Microsecond Interaural Time Difference Discrimination Restored by Cochlear Implants After Neonatal Deafness

Nicole Rosskothen-Kuhl[1,2*], Alexa N Buck[1], Kongyan Li[1], Jan W H Schnupp[1*]

1) Department of Biomedical Sciences, City University of Hong Kong, Hong Kong (SAR China);

2) Neurobiological Research Laboratory, Section for Clinical and Experimental Otology, University Medical Center Freiburg, Freiburg, Germany

*Correspondence: nicole.rosskothen@uniklinik-freiburg.de; wschnupp@cityu.edu.hk

Contact Info

Corresponding authors:

Dr. Nicole Rosskothen-Kuhl

Neurobiological Research Laboratory,

Section for Clinical and Experimental Otology,

University Medical Center Freiburg,

Killianst. 5, 79106 Freiburg i. Br., Germany

Phone: +49 761 27042650

nicole.rosskothen@uniklinik-freiburg.de

Prof. Dr. Jan W H Schnupp

Department of Biomedical Sciences

City University of Hong Kong

31 To Yuen Street
Kowloon, Hong Kong
wschnupp@cityu.edu.hk

Keywords

Deafness; prosthetics; cochlear implant; binaural hearing; interaural time difference; psychoacoustics; hearing experience; inferior colliculus

Abstract

Cochlear implants (CIs) can restore a high degree of functional hearing in deaf patients but enable only poor spatial hearing or hearing in noise. Early deaf CI users are essentially completely insensitive to interaural time differences (ITDs). A dearth of binaural experience during an early critical period is often blamed for this shortcoming. However, here we show that neonatally deafened rats provided with precisely synchronized CI stimulation in adulthood can be trained to localize ITDs with essentially normal behavioral thresholds near 50 μs. Furthermore, neonatally deaf rats show high physiological sensitivity to ITDs immediately after binaural implantation in adulthood. This suggests that the insensitivity to ITDs seen in human children who are born deaf is similarly unlikely to be caused by lack of early auditory experience, and more likely due to prolonged stimulation with CI processors which do not encode sub-millisecond temporal fine structure of sounds.

The World Health Organization reported 466 million people with disabling hearing loss, making it the most common sensory impairment of our age. For people with severe to profound sensorineural hearing loss, cochlear implants (CIs) can be enormously beneficial routinely allowing near normal spoken language acquisition particularly when CI implantation takes place early in life [1]. Nevertheless the performance of CI users remains variable, and falls short of natural hearing.

Good speech understanding with competing sound sources requires the ability to separate speech from background. This is aided by “spatial release from masking”, which relies on the brain’s ability to process binaural spatial cues, including interaural level and time differences (ILDs & ITDs) [2]. Bilateral cochlear implantation is becoming commonplace to provide benefits of binaural hearing to the deaf [3-5], but binaural CI recipients perform poorly in sound localization and auditory scene analysis tasks, particularly when multiple sound sources are present [6,7]. The parameters that would allow CI patients to derive maximum benefits from binaural spatial cues are only partially understood. A number of technical problems (see [8], chapter 6) limit the fidelity with which CIs can encode ITDs in particular. Contemporary CI speech processors were originally designed for monaural, not binaural, hearing, and this likely contributes to the observed deficits in bilateral CI users [3]. Standard CI processors provide pulsatile stimulation which is not locked to the temporal fine structure of incoming sounds, and the timing of electrical pulses is not synchronized between both ears, making these devices incapable of encoding the temporal fine structure and ITDs with the required resolution of a few tens of μs. While normal human listeners may be able to detect ITDs as small as 10 μs [9], ITD sensitivity of CI patients is generally very poor, even when tested with synchronized experimental processors delivering synchronized pulses with sub-millisecond precision [3,5-7,10,11].

Whether CI patients can detect ITDs at all depends largely on their history. Pre-lingually deaf CI users invariably appear to exhibit no ITD sensitivity at all, but many post-lingually

deaf CI users show at least some degree of ITD sensitivity [4,5,11-13]. This led to the suggestion that early auditory deprivation during a sensitive period may prevent the development of ITD sensitivity irrecoverably [1,13,14]. If this hypothesis is correct, then developing more sophisticated binaural CI processors might not benefit patients with hearing loss early in life. At the time of surgery these patients would already have missed out on the formative sensory input needed to develop the brain circuitry required for binaural processing with microsecond precision. This possibility is supported by immunohistochemical studies showing degradation of the tonotopic organization [15,16] and stimulation-induced molecular, morphological, and electrophysiolological plasticity altered in neonatally deafened rats compared to CI-stimulated rats with normal auditory development [15-19]. Furthermore, early acoustic experience does alter ITD tuning curves in key brainstem nuclei of gerbils [20], probably by shaping the precise timing of inhibitory inputs into superior olivary nuclei [20,21].

However, it is not impossible that the unstimulated auditory pathway could retain an innate ability to encode ITD during early deafness, which is only lost as a result of maladaptive plasticity after a period of binaural CI stimulation which conveys no useful ITD information. These possibilities cannot be distinguished based on clinical data, as there are no binaural CI processors in clinical use capable of resolving sub-millisecond ITDs. Thus, animal experimentation is needed to distinguish these possibilities. Previous animal studies investigating binaural sensitivity after early deafness have been limited to acute electrophysiological experiments on cats and rabbits. These studies have reported reduced ITD sensitivity in the inferior colliculus (IC) [22-24] and auditory cortex (AC) [26,27]compared to hearing experienced animals. There have been no previous attempts to train neonatally deaf animals to discriminate sub-millisecond ITDs across delivered with CIs fitted in adulthood. Here, we show that cohorts of neonatally deafened rats which

received synchronized bilateral CI stimulation in young adulthood can exhibit essentially normal ITD sensitivity, both behaviorally and physiologically.

Results

Fourteen female Wistar rats were divided into three groups: 1) neonatally deafened (ND) rats (n=5) who received chronic bilateral CIs in young adulthood and were trained on ITD discrimination with electric stimulation; 2) normal hearing (NH) rats (n=5) trained in young adulthood on ITD discrimination with acoustic stimuli; and 3) ND rats (n=4) who received bilateral CIs in young adulthood (postnatal weeks 10-14), followed immediately by acute, terminal IC recording under anesthesia. Care and use of all rats reported here were approved by Department of Health of Hong Kong (#16-52 DH/HA&P/8/2/5) or Regierungspräsidium Freiburg (#35-9185.81/G-17/124).

Early deaf CI rats discriminate ITD as accurately as their normally hearing litter mates.

We trained five ND and five NH rats in a simple two-alternative forced choice (2AFC) ITD lateralization task. Animals initiated trials by licking a center “start spout”, and responded to 200 ms long 50 Hz binaural pulse trains by licking either a left or a right “response spout” to receive drinking water as positive reinforcement (Figs. S2a, S3b). Which response spout would give water was indicated by the ITD of the stimulus. We used pulses of identical amplitude in each ear, so that systematic ITD differences were the only reliable cue available (Fig. S2c-d). ND rats were stimulated with biphasic electrical pulse trains delivered through chronic CIs, NH rats received acoustic pulse trains through near-field sound tubes positioned next to each ear when the animal was at the start spout (Fig. S3a). During testing, stimulus ITDs varied randomly. The behavioral performance of each rat is shown in Figure 1, using light blue for NH (top) and dark blue for ND (bottom) animals.

Figure 1 clearly demonstrates that all rats, whether NH or ND with CIs, were capable of lateralizing ITDs. As might be expected, the behavioral sensitivity varied from animal to animal. To quantify the behavioral ITD sensitivity of each rat we fitted psychometric curves (see Methods, red lines in Fig. 1) to the raw data and calculated the slope of that curve at ITD=0. Figure 1k summarizes these slopes for NH (light blue) and ND CI (dark blue) animals. The slopes for both groups fell within the same range. Remarkably, the observed mean sensitivity for the ND animals (0.601 %/μs) was slightly better than that of the NH (0.489 %/μs), although the differences in means between experimental groups (0.112 %/μs) were so much smaller than the animal-to-animal variance (~0.56 $\%^2/\mu s^2$). Prohibitively large cohorts of animals would be required to have any reasonable prospect of finding a significant difference. Similarly, both cohorts showed similar 75% correct lateralization thresholds (median NH: 45.4 μs; ND: 57.8 μs; mean NH: 80.9 μs; ND: 60.3 μs). Remarkably, the ITD thresholds of our CI rats are thus orders of magnitude better than those reported for early deaf human CI patients, who typically have ITD thresholds too large to measure, in excess of 3000 μs [5,28]. Indeed, their thresholds are not dissimilar from the approx. 10-60 μs range of 75% correct ITD discrimination thresholds reported for normal human subjects tested with noise bursts [29], and pure tones [9], or the ≈ 40 μs thresholds reported for normally hearing ferrets tested with noise bursts [30].

