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

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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 these shortcomings. However, here we show that neonatally deafened rats which are fitted with binaural CIs in early adulthood are highly sensitive to ITDs immediately after implantation. Under binaural synchronized stimulation they can be trained to localize ITDs with essentially normal behavioral thresholds near 50 µs. This suggests that the deficits seen in human patients are unlikely to be caused by lack of experience during their period of deafness. It may instead be due to months or years of CI stimulation with inappropriate binaural parameters provided by CI processors which do not provide sub-millisecond temporal fine structure of sounds.

The World Health Organization reports that about 466 million people suffer from 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, quite routinely allowing near normal spoken language acquisition, particularly when CI implantation takes place early in life [1]. Never the less the performance of CI users remains variable, and even in the best cases falls short of natural hearing.

Good speech understanding in multi-sound environment requires the ability to separate speech from background, which relies in part on a phenomenon known as “spatial release from masking”. This relies on the brain’s ability to process binaural spatial cues, including interaural level and interaural time differences (ILDs/ITDs) [2]. To benefit from binaural cues in everyday life, bilateral cochlear implantation is becoming increasingly common for deaf patients [3-5] . However, even binaural CI patients perform much below the level of normal listeners in sound localization or 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 still only partially understood. A number of technical problems (see [8], chapter 6) limit the fidelity with which CIs can encode binaural cues, particularly ITDs. The fact that contemporary CI speech processors were originally designed for monaural, rather than binaural, hearing likely contributes the observed deficits in ITD performance of bilateral CI users [3]. Standard CI processors provide pulsatile stimulation which is not locked to the temporal fine structure of the incoming sounds, and the timing of the electrical pulses is not synchronized between both ears, which makes these devices fundamentally incapable of encoding sub-millisecond binaural time structure. To be useful, ITDs as small as a few tens of µs need to be resolved. Under optimal conditions, normal human listeners may be able to detect ITDs not much larger than 10 µs [9]. In contrast, the ITD sensitivity of CI patients is highly variable and generally very poor, even when tested with experimental processors capable of delivering synchronized stimulus pulses with sub-millisecond resolution [3,5-7,10,11].

The binaural performance of CI patients depends to a fair extent on the patients’ history. Importantly, pre-lingually deaf CI users invariably appear to exhibit no ITD sensitivity at all, whereas many post-lingually deaf CI users do exhibit at least some degree of ITD sensitivity [4,5,11-13]. This has led to the suggestion that early auditory deprivation during a sensitive period may prevent the development of ITD sensitivity, and that this cannot be recovered with later binaural stimulation using state-of-the-art speech processors [1,13,14]. If that hypothesis is correct, then developing more sophisticated binaural CI processors might not benefit the many patients who are born deaf or lose their hearing very early in life. By the time these patients are old enough to receive implants, they may already have missed out on the formative sensory input needed to develop the brain circuitry required for binaural processing with microsecond precision. This possibility seems particularly plausible given that immunohistochemical studies have shown that the tonotopic organization is degraded [15,16] and that stimulation-induced molecular, morphological, and electrophysiolological plasticity is altered in neonatally deafened rats compared to CI-stimulated rats with normal auditory development [15-19]. Furthermore, it has been shown that early acoustic experience shapes 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 also possible that the unstimulated auditory pathway may retain the ability to encode ITDs during a period of early deafness, and may only lose it as a result of maladaptive plasticity after a period of CI stimulation which conveys no useful ITD information. These possibilities cannot be distinguished based on clinical data, as there are no binaural CI processors capable of resolving sub-millisecond ITDs which are currently available for implantation in neonatally deaf children. To find out what level of binaural performance might be achievable with different stimulation strategies therefore requires animal experimentation. So far, studies investigating binaural sensitivity with CIs in adult, early deaf animals have been limited to acute electrophysiological experiments on cats, and these studies have reported significant amounts of ITD sensitivity in the inferior colliculus (IC) [22-24] and auditory cortex (AC) [25,26], even if that sensitivity appeared reduced compared to that seen with acoustic stimulation in normal animals. However, there have been no previous attempts to measure the extent to which chronic, precisely synchronized, bilateral CI stimulation might restore the ability of an adult implanted, neonatally deaf animal to use ITDs across the normal, sub-millisecond physiological range to guide behavior. We here address this question by investigating ITD sensitivity, both physiologically and behaviorally, in cohorts of neonatally deafened rats which received synchronized bilateral CIs in young adulthood.

