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Temporal Spatial Perception under Electric Hearing
人工耳蝸電刺激下顳的空間感知

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Abstract

Spatial hearing in cochlear implant (CI) patients remains a major challenge with many early deaf users reported to have no measurable sensitivity to interaural time differences (ITDs). This thesis aims to investigate influencing factors in ITD sensitivity under bilateral electric hearing.

Deprivation of binaural experience during an early critical period is often hypothesized to be one of the major causes of temporal spatial perceptual shortcomings in CI users. Additional influencing factors include: 1) carrier rates, where typical clinical speech processor rates are thought to be too fast to encode ITDs; 2) the prevalence of onset dominance for these ITD cues, which is known to be a prominent feature under normal hearing circumstances but has not bee elucidated in electric hearing and 3) the ability to make use of ITDs carried on the extracted sound amplitude envelopes.

In order to address these ITD influencing factors in the work presented in this thesis I have investigated the following questions: does ITD sensitivity have a critical period?, what are the effects of hearing experience on ITD sensitivity?, does ITD sensitivity exist at clinically relevant pulse rates under appropriate stimulation?, does ITD sensitivity show onset dominance in the absence of early hearing experience? and is ITD sensitivity more reliably carried on the fixed rate pulses or the modulating amplitude?

These studies were all conducted in a newly developed animal model together with a novel behavioural setup and design in order to assess awake, behaving ITD sensitivity under bilateral CI. This enabled the control of several confounding variables in particular: aetiology of deafening, age of onset, age of implantation and therefore duration of auditory deprivation together with stimulation strategy not limited to clinical speech processor technology.

My research conducted in pursuance of this thesis has demonstrated that, even in the absence of early hearing experience, and while using high carrier rates, CI users are capable of developing good ITD sensitivity when stimulated appropriately. These results are of clinical importance as they prove that uncontrollable biological factors, such as age of deafness and length of period of deprivation, are most likely not the limiting factors for developing usable ITD sensitivity under CI stimulation which they have hitherto been suspected to be. Rather, better control of the stimulation strategy to improve pulse time delivery is what is needed.

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Chapter 1: Introduction

Cochlear implants (CIs) have been used to restore hearing to patients for almost half a century. As the first human machine interface it was the innovation of its time and is largely successful in enabling deaf users to hear in quiet environments, significantly improving their quality of life. However, these devices are far from perfect and much remains to be understood of the effects of this altered input to the auditory system and the altered system itself.

CIs consist of an electrode within the cochlea to stimulate the auditory nerve, a radio receiver on the skull to receive electric signals from a speech processor which translates acoustic input captured by a microphone into an electric stimulation strategy. Intra-cochlear electrodes can consist of between 8 – 24 contact channels. Several speech processor algorithms exist, although CIS (continuous interleaved sampling), or similar algorithms derived from it, are the most common in the industry. The starting point for most strategies involves sound wave envelope extraction and subsequent band pass filtering. The further processing and delivery of these electric signals then depends on the strategy. CIS involves mapping the electrodes to a stimulation sequence so that there is a temporal offset between the firing of adjacent electrodes, thus limiting the overlap in electric fields and significantly improving speech recognition thresholds (Wilson et al. 1991).

That the vast majority of CI strategies discard the “fine structure” of the acoustic input and only encode the envelopes in different frequency bands during the initial stage of processing which makes any temporal processing difficult, if not impossible in many cases, for CI users. Binaural temporal precision is further impaired by the fact that CIs were originally designed for monaural use, and thus have no integration between inputs to the two ears in bilateral CI users. The onset of the continuous pulses at a fixed carrier rate is determined by the internal clock-time of the individual processor, which can have a jitter resulting in the pulses being asynchronous between ears. Thus not only can temporal precision not be delivered with fine structure, but the timing of the fixed rate pulses, what might be called the “fine structure of CI stimulus pulse trains”, is also randomly out of sync between ears.

One important cue that is thus greatly disturbed is the interaural time difference (ITD), which is the difference in arrival times of the sound between the two ears. This, together with interaural level differences (ILDs), the difference in loudness between the two ears, are the major localisation cues for humans and most mammals in the horizontal plane, and both require intact binaural processing. Unlike ITDs, ILDs are, at least to an appreciable degree, usable by CI listeners, although in many cases performance is still below normal hearing peers (Litovsky et al. 2010). ITD performance on the other hand is dismal, with many CI users failing to obtain any threshold and many more having thresholds orders of magnitude higher than what an acoustic listener would be able to achieve.

Beyond the technology limitations of the CI itself there are a number of other reasons thought to account for CI users inability, for the most part, to use ITDs. Cost limitations and healthcare policies across different countries have resulted in many deaf patients having only one CI, monoaural stimulation, for extended periods of time. Gordon et al. (2014) found that children who received their second implant more than 18 months after the first were found to have a midline shift in auditory perceptual space towards the first implant. Additional asymmetries may exist in spiral ganglion survival, depending on the aetiology of deafness, or surgical implantation technique both of which could potentially disrupt delivery of appropriate ITD cues.

Beyond the issues of symmetry and synchronisation, there are additional elements that are though to play a role in ITD perception. ITD is primarily considered a low frequency cue, while ILDs tend to take over localisation for sounds > 1500 Hz (Zwislocki and Feldman 1956) although it is worth mentioning that this dichotomy, or 'duplex theory', is somewhat overly simplistic as listeners can have good sensitivity to ITDs conveyed in modulated envelopes at high frequencies (Henning 1974; McFadden and Pasanen 1976a). In fact Bernstein and Trahiotis (2002) demonstrated that high frequency channels could still support good ITD sensitivity if they are 'transposed' in such away that the envelopes carry sufficient ITD information whereby half-rectification and low pass filtering were found to capture the loss of neural synchrony to fine structure with increasing central frequency(Bernstein and Trahiotis 1996; Bernstein et al. 1999). Never the less the apical region of the cochlea, the low frequency region of the basement membrane, is still thought to be of particular importance. However, the apical region is the furthest from the round window which is the most common entry point for the CI electrode array insertion and even the longest electrode arrays frequently are unable to adequately reach this region without increasing the risk of surgical trauma and potential scarring which can affect contact points and signal transduction to the spinal ganglion neurons as well as affecting their survival. However, Ihlefeld et al. (2014) found no difference in ITD sensitivity between basal, apical or basal and apical stimulation configurations and place of stimulation was not found to affect ITD sensitivity in a systematic way (Ihlefeld et al. 2015) In addition Kan et al. (2015) show that, not only is apical electrode stimulation no better than basilar electrode stimulation in terms of ITD discrimination, but in fact multiple electrode stimulation along the full length of the array proved to be the best in terms of ITD performance. This invites the conclusion that ITD perception does not rely on apical stimulation. However, whether this stimulation pattern allows for greater activation of the surviving spinal ganglion neurons in general, better synchronised neural activity or greater frequency spread is not known.