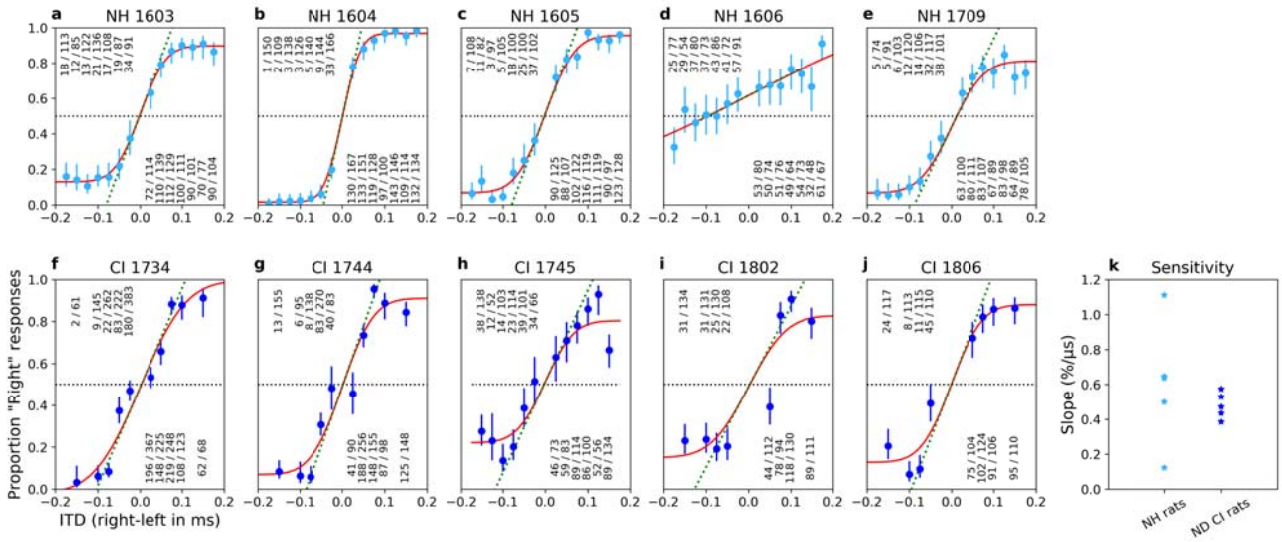

Figure 1: Early deaf CI rats discriminate ITD as accurately as their normally hearing litter mates. **a-j** ITD psychometric curves of normal hearing (**a-e**) and neonatally deafened CI rats (**f-j**). Panel titles show corresponding animal IDs. Y-axis: proportion of responses to the right-hand side. X-axis: Stimulus ITD in ms, with negative values indicating left ear leading. Blue dots: observed proportions of "right" responses for the stimulus ITD given by the x-coordinate. Number fractions shown above or below each dot indicate the absolute number of trials and "right" responses for corresponding ITDs. Blue error bars show Wilson score 95% confidence intervals for the underlying proportion "right" judgments. Red lines show sigmoid psychometric curves fitted to the blue data using maximum likelihood. Green dashed lines show slopes of psychometric curves at x=0. Slopes serve to quantify the behavioral sensitivity of the animal to ITD. Panel **k** summarizes the ITD sensitivities (psychometric slopes) across the individual animal data shown in **a-j** in units of % change in animal's' "right" judgments per µs change in ITD.

IC neurons of ND rats exhibit varying degrees and types of ITD sensitivity immediately after adult cochlear implantation.

To determine if the physiological ITD sensitivity of hearing inexperienced rat brains reflects the behavior we found we recorded in the IC of ND rats responses of n=1230 multiunits to isolated, bilateral CI pulse stimuli with ITDs varying randomly over a ±160 μs range (ca 123% of the rat's physiological range [31]). The stimuli were again biphasic current pulses of identical amplitude in each ear, so that systematic differences in responses can only be attributed to ITD sensitivity (see Fig. S2). Responses of IC neurons were detected for currents as low as 100 μA. Figure 2 shows a selection of responses as raster plots (Fig. 2a) and corresponding ITD tuning curves (Fig. 2b). As shown in previous studies investigating the IC of early deaf animals [22,24-26] we identified multiunits that exhibited ITD sensitivity. However, for the first time, we observed that the large majority of multiunits (1050/1230 ≈ 85%) showed substantial degrees of ITD tuning.

The manner in which varying ITD changed neural discharge patterns was highly variable from one recording site to the next. While many multiunits showed typical short-latency onset responses to the stimulus with varying response amplitudes (Fig. 2a, #2, #3, #6, #9), some showed sustained, but still clearly tuned, responses extending for up to 80 ms or longer post-stimulus (Fig. 2a, #5, #7, #8). The shapes of ITD tuning curves we observed in rat IC (Fig. 2b) resembled the "peak", "biphasic" or "sigmoid", and "multi-peak" shapes previously described in the IC of cats [32].

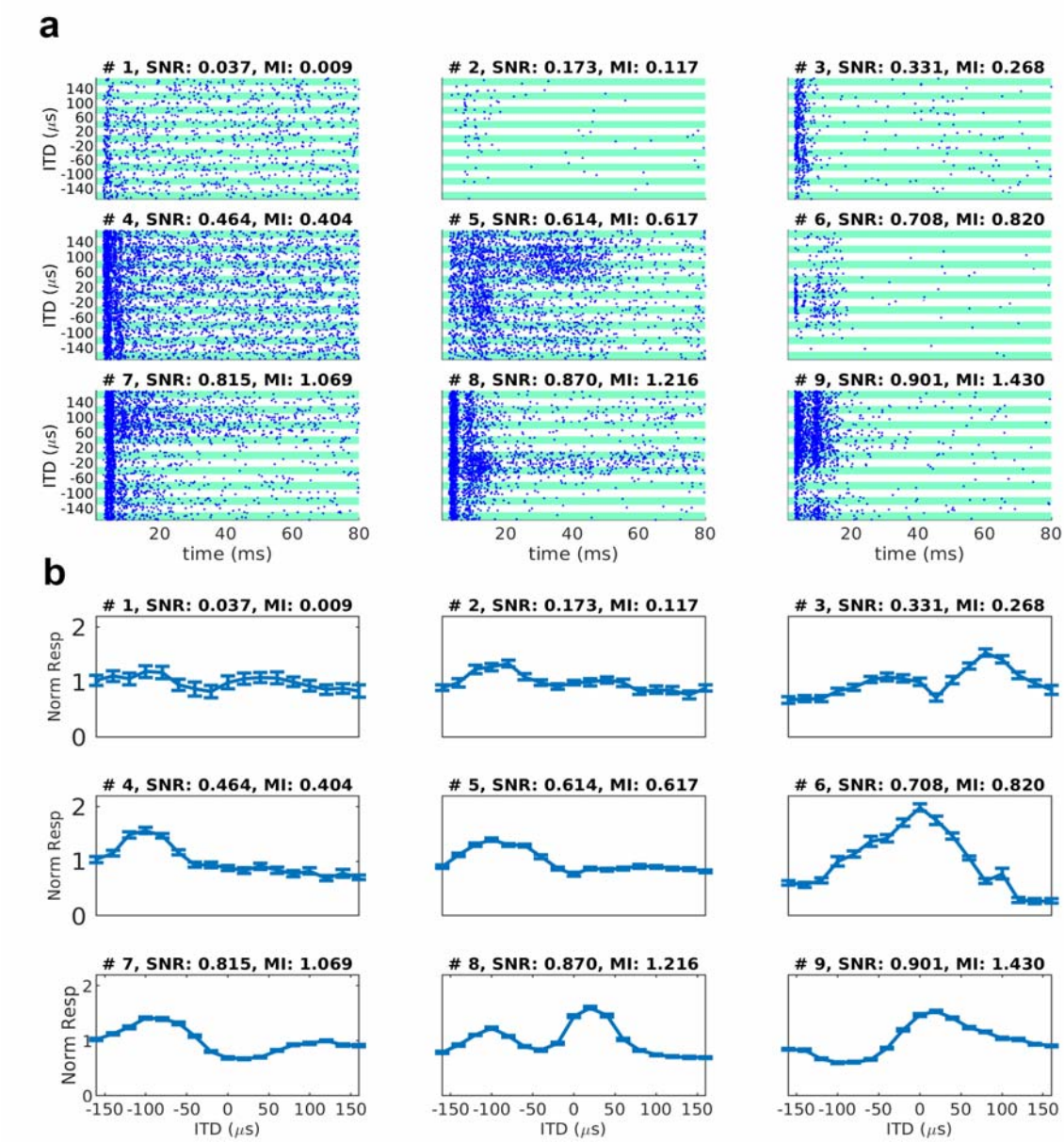

Figure 2: IC neurons of ND rats exhibit varying degrees and types of ITD sensitivity immediately after adult cochlear implantation. Dot raster plots (**a**) and corresponding ITD tuning curves (**b**) for multiunits selected to illustrate some of the variety of ITD tuning depths and types observed. **a** Each blue dot shows one spike. Alternating white and green bands show responses to n=30 repeats at each ITD shown. **b** Corresponding multiunit tuning curves, showing the response amplitudes above baseline, normalized relative to the maximum response, during a period of 3-80 ms post stimulus onset, as a function of stimulus ITD. Error bars show SEM. Above each sub-panel we show signal-to-noise (SNR)

and mutual information (MI) values to quantify ITD tuning. Sub-panels are arranged by increasing SNR and MI. ITD>0: ipsilateral ear leading; ITD<0: contralateral ear leading.