Results

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

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

To measure the physiological ITD sensitivity of hearing inexperienced rat brains, we recorded responses to isolated, bilateral CI pulse stimuli with ITDs varying randomly over a ±160 μs range (ca 130% of the rat's physiological range [27]). We recorded from n=1230 multi-units in the IC of four ND rats. The binaural stimuli were simple biphasic current pulses of identical amplitude in each ear. The only parameter that varied from trial to trial was the interaural timing, and any 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 or less. Figure 1 shows a selection of responses as raster plots

(Fig. 1a) and the corresponding ITD tuning curves (Fig. 1b). As might be expected in light of previous studies investigating ITD sensitivity in the IC [22,24,28,29], we observed that the large majority of multi-units exhibited at least some, and at times substantial degrees of tuning to stimulus ITD.

The manner in which changes in ITD changed neural discharge patterns was also highly variable from one recording site to the next. While many multi-units showed typical short-latency onset responses to the stimulus which varied in response amplitude (Fig. 1a, #2, #3, #6, #9), some showed sustained, but still clearly tuned, responses extending for up to 80 ms or longer post-stimulus (Fig. 1a, #5, #7, #8). The shapes of ITD tuning curves we observed in rat IC (Fig. 1b) resembled the “peak”, “biphasic” or “sigmoid”, and “multi-peak” shapes previously described in the IC of cats [28].

Signal-to-noise and mutual information values show that substantial ITD tuning is widespread in the IC of ND 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. The first, a signal to noise ratio (SNR), was calculated as described by [22], and simply quantifies the proportion of the trial-to-trial response variance that can be accounted for by changes in ITD (see Methods for details). The second, a mutual information (MI) measure, quantifies the mutual information between trial-to-trial response amplitude and stimulus ITD in bits per response. It was calculated using a direct method with shuffling for bias correction (see Methods for details). Each sub-panel of Figure 1 indicates the SNR and MI values obtained for the corresponding multi-unit, while Figure 2 shows the distributions of SNR (Fig. 2a) and MI (Fig. 2b) values, respectively. For comparison, Figure 2a also shows the SNR values reported by [22] for the IC of congenitally deaf cats. As can be readily seen from Figure 2, multi-units with quite substantial ITD tuning (SNRs or MI values ≥ 0.5) are by no means rare exceptions. The amount of ITD tuning we observed in the IC of neonatally deafened, adult CI-implanted rats is about the same as reported for deaf cats, although the proportion of units with ITD SNR > 0.5 is higher in our rats. Furthermore, the great majority (1050/1230 ≈ 85%) of multi-units 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 1 and 2 clearly illustrate that the auditory midbrain of adult implanted ND rats exhibits substantial amounts of tuning to changes in ITDs of CI pulse stimuli of just a few tens of μs. Behavioral experiments described next 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.

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

We trained five ND, adult implanted rats and five NH rats in a simple two-alternative forced choice (2AFC) ITD lateralization task. The animals had to initiate trials by licking a center

"start spout", and then respond to 200 ms long 50 Hz binaural pulse trains by licking one of two "response spouts" positioned to either side to receive drinking water as a positive reinforcer (Figs. S2a, S3b). Which response spout would give water was signaled by the ITD of the stimulus. Again, we used simple biphasic pulses of identical amplitude in each ear, so that systematic ITD differences were the only reliable cue available to the animal (Fig. S2c-d). While the ND rats were stimulated with electrical pulse trains delivered through chronic CIs, the NH rats were stimulated with acoustic pulse trains delivered through near-field sound tubes positioned next to each ear when the animal was lined up to the start spout (Fig. S3a). During testing, stimulus ITDs varied randomly, and the discrimination performance of each rat as a function of ITD was fitted with sigmoid psychometric functions. Further details are given in the Methods section. The behavioral performance of each animal is shown in Figure 3, using light blue for NH (top) and dark blue for ND (bottom) animals.