Additional factors seem to include age of onset of deafness. Post-lingual CI users' ITD performance thresholds tend to be significantly better in ITD tasks compared to pre-lingually deafened CI users (Litovsky et al. 2012). Due to the development of the skull CIs can not be implanted much before 2 years of age at which point, even if bilateral CIs are implanted simultaneously, has resulted in significant auditory deprivation. There is a widely held belief that this period of deprivation may already be too long for these children to ever gain ITD sensitivity and at least the clinical psychometric studies would agree with this argument. This suggests that there is a critical period

during development for ITD sensitivity which if missed or distorted in some way would prevent ITD perception ever being possible to a physiologically relevant degree. We therefore investigated whether ITD sensitivity does in fact have a critical period by eliminating auditory input during the developmental period following which auditory input was restored with bilateral CI stimulation and ITD sensitivity was tested using a two-alternate forced choice task in a newly developed animal model and behavioural setup. Our research suggests that this critical period does not exist and in fact ITDs sensitivity is comparable both behaviourally and physiologically to normal hearing peers (see Chapter 2 and 3).

That ITDs are considered a low frequency cue does not only relate to the location of stimulation on the basilar membrane, which does not seem to be relevant at least for CI stimulation, but it also relates to the frequency of the sound. In terms of acoustic signals, the word frequency can be ambiguous, referring to pure tones or central narrow band frequencies or components of a Fourier spectrum, but also to the rate of click trains or other periodic signals. Acoustic click trains are to some extent similar to the fixed rate pulses delivered to CIs, in that they deliver periodic stimulus pulses to fairly wide regions of the basilar membrane. CI pulse trains usually have pulse ("carrier") rates between 900 - 1500 Hz in clinical processors (Wilson 2004). The carrier rates for CIs are required to be high enough to adequately sample the sound envelopes picked up by the microphone, most importantly for speech. However, these rates much above 100 Hz are thought to be too high for ITD perception in most CI users, even post-linguilly deafened. Clinical psychoanalysis studies have shown that, for constant amplitude pulse trains, without envelope modulation, even with the use of bilateral synchronised research interfaces, CI users ITD performance peaks at 50 – 100 Hz and dramatically deteriorates beyond 300-600 Hz, or pulses per second (pps) (van Hoesel 2007; Laback et al. 2007). Thus CI manufacturers appear to be facing a paradox. On the one hand carrier rates need to adequately sample speech envelopes at higher rates while on the other carrier rates need to be slow enough to convey ITDs. We therefore asked how pulse rates affect the good ITD sensitivity found in our animal behavioural model with bilateral CIs in the absence of early hearing experience. Our results show that ITD perception is possible even at clinically relevant pulse rates when provided with bilaterally synchronised ITDs from the moment of implantation (see Chapter 3).

With the standing technical limitations of clinical speech processors one alternative to deliver ITDs at a slow rate, while still having adequate envelope sampling, is using amplitude modulation. At higher frequencies (>1.5 kHz) normal hearing listeners are still highly sensitive to ITDs when a slow modulated envelope is present (Henning 1974; McFadden and Pasanen 1976b). And in fact under CI stimulation ITD sensitivity up to 5000 pps can be obtained under amplitude modulation (Smith and Delgutte 2008). This has lead to the theory that, while fines structure ITDs are undeliverable, ITDs carried in the amplitude envelopes could be. However, several studies have shown that in fact sensitivity to the envelope requires the envelope to have a very sharp onset (Laback et al. 2004; van Hoesel et al. 2009; Laback et al. 2011; Noel and Eddington 2013). It follows that ITD perception

has an onset weighting which implies that the precedence effect plays a role in ITD sensitivity (Litovsky et al. 1999).

Brown and Stecker (2010) demonstrate the presence of onset dominance in ITD sensitivity in normal hearing listeners which appears to become more striking with increasing pulse rates. van Hoesel (2008) further shows that this appears to be present at least in post-linguilly deafened CI listeners at carrier rates above 100 pps. However, a comparative study with normal hearing peers as well as the effects of early onset deafness had yet to be evaluated. The importance of onset cues and the precedence effect in our daily environment allows us to ignore cues that are less salient. This is of particular importance in complex sound environments with competing noises. We thus investigated whether in our early onset bilateral CI animal model we see onset ITDs. That ITDs show onset dominance does not appear to be experience dependent but this is not the case for the strength of this response and the effects of increasing pulse rate (see Chapter 4).

The importance of this onset response lead Laback and Majdak (2008) as well as Goupell et al. (2009) to attribute improved ITD performance under jittered pulse timing to a restarting phenomenon. However, as discussed in van Hoesel (2008) and Brown and Stecker (2010) this would result in jittered pulse trains showing equal weigting across pulses, in other words no onset dominance. However, reduced, not eliminated, onset weighting was only found for 400 Hz click trains while at 800 Hz onset dominance prevailed at least for normal hearing listeners (Brown and Stecker 2010). Thus these authors hypothesised that the improved ITD performance under jittered pulse trains was in fact due to the second order envelope modulation that these faster and slower pulses would introduce which again alludes to the importance of ITDs carried on the envelopes. However, envelope modulation does not seem to be all that effective in CI users even with synchronised input from a research interface and the performance still deteriorates with increasing pulse rate and increasing modulation rate with better performance with unmodulated pulse trains even at the highest carrier rate (van Hoesel et al. 2009). However, with very slow modulation rates (12.5 Hz) CI listeners were found to be sensitive to ITDs carried on the electric pulses presented with a research interface up to 800 pps, although with high variability amongst subjects (Majdak et al. 2006). The same study also showed a significant improvement in lateralisation ability from envelope only ITDs to full waveform ITDs (ITDs presented on both the envelope and the pulses). However, again there was great subject variability and although all subjects were post-linguilly deafened too many confounding variables were present to fully understand the factors at play. Thus our neonatally deafened animal model was ideal to remove these confounds (see Chapter 5).

