Hearing after Congenital Deafness: Central Auditory Plasticity and Sensory Deprivation

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The congenitally deaf cat suffers from a degeneration of the inner ear. The organ of Corti bears no hair cells, yet the auditory afferents are preserved. Since these animals have no auditory experience, they were used as a model for congenital deafness. Kittens were equipped with a cochlear implant at different ages and electrostimulated over a period of 2.0–5.5 months using a monopolar single-channel compressed analogue stimulation strategy (VIENNA-type signal processor). Following a period of auditory experience, we investigated cortical field potentials in response to electrical biphasic pulses applied by means of the cochlear implant. In comparison to naive unstimulated deaf cats and normal hearing cats, the chronically stimulated animals showed larger cortical regions producing middle-latency responses at or above 300 μV amplitude at the contralateral as well as the ipsilateral auditory cortex. The cortex ipsilateral to the chronically stimulated ear did not show any signs of reduced responsiveness when stimulating the 'untrained' ear through a second cochlear implant inserted in the final experiment. With comparable duration of auditory training, the activated cortical area was substantially smaller if implantation had been performed at an older age of 5–6 months. The data emphasize that young sensory systems in cats have a higher capacity for plasticity than older ones and that there is a sensitive period for the cat's auditory system.

Introduction

Maturation of brain function requires sensory input. Sensory deprivation during infancy results in serious central nervous deficits in the respective structures (Moore and Kitzes, 1985; Fox, 1995; Hartmann *et al.*, 1997; Katz, 1999; Kral *et al.*, 2000; Klinke *et al.*, 2001a,b). In the central auditory system, investigating these deficits and possible repair mechanisms is difficult. The ear canals would have to be blocked at an early age and later reopened. This, however, does not lead to deafness since sounds, in particular self-produced sounds (chewing, scratching, vocalizations), still reach the cochlea by bone conduction. If the cochlea is damaged by ototoxic agents or section of the VIIIth nerve, testing the auditory system will be impossible at later stage in life. Electrical stimulation of the auditory nerve by cochlear implants is currently the only way to overcome these difficulties. Chronic electrostimulation through cochlear implants in congenitally deaf animals thus provides an opportunity to study delayed maturation processes and plasticity in the central auditory system of acoustically deprived animals. Studies of this type are of particular interest as cochlear implantation in deaf infants has become a promising tool for auditory rehabilitation. They can provide an answer to certain aspects of clinical interest (Klinke *et al.*, 2001a,b) and to the question of whether existing implantation strategies should be modified. Details about central maturation processes triggered by cochlear implantation, sensitive periods and the capacity for plastic reorganizations in the central auditory system are of particular interest.

The congenitally deaf cat (CDC) is a suitable model for such studies (Heid *et al.*, 1998; Klinke *et al.*, 1999). These animals suffer from a cochlear degeneration even before hearing takes place. The auditory nerve, however, is quite well preserved compared to animals neonatally deafened by ototoxic agents (Shepherd and Martin, 1995; Leake *et al.*, 1999). Electrostimulation of the auditory nerve in adult, naive CDCs leads to central responses and reveals rudimentary cochleotopic representation in the primary auditory cortex (Hartmann *et al.*, 1997), showing that afferent pathways are present and to some extent functional (Heid *et al.*, 1997). Nevertheless, synaptic activity in different cortical layers suggests that there are substantial functional deficits in the primary auditory cortex of these cats (Kral *et al.*, 2000).

In the present study, changes of cochlear representations following meaningful cochlear electrostimulation in CDCs were evaluated after different stimulation periods. One group of animals was cochlea-implanted at an early age (2.5–5 months) and stimulated using a portable signal processor.

A second group of animals was implanted after their fifth month ('late-implanted animals'). In hearing cats, cortical functional maturation is completed with 5 months of birth (Eggermont, 1996). We thus tested whether the success of cochlear implantation is limited after that age.

Material and Methods

Animals

For the present study, 10 congenitally deaf and five hearing cats were used. Deafness of the CDCs was verified measuring their auditory-evoked brainstem responses to clicks and tone-pips of intensities up to 125 dB SPL (Heid *et al.*, 1998). Four naive CDCs were investigated at 4, 6, 8 and 26 months of age; the remaining six CDCs were implanted and chronically stimulated. Two adult hearing controls (HC 1 and 2) were acutely deafened by intrascalar application of neomycin at the beginning of the final experiment (Hartmann *et al.*, 1984). Two additional littermates of normal cats were deafened neonatally (NCs). For this purpose, kanamycin and etacrynic acid (kanamycin 300 mg/kg s.c., 30 min later etacrynic acid 30 mg/kg i.v.) (Xu *et al.*, 1993) were applied on postnatal days P10 and P11. One of these neonatally deafened kittens was kept naive (NC 1) and the other was chronically electrostimulated (csNC 3). Thus, in total, there were seven chronically stimulated (cs) animals used (see Table 1): six CDCs (csCDCs) and one neonatally deafened normal kitten (csNC 3). One of the normal hearing kittens was used as a control for conditioning.

Cochlear Implant and Implantation Procedure

The chronically stimulated animals were equipped with a custom-made cochlear implant at the age of 2.5–6.5 months. Five animals were implanted at age 2.5–5.0 months – these were the early implanted cats. Two animals were implanted after their fifth month of life (late-implanted cats, csCDC 6 and csCDC 7). The implanted animals were stimulated over a period of 2.0–5.5 months. The implant consisted of a medical-grade silicone tube with three electrical contacts. There were two intrascalar gold contacts: a small ball at the tip (diameter 0.6 mm) and a ring, with a distance of 2–5 mm between ball and ring (Behrendt, 1999). The

Table 1
Overview on experimental animals

Animal	Age at implantation	Stimulation duration	Age at experiment	Strain
csCDC 1	2.5	2	4.5	CDC
csCDC 2	3.5	2	5.5	CDC
csNC 3	3.5	3	6.5	Normal, neonate deafened
csCDC 4	5	5.5	10.5	CDC
csCDC 5	3.5	5	8.5	CDC
csCDC 6	6	5	11	CDC
csCDC 7	6.5	2	8.5	CDC
CDC 1	–	–	4	CDC
CDC 2	–	–	6	CDC
CDC 3	–	–	8	CDC
CDC 4	–	–	26	CDC
NC 1	–	–	6.5	Normal, neonate deafened
HC 1	–	–	10	Normal hearing
HC 2	–	–	58	Normal hearing

csCDCs are the chronically stimulated CDCs; csNC 3 is the chronically stimulated neonatally deafened cat; NC 1 is the naive neonatally deafened cat; HCs are hearing controls. Ages are given in months.

intrascalar part of the implant was tapered in the apical direction from a diameter of 1.6 mm to 0.6 mm. The extracochlear silicone tube had a diameter of 1.6 mm. An indifferent electrode (ring) was located extracochlearly at the neck after implantation. The gold contacts were connected to a seven-strand, teflon-coated, stainless-steel braided wire. The stimulation mode was monopolar. The most apical intrascalar electrode was selected for stimulation.

For implantation under ketamine anesthesia, the bulla was exposed through a cutaneous incision behind the ear. A small hole was drilled into the bulla. The membrane of the round window was carefully removed. The implant was inserted 4 mm deep. Intactness of the cochlear structures was verified histologically after the final experiment. The implant was fixed using a suture (non-resorbable thread) at the dorsal thickened part of the bulla. The bulla was tightly closed using dental acrylic, fixing the implant at the same time. The leads of the implant were fed subcutanaously, additionally fixed with a suture at the lambdoideal crista, and led transcutaneously into the interscapular line. The transcutaneous feed-through was covered with a jacket which also carried the sound-processor. Plugs connected the implant with the sound processor. The animals were treated with ampicillin (100 mg s.c.) for 7 days after surgery. After implantation, the animals could move freely. The impedance of the implanted electrodes was ~5 kΩ at 125 Hz. The impedance was tested at regular intervals (directly after implantation, 3 days post-implantation, 4 days post-implantation and then once every 2 weeks). A constant impedance indicated correct functioning of the implanted electrode.