It is readily apparent from Figure 3 that all rats, whether NH or ND with CIs, were capable of lateralizing ITDs. As might be expected, the behavioral sensitivity and performance was variable between individuals, with some animals (e.g. NH 1604 or CI 1734) exhibiting very few lapses and near perfect performance at ITDs larger than 0.1 ms, while others (e.g. NH 1606) had higher error rates and a less steep dependence of responses on stimulus ITD. To quantify the behavioral sensitivity of each rat to ITD we fitted psychometric curves (red lines in Fig. 3) to the raw behavioral data and calculated the slope of that curve at ITD=0. Figure 3k summarizes these slopes for NH (light blue) and ND CI (dark blue) animals. The slopes for ND CI rats and NH rats fall within the same range. The differences in mean slope were so small between both experimental groups (NH: 0.489 %/μs, ND CI: 0.601 %/μs) that very large cohorts of animals would be required to have any reasonable prospect of finding a significant difference. Similarly, the two cohorts showed quite similar 75% correct lateralization performance: NH rats with median of 45.4 μs and mean of 80.9 μs; ND CI rats with median of 57.8 μs and mean of 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 [5,30]. 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 [31], and pure tones [9], or the ≈ 40 μs thresholds reported for normally hearing ferrets tested with noise bursts [32].

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 subjects supplied with CIs in adulthood. These results may well generalize to other mammalian species, with major potential implications: If early deaf human CI patients cannot achieve accurate ITD discrimination, but early deaf CI rats can, then we should review with some urgency the manner in which we supply early deaf human patients with binaural CI stimulation.

But before we discuss these potential implications, we should address three aspects of this study which colleagues in this field of research may find surprising:

Firstly, some studies deemed rats to be generally poor at processing ITDs [33,34]. However, the only previous behavioral study in rats 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 [35,36]. That may also explain why our CI rats showed good ITD sensitivity even though our CIs targeted the mid-frequency region of their cochleae, and not the apical region normally associated with low frequency hearing. Recent studies in human CI patients who suffered late deafness have shown that ITDs delivered to mid, and even high-frequency parts of the cochlea can be detected behaviorally [5,37].

Secondly, previous electrophysiological studies on congenitally deaf CI cats reported a substantially reduced ITD sensitivity relative to that seen in NH animals [22,25,26]. These studies recorded neural tuning relatively high up in the auditory pathway (AC and IC respectively), so one cannot be certain whether the relatively reduced sensitivity seen reflects a fundamental degradation of ITD processing in the olivary nuclei, or merely a poor maturation of connections from there to higher order areas which might 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% previously reported for congenitally deaf cats [22]. The proportion of ITD sensitive sites in our ND rats is thus more similar to reported proportions in adult deafened cats (84%-86%; [22,28]), rabbits (73%; [38]) or gerbils (at least 74%; [29]). Our Figure 2a also shows a relatively greater proportion of units showing ITD SNRs above 0.6 for our ND rats than for ND cats of [22]. These relatively modest differences in proportions of sensitive sites are probably at least in large part to methodological differences. For example, Hancock et al. [22] recorded single-unit data, while we report analog multi-unit data which is likely to give better SNRs, and hence also a higher proportion of units above significance threshold, simply by pooling responses over multiple, similarly tuned neighboring units.

