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

Nicole Rosskoth-Kuhl^{1,2*#}, Alexa N Buck^{1#}, Kongyan Li¹, 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

#: divided first author ship

Contact Info

Corresponding authors:

Dr. Nicole Rosskoth-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

29 **Keywords**

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

32 Abstract

33 Cochlear implants (CIs) can restore a high degree of functional hearing in deaf patients
 34 however spatial hearing remains poor, with many early deaf CI users reported to have no
 35 measurable sensitivity to interaural time differences (ITDs) at all. Deprivation of binaural
 36 experience during an early critical period is often blamed for this shortcoming. However,
 37 we show that neonatally deafened rats provided with precisely synchronized CI stimulation
 38 in adulthood can be trained to localize ITDs with essentially normal behavioral thresholds
 39 near 50 μ s. Furthermore, neonatally deaf rats show high physiological sensitivity to ITDs
 40 immediately after binaural implantation in adulthood. The fact that our neonatally deaf CI
 41 rats achieved very good behavioral ITD thresholds while prelingually deaf human CI
 42 patients usually fail to develop a useful sensitivity to ITD raises urgent questions about
 43 whether shortcomings in technology or treatment may be behind the usually poor binaural
 44 outcomes for current binaural CI patients.

45 For people with severe to profound sensorineural hearing loss, cochlear implants (CIs) can
 46 be enormously beneficial routinely allowing near normal spoken language acquisition
 47 particularly when CI implantation takes place early in life [1]. Nevertheless the
 48 performance of CI users remains variable, and falls short of natural hearing.

49 Good speech understanding with competing sound sources requires the ability to separate
 50 speech from background. This is aided by “spatial release from masking”, which relies on
 51 the brain’s ability to process binaural spatial cues, including interaural level and time
 52 differences (ILDs & ITDs) [2]. Bilateral cochlear implantation is becoming commonplace to
 53 provide benefits of binaural hearing to the deaf [3-5], but binaural CI recipients perform
 54 poorly in sound localization and auditory scene analysis tasks, particularly when multiple
 55 sound sources are present [6,7]. The parameters that would allow CI patients to derive
 56 maximum benefits from binaural spatial cues are only partially understood. A number of
 57 technical problems (see [8], chapter 8) limit the fidelity with which CIs can encode ITDs in
 58 particular. Contemporary CI speech processors were originally designed for monaural, not
 59 binaural, hearing, and this likely contributes to the observed deficits in bilateral CI users
 60 [3]. Standard CI processors provide pulsatile stimulation which is not locked to the
 61 temporal fine structure of incoming sounds, and the timing of electrical pulses is not
 62 synchronized between both ears, making these devices incapable of encoding the
 63 temporal fine structure and ITDs with the required resolution of a few tens of μ s. While
 64 normal hearing human listeners may be able to detect ITDs as small as 10 μ s [9], ITD
 65 sensitivity of CI patients is poor or completely missing [3,5-7,10-12].

66 Whether CI patients can detect ITDs at all depends largely on their history: Prelingually
 67 deaf CI users invariably exhibit poor or no ITD sensitivity at all (rare star performers at best
 68 achieving thresholds of a few hundred μ s), but many postlingually deaf CI users show at
 69 least some degree of ITD sensitivity [4,5,11-15]. This led to the suggestion that early
 70 auditory deprivation during a sensitive period may prevent the development of ITD

71 sensitivity irrecoverably [1,15,16]. If this hypothesis is correct, then developing CI
 72 processors with better ITD coding might not benefit patients with hearing loss early in life
 73 because, by the time of implantation these patients would already have missed out on the
 74 formative sensory input needed to develop the brain circuitry required for binaural
 75 processing with microsecond precision. Various lines of evidence make this critical period
 76 hypothesis plausible, including immunohistochemical studies which have shown degraded
 77 tonotopic organization [17,18] and changes in stimulation-induced molecular,
 78 morphological, and electrophysiological properties of the auditory pathway of neonatally
 79 deafened (ND) CI-rats [17-21]. Additional studies demonstrate that abnormal sensory input
 80 during early development can alter ITD tuning curves in key brainstem nuclei of gerbils
 81 [22,23].

82 However, the “critical period hypothesis” of poor ITD sensitivity in CI patients has not been
 83 rigorously tested, and it is possible that the ND auditory pathway could retain an innate
 84 ability to encode ITD, which may then only be lost as a result of maladaptive plasticity after
 85 a period of binaural CI stimulation which conveys no useful ITD information. These
 86 possibilities cannot be distinguished based on clinical data, as there are no binaural CI
 87 processors in clinical use capable of encoding microsecond ITDs effectively. Thus, animal
 88 experimentation is needed, in a first instance, to examine how much functional ITD
 89 sensitivity can be achieved through bilaterally synchronized CI stimulation in a mature ND
 90 animal. Previous animal studies investigating binaural sensitivity after early deafness have
 91 been limited to acute electrophysiological experiments on cats and rabbits. These studies
 92 have reported reduced ITD sensitivity in the inferior colliculus (IC) [24-27] and auditory
 93 cortex (AC) [28,29] compared to hearing experienced animals. There have been no
 94 previous attempts to train ND animals to discriminate sub-millisecond ITDs across the
 95 physiological range delivered with CIs fitted in adulthood. Here, we show that cohorts of
 96 ND rats which received synchronized bilateral CI stimulation in young adulthood not only

exhibit a great deal of physiological ITD sensitivity in their IC straight after implantation but they can also be trained easily and quickly to lateralize ITDs behaviorally, achieving thresholds as low as ~50 μ s, comparable to their normal hearing (NH) litter mates.

Results

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

To test whether ND rats can learn to discriminate ITDs of CI stimuli, we trained five ND rats who received chronic bilateral CIs in young adulthood (postnatal weeks 10-14) in a simple two-alternative forced choice (2AFC) ITD lateralization task, and we compared their performance against behavioral data from five age-matched NH rats trained to discriminate the ITDs of acoustic pulse trains [30]. 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 (Figs. S2c-d; S3f). 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 behavioural data (Fig. 1) were collected over a testing period of around 14 days. For CI rats, the initial lateralization training started usually one day after CI implantation. On average, rats were trained for maximum eight days before we started to test them on ITD sensitivity. The behavioral performance of each rat is shown in Figure 1, using light blue for NH (a-e) and dark blue for ND (f-j) 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 (0.487 %/ μ s) is only about 20% worse than that of the NH (0.657 %/ μ s). Furthermore, the differences in means between experimental groups (0.17 %/ μ s) were so much smaller than the animal-to-animal variance ($\sim 0.73\%/\mu\text{s}^2$) that 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: 41.5 μ s; ND: 54.8 μ s; mean NH: 79.9 μ s; ND: 63.5 μ s). Remarkably, the ITD thresholds of our ND CI rats are thus orders of magnitude better than those reported for prelingually deaf human CI patients, who usually have ITD thresholds too large to measure, often in excess of 3000 μ s [5,31]. Indeed, their thresholds are not dissimilar from the approx. 10-60 μ s range of 75% correct ITD discrimination thresholds reported for normal human subjects tested with noise bursts [32], and pure tones [9], or the $\approx 40\ \mu$ s thresholds reported for normally hearing ferrets tested with noise bursts [33].

