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Single-sided deafness leads to unilateral aural preference within an early sensitive period

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Unilateral deafness has a high incidence in children. In addition to children who are born without hearing in one ear, children with bilateral deafness are frequently equipped only with one cochlear implant, leaving the other ear deaf. The present study investigates the effects of such single-sided deafness during development in the congenitally deaf cat. The investigated animals were either born with unilateral deafness or received a cochlear implant in one ear and were subjected to chronic monaural stimulation. In chronically stimulated animals, implantation ages were at the following three critical developmental points: 'early' during the peak of functional cortical synaptogenesis in deaf animals; 'intermediate' at the age when synaptic activity in the deaf cats dropped to the level of hearing control cats and finally, 'late' at the age when the evoked synaptic activity fell below the level of hearing control cats. After periods of unilateral hearing, local field potentials were recorded from the cortical surface using a microelectrode at ~100 recording positions. Stimulation was with cochlear implants at both ears. The measures evaluated were dependent only on the symmetry of aural input: paired differences of onset latencies and paired relations of peak amplitudes of local field potentials. A massive reorganization of aural preference in favour of the hearing ear was found in these measures if the onset of unilateral hearing was early (before or around the peak of functional synaptogenesis). The effect was reduced if onset of unilateral hearing was in the intermediate period, and it disappeared if the onset was late. In early onset of unilateral deafness, the used ear became functionally dominant with respect to local field potential onset latency and amplitude. This explains the inferior outcome of implantations at the second-implanted ear compared with first-implanted ear in children. However, despite a central disadvantage for the deaf ear, it still remained capable of activating the auditory cortex. Appropriate training may thus help to improve the performance at the second-implanted ear. In conclusion, periods of monaural stimulation should be kept as short as possible, and training focused on the deaf ear should be introduced after delayed second implantation in children.

Keywords: congenital single-sided deafness; asymmetric hearing; deaf white cat; cochlear implant; plasticity; development; sensitive period

Abbreviation: CDC = congenitally deaf cat

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Introduction

Most cortical synapses appear during post-natal life [humans: the first 1–2 years (Huttenlocher and Dabholkar, 1997); cats: the first 4–8 weeks (Winfield, 1983; Kral *et al*., 2005)]. The cortical developmental sequence is severely affected by total absence of hearing experience (deafness), where the development of functional synapses is delayed and subsequent functional synaptic elimination is enhanced, resulting in numerous processing deficits (Kral *et al*., 2005; Kral and Sharma, 2012). Consequently, the developing auditory system is vulnerable to manipulation of auditory experience.

Unilateral hearing loss is frequent in newborns (0.5/1000 newborns; Eiserman *et al*., 2008; Watkin and Balwin, 2012), and the incidence increases with age (Tharpe and Sladen, 2008; Shargorodsky *et al*., 2010). It affects speech recognition (Lieu *et al*., 2010) and, consequently, requires therapy. The most extreme form of asymmetric hearing loss is unilateral deafness. Moreover, the majority of cochlear-implant recipients are implanted in only one ear. In both of these conditions, the central auditory system receives highly imbalanced input from the two ears, potentially reorganizing the central auditory system. Recent studies on cochlear-implant recipients demonstrate the advantage of binaural versus monaural implants, and also that binaural implant users have some access to spatial cues (Litovsky *et al*., 2009, 2010; Chadha *et al*., 2011). In children, sequential implantations lead to speech recognition benefit in the second-implanted ear that is inferior to the first implanted ear (Peters *et al*., 2007; Firszt *et al*., 2008; Graham *et al*., 2009; Gordon *et al*., 2011). The outcome critically depends on age at second implantation (Graham *et al*., 2009; Van Deun *et al*., 2009), which could reflect the length of the time spent without hearing on one side. First data from human imaging studies of binaural cochlear implantees support more simultaneous implantations (Gordon *et al*., 2010). The present study investigates the neuronal substrate of this effect in an animal model.

Windows of developmental plasticity were identified in animals and humans when cochlear implantation is capable of inducing cortical maturation (Klinke *et al*., 1999; Kral *et al*., 2002; Sharma *et al*., 2005, 2007). Nonetheless, previous studies either concentrated on the cortex contralateral to the implanted ear (Klinke *et al*., 1999; Fallon *et al*., 2009; Kral *et al*., 2009; Beitel *et al*., 2011) or were—owing to the technology used—not able to differentiate and localize the effects on the contralateral and ipsilateral hemisphere (Sharma *et al*., 2007) and only recently have investigations on hemispheric contributions been initiated (Gilley *et al*., 2008; Gordon *et al*., 2010). Here, we systematically investigate the cortex ipsilateral to the implanted ear.

The present study uses an animal model with well-controlled auditory experience, the congenitally deaf white cat (CDC; Mair and Elverland, 1977; Heid *et al*., 1998). In CDCs, numerous deficits in the auditory system have been described and shown to be reversible with chronic cochlear-implant stimulation (reviewed in Kral and Sharma, 2012). In the present study, CDCs were monaurally equipped with a cochlear implant and were chronically stimulated using a portable stimulator that converted natural sounds into electrical signals. Implantations were performed based on cortical synaptic developmental sequence in CDCs (described in Kral *et al*., 2005), during the peak in synaptic activity (functional 'synaptic overshoot') in the naive auditory cortex, during the time when the synaptic activity falls to the level of hearing control cats and, finally, during the time when it dropped below the level of hearing control cats (Kral *et al*., 2005). However, it has not been possible to implant animals within the first 6 weeks of life (i.e. before and during the process of cortical synaptogenesis) owing to the thin and partially non-calcified cranium that cannot support the implant at such an early stage. Therefore, to investigate effects of unilateral deafness from the first post-natal days, we compared the results from implanted animals to those from the rare animals that were born deaf in one ear and had normal hearing in the other ear (incidence ~1%; Geigy *et al*., 2007).

The present experiments demonstrate that the cortex ipsilateral to the 'hearing' ear consistently shows an extensive reorganization during an early sensitive developmental period, leading to an aural preference for the 'hearing' ear and 'weakness' of the representation of the 'deaf' ear.

Materials and methods

Animals

Experiments were performed on 21 cats (supplementary control data were obtained from additional 11 cats, see Supplementary material). All investigated animals had no signs of infection in the bulla, middle ear and cochlea. Fourteen cats had symmetrical hearing, of which seven animals were congenitally deaf and did not receive any chronic stimulation (naïve, CDCs) and seven cats had normal hearing (hearing thresholds <40 dB sound pressure level) and had a normal hearing experience up to the time of the acute experiment (hearing control cats). Seven animals had unilateral hearing (Table 1), of which two animals were congenitally deaf in one ear with normal hearing on the other ear (hearing thresholds <40 dB sound pressure level; unilateral CDC group) and the remaining five were congenitally deaf in both ears but received chronic electrostimulation unilaterally (chronic electrostimulation CDC group). The implantation ages of unilateral animals are given in Table 1. All animals obtained from the colony of deaf white cats underwent hearing screening within the fourth week of life. The screening procedure was based on a longitudinal study of hearing in deaf white cats recorded every 2 days after birth and is described in detail elsewhere (Heid *et al*., 1998).

All experiments were approved by the local state authorities and were performed in compliance with the guidelines of the European Community for the care and use of laboratory animals (EU VD 86/609/EEC) and the German law for protection of animals.