Thirdly, we don’t really know how much ITD tuning in the IC or AC is really necessary to make ITD discrimination thresholds of ≈ 50 µs possible. Even if the amount of ITD sensitivity reported in the IC [22] and AC [25,26] of congenitally deaf cats is somewhat less than that in normal cats, it may still be sufficient to permit accurate localization behavior, and it might improve with training. Thus, while our finding of apparently normal behavioral ITD sensitivity in ND rats may appear surprising, it is not in contradiction with previously published animal work [22,24-26].

Finally, the biggest difference between our results and that from previously published studies remains the vastly better behavioral ITD discrimination we see in our ND CI rats compared to that reported for early deaf human CI patients [5,13]. Previous authors have put forward a number of possible explanations for the very poor performance seen in these human patients, including “factors such as auditory deprivation, in particular, lack of early exposure to consistent timing differences between the ears” [5]. However, our ND rats

achieved very good performance despite lack of early exposure, which makes that explanation appear substantially less likely. Admittedly, there may be species differences at play here. Our ND animals were implanted in young adulthood and thus were severely deprived of auditory input throughout their childhood. But humans mature much more slowly so that even human patients implanted at a very young age will have been deprived of auditory input for a substantially longer absolute time period compared with our rats. Nevertheless, our results strongly hint at the possibility that the complete insensitivity of current early deaf, binaural CI patients to ITD cues may be not so much the "lack of exposure to consistent timing differences", but rather the massive and prolonged exposure to entirely inconsistent ITDs they will experience as soon as they are bilaterally fitted with standard implants which do not synchronize inputs between ears. In addition, most binaural CI patients receive their CIs sequentially, and their initial, potentially formative, auditory experience is therefore monaural.

Developmental anatomical 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 [39]. Similarly, the highly specialized calyx of held synapses which are thought to play key roles in relaying precisely timed information in the binaural circuitry of the brainstem have also been shown to mature before the onset of hearing in mice [40]. Admittedly, it has been shown in gerbils that 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 [20,32,41-43], but there are no studies demonstrating that critical periods in the ITD pathways will irrevocably close if sensory input is simply absent. These data are therefore also compatible with our interpretation that inappropriate input, rather than a lack of experience, may be the predominant reason why neonatally deaf CI users fail to develop ITD sensitivity.

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, but that it also adapts strongly to changes in these cues and can re-weight them depending on their reliability [26,44,45]. Current standard CI processors produce pulsatile stimulation based on fixed rate interleaved sampling, which is neither synced to stimulus fine structure nor synchronized between the ears. Consequently these processors only ever provide uninformative ITDs to the children fitted with these devices. In sharp contrast, for our ND CI rats, binaural cues were essentially the only form of useful auditory input they ever experienced, and they quickly learned to make effective use of them. Thus, the brainstem circuits of human children fitted with conventional binaural CIs may simply "learn" to ignore inputs that aren't helpful. That would be adaptive to them given that the only ITDs they ever receive carry no useful information about the external world.

In the light of our data, we suggest that the mammalian auditory system develops some sensitivity to ITD cues in the absence of early sensory input, which is then either refined or lost depending on whether the inputs received once hearing starts are appropriate and informative or not. For the visual system it has already been shown that orientation selective neuronal responses exist at eye-opening and thus are established without visual

input [46]. Whether human CI patients are able to recover near 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. 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 a lack of sensory experience [47].

While these 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 early deaf binaural CI patients, one must nevertheless acknowledge that it may be difficult to change established CI processing strategies without at the same time compromising the CI's effectiveness in encoding speech formant information. The continuous interleaved sampling (CIS) paradigm [48] from which almost all current CI speech processing 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" in the inner ear which might further reduce the accuracy of the already quite limited tonotopic place coding which CIs can deliver. At the same time, CI processors routinely run at relatively high pulse rates (900 Hz and above), which seems to be necessary to encode enough information about amplitude modulations (AM) in speech signals to facilitate accurate word recognition [49]. Here, the needs for speech encoding and ITD encoding seem to diverge, as previous studies on humans [50,51] and animals [38] have shown that ITD discrimination deteriorates dramatically when pulse rates exceed a few hundred Hz. This fact is likely related to the physiological observation that the ability of superior olivary neurons to encode envelope ITDs declines at envelope rates exceeding several hundred Hz [52]. Our own behavioral experiments described here were conducted with very low pulse rates of only 50 Hz, and it is doubtful that our animals would have been able to perform the task nearly as well at pulse rates close to 1 kHz.