Adjustment of Stimulation Currents and Chronic Stimulation

In order to adjust the currents delivered by the sound processor, the thresholds for pinna and head orientation reflexes were assessed 3–7 days after implantation. These reflexes appear in response to activity in the auditory brainstem, both in hearing cats and in CDCs (Ehret, 1985; Klinke *et al*., 1999). These reflexes were tested in unrestrained unanaesthetized animals in two to four sessions at stimulation frequencies of 125, 250, 500, 1000, 2000, 4000 and 8000 Hz with monopolar stimulation. The sessions were videotaped. An electrical signal of 500 ms duration, 5 ms rise/fall was used for stimulation, presented at a repetition rate of 0.3/s. Using this repetition rate, the animals were able to respond to each stimulus presentation with movement of pinna and/or head. If there were reliable reflexes, the actual current was taken as the threshold at the given stimulus frequency.

The Signal Processor for Chronic Electrostimulation

For chronic electrostimulation, a portable one-channel signal processor, comparable to VIENNA-type human speech processors (Burian *et al*., 1986), was developed. The sound signals were recorded by a Sennheiser KE4 microphone. The signal was fed into an automatic gain control, adjustable in offset and gain. Two independent bandpass filters operating in frequency ranges of 100–500 and 500–8000 Hz were used to adjust the processor output to the individual threshold curve of the animal. The device was 4 × 3 × 1 cm and weighed 24.4 g.

In order to avoid uncomfortable current levels, automatic gain control was used to limit the maximal current to 10 dB above threshold. The signal processor was adjusted so that thresholds for each frequency were reached at 60 dB SPL. Animals were chronically stimulated in a monopolar mode 24 h a day, 7 days a week.

Conditioning of the Chronically Stimulated CDCs

On a daily basis, the animals were conditioned to acoustic stimuli consisting of 500 ms tones of 437 Hz (5 ms rise/fall) presented at random intensities between 70 and 100 dB SPL. The animals were tested in a sound-shielded room. They were separated from the experimenter by a wall and were observed using a video camera. Sessions were videotaped. Special food pellets were presented by a rotating plate as a reward for correct responses. Only 10–20 stimulus presentations were used during each session. The animals were not deprived of food, but food was restricted before conditioning. Access to food was unlimited after conditioning. A normal hearing cat was used for comparison of the conditioning results.

In addition to conditioning, the performance of the stimulation system was verified by a casual wake-up test (at least every second or third day). Care was taken that the stimuli could not be perceived by other senses (e.g. vibration). All implanted and chronically stimulated animals could be reliably woken up by moderate acoustic stimuli, except when the signal processor was not functional.

To gain further auditory experience, the animals were exposed to all ambient and self-produced sounds (before and during feeding, vocalizations, etc.). Toys that produce sounds when moved were used. In total, the cats experienced an acoustically enriched animal house environment. The implanted animals could interact with each other under supervision to prevent damage to the processor or the implant. Occasionally, the behaviour of the cats in the animal house was videotaped.

Final Experiments

The auditory cortex of each animal was investigated in a final experiment after 2.0–5.5 months of auditory experience with the cochlear implant. One animal (csCDC 2) was investigated the day after the lead broke. For the experiments, the animals were premedicated with 0.25 mg atropine i.p. and first anaesthetized with ketamin hydrochloride (24.5 mg/kg; Ketavet, Parker-Davis, Germany) and propionylpromazine phosphate (2.1 mg/kg; Combelen, Bayer, Germany). The animals were then tracheotomized and artificially respirated with 50% O_2 and 50% N_2O, with the addition of 0.2–1.0 % concentration isoflurane (Lilly, Germany) to maintain a controlled depth of anesthesia (Kral *et al*., 1999). End-tidal CO_2 was monitored and kept <4%. A modified Ringer's solution containing glucose was infused i.v. Core temperature was kept constant between 37.5 and 38°C using a homeothermic blanket. The skull above the auditory cortices was opened and both bullae and ear canals were exposed (in the chronically stimulated animals the chronic cochlear electrode was not touched). The head of the animal was then fixed in a stereotactic holder (Horsley-Clark). In order to record electrically evoked auditory brainstem responses a small hole was drilled into the skull at the vertex and a silver-ball electrode (diameter 1 mm) was attached epidurally. The indifferent electrode used for the recordings was positioned medially in the mouth; the indifferent electrode for stimulation was inserted medially into the neck muscles. Trephination was performed above the auditory cortex and the dura was opened. The cortex was photographed for documentation of the recording positions. The following nomenclature was defined for orientation in the anatomy of the chronically stimulated CDCs: 'contralateral' is the side opposite to the chronically stimulated ear and 'ipsilateral' is the same side as the chronically stimulated ear (see Fig. 1). In naive CDCs, the ipsilateral is the side of the acutely implanted ear and contralateral the opposite side.

For stimulation during the electrophysiological experiment, charge-balanced pulses (200 ms/phase, repetition rate 2 Hz) were applied to the cochlear implant (monopolar stimulation).

Recordings were started ~4 h after the onset of anesthesia. Using an *x–y–z* micromotor (enabling movements in all three direction with a

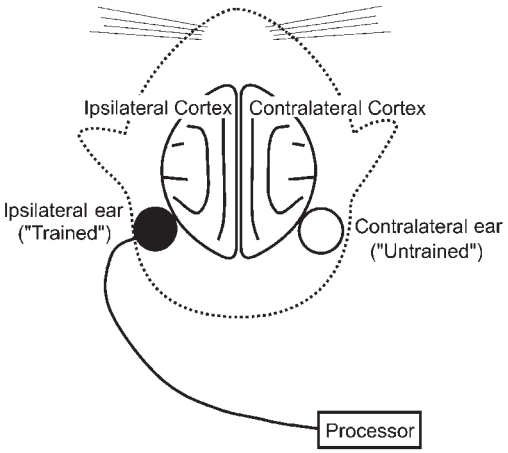

Figure 1. Schematic illustration of the head of a cat seen from dorsal. The bulla (circle) at the chronically implanted side is marked black. Contralateral and ipsilateral always refer to the chronically implanted side (for details see Materials and Methods). In the final experiments, four chronically stimulated animals were also contralaterally implanted and stimulated.

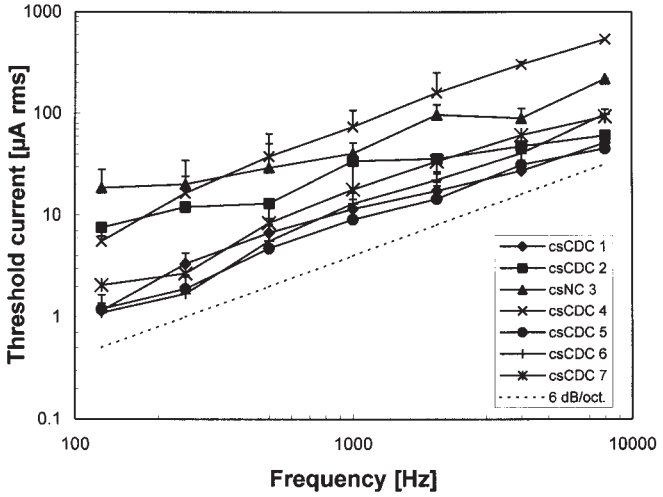

Figure 2. Pinna reflex threshold currents in all chronically stimulated animals. Stimulus 500 ms duration, 5 ms rise/fall, presentation rate 0.3/s. The threshold currents increase by 6 dB/octave with increasing stimulation frequency.

precision of 1 µm), a silver-ball macroelectrode (diameter 1 mm) was positioned at six to nine cortical positions on the primary auditory cortex. The dorsal end of the posterior ectosylvian sulcus was used as a reference point. For the recordings, a differential amplifier (filters 0.01–10 kHz, 6 dB/oct.; Tektronix 5A22N) and a signal averaging computer (Macintosh II or IBM PC, 50 sweeps, repetition rate 2 Hz) were used. The cortical field potentials were recorded and their thresholds were evaluated at all recording positions with a precision of ±1 dB. These recordings determined the minimal stimulation current to evoke a cortical response at one or more of the recording positions (threshold current). Further technical details are given in previously published work (Hartmann *et al.*, 1984, 1997).