To investigate developmental plasticity in animals with unilateral hearing, chronic stimulation in the present study was initiated at three different ages based on the cortical synaptic development in CDCs (Kral *et al*., 2005, Fig. 1C) (i) early (2.5 and 3.5 months, early implanted animals), when the naïve cortex shows a developmental peak in evoked synaptic activity; (ii) intermediate (4.2 months), when synaptic activity in the naïve auditory cortex has decreased to adult hearing levels; and (iii) late (after 6.0 months), when synaptic activity in deaf animals fell below the level of hearing control cats and

Table 1 Overview of the seven unilateral animals used in the present study

Animal	Age at onset of unilateral hearing (months)	Age at experiment (months)	Hearing ear	Contralateral cortex	Ipsilateral cortex
uCDC 1	Congenital	>12	Left		•
uCDC 2	Congenital	>12	Right	•	•
csCDC 1	2.5	4.5	Left	•	•
csCDC 2	3.5	9	Left	•	•
csCDC 3	4.2	9.2	Left		•
csCDC 4	6.0	11	Left	•	•
csCDC 5	6.0	8	Left	•	•

For chronic electrostimulation of CDCs, the age at onset unilateral hearing corresponds to implantation age. Consequently, chronic electrostimulation CDC 1 and 5 were stimulated for 2 months and chronic electrostimulation CDCs 2, 3 and 4 for 5 months. All control cats (hearing control cats and CDCs) were adult.
csCDC = chronic electrostimulation CDC; uCDC = unilateral CDC.

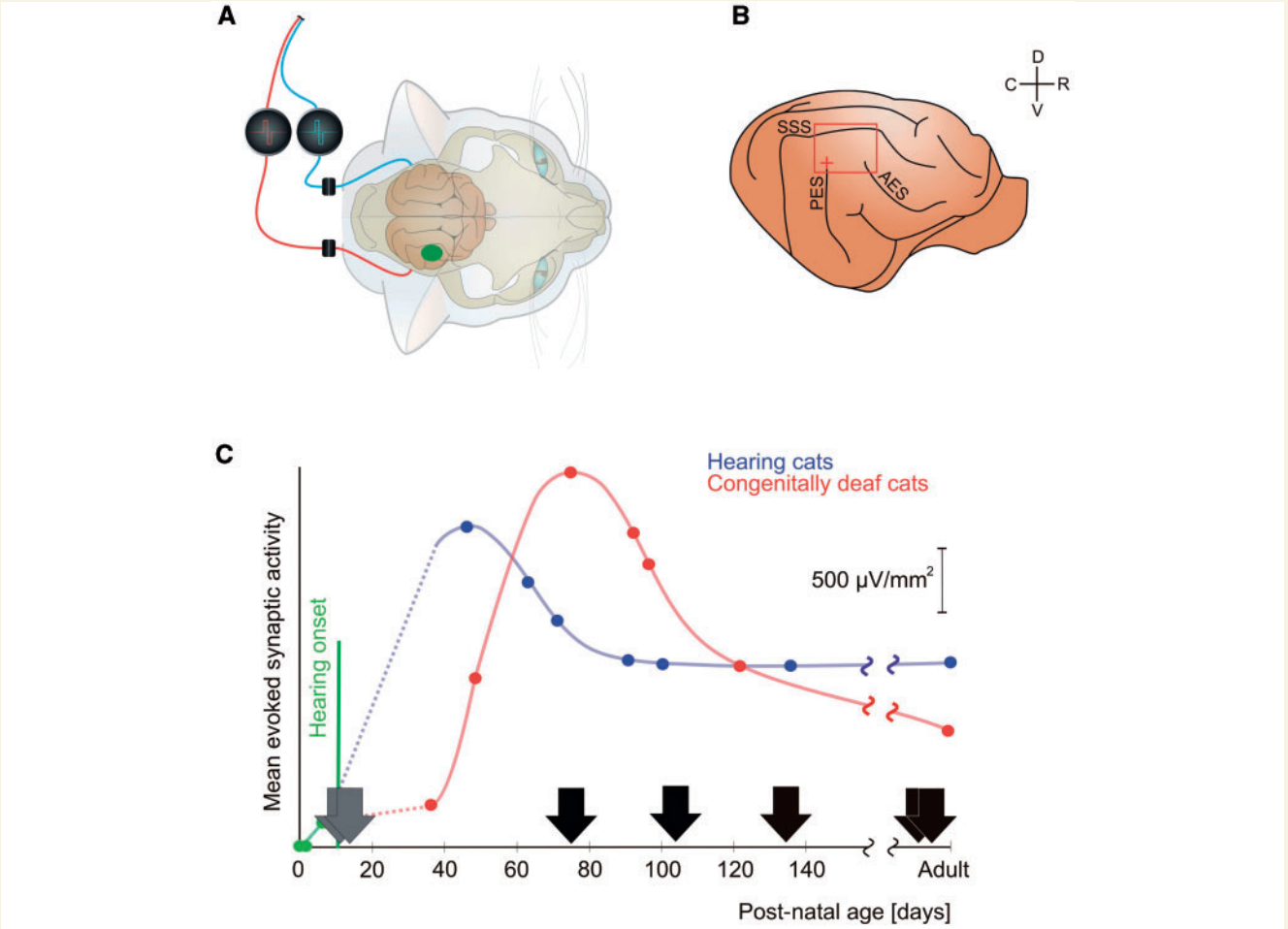

Figure 1 Methodology. (**A**) In the final experiment, all animals were implanted binaurally and stimulated with biphasic pulses, 200 µs/phase charged-balanced, applied through the apical-most electrode of the implant in monopolar configuration at 10 dB above lowest cortical threshold. The cortex was exposed in unilateral animals at the site ipsilateral to the trained ear. (**B**) The primary auditory cortex and the adjoining regions of surrounding areas were mapped, as shown by the red rectangle. Reference structures were the dorsal end of the posterior ectosylvian sulcus (cross), the anterior ectosylvian sulcus and the superior sylvian sulcus. (**C**) Onset of unilateral hearing in seven single-sided animals (two unilateral CDCs: grey arrows; five chronic electrostimulation CDCs: black arrows) related to the developmental change in the mean evoked synaptic activity (quantified from current source density signals) determined in congenitally deaf cats in a previous study (Kral *et al*., 2005, parts of C modified and reproduced with permission from Kral and O'Donoghue, 2010). For details on stimulation duration, see Table 1. SSS = superior sylvian sulcus; PES = posterior ectosylvian sulcus; AES = anterior ectosylvian sulcus; C = caudal; R = rostral; D = dorsal; V = ventral.

expressed the deficits in cortical microcircuitry as described previously (Kral *et al*., 2005).

Chronic stimulation was performed using single-channel portable processors with a compressed analogue coding strategy in monopolar stimulation. Stimulation was applied on a 24/7 basis (Kral *et al*., 2006; Supplementary material). To may consider the effects of stimulation duration, two animals were stimulated for 2 months (~1440 h of implant stimulation) and three animals were stimulated for 5 months (~3600 h of implant stimulation).

Acute experiments: stimulation and recording

For acute experiments, all animals were premedicated with 0.25 mg atropine intraperitoneally and were initially anaesthetized with ketamin hydrochloride (24.5 mg/kg Ketavet, Parker-Davis) and propionylpromazine phosphate (2.1 mg/kg Combelen, Bayer) or xylazine hydrochloride (1 mg/kg, Bayer). These animals were then tracheotomized and artificially respirated with 50% O_2 and 50% N_2O, with a 0.2–1.5% concentration of isoflurane (Lilly) added to maintain a controlled depth of anaesthesia. Animals were monitored using heart-rate, end-tidal CO_2, muscle tone and EEG signals. End-tidal CO_2 was maintained $<4\%$. Core temperature was kept $>37.5^{\circ}C$ using a homeothermic blanket. The animals' status was further monitored by blood–gas concentration measurements, pH, bicarbonate concentration and base excess, glycaemia and oxygen saturation. A modified Ringer's solution containing bicarbonate (according to the base excess) was infused intravenously. The internal state was monitored by testing capillary blood every 12 h.