Thus, designers of novel human binaural CI speech processors face seemingly irreconcilable demands: They must invent devices which fire each of 20 or more electrode channels in turn, at rates that are at the same time fast, so as to encode speech AM in fine detail, but also slow, so as not to overtax the brainstem's ITD extraction mechanisms. In addition, they must make the timing of at least some of these pulses encode stimulus fine structure and ITDs. While that is difficult, it may not be impossible, and promising lines of research are already pursued, which either use a mixture of different pulse rates for different electrode channels [53] or "reset" the brain's ITD extraction mechanisms by introducing occasional "double pulses" into the stimulus regime [54]. However, a detailed discussion of such approaches is beyond the scope of this paper. Our findings raise the hope that even early deafened patients may be able to develop useful ITD sensitivity, if informative ITD cues are made available to them right after implantation and they are not subjected to prolonged CI stimulation with ITDs which are uninformative.

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 [17,55,56] while keeping the number of spiral ganglion cells comparable to that in untreated control rats [56]. We verified that this procedure provoked profound hearing loss (> 90 dB) by first, the loss of Preyer's reflex [57], before the onset of neural auditory brainstem response (ABRs) to pure tone pips [58], 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) [20,41].

CI implantation, stimulation and testing

All surgical procedures, including CI implantation and craniotomy, were performed under anaesthesia 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 [15,59-62]. 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 +/- 120 μs [27], 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 [32,42,43]. 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 [42,63], 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. [32,64]. We used a 3D printed “rat kemar head” 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 [61].

Multi-unit 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; [65]).

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

453 times at each recording site. The inter-stimulus interval was 500 ms. At the end of the
454 recording session the animals were overdosed with pentobarbitone.

455 Data analysis

456 To quantify the extracellular multi-unit responses we calculated the average activity for
457 each stimulus over a response period (3-80 ms post stimulus onset) as well as baseline
458 activity (300-500 ms after stimulus onset) at each electrode position. The first 2.5 ms post
459 stimulus onset were dominated by electrical stimulus artifacts and were discarded. For
460 display purposes of the raster plots in Figure 1 we extracted multi-unit spikes by simple
461 threshold crossings of the bandpassed (300Hz-6kHz) electrode signal with a threshold set
462 at four standard deviation of the signal amplitude. To quantify responses for tuning curves,
463 instead of counting spikes by threshold crossings we instead computed an analog
464 measure of multi-unit activity (AMUA) amplitudes as described in [66]. The mean AMUA
465 amplitude during the response and baseline periods was computed by bandpassing
466 (300Hz-6kHz), rectifying (taking the absolute value) and lowpassing (6 kHz) the electrode
467 signal. This AMUA value thus measures the mean signal amplitude in the frequency range
468 in which spikes have energy. As illustrated in Figure 1 of [66], this gives a less noisy
469 measure of multi-unit neural activity than counting spikes by conventional threshold
470 crossing measures because the later are subject to errors due to spike collisions, noise
471 events, or small spikes sometimes reach threshold and sometimes not. The tuning curves
472 shown in the panels of Figure 1b were measured using this AMUA measure. It is readily
473 apparent that changes in the AMUA amplitudes track changes in spike density.