Using a Ringer-filled glass microelectrode (impedance < 6 MΩ), field potentials on the cortical surface were recorded at 100–150 cortical positions during stimulation with the cochlear implant using biphasic pulses (200 µs/phase, stimulation current 10 dB above the lowest cortical threshold determined with the macroelectrode). After the experiment, amplitudes of middle-latency responses (peak to baseline) were used to construct cortical activation maps (Kriging method, 100–150 recording positions, Surfer v. 6.04, ©Golden Software 1997).

In five animals, responses were additionally collected at the ipsilateral cortex. Again, threshold currents were first assessed with macroelectrodes. Furthermore, during the final experiment, four chronically stimulated CDCs (csCDC 1, 5, 6 and 7) were acutely implanted with a second implant on the contralateral cochlea. Subsequently, the same recordings were performed on the ipsilateral cortex with stimulation of the contralateral ear.

The responses of the contralateral cortex to ipsilateral stimulation were obtained 5–15 h after initiation of anesthesia. All other recordings were carried out thereafter.

Brain size differs with age. Therefore, in order to compare how much of the surface of the primary auditory cortex had been activated by cochlear electrostimulation (activated area) in different animals, the computed area of the cortex with responses >300 µV was normalized using the formula

$$\text{activated area (r.u.)} = \frac{\text{area (mm}^2\text{)}}{\text{weight}^{2/3}\text{ (kg)}}$$

This formula reflects the relation of the surface area to the volume in a sphere and is assumed to approximate the relation of body weight and brain surface.

After the experiment, the animals were transcardially perfused with 2.5% glutaraldehyde and 2% formaldehyde (Heid *et al.*, 1998). The bulla was checked for proper location of the implant in the cochlea. The cochlea and spiral ganglion of the animals were evaluated in midmodiolar sections of the cochlea stained with 0.25% toluidine blue (Heid *et al.*, 1998).

Results

For adjustment of the signal processors, hearing thresholds were assessed using pinna and head orientation reflexes in unanaesthetized implanted CDCs (Table 1). The thresholds were up to 20 μA_{rms} for a sinusoidal stimulus of 125 Hz and showed a rise of 6 dB/octave with increasing stimulation frequency (Fig. 2). The portable signal processors compensated for this rise. The chronically stimulated animals learned to react to acoustic stimuli. They actively searched for sound sources, reacted to voices and could consistently be woken up by sound stimuli. The classical conditioning procedure was effective after 1–4 weeks of training. Animals implanted between 2.5 and 3.5 months of age reached a success rate of 90–100% after the second week of training. Animals implanted at the ages of 5 or 6 months learned more slowly (90–100% after 4 weeks).

Contralateral Cortex

The cortical field potentials with the largest amplitudes at the contralateral cortex were of similar shape in all chronically stimulated CDCs. Two prominent peaks were observed (Fig. 3, top): a middle latency response (<80 ms) and a long-latency response (latency >80 ms). The amplitude-intensity functions of the middle-latency responses increased steeply with a dynamic range of 2–6 dB (Fig. 3, middle). The long-latency responses had a slightly higher threshold and a smaller amplitude than the middle-latency responses (Fig. 3, bottom).

Threshold currents (lowest stimulation currents needed to measure cortical field potentials with silver-ball macroelectrodes) were not significantly different between naive CDCs and chronically stimulated CDCs (naive, –31.5 ± 1.9 dB re 3 mA_{pp}, n = 4; stimulated, –33.7 ± 3.5 dB re 3 mA_{pp}, n = 7; two-tailed t-test, α = 5%). The late-implanted animals had thresholds similar to those of early implanted cats (csCDC 6, –32 dB; csCDC 7, –38 dB). When assessed with macroelectrodes at the cortical positions mentioned above (see Materials and Methods), the thresholds did not differ by >2–4 dB in individual animals.

The spatial distribution of the amplitudes of the middle-latency responses showed two prominent regions with large amplitudes – 'hot-spots' – and a less-activated ridge in between in the primary auditory cortex (Figs 4 and 5). Outside of the 'hot-spots' the shape of the field potentials varied (Fig. 4). Here