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.

Varying degrees and types of ITD tuning are pervasive in the neural responses in the IC of ND rats immediately after adult cochlear implantation.

To investigate the amount of physiological ITD sensitivity present in the hearing inexperienced rat brain, we recorded responses of $n=1140$ multi-units in the IC of four young adult ND rats (Fig. 2, left) to isolated, bilateral CI pulse stimuli with ITDs varying randomly over a $\pm 160 \mu\text{s}$ range (ca 123% of the rat’s physiological range [34]). For comparison, we also recorded responses of $n=1312$ IC multi-units in four age-matched NH rats (Fig. 2, right), using identical stimulation. For both cohorts, 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. S2c-d). Responses of IC

neurons were detected for currents as low as 100 μ A. Figure 2 shows a selection of responses as raster plots and corresponding ITD tuning curves for both cohorts (Fig. 2, #1-8).

Both for the ND and the NH animals, the manner in which varying ITD changed neural discharge patterns varied from one recording site to the next. But the extent to which discharge patterns depend on stimulus ITD is not obviously very different in the ND and the NH examples shown. While many multi-units showed typical short-latency onset responses to the stimulus with varying response amplitudes (Fig. 2, #1, #3, #6, #7), some showed sustained, but still clearly tuned, responses extending for up to 80 ms or longer post-stimulus (Fig. 2, #4). The shapes of ITD tuning curves we observed in rat IC (Fig. 2) resembled mostly the “peak”, “monotonic sigmoid”, “trough”, and “multi-peak” shapes previously described in the IC of cats [35].

Figure 2: IC neurons of ND rats were ITD sensitive immediately following adult cochlear implantation. Examples of ITD tuning curves of neonatally deafened (ND) rats (red, left) and normal hearing (NH) rats (blue, right) with varying degrees and types of ITD sensitivity. Dot raster plots are shown next to corresponding ITD tuning curves. The multi-units shown were selected to illustrate some of the variety of ITD tuning curve depths and types observed. In the raster plots, each blue dot shows one spike. Alternating white and green bands show responses to n=30 repeats at each ITD shown. Tuning curve response amplitudes are baseline corrected and normalized relative to the maximum of the mean response across all trials, during a period of 3-80 ms post stimulus onset. Error bars show SEM. Above each sub-panel we show signal-to-noise (SNR) values to quantify ITD tuning. Panels are arranged top to bottom by increasing SNR. ITD>0: ipsilateral ear leading; ITD<0: contralateral ear leading.

190

To quantify how strongly the neural responses recorded at any one site depended on stimulus ITD, a “signal-to-noise ratio” (SNR) value was calculated as described in [24]. It quantifies the proportion of response variance that can be accounted for by stimulus ITD (see Methods). Each sub-panel of Figure 2 indicates SNR values obtained for the corresponding multi-unit, while Figure 3 shows the distributions of SNR values for both ND (dark red) and NH cohorts (light red). Figure 3 also shows the SNR values reported by Hancock et al. [24] for the IC of congenitally deaf (dark blue) and hearing experienced (light blue) cats. When comparing the distributions shown, it is important to be aware that there are significant methodological, as well as species, differences between our study and the study that produced the cat data shown in [24], so the cross-species comparison in particular must be done with care. Nevertheless, the distributions clearly show that ITD SNRs in our ND and NH rats are broadly similar, and also broadly in line with the values reported by others using similar methodologies. It is noticeable, and perhaps surprising,

19

10

20

204 that the proportion of multi-units with relatively large SNRs values (substantial ITD tuning)
 205 is if anything slightly higher among the ND rats compared to the NH rats, and the median
 206 SNR value for ND rat IC multi-units (0.37) was in fact larger than that observed in NH rats
 207 (0.25). The proportion of rat multi-units which showed statistically significant ITD tuning
 208 ($p \leq 0.01$), as determined by ANOVA (see Methods), was also similarly very large in both
 209 ND (1041/1140 $\approx$ 91%) and NH CI-stimulated rats (1154/1312 $\approx$ 88%). Thus, for our rats
 210 which were kanamycin deafened before the onset of hearing, a lack of early auditory
 211 experience did not produce a measurable decline in overall sensitivity of IC neurons to the
 212 ITD of CI stimulus pulses. This is perhaps unexpected given that previous studies
 213 comparing ITD tuning in the IC of congenitally deaf white cats and with that in wild type
 214 cats did report noticeably worse ITD tuning in the congenitally deaf cats [26].

215 Nevertheless, the results in Figures 2 and 3 clearly show that many IC neurons in the
 216 inexperienced, adult midbrain of ND rats are quite sensitive to changes in ITD of CI pulse
 217 stimuli by just a few tens of μ s, and our behavioral experiments showed that ND rats (Fig.
 218 1, f-j) can readily learn to use this neural sensitivity to perform behavioral ITD
 219 discrimination with an accuracy similar to that seen in their NH litter mates (Fig. 1, a-e).

220

Figure 3: IC multi-units with good ITD tuning, as measured by high signal-to-noise ratio (SNR) values, are not less common in ND than in NH rats. Bar chart shows distributions of ITD SNR values for ICs multi-units of ND (red) and NH (light red) rats. SNR value distributions for IC single unit data recorded by Hancock et al. [24] for congenitally deaf (dark blue) and hearing experienced cats (light blue) are also shown for comparison.

Discussion

This study is the first demonstration that, at least in rats, severely degraded auditory experience in early development does not inevitably lead to impaired binaural time processing in adulthood. In fact, the ITD thresholds of our ND rats ($\approx 50 \mu\text{s}$) were as good as the ITD thresholds of NH rats [30], and many times better than those typically reported for early deaf human CI patients with thresholds often too large to measure [5,14,30,31]. The surprisingly good performance exhibited by our ND animals raises the important question of whether early deaf human CI patients might perhaps also be able to achieve near normal ITD sensitivity if supplied with better binaural CI stimulation from the

beginning of implantation. But before we consider translational questions that might be raised by our results, we should address two aspects of this study which colleagues may find surprising:

Firstly, some studies deemed rats to be generally poor at processing ITDs [36,37]. However, the only previous rat behavioral study outside of our lab tested interaural phase sensitivity only 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 [38,39]. 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 [5,40].

