ranges tend to be lower than those observed for the more apical electrode pair (1,2). Also, the thresholds, widths and dynamic ranges for electrode pair 3,4 tend to have greater intersubject variability than those observed for electrode pair 1,2. Consequently, with the exception of the analyses of the cochleotopic organization in the IC, only data from stimulation with the apical electrode pair 1,2 are reported in the present study. The stimulating contacts (~290 μm in diameter) comprising the apical electrode pair were separated from each other by 1 mm; they were arranged in an offset-radial orientation and were located on average at 49% (electrode 1) and 45% (2) of basilar membrane distance from the cochlear base. In the normal cochlea the stimulating electrodes would have represented frequencies of ~5–6.3 kHz. These frequency assignments are calculated based on Greenwood’s frequency-position function (Greenwood 1974, 1990) using the revised constants for the cat cochlea suggested by Liberman (1982).

Chronic stimulation (LDS cats)

In the LDS cats, chronic electrical stimulation was applied for 4 h/day, 5 day/wk for a mean duration of 21 ± 11 (SD) wk. EABR thresholds were determined as described previously (Moore et al. 2002), and chronic stimulation levels were set with maximum signal intensity adjusted to 2 dB above EABR threshold for each individual subject. All LDS animals were stimulated with the apical electrode pair 1,2. Due to lead failure, however, subjects CD393 and CH539 were stimulated with electrode pairs 2,3 and 1,4, respectively, during the final weeks of stimulation.

Electrical stimulation was delivered either by an analogue speech processor (SP) that transcended ambient environmental sounds into electrical signals delivered to the implanted electrodes or by computer-generated amplitude modulated pulse trains. For stimulation with the SP, the frequency spectrum of the analogue stimulation was band-pass filtered from 250 Hz to 3 kHz with a roll-off at the shoulder frequencies of 6 dB/octave. The processor output was logarithmically amplitude-compressed to a dynamic range of 6 dB. The maximum peak-to-peak output was set to 6 dB above the animals’ individual
EABR thresholds. The peak intensity of the pulsatile signals was set to 2 dB above EABR threshold. The computer-generated signal was a continuous train of electrical pulses (200 μs/phase, charge-balanced biphasic square-wave pulses) delivered at a 300pps carrier rate and sinusoidally amplitude modulated (SAM) at a frequency of 30 Hz with a modulation depth of 100% (300/30 SAM). The choice of these stimuli was based on previous studies showing that chronic electrical stimulation of the developing and long-deafened adult auditory system using these signals resulted in a significant increase in temporal resolution of ICC neurons (Snyder et al. 1995; Vollmer et al. 1999, 2005).

One animal (CH611) received initial stimulation with an unmodulated pulse train at 80 pps that was delivered by a backpack stimulator for a period of 2 wk. This animal did not tolerate stimulation outside its home cage, and the 80 pps stimulation was used until an analogue SP became available as a backpack stimulator for use in the home cage.

All but one LDS cat received additional stimulation during behavioral training sessions (5 day/wk; see Table 1). These training sessions generally lasted about one hour, although the total duration of suprathreshold electrical stimulation during the behavioral sessions was brief (a total of usually <30 s).

Electrophysiological procedures

EABR and IC thresholds (0 dB = 1 μA peak-to-peak) were estimated for each subject, and final acute electrophysiological experiments were conducted using tungsten microelectrodes to record responses of multi-neuronal clusters and single neurons in the IC. Several penetrations through the IC were made, and response thresholds were recorded at intervals of 100 μm. Responses to biphasic electrical pulses (200 μs/phase) and to three cycles of a 100-Hz sinusoid were recorded. To estimate thresholds, the intensities just sufficient to activate the neuron(s) were determined using audiovisual criteria. Thresholds were plotted as a function of IC depth along the tonotopic gradient of the IC to obtain STCs (Fig. 1). As reported previously, despite intra- and interindividual variability in shapes and widths, STCs are typically W-shaped (e.g., Leake et al. 2000; Moore et al. 2002; Rebscher et al. 2001; Snyder et al. 1990; Vollmer et al. 1999, 2000). The highest threshold region between the two locations of minimum thresholds was defined as the border between the two nuclei (see vertical - - - in Fig. 1) and allowed neurons to be assigned to either ICX or ICC. The location of minimum threshold within the IC (“best location”) for stimulation with a given electrode/electrode pair is an indirect measure of the cochleotopic organization of the IC. To evaluate the cochleotopic organization after different durations of deafness, the best locations were estimated and compared for stimulation with the apical electrode pair (1,2) and the basal electrode pair (3,4). The best locations were separately determined for the ICX and the ICC.

The widths of the STCs were measured for stimulation with the apical electrode pair (1,2) at 6 dB above the minimum ICC threshold for sines and at 2 dB above minimum ICC threshold for pulses to evaluate the extent of excitation across the tonotopic gradient. Because intensities of 6 dB above minimum pulse threshold exceeded the dynamic range of most of the STCs for LD animals, 6 dB STC widths for pulses could not be calculated in many instances, and these data are not included in this report.

In addition, the difference between minimum ICC threshold and the higher threshold recorded at the border between ICX and ICC was determined to study the range of intensities over which differences in the spatial extent of excitation were elicited as an estimate of the neural dynamic range for electrical stimulation in the ICC (Fig. 1). At suprathreshold intensities that exceeded the dynamic range, continuous regions of both ICX and ICC were activated.