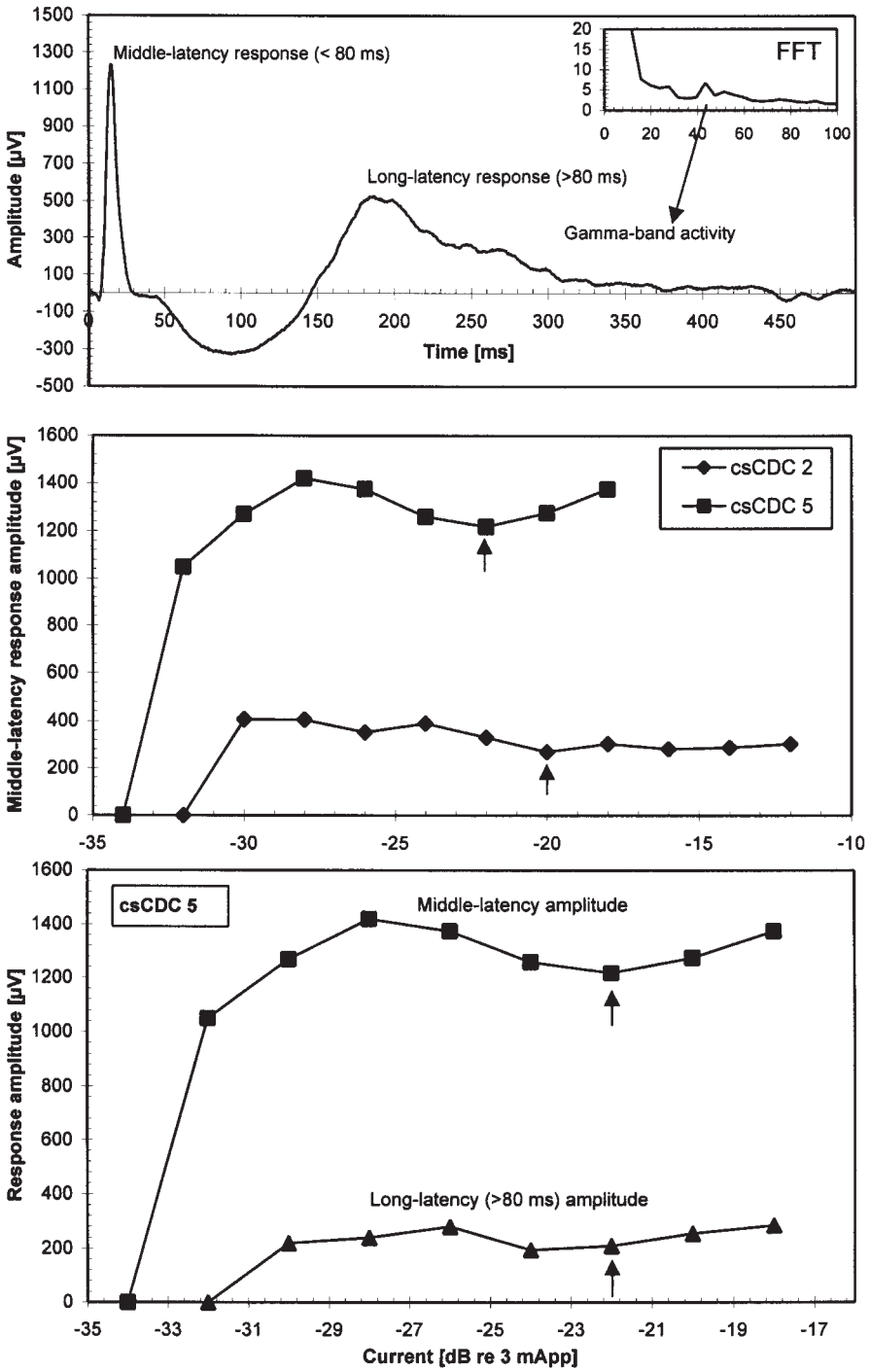

Figure 3. Top panel: example of a cortical field potential in response to a biphasic charge-balanced pulse applied by the cochlear implant (csCDC 4). The response consists of a large middle-latency wave and a smaller long-latency wave. Gamma-band activity was observed after the long-latency response, but levelled off by the averaging procedure. Inset shows the fast Fourier transformation of the averaged curve between 250 and 500 ms poststimulus. The peak at 45 Hz illustrates gamma activity. Middle panel: amplitude intensity function (contralateral cortex) of the responses of two animals implanted at 3.5 months, one stimulated at 2 months (csCDC 2) and the at other 5 months (csCDC 5). Both recordings at the position with largest responses, stimulation ipsilateral, monopolar, biphasic charge-balanced pulses 200 µs/phase, repetition rate 2 Hz. Amplitude-intensity functions show steep rise; the amplitudes saturate 2–6 dB above threshold. Arrows indicate stimulation intensity for the surface recordings (10 dB above threshold). The animal with less auditory experience shows lower amplitudes and higher thresholds. Bottom panel: comparison of the middle-latency and long-latency amplitude-intensity functions (csCDC 5, same recording position, same stimulation as middle panel). The long-latency response has a 2 dB higher threshold and smaller amplitude.

field potentials with two middle-latency peaks were recorded. The maximum amplitudes of the middle-latency responses differed considerably, even when naive CDCs were compared to each other (from 400 to 700 μV_{peak}). There was a trend towards larger maximum amplitudes in early implanted chronically stimulated CDCs with longer stimulation duration (Fig. 5). Long-latency responses had a maximum amplitude in the hot spot, but were also found at other recording positions (Fig. 6).

To evaluate how cortical representations change with hearing experience, the spatial extent of excitation at the contralateral

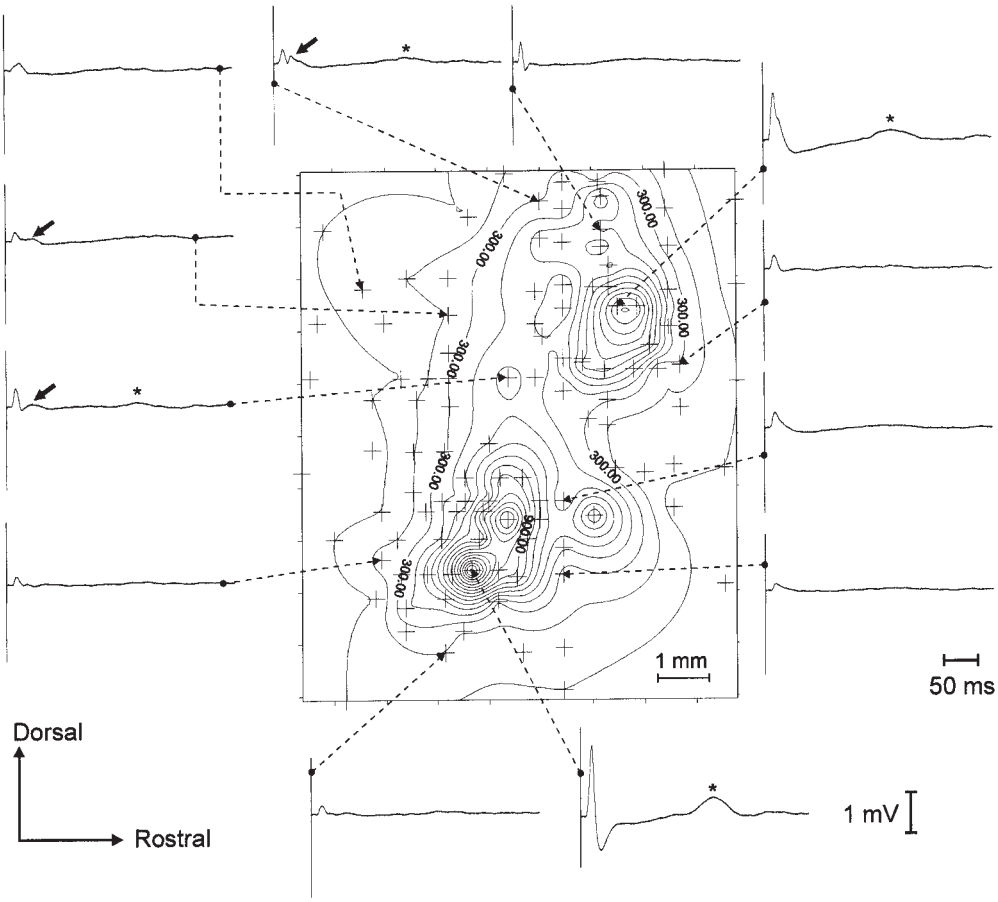

Figure 4. Map of the middle-latency response amplitudes at the contralateral cortical surface in animal csCDC 5 (stimulation: ipsilateral ear, monopolar, biphasic charge-balanced pulse 200 μs/phase, 10 dB above threshold current, repetition rate 2 Hz). The contour lines are shown in 100 μV steps. Recording positions are given as crosses. Recordings were not possible at all locations because of blood vessels. Field potentials at selected positions are shown at the margin. At the beginning of each field potential, the electrical artefact from stimulation appears. Long-latency responses are marked by an asterisk. At some border positions a second middle-latency peak is discernible (marked by an arrow).

cortex activated by stimulation through the cochlear implant was compared between different animals (Fig. 5, Table 2). Naive CDCs (Fig. 5*a*,*b*,*c*) did not differ in activated areas from hearing controls (naive, 2.8 ± 0.6 r.u.; hearing 2.6 ± 0.6 r.u.; two-tailed Wilcoxon–Mann–Whitney test, α = 5 %). The early implanted animals showed increasing activated areas with increasing duration of stimulation (Fig. 7, significant differences, two-tailed Kruskal–Wallis test, α = 5%). Pooling activated areas of all early implanted chronically stimulated animals (examples in Fig. 5*d*,*e*,*f*) resulted in significantly larger mean activated area (10.0 ± 5.7 r.u., n = 5) than in naive CDCs (2.8 ± 0.6 r.u.; two-tailed Wilcoxon–Mann–Whitney test, α = 5%). The pooled activated areas of late-implanted animals (example in Fig. 5*g*) yielded a smaller mean activated area (3.3 ± 4.6 r.u., n = 2), which was not significantly different from the one in naive animals (two-tailed Wilcoxon–Mann–Whitney test, α = 5%).