ITD sensitivity is pervasive in the IC of neonatally deaf rats.

To quantify how strongly the neural responses recorded at any one site depended on stimulus ITD we used two measures previously described in the literature. Signal-to-noise ratio (SNR), was calculated as described in [22]. It quantifies the proportion of response variance that can be accounted for by stimulus ITD (see Methods). We also computed the mutual information (MI) between response amplitude and stimulus ITD in bits per response, using a direct method with shuffling for bias correction [33] (see Methods). Each sub-panel of Figure 2 indicates SNR and MI values obtained for the corresponding multiunit, while Figure 3 shows the distributions of SNR (Fig. 3a) and MI (Fig. 3b) values, respectively. Figure 3a also shows the SNR values reported by [22] for the IC of congenitally deaf cats and readily demonstrates that multiunits with substantial ITD tuning (SNRs or MI values ≥ 0.5) are not rare exceptions. The proportion of IC units with ITD SNR > 0.5 is higher in our neonatally deafened, adult CI-implanted rats than in deaf cats. Furthermore, the majority (1050/1230 ≈ 85%) of mulitunits showed statistically significant ITD tuning ($p \leq 0.01$), as determined by MI values significantly greater than zero (permutation test, $\alpha=0.01$).

The results in Figures 2 and 3 clearly illustrate that the inexperienced, adult midbrain of ND rats exhibits substantial sensitivity to changes in ITD of CI pulse stimuli by just a few tens of μs, and our behavioral experiments showed that ND rats can readily learn to use this neural sensitivity to perform behavioral ITD discrimination with an accuracy similar to that seen in their NH litter mates.

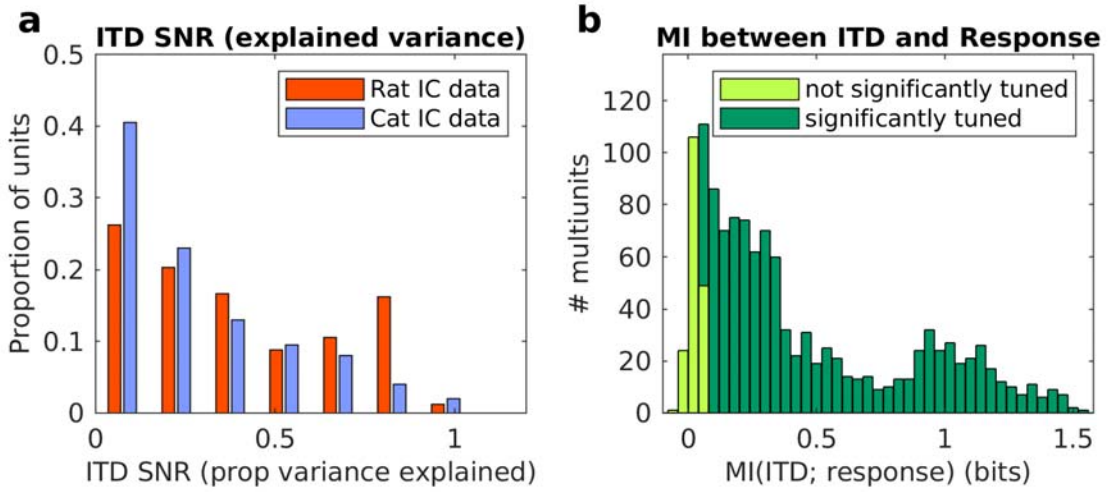

Figure 3: Signal-to-noise (SNR) and mutual information (MI) values show widespread, substantial ITD tuning, in IC of ND rats. **a** Distribution of ITD SNR values recorded in ICs for multiunits of ND, CI-stimulated rats (red columns) and single units in congenitally deaf CI cats (blue columns) by [22]. **b** Distribution of MI values in bits/response for MI between response amplitude and stimulus ITD. Light green bars: MI values which were not significantly greater than zero (permutation test, α=0.01).

Discussion

This study is the first demonstration that, at least in rats, a lack of auditory experience in early development does not inevitably lead to impaired binaural time processing in adulthood. These results may well generalize to other mammalian species, with potentially major implications: Early deaf human CI patients might also be able to achieve near normal ITD sensitivity if supplied with better binaural CI stimulation.

Prior to this discussion we should address three aspects of this study which colleagues may find surprising:

Firstly, some studies deemed rats to be generally poor at processing ITDs [34,35]. However, the only previous rat behavioral study only tested interaural phase sensitivity of

relatively low frequency tones. We focused on broad-band acoustic or electrical pulse stimuli which provide plenty of "onset" and "envelope" ITDs, and which are processed well even at high carrier frequencies [36,37]. That may also explain why our CI rats showed good ITD sensitivity even though our CIs targeted the cochleas' mid-frequency region, and not the apical region associated with low frequency hearing. Recent studies in CI patients with late deafness have shown that ITDs delivered to mid and high-frequency cochlear regions can be detected behaviorally [5,38].

Secondly, electrophysiological studies on congenitally deaf CI cats reported a substantially reduced ITD sensitivity relative to NH animals [22,26,27]. These studies recorded neural tuning higher up in the auditory pathway (AC and IC), so one cannot be certain whether the reduced sensitivity reflects a fundamental degradation of ITD processing in the olivary nuclei, or merely poor maturation of connections to higher order areas, which may be reversed with experience and training. In the IC of our ND rats we found significant ITD sensitivity in 85% of recordings sites, compared to only 48% reported for early deaf cats [22] or 62% for early deaf rabbits [25]. The proportion of ITD sensitive sites in ND rats is thus more similar to proportions in adult deafened cats (84%-86%; [22,32],~75%; [39] [25,39] or gerbils (~74%; [40]). Figure 3a suggests that the ITD sensitivity seen in our ND rats compares favorably with that previously reported for congenitally deaf cats [22] but these relatively modest differences are probably in large part due to methodological differences. Hancock et al. [22] recorded single-unit data, while we report analog multiunit data, which may give better SNRs by pooling responses over multiple, similarly tuned neighboring units.

Thirdly, we don't know how much ITD tuning in the IC or AC is necessary to make behavioral ITD discrimination thresholds of ≈ 50 μs possible. Even if the amount of ITD sensitivity for the IC [25,39] and AC [26,27] of early deaf animals is reportedly less than that in normal animals, it may still be sufficient for accurate localization behavior, and it

may improve with training. Thus, our finding of apparently normal behavioral ITD sensitivity in ND rats may appear surprising, but it does not contradict previous studies [22,24-27].

The biggest difference between our results and that from published works remains the vastly better behavioral ITD discrimination in ND CI rats compared to that of early deaf CI patients [5,13]. Previous authors have proposed that the very poor performance seen in these patients may be due to “factors such as auditory deprivation, in particular, lack of early exposure to consistent timing differences between the ears” [5]. However, a lack of early exposure did not prevent our ND rats from achieving very good ITD discrimination performance. Admittedly, there may be species differences at play here. Our ND rats were implanted as young adults, and were severely deprived of auditory input throughout their childhood, but humans mature much more slowly, so even patients implanted at a very young age will have suffered auditory deprivation for a substantially longer absolute time period than our rats. Nevertheless, our results strongly suggest that the ITD insensitivity of early deaf patients may not be caused by the “lack of exposure to consistent timing differences”, but rather by the prolonged exposure to entirely inconsistent ITDs delivered by current implant processors, which do not synchronize pulses between ears. In addition, most binaural patients receive their CIs sequentially, and their initial, potentially formative, auditory experience is monaural.

Developmental studies in ferrets have shown that the formation of afferent synapses to medial superior olive, one of the main brainstem nuclei for ITD processing, is essentially complete before the onset of hearing [41]. In mice, the highly specialized calyx of held synapses which are thought to play key roles in relaying precisely timed information in the binaural circuitry have been shown to mature before the onset of hearing [42]. In gerbils, key parts of the binaural ITD processing circuitry in the auditory brainstem will fail to mature when driven with strong, uninformative omnidirectional white noise stimulation during a critical period [20,30,43-45], but no studies have demonstrated that critical

periods in the ITD pathways will irrevocably close if sensory input is simply absent. These data are therefore not incompatible with our hypothesis that inappropriate input, rather than its absence, may cause the loss of ITD sensitivity in early deaf CI users.

It is well known that the normal auditory system not only combines ITD information with ILD and monaural spectral cues to localize sounds in space, it also adapts strongly to changes in these cues, and can re-weight them depending on their reliability [27,46,47]. Current CI processors produce pulsatile stimulation based on fixed rate interleaved sampling, which is neither synced to stimulus fine structure nor synchronized between ears. Consequently, they only ever provide uninformative ITDs to the children using them. The brainstem circuits of children fitted with conventional binaural CIs may simply “learn” to ignore unhelpful inputs which would be adaptive to them given that no useful information comes from the ITDs received. In contrast, precise ITD cues were essentially the only form of useful auditory input that our ND CI rats experienced, and they quickly learned to use them.