This thesis thus aims to investigate influencing factors in ITD sensitivity and answers the following questions: does ITD sensitivity have a critical period? (see Chapter 2), what are the effects of hearing experience on ITD sensitivity? (see Chapter 3), does ITD sensitivity exist at clinically relevant pulse rates under appropriate stimulation? (see Chapter 4), does ITD sensitivity show onset dominance in the absence of early hearing experience? (see Chapter 5) and is ITD sensitivity more reliably carried on the fixed rate pulses or the modulating amplitude? (see Chapter 6).

Overall the studies here in emphasis the importance of controlling for confounding variables and the value of an appropriate and established animal model. In particular: aetiology of deafening, age of onset, age of implantation and therefore duration of auditory deprivation together with stimulation strategy not limited to clinical speech processor technology can all be controlled and kept constant between subjects allowing us to clearly answer fundamental questions on ITD sensitivity under electric hearing.

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Chapter 2: Microsecond Interaural Time Difference Discrimination Restored by Cochlear Implants After Neonatal Deafness

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Abstract

Spatial hearing in cochlear implant (CI) patients remains a major challenge with many early deaf users reported to have no measurable sensitivity to interaural time differences (ITDs). Deprivation of binaural experience during an early critical period is often hypothesized to be the cause of this shortcoming. However, we show that neonatally deafened (ND) rats provided with precisely synchronized CI stimulation in adulthood can be trained to lateralize ITDs with essentially normal behavioral thresholds near 50 μs. Furthermore, comparable ND rats show high physiological sensitivity to ITDs immediately after binaural implantation in adulthood. Our result that ND CI rats achieved very good behavioral ITD thresholds while prelingually deaf human CI patients often fail to develop a useful sensitivity to ITD raises urgent questions concerning the possibility that shortcomings in technology or treatment, rather than missing input during early development, may be behind the usually poor binaural outcomes for current CI patients.

Introduction

For patients with severe to profound sensorineural hearing loss, cochlear implants (CIs) can be enormously beneficial, as they often permit spoken language acquisition, particularly when CI implantation takes place early in life (Kral and Sharma 2012). Nevertheless the auditory performance achieved by CI users remains variable and falls a long way short of natural hearing.

For example, good speech understanding in the presence of competing sound sources requires the ability to separate speech from background. This is aided by “spatial release from masking”, a binaural phenomenon, which relies on the brain’s ability to process binaural spatial cues, including interaural level and time differences (ILDs & ITDs) (Ellinger et al. 2017). While bilateral cochlear implantation is becoming more common (Litovsky 2010; Conti-Ramsden et al. 2012; Ehlers et al. 2017), bilateral CI recipients still perform poorly in binaural tasks such as sound localization and auditory scene analysis, particularly when multiple sound sources are present (van Hoesel 2004; van Hoesel 2012). Indeed, while normal hearing human listeners may be able to detect ITDs as small as 10 μs (Zwislocki and Feldman 1956), ITD sensitivity of CI patients, particularly with prelingual onset of deafness, is often poor and sometimes seems completely absent (van Hoesel 2004; Litovsky 2010; van Hoesel 2012; Kerber and Seeber 2012; Litovsky et al. 2012; Laback et al. 2015; Ehlers et al. 2017).

The reasons for the poor binaural sensitivity of CI recipients are only poorly understood, but two main factors are generally thought to be chiefly responsible, namely: 1) technical limitations of current CI devices, and 2) neurobiological factors, such as when the neural circuitry responsible for processing binaural cues fails to develop due to a lack of experience during a presumed “critical period” in early life, or when it degenerates during a period of late deafness. These presumed factors could act alone or in combination. Let us first consider the technological issues. The vast majority of CI devices in clinical use

operate stimulation which are variants of the “continuous interleaved sampling” (CIS) method (Wilson et al. 1991). While these technical limitations are substantial, currently few researchers believe that they alone can be fully responsible for the poor binaural acuity observed in CI patients, because it is possible to test patients with experimental processors that overcome some of the shortcomings of standard issue clinical devices. When tested with such experimental devices, many postlingually deaf CI users show better ITD sensitivity, with some of the best performers achieving thresholds comparable to those seen in normal hearing peers. In contrast, the ITD performance of prelingually deaf CI users remains invariably poor, with even rare star performers only achieving thresholds of a few hundred µs (Poon et al. 2009; Conti-Ramsden et al. 2012; Litovsky et al. 2012; Gordon et al. 2014; Laback et al. 2015; Litovsky and Gordon 2016; Ehlers et al. 2017). It is this poor performance of prelingually deaf patients even under optimized experimental conditions that led to the suggestion that the absence of binaural inputs during a presumed "critical" period in early childhood may prevent the development of ITD sensitivity (Kral and Sharma 2012; Kral 2013; Litovsky and Gordon 2016; Yusuf et al. 2017).

In this context it is however important to remember that the terms “sensitive” or “critical” period do not have simple, universally accepted definitions, which may create uncertainty about what exactly a “critical period hypothesis of binaural hearing” proposes. Some authors distinguish “strong” and “weak” critical periods. Both types of critical period are developmental periods during which the acquisition of a new sensory or sensory-motor faculty appears to be particularly easy. However, after “weak” critical periods, a full mastery of a faculty may still be acquired with a little more effort (Kilgard and Merzenich 1998), but missing essential experience during a “strong” critical period leads to substantial and irreparable limitations later in life (Knudsen et al. 1984). Perhaps the best studied example of a strong critical period disorder is amblyopia. Amblyopic patients experience an uneven or unbalanced binocular visual stimulation in early life, which leads

to a failure of the normal development of the brain's binocular circuitry. This, in turn, causes sometimes dramatic impairments in the visual acuity in the "weaker eye", as well as in stereoscopic vision. These impairments can only be fully reversed if diagnosed and treated prior to critical period closure, and despite substantial research efforts, no interventions performed after critical period closure can offer more than partial remediation of the deficits (Tsirlin et al. 2015). If we hypothesize that binaural hearing development exhibits a similarly strong critical period, then developing clinical CI processors with better ITD coding might not benefit patients with hearing loss early in life, as it might not be possible to implant these patients early enough to provide them with suitable binaural experience during their (strong) critical period. Their brains would then be unable to learn to take full advantage of the binaural cues that improved CIs provided later in life might deliver.

For neonatally deaf patients, periods of sensory deprivation during development are the norm, because profound bilateral hearing loss is hard to diagnose in neonates and measurements of auditory brainstem responses have to be repeated to exclude delayed maturation of the auditory brainstem (Jöhr et al. 2008; Cosetti and Roland 2010; Arndt et al. 2014). Also, before CI surgery is considered non-invasive alternatives such as hearing aids may be tried first. Finally, risks associated with anesthesia in young babies provide another disincentive for very early implantation (Dettman et al. 2007; Jöhr et al. 2008; Cosetti and Roland 2010). Altogether, this means by the time of implantation, neonatally deaf pediatric CI patients will typically already have missed out on many months of the auditory input. Consequently, if there is a strong binaural critical period, then this lack of early experience might put near normal binaural hearing performance forever out of their reach.