Secondly, electrophysiological studies on congenitally deaf CI cats reported a substantially reduced ITD sensitivity relative to wild type, hearing experienced cats [24,28,29]. These studies recorded neural tuning high 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 91% of recordings sites, compared to only 48% reported for congenitally deaf cats [24] or 62% for early deaf rabbits [27]. The proportion of ITD sensitive sites in ND rats is thus more similar to proportions in adult deafened CI-stimulated cats (84%-86%; [24,35], rabbits (~75%; [27,41]) or gerbils (~74%; [42]) and is comparable with our own NH rats (88%). Figure 3 suggests that the ITD SNR seen in our ND and NH CI-rats fall in a similar range of the ITD SNRs previously reported for congenitally deaf and hearing experienced CI-cats [24]. While for cats, the proportion of IC multi-units with large ITD SNR values appears to be reduced in animals lacking early

auditory experience, the same does not appear to be the case in our rats. Whether these quantitative differences in physiological ITD sensitivity are due to methodological and/or species differences is not determinable, but we believe that these apparent differences are ultimately unlikely to be important, because even the congenitally deaf cats still have a decent number of IC units showing fairly large amounts of ITD sensitivity. In fact, more than 20% of the congenitally deaf cat IC units have SNR values of 0.5 or higher, which indicates really rather good ITD sensitivity. It is important to remember that it is essentially unknown how much ITD tuning in the IC or AC is necessary, or whether this is species specific, to make behavioral ITD discrimination thresholds of $\approx 50 \mu\text{s}$ possible, but multi-units such as #3 and #4 shown in Figure 2 change their firing rates substantially when ITDs change by only a few tens of microseconds, and these multi-units have SNRs that are not outside the range reported for congenital cats. This level of physiological sensitivity probably ought to be sufficient to enable quite good behavioral ITD discrimination performance if only these animals could be trained and tested on an appropriate task.

Thus, in our opinion, any previously reported reductions in physiological ITD sensitivity seen in the IC [27,41] or AC [28,29] of early deaf animals simply does not seem nearly large enough to fully explain the extremely poor behavioral ITD thresholds seen in most early deaf humans and the observation that the physiological ITD sensitivity in our ND rats is comparable to that in NH animals [30] emphasizes the existence of other causes.

Consequently, why in congenitally deaf cats there appears to be a relatively modest reduction in neural ITD sensitivity while in ND rats that appears not to be the case is not a pressing question, given that the available evidence suggests that both have quite a lot of innate or residual ITD sensitivity in their midbrains, and consequently ought to be able to learn to make use of that binaural cue. Thus, our finding of apparently normal behavioral ITD sensitivity in ND CI-rats may appear surprising, but it does not contradict previous studies [24,26-29].

289 The most striking difference between our results and other previously published work
 290 remains the vastly better behavioral ITD discrimination in ND CI rats compared to that of
 291 early deaf CI patients [5,14,15]. Previous authors have proposed that the very poor
 292 performance seen in these patients may be due to “factors such as auditory deprivation, in
 293 particular, lack of early exposure to consistent timing differences between the ears” [5].
 294 However, a lack of early exposure did not prevent our ND rats from achieving very good
 295 ITD discrimination performance. Furthermore, our rats were neonatally deafened and
 296 implanted with CI in early adulthood thus not only lacking auditory experience during a so
 297 called ‘critical period’ but also having prolonged deprivation. This is comparable with
 298 prelingually deafened CI users who receive CIs as adults. However, Litovsky et al. [11]
 299 demonstrated that this cohort too had worse ITD performance as compared with adult-
 300 onset deafened CI users. Admittedly, there may be species differences at play here. Our
 301 ND rats were implanted as young adults, and were severely deprived of auditory input
 302 throughout their childhood, but humans mature much more slowly, so even patients
 303 implanted at a very young age will have suffered auditory deprivation for a substantially
 304 longer absolute time period than our rats. Nevertheless, our results raise the possibility
 305 that the poor ITD sensitivity of early deaf patients may perhaps not be caused by the “lack
 306 of exposure to consistent timing differences” and other factors might be to blame, such as
 307 the prolonged exposure to entirely inconsistent ITDs delivered by current clinical CI
 308 processors, which do not synchronize pulses between ears. This argument is supported by
 309 Zheng et al. [43] who found that CI implanted children with bilateral experience (>4 years)
 310 still show a higher percentage of errors than age-matched NH peers and Litovsky and
 311 Gordon [15] describe that “even the bilateral CI users who have had >6 years of
 312 experience listening with their CIs did not perform as well as the children with NH”.
 313 Additionally, most binaural patients receive their CIs sequentially, and their initial,
 314 potentially formative, auditory experience is monaural. In contrast, our rats received highly
 315 precise and informative ITDs right from the start.

316 Developmental studies in ferrets have shown that the formation of afferent synapses to
 317 medial superior olive, one of the main brainstem nuclei for ITD processing, is essentially
 318 complete before the onset of hearing [44]. In mice, the highly specialized calyx of held
 319 synapses which are thought to play key roles in relaying precisely timed information in the
 320 binaural circuitry have been shown to mature before the onset of hearing [45]. In gerbils,
 321 key parts of the binaural ITD processing circuitry in the auditory brainstem will fail to
 322 mature when driven with strong, uninformative omnidirectional white noise stimulation
 323 during a critical period [22,33,46-48], but no studies have demonstrated that critical
 324 periods in the ITD pathways will irrevocably close if sensory input is simply absent. In fact
 325 Tirko and Ryugo [49] show that inhibitory pathways in the medial superior olive, which are
 326 thought to be essential for ITD encoding [50], are significantly reduced in congenitally deaf
 327 cats at postnatal day 90, compared to normal hearing peers, and can be fully restored with
 328 the advent of CI stimulation after only 3 months. These data are therefore not incompatible
 329 with our hypothesis that inappropriate input, rather than its absence, may cause the loss of
 330 ITD sensitivity in early deaf CI users.

331 It is well known that the normal auditory system not only combines ITD information with
 332 ILD and monaural spectral cues to localize sounds in space, it also adapts strongly to
 333 changes in these cues, and can re-weight them depending on their reliability [29,51-53].
 334 Current CI processors produce pulsatile stimulation based on fixed rate interleaved
 335 sampling, which is neither synced to stimulus fine structure nor synchronized between
 336 ears. Consequently, they only ever provide uninformative ITDs to the children using them.
 337 Perhaps brainstem circuits of children fitted with conventional binaural CIs simply “learn” to
 338 ignore unhelpful inputs which would be adaptive to them given that no useful information
 339 comes from the ITDs received. In contrast, precise ITD cues were essentially the only form
 340 of useful auditory input that our ND CI rats experienced, and they quickly learned to use
 341 them. Thus, our data raise the possibility that the mammalian auditory system may

342 develop ITD sensitivity in the absence of early sensory input, and that this sensitivity is
 343 then either refined or lost depending on how informative binaural input turns out to be. The
 344 inability of early deaf CI patients to use ITDs may thus be somewhat similar to conditions
 345 such as amblyopia or failures of stereoscopic depth vision development, pathologies which
 346 are caused more by unbalanced or inappropriate inputs than by a lack of sensory
 347 experience [54]. For the visual system, it has been shown that orientation selective
 348 neuronal responses exist at eye-opening and thus are established without visual input [55].
 349 If this hypothesis is correct, then it may be possible to “protect” ITD sensitivity in young
 350 binaural CI users by exposing them to regular periods of precise ITD information from the
 351 beginning of binaural stimulation. Whether CI patients are able to recover normal ITD
 352 sensitivity much later if rehabilitated with useful ITDs for prolonged periods, or whether
 353 their ability to process microsecond ITDs atrophies irreversibly, is unknown.