Histology

After completion of the electrophysiological experiment, the cochleas of all short- and long-deafened animals were prepared for histological analyses. The methods for the preparation of cochlear specimens were identical to those described by Leake et al. (1999) and will be described here only briefly. The cochleae were perfused through the scalae with mixed aldehyde fixative, postfixed in osmium tetroxide, decalcified briefly, embedded in LX resin and mounted on glass slides as block surface preparations. Semithin sections (1–2 μm) were cut at ~2-mm intervals along the basilar membrane, stained with toluidin-blue and examined in light microscopy to assess the condition of the organ of Corti and the survival of SGCs. SGC volume ratio (a measure of relative cell density) in Rosenthal’s canal was determined.
using a point-counting method (Leake and Hradek 1988; Leake et al. 1999). Earlier studies in normal hearing animals using this method provided normative data for the cat spiral ganglion (Leake and Hradek 1988). These data served as a control reference in the present study and allowed the SGC density of the SDU and LD cats to be expressed as percent of normal.

Data analysis

For descriptive statistics of normally distributed data, the mean ± SD are reported. If the data were not normally distributed, the median (MDN) and the quartile deviation (Q) are reported. The t-test was used for comparisons between two independent groups. If the data did not meet the criteria for normality and equal variance, the nonparametric Mann Whitney-U test was used for comparisons. If the difference between LDU and LDS animals was not statistically significant (t-test; \( t = -3.123, df = 10, P < 0.05 \)), the mean SGC density in the SDU group is expressed as percent of normal.

SGC survival between LDU and LDS animals is statistically significant (t-test; \( t = -3.123, df = 10, P < 0.05 \))

Cochleotopic organization

To study the effects of deafness on the tonotopic frequency organization in the IC, we determined the best locations for pulsatile and sinusoid bipolar stimulation with the apical electrode pair (1,2) that is centered on average at a location that would represent ~5.5 kHz in the normal cochlea and a basal electrode pair (3,4) centered at ~12 kHz. The best locations in the midbrain were estimated separately for the ICX and the ICC. As demonstrated for the ICC in Fig. 4, the best locations for pulsatile and sinusoidal stimulation were virtually identical for electrode pair 1,2 (A), and the same was true for electrode pair 3,4 (B; paired t-test and Wilcoxon signed-rank test; \( P > 0.07 \) for all groups).

Thresholds for pulsatile stimuli were not measured in some animals, and in other animals, pulsatile thresholds were not measured throughout the recording experiment or consistently along an electrode penetration. Furthermore, because of the limited dynamic range and broad tuning, STCs for pulsatile stimulation, especially for LD animals, often did not allow a clear definition of the border between ICX and ICC or of the
best locations for given electrode combinations. In contrast, STCs for sinusoidal stimulation are typically more sharply tuned than those for pulses (see Fig. 1) and allow a more precise estimation of the best locations. For these reasons, the number of best locations derived for sinusoidal stimulation is substantially larger than those for pulsatile stimulation. The following comparisons of best locations are limited to those based on sinusoidal stimulation.

Figure 5 compares the best locations for sinusoidal stimulation with electrode pairs 1,2 and 3,4 in the ICX (A) and the ICC (B). Generally, the best locations in the ICX (Fig. 5A) for the apical electrode pair 1,2 are at equal or deeper locations than those for the basal electrode pair 3,4. In the LDU (t = 2.862, df = 4) and LDS animals (t = 4.078, df = 6) the mean best locations for pair 1,2 [1,188 ± 460.29 and 1,271.43 ± 467.13 (SD) μm, respectively] were significantly deeper than those for pair 3,4 [1,134 ± 436.84 and 914.29 ± 333.81 (SD) μm, respectively; paired t-test; P < 0.05]. In control and SDU animals, the best locations for pair 1,2 [mean: 1,671.25 ± 788.62 (SD) μm and median: 870 ± 222.5 (Q) μm, respectively] were also deeper than those for pair 3,4 [mean: 1,498.75 ± 805.03 (SD) μm and median: 815 ± 210 (Q) μm, respectively], but these differences did not achieve statistical significance (t-test and Wilcoxon signed-rank test, respectively; P > 0.05).

When the best locations in the ICC for stimulation with the basal electrode pair 3,4 are plotted against the best locations for stimulation with the apical electrode pair 1,2, most data points lie above the diagonal (Fig. 5B), i.e., the best locations for stimulation with the apical electrode pair 1,2 tend to be more superficial than those for stimulation with the basal electrode pair 3,4. Statistical comparisons show that for all four groups of animals, the best locations for electrode pair 1,2 are significantly more superficial than those for stimulation with the basal electrode pair 3,4 (paired t-test; P < 0.01 for all groups). Moreover, these differences in the median best locations for electrode pair 1,2 versus pair 3,4 were virtually identical for the control [median: 500 ± 213.75 (Q) μm], SDU [mean: 400 ± 170 (SD) μm], and LD animals [mean: 700 ± 328.75 (SD) μm; Kruskal-Wallis; P > 0.05]. These results suggest consistent activation of higher frequency areas with the more basal electrode pair and activation of lower frequency areas with the apical electrode pair for all groups of animals.

In summary, the cochleotopic organization of the ICC is inverse to that of the ICX, and this organization appears to be maintained independent of the duration of deafness.

Response thresholds

An important issue in the present study is whether progressive duration of deafness and the consequent loss of SGCs lead to changes in neuronal response sensitivity. To address this issue, EABR thresholds to pulses were measured, and for each STC, the minimum neuronal response thresholds in ICX and ICC to pulses and sines were determined. First, to characterize global trends in the data, minimum neuronal thresholds for sinusoidal stimulation (apical electrode pair 1,2) are pooled for all experimental groups, and the
resulting analysis shows that thresholds in the ICX and ICC are strongly correlated ($R^2 = 0.7642, P < 0.001$). In addition, mean thresholds of ICC neurons pooled for all animals [34 ± 6.5 (SD) dB] are only slightly lower than ICX thresholds [35.2 ± 7 (SD) dB], although this small difference in threshold is significant (paired t-test; $t = 2.325, df = 47, P < 0.05$). In view of the previously reported differences in the physiological response properties to auditory stimulation between ICX and ICC neurons (e.g., higher frequency following ability, lower response latencies in the ICC) (Vollmer et al. 1999) and the somatosensory and efferent cortical inputs known to influence responses in the ICX (e.g., Aitkin 1986), the following results focus on data obtained from the ICC.