The animal's head was fixed in a stereotactic holder (Horsley-Clarke). Both bullae and ear canals were exposed. To record evoked auditory brainstem responses, a small trephination was drilled at the vertex, and a silver-ball electrode (diameter 1 mm) was attached epidurally. Hearing status was tested at the beginning of the experiments. So as to prevent electrophonic responses, the hair cells in normal-hearing animals were destroyed by intracochlear instillation of 300 µl of 2.5% neomycin sulphate solution over a 5-min period and subsequent rinsing using Ringer's solution. The absence of hearing was subsequently confirmed by the absence of brainstem-evoked responses.

Stimulation in the final acute experiments was performed using cochlear implants inserted bilaterally into the cochlea. The stimulus was a biphasic pulse (200 µs/phase) applied through the apical-most electrode contact at 10 dB above the lowest cortical threshold for the stimulation at the given ear (Kral *et al*., 2009; Supplementary material). Relating stimulation level to the cortical threshold for stimulation at each ear assured balanced levels of cortical activity for each ear during stimulation.

For recording, a trephination above the auditory cortex was performed, and the dura was opened (Fig. 1A and B). Mapping of cortical responses was performed using glass microelectrodes ($Z \sim 6$ MΩ) that were moved along the auditory cortex with a micromanipulator (1 µm precision) at the cortical surface. The signals were amplified 5000–10 000 times, bandpass filtered (0.01–10 kHz), digitized (with sampling rate of 25 kHz) and 50 responses were averaged. The activation maps were constructed from ~100 recording positions per animal (Kral *et al*., 2009). Averaged signals were processed further. For details, see Kral *et al*. (2009) and Supplementary material.

Data processing

From the recordings at the cortical surface within field A1 and adjacent fields, cortical activation maps were constructed (Fig. 2).

Cochlear-implant stimulation results in electrical artefacts in the recordings. These occurred between 0 and 0.6 ms after stimulus onset and were blanked before further processing. The signal after the artefact and before the first cortical evoked response (500 ms duration in each animal) was characterized by computing its mean and standard deviation. The threshold of mean $\pm 4 \times$ standard deviation was then used for detecting neuronal responses. The threshold attained absolute values of 10–20 µV. To check the consistence of this measure, any suprathreshold values within 5 ms after the stimulus onset (before cortical responses appear) were reported by the software. This happened in 11 local field potentials in three animals owing to recording artefacts (disturbances in the electric circuit or muscle artefacts). In these few cases, the artefacts were eliminated by removing the corresponding trials before averaging.

Using the above threshold, onset latencies were detected for both the first negative response (N_a component) and first positive response (P_a component) of the local field potentials. For each recording position of the surface maps, these data were determined for responses evoked by stimulation at the ipsilateral and the contralateral ear. Afterwards, from all recording positions in each animal, a paired comparison was performed and statistically tested. Normality of the data was tested using the Jarque–Bera test (5% level) and if confirmed, a paired *t*-test was carried out; if it failed, a paired Wilcoxon test (both two-tailed at 5% significance level) was used. Additionally, for each position, a paired difference of the onset latency was computed. The medians were used as population measures, as the latency values showed a significantly skewed distribution. Comparisons between the experimental groups were performed, depending on normality of the data, with *t*-tests or Wilcoxon–Mann–Whitney test (both two-tailed, 5% significance level).

Peak amplitudes of P_a components were determined using an automated procedure (based on the time derivatives of the signals). Amplitudes <50 µV were discarded from the processing to minimize the effect of noise on small amplitude signals. First, the activated area of the cortex (with responses >50 µV) was determined in all animals and expressed in relative units (same procedure as in Kral *et al*., 2002). Secondly, the contralaterality index was computed for each recording position (Kral *et al*., 2009):

$$CI = \frac{LFP_c}{LFP_c + LFP_i}$$

The contralaterality index (CI) represents the fraction of the amplitude obtained with contralateral stimulation, divided by the sum of the amplitudes obtained with contralateral stimulation and ipsilateral stimulation. $CI > 0.5$ represents a greater contralateral than ipsilateral response, and $CI < 0.5$ represents the reverse. The significance of the CI was determined from paired tests of the peak amplitudes from all recording positions. Normality of the data was tested using the Jarque–Bera test (5% level), and if confirmed, a paired *t*-test was performed; if it failed, a paired Wilxocon test was used (both two-tailed at 5% significance level). From all values in each animal, means were calculated and statistically compared between groups, depending on normality of the data, with *t*-test or Wilcoxon–Mann–Whitney test (both two-tailed, 5% significance level). Some analyses were performed exclusively from six positions within the area with the largest responses (the 'hot-spot'; Kral *et al*., 2009).

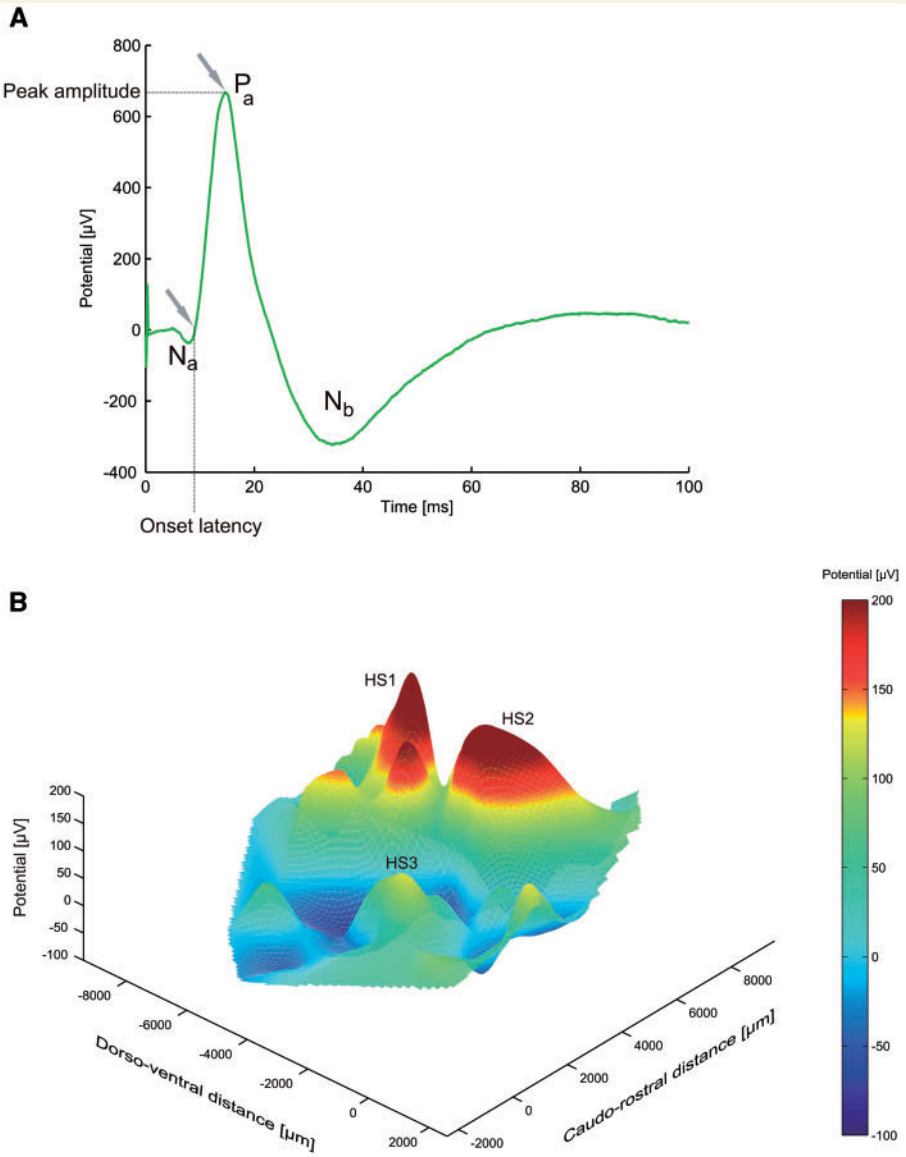

Figure 2 (**A**) Morphology of local field potentials in the middle-latency range. The three prominent components (N_a, P_a and N_b) can be observed with electrical stimulation in all groups of animals at different cortical recording positions. The first two components were processed, whereas statistical analysis concentrated on P_a components. Onset latencies and peak amplitudes were quantified. (**B**) Distribution of Pa amplitudes in response to cochlear electrical stimulation is characterized by three 'hot spots' in a healthy control animal (Kral *et al*., 2009). In chronic electrostimulation CDCs, mainly hot spot 1 (HS1) could be differentiated (data not shown). Coordinate (0,0) corresponds to the dorsal end of the posterior ectosylvian sulcus (Fig. 1B).