474 Signal-to-noise ratio (SNR) calculation

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

482 Mutual information (MI) calculation

483 MI quantifies the statistical dependence between stimulus and response amplitude in bits
484 per response according to the formula

485 $$MI(S;R)=\sum_{s\in S}\sum_{r\in R}\log_2\left(\frac{p(r,s)}{p(r)\cdot p(s)}\right). \qquad (1)$$

486 Here *p(r)* is the probability that the response of a given trial is of magnitude *r, p(s)* is the
487 probability that the ITD stimulus parameter of a given trial is *s*, and *p(r,s)* is the probability
488 that response *r* and stimulus *s* co-occurred in a given trial. It is common practice to bin the
489 set of possible responses into a suitable number of discrete steps. We performed this
490 binning using the function *binr()* of the “information breakdown toolbox” [67] 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 [68]. As described in [69] 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 [70], 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 multi-unit, and subtracted the mean bias from the original, "raw" MI value to obtain the bias corrected values (Fig. 2b). We also used the distribution of bias estimates to assess whether the tuning of a multi-unit to ITD was statistically significant. Only multi-units 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 [71,72]. 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 3a-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 3k. That slope is easily calculated using the equation

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

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.

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Author Contributions

N.R.K. and J.W.H.S. designed the study. 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. N.R.K. and J.W.H.S wrote the article. All authors approved the final manuscript.

Declaration of Interests

The authors declare no competing interests.