A pairwise comparison between minimum response thresholds for sines and for pulses is illustrated in Fig. 6A for all groups of animals. Response thresholds vary over a wide range of stimulus amplitudes. LD animals generally show higher response thresholds than control animals. At low intensities, sinusoidal and pulsatile response thresholds have a tendency to approach equal charge per phase (---). At higher threshold levels, sinusoidal thresholds tend to increase more rapidly than pulsatile thresholds, and the linear regression line approaches the equal intensity line (/). Also, at higher response thresholds the scatter of the data decreases. However, minimum sinusoidal thresholds are always lower than minimum pulsatile thresholds. Because of the low number of threshold pairs ($n = 2$), the SDU animals were excluded from the statistical comparison. For all other groups, the differences between minimum sinusoidal and pulsatile thresholds are significant (LDU, LDS: paired $t$-test; controls: Wilcoxon signed-rank test; $P < 0.001$ for all groups).

Figure 6B shows the relationship between the lowest minimum ICC threshold determined for a given animal and its EABR threshold for stimulation with the identical stimulus (200 μs/phase pulses). The two thresholds are significantly correlated ($R^2 = 0.7653, P < 0.001$). With the exception of one control animal (CH645) that demonstrated identical EABR and minimum ICC pulse thresholds, EABR thresholds are consistently higher than the lowest ICC thresholds. The mean difference between the two thresholds [4.39 ± 3.43 (SD) dB] is relatively constant across groups. Again, the long-deafened animals generally show a tendency for higher ICC and EABR thresholds compared with both SDU and control animals.

To examine the effect of duration of deafness on response thresholds in greater detail, Fig. 7 displays final EABR thresholds as a function of the number of months of deafness, i.e., the age at which each of these neonatally deafened animals was studied physiologically. EABR thresholds increase progressively with longer durations of deafness. EABR thresholds from SDU animals are well within the variability of thresholds of control animals (grey area: ±SD of mean EABR thresholds for control animals), whereas all EABR thresholds from LD animals with durations of deafness > 30 mo (vertical ----) exceed the variability of the controls. Paired comparisons of EABR thresholds of LDU (K33: 48 dB and K51: 50 dB) and LDS animals (CH611: 49 dB and CD393: 52 dB) with similar durations of deafness (51 and 78 mo vs. 50 and 79 mo, respectively) show similar threshold values for both groups of animals ($t$-test; $P > 0.05$). Thus chronic stimulation appears not to affect EABR thresholds. However, given the small number of comparisons ($n = 2$), this statistical finding must be interpreted with caution.

When plotted as a function of SGC density (Fig. 7B), EABR thresholds show a progressive elevation with lower SGC density. Severe reductions in SGC density in LD animals to less than around 14% (vertical ----) are associated with thresholds that exceed the variability of control thresholds. Generally, similar trends are also observed for ICC thresholds to sinusoidal and pulsatile stimulation as a function of deafness duration and SGC density (results not shown).

Figure 8, A–C, summarizes the mean EABR thresholds (A), the median minimum ICC thresholds for pulsatile stimulation (B), and the median minimum ICC thresholds for sinusoidal stimulation (C) for control and experimental animals. In Fig. 8, the data for the LDU and LDS animals have been pooled (LD group). This was done because, as previously mentioned, there was no difference in EABR thresholds between two pairs of age-matched LDU and LDS animals (K33 and K51 vs. CH611 and CD393), and further comparisons of these same age-matched pairs showed that there was no difference in ICC thresholds for pulses and sines ($t$-test; pulses: $t = 1.426, df = 16$; sines: $t = 1.768, df = 11$; both $P > 0.05$). These additional results strengthen the hypothesis that chronic stimulation has no effect on response thresholds in LDS animals.

ANOVA showed that the differences in the mean EABR thresholds (Fig. 8A) among control, SDU, and LD animals are significant ($F = 14.11, df = 2, P < 0.001$). A subsequent Tukey test showed that there was no significant difference in EABR thresholds between control [mean: 41.17 ± 6.53 (SD) dB] and SDU [mean: 41.60 ± 2.61 (SD) dB] animals.
In contrast, LD animals had significantly higher EABR thresholds (mean: 51.6 ± 2.84 (SD) dB) than both control and SDU animals (P < 0.05).

Because minimum ICC thresholds for pulsatile stimulation were available for only two subjects in the SDU group (Fig. 8B), this group was not included in the statistical comparisons. The data indicate that LD animals have significantly higher thresholds for pulses than the control animals (Mann-Whitney ranked-sum test; t = 171.50, P < 0.001).

In addition, the differences in the median ICC thresholds for sines (Fig. 8C) among the control, SDU, and LD animals were significant (Kruskal-Wallis ANOVA on ranks; H = 15.87, df = 2, P < 0.001). In close agreement to the EABR thresholds, an all pairwise multiple comparison procedure (Dunn’s method) showed that there was no difference in median minimum ICC thresholds between control and SDU animals [31.5 ± 3.5 (Q) dB] and LD animals [32 ± 5.25 (Q) dB; P > 0.05]. In contrast, median minimum sinusoidal ICC thresholds from LD animals [39 ± 5.25 (Q) dB] were significantly higher than those from control and SDU animals.