The latency of the first positive waves (P_a waves) of the cortical field potentials differed between animals. All animals stimulated 2 months had same P_a latencies (two-tailed *t*-test, α = 5%; pooled mean 16.5 ± 2.4 ms). They were not significantly different from naive CDCs of comparable age (pooled mean 16.5 ± 2.9 ms) nor from hearing controls (pooled mean 16.8 ± 2.6 ms; two-tailed *t*-test, α = 5%). After 5 months of stimulation, P_a latencies became significantly shorter in the animal implanted at 3.5 months (csCDC 5, 13.7 ± 2.0 ms). The animal implanted at 5 months had P_a latencies significantly longer than csCDC 5 (csCDC 4, 15.5 ± 1.8 ms); however, they were significantly shorter than those of naive CDCs (two-tailed *t*-test, α = 5%). In the late-implanted animal (csCDC 6), the P_a latencies were no longer different from naive CDCs despite 5 months of stimulation (16.9 ± 4.5 ms). Compared to both early implanted animals, the difference was significant. Consequently, P_a latencies significantly correlate with implantation age after 5 months of stimulation (r = +0.999; two-tailed test at α = 5%).

Early implanted, chronically stimulated animals showed long-latency responses (peaks with latencies >80 ms) in the field potentials, which have rarely been observed in adult naive CDCs (Klinke *et al.*, 1999). Long-latency responses were most frequently found at positions with the largest middle-latency responses, but the shapes of the activation maps were different (Fig. 6). Long-latency responses were statistically evaluated in a region of interest with dimensions of 1 × 1.5 mm at the position with the largest middle-latency responses (corresponding to the 'hot-spot' – see above). The animals stimulated 2 months (csCDC 1, csCDC 2 and csCDC 7) showed only small amplitudes of the long-latency responses in the hot-spot. The amplitudes were in the range of 16–88 μV (non-significant differences between animals; two-tailed Wilcoxon–Mann–Whitney test, α = 5%).

Early implanted animals stimulated 5 months (csCDC 4, 5) had similar amplitudes of long-latency responses (66–562 μV in the hot spot, non-significant difference; two-tailed Wilcoxon–

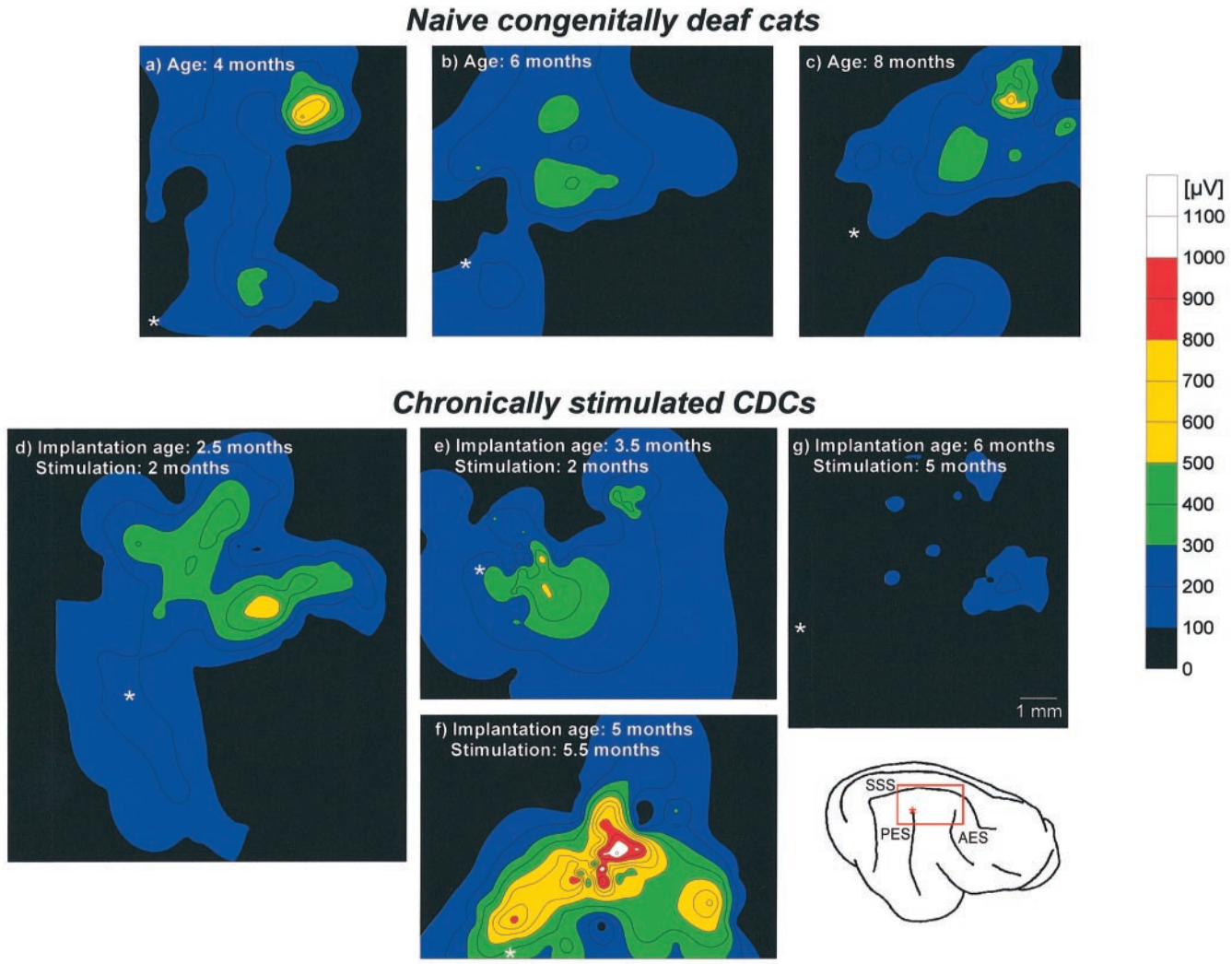

Figure 5. Color-coded middle-latency amplitudes at the auditory cortex of the naive CDCs and chronically stimulated CDCs (stimulation: ipsilateral ear, monopolar, biphasic pulse 200 μs/phase, 10 dB over threshold current, repetition rate 2 Hz). Investigated cortical region is shown in the bottom right inset. PES, posterior ectosylvian sulcus; AES, anterior ectosylvian sulcus; SSS, superior ectosylvian sulcus. Dorsal end of the PES is marked by an asterisk. (*a–c*) Naive CDCs show reproducible activated areas. Two spots of higher activity with a less active region in between. (*d*) csCDC 1. (*e*) csCDC 2. (*f*) csCDC 4. The chronically stimulated CDCs show larger amplitude responses and larger activated regions. (*g*) csCDC 6 (late-implanted animal) shows no expansion of the activated area.

Mann–Whitney test, $\alpha = 5\%$). The late-implanted animal (csCDC 6) had no long-latency responses in the hot-spot. There were, however, long-latency responses at 20 recording positions outside the hot-spot (P1 amplitudes 8–41 μV, N1 amplitudes –3 to –84 μV).

Ipsilateral Cortex

The ipsilateral activated areas with stimulation of the trained ear were always smaller than the contralateral activated areas (Fig. 8). The early implanted animal csCDC 5 showed a large ipsilateral activated area. When stimulating the untrained ear with an 'acute' cochlear implant and recording the responses on the cortex ipsilateral to the chronically stimulated ear, the mean activated area for the early implanted cats was 5.3 ± 3.1 r.u. This was not significantly different from the activated areas of naive CDCs (2.8 ± 0.6 r.u.; two-tailed Wilcoxon–Mann–Whitney test, $\alpha = 5\%$). Consequently, there seems to be no suppression of the responses of the untrained ear at the ipsilateral cortex after months of unilateral auditory experience in early implanted animals.

As far as the implantation age is concerned, the ipsilateral activated areas were consistently smaller in late-implanted animals than in early implanted animals, both for stimulation at the 'trained' and 'untrained' ear (Fig. 8). The ratio between the ipsilateral activated area (stimulation at 'untrained' ear) and contralateral activated area (stimulation at 'trained' ear) decreased with increasing implantation age, irrespective of the stimulation duration ($r = -0.999$, significant; two-tailed test at $\alpha = 5\%$).