Results

Local field potentials in the middle latency range were typically characterized by the following three components: N_a, P_a and N_b (Fig. 2A). Owing to the inconsistency of appearance of N_a waves, this component could not be compared in all animals. The analysis, therefore, concentrated on P_a components. All animals had mature P_a latencies at the time of the acute (final) experiment (for post-natal development in deaf animals see Supplementary Fig. 1; for hearing animals see Eggermont, 1996). Activation maps revealed that the cortical responses to cochlear implants are grouped in two to three hot spots in field A1 (Fig. 2B). The largest amplitudes were localized in the rostral part of the field A1. Because of the cochleotopic organization of field A1, the rostral A1 corresponds to the position of the cochlear implant in the base of the cochlea (Kral *et al*., 2009).

Although statistical testing was not possible for cortical areas (yielding individual values for each animal), the two early implanted (unilateral) animals had nominally larger cortical activated areas at the cortex ipsilateral to the trained ear than animals with symmetric hearing (hearing control cats and CDCs, Supplementary Fig. 2). This is known to be the consequence of single-channel

electrostimulation (see 'Discussion' section) and corresponds to previous observations on a sensitive period for expansion of activated areas in early implanted chronically stimulated cats (Klinke *et al*., 1999; Kral *et al*., 2006).

In adult hearing control cats and CDCs (i.e. animals with symmetrical hearing), responses for stimulation at the contralateral ear had larger P_a components than for stimulation at the ipsilateral ear (Fig. 3). The onset latencies were nominally shorter for the

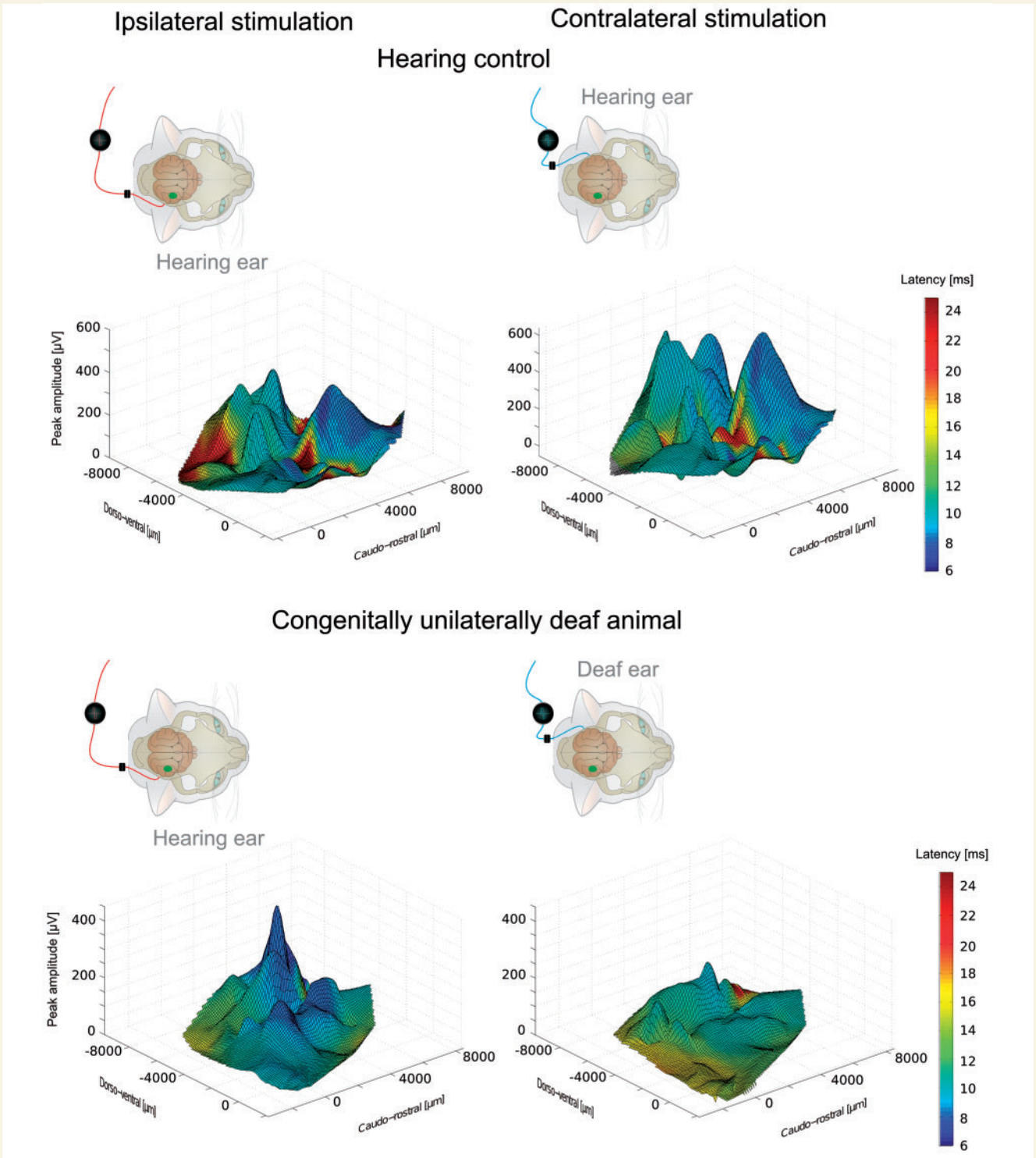

Figure 3 Distribution of P_a amplitude and onset latency along the auditory cortex, latency indicated by colour. Top: In a hearing control, contralateral stimulation results in larger amplitudes and slightly shorter onset latencies. Bottom: In the congenitally unilaterally deaf cat, the situation is reversed; with ipsilateral stimulation, larger amplitudes are found and latencies are considerably shorter.