Overall these results confirm that very long durations of deafness lead to significant increases in neuronal response thresholds. These increases were demonstrated both in far-field (EABR) and near-field recordings. Chronic stimulation had no apparent effect on response thresholds. However, because of the limited number of comparisons between age-matched LDU and LDS animals, this finding has to be treated with caution.

**Dynamic range**

Neural dynamic range is an estimate of the range of intensities between the minimum threshold for electrical excitation in an STC function and the suprathreshold intensity at which major continuous regions of the ICX and ICC are activated. Once the stimulus intensity exceeds the dynamic range, selective activation of neural populations is impossible, and stimulating channels in a multi-channel CI would presumably lose their functional independence. An important goal of the present study was to examine the effects of duration of deafness and electrical stimulation on the dynamic range of CI subjects. Dynamic range was studied for both pulsatile and sinusoidal stimulation.

Due to the difference in phase durations, STCs obtained with 100-Hz sinusoidal stimuli (5 ms/phase) generally have lower thresholds, markedly sharper tuning (Moore et al. 2002) and larger dynamic ranges than those obtained with pulses (biphasic pulses, 200 µs/phase; Fig. 1, A and B). Because STC widths tend to be very broad (Figs. 1B and 11) and dynamic ranges very small in LD animals (Figs. 1B and 9), a clear W shape of the STCs and a border between ICX and ICC were sometimes not identified. As a consequence, data on the dynamic ranges of STCs, particularly for pulsatile stimulation, are more limited for the long-term deafened animals. Figure 9 A summarizes the mean dynamic range for pulsatile stimulation in the control and LD animals. Because only one measure of dynamic range for pulsatile stimulation was available for the SDU animals, this

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**FIG. 7.** EABR thresholds for electrode pair 1,2 as a function of duration of deafness (A) and SGC density (B). Mean EABR thresholds for control animals are summarized in 1 symbol (○), grey area, ±SD of mean EABR thresholds for the control animals. —, linear regression line in A, power function in B. *-*, deafness duration (A) and SGC density (B) at which thresholds exceed SD of EABR thresholds for control animals. N, number of animals.

**FIG. 8.** Mean EABR thresholds (A), median minimum ICC thresholds for pulsatile stimulation (B) and median minimum ICC thresholds for sinusoidal stimulation (C) are shown for control, SDU, and LD animals. Electrode pair 1,2 was used for stimulation in all cases. Bars indicate SD in A and quartile deviation Q in B and C. * statistical significance (P < 0.05). Because of the low number of threshold measures to pulsatile stimulation, SDU animals in B were excluded from statistical analyses. Numbers in data bars indicate numbers of EABR and minimum ICC threshold measures included in the data set. LD, pooled long-deafened group, including LDU and LDS animals.
group is not included in the statistical analyses. There is no difference in dynamic ranges for pulses between the age-matched LDU and LDS animals (K33, K51 vs. CH611, CD393; t-test; \( t = 1.735, df = 5, P > 0.05 \)). Thus chronic stimulation does not appear to affect dynamic ranges in LD animals. The data from LDU and LDS animals were, therefore pooled for statistical analysis.

For pulsatile stimulation, the mean dynamic range from LD animals [4.35 ± 3.43 (SD) dB] is statistically smaller than that from control animals [14.76 ± 7.11 (SD) dB; t-test; \( t = 5.49, df = 29, P < 0.001 \)]. Because Fig. 9A excludes cases in which the dynamic ranges of STCs to pulsatile stimulation could not be assessed, it actually overestimates the dynamic ranges especially for LD animals. That is, the dynamic ranges of these animals would be even more severely limited if cases were included in which the dynamic ranges were so small that the criteria established to define this measure were not met.

It is interesting to note that when the dynamic ranges of all, i.e., not age-matched, LDU and LDS animals are compared (data not shown), LDS animals have significantly smaller dynamic ranges for pulses [mean: 6.72 ± 4.27 (SD) dB] than LDU animals [mean: 3.26 ± 2.45 (SD) dB]. Because there is no difference in dynamic range between the age-matched LDU and LDS animals, this result in the larger groups may be due to the longer duration of deafness in the LDS animals.

For stimulation with 100-Hz electrical sinusoids (Fig. 9B), a statistical comparison of dynamic ranges between age-matched LDU and LDS animals was not possible because of insufficient data (\( n = 6 \) and \( n = 1 \), respectively). Thus we cannot fully exclude the possibility of confounding effects of chronic electric stimulation or duration of deafness on dynamic ranges for sinusoids. However, comparisons of mean dynamic ranges for sinusoidal stimulation between all LDU [9.14 ± 7.621 (SD) dB] and LDS [5.73 ± 4.29 (SD) dB] animals included in the present study did not show a significant difference (t-test; \( t = 1.04, df = 25, P > 0.05 \)). The data for LDU and LDS animals were therefore pooled for statistical comparison. The differences in mean dynamic range among the control, SDU and LD animals are significant (ANOVA; \( F = 10.02, df = 2/80, P < 0.001 \)). A subsequent pairwise comparison shows that there is no difference in dynamic ranges for sinusoidal stimulation between control and SDU animals [means: 17.13 ± 10.10 (SD) dB and 18.84 ± 7.09 (SD) dB, respectively; Tukey test; \( P > 0.05 \)]. In contrast, LD animals have significantly smaller dynamic ranges for sinusoidal stimulation (mean: 8.39 ± 7.09 dB) than both control and SDU animals (\( P < 0.05 \)).