Thus, our data suggest that the mammalian auditory system develops ITD sensitivity in the absence of early sensory input, and this is then either refined or lost depending on how informative it turns out to be. The inability of early deaf CI patients to use ITDs may thus be somewhat similar to conditions such as amblyopia or failures of stereoscopic depth vision development, pathologies which are caused more by unbalanced or inappropriate inputs than by lack of sensory experience [48]. For the visual system it has been shown that orientation selective neuronal responses exist at eye-opening and thus are established without visual input [49]. Whether CI patients are able to recover normal ITD sensitivity much later if rehabilitated with useful ITDs for prolonged periods, or whether their ability to process microsecond ITDs atrophies irreversibly, is unknown [48].

While the interpretations of our findings would lead us to argue strongly that binaural CI processing strategies ought to change to make microsecond ITD information available to

CI patients, one must nevertheless acknowledge the difficulty in changing established CI processing strategies. The continuous interleaved sampling (CIS) paradigm [50] from which most processor algorithms are derived, times the stimulus pulses so that only one electrode channel delivers a pulse at any one time. This is thought to minimize “current spread” which might compromise the already quite limited tonotopic place coding of CIs. Additionally, CI processors run at high pulse rates (≧900 Hz), which seems necessary to encode sufficient amplitude modulations (AM) for speech recognition [51]. However, ITD discrimination deteriorates when pulse rates exceeded a few hundred Hz in humans [52,53] and animals [39]. This is likely related to the observation that the ability of superior olivary neurons to encode envelope ITDs declines at envelope rates exceeding several hundred Hz [54]. Our own behavioral experiments described here were conducted with low pulse rates (50 Hz), and it is unknown whether performances would be as good at pulse rates close to 1 kHz.

Thus, designers of novel binaural CI speech processors may face conflicting demands: They must invent devices which fire each of 20 or more electrode channels in turn, at rates that are both fast, so as to encode speech AM in fine detail, but also slow, so as not to overtax the brainstem’s ITD extraction mechanisms, and they must make the timing of at least some of these pulses encode stimulus fine structure and ITDs. While difficult, this may not be impossible, and promising research is underway which either uses a mixture of different pulse rates for different electrode channels [55], or aims to “reset” the brain’s ITD extraction mechanisms by introducing occasional “double pulses” into the stimulus [56]. A detailed discussion is beyond the scope of this paper. Our results underscore the need to pursue this work with urgency, as it may save many thousands of deaf patients from a loss of ITD sensitivity that may be caused by sub-optimal stimulation.

STAR Methods

Deafening

Rats were neonatally deafened by daily intraperitoneal (i.p.) injections of 400 mg/kg kanamycin from postnatal day 9 to 20 inclusively [15,17]. This is known to cause widespread death of inner and outer hair cells [17,57,58] while keeping the number of spiral ganglion cells comparable to that in untreated control rats [58]. We verified that this procedure provoked profound hearing loss (> 90 dB) by first, the loss of Preyer's reflex [59], before the onset of neural auditory brainstem response (ABRs) to pure tone pips [60], and second, the absence of ABRs (Fig. S1b). ABRs were measured as described in [19]: under ketamine (80mg/kg) and xylazine (12 mg/kg) anesthesia each ear was stimulated separately through hollow ear bars with 0.5 ms broad-band clicks with peak amplitudes up to 130 dB SPL delivered at a rate of 23 Hz. ABRs were recorded by averaging scalp potentials measured with subcutaneous needle electrodes between mastoids and the vertex of the rat's head over 400 click presentations. While normal rats typically exhibited click ABR thresholds near 30 dB SPL (Fig. S1a), deafened rats had very high click thresholds of ≥130 dB SPL; Fig. S1b) [20,43].

CI implantation, stimulation and testing

All surgical procedures, including CI implantation and craniotomy, were performed under anesthesia induced with i.p. injection of ketamine (80mg/kg) and xylazine (12 mg/kg). For maintenance of anesthesia during electrophysiological recordings, a pump delivered an i.p. infusion of 0.9% saline solution of ketamine (17.8 mg/kg/h) and xylazine (2.7 mg/kg/h) at a rate of 3.1 ml/h. During surgical and experimental procedures the body temperature was maintained at 38°C using a feedback-controlled heating pad (RWD Life Sciences,

Shenzhen, China). Further detailed descriptions of our cochlear implantation methods can be found in previous studies [15,61-64]. In short, two to four rings of an eight channel electrode carrier (ST08.45, Peira, Beerse, Belgium) were fully inserted through a cochleostomy in medio-dorsal direction into the middle turn of both cochleae.

Electrically evoked ABRs (EABRs) were measured for each ear individually to verify that both CIs were successfully implanted and operated at acceptably low electrical stimulation thresholds, usually around 100 µA (Fig. S1c). EABR recording used isolated biphasic pulses (see below) with a 23 ms inter-pulse interval. EABR mean amplitudes were determined by averaging scalp potentials over 400 pulses for each stimulus amplitude. For electrophysiology experiments, EABRs were also measured immediately before and after IC recordings, and for the chronically implanted rats, EABRs were measured once a week under anesthesia to verify that the CIs functioned properly and stimulation thresholds were stable.

Electric and acoustic stimuli

The electrical stimuli used to examine the animals' EABRs, the physiological, and the behavioral ITD sensitivity were generated using a Tucker Davis Technology (TDT, Alachua, Florida, US) IZ2MH programmable constant current stimulator at a sample rate of 48,828.125 Hz. The most apical ring of the CI electrode served as stimulating electrode, the next ring as ground electrode. All electrical intracochlear stimulation used biphasic current pulses similar to those used in clinical devices (duty cycle: 61.44 µs positive, 40.96 µs at zero, 61.44 µs negative), with peak amplitudes of up to 300 µA, depending on physiological thresholds or informally assessed behavioral comfort levels (rats will scratch their ears frequently, startle or show other signs of discomfort if stimuli are too intense). For behavioral training we stimulated all CI rats 6 dB above these thresholds.

Acoustic stimuli used to measure behavioral ITD sensitivity in NH rats were single sample pulse clicks generated at a sample rate of 48,000 Hz via a Raspberry Pi 3 computer connected to a USB sound card (StarTech.com, Ontario Canada, part # ICUSBAUDIOMH), amplifier (Adafruit stereo 3.7W class D audio amplifier, New York City, US, part # 987) and miniature high fidelity headphone drivers (GQ-30783-000, Knowles, Itasca, Illinois, US) which were mounted on hollow tubes. Stimuli were delivered at sound intensities of ≈ 80 dB SPL.

To produce electric or acoustic stimuli of varying ITDs spanning the rat's physiological range of ± 130 μs [31], stimulus pulses of identical shape and amplitude were presented to each ear, with the pulses in one ear delayed by an integer number of samples. Given the sample rates of the devices used, ITDs could thus be varied in steps of 20.48 μs for the electrical, and 20.83 μs for the acoustic stimuli. The physiological experiments described here used single pulse stimuli presented in isolation, while the behavior experiments used 200 ms long 50 Hz pulse trains.

Animal psychoacoustic testing

We trained our rats on 2AFC sound lateralization tasks using methods similar to those described in [30,44,45]. The behavioral animals were put on a schedule with six days of testing, during which the rats obtained their drinking water as a positive reinforcer, followed by one day off, with *ad-lib* water. The evening before the next behavioral testing period, drinking water bottles were removed. During testing periods, the rats were given two sessions per day. Each session lasted 25-30 min, which typically took 150-200 trials during which ≈ 10 ml of water were consumed.

One of the walls of each behavior cage was fitted with three brass water spouts, mounted ≈ 6-7 cm from the floor and separated by ≈ 7.5 cm (Fig. S2a-b). We used one center "start spout" for initiating trials and one left and one right "response spout" for indicating whether

the stimulus presented during the trial was perceived as lateralized to that side. Contact with the spouts was detected by capacitive touch detectors (Adafruit industries, New York City, US, part # 1362). Initiating a trial at the center spout triggered the release of a single drop of water through a solenoid valve. Correct lateralization triggered three drops of water as positive reinforcement. Incorrect responses triggered no water delivery but caused a 5-15 s timeout during which no new trial could be initiated. Timeouts were also marked by a negative feedback sound for the NH rats, or a flashing LED for the ND CI rats. After each correct trial a new ITD was chosen randomly from a set spanning ±160 μs in 25 μs steps, but after each incorrect trial the last stimulus was repeated in a “correction trial”. Correction trials prevent animals from developing idiosyncratic biases favoring one side [44,65], but since they could be answered correctly without attention to the stimuli by a simple “if you just made a mistake, change side” strategy, they are excluded from the final psychometric performance analysis.