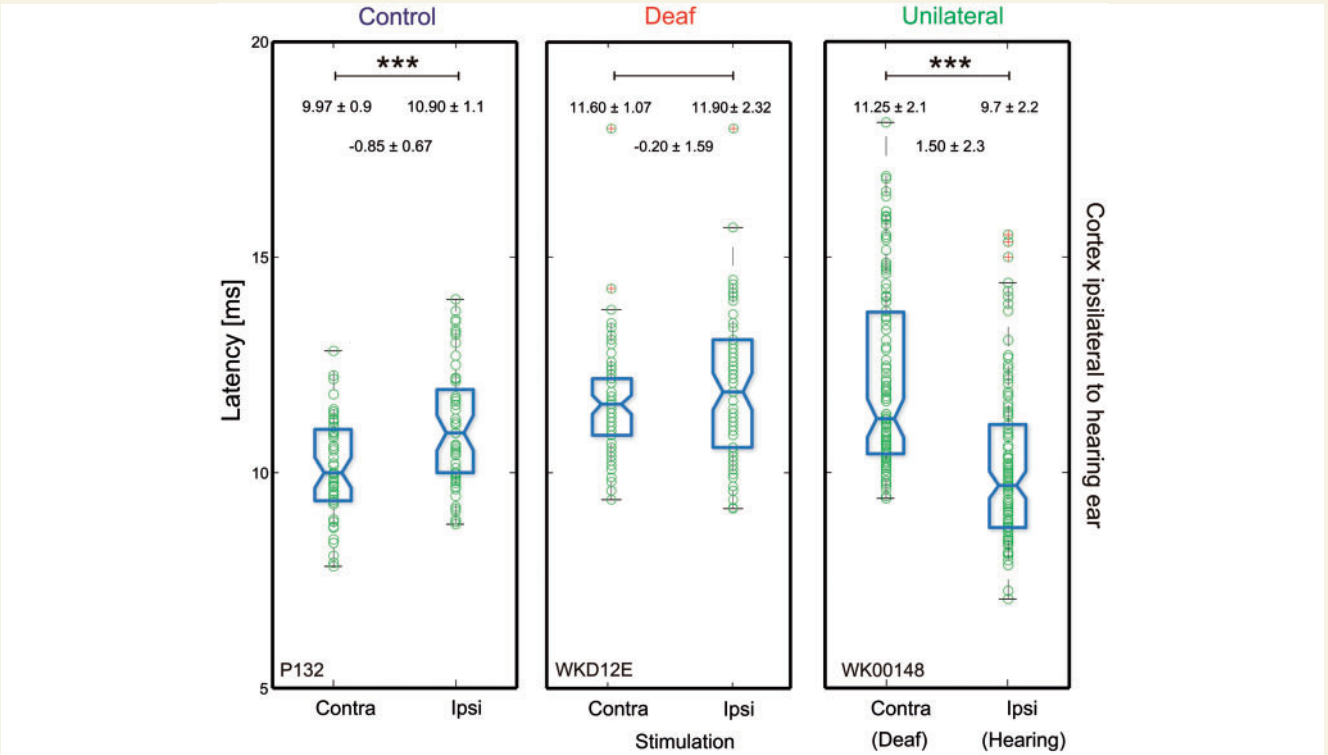

Figure 4 Statistical analysis of onset latencies in three example animals. *Left*: Hearing control. From > 100 recording positions, onset latencies were determined for contralateral and ipsilateral stimulation, and medians with their absolute deviations are shown above. Pairwise differences resulted in the median and its absolute deviation of -0.85 ± 0.67 ms (contralateral shorter). *Middle*: CDC. Contralateral and ipsilateral stimulation resulted in no difference in paired onset latency (-0.2 ± 1.59 ms). *Right*: Unilaterally congenitally deaf animal. In this animal, the paired difference was reversed (1.5 ± 2.3 ms) and was highly significant. Ipsilateral response had a shorter latency at the cortex ipsilateral to the hearing ear.

contralateral ear in hearing control cats. In CDCs, this difference was less prominent. Animals with the 'early' single-sided hearing (unilateral CDCs and chronic electrostimulation CDCs implanted before the fourth month of life) showed the opposite pattern at the cortex ipsilateral to the hearing (or electrostimulated, 'trained') ear (Fig. 3); the responses to the ipsilateral, 'hearing' ear were larger than the responses to the contralateral, 'deaf' ear. The latencies were shorter with stimulation of the 'hearing' (ipsilateral) ear in unilateral animals. This was not observed in any of the 14 control cats (hearing control cats and CDCs). Similar results were obtained for peak latencies; however, they were delayed by ~4 ms compared with onset latencies (data not shown).

To quantify this observation, paired differences of onset latencies at each recording position were statistically evaluated (three individual animals shown in Fig. 4). In six hearing control animals, significantly shorter latency for contralateral stimulation was found (paired Wilcoxon two-tailed test, $P < 0.01$); in the last one, the difference was not statistically significant, but it was of similar order of magnitude. When pooled together for all animals, this resulted in the grand mean paired difference of -0.84 ± 0.44 ms (Fig. 5). In CDCs, no animal had significant paired difference of latencies (paired two-tailed Wilcoxon test, $P > 0.05$). The resulting grand mean paired difference was 0.04 ± 0.29 ms (Fig. 5; significantly different from hearing control cats, two-tailed Wilcoxon–Mann–Whitney test, $P = 0.00058$). In both unilateral CDCs, the ipsilateral stimulation (of the trained ear) resulted in significantly shorter latencies than contralateral stimulation, completely reversing the condition in hearing control cats (Figs 4 and 5).

Thus, the contralateral latency preference in hearing control cats (shorter latency for contralateral stimulation) was lost in CDCs and reversed in unilateral CDCs (Figs 4 and 5). When compared with medians of chronic electrostimulation CDCs, a developmental dependence of onset latency on implantation age became apparent, with statistically significant reversals at early implantation age only (Fig. 5). All three animals implanted after fourth month of life (intermediate and late implantations) showed no significant difference in onset latencies between ipsilateral and contralateral stimulation, and their medians fell within the range of naïve CDCs. The paired difference in onset latencies thus showed a general decrease with increasing age at onset of unilateral deafness (correlation coefficient: -0.9511, $P = 0.00078$), demonstrating a sensitive period for reorganization of aural preference at the ipsilateral cortex.

The duration of stimulation did not correlate with paired differences of onset latencies (correlation coefficient: 0.645, $P = 0.118$). Consequently, stimulation duration was less critical for the outcome than age at onset of unilateral hearing. This further confirms

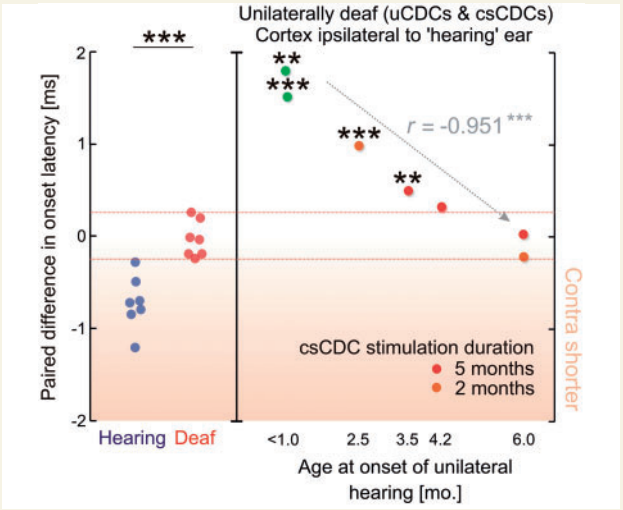

Figure 5 Medians of the paired differences in onset latencies for all animals. *Left*: Control animals (hearing control cats and CDCs). Six of the seven hearing control cats (HC, 86%) showed a significant difference in of onset latency, with shorter latency for contralateral stimulation; none of the CDCs had a statistically significant difference between contralateral and ipsilateral latency. In consequence, the pooled medians showed a significant difference between hearing and deaf animals (see text). The dotted lines mark the range observed in naïve CDCs. *Right*: Single-sided animals reorganized the aural preference to the ipsilateral (trained) ear, whereas the medians were significantly different for both unilateral CDCs (uCDC, green) and both early implanted chronic electrostimulation CDCs (csCDC). The paired difference in latency significantly correlated with age of onset of unilateral hearing. ***$\sim p < 0.001$.

that the selected stimulation durations in chronic electrostimulation CDCs were sufficiently long for resolving the investigated developmental effects. Large effects were already evident after the first 2 months of unilateral hearing in the early implanted animal. Such rapid reorganization may be because of the fact that onset latency approaches a floor level below which it cannot further decrease, determined by the number of synapses involved and their minimal synaptic delays.

To evaluate P_a amplitude differences, the contralaterality index was determined for each recording position and was statistically compared between animals. The contralaterality index is highest within hot spots 1 and 2 and at their borders and lower elsewhere in hearing control cats and CDCs. Additionally, it has been previously shown that CDCs have a lower contralaterality index (Kral *et al*., 2009). In the present data, too (Fig. 6), a difference was observed depending on hearing experience; all hearing control cats had a mean CI > 0.5, with grand CI of 0.66 ± 0.04 (all paired amplitude differences were significant, two-tailed Wilcoxon test, $P < 0.001$). Also CDCs showed a significant contralateral preference (grand mean CI 0.61 ± 0.03; all paired differences were significant, $P < 0.001$), although significantly smaller than hearing control cats (comparison of pooled data, two-tailed Wilcoxon–Mann–Whitney test, $P = 0.017$; Fig. 6).