To better illustrate the relationship between response sensitivity and dynamic range, Fig. 10 displays the quantitative distribution of the ratios of minimum response thresholds (sinusoidal stimulation) divided by the corresponding dynamic ranges separately for the control, SDU and LD animals. LDU and LDS animals are pooled as LD animals because there is no significant difference in the median ratio values between the two groups (Mann-Whitney \( U \); \( P = 0.924 \)). The ratios of LD animals (C) are clearly shifted toward higher values as compared with those from control (A) and SDU animals (B). The differences in the median threshold/dynamic range ratio values between control, SDU and LD animals are significant (Kruskal-Wallis on ranks; \( H = 15.781, df = 2, P < 0.001 \)). Subsequent comparisons (Dunn’s method) show that the median threshold/dynamic range ratios of control (A) and SDU animals (B) are not different (\( P > 0.05 \)). In contrast, the median ratio of the LD animals was significantly higher [median: 4.82 ± 2.86 (Q); \( P < 0.05 \) compared with both control and SDU animals. These results suggest that long-term deafness leads to a relative increase in threshold and a relative decrease in dynamic range.

**Spread of activation and STC widths**

Measures of STC widths reflect the spread of activation across the ICC at a given intensity above threshold. These measures provide an estimate of the selectivity of activation with respect to the cochleotopic gradient of the central auditory system. Figure 11A summarizes the mean STC widths for stimulation with electrical pulses delivered at 2 dB above minimum threshold for electrode pair 1.2. Data from SDU animals are not included in the statistical analysis because of the small number of available measures (\( n = 2 \)). The data for LDU and LDS animals are pooled as LD animals because there is no significant difference between the age-matched animals (t-test; \( P > 0.05 \)). Thus in accordance to the reported findings for thresholds and dynamic ranges, there is no apparent effect of chronic stimulation on STC width for pulses. Further, there is no difference when the data from all LDU and LDS animals are compared (t-test; \( P > 0.05 \)). For pulsatile electrical stimulation, LD animals exhibit a significantly broader extent of excitation [mean: 1,166.3 ± 404.86 (SD) \( \mu \)m] compared with control animals [mean: 667.14 ± 337.87 (SD) \( \mu \)m; t-test; \( t = 2.86 (Q); P < 0.05 \)].
sinusoidal stimulation, a statistical comparison between the age-matched LDU and LDS animals was not possible because of insufficient data (n = 7 and n = 1, respectively). However, when all LDU and LDS animals were compared, there was no significant difference in spread of activation as measured by the STC widths (t-test; P > 0.05). Therefore the data from the two groups were pooled for statistical comparisons (LD group). The differences in median 6 dB widths for sines among the control, SDU and LD animals are significant (Kruskal-Wallis on ranks; H = 8.09, df = 2, P < 0.05). In subsequent comparisons, there is no significant difference between control [median: 870 μm ± 365 (Q) dB] and SDU animals [median: 840 μm ± 261.25 (Q) dB] (Dunn’s method; P > 0.05). In contrast, LD animals have significantly broader 6 dB STC widths for sines [median: 1,320 μm ± 580 (Q) dB] than both the control and SDU animals (P < 0.05).

Figure 12 illustrates the relationship between the 6 dB STC widths for sines and the corresponding dynamic ranges of the same STCs for all groups of animals. The slope of the regression line (power function) is negative, and the correlation coefficient of the data is relatively high (R = 0.71). These results indicate a systematic relationship between broader, less selective electrical activation (i.e., larger STC widths) and smaller dynamic ranges. Conversely, relatively selective or narrow STCs have larger neural dynamic ranges. Because dynamic ranges are particularly limited and STC widths are particularly broad in long-deafened animals, the results reflect a marked degradation in spatial selectivity of ICs after long durations of deafness, again suggesting that greater channel interaction would occur in these animals (see summaries in Figs. 9 and 11).

**DISCUSSION**

The present study provides evidence that prolonged duration of deafness results in severe degenerative changes in the auditory periphery and a loss of response sensitivity and spatial selectivity of neurons to sinusoidal and pulsatile electrical activation in the inferior colliculus. Further, the findings also suggest that chronic single-channel electrical stimulation of the long-deafened auditory system has no apparent effect on response thresholds and spatial selectivity.

**Cochlear pathology**

Peripheral pathology is a likely factor affecting auditory perception of cochlear implant recipients. In an animal model of neonatal deafness, we observed progressive loss of SGCs with increasing durations of deafness. SDU animals had an average SGC density of ~45% of normal. After prolonged periods of deafness, the SGC density in LDU animals was severely reduced to an average of ~10% of normal and in LDS animals to an average of only ~3% of normal. These results reflect previous findings in a partially overlapping set of SDU and LD animals (Rebscher et al. 2001; Vollmer et al. 2000, 2005). It is important to note that the mean SGC survival in the LDU animals was significantly lower than that in the LD animals. Presumably, this difference is due to the significantly longer duration of deafness in the LDS animals (mean: ~69 mo) compared with the LDU animals (mean: ~44 mo; t-test; t = −2.663, df = 10, P < 0.05). These results
are consistent with other studies that have reported progressive loss of SGCs and radial nerve fibers for many years after aminoglycoside-induced hair cell loss (e.g., Hardie and Shepherd 1999; Leake and Hradek 1988; Lustig et al. 1994; Xu et al. 1993).

A trophic effect of chronic electrical stimulation in promoting SGC survival, as demonstrated in neonatally deafened, early stimulated animals (e.g., Leake et al. 1999), was not observed in the LDS animals, presumably because of the already severe reduction in SGC count after >3.5 yr of deafness. It is interesting to note that the pathology and neuronal degeneration seen in these cat cochleae after several years of deafness appears to be considerably more severe than the alterations one would expect in the human cochlea after equivalent periods of profound deafness even after congenital deafness (e.g., Linthicum and Anderson 1991; Nadol et al. 2001). The extent and progression of hair cell loss and SGC degeneration are likely dependent on the extent and rapidity of onset of aminoglycoside-induced damage to the cochlea and possibly also on species-specific differences in neuronal survival patterns (Forge and Schacht 2000; Hinojosa et al. 2001; Johnsson et al. 1981; McFadden et al. 2004; Sone et al. 1998). The dosage of aminoglycosides in our experimental design was intentionally higher than would be used clinically to reduce the dosage of aminoglycosides in our experimental design was intended to model the extreme condition of very severe pathology to examine the functional consequences.