354 While the interpretations of our findings would lead us to argue that binaural CI processing
 355 strategies may need to change to make microsecond ITD information available to CI
 356 patients, one must nevertheless acknowledge the difficulty in changing established CI
 357 processing strategies. The continuous interleaved sampling (CIS) paradigm [56] from
 358 which most processor algorithms are derived, times the stimulus pulses so that only one
 359 electrode channel delivers a pulse at any one time. This is thought to minimize cross-
 360 channel interactions due to “current spread” which might compromise the already quite
 361 limited tonotopic place coding of CIs. Additionally, CI processors run at high pulse rates
 362 (≥ 900 Hz), which seems necessary to encode sufficient amplitude modulations (AM) for
 363 speech recognition [57]. However, ITD discrimination deteriorates when pulse rates
 364 exceeded a few hundred Hz in humans [58,59] and animals [41]. This is likely related to
 365 the observation that the ability of superior olivary neurons to encode envelope ITDs
 366 declines at envelope rates exceeding several hundred hertz [60]. Our own behavioral
 367 experiments described here were conducted with low pulse rates (50 Hz), and future work

368 will need to determine whether ITD discrimination performance would be as good at pulse
 369 rates close to 1 kHz. Thus, designers of novel binaural CI speech processors may face
 370 conflicting demands: They must invent devices which fire each of 20 or more electrode
 371 channels in turn, at rates that are both fast, so as to encode speech AM in fine detail, but
 372 also slow, so as not to overtax the brainstem's ITD extraction mechanisms, and they must
 373 make the timing of at least some of these pulses encode stimulus fine structure and ITDs.
 374 While difficult, this may not be impossible, and promising research is underway which
 375 either uses a mixture of different pulse rates for different electrode channels [61], or aims
 376 to "reset" the brain's ITD extraction mechanisms by introducing occasional "double pulses"
 377 into the stimulus [62]. A detailed discussion is beyond the scope of this paper. Our results
 378 underscore the need to pursue this work with urgency, as it might just save many
 379 thousands of deaf patients from a loss of ITD sensitivity that could be caused by sub-
 380 optimal binaural CI-stimulation.

382

383 **Material and Methods**

384 All procedures involving experimental animals reported here were approved by the
385 Department of Health of Hong Kong (#16-52 DH/HA&P/8/2/5) or Regierungspräsidium
386 Freiburg (#35-9185.81/G-17/124), as well as by the appropriate local ethical review
387 committee.

388 **Deafening**

389 Rats were neonatally deafened by daily intraperitoneal (i.p.) injections of 400 mg/kg
390 kanamycin from postnatal day 9 to 20 inclusively [17,63]. This is known to cause
391 widespread death of inner and outer hair cells [63-65] while keeping the number of spiral
392 ganglion cells comparable to that in untreated control rats [63,65]. Osako et al. [63] have
393 shown that rat pups treated with this method achieve hearing thresholds around 70 dB for
394 only a short period (~p14-16) and are severely to profoundly hearing impaired thereafter,
395 resulting in widespread disturbances in the histological development of their central
396 auditory pathways, including a nearly complete loss of tonotopic organisation [17,18,21].
397 We verified that this procedure provoked profound hearing loss (> 90 dB) by the loss of
398 Preyer's reflex [66], and the absence of auditory brainstem responses (ABRs) to
399 broadband click stimuli (Fig. S1b). ABRs were measured as described in [21]: under
400 ketamine (80mg/kg) and xylazine (12 mg/kg) anesthesia each ear was stimulated
401 separately through hollow ear bars with 0.5 ms broadband clicks with peak amplitudes up
402 to 130 dB SPL delivered at a rate of 43 Hz. ABRs were recorded by averaging scalp
403 potentials measured with subcutaneous needle electrodes between mastoids and the
404 vertex of the rat's head over 400 click presentations. While normal rats typically exhibited
405 click ABR thresholds near 30 dB SPL (Fig. S1a), deafened rats had very high click
406 thresholds of ≥ 130 dB SPL; Fig. S1b).

37

19

38

407 **CI implantation, stimulation and testing**

408 All surgical procedures, including CI implantation and craniotomy, were performed under
 409 anesthesia induced with i.p. injection of ketamine (80mg/kg) and xylazine (12 mg/kg). For
 410 maintenance of anesthesia during electrophysiological recordings, a pump delivered an
 411 i.p. infusion of 0.9% saline solution of ketamine (17.8 mg/kg/h) and xylazine (2.7 mg/kg/h)
 412 at a rate of 3.1 ml/h. During surgical and experimental procedures the body temperature
 413 was maintained at 38°C using a feedback-controlled heating pad (RWD Life Sciences,
 414 Shenzhen, China). Further detailed descriptions of our cochlear implantation methods can
 415 be found in previous studies [17,67-70]. In short, two to four rings of an eight channel
 416 electrode carrier (ST08.45, Peira, Beerse, Belgium) were fully inserted through a
 417 cochleostomy in medio-dorsal direction into the middle turn of both cochleae. Electrically
 418 evoked ABRs (EABRs) were measured for each ear individually to verify that both CIs
 419 were successfully implanted and operated at acceptably low electrical stimulation
 420 thresholds, usually around 100 μ A (Fig. S1c). EABR recording used isolated biphasic
 421 pulses (see below) with a 23 ms inter-pulse interval. EABR mean amplitudes were
 422 determined by averaging scalp potentials over 400 pulses for each stimulus amplitude. For
 423 electrophysiology experiments, EABRs were also measured immediately before and after
 424 IC recordings, and for the chronically implanted rats, EABRs were measured once a week
 425 under anesthesia to verify that the CIs functioned properly and stimulation thresholds were
 426 stable.