A reversal of aural preference was found in unilateral CDCs, with a preference for the ipsilateral (trained) ear (grand mean CI 0.45 ± 0.01); the amplitude difference was significant in both animals (paired two-tailed Wilcoxon test, $P < 0.001$). In chronic electrostimulation CDCs, only the early implanted animal with 5 months stimulation showed a similar reversal of aural preference (Fig. 6). The CI distribution in the cortex of chronic electrostimulation CDCs was highly unusual; within hot spot 1, the lowest CIs were found (Supplementary Fig. 3), something never observed in hearing control cats and CDCs (see also Kral *et al*., 2009). This indicates that a change in contralaterality was initiated within the hot spot. As activated areas (and hot spots) expand during stimulation (Kral *et al*., 2006; Supplementary Fig. 2), contralaterality was also quantified within the hot spot (four to six recording positions with largest responses). The values obtained correlated significantly with onset of unilateral hearing (correlation coefficient: 0.93, $P = 0.0025$). Despite the change in contralaterality, the untrained ear remained capable of activating the cortex in all investigated animals (*cf*. Fig. 3), demonstrating that the weaker ear was not completely suppressed in unilateral deafness. Although in the early implanted chronic electrostimulation CDCs stimulation duration affected the outcome (Fig. 6), for the whole group of unilateral animals, the contralaterality index did not correlate with stimulation duration (correlation coefficient: -0.660, $P = 0.107$). Thus, also here, the effect of stimulation duration was less critical than age at onset of unilateral deafness.

Morphology of local field potentials (Fig. 7) carries information on the time course of the underlying synaptic currents as well as their location relative to the cortical surface. Consequently, differences in synapses generating the local field potential (with respect to their position and gating properties) should result in difference of morphology of local field potentials, irrespective of their amplitude difference. In hearing control cats, morphology of local field potentials evoked by stimulation at the ipsilateral and contralateral ear in the hot spot differ (Fig. 7A; Kral *et al*., 2009). This is, however, not the case for CDCs (Fig. 7B; Kral *et al*., 2009). When such local field potentials (ipsilateral versus contralateral stimulation) were compared in animals with unilateral hearing, similarity of the morphology within was observed, despite differences in amplitude and latency (Fig. 7C–E). This excludes more substantial differences in generator currents and indicates that stimulation at the ipsilateral and contralateral ear activates an overlapping neuronal population in the cortex.

Discussion

Onset latencies showed significant and rapid shifts towards shorter values for the hearing ear in early unilateral deafness. A similar but weaker effect was observed with peak amplitudes of local field potentials, together resulting in the preference of the cortex for the hearing ear compared with the deaf ear with respect to these measures. The present data additionally demonstrate a sensitive period for such cortical aural reorganization after unilateral deafness. The sensitive period covered the first 4 months and correlated with the developmental peak of evoked synaptic activity in the naïve cat auditory cortex (Fig. 1C).

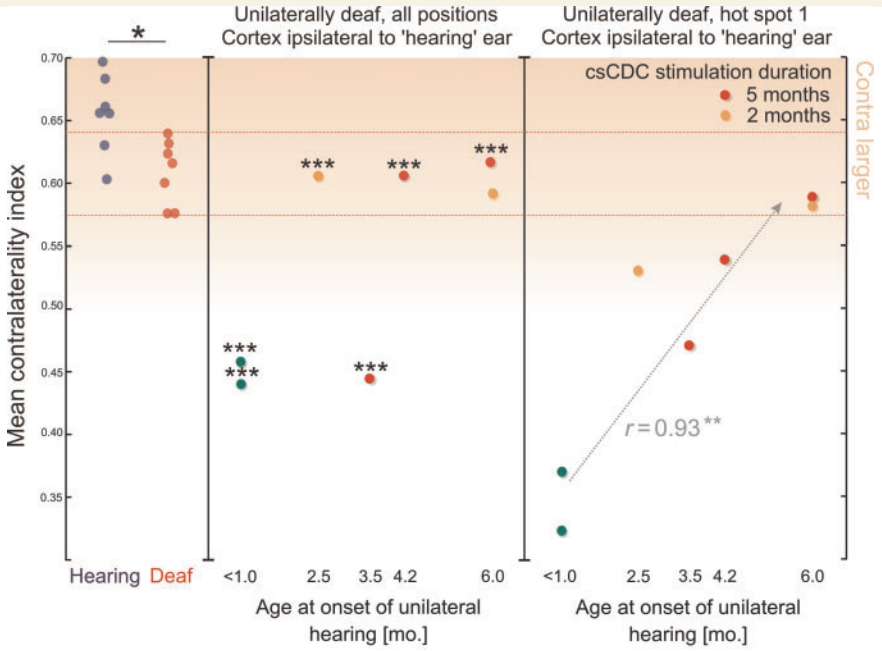

Figure 6 Statistical analysis of P_a amplitudes according to contralaterality index. In both CDCs and hearing control cats, the CI is >0.5 and shows a statistically significant difference between ipsilateral and contralateral responses; however, in the grand means, the hearing control cats have a slightly higher CI, and thus a higher contralateral specificity in the cortex (*left* panel, see text). The dotted lines mark the range observed in naïve CDCs. In the unilateral animals, when CI was computed from all recording positions (*middle* panel), reversals of CI to the ipsilateral preference were found only in unilateral CDCs (green) and the early implanted chronic electrostimulation CDC (csCDC) stimulated for 5 months (*middle* panel). If CI was computed only from the hot spot (*right* panel), a significant correlation of the CI with onset of unilateral hearing was found, again with reversals of contralaterality in unilateral CDCs and the early implanted long-term stimulated chronic electrostimulation CDC only. However, the other early implanted chronic electrostimulation CDC and the chronic electrostimulation CDC implanted at intermediate age also had CIs below the range found in naïve CDCs. *~$p < 0.05$; ***~$p < 0.001$.

The demonstrated reorganization is adaptive for unilateral hearing, as it attributes larger neuronal resources to the hearing ear at the expense of the deaf ear, but it is disadvantageous for the later use of the deaf ear. However, despite reorganization in favour of the hearing ear, the representation of the deaf ear was in no case completely eliminated at the cortex ipsilateral to the hearing ear.

Methodological considerations

Unilateral deafness is common in species with spontaneous deafness, particularly in white cats, with a prevalence of 12.1% in strains bred with the aim of obtaining hearing animals (Strain, 2007). The cochlear deficits include a displacement of the marginal cells and consequent degeneration of the organ of Corti with the scala media collapsing, resulting in congenital deafness (Mair and Elverland, 1977). In our population of deaf white cats (bred specifically for congenital deafness), the unilateral deafness was, however, extremely rare (~1%, Geigy *et al*., 2007), such that in 15 years of breeding, only two animals met the condition of unilateral deafness used here.

The present data on unilateral hearing are based on both unilateral cochlear-implanted and unilaterally congenitally deaf animals. The unilateral CDCs allowed surgical difficulties with cochlear implants in young animals to be overcome, and, for the first time, they allowed insights into the plasticity of aural preference before or during cortical synaptogenesis. Obviously, single-channel cochlear implants do not provide the same amount of information as normal unilateral hearing. Nonetheless, all comparisons were based on measures depending solely on the balance of binaural inputs (paired differences in latency and paired relations of field potential amplitudes). Direct pairwise statistical comparison was performed and statistically tested in each single animal. Thus, interindividual differences could be minimized. In the developmental time course of paired latency differences and contralaterality indices, the unilateral CDCs and chronic electrostimulation CDCs linearly depended on age at onset of unilateral hearing, showing consistency of results throughout the unilateral group. Finally, mild to moderate hearing loss also leads to plastic reorganization in the auditory system (Nodal *et al*., 2010; Popescu and Polley, 2010).