Various lines of animal experimentation make such a critical period hypothesis plausible, including immunohistochemical studies which have shown degraded tonotopic

organization (Rosskothen-Kuhl and Illing 2012; Rauch et al. 2016) and changes in stimulation-induced molecular, cellular, and morphological properties of the auditory pathway of neonatally deafened (ND) CI rats (Illing and Rosskothen-Kuhl 2012; Rosskothen-Kuhl and Illing 2012; Jakob et al. 2015; Rauch et al. 2016; Rosskothen-Kuhl et al. 2018). Additional studies demonstrate that abnormal sensory input during early development can alter ITD tuning curves in key brainstem nuclei of gerbils (Seidl and Grothe 2005; Beiderbeck et al. 2018). Furthermore, numerous electrophysiological studies on cats and rabbits have reported significantly lower ITD sensitivity to CI stimulation in the inferior colliculus (IC) (Hancock et al. 2010; Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2019) and auditory cortex (AC) (Tillein et al. 2009; Tillein et al. 2016) after early deafening compared to what is observed in hearing experienced controls.

However, although the “strong critical period hypothesis” of poor ITD sensitivity in CI patients is plausible, it has not yet been rigorously tested. The previous animal studies just mentioned have not investigated perceptual limits of binaural function in behavioral experiments using optimized binaural inputs. Similarly, while we do know that CI patients with normal hearing experience in early childhood usually have a better ITD sensitivity than patients without (Litovsky 2010; Laback et al. 2015; Ehlers et al. 2017) we do not yet know whether early deaf patients could develop good ITD sensitivity after implantation later in life if they were fitted with CI processors providing with optimized binaural stimulation from the outset. Currently, only research interfaces which are unsuitable for everyday clinical use can deliver the high quality binaural inputs needed to investigate this question. Consequently, there are currently no patient cohorts who experienced through their CIs the long periods of high quality ITD information that may be needed for them to become expert at using ITDs, irrespective of any hypothetical critical periods. We cannot at present exclude the possibility that the ND auditory pathway may retain a substantial innate ability to encode ITD even after long periods of neonatal deafness, but that this

ability may atrophy after countless hours of binaural CI stimulation through conventional clinical processors which convey no useful ITD information.

Since these possibilities cannot currently be distinguished based on clinical data, animal experimentation is needed, which can measure binaural acuity behaviorally. The first objective here is to examine how much functional ITD sensitivity can be achieved in mature ND animals which receive bilaterally synchronized CI stimulation capable of delivering ITD cues with microsecond accuracy. Achieving this first objective was the aim of this paper. In essence, we attempted to disprove the “strong critical period hypothesis for ITD sensitivity development” by examining whether experimental animals fitted with binaural CIs may be able to achieve good ITD sensitivity without excessive training or complicated interventions, even after severe hearing loss throughout infancy. To achieve this we used a stimulation optimized for ITD encoding straight after implantation.

We therefore established a new behavioral bilateral CI animal model and setup capable of delivering microsecond precise ITD cues to cohorts of ND rats (early-onset deafness) which received training with synchronized bilateral CI stimulation in young adulthood. These young adult rats learned easily and quickly to lateralize ITDs behaviorally, achieving thresholds as low as ~50 µs, comparable to those of their normal hearing (NH) litter mates. We also observed that such ND rats exhibit a great deal of physiological ITD sensitivity in their IC straight after implantation. Our results therefore indicate that, at least in rats, there appears to be no strong critical period for ITD sensitivity.

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 two-alternative forced choice (2AFC) ITD lateralization task (NDCI-B; see Fig. 1), and we compared their performance against behavioral data from five age-matched NH rats trained to discriminate the ITDs of acoustic pulse trains (NH-B; see Fig. 1;Li et al. (2019)). 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. S1a, S2b; Video 1). 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. S1c-d; S2f). NDCI-B rats were stimulated with biphasic electrical pulse trains delivered through chronic CIs, NH-B rats received acoustic pulse trains through a pair of “open stereo headphones” implemented as near-field sound tubes positioned next to each ear when the animal was at the start spout (Fig. S2a, see Li et al. (2019) for details). During testing, stimulus ITDs varied randomly.

The behavioral data (Fig. 2) were collected over a testing period of around 14 days. For NDCI-B rats, the initial lateralization training started usually one day after CI implantation. On average, rats were trained for eight days before we started to test them on ITD sensitivity. The behavioral performance of each rat is shown in Figure 2, using light blue for NH-B (a-e) and dark blue for NDCI-B (f-j) animals. Figure 2 clearly demonstrates that all rats, whether NH with acoustic stimulation or ND with CI stimulation, 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. 2) to the raw data and calculated the slope of that curve at

ITD=0. Figure 2k summarizes these slopes for NH-B (light blue) and NDCI-B (dark blue) animals.

The slopes for both groups fell within the same range. Remarkably, the observed mean sensitivity for the NDCI-B animals (0.487 %/μs) is only about 20% worse than that of the NH-B (0.657 %/μs). Furthermore, the differences in means between experimental groups (0.17 %/μs) were so much smaller than the animal-to-animal variance (~0.73 $\%^2/\mu s^2$) that prohibitively large cohorts of animals would be required to have any reasonable prospect of finding a significant difference. Indeed, we performed a Wilcoxon test on the slopes and found no significant difference (p=0.4375). Similarly, both cohorts showed similar 75% correct lateralization thresholds (median NH-B: 41.5 μs; median NDCI-B: 54.8 μs; mean NH-B: 79.9 μs; mean NDCI-B: 63.5 μs). 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 often have ITD thresholds too large to measure and often in excess of 3000 μs (Litovsky et al. 2010; Ehlers et al. 2017). Thresholds in ND rats were not dissimilar from the approx. 10-60 μs range of 75% correct ITD discrimination thresholds reported for normal human subjects tested with noise bursts (Klumpp and Eady 1956), and pure tones (Zwislocki and Feldman 1956), or the ≈ 40 μs thresholds reported for normal hearing ferrets tested with noise bursts (Keating et al. 2013a).