The NH rats received their acoustic stimuli through stainless steel hollow ear tubes placed such that, when the animal was engaging the start spout, the tips of the tubes were located right next to each ear of the animal to allow near-field stimulation (Fig. S3a). The pulses resonated in the tubes, producing pulse-resonant sounds, resembling single-formant artificial vowels with a fundamental frequency corresponding to the click rate. Note that this mode of sound delivery is thus very much like that produced by “open” headphones, such as those commonly used in previous studies on binaural hearing in humans and animals, e.g. [30,66]. We used a 3D printed “rat acoustical manikin” with miniature microphones in the ear canals (Fig. S3c). It produced a frequency dependent channel separation between ears of ≥ 20dB at the lowest, fundamental frequency and around 40 dB overall (data not shown). The ND CI rats received their auditory stimulation via bilateral CIs described above, connected to the TDT IZ2MH stimulator via a custom-made, head mounted connector and commutator, as described in [63].

Multiunit recording from IC

Anesthetized rats were head fixed in a stereotactic frame (RWD Life Sciences), craniotomies were performed bilaterally just anterior to lambda. The animal and stereotactic frame were positioned in a sound attenuating chamber, and a single-shaft, 32-channel silicon electrode array (ATLAS Neuroengineering, E32-50-S1-L6) was inserted stereotactically into the left or right IC through the overlying occipital cortex using a micromanipulator (RWD Life Sciences). Extracellular signals were sampled at a rate of 24.414 Hz with a TDT RZ2 with a NeuroDigitizer headstage and BrainWare software. Our recordings typically exhibited short response latencies (≈ 3-5 ms), which suggests that they may come predominantly from the central region of IC. Responses from non-lemniscal sub-nuclei of IC have been reported to have longer response latencies (≈ 20ms; [67]).

At each electrode site, we first measured neural rate/level functions, varying stimulation currents in each ear to verify that the recording sites contained neurons responsive to cochlear stimulation, and to estimate threshold stimulus amplitudes. Thresholds rarely varied substantially from one recording site to another in any one animal. We then measured ITD tuning curves by presenting single pulse binaural stimuli with equal amplitude in each ear, ≈ 10 dB above the contralateral ear threshold, in pseudo-random order. ITDs varied from 163.84 μs (8 samples) contralateral ear leading to 163.84 μs ipsilateral ear leading in 20.48 μs (one sample) steps. Each ITD value was presented 30 times at each recording site. The inter-stimulus interval was 500 ms. At the end of the recording session the animals were overdosed with pentobarbitone.

Data analysis

To quantify the extracellular multiunit responses we calculated the average activity for each stimulus over a response period (3-80 ms post stimulus onset) as well as baseline

activity (300-500 ms after stimulus onset) at each electrode position. The first 2.5 ms post stimulus onset were dominated by electrical stimulus artifacts and were discarded. For display purposes of the raster plots in Figure 2 we extracted multiunit spikes by simple threshold crossings of the bandpassed (300Hz-6kHz) electrode signal with a threshold set at four standard deviation of the signal amplitude. To quantify responses for tuning curves, instead of counting spikes by threshold crossings we instead computed an analog measure of multiunit activity (AMUA) amplitudes as described in [68]. The mean AMUA amplitude during the response and baseline periods was computed by bandpassing (300Hz-6kHz), rectifying (taking the absolute value) and lowpassing (6 kHz) the electrode signal. This AMUA value thus measures the mean signal amplitude in the frequency range in which spikes have energy. As illustrated in Figure 1 of [68], this gives a less noisy measure of multiunit neural activity than counting spikes by conventional threshold crossing measures because the later are subject to errors due to spike collisions, noise events, or small spikes sometimes reach threshold and sometimes not. The tuning curves shown in the panels of Figure 2b were measured using this AMUA measure. It is readily apparent that changes in the AMUA amplitudes track changes in spike density.

Signal-to-noise ratio (SNR) calculation

SNR values are a measure of the strength of tuning of neural responses to ITD which we adopted from [22] to facilitate comparisons from previous work. The SNR is the proportion of trial-to-trial variance in response amplitude explained by changes in ITD. It is calculated by computing a one-way ANOVA (α=0.01) of responses grouped by ITD value and dividing the total sum of squares by the group sum of squares. The n for each ITD was 30 with a degree of freedom (df) of 29. This yields values between 0 (no effect of ITD) and 1 (response amplitudes completely determined by ITD).

Mutual information (MI) calculation

MI quantifies the statistical dependence between stimulus and response amplitude in bits per response according to equation (1)

$$MI(S;R)=\sum_{s\in S}\sum_{r\in R}\log_2\left(\frac{p(r,s)}{p(r)\cdot p(s)}\right). \qquad (1)$$

Here *p(r)* is the probability that the response of a given trial is of magnitude *r, p(s)* is the probability that the ITD stimulus parameter of a given trial is *s*, and *p(r,s)* is the probability that response *r* and stimulus *s* co-occurred in a given trial. It is common practice to bin the set of possible responses into a suitable number of discrete steps. We performed this binning using the function *binr()* of the “information breakdown toolbox” [69] with equipopulated binning. The probabilities *p(s)*, *p(r)* and *p(r,s)* are not know exactly and must be estimated from the observed frequencies of stimuli and responses in the data set. It is well established that sampling errors in these probability estimates lead to a somewhat inflated (positively biased) estimate of the true MI [70]. As described in [33] a number of methods have been proposed to correct for this bias. Here we bias corrected our MI estimates by a permutation test at α=0.01 as described in [71], where stimulus-response pairings are randomly reshuffled. This should destroy any underlying association between stimulus and response and thereby, in theory, lead to an MI of zero. In practice, the shuffled data yield small positive MI values which serve as bootstrap estimates for the size of the bias. By repeating the random reshuffling 1000 times we calculated a distribution of bias estimates for each multiunit, and subtracted the mean bias from the original, "raw" MI value to obtain the bias corrected values (Fig. 3b). We also used the distribution of bias estimates to assess whether the tuning of a multiunit to ITD was statistically significant. Only multiunits whose raw MI values exceeded 99% of the bias estimates were deemed significantly tuned at α<0.01.

Psychometric curve fitting

In order to derive summary statistics that could serve as measures of ITD sensitivity from the thousands of trials performed by each animal we fitted psychometric models to the observed data. It is common practice in human psychophysics to fit performance data with cumulative Gaussian functions [72,73]. This practice is well motivated in signal detection theory, which assumes that the perceptual decisions made by the experimental subject are informed by sensory signals which are subject to multiple, additive, and hence approximately normally distributed sources of noise. When the sensory signals are very large relative to the inherent noise then the task is easy and the subject will make the appropriate choice with near certainty. For binaural cues closer to threshold, the probability of choosing “right” (p_R) can be modeled by the function

$$p_R = \Phi(ITD \cdot \alpha) \qquad (2)$$

where, Φ is the cumulative normal distribution, *ITD* denotes the interaural time difference (arrival time at left ear minus arrival time at right ear, in ms), and α is a sensitivity scale parameter which captures how big a change in the proportion of “right” choices a given change in ITD can provoke, with units of 1/ms.

Functions of the type in equation (2) tend to fit psychometric data for 2AFC tests with human participants well, where subjects can be easily briefed and lack of clarity about the task, lapses of attention or strong biases in the perceptual choices are small enough to be explored. However, animals have to work out the task for themselves through trial and error, and may spend some proportion of trials on “exploratory guesses” rather than direct perceptual decisions. If we denote the proportion of trials during which the animal makes such guesses (the “lapse rate”) by γ, then the proportion of trials during which the animal’s responses are governed by processes which are well modeled by equation (2) is reduced to (1-γ). Furthermore, animals may exhibit two types of bias: an “ear bias” and a “spout

bias". An "ear-bias" exists if the animal hears the mid-line (50% right point) at ITD values which differ from zero by some small value β. A "spout bias" exists if the animal has an idiosyncratic preference for one of the two response spouts or the other, which may increase its probability of choosing the right spout by δ (where δ can be negative if the animal prefers the left spout). Assuming the effect of lapses, spout and ear bias to be additive, we therefore extended eqn (2) to the following psychometric model:

$$p_R = \Phi(ITD \cdot \alpha + \beta) \cdot (1-\gamma) + \gamma/2 + \delta \qquad (3)$$

We fitted the model in equation (3) to the observed proportions of "right" responses as a function of stimulus ITD using the scipy.optimize.minimize() function of Python 3.4, using gradient descent methods to find maximum likelihood estimates for the parameters α, β, γ and δ given the data. This cumulative Gaussian model fitted the data very well, as is readily apparent in Figure 1a-j. We then used the slope of the psychometric function around zero ITD as our maximum likelihood estimate of the animal's ITD sensitivity, as plotted in Figure 1k. That slope is easily calculated using the equation (4)

$$slope = \varphi(0) \cdot \alpha \cdot (1-\gamma) \qquad (4)$$

which is obtained by differentiating equation (3) and setting ITD=0. $\varphi(0)$ is the Gaussian normal probability density at zero (≈0.3989).

Seventy-five % correct thresholds were computed as the mean absolute ITD at which the psychometric dips below 25% or rises above 75% "right" responses respectively.

Acknowledgements

We thank A. Hyun Jung for assisting behavioral training of CI rats, P. Ruther and the *Cluster of Excellence BrainLinks-BrainTools* (German Research Foundation, grant number EXC1086) for the support by recording electrodes. Work leading to this publication was supported by a grant from the Vice President of Research and Technology (VPRT) of the City University of Hong Kong, the German Academic Exchange Service (DAAD) with funds from the German Federal Ministry of Education and Research (BMBF) and the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement n° 605728 (P.R.I.M.E. – Postdoctoral Researchers International Mobility Experience), and friends' association "Taube Kinder lernen hören e. V.".