427 **Electric and acoustic stimuli**

428 The electrical stimuli used to examine the animals' EABRs, the physiological, and the
 429 behavioral ITD sensitivity were generated using a Tucker Davis Technology (TDT,
 430 Alachua, Florida, US) IZ2MH programmable constant current stimulator at a sample rate of
 431 48,828.125 Hz. The most apical ring of the CI electrode served as stimulating electrode,
 432 the next ring as ground electrode. All electrical intracochlear stimulation used biphasic

433 current pulses similar to those used in clinical devices (duty cycle: 61.44 μ s positive, 40.96
434 μ s at zero, 61.44 μ s negative), with peak amplitudes of up to 300 μ A, depending on
435 physiological thresholds or informally assessed behavioral comfort levels (rats will scratch
436 their ears frequently, startle or show other signs of discomfort if stimuli are too intense).
437 For behavioral training we stimulated all CI rats 6 dB above these thresholds. For details
438 on the calibration which confirmed that our CI setup delivered the desired ITDs and no
439 useable intensity cues, see supplementary Figure S2. Acoustic stimuli used to measure
440 behavioral ITD sensitivity in NH rats were single sample pulse clicks generated at a
441 sample rate of 48,000 Hz via a Raspberry Pi 3 computer connected to a USB sound card
442 (StarTech.com, Ontario Canada, part # ICUSBAUDIOMH), amplifier (Adafruit stereo 3.7W
443 class D audio amplifier, New York City, US, part # 987) and miniature high fidelity
444 headphone drivers (GQ-30783-000, Knowles, Itasca, Illinois, US) which were mounted on
445 hollow tubes. Stimuli were delivered at sound intensities of $\approx$ 80 dB SPL. For details on the
446 calibration of the acoustic setup delivered the desired ITDs and no useable intensity cues,
447 see supplementary Figure S3 and [30].

448 To produce electric or acoustic stimuli of varying ITDs spanning the rat's physiological
449 range of $\pm$ 130 μ s [34], stimulus pulses of identical shape and amplitude were presented to
450 each ear, with the pulses in one ear delayed by an integer number of samples. Given the
451 sample rates of the devices used, ITDs could thus be varied in steps of 20.48 μ s for the
452 electrical, and 20.83 μ s for the acoustic stimuli. The physiological experiments described
453 here used single pulse stimuli presented in isolation, while the behavior experiments used
454 200 ms long 50 Hz pulse trains.

455 **Animal psychoacoustic testing**

456 We trained our rats on 2AFC sound lateralization tasks using methods similar to those
457 described in [30,33,47,48]. The behavioral animals were put on a schedule with six days of
458 testing, during which the rats obtained their drinking water as a positive reinforcer, followed

459 by one day off, with *ad-lib* water. The evening before the next behavioral testing period,
460 drinking water bottles were removed. During testing periods, the rats were given two
461 sessions per day. Each session lasted 25-30 min, which typically took 150-200 trials
462 during which ≈ 10 ml of water were consumed.

463 One of the walls of each behavior cage was fitted with three brass water spouts, mounted
464 ≈ 6 -7 cm from the floor and separated by ≈ 7.5 cm (Figs. S2a-b; S3a-c). We used one
465 center “start spout” for initiating trials and one left and one right “response spout” for
466 indicating whether the stimulus presented during the trial was perceived as lateralized to
467 that side. Contact with the spouts was detected by capacitive touch detectors (Adafruit
468 industries, New York City, US, part # 1362). Initiating a trial at the center spout triggered
469 the release of a single drop of water through a solenoid valve. Correct lateralization
470 triggered three drops of water as positive reinforcement. Incorrect responses triggered no
471 water delivery but caused a 5-15 s timeout during which no new trial could be initiated.
472 Timeouts were also marked by a negative feedback sound for the NH rats. Given that CI
473 stimulation can be experienced as strenuous and tiring by human patients [71], the ND CI
474 rats received a flashing LED as an alternative negative feedback stimulus. After each
475 correct trial a new ITD was chosen randomly from a set spanning ± 160 μ s in 25 μ s steps,
476 but after each incorrect trial the last stimulus was repeated in a “correction trial”. Correction
477 trials prevent animals from developing idiosyncratic biases favoring one side [47,72], but
478 since they could be answered correctly without attention to the stimuli by a simple “if you
479 just made a mistake, change side” strategy, they are excluded from the final psychometric
480 performance analysis.

481 The NH rats received their acoustic stimuli through stainless steel hollow ear tubes placed
482 such that, when the animal was engaging the start spout, the tips of the tubes were
483 located right next to each ear of the animal to allow near-field stimulation (Fig. S3a). The
484 pulses resonated in the tubes, producing pulse-resonant sounds, resembling single-

485 formant artificial vowels with a fundamental frequency corresponding to the click rate. Note
 486 that this mode of sound delivery is thus very much like that produced by “open”
 487 headphones, such as those commonly used in previous studies on binaural hearing in
 488 humans and animals, e.g. [33,73]. We used a 3D printed “rat acoustical manikin” with
 489 miniature microphones in the ear canals (Fig. S3c). It produced a channel separation
 490 between ears of ≥ 20 dB at the lowest, fundamental frequency and around 40 dB overall.
 491 Further details on the acoustic setup and procedure are described in [30]. The ND CI rats
 492 received their auditory stimulation via bilateral CIs described above, connected to the TDT
 493 IZ2MH stimulator via a custom-made, head mounted connector and commutator, as
 494 described in [74].

495 **Multi-unit recording from IC**

496 Anesthetized rats were head fixed in a stereotactic frame (RWD Life Sciences),
 497 craniotomies were performed bilaterally just anterior to lambda. The animal and
 498 stereotactic frame were positioned in a sound attenuating chamber, and a single-shaft, 32-
 499 channel silicon electrode array (ATLAS Neuroengineering, E32-50-S1-L6) was inserted
 500 stereotactically into the left or right IC through the overlying occipital cortex using a
 501 micromanipulator (RWD Life Sciences). Extracellular signals were sampled at a rate of
 502 24.414 kHz with a TDT RZ2 with a NeuroDigitizer headstage and BrainWare software. Our
 503 recordings typically exhibited short response latencies (≈ 3 -5 ms), which suggests that
 504 they may come predominantly from the central region of IC. Responses from non-
 505 lemniscal sub-nuclei of IC have been reported to have longer response latencies (≈ 20 ms;
 506 [75]).

507 At each electrode site, we first measured neural rate/level functions, varying stimulation
 508 currents in each ear to verify that the recording sites contained neurons responsive to
 509 cochlear stimulation, and to estimate threshold stimulus amplitudes. Thresholds rarely
 510 varied substantially from one recording site to another in any one animal. We then

511 measured ITD tuning curves by presenting single pulse binaural stimuli with equal
512 amplitude in each ear, ≈ 10 dB above the contralateral ear threshold, in pseudo-random
513 order. ITDs varied from 163.84 μ s (8 samples) contralateral ear leading to 163.84 μ s
514 ipsilateral ear leading in 20.48 μ s (one sample) steps. Each ITD value was presented 30
515 times at each recording site. The inter-stimulus interval was 500 ms. At the end of the
516 recording session the animals were overdosed with pentobarbitone.