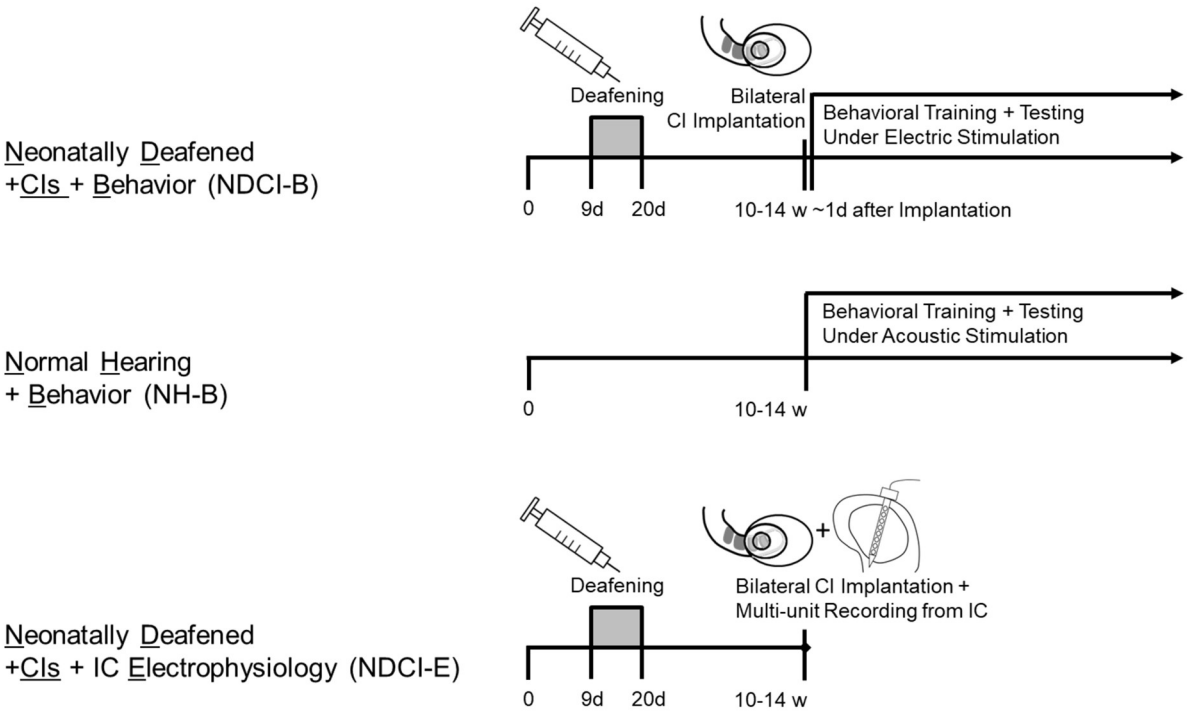

Figure 1: Timeline and experimental treatment of our three cohorts. NDCI-B and NDCI-E rats were both neonatally deafened by kanamycin and bilaterally implanted as young adults. Around half of them went into a behavioral training and testing (NDCI-B) while the other half were used for multi-unit recordings of IC neurons directly after bilateral CI implantation. NH-B rats were normal hearing and started a behavioral training and testing as young adults. w: weeks. d: days.