Author Contributions

N.R.K. and J.W.H.S. designed the study and wrote the article. N.R.K., A.N.B., K.L., and J.W.H.S. performed the experiments. J.W.H.S., N.R.K., and A.N.B. evaluated the data. All authors approved the final manuscript.

Declaration of Interests

The authors declare no competing interests.

Supplementary Figures

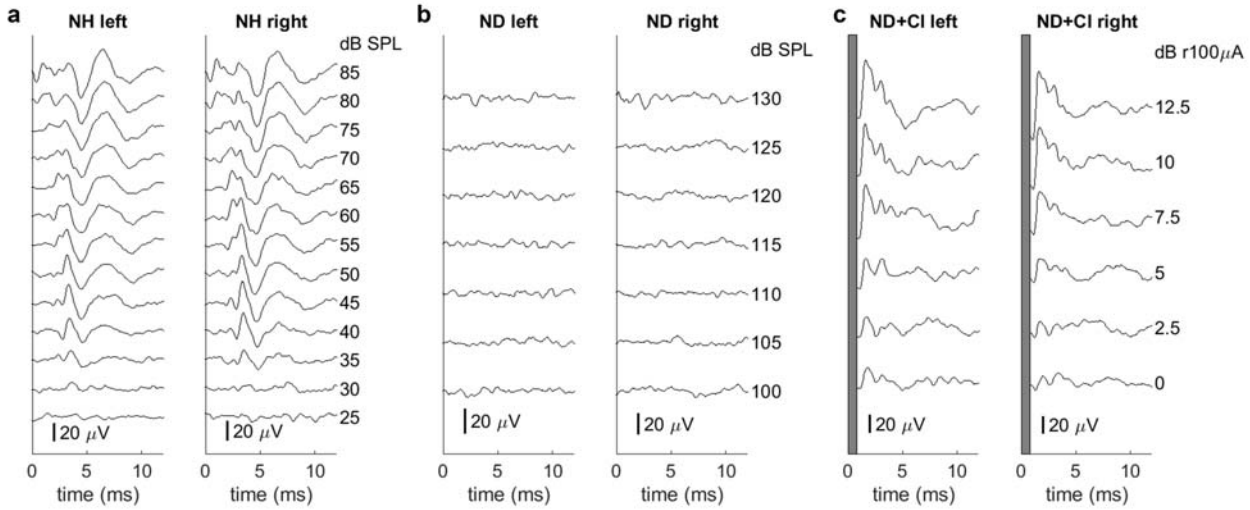

Figure S1: Brainstem recordings to verify normal hearing or loss of hearing function as well as the symmetrical placement of CIs. **a** Auditory brainstem responses of an acoustically stimulated normal hearing (NH) rat. ABRs are symmetrical for both ears and show clear differentiation. **b** ABRs of a neonatally deafened (ND) rat. No hearing thresholds were detectable up to 130 dB SPL. **c** Electrically evoked ABRs under CI stimulation of a deafened rat. Each subpanel includes measurements for the left and the right ear, respectively, under acoustic (**a-b**) or electric stimulation (**c**). In (c) the first millisecond (electrical stimulus artifact) is blanked out.

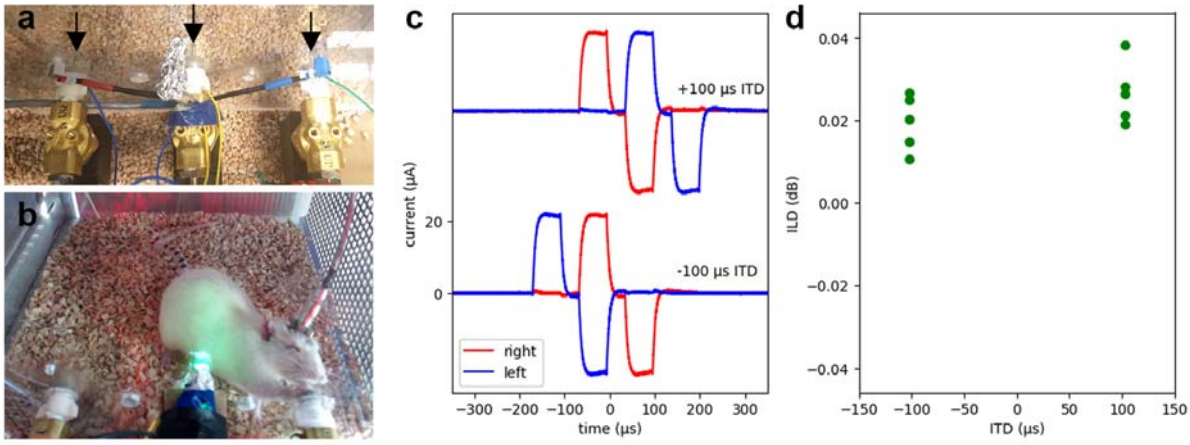

Figure S2: Binaural electrical intracochlear stimulation of CI rats. **a** Close-up of the training setup for CI rats. The central "start" and lateral "response" spouts deliver the water reward and are indicated by arrows. **b** CI rat during a testing session, making a response to the left by making contact with the left reward spout. **c** Calibration measurements were performed by connecting the stimulator cable to 10 kOhm resistors instead of the in-vivo electrodes and recording voltages using a Tektronix MSO 4034B oscilloscope with 350 MHz and 2.5 GS/s. Recordings of stimulus pulses are shown with 100 µs ITD leading in the right ear (top) or the left ear (bottom) respectively. Pulses delivered to the right ear are shown in red, those delivered in the left ear in blue. The stimulator was programmed to produce biphasic rectangular stimulus pulses with a 20 µA amlitude (y-axis) and a 23 µs inter-pulse interval. **d** Measured calibration pulses such as those shown in (**c**) were used to verify that electric ILDs were negligible and did not vary systematically with ITD. ILDs were computed as the difference in root mean square (RMS) power of the signals in (**d**). Data from five presentations of ITDs of + or – 100 µs are shown by the green dots. These residual ILDs produced by device tolerances in our system are not only an order of magnitude smaller than the ILD thresholds for human CI subjects reported in the literature (~0.1 dB [74]), they also do not covary with ITD. We can therefore be certain that sensitivity to ILDs can not account for our behavior data.