Discussion

The present data demonstrate the following:

1. Long-term electrical stimulation with single-channel cochlear implants leads to a gradual recruitment of cortical regions for processing of auditory stimuli. The extent of this recruitment correlates with the duration of stimulation in early implanted animals.
2. Following chronic electrical stimulation, the auditory cortex develops long-latency responses.

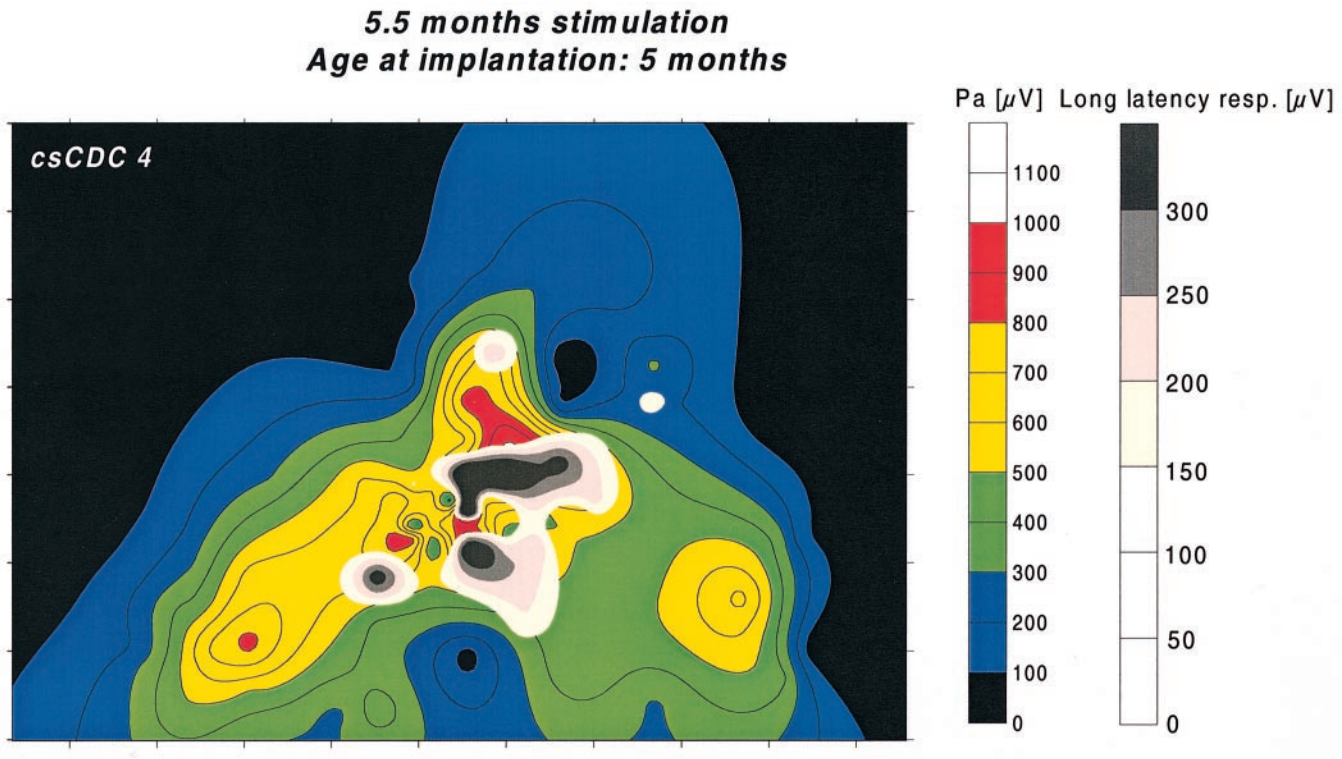

Figure 6. Overlap of the contralateral middle-latency and long-latency responses in csCDC 4. The positions with largest amplitudes overlap only partially (stimulation: ipsilateral ear, monopolar, biphasic pulse 200 μs/phase, 10 dB over threshold, repetition rate 2 Hz).

3. The ipsilateral cortex also shows considerable expansions of activated areas for the stimulation of both the trained and untrained ear in early implanted animals. The effect is smaller in late-implanted animals.

Cortical Field Potentials of Chronically Stimulated CDCs Resemble those of Hearing Cats

The shape of the field potentials in chronically stimulated CDCs electrically stimulated with pulses resembles the shape of field potentials in hearing cats in response to acoustic clicks (Hartmann *et al.*, 1997; Klinke *et al.*, 1999) and the one of field potentials of normal hearing human subjects (Howard *et al.*, 2000).

In normal hearing cats, long-latency cortical responses first appear around the third postnatal week, thus later than the middle-latency responses (König *et al.*, 1972; Eggermont, 1992). As a rule, in the present experiments long-latency responses were only found in chronically stimulated CDCs. They had a large amplitude after 5 months of auditory experience. These data support the hypothesis that long-latency responses are dependent on auditory experience (Klinke *et al.*, 1999). Long-latency cortical responses have also been found with intracellular recordings in AI of the normal hearing cat and represent a rebound from intracortical inhibition (de Ribaupierre *et al.*, 1972; Volkov and Galazjuk, 1991; Eggermont, 1992; Metherate and Cruikshank, 1999). This inhibition seems to be strongly influenced by the thalamus (Grenier *et al.*, 1998; Cotillon *et al.*, 2000).

Long-latency responses increase in amplitude after conditioning (Mercado *et al.*, 2000). They probably represent a memory trace in response to stimulation, which makes it possible to associate stimuli with succeeding ones by self-sustained oscillations in thalamocortical loops (Steriade and Llinas, 1988; Dinse *et al.*, 1997; Steriade 1999). Deficits in these loops should have perceptual correlates in prelingually deaf patients implanted late (as adults). Psychophysical studies have indeed revealed deficiencies in counting abilities for auditory stimuli in prelingually deaf patients implanted as adults (Busby *et al.*, 1992). Counting involves short-term memory which, in turn, is supposed to rely upon thalamocortical loops.

Table 2
Activated areas of the chronically stimulated CDCs at the contralateral and ipsilateral cortex

Animal	Age at implantation	Stimulation duration	Contralateral area	Ipsilateral area	Ipsilat. area, contralat. stimulation
csCDC 1	2.5	2	6.18	0.84	3.11
csCDC 2	3.5	2	4.73	–	–
csNC 3	3.5	3	8.05	–	–
csCDC 5	3.5	5	18.36	10.5	7.46
csCDC 4	5	5	13.98	0.87	–
CSCDC 6	6	5	0.00	0.00	0.09
csCDC 7	6.5	2	6.49	0.31	1.02

Stimulation was always ipsilateral (see Fig. 1 for definition) except for the last column, where the contralateral ear was stimulated. Ages are given in months, activated areas in relative units (see Materials and Methods).