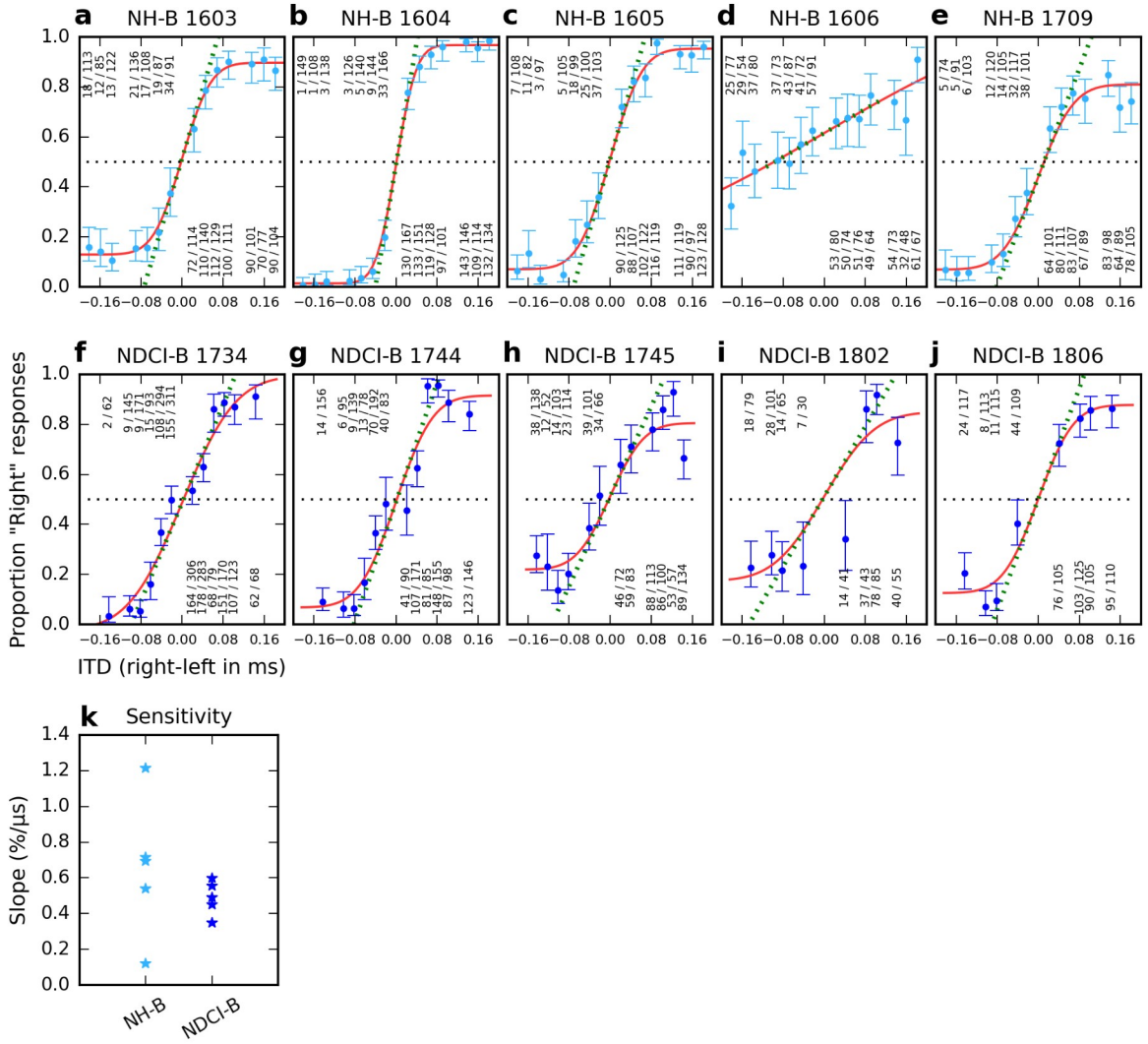

Figure 2: a-j ITD psychometric curves of normal hearing acoustically stimulated (NH-B, **a-e**) and neonatally deafened CI-stimulated rats (NDCI-B, **f-j**). Panel titles show corresponding animal IDs. Y-axis: proportion of responses to the right-hand side. X-axis: Stimulus ITD in ms, with negative values 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 animals' "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 (NDCI-E; see Figs. 1 and 3). These rats were litter mates of the behavioral ND animals (NDCI-B) and were stimulated by isolated, bilateral CI pulses with ITDs varying randomly over a ±160 µs range (ca 123% of the rat's physiological range (Koka et al. 2008). For the cohort of neonatally deafened rats (NDCI-E), the CI implantation and the electrophysiology measurements in the IC were performed on the same day with no prior electric hearing experience. 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. S1c-d). Responses of IC neurons were detected for currents as low as 100 µA. Figure 3 shows a selection of responses as raster plots and corresponding ITD tuning curves, as a function of firing rate (Fig. 3, #1-4).

For NDCI-E animals, ITD tuning varied from one recording site to the next both in shape and magnitude and firing rates clearly varied as a function of ITD values (Fig. 3). While many multi-units showed typical short-latency onset responses to the stimulus with varying response amplitudes (Fig. 3, #1, #3), some showed sustained, but still clearly tuned, responses extending for up to 80 ms or longer post-stimulus (Fig. 3, #4). Although the interpretation of tuning curves is complex the shapes of ITD tuning curves we observed in

rat IC (Fig. 3) resembled mostly the “peak”, “monotonic sigmoid”, “trough”, and “multi-peak” shapes previously described in the IC of cats (Smith and Delgutte 2007).

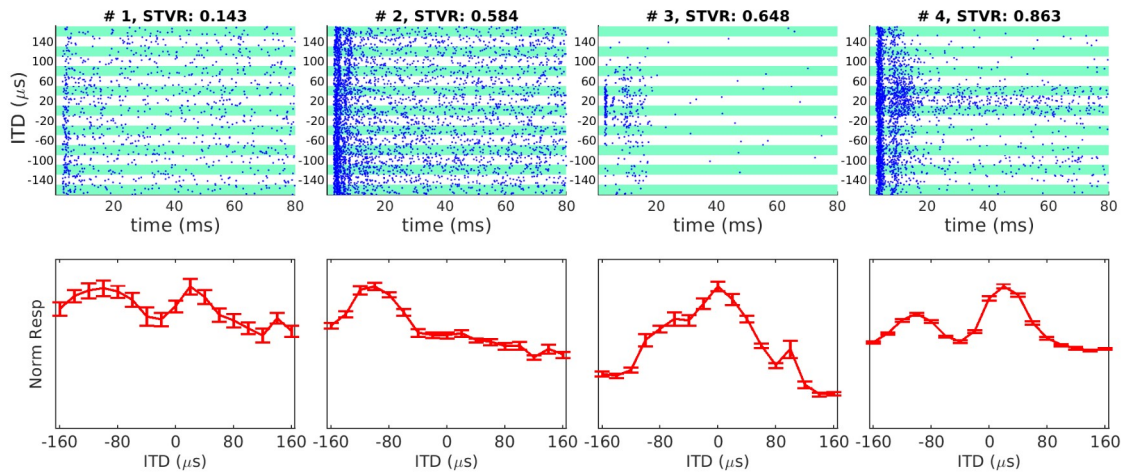

Figure 3: Examples of ITD tuning curves of neonatally deafened CI rats (NDCI-E) as a function of ITD. Dot raster plots are shown above the corresponding ITD tuning curves. The multi-units shown were selected to illustrate some of the variety of ITD tuning curve depths and shapes observed. In the raster 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-total variance ratio (STVR) values to quantify ITD tuning. Panels are arranged top to bottom by increasing STVR. ITD>0: ipsilateral ear leading; ITD<0: contralateral ear leading.

To quantify how strongly the neural responses recorded at any one site depended on stimulus ITD, signal-to-total variance ratio (STVR) values were calculated as described in Hancock et al. (2010). It quantifies the proportion of response variance that can be accounted for by stimulus ITD (see Methods). Each sub-panel of Figure 3 indicates STVR

values obtained for the corresponding multi-unit, while Figure 4 shows the distributions of STVR values for the NDCI-E cohort (red). For comparison with a similar previous bilateral CI study, Figure 4 also shows the STVR values for the IC of congenitally deaf (blue) cats reported by Hancock et al. (2010) and in which they are referred to as SNR values. 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 Hancock et al. (2010), so the cross-species comparison in particular must be done with care. Nevertheless, the distributions clearly show that ITD STVRs in our NDCI-E rats are very good, and also in line with the values reported by others using similar methodologies. For interpretation purposes an STVR >0.5 is considered good ITD sensitivity. It is noticeable that the proportion of multi-units with relatively large STVRs values (substantial ITD tuning) is high among the NDCI-E rats with a median STVR value for IC multi-units of 0.362. In comparison, Hancock et al. (2010) showed a lower median STVR (referred to as SNR) for congenitally deaf cats (0.19) as compared to adult deafened cats (0.45). The proportion of rat multi-units which showed statistically significant ITD tuning ($p \leq 0.01$), as determined by ANOVA (see Methods), was also very large in ND (1125/1229 ≈ 91%) CI-stimulated rats. Thus, for our rats which were deafened before the onset of hearing, a lack of early auditory experience during what ought to have been a critical period for ITD sensitivity, did not produce a measurable decline in overall sensitivity of IC neurons to the ITD of CI stimulus pulses. This is perhaps unexpected given that previous studies comparing ITD tuning in the IC of congenitally deaf white cats with that of hearing experienced, adult deafened wild type cats did report noticeably worse ITD tuning in the congenitally deaf cats (Hancock et al. 2013). Note that congenitally deaf white cats lose hair-cell function between postnatal days 3 and 10 (Mair and Elverland 1977).