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Figures plus Figure Legends

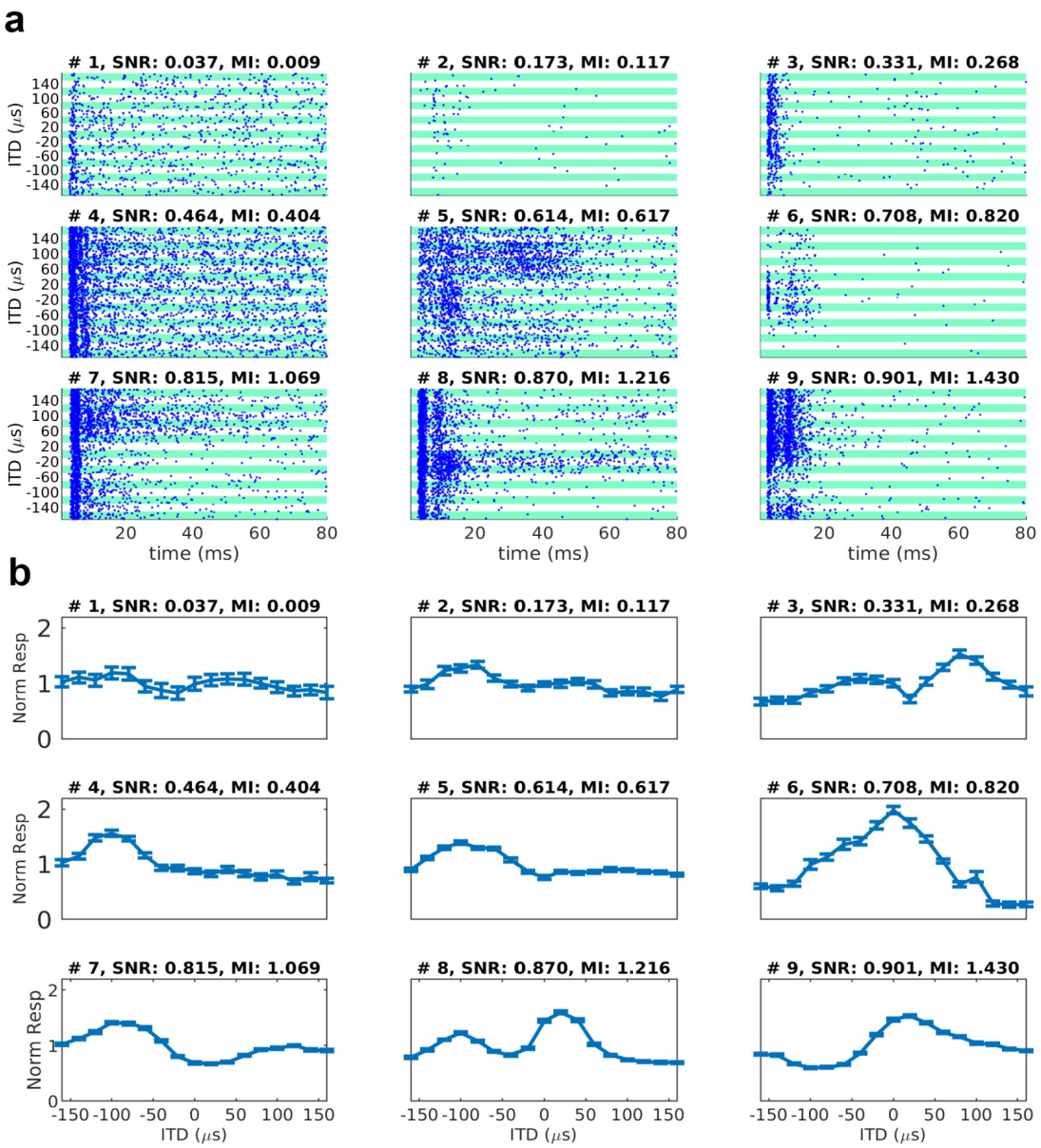

Figure 1: IC neurons of ND rats exhibit varying degrees and types of ITD sensitivity immediately after adult cochlear implantation. Dot raster plots (**a**) and their corresponding ITD tuning curves (**b**) for a number of multi-units selected to illustrate some of the variety of ITD tuning depths and types observed in this study. **a** Each blue dot shows the timing of one spike. The alternating white and green bands show responses to n=30 repeats each of CI binaural pulse stimuli at the ITDs shown along the left margins. **b** Corresponding multi-unit tuning curves, showing the response amplitudes above baseline and 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 the signal-to-noise (SNR) and mutual information (MI) values calculated to quantify the strength of

the tuning to ITD (see Methods). Sub-panels are arranged by increasing SNR and MI. ITD>0: ipsilateral ear leading; ITD<0: contralateral ear leading.