517 **Data analysis**

518 To quantify the extracellular multi-unit responses we calculated the average activity for
519 each stimulus over a response period (3-80 ms post stimulus onset) as well as baseline
520 activity (300-500 ms after stimulus onset) at each electrode position. The first 2.5 ms post
521 stimulus onset were dominated by electrical stimulus artifacts and were discarded. For
522 display purposes of the raster plots in Figure 2 we extracted multi-unit spikes by simple
523 threshold crossings of the bandpassed (300 Hz - 6 kHz) electrode signal with a threshold
524 set at four standard deviation of the signal amplitude. To quantify responses for tuning
525 curves, instead of counting spikes by threshold crossings we instead computed an analog
526 measure of multi-unit activity (AMUA) amplitudes as described in [76]. The mean AMUA
527 amplitude during the response and baseline periods was computed by bandpassing (300
528 Hz - 6 kHz), rectifying (taking the absolute value) and lowpassing (6 kHz) the electrode
529 signal. This AMUA value thus measures the mean signal amplitude in the frequency range
530 in which spikes have energy. As illustrated in Figure 1 of [76], this gives a less noisy
531 measure of multi-unit neural activity than counting spikes by conventional threshold
532 crossing measures because the later are subject to errors due to spike collisions, noise
533 events, or small spikes sometimes reach threshold and sometimes not. The tuning curves
534 shown in the panels of Figure 2 were measured using this AMUA measure. It is readily
535 apparent that changes in the AMUA amplitudes track changes in spike density.

536 **Signal-to-noise ratio (SNR) calculation**

537 SNR values are a measure of the strength of tuning of neural responses to ITD which we
 538 adopted from [24] to facilitate quantitative comparisons. The SNR is defined in [24] as the
 539 proportion of trial-to-trial variance in response amplitude explained by changes in ITD. The
 540 SNR is calculated by computing a one-way ANOVA of responses grouped by ITD value
 541 and dividing the total sum of squares by the group sum of squares. This yields values
 542 between 0 (no effect of ITD) and 1 (response amplitudes completely determined by ITD).
 543 P-values were also computed from the one-way ANOVA and $p < 0.01$ served as a criterion
 544 to determine whether the ITD tuning of a given multi-unit was deemed statistically
 545 significant. The number of responses for each ITD value was 30, yielding with a degree of
 546 freedom (df) for the ANOVA of 29.

547 **Psychometric curve fitting**

548 In order to derive summary statistics that could serve as measures of ITD sensitivity from
 549 the thousands of trials performed by each animal we fitted psychometric models to the
 550 observed data. It is common practice in human psychophysics to fit performance data with
 551 cumulative Gaussian functions [77,78]. This practice is well motivated in signal detection
 552 theory, which assumes that the perceptual decisions made by the experimental subject are
 553 informed by sensory signals which are subject to multiple, additive, and hence
 554 approximately normally distributed sources of noise. When the sensory signals are very
 555 large relative to the inherent noise then the task is easy and the subject will make the
 556 appropriate choice with near certainty. For binaural cues closer to threshold, the probability
 557 of choosing “right” (p_R) can be modeled by the function

$$558 \quad p_R = \Phi(ITD \cdot \alpha) \quad (2)$$

559 where, Φ is the cumulative normal distribution, ITD denotes the interaural time difference
 560 (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 $(1-\gamma)$. Furthermore, animals may exhibit two types of bias: an “ear bias” and a “spout bias”. An “ear-bias” exists if the animal hears the midline (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:

$$p_R = \Phi(ITD \cdot \alpha + \beta) \cdot (1 - \gamma) + \frac{\gamma}{2} + \delta \quad (3)$$

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)

586 $slope = \varphi(0) \cdot \alpha \cdot (1 - \gamma) \quad (4)$

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

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

591 **Acknowledgements**

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

602 **Author Contributions**

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

606 **Declaration of Interests**

607 The authors declare no competing interests.

609

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 sub-panel 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 amplitude (y-axis) and a 20.5 μs interval between the positive and the negative phase. **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 [79]), 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. Note that the setup is identical to that described in Li et al. [30] and this supplementary figure is similar to Figure 1 of that paper. **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

654 (RMS) power of the signals in panel (d). Data were recorded from 10 presentations of
 655 each ITD stimulus, and each dot represents one trial (a random amount of scatter along
 656 the x-axis was added for ease of visualization). Note that the residual ILDs are much
 657 smaller than the reported behavioral thresholds for ferrets (~ 1.3 dB, dotted line, [33]) or
 658 rats (~3 dB [37]). We can therefore be certain that sensitivity to ILDs cannot account for
 659 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. Res.* **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. Neurotol.* **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. Litovsky, R. Y., Goupell, M. J., Godar, S., Grieco-Calub, T., Jones, G. L., et al Studies on bilateral cochlear implants at the University of Wisconsin's Binaural Hearing and Speech Laboratory. *J. Am. Acad. Audiol.* **23**, 476-494 (2012)
12. Laback, B., Egger, K. & Majdak, P. Perception and coding of interaural time differences with bilateral cochlear implants. *Hear. Res.* **322**, 138-150 (2015)
13. 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)
14. Gordon, K. A., Deighton, M. R., Abbasalipour, P. & Papsin, B. C. Perception of binaural cues develops in children who are deaf through bilateral cochlear implantation. *PLoS One* **9**, e114841 (2014)
15. 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)
16. Yusuf, P. A., Hubka, P., Tillein, J. & Kral, A. Induced cortical responses require developmental sensory experience. *Brain* **140**, 3153-3165 (2017)
17. Rosskothén-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)