Naive and Hearing Cats show Similar Activation Areas in AI

The present data did not demonstrate significant differences in middle-latency responses recorded at the cortical surface between naive CDCs and hearing controls. Also, the activated cortical areas were identical. However, this does not imply that the naive auditory cortex does not show functional deficits. A previous study revealed that synaptic activity was significantly

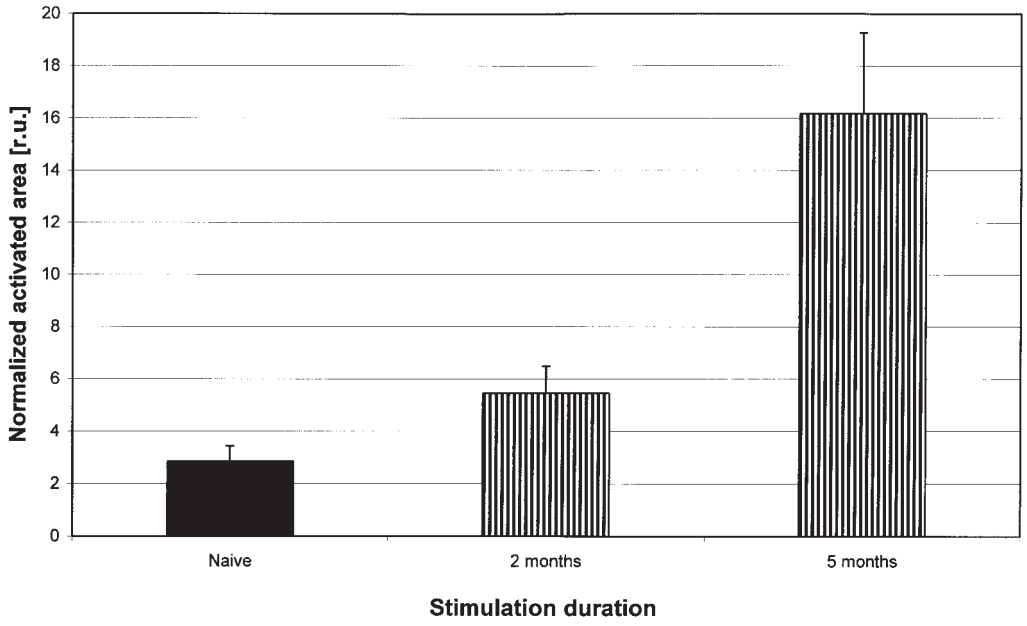

Figure 7. Effect of chronic electrical stimulation on the contralateral activated areas of early implanted chronically stimulated animals (compared are all naive animals and csCDC 1, 2, 4, 5). Stimulation: ipsilateral ear, monopolar, biphasic pulse 200 μs/phase, 10 dB above threshold current, repetition rate 2 Hz. Longer stimulation duration results in an increase of the activated area (significant; two-tailed Kruskal–Wallis test, $\alpha = 5\%$).

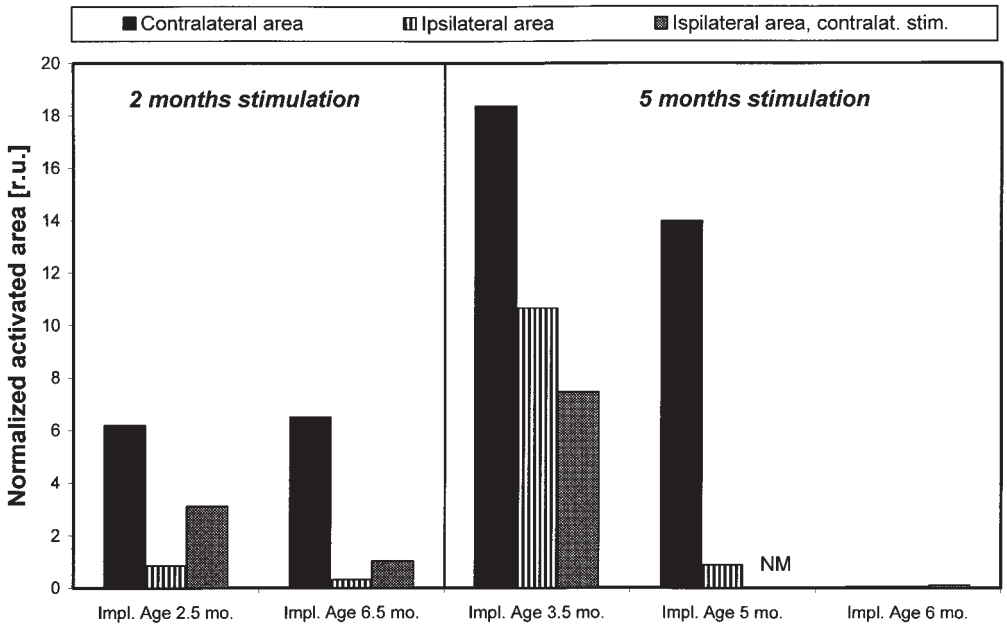

Figure 8. Effect of age at implantation on activated areas. Left: animals after 2 months of stimulation (early implanted animal csCDC 1 and late-implanted animal csCDC 7). Right: animals after 5 months of stimulation (early implanted animal csCDC 5, animal implanted with 5 months csCDC 4 and the late-implanted animal csCDC 6; NM, not measured). Black bars represent contralateral activated areas with ipsilateral stimulation; dashed bars represent ipsilateral activated areas with ipsilateral stimulation; grey bars represent ipsilateral activated areas with contralateral stimulation. Stimulation: monopolar, biphasic pulse 200 μs/phase, 10 dB above the respective cortical threshold, repetition rate 2 Hz. Later implantation results in smaller ipsilateral activated areas in all animals.

lower in naive CDCs when compared to hearing cats (Kral *et al.*, 2000). The low level of activity was prominent mainly in infragranular layers of the auditory cortex and at latencies >30 ms. This explains why no differences were observed between naive CDCs and hearing cats in activated areas computed from the first peak of surface-recorded, middle-latency responses. Additionally, the electrical stimulus is an 'inadequate' stimulus for hearing cats, as their auditory system was trained to process acoustically evoked cochlear activity characterized by much more complex discharge patterns.

As in the present study, two regions of lower thresholds were found in an earlier study (Raggio and Schreiner, 1999) using multi-unit recordings at the middle cortical layers in neonatally deafened cats. Raggio and Schreiner found differences between long-term neonatally deafened cats and hearing cats. The long-term deafened animals had significantly larger 'activated areas'

than hearing controls. The data presented here do not reveal such differences, most likely because different parameters were compared. Raggio and Schreiner compared multi-unit thresholds, whereas the present study compared amplitudes of the middle-latency responses with a stimulation current 10 dB over threshold (saturation of middle-latency amplitudes). Also, the preservation of auditory afferents is larger in CDCs than in neonatally deafened cats (Heid *et al*., 1998; Leake *et al*., 1999).

Topographic Representation of the Stimulated Cochlear Region Expands in Chronically Stimulated CDCs

In cortical primary sensory areas, anatomically neighbouring receptors efficiently activate neighbouring cortical locations. The representation of the receptors in the sensory cortex also depends on the biological importance of the conveyed signals. Therefore, more active afferents or receptors transducing more important stimuli are mapped to a larger set of neurons at the sensory cortex (Buonomano and Merzenich, 1998). It is likely that our stimuli were not sufficient to activate all fibres of the auditory nerve. This is concluded from spatial excitation curves recorded in the auditory nerve with monopolar stimulation (Kral *et al*., 1998) and the 10 dB dynamic range of the signal processors used in the present study. Partitions of the auditory nerve (located at the apex of the cochlea) were most likely not reached in our chronically stimulated CDCs. By long-term stimulation, activity invaded into these inactive regions of the primary auditory cortex and the representation of the chronically stimulated cochlear region expanded. Activated areas in chronically stimulated CDCs were even larger than in hearing cats. This is not surprising. Given the normal auditory experience of hearing cats, the acute electrical stimulation of a certain cochlear region is an inadequate stimulus. In hearing cats, the primary auditory cortex has been trained to process activity from all portions of the cochlea. All portions of the cochlea have similar significance and therefore similar representations in the cortex. The acute electrical stimulation of only one part of the cochlea of hearing animals consequently renders an activity the animal is not used to processing. The functional organization of the cortex in chronically stimulated CDCs thus differs from that in hearing cats.