The present study did not investigate the histology of the animals' brains and, consequently, cannot directly disentangle effects of synaptic conduction times, myelination and axon diameter, all of which may contribute to differences in response latency. With regard to the aforementioned aspects, cortical neurons appear morphologically developed between 5–6 months post-natally in the feline visual cortex (Haug *et al*., 1976). Based on the age of the investigated animals, based on the fact that myelination in the auditory periphery does not directly explain cortical response latency development in cats (Eggermont, 1996) and based on the

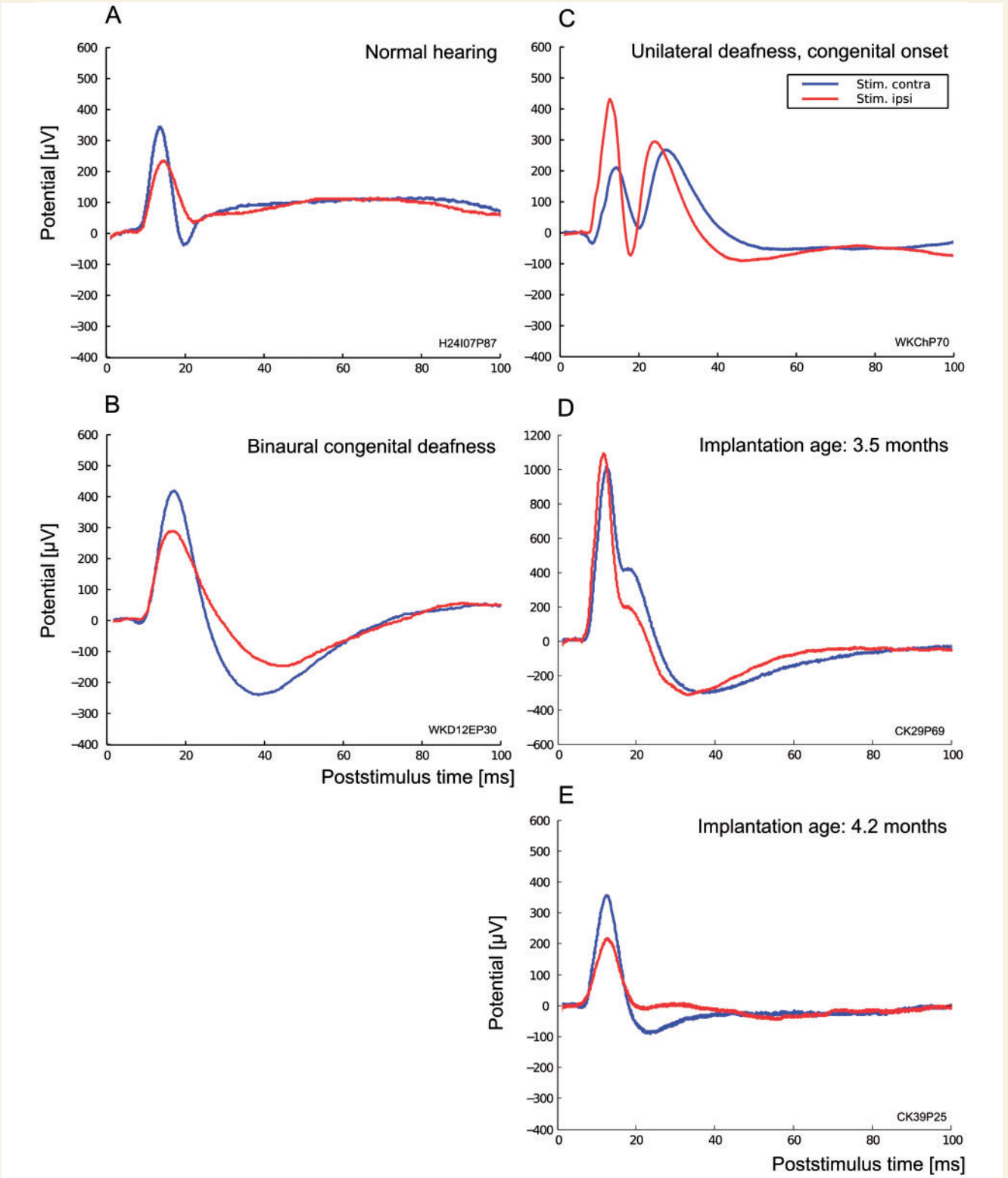

Figure 7 Examples of local field potentials from the hot spots during contralateral (blue) and ipsilateral (red) stimulation, recorded in a hearing control animal (**A**), a CDC (**B**), unilateral CDC (**C**), early implanted chronic electrostimulation CDC (**D**) and intermediate-implanted chronic electrostimulation CDC (**E**), the latter two being stimulated for 5 months. Hearing experience in **C**–**E** was through the ipsilateral ear. Stimulation in final experiments was contralateral (blue) and ipsilateral (red). Stimulation artefacts were blanked. Responses with contralateral stimulation are smaller in **C** and **D** and larger in **A**, **B** and **E**. Onset latencies are larger with contralateral stimulation in **C** and **D** and smaller in **A**, **B** and **E**. Morphology of local field potentials is, despite these differences, well-comparable between ipsilateral and contralateral stimulation in all unilateral animals, whereas hearing control cats show some difference in morphology (details on hearing control cats and CDCs in Kral *et al*., 2009).

high speed of changes observed here (saturating in <2 months of experience), we assume that the most crucial factor contributing to the present observations is changes in synaptic conduction. However, effects of deprivation on myelination are likely (Emmorey *et al*., 2003), and thus an influence of myelination on the present results cannot be ruled out.

Analysis of results

In the present experiments with unilateral deafness, onset latency demonstrated pronounced and rapid reorganization at the primary auditory cortex. The reason for this is likely to be the large number of synapses involved. Although cortical plasticity is in principle more flexible than subcortical plasticity in moderate asymmetric hearing loss (Popescu and Polley, 2010), it is likely that subcortical effects are a factor in complete deafness, as deafness-related effects have been described in the cochlear nucleus (Ryugo *et al*., 2005; Baker *et al*., 2010; O'Neil *et al*., 2010) as well as in the inferior colliculus (Snyder *et al*., 1991; Shepherd *et al*., 1999). However, it can be safely ruled out that the first synapses in the cochlear nucleus are the sole contributory factor in the present results, as a decrease in onset latency within the millisecond range cannot be achieved by a single (or a few) synapse(s).

We assume two steps in the adaptation to unilateral deafness, as follows. The first and most rapid change after unilateral deafness is the decrease in latency for the responses to the hearing ear that is not being accompanied by a corresponding decrease for the deaf ear. The decrease in onset latency will eventually reach a minimum (floor) level. When that point is approached, stimulation applied to the trained ear results in more synchronized cortical activity that further boosts synaptic plasticity. This is most apparent in the portion of the cortex receiving strongest excitation, namely, the hot spot. The rise of local field potential amplitudes in response to stimulation of the hearing ear (considered the other step) is a slower process likely related to the aforementioned increase in response synchrony. At the hot spot, the responses rose most rapidly for the trained ear when compared with other portions of the cortex. Thus, a change in contralaterality is caused first in the hot spot, with other cortical regions following. It is most likely that some of the synapses not activated by the deaf ear are ultimately replaced by synaptic contacts from the active hearing ear. The aforementioned two steps, however, represent two aspects of the same synaptic plasticity.