- 698 18. Rauch, A.-K., Rosskoth-Kuhl, N. & Illing, R.-B. Counter-regulation of the AP-1 monomers
699 pATF2 and Fos: Molecular readjustment of brainstem neurons in hearing and deaf adult rats after
700 electrical intracochlear stimulation. *Neuroscience* **313**, 184-198 (2016)
- 701 19. Illing, R.-B. & Rosskoth-Kuhl, N. *The cochlear implant in action: molecular changes*
702 *induced in the rat central auditory system*. (INTECH Open Access Publisher, Freiburg, 2012)
- 703 20. Jakob, T. F., Dörmann, U. & Illing, R.-B. The pattern of Fos expression in the rat auditory
704 brainstem changes with the temporal structure of binaural electrical intracochlear stimulation. *Exp.*
705 *Neurol.* **266**, 55-67 (2015)
- 706 21. Rosskoth-Kuhl, N., Hildebrandt, H., Birkenhäger, R. & Illing, R.-B. Astrocyte Hypertrophy
707 and Microglia Activation in the Rat Auditory Midbrain Is Induced by Electrical Intracochlear
708 Stimulation. *Front. Cell. Neurosci.* **12**, (2018)
- 709 22. Seidl, A. H. & Grothe, B. Development of sound localization mechanisms in the mongolian
710 gerbil is shaped by early acoustic experience. *J. Neurophysiol.* **94**, 1028-1036 (2005)
- 711 23. Beiderbeck, B., Myoga, M. H., Müller, N. I. C., Callan, A. R., Friauf, E., et al Precisely timed
712 inhibition facilitates action potential firing for spatial coding in the auditory brainstem. *Nat.*
713 *Commun.* **9**, (2018)
- 714 24. Hancock, K. E., Noel, V., Ryugo, D. K. & Delgutte, B. Neural coding of interaural time
715 differences with bilateral cochlear implants: effects of congenital deafness. *J. Neurosci.* **30**, 14068-
716 14079 (2010)
- 717 25. Hancock, K. E., Chung, Y. & Delgutte, B. Neural ITD coding with bilateral cochlear implants:
718 effect of binaurally coherent jitter. *J. Neurophysiol.* **108**, 714-728 (2012)
- 719 26. Hancock, K. E., Chung, Y. & Delgutte, B. Congenital and prolonged adult-onset deafness cause
720 distinct degradations in neural ITD coding with bilateral cochlear implants. *JARO* **14**, 393-411
721 (2013)
- 722 27. Chung, Y., Buechel, B. D., Sunwoo, W., Wagner, J. D. & Delgutte, B. Neural ITD Sensitivity
723 and Temporal Coding with Cochlear Implants in an Animal Model of Early-Onset Deafness..
724 *Journal of the Association for Research in Otolaryngology : JARO* **20**, 37-56 (2019)
- 725 28. Tillein, J., Hubka, P., Syed, E., Hartmann, R., Engel, A., et al Cortical representation of
726 interaural time difference in congenital deafness. *Cereb. Cortex* **20**, 492-506 (2009)
- 727 29. Tillein, J., Hubka, P. & Kral, A. Monaural Congenital Deafness Affects Aural Dominance and
728 Degrades Binaural Processing.. *Cereb. Cortex* **26**, 1762-1777 (2016)
- 729 30. Li, K., Chan, C. H. K., Rajendran, V. G., Meng, Q., Rosskoth-Kuhl, N., et al Microsecond
730 sensitivity to envelope interaural time differences in rats.. *The Journal of the Acoustical Society of*
731 *America* **145**, EL341 (2019)
- 732 31. Litovsky, R. Y., Jones, G. L., Agrawal, S. & van Hoesel, R. Effect of age at onset of deafness
733 on binaural sensitivity in electric hearing in humans. *J. Acoust. Soc. Am.* **127**, 400-414 (2010)
- 734 32. Klumpp, R. & Eady, H. Some measurements of interaural time difference thresholds. *J. Acoust.*
735 *Soc. Am.* **28**, 859-860 (1956)
- 736 33. Keating, P., Nodal, F. R., Gananandan, K., Schulz, A. L. & King, A. J. Behavioral sensitivity to

- 737 broadband binaural localization cues in the ferret. *JARO* **14**, 561-572 (2013)
- 738 34. Koka, K., Read, H. L. & Tollin, D. J. The acoustical cues to sound location in the rat:
739 measurements of directional transfer functions. *J. Acoust. Soc. Am.* **123**, 4297-4309 (2008)
- 740 35. Smith, Z. M. & Delgutte, B. Sensitivity to interaural time differences in the inferior colliculus
741 with bilateral cochlear implants. *J. Neurosci.* **27**, 6740-6750 (2007)
- 742 36. Grothe, B. & Klump, G. M. Temporal processing in sensory systems. *Curr. Opin. Neurobiol.*
743 **10**, 467-473 (2000)
- 744 37. Wesolek, C. M., Koay, G., Heffner, R. S. & Heffner, H. E. Laboratory rats (*Rattus norvegicus*)
745 do not use binaural phase differences to localize sound. *Hear. Res.* **265**, 54-62 (2010)
- 746 38. Joris, P. X. & Yin, T. C. Envelope coding in the lateral superior olive. I. Sensitivity to interaural
747 time differences. *J. Neurophysiol.* **73**, 1043-1062 (1995)
- 748 39. Bernstein, L. R. Auditory processing of interaural timing information: new insights. *J.*
749 *Neurosci. Res.* **66**, 1035-1046 (2001)
- 750 40. Kan, A., Jones, H. G. & Litovsky, R. Y. Lateralization of interaural timing differences with
751 multi-electrode stimulation in bilateral cochlear-implant users. *J. Acoust. Soc. Am.* **140**, EL392
752 (2016)
- 753 41. Chung, Y., Hancock, K. E. & Delgutte, B. Neural Coding of Interaural Time Differences with
754 Bilateral Cochlear Implants in Unanesthetized Rabbits. *J. Neurosci.* **36**, 5520-5531 (2016)
- 755 42. Vollmer, M. Neural processing of acoustic and electric interaural time differences in normal-
756 hearing gerbils. *J. Neurosci.* **38**, 6949-6966 (2018)
- 757 43. Zheng, Y., Godar, S. P. & Litovsky, R. Y. Development of Sound Localization Strategies in
758 Children with Bilateral Cochlear Implants.. *PLoS One* **10**, e0135790 (2015)
- 759 44. Brunso-Bechtold, J. K., Henkel, C. K. & Linville, C. Ultrastructural development of the medial
760 superior olive (MSO) in the ferret. *J. Comp. Neurol.* **324**, 539-556 (1992)
- 761 45. Hoffpauir, B. K., Grimes, J. L., Mathers, P. H. & Spirou, G. A. Synaptogenesis of the calyx of
762 Held: rapid onset of function and one-to-one morphological innervation. *J. Neurosci.* **26**, 5511-5523
763 (2006)
- 764 46. Kapfer, C., Seidl, A. H., Schweizer, H. & Grothe, B. Experience-dependent refinement of
765 inhibitory inputs to auditory coincidence-detector neurons.. *Nat. Neurosci.* **5**, 247-253 (2002)
- 766 47. Walker, K. M., Schnupp, J. W., Hart-Schnupp, S. M., King, A. J. & Bizley, J. K. Pitch
767 discrimination by ferrets for simple and complex sounds. *J. Acoust. Soc. Am.* **126**, 1321-1335
768 (2009)
- 769 48. Bizley, J. K., Walker, K. M. M., Nodal, F. R., King, A. J. & Schnupp, J. W. H. Auditory cortex
770 represents both pitch judgments and the corresponding acoustic cues. *Curr. Biol.* **23**, 620-625
771 (2013)
- 772 49. Tirko, N. N. & Ryugo, D. K. Synaptic plasticity in the medial superior olive of hearing, deaf,
773 and cochlear-implanted cats.. *The Journal of comparative neurology* **520**, 2202-2217 (2012)
- 774 50. Pecka, M., Brand, A., Behrend, O. & Grothe, B. Interaural time difference processing in the
775 mammalian medial superior olive: the role of glycinergic inhibition.. *The Journal of neuroscience* :
69 35