Nevertheless, the results in Figures 3 and 4 clearly show that many IC neurons in the inexperienced, adult midbrain of NDCI-E rats are quite sensitive to changes in ITD of CI pulse stimuli by just a few tens of μs, and our behavioral experiments showed that NDCI-B rats (Fig. 2, f-j) can readily learn to use this neural sensitivity to perform behavioral ITD discrimination with an accuracy similar to that seen in their NH-B litter mates (Fig. 2, a-e).

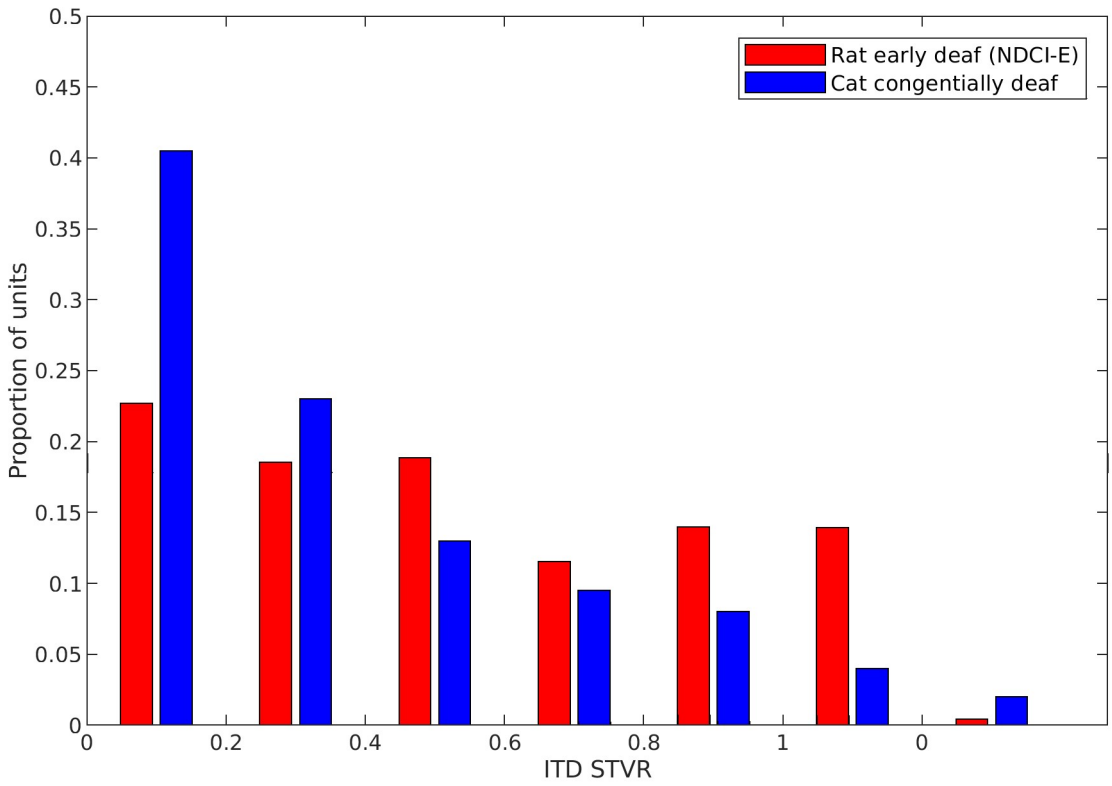

Figure 4: Bar chart shows distributions of ITD STVR values for ICs multi-units of neonatally deafened CI-stimulated rats (NDCI-E, red). STVR value distributions for IC single-unit data recorded by Hancock et al. (2010) for congenitally deaf cats (blue) under CI stimulation are also shown for comparison and are referred to as SNR in this cat study.

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 NDCI-B rats (≈ 50 µs) were as good as the ITD thresholds of NH-B rats Li et al. (2019), and many times better than those typically reported for early deaf human CI patients with thresholds often too large to measure (Litovsky et al. 2010; Gordon et al. 2014; Ehlers et al. 2017). The good performance exhibited by our NDCI-B 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 optimal bilateral CI stimulation capable of delivering adequate ITDs from the first electric stimulation even in the absence of hearing experience during a period what has been thought to be critical for the development of ITD sensitivity. 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 a poor model for ITD processing due to MSOs with less ITD sensitive neurons and their limited low-frequency hearing which may result in limited ITD perception (Grothe and Klump 2000; Wesolek et al. 2010). However, in animals with relatively high frequency hearing, such as rats, envelope ITD coding through the lateral superior olive is likely to make important contributions (Joris and Yin 1995). The only previous behavioral study of ITD sensitivity in rats outside of our lab (Wesolek et al. 2010) concluded that rats are unlikely to be sensitive to the interaural phase of relatively low frequency tones. High frequency “envelope” ITD sensitivity is also bound to be of great importance in prosthetic hearing given that CIs rarely reach the apex of the cochlea. In Li et al. (2019) we recently demonstrate that NH rats can use ITD cues for 2AFC sound lateralization tasks and thus conclude that, at least to broadband clicks, rats show ITD sensitivity. Here, 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 (Joris and Yin 1995; Bernstein 2001). That may also explain why our CI rats showed good ITD sensitivity even though our CIs targeted the lower mid-frequency region in each ear, and not the apical region associated with low frequency hearing. Recent studies in CI patients with late deafness in adults and children have shown that ITDs delivered to mid- and high-frequency cochlear regions can be detected behaviorally (Kan et al. 2016; Ehlers et al. 2017).