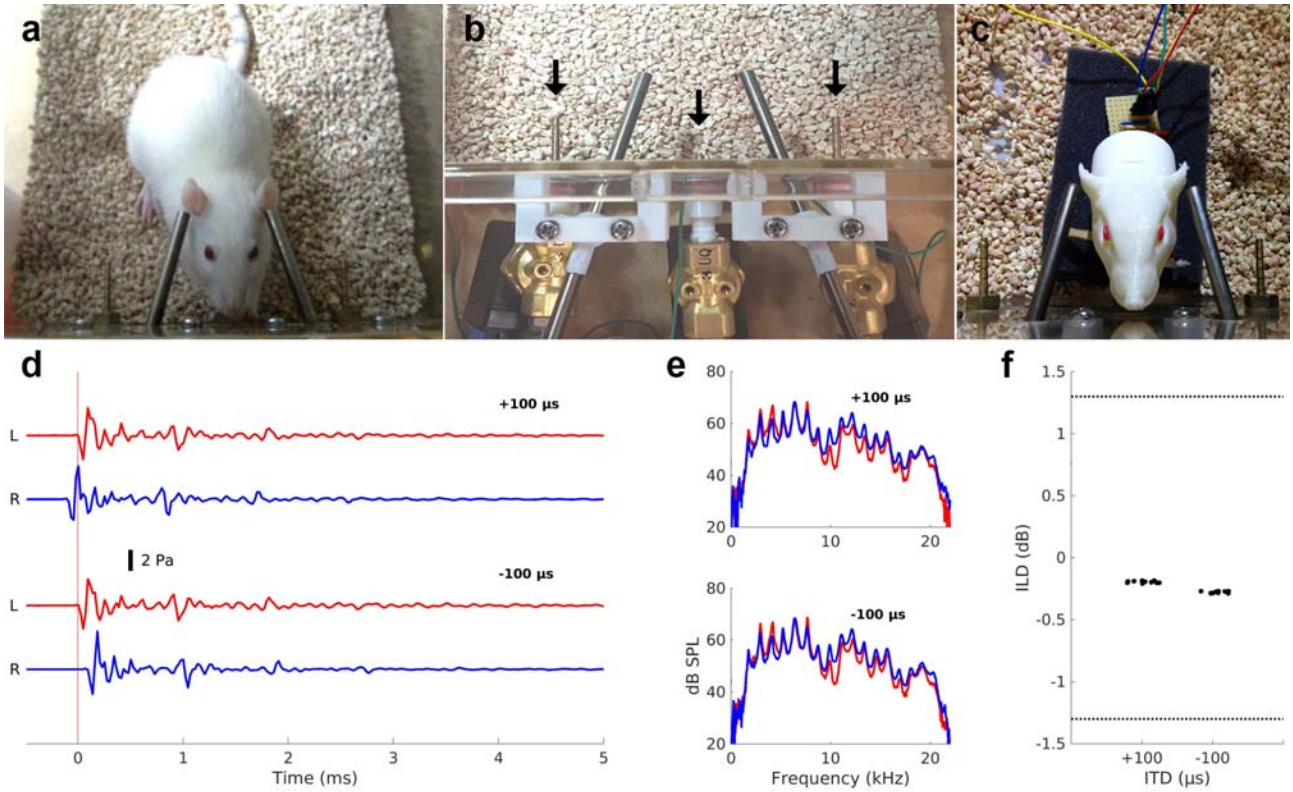

Figure S3: Binaural psychoacoustics near-field setup for NH rats. **a** NH rat during a testing session, initiating a trial by making contact with the central “start” spout. Steel tube phones are positioned close to each ear. **b** Close-up of the assembly. The central “start” and lateral “response” spouts deliver the water reward and are indicated by arrows. Also visible are the custom ball joints for adjusting the tube phone positions. **c** 3D printed “rat acoustical manikin” with miniature microphones in each ear canal, used for validating the setup. **d** Validation data for acoustic click stimuli as recorded from the microphones inside each ear canal of the 3D printed “rat acoustical manikin” (L: left ear, R: right ear) in response to the +/- 100 µs ITD conditions (top and bottom pair of traces, respectively). **e** Frequency spectra of the sound waveforms recorded by the microphones in each ear for the +100 µs (top) and -100 µs (bottom) conditions. **f** Acoustic ILDs (y-axes) measured through the “rat acoustical manikin” microphones for the +/- 100 µs ITD conditions. ILDs were computed as the difference in root mean square (RMS) power of the signals in panel (**d**). Data were recorded from 10 presentations of each ITD stimulus, and each dot represents one trial (a random amount of scatter along the x-axis was added for ease of

visualization). Note that the residual ILDs are much smaller than the reported behavioral thresholds for ferrets (~ 1.3 dB, dotted line, [30]) or rats (~3 dB [35]). We can therefore be certain that sensitivity to ILDs cannot account for our behavior data.

References

1. Kral, A. & Sharma, A. Developmental neuroplasticity after cochlear implantation. *Trends Neurosci.* **35**, 111-122 (2012)
2. Ellinger, R. L., Jakien, K. M. & Gallun, F. J. The role of interaural differences on speech intelligibility in complex multi-talker environments. *J. Acoust. Soc. Am.* **141**, EL170 (2017)
3. Litovsky, R. Bilateral Cochlear Implants. *ASHA Leader* **15**, 14 (2010)
4. Conti-Ramsden, G., St Clair, M. C., Pickles, A. & Durkin, K. Developmental trajectories of verbal and nonverbal skills in individuals with a history of specific language impairment: from childhood to adolescence.. *J. Speech. Lang. Hear. Rees* **55**, 1716-1735 (2012)
5. Ehlers, E., Goupell, M. J., Zheng, Y., Godar, S. P. & Litovsky, R. Y. Binaural sensitivity in children who use bilateral cochlear implants. *J. Acoust. Soc. Am.* **141**, 4264-4277 (2017)
6. van Hoesel, R. J. M. Exploring the Benefits of Bilateral Cochlear Implants. *Audiol. Neurootol.* **9**, 234-246 (2004)
7. van Hoesel, R. J. M. Contrasting benefits from contralateral implants and hearing aids in cochlear implant users. *Hear. Res.* **288**, 100-113 (2012)
8. Schnupp, J., Nelken, I. & King, A. *Auditory neuroscience : making sense of sound.* (MIT Press, Cambridge, Mass. ; London, 2011)
9. Zwislocki, J. & Feldman, R. S. Just Noticeable Dichotic Phase Difference. *J. Acoust. Soc. Am.* **28**, 152-153 (1956)
10. Kerber, S. & Seeber, B. U. Sound Localization in Noise by Normal-Hearing Listeners and Cochlear Implant Users. *Ear Hear.* **33**, 445-457 (2012)
11. Laback, B., Egger, K. & Majdak, P. Perception and coding of interaural time differences with bilateral cochlear implants. *Hear. Res.* **322**, 138-150 (2015)
12. Poon, B. B., Eddington, D. K., Noel, V. & Colburn, H. S. Sensitivity to interaural time difference with bilateral cochlear implants: Development over time and effect of interaural electrode spacing. *J. Acoust. Soc. Am.* **126**, 806-815 (2009)
13. Litovsky, R. Y. & Gordon, K. Bilateral cochlear implants in children: Effects of auditory experience and deprivation on auditory perception. *Hear. Res.* **338**, 76-87 (2016)
14. Yusuf, P. A., Hubka, P., Tillein, J. & Kral, A. Induced cortical responses require developmental sensory experience. *Brain* **140**, 3153-3165 (2017)
15. Rosskothen-Kuhl, N. & Illing, R.-B. The impact of hearing experience on signal integration in the auditory brainstem: A c-Fos study of the rat. *Brain Res.* **1435**, 40-55 (2012)
16. Rauch, A.-K., Rosskothen-Kuhl, N. & Illing, R.-B. Counter-regulation of the AP-1 monomers

pATF2 and Fos: Molecular readjustment of brainstem neurons in hearing and deaf adult rats after electrical intracochlear stimulation. *Neuroscience* **313**, 184-198 (2016)

17. Osako, S., Tokimoto, T. & Matsuura, S. Effects of kanamycin on the auditory evoked responses during postnatal development of the hearing of the rat. *Acta Otolaryngol. (Stockh.)* **88**, 359-368 (1979)
18. Illing, R.-B. & Rosskothen-Kuhl, N. *The cochlear implant in action: molecular changes induced in the rat central auditory system*. (INTECH Open Access Publisher, Freiburg, 2012)
19. Rosskothen-Kuhl, N., Hildebrandt, H., Birkenhäger, R. & Illing, R.-B. Astrocyte Hypertrophy and Microglia Activation in the Rat Auditory Midbrain Is Induced by Electrical Intracochlear Stimulation. *Front. Cell. Neurosci.* **12**, (2018)
20. Seidl, A. H. & Grothe, B. Development of sound localization mechanisms in the mongolian gerbil is shaped by early acoustic experience. *J. Neurophysiol.* **94**, 1028-1036 (2005)
21. Beiderbeck, B., Myoga, M. H., Müller, N. I. C., Callan, A. R., Friauf, E., et al Precisely timed inhibition facilitates action potential firing for spatial coding in the auditory brainstem. *Nat. Commun.* **9**, (2018)
22. Hancock, K. E., Noel, V., Ryugo, D. K. & Delgutte, B. Neural coding of interaural time differences with bilateral cochlear implants: effects of congenital deafness. *J. Neurosci.* **30**, 14068-14079 (2010)
23. Hancock, K. E., Chung, Y. & Delgutte, B. Neural ITD coding with bilateral cochlear implants: effect of binaurally coherent jitter. *J. Neurophysiol.* **108**, 714-728 (2012)
24. Hancock, K. E., Chung, Y. & Delgutte, B. Congenital and prolonged adult-onset deafness cause distinct degradations in neural ITD coding with bilateral cochlear implants. *JARO* **14**, 393-411 (2013)
25. Chung, Y., Buechel, B. D., Sunwoo, W., Wagner, J. D. & Delgutte, B. Neural ITD Sensitivity and Temporal Coding with Cochlear Implants in an Animal Model of Early-Onset Deafness.. *Journal of the Association for Research in Otolaryngology : JARO* **20**, 37-56 (2019)
26. Tillein, J., Hubka, P., Syed, E., Hartmann, R., Engel, A., et al Cortical representation of interaural time difference in congenital deafness. *Cereb. Cortex* **20**, 492-506 (2009)
27. Tillein, J., Hubka, P. & Kral, A. Monaural Congenital Deafness Affects Aural Dominance and Degrades Binaural Processing.. *Cereb. Cortex* **26**, 1762-1777 (2016)
28. Litovsky, R. Y., Jones, G. L., Agrawal, S. & van Hoesel, R. Effect of age at onset of deafness on binaural sensitivity in electric hearing in humans. *J. Acoust. Soc. Am.* **127**, 400-414 (2010)
29. Klumpp, R. & Eady, H. Some measurements of interaural time difference thresholds. *J. Acoust. Soc. Am.* **28**, 859-860 (1956)
30. Keating, P., Nodal, F. R., Gananandan, K., Schulz, A. L. & King, A. J. Behavioral sensitivity to

broadband binaural localization cues in the ferret. *JARO* **14**, 561-572 (2013)