Although there is no clear evidence that the degree of SGC degeneration is a predictor of speech perception (e.g., Fayad and Linthicum 2006; Khan et al. 2005a,b), it is generally assumed that SGC survival plays a critical role for word recognition, especially if the number of SGCs is very low (Clopton et al. 1980; Incesulu and Nadol 1998; Khan et al. 2005b; Nadol 1984; Nadol et al. 1989; Otte et al. 1978). However, many other variables, especially including alterations in the central auditory pathway and its signal processing capacity, likely play important roles in the success of cochlear implantation.

Cochleotopy

The estimation of the cochleotopic organization of the IC was based on the best location for stimulation with different electrode pairs. In contrast to observations in the cortex by Raggio and Schreiner (2003), differences in waveform (pulses vs. sines) did not contribute to differences in the location of highest stimulus sensitivity. Thus at the level of the auditory midbrain, specific properties of the electrical stimulus, including differences in stimulus rise time and stimulus duration, did not influence the most sensitive response location relative to the cochleotopic organization.

Some earlier studies have reported only vague indications that the characteristic frequencies of ICX neurons are tonotopically organized with high frequencies being located more superficially in the ICX and low frequencies being represented deeper in the ICX (e.g., cat: Aitkin et al. 1994; guinea pig: Binns et al. 1992). In contrast, other anatomical and physiological studies suggest solid evidence that all subdivisions of the IC, i.e., including the ICX, exhibit a tonotopic organization (cat: Andersen et al. 1980; rat: Saldaña et al. 1996). When the data from all animal groups were pooled, the present study supports the latter finding. For all groups of animals, including the long-deafened animals, a trend was observed that the best locations for higher frequencies, i.e., more basal stimulating electrodes, were located more superficially in the ICX than those for lower frequencies. However, this trend did not
achieve statistical significance in all groups. At least two potential factors may play a role. First, the depth of the ICX is relatively shallow [mean across all groups: 1.646 ± 578 (SD) μm, unpublished observations], and the estimation of response thresholds at intervals of 100 μm may be too coarse to detect small differences in best location. Second, the surgical access to the IC and its exposure over a period of several days as required for the completion of these experiments may result in traumatic or inflammatory changes near the surface of the IC that could affect responses, particularly in the ICX.

The ICX, in contrast, exhibited for all groups of animals a clear cochleotopic frequency gradient that was systematically related to ICX depth. These results are in agreement with data from normal-hearing cats (e.g., Brown et al. 1997; Merzenich and Reid 1974; Oliver 1987; Oliver and Morest 1984; Rose et al. 1966) and neonatally deafened cats that were either unstimulated (deafness durations pooled over 0.5–2.6 yr, including a single long-deafened animal) or implanted and stimulated at a young age (Snyder et al. 1990, 1991). In the present study, cochleotopic organization in the ICC was maintained even after very prolonged periods of deafness. This finding is in contrast to previous studies in the auditory cortex (Dinse et al. 1997; Hartmann et al. 1997; Klinke et al. 1999; Raggio and Schreiner 1999, 2003; Taniguchi et al. 1997) suggesting that sustained lack of auditory input and severe degeneration of peripheral innervation result in a degradation of cortical cochleotopic organization. The present results suggest that the cochleotopicity of the ICC is less affected by long-term auditory deprivation than that of the auditory cortex. This difference may relate to the larger range of sources of subcortical and cortical inputs to the primary auditory cortex that can be altered in their response specificity by long-term deafness.

**Thresholds**

**ICX VERSUS ICC.** Across all animals minimum sinusoidal thresholds in the ICC were slightly (~1 dB) but significantly lower than those estimated in the ICX. This difference is in close agreement with ICX/ICC threshold comparisons in our laboratory for a large number of animals with various deafness durations and stimulation histories [number of threshold comparisons = 109; mean difference: 1.69 ± 4.12 (SD) dB; unpublished data]. The reason for the higher minimum threshold values in the ICX may be related to the additional somatosensory (e.g., Aitkin 1986) or descending inputs from both primary and nonprimary cortices (e.g., Anderson et al. 1980; Coleman and Clerici 1987; Faye-Lund 1985; Oliver and Huerta 1992). Such multisensory and multisource cortical inputs may lead to a decreased synchrony of neural responses and thus to increased response thresholds. Furthermore, the lower response sensitivity of ICX neurons may simply reflect an increased risk of mechanical trauma to the ICX during surgical exposure of the auditory midbrain for recording.

**PULSES VERSUS SINES.** The present study evaluated the effects of duration of deafness on response sensitivity and spatial selectivity of sinusoidal and pulsatile electrical activation in the IC of adult cats. Comparisons of thresholds derived from animals for which the responses to both pulsatile and sinusoidal stimuli were examined demonstrated some stimulus-specific differences in IC responses. When expressed in peak-to-peak current, minimum response thresholds for sinusoidal stimulation were significantly lower than those for pulsatile stimulation. There was no significant difference in mean threshold difference among the different groups of animals, and the mean threshold difference across all animals was 13.54 ± 6.99 (SD) dB. This difference is in agreement with previous reports about threshold differences for varying phase durations in the auditory nerve (Hartmann et al. 1984; Shepherd and Javel 1997) and the inferior colliculus (Leake et al. 2000; Moore et al. 2002; Snyder et al. 1990), the auditory cortex (Raggio and Schreiner 2003) and reports of psychophysical threshold estimates for different phase durations (Beitel et al. 2000a,b; Moon et al. 1993; Pfingst and Morris 1993; Smith and Finley 1997; Smith et al. 1994).