In addition to the expansion of the activated areas, the latencies of middle-latency responses decreased with chronic electrostimulation. Cortical latencies also decrease during postnatal development of normal hearing kittens (Eggermont, 1996). However, in chronically stimulated CDCs, the latencies became even shorter than in hearing cats. This effect can be attributed to the artificial electrical stimulation, which is known to lead to more synchronous afferent activity than acoustical stimulation (Hartmann *et al*., 1984). Higher spike synchronization probably leads to a stronger effect on synaptic efficacies in the afferent auditory pathway.

The extent to which cortical auditory fields other than AI were involved was not investigated in this study. The second middle-latency peak and the long-latency response in the chronically stimulated CDCs, however, indicate a more complex processing of the stimuli than in naive CDCs.

Contralateral and Ipsilateral Expansions

The activated areas were larger in the contralateral than in the ipsilateral cortex. This is possibly a consequence of the projection patterns from the cochlea to the ipsilateral and contralateral cortex. The majority of afferents from the cochlea project to the contralateral cortex (Aitkin, 1990). Previous studies have shown that excitatory–excitatory interactions in the auditory cortex mainly result from callosal input, whereas excitatory–inhibitory interactions mainly result from thalamic input (Imig and Brugge, 1978; Middlebrooks *et al*., 1980). Inhibitory–excitatory interactions are rare (Middlebrooks *et al*., 1980). Potentials evoked at the contralateral cortex have larger amplitudes (Kelly and Judge, 1994) and the BOLD response obtained in functional magnetic resonance imaging is also larger at the contralateral cortex in humans (Scheffler *et al*., 1998); for cats, see Thierfelder *et al*. (Thierfelder *et al*., 2000).

The ipsilateral cortex (Fig. 1), despite having smaller activated areas than the contralateral cortex, none the less showed expansions of the representations of the chronically stimulated cochlear region (ipsilateral ear) in early implanted animals. Similar functional changes have been described after unilateral neonatal cochlear ablation in cats (Reale *et al*., 1987). In those cats, the non-ablated ear activated the ipsilateral cortex more effectively than in normal controls. The stimulation thresholds were lower and the proportion of units activated by the non-ablated ear was higher. Similar changes have also been demonstrated in the inferior colliculus of gerbils (Kitzes and Semple, 1985) and ferrets (McAlpine *et al*., 1997). The cortical neurons had larger dendritic trees after unilateral cochlear ablation in rabbits (McMullen *et al*., 1988). Unfortunately, unilateral cochlear ablation represents a different condition than inborn bilateral cochlear dysplasia. With unilateral ablation, the afferent auditory system completely loses all input from that side, including spontaneous activity and trophic influences. Therefore, the unablated side will have an advantage over the ablated ear in the competition for neuronal targets. In CDCs, both ears degenerate slowly in a comparable time frame. Hence, projections from both ears have equal potential in the competition for neuronal targets and therefore have the same targets during early postnatal development. The connectivity of the afferent auditory system is basically intact in CDCs (Heid *et al*., 1997). Unilateral stimulation was initiated after several weeks of complete bilateral deprivation in this study, which corresponds to cochlear-implanted congenitally deaf children, but not to the neonatal unilateral ablation models mentioned above.

The brainstem projections after unilateral ablation are rewired: projections from the non-ablated ear include parts normally innervated by the ablated cochlea [cf. ferret (Moore *et al*., 1993, 1995; Moore, 1994) and gerbil (Kitzes *et al*., 1995)]. The connections in the auditory system in CDCs following chronic electrostimulation are as yet unknown.

Contralateral ('Untrained') Ear Activates Ipsilateral Cortex

In addition, after months of unilateral auditory experience there was no functional suppression of the projections from the untrained ear to the cortex, contrary to monocular deprivation (Rauschecker, 1991). The possible explanation is a large binaural convergence at the level of the brainstem in the auditory system. Part of the expansions of activated areas of the primary auditory cortex are thus possibly based on subcortical changes, which take place in addition to (or as a consequence of) the cortical ones. Expansion of the 'activated area' has also been observed in the inferior colliculus of neonatally deafened, cochlea-implanted and chronically stimulated animals (Snyder *et al*., 1990, 1991). Whether these changes were cortically induced (Ergenzinger *et al*., 1998; Parker and Dostrovsky, 1999) remains to be clarified. The influence of callosal projections in the cortical expansions documented here is unknown. The fact that the untrained ear strongly activates the ispilateral cortex in chronically stimulated

CDCs (Fig. 8) implies that connections from the untrained ear are not replaced by those of the trained ear. These findings suggest that there is a difference compared to unilateral cochlear ablation [cf. gerbil (Moore and Kitzes, 1985; Kitzes *et al.*, 1995)] and indicate that trophic influences and activity, possibly even spontaneous activity, in early postnatal development are of substantial importance [cf. gerbil (Tierney *et al.*, 1997)]. In other experiments (Reale *et al.*, 1987), it was impossible to stimulate the ablated ear, so that a direct comparison between the results of this study and their results is not possible.

A Sensitive Period in the Cat Auditory System

With implantation after the fifth month of age, the effect of chronic stimulation on the auditory system decreased (e.g. smaller activated areas, longer shortest latencies, smaller long-latency responses), indicating a developmental window for plasticity. Similar conclusions were drawn from neonatal cochlear manipulations (Harrison *et al.*, 1991), although this condition differs from congenital deprivation. In the cat's visual system, the sensitive period ends at 4–8 months of life (Cynader and Mitchell, 1980; Fregnac and Imbert, 1984). Age-dependency appears to be stronger for the plasticity at the cortex ipsilateral to the stimulated ear (Fig. 8). This can be explained with the corticopetal projection pattern showing more abundant excitatory projections to the contralateral cortex (see above). The stronger effect of deprivation on the plasticity of the ipsilateral cortex has also been demonstrated in the visual system of the mouse (Antonini *et al.*, 1999).

The amplitudes of middle-latency responses displayed a large variability, especially in late-implanted animals at the contralateral cortex. The late-implanted animal csCDC 7 had a small ipsilateral activated area, but the contralateral activated area was larger than the mean of naive CDCs. In that sense, csCDC 7 was more similar to csCDC 4 (implantation age 5 months, large contralateral area) than to csCDC 6 (implantation age 6 months, small contralateral area). Therefore, a substantial decrease in the contralateral activated area in case of an implantation age of >5 months cannot be safely concluded. Decreasing ipsilateral activated areas with increasing implantation age were consistent in all five animals (Fig. 8) and demonstrate the existence of a sensitive period in the auditory cortex of CDCs.

A decrease in the amplitude of cortical field potentials recorded at the cortical surface with implantation age does not necessarily imply a decrease in overall activity in the cortex. Changes in amplitude and shape of surface field potentials can also be a consequence of rearranged localization and latency of synaptic currents in the cortical column.

In humans, it has been shown that the activated area correlates with speech performance in cochlear implant patients and that it expands with duration of auditory experience through a cochlear implant (Lee *et al.*, 2001). This indicates that the cortical activated area represents a good neurophysiological measure of auditory competence. The results of the present study correspond to the human data. The auditory performance of congenitally deaf cochlear implant users also depends on implantation age and shows a sensitive period (Busby *et al.*, 1992, 1993, 1998; Fryauf-Bertschy *et al.*, 1997; Ponton *et al.*, 1999; Kral *et al.*, 2001).

Cellular Mechanisms

It has been demonstrated that in naive CDCs neurons in AI have fewer primary and secondary dendrites than in hearing cats (Wurth *et al.*, 1999), something which correlates with smaller synaptic currents (Kral *et al.*, 2000). Dendritic and axonal growth (Darian-Smith and Gilbert, 1994) is a candidate for the expansions of cortical activity reported in this paper. The large time frame demonstrated here (weeks to months) also indicates that morphological changes are involved. No conclusion can be drawn about the cellular and molecular mechanisms that lead to cortical expansions in these animals as yet; however, a detailed review of possible neural mechanisms has been published (Kral *et al.*, 2001).

Notes

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