31. Koka, K., Read, H. L. & Tollin, D. J. The acoustical cues to sound location in the rat: measurements of directional transfer functions. *J. Acoust. Soc. Am.* **123**, 4297-4309 (2008)
32. Smith, Z. M. & Delgutte, B. Sensitivity to interaural time differences in the inferior colliculus with bilateral cochlear implants. *J. Neurosci.* **27**, 6740-6750 (2007)
33. Nelken, I., Chechik, G., Mrsic-Flogel, T. D., King, A. J. & Schnupp, J. W. Encoding stimulus information by spike numbers and mean response time in primary auditory cortex. *J. Comput. Neurosci.* **19**, 199-221 (2005)
34. Grothe, B. & Klump, G. M. Temporal processing in sensory systems. *Curr. Opin. Neurobiol.* **10**, 467-473 (2000)
35. Wesolek, C. M., Koay, G., Heffner, R. S. & Heffner, H. E. Laboratory rats (Rattus norvegicus) do not use binaural phase differences to localize sound. *Hear. Res.* **265**, 54-62 (2010)
36. Joris, P. X. & Yin, T. C. Envelope coding in the lateral superior olive. I. Sensitivity to interaural time differences. *J. Neurophysiol.* **73**, 1043-1062 (1995)
37. Bernstein, L. R. Auditory processing of interaural timing information: new insights. *J. Neurosci. Res.* **66**, 1035-1046 (2001)
38. Kan, A., Jones, H. G. & Litovsky, R. Y. Lateralization of interaural timing differences with multi-electrode stimulation in bilateral cochlear-implant users. *J. Acoust. Soc. Am.* **140**, EL392 (2016)
39. Chung, Y., Hancock, K. E. & Delgutte, B. Neural Coding of Interaural Time Differences with Bilateral Cochlear Implants in Unanesthetized Rabbits. *J. Neurosci.* **36**, 5520-5531 (2016)
40. Vollmer, M. Neural processing of acoustic and electric interaural time differences in normal-hearing gerbils. *J. Neurosci.* **38**, 6949-6966 (2018)
41. Brunso-Bechtold, J. K., Henkel, C. K. & Linville, C. Ultrastructural development of the medial superior olive (MSO) in the ferret. *J. Comp. Neurol.* **324**, 539-556 (1992)
42. Hoffpauir, B. K., Grimes, J. L., Mathers, P. H. & Spirou, G. A. Synaptogenesis of the calyx of Held: rapid onset of function and one-to-one morphological innervation. *J. Neurosci.* **26**, 5511-5523 (2006)
43. Kapfer, C., Seidl, A. H., Schweizer, H. & Grothe, B. Experience-dependent refinement of inhibitory inputs to auditory coincidence-detector neurons.. *Nat. Neurosci.* **5**, 247-253 (2002)
44. Walker, K. M., Schnupp, J. W., Hart-Schnupp, S. M., King, A. J. & Bizley, J. K. Pitch discrimination by ferrets for simple and complex sounds. *J. Acoust. Soc. Am.* **126**, 1321-1335 (2009)
45. Bizley, J. K., Walker, K. M. M., Nodal, F. R., King, A. J. & Schnupp, J. W. H. Auditory cortex represents both pitch judgments and the corresponding acoustic cues. *Curr. Biol.* **23**, 620-625

(2013)
46. Keating, P., Dahmen, J. C. & King, A. J. Context-specific reweighting of auditory spatial cues following altered experience during development. *Current biology : CB* **23**, 1291-1299 (2013)
47. Keating, P., Dahmen, J. C. & King, A. J. Complementary adaptive processes contribute to the developmental plasticity of spatial hearing. *Nat. Neurosci.* **18**, 185-187 (2015)
48. Levi, D. M., Knill, D. C. & Bavelier, D. Stereopsis and amblyopia: a mini-review. *Vision Res.* **114**, 17-30 (2015)
49. Ko, H., Cossell, L., Baragli, C., Antolik, J., Clopath, C., et al The emergence of functional microcircuits in visual cortex. *Nature* **496**, 96-100 (2013)
50. Wilson, B. S., Finley, C. C., Lawson, D. T., Wolford, R. D., Eddington, D. K., et al Better speech recognition with cochlear implants. *Nature* **352**, 236-238 (1991)
51. Loizou, P. C., Poroy, O. & Dorman, M. The effect of parametric variations of cochlear implant processors on speech understanding. *J. Acoust. Soc. Am.* **108**, 790-802 (2000)
52. van Hoesel, R. J. M. Sensitivity to binaural timing in bilateral cochlear implant users. *J. Acoust. Soc. Am.* **121**, 2192-2206 (2007)
53. Laback, B., Majdak, P. & Baumgartner, W.-D. Lateralization discrimination of interaural time delays in four-pulse sequences in electric and acoustic hearing. *J. Acoust. Soc. Am.* **121**, 2182-2191 (2007)
54. Joris, P. X. & Yin, T. C. Envelope coding in the lateral superior olive. III. Comparison with afferent pathways. *J. Neurophysiol.* **79**, 253-269 (1998)
55. Thakkar, T., Kan, A., Jones, H. G. & Litovsky, R. Y. Mixed stimulation rates to improve sensitivity of interaural timing differences in bilateral cochlear implant listeners. *J. Acoust. Soc. Am.* **143**, 1428 (2018)
56. Srinivasan, S., Laback, B., Majdak, P. & Delgutte, B. Introducing Short Interpulse Intervals in High-Rate Pulse Trains Enhances Binaural Timing Sensitivity in Electric Hearing. *JARO* **19**, 301-315 (2018)
57. Matsuda, K., Ueda, Y., Doi, T., Tono, T., Haruta, A., et al Increase in glutamate-aspartate transporter (GLAST) mRNA during kanamycin-induced cochlear insult in rats. *Hear. Res.* **133**, 10-16 (1999)
58. Argence, M., Vassias, I., Kerhuel, L., Vidal, P.-P. & de Waele, C. Stimulation by cochlear implant in unilaterally deaf rats reverses the decrease of inhibitory transmission in the inferior colliculus. *Eur. J. Neurosci.* **28**, 1589-1602 (2008)
59. Jero, J., Coling, D. E. & Lal, A. K. The Use of Preyer's Reflex in Evaluation of Hearing in Mice. *Acta Otolaryngol. (Stockh.)* **121**, 585-589 (2001)
60. Blatchley, B., Cooper, W. & Coleman, J. Development of auditory brainstem response to tone

pip stimuli in the rat. *Dev. Brain Res.* **32**, 75 - 84 (1987)

61. Rosskothen, N., Hirschm{\"u}ller-Ohmes, I. & Illing, R.-B. AP-1 activity rises by stimulation-dependent c-Fos expression in auditory neurons. *Neuroreport* **19**, 1091-1093 (2008)
62. Rosskothen-Kuhl, N. & Illing, R.-B. Nonlinear development of the populations of neurons expressing c-Fos under sustained electrical intracochlear stimulation in the rat auditory brainstem. *Brain Res.* **1347**, 33-41 (2010)
63. Rosskothen-Kuhl, N. & Illing, R.-B. Gap43 transcription modulation in the adult brain depends on sensory activity and synaptic cooperation. *PLoS One* **9**, e92624 (2014)
64. Rosskothen-Kuhl, N. & Illing, R.-B. The utilization of brain plasticity by cochlear implants : Molecular and cellular changes due to electrical intracochlear stimulation. *HNO* **63**, 94-103 (2015)
65. Keating, P., Nodal, F. R. & King, A. J. Behavioural sensitivity to binaural spatial cues in ferrets: evidence for plasticity in the duplex theory of sound localization. *Eur. J. Neurosci.* **39**, 197-206 (2014)
66. Wightman, F. L. & Kistler, D. J. The dominant role of low-frequency interaural time differences in sound localization.. *J. Acoust. Soc. Am.* **91**, 1648-1661 (1992)
67. Syka, J., Popelár, J., Kvasnák, E. & Astl, J. Response properties of neurons in the central nucleus and external and dorsal cortices of the inferior colliculus in guinea pig. *Exp. Brain Res.* **133**, 254-266 (2000)
68. Schnupp, J. W. H., Garcia-Lazaro, J. A. & Lesica, N. A. Periodotopy in the gerbil inferior colliculus: local clustering rather than a gradient map. *Front. Neural Circuits* **9**, 37 (2015)
69. Magri, C., Whittingstall, K., Singh, V., Logothetis, N. K. & Panzeri, S. A toolbox for the fast information analysis of multiple-site LFP, EEG and spike train recordings. *BMC neuroscience* **10**, 81 (2009)
70. Treves, A. & Panzeri, S. The upward bias in measures of information derived from limited data samples. *Neural Comput.* **7**, 399-407 (1995)
71. Schnupp, J. W. H., Hall, T. M., Kokelaar, R. F. & Ahmed, B. Plasticity of temporal pattern codes for vocalization stimuli in primary auditory cortex. *J. Neurosci.* **26**, 4785-4795 (2006)
72. Wickens, T. D. *Elementary signal detection theory*. (Oxford University Press, USA, , 2002)
73. Schnupp, J. W., Dawe, K. L. & Pollack, G. L. The detection of multisensory stimuli in an orthogonal sensory space. *Exp. Brain Res.* **162**, 181-190 (2005)
74. van Hoesel, R. J. & Tyler, R. S. Speech perception, localization, and lateralization with bilateral cochlear implants. *The Journal of the Acoustical Society of America* **113**, 1617-1630 (2003)