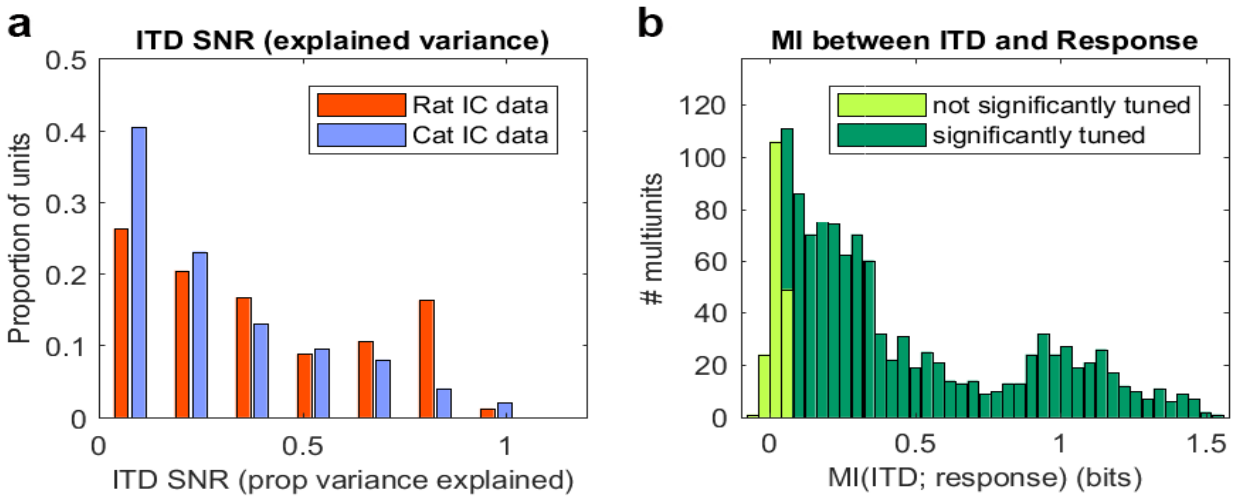

Figure 2: Signal-to-noise (SNR) and mutual information (MI) values show that substantial ITD tuning is widespread in the IC of ND rats. **a** Distribution of ITD SNR values for multi-units recorded in the ICs of our ND, CI-stimulated rats (red columns). For comparison, IC single-unit SNR values recorded in congenitally deaf CI cats by [22] (blue columns). **b** Distribution of MI values in bits / response for mutual information between response amplitude and stimulus ITD. MI values which were not significantly greater than zero (permutation test, α=0.01) are shown in light green.

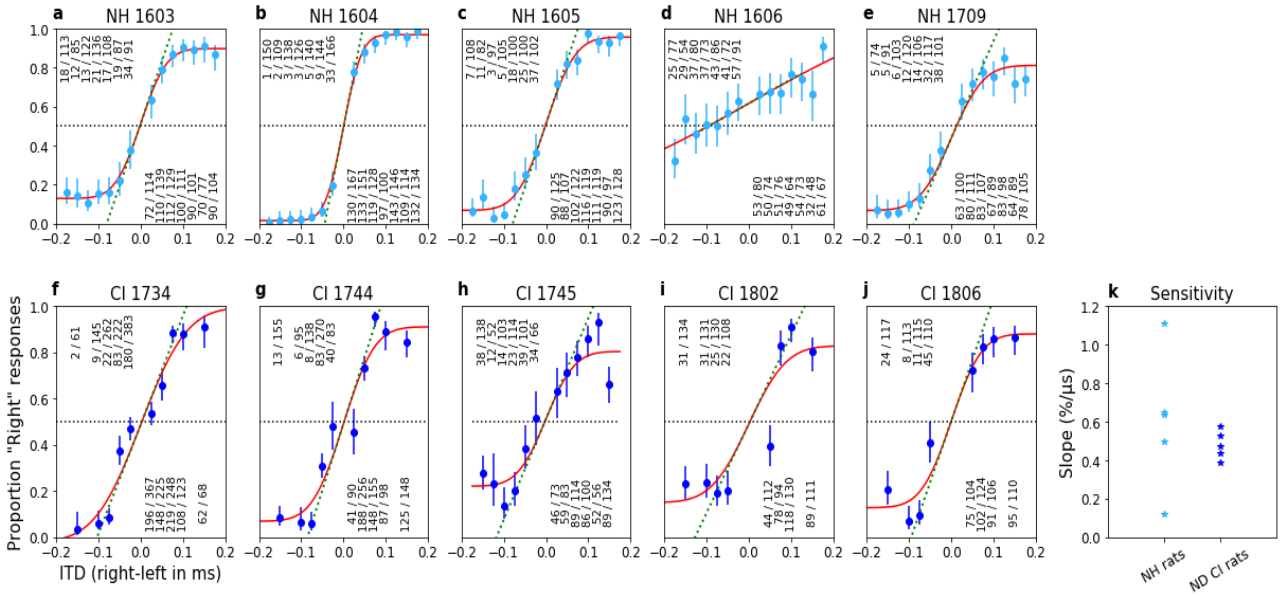

Figure 3: Early deaf CI rats discriminate ITD as accurately as their normally hearing litter mates. **a-j** ITD psychometric curves of normal hearing (**a-e**) and neonatally deafened CI rats (**f-j**). The titles above the panels show the ID number of the corresponding experimental animal. Y-axis: proportion of responses to the right-hand side. X-axis: Stimulus ITD in ms, with negative values indicating that the left ear stimulus is 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 the corresponding ITD. 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. The green dashed lines show the slopes of the psychometric curves at x=0. These 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 the animals’ “right” judgments per µs change in ITD.