An aural reorganization process of this kind involves small changes in latency (in the range of milliseconds) as a first adaptation to unilateral deafness. In general, it is well known that timing in the millisecond range is a critical property for further processing in the auditory cortex (Yang *et al*., 2008). The timing of activity in the auditory cortex is reliable (Wehr and Zador, 2003) and involves complex spatiotemporal patterns (Reimer *et al*., 2011). Thus, changes in the timing of cortical responses between the ipsilateral and contralateral ear at the ipsilateral cortex imply effects in cortical processing and perception, especially under binaural stimulation.

The present effects on latency have considerable implications, namely, it is crucial which neuronal elements within a neuronal network respond first. Neurons active first will determine (or co-determine) the successive processing within the network and, hence, the interpretation of the succeeding inputs. If one ear is consistently at an advantage with respect to these temporal relations, it may perceptually complicate the accessibility to cues presented to the other ear. In consequence, binaural synchronous inputs are likely to result in predominant processing of the trained ear at the ipsilateral cortex, putting the untrained ear at a disadvantage. The effect is further emphasized by a shift in amplitude relations.

The present data compare well with those from studies with unilateral cochlear ablation in neonatal animals (generally studied as adults), demonstrating a morphological reorganization of projections from the used (hearing) ear to the brainstem (Nordeen *et al*., 1983; Moore and Kitzes, 1985; Kitzes *et al*., 1995), but with additional degeneration induced by the ablation (Moore and Kitzes, 1985). A reduced number of central projections from the cochlear nucleus of the side ipsilateral to the ablated cochlea have also been shown (Nordeen *et al*., 1983). However, more recent data indicate that the strong reorganization of aural input to the cochlear nucleus takes place during the few days preceding hearing onset (Russell and Moore, 1995) and is, therefore, not likely to be dependent on auditory input, but rather the consequence of the anatomical withdrawal of spontaneous activity and trophic factors from the ablated ear. More central projections (from the cochlear nucleus to the midbrain) are also altered after cochlear ablation (Moore *et al*., 1995). Recordings with stimulation of the intact ear have demonstrated stronger responses for stimulation of the hearing ear when compared with normal control cats (Nordeen *et al*., 1983; Kitzes and Semple, 1985; Reale *et al*., 1987). Additionally, the data demonstrated that the reorganized response areas in the midbrain had otherwise normal characteristics (Kitzes and Semple, 1985). A shortening of latencies of the inputs from the hearing ear at the ipsilateral cortex (Kitzes and Semple, 1985) has occurred to a similar extent (i.e. few milliseconds) as in the present study. Unfortunately, cochlear ablation does not allow stimulation of the ablated ear; therefore, direct functional comparisons between the ears were impossible in previous studies. Ablations were performed at around the onset of hearing; developmental periods have not been investigated. Recently, mild to moderate unilateral hearing loss during development has been correspondingly observed to reorganize cortical aural representation (Popescu and Polley, 2010; for behaviour see King *et al*., 2001). Finally, an early critical period for cellular loss in the cochlear nucleus after early ablation of the cochlea has been described (Tierney *et al*., 1997). However, this process has not been observed in CDCs, despite dystrophic and functional changes in the cochlear nucleus (O'Neil *et al*., 2010).

In the visual system, monocular deprivation leads to suppression of the representation of the deprived eye in the visual cortex, resulting in reduced acuity of the deprived eye (Daw, 2009). Although the present study supports an aural preference for the trained ear after periods of single-sided deafness from early age (shift in latency and amplitudes of field potentials), even in unilateral CDCs, responses were also found for the untrained ear, demonstrating the presence of activity at the ispilateral cortex after stimulation of the untrained ear. This may be the consequence of binaural convergence in the auditory system and at

least a partial preservation of functional connections from each ear. Monocular deprivation, on the other hand, leads in the most extreme case to central blindness. The visual cortex differs from the auditory cortex in the high extent of reciprocal inhibition between the representation of both eyes that affects the outcome of monocular deprivation (Maffei and Turrigino, 2008; Morishita and Hensch, 2008). This state favours suppression of the non-used input where sight is asymmetric. Although in the auditory cortex excitatory–inhibitory interactions are common (at the ipsilateral cortex, inhibition would be exerted by the trained ear), excitatory–excitatory interactions are abundant as well (Middlebrooks *et al*., 1980; Zhang *et al*., 2004; Mrsic-Flogel *et al*., 2005). Consequently, the strong inhibition observed in the visual cortex does not operate exclusively in the auditory cortex, but is complemented by many other types of interactions, including excitatory–excitatory ones. Periods of complete deafness before the onset of unilateral hearing, such as in chronic electrostimulation CDCs, are likely to downregulate inhibitory transmission (Kral *et al*., 2005; Kotak *et al*., 2008), further weakening such reciprocal inhibition. This and some preserved subcortical activity may explain why the auditory system preserves some input from the deaf ear in unilateral hearing.

In bilaterally implanted patients with early first implantations and long delays until the second implantation, the second ear retained the ability to activate the auditory system through the second-implanted ear (Key *et al*., 2010; Gordon *et al*., 2011), further supporting the present conclusions.

Interestingly, the differential effect of experience on the representation of each ear at the ipsilateral cortex strongly indicates the existence of separate monaural pathways. On the other hand, similarity of the morphology of local field potentials evoked by stimulation of the ipsilateral and contralateral ear (Fig. 7; Kral *et al*., 2009) additionally indicates a convergence of the monaural inputs to the same neuronal populations in the cortex. Although single neuron recordings would be required to confirm this conclusion, some transfer of experience-evoked reorganization can be expected after the second implantation, yet access to the information is initially weaker for the untrained ear.

Clinical significance

Early unilateral hearing experience involves switching of aural preference, leaving the used ear preferentially represented in the cortex. This explains the clinical findings of worse outcome at the second-implanted ear in bilaterally implanted children (Peters *et al*., 2007; Firszt *et al*., 2008; Graham *et al*., 2009; Gordon *et al*., 2011). Early implantations, therefore, require a symmetric restoration of hearing as soon as possible. Similarly, in cochlear-implanted humans, first data confirm that restoration of normal activity patterns seems more rapid if implantations are more simultaneous (Gordon *et al*., 2010). Based on the present data, in combination with the published outcomes from patients (Sharma *et al*., 2005; Gordon *et al*., 2010), training concentrated on the use of the previously deaf ear (avoiding competition with the previously dominant ear, e.g. by unilateral speech training) is required to counteract the consequences of unilateral experience in binaural implantations. One theoretical possibility is to perform training with the implant in the more experienced ear switched off; however, binaural training of spatial localization should additionally be considered to prevent elimination of binaural interactions. Finally, a complete suppression of the representation of the deaf ear was never observed in the present study.

Although the consequence of unilateral hearing was less severe with increasing age of onset, late first implantations are not favourable in cases of prelingual deafness, as the cortical adaptations to the cochlear implant (e.g. in the cortical activated area, long latency responses and other aspects of neuronal activity) decrease with increasing implantation age (Kral *et al*., 2002; Sharma *et al*., 2002), with related decreasing speech understanding (Niparko *et al*., 2010). The present results additionally reveal that the changes in the ipsilateral cortex need to be considered when assessing the effects of cochlear implantation in one ear, as those changes represent adequate adaptation for the unilateral hearing condition, but not for the later use of the second ear.

Finally, the present data advocate the identification of asymmetric hearing during neonatal hearing screening to prevent the described aural preference in single-sided deafness.

Conclusion

The outcome of a second cochlear implantation is dependent on the age at onset of unilateral deafness (first implantation). This sensitive period spans the time before and at the developmental functional 'synaptic overshoot' in the auditory cortex. It is related to the reorganization in response latency and amplitude at the cortex ipsilateral to the hearing ear. In cases of early onset of unilateral deafness, focused trainig on the previously deaf ear may be necessary after the asymmetry has been eliminated by implanting on the deaf side. The training may help to overcome the cortical aural preference for the first hearing ear.

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Supplementary material

Supplementary material is available at *Brain* online.

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