The differences in thresholds for sinusoidal and pulsatile stimulation can be partially explained by the different stimulus durations (He 1997) and phase durations, i.e., the total charge per phase rather than the peak amplitude. Although the scatter of the data in Fig. 6A was relatively large for low sinusoidal response thresholds, sinusoidal and corresponding pulsatile thresholds tended to approach equal charge per phase. At higher stimulation current levels, a more rapid growth of sinusoidal thresholds relative to the pulsatile thresholds is observed. That is, at these higher intensities, the charge per phase required to reach thresholds is lower for pulsatile stimulation than for sinusoidal stimulation. Thus a simple charge-integrator-model is not valid for higher minimum response thresholds. However, the peak current for sinusoidal thresholds remains below that for pulsatile thresholds. A similar compression of the pulsatile or expansion of the sinusoidal efficacy with increasing response thresholds was also observed in the auditory cortex by Raggio and Schreiner (2003). It is possible that even near threshold the fast rise time of current in pulsatile stimulation leads to a higher temporal synchronization of neural inputs (Heil 1997) and thus to lower response thresholds when expressed relative to charge per phase. The higher degree of synchrony may also contribute to the overall reduction in scatter in the corresponding thresholds at higher intensities. It is also possible that the temporal integration of longer-duration sinusoidal stimuli is more affected by prolonged durations of deafness (that are typically associated with higher thresholds) and peripheral loss of SGCs than that for pulsatile stimulation with shorter phase and shorter stimulus durations (van den Honert and Stypulkowski 1984).

**ICC VERSUS EABR THRESHOLDS.** When measured in the same animal, minimum response thresholds in the ICC were lower than EABR thresholds, and the two measures were strongly correlated. The mean threshold difference was on the order of ~4.5 dB. These data are consistent with previously published data from other studies in our laboratory (Beitel et al. 2000a,b; Moore et al. 2002; Vollmer et al. 2000). This difference can be explained by the intrinsic differences in the recording methods: EABR thresholds are based on the synchronized and averaged responses of a large number of neurons that are recorded in a far-field condition, whereas minimum ICC thresholds are based on the most sensitive responses from single neurons or a small group of neurons that are located close to the recording electrode (near-field recordings). Although long-deafened animals demonstrated an overall increase in both EABR and ICC thresholds and despite the possibility of undersampling the ICC.
with respect to recording from the most sensitive neurons, the difference between the two thresholds was relatively consistent across all groups. Thus the duration of deafness and, consequently, the number of surviving SGCs do not appear to affect the intrinsic relationship between average EABR and minimum ICC response measures.

**EFFECT OF DEAFNESS DURATION ON RESPONSE_THRESHOLDS.** The duration of deafness and SGC survival appear to influence the overall response sensitivity of neurons. It has been reported previously that long durations of deafness and severe loss of SGCs result in higher response thresholds (Shepherd and Javel 1997; Vollmer et al. 2000). The present study confirms this finding and, moreover, suggests that the deafness-induced reduction in response sensitivity affects both far-field EABR and near-field ICC measures and is independent of the stimulus waveform (pulsatile or sinusoid). In contrast, Rebscher et al. (2001) did not observe a significant increase in IC thresholds for sinusoidal stimulation in long-deafened animals. The reason for this discrepancy in the data may be differences in the distributions of deafness durations in the long-deafened animals. The mean duration of deafness in Rebscher and colleagues’ group of long-deafened animals was ~46 mo and corresponded to the LDU group in the present study. The present study included LDS animals with a significantly longer mean duration of deafness (overall mean for all LD animals ~57 mo) that likely contributed to the increases in EABR and ICC thresholds.

Threshold estimates are affected by a large number of additional variables, including signal-to-noise ratios, intracochlear electrode locations, visual threshold detection procedures, and neural temporal synchronization (Elberling and Don 1987; van den Honert and Stypulkowski 1986). As a result, relatively large variations in threshold estimates were observed in the present study. Consequently, very long durations of deafness and severe reductions in SGC survival were required to result in significant increases in thresholds compared with normal animals.

As noted previously, the LDS animals had a significantly longer duration of deafness than the LDU animals. In addition to the differences in deafness duration between the two groups, chronic electrical stimulation of the LDS animals may have contributed to differences and changes in response properties. However, age-matched animals from the two groups did not show any significant difference in EABR or IC thresholds. This suggests that chronic ICES does not significantly affect response sensitivity in the long-deafened auditory system.

The overall increase in thresholds in long-deafened animals may be explained by a number of different mechanisms. Among the possible explanations are the loss of myelin and partial neural degeneration that not only lead to a larger distance between the stimulating contacts and the population of excitable neural targets but also to prolonged refractory periods and an increased vulnerability of the propagating spike. In the central auditory system, a weakening of individual excitatory synapses (Kotak and Sanes 1997), a decrease in excitatory neurotransmitter release (Vale and Sanes 2002), a reduction in the volume of the cochlear nuclei, reduced size and/or loss of auditory brain stem neurons and a decrease in synaptic density in the IC (Hardie et al. 1998; Nadol et al. 1989; Nishiyama et al. 2000; Otte et al. 1978; Saada et al. 1996) may contribute to an overall reduction in conduction, synaptic efficacy, and synchrony of afferent connections along the ascending central auditory system and thus to increased response thresholds.