- 776 *the official journal of the Society for Neuroscience* **28**, 6914-6925 (2008)
- 777 51. Keating, P., Dahmen, J. C. & King, A. J. Context-specific reweighting of auditory spatial cues
778 following altered experience during development. *Current biology : CB* **23**, 1291-1299 (2013)
- 779 52. Keating, P., Dahmen, J. C. & King, A. J. Complementary adaptive processes contribute to the
780 developmental plasticity of spatial hearing. *Nat. Neurosci.* **18**, 185-187 (2015)
- 781 53. Kumpik, D. P., Campbell, C., Schnupp, J. W. H. & King, A. J. Re-weighting of Sound
782 Localization Cues by Audiovisual Training.. *Front. Neurosci.* **13**, 1164 (2019)
- 783 54. Levi, D. M., Knill, D. C. & Bavelier, D. Stereopsis and amblyopia: a mini-review. *Vision Res.*
784 **114**, 17-30 (2015)
- 785 55. Ko, H., Cossell, L., Baragli, C., Antolik, J., Clopath, C., et al The emergence of functional
786 microcircuits in visual cortex. *Nature* **496**, 96-100 (2013)
- 787 56. Wilson, B. S., Finley, C. C., Lawson, D. T., Wolford, R. D., Eddington, D. K., et al Better
788 speech recognition with cochlear implants. *Nature* **352**, 236-238 (1991)
- 789 57. Loizou, P. C., Poroy, O. & Dorman, M. The effect of parametric variations of cochlear implant
790 processors on speech understanding. *J. Acoust. Soc. Am.* **108**, 790-802 (2000)
- 791 58. van Hoesel, R. J. M. Sensitivity to binaural timing in bilateral cochlear implant users. *J. Acoust.*
792 *Soc. Am.* **121**, 2192-2206 (2007)
- 793 59. Laback, B., Majdak, P. & Baumgartner, W.-D. Lateralization discrimination of interaural time
794 delays in four-pulse sequences in electric and acoustic hearing. *J. Acoust. Soc. Am.* **121**, 2182-2191
795 (2007)
- 796 60. Joris, P. X. & Yin, T. C. Envelope coding in the lateral superior olive. III. Comparison with
797 afferent pathways. *J. Neurophysiol.* **79**, 253-269 (1998)
- 798 61. Thakkar, T., Kan, A., Jones, H. G. & Litovsky, R. Y. Mixed stimulation rates to improve
799 sensitivity of interaural timing differences in bilateral cochlear implant listeners. *J. Acoust. Soc.*
800 *Am.* **143**, 1428 (2018)
- 801 62. Srinivasan, S., Laback, B., Majdak, P. & Delgutte, B. Introducing Short Interpulse Intervals in
802 High-Rate Pulse Trains Enhances Binaural Timing Sensitivity in Electric Hearing. *JARO* **19**, 301-
803 315 (2018)
- 804 63. Osako, S., Tokimoto, T. & Matsuura, S. Effects of kanamycin on the auditory evoked responses
805 during postnatal development of the hearing of the rat. *Acta Otolaryngol. (Stockh.)* **88**, 359-368
806 (1979)
- 807 64. Matsuda, K., Ueda, Y., Doi, T., Tono, T., Haruta, A., et al Increase in glutamate-aspartate
808 transporter (GLAST) mRNA during kanamycin-induced cochlear insult in rats. *Hear. Res.* **133**, 10-
809 16 (1999)
- 810 65. Argence, M., Vassias, I., Kerhuel, L., Vidal, P.-P. & de Waele, C. Stimulation by cochlear
811 implant in unilaterally deaf rats reverses the decrease of inhibitory transmission in the inferior
812 colliculus. *Eur. J. Neurosci.* **28**, 1589-1602 (2008)
- 813 66. Jero, J., Coling, D. E. & Lal, A. K. The Use of Preyer's Reflex in Evaluation of Hearing in
814 Mice. *Acta Otolaryngol. (Stockh.)* **121**, 585-589 (2001)

815 67. Rosskothén, N., Hirschmüller-Ohmes, I. & Illing, R.-B. AP-1 activity rises by stimulation-
816 dependent c-Fos expression in auditory neurons. *Neuroreport* **19**, 1091-1093 (2008)

817 68. Rosskothén-Kuhl, N. & Illing, R.-B. Nonlinear development of the populations of neurons
818 expressing c-Fos under sustained electrical intracochlear stimulation in the rat auditory brainstem.
819 *Brain Res.* **1347**, 33-41 (2010)

820 69. Rosskothén-Kuhl, N.; Hildebrandt, H.; Birkenhaefer, R. and Illing, R.-B. Hearing Experience
821 Changes Neuron-Glia Interaction in the Midbrain of Adult Rats, (2014).

822 70. Rosskothén-Kuhl, N. & Illing, R. The utilization of brain plasticity by cochlear implants:
823 Molecular and cellular changes due to electrical intracochlear stimulation. *HNO* **63**, 94-103 (2015)

824 71. Perreau, A. E., Wu, Y.-H., Tatge, B., Irwin, D. & Corts, D. Listening Effort Measured in Adults
825 with Normal Hearing and Cochlear Implants.. *J. Am. Acad. Audiol.* **28**, 685-697 (2017)

826 72. Keating, P., Nodal, F. R. & King, A. J. Behavioural sensitivity to binaural spatial cues in ferrets:
827 evidence for plasticity in the duplex theory of sound localization. *Eur. J. Neurosci.* **39**, 197-206
828 (2014)

829 73. Wightman, F. L. & Kistler, D. J. The dominant role of low-frequency interaural time differences
830 in sound localization.. *J. Acoust. Soc. Am.* **91**, 1648-1661 (1992)

831 74. Rosskothén-Kuhl, N. & Illing, R.-B. Gap43 transcription modulation in the adult brain depends
832 on sensory activity and synaptic cooperation. *PLoS One* **9**, e92624 (2014)

833 75. Syka, J., Popelár, J., Kvasnák, E. & Astl, J. Response properties of neurons in the central
834 nucleus and external and dorsal cortices of the inferior colliculus in guinea pig. *Exp. Brain Res.* **133**,
835 254-266 (2000)

836 76. Schnupp, J. W. H., Garcia-Lazaro, J. A. & Lesica, N. A. Periodotopy in the gerbil inferior
837 colliculus: local clustering rather than a gradient map. *Front. Neural Circuits* **9**, 37 (2015)

838 77. Wickens, T. D. *Elementary signal detection theory*. (Oxford University Press, USA, , 2002)

839 78. Schnupp, J. W., Dawe, K. L. & Pollack, G. L. The detection of multisensory stimuli in an
840 orthogonal sensory space. *Exp. Brain Res.* **162**, 181-190 (2005)

841 79. van Hoesel, R. J. & Tyler, R. S. Speech perception, localization, and lateralization with bilateral
842 cochlear implants. *The Journal of the Acoustical Society of America* **113**, 1617-1630 (2003)