Based on similar mechanisms that have been suggested for the reversal of degraded temporal resolution in long-deafened animals after the introduction of chronic stimulation (Vollmer et al. 2005), one could hypothesize that ICES would result in an increase in neuronal synchrony in the central auditory system. Contrary to our present findings, this could lead to a decrease in response thresholds after ICES. However, the degenerative changes in the peripheral and central auditory system may be too severe to sustain any effects of central synchrony on response sensitivity.

**Spatial selectivity**

It is presumed that the activation of spatially restricted neural populations is essential for successful CI channel separation and thus for optimum speech discrimination performance in multichannel cochlear implant users (Chatterjee and Shannon 1998; Henry et al. 2000; Townsend et al. 1987; Throckmorton and Collins 1999; Zwolan et al. 1997). To investigate the effects of long-term deafness on spatial selectivity, we determined the STC widths and dynamic ranges of ICC responses.

Long-term deafness resulted in a marked degradation of spatial selectivity with a significant expansion of STCs and reduction in neural dynamic ranges. These changes were independent of the waveform of the electrical stimulus (pulsatile or sinusoidal). The observed degradation of spatial selectivity is consistent with earlier publications from our laboratory (Rebscher et al. 2001; Vollmer et al. 2000) and is supported by computational models (Briaire and Frijns 2006; Frijns et al. 1998). In contrast to the present findings, Shepherd and colleagues (Shepherd and Javel 1997; Shepherd et al. 1999) indicate that degeneration of spiral ganglion neurons results in decreased response selectivity. Loss of peripheral auditory nerve fibers, ganglion cell somata, and the larger distance between the location of the stimulating contacts and the neural targets can lead to increased thresholds and, as a result, to larger electrical fields at suprathreshold levels. Further, the reduced separation of peripheral processes and SGCs may also provide a low impedance pathway and, consequently, increased spread of the current into the modiolus (Frijns 1995). As a result auditory neurons over a broad range of frequencies will be excited, and the dynamic range will be limited to relatively low intensities above threshold. Also deafness-induced changes in the central auditory system may contribute to the decreased spatial selectivity after long-term deafness. Such changes include alterations in the balance between excitatory and inhibitory inputs to the ICC (Raggio and Schreiner 1999; Schreiner and Raggio 1996) and decreases in the synaptic density in the IC of neonatally deafened animals (Hardie et al. 1998). In contrast to the present findings, Shepherd and colleagues (Shepherd and Javel 1997; Shepherd et al. 1999) observed increased dynamic ranges following long-term deafness, although it must be noted that this result was obtained from only one experimental animal that was deafened as a juvenile. Thus these data may not be fully representative of the functional changes after *neonatally* induced long-term deafness.

The degradation of spatial selectivity in these long-deafened animals was not reversed by either chronic stimulation or by...
behavioral training to detect electrical signals. Our earlier studies have reported that chronic electric stimulation delivered on a single channel of a CI leads to an expansion of the STC width in animals that were deafened neonatally or as adults and chronically stimulated thereafter (e.g., Leake and Rebscher 2004; Leake et al. 2000; Moore et al. 2002; Snyder et al. 1991). However, due to the longer durations of deafness, the long-deafened animals reported in the present study demonstrated an even more pronounced degradation in spatial selectivity than that reported in any of those previous studies.

The same mechanisms that could lead to the marked increase in temporal resolution after chronic stimulation in the long-deafened animal (e.g., axonal sprouting and increased synchrony of auditory nerve inputs), could contribute also to an additive negative effect of both deafness-induced degenerative functional and anatomical changes and stimulation-induced changes on spatial selectivity of ICC neurons. However, despite the limitation of a small number of subjects, it is noteworthy that the comparison of both STC widths and dynamic ranges between age-matched LDU and LDS animals did not reveal an additional effect of ICES on spatial selectivity. The deafness-induced morphological and functional degenerations in the peripheral and central auditory system may be the dominant factors contributing to the loss of spatial selectivity in the long-deafened auditory system and may mask any effects of ICES on spatial signal representation. Further, if the goal was to improve (sharp) the degraded spatial selectivity in the long-deafened auditory system, other stimulation parameters (e.g., introduction of competing inputs from dual channel stimulation) (see Leake et al. 2000) would be more appropriate. Clearly this is an issue requiring additional study in the future.

Conclusion

The present results demonstrate that long-term profound sensorineural hearing loss leads to severe loss of SGCs and auditory nerve fibers and can effectively alter the representation and processing of intracochlear electrical signals in the central auditory system. Although a modular functional organization of the ICC was still maintained (cochleotopicity), long-term deafness (>2.5 yr) resulted in significant increases in thresholds and marked degradation in spatial selectivity (i.e., broader STC width and smaller dynamic range) of electrical stimulation in the central auditory system. These parameters may lead to a greater extent of channel interaction in multichannel implants and thus poorer speech discrimination performance in CI users with congenital or very early acquired deafness who are implanted as adults.

Unlike the degraded temporal resolution of ICC neurons, these changes in spatial selectivity and response sensitivity were not reversible by chronic electric stimulation. Thus in long-deafened subjects, the increases in threshold and degraded spatial selectivity may be the dominant factors contributing to poor speech discrimination performance. Improvements in speech discrimination performance over time are probably due to increasing temporal resolution in the central auditory system and cognitive learning with auditory experience.

In contrast, shorter durations of deafness (<1.5 yr) with more moderate degrees of degenerative anatomical changes did not alter the response sensitivity and spatial selectivity of electrical signals in the central auditory system. However, it is not clear at present to what extent early chronic stimulation by itself can prevent, or even cause, negative effects on spatial selectivity and thus increased channel interactions.

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