Secondly, electrophysiology studies on congenitally deaf CI cats reported a substantially reduced ITD sensitivity relative to wild type, hearing experienced cats acutely deafened as adults (Tillein et al. 2009; Hancock et al. 2010; Tillein et al. 2016). These studies recorded neural tuning high up in the auditory pathway (AC and IC), therefore 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, the latter of which may be reversible 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 (Hancock et al. 2010) or 62% for neonatally deafened rabbits (Chung et al. 2019). When tested under optimal stimulation to deliver microsecond precise ITD cues in a naive auditory system, the proportion of ITD sensitive sites in NDCI-E rats is thus more similar to proportions in adult deafened CI-stimulated cats (84%-86%; (Smith and Delgutte 2007; Hancock et al. 2010), rabbits (~75%; (Chung et al. 2016; Chung et al. 2019)) or gerbils (~74%; (Vollmer 2018)). Figure 4 suggests that the ITD STVR seen in our ND CI rats fall in a similar range of the ITD STVRs previously reported for congenitally deaf CI-cats (Hancock et al. 2010). While for cats, the proportion of IC multi-units with large ITD STVR values (>0.5) 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 STVR values of 0.5 or higher, which indicates rather good ITD sensitivity. It is important to remember that it is 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 ≈ 50 μs possible, as we see in our NDCI-B cohort (Fig. 2). However, multi-units such as #3 and #4 shown in Figure 3 change their firing rates as a function of ITD substantially between steps of only 20 μs. These multi-units have STVRs that are not outside the range reported for congenital deaf cats. Thus we cannot conclude from the electrophysiology data alone whether the quantitative differences in ITD sensitivity between these studies would equate to difference in behavioral lateralization performances. The level of physiological ITD sensitivity previously observed in cats (Tillein et al. 2009; Hancock et al. 2010; Tillein et al. 2016) and rabbits (Chung et al. 2019) could be sufficient to enable 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 (Chung et al. 2016; Chung et al. 2019) or AC (Tillein et al. 2009; Tillein et al. 2016) of early deaf animals does not seem nearly large enough to fully explain the very poor behavioral ITD thresholds seen in most early deaf humans. And indeed, our own findings that the behavioral ITD sensitivity of our NDCI-B rats compares favorably with that in NH-B animals strongly suggests that the poor ITD sensitivity in human CI patients may well have causes beyond the lack of auditory experience during a presumed critical period.

It is unclear why congenitally deaf cats (Hancock et al. 2010; Hancock et al. 2013) show a modest reduction in neural ITD sensitivity, while NDCI-E rats in the present study seem not to. There are numerous methodological and species differences that might account for

this, ultimately relatively small discrepancy. More pertinent for the present discussion is that both preparations exhibit a lot of innate residual ITD sensitivity in their midbrains despite severe hearing impairment throughout their development, (Tillein et al. 2009; Hancock et al. 2010; Hancock et al. 2013; Tillein et al. 2016; Chung et al. 2019). We would find it surprising if this physiological ITD sensitivity of IC neurons could not ever be harnessed to inform perceptual decisions in the cats' and rabbits' brains. Thus, in light of our new behavioral results in rats, it seems reasonable to expect that, with appropriate rehabilitation and training, neonatally deaf cats and rabbits (and perhaps even humans), might be able to learn to make use of their residual innate physiological ITD sensitivity to perform very well in binaural hearing tasks.

The most striking difference between our results and other previously published work remains that the behavioral ITD discrimination thresholds of our NDCI-B rats are an order of magnitude or more better than those of early deaf human CI patients (Gordon et al. 2014; Litovsky and Gordon 2016; Ehlers et al. 2017). As mentioned in the introduction, previous authors have proposed that the very poor performance typical of early deaf human CI patients may be due to “factors such as auditory deprivation, in particular, lack of early exposure to consistent timing differences between the ears” (Ehlers et al. 2017), in other words, the critical period hypothesis. However, neonatal deafening and severe hearing loss until reaching developmental maturity did not prevent our NDCI-B rats from achieving very good ITD discrimination performance. Admittedly, there may be species differences at play here. Our ND rats were implanted as young adults, and were severely deprived of auditory input throughout their childhood, but humans mature much more slowly, so even patients implanted at a very young age will have suffered auditory deprivation for a substantially longer absolute time period than our rats. Nevertheless, our results on early deafened CI rats show that lack of auditory input during early development

does not need to result in poor ITD sensitivity and is therefore unlikely to be a sufficient explanation for the poor ITD sensitivity found in early deaf CI patients.

Previous studies of the development of the binaural circuitry in animal models also have not provided any strong evidence for a critical period, even if they have pointed to the important role that early experience can have in shaping this circuitry. Most of these studies have focused on low frequency fine structure ITD pathways through the MSO, rather than LSO envelope ITD pathways that are likely to be of particular relevance for the CI ITD processing we are studying here. But even if they may not be directly applicable, they are nonetheless somewhat informative for the present discussion. For example, developmental studies in ferrets have shown that the formation of afferent synapses to medial superior olive (MSO), one of the main brainstem nuclei for ITD processing, is essentially complete before the onset of hearing (Brunso-Bechtold et al. 1992). In mice, the highly specialized calyx of Held synapses which are thought to play key roles in relaying precisely timed information in the binaural circuitry have been shown to mature before the onset of hearing (Hoffpauir et al. 2006). In both cases crucial binaural circuitry elements are completed before any sensory input dependent plasticity can take place. However, there are also studies which do indicate that the developing binaural circuitry can respond to changes in input. For example, in gerbils, key parts of the binaural ITD processing circuitry in the auditory brainstem will fail to mature when driven with strong, uninformative omnidirectional white noise stimulation during development (Kapfer et al. 2002; Seidl and Grothe 2005), which shows that inappropriate or uninformative sensory input can disturb the development of binaural brainstem pathways. A perhaps related finding by Tirko and Ryugo (2012) shows that inhibitory pathways in the MSO, which are thought to be essential for ITD encoding, are significantly reduced in congenitally deaf cats at postnatal day 90, compared to normal hearing peers, but they can be fully restored with

the advent of CI stimulation after only three months. Finally, Pecka et al. (2008) demonstrated the importance of glycinergic inhibition and its timing in the MSO in controlling binaural excitation by fine tuning the delay between arrival from the two ears, which could allow ITD pathways to be "tuned", possibly in an experience dependent manner. Overall, these studies point to varying extents of experience dependence of the developing binaural pathway, but none of them would suggest that the absence of stimulation early in life would necessarily prevent the restoration of effective binaural processing after the closure of some presumed critical period. None of the published papers we could find point to a biological mechanism for a critical period that could explain the loss of ITD sensitivity in early deaf CI users merely as a consequence of an absence of input in early life.

It is well known that the normal auditory system not only combines ITD information with ILD and monaural spectral cues to localize sounds in space, it also adapts strongly to changes in these cues, and can re-weight them depending on their reliability (Keating et al. 2013b; Keating et al. 2015; Tillein et al. 2016; Kumpik et al. 2019). Similarly, Jones et al. (2011) demonstrated changes in ITD and ILD thresholds as head size and pinnae grow for up to six weeks postnatally in chinchillas. Again this highlights the importance of plasticity of binaural hearing during development. However, no studies have demonstrated that critical periods in the ITD pathways will irrevocably close if sensory input is simply absent, rather than altered. By using the rat model, which allowed us to study ITD sensitivity behaviorally, we were able to show conclusively that the ability to use ITD cues perceptually does not disappear permanently after hearing loss during a presumed critical period.

Given that our results cast doubts on the critical period hypothesis, it may be time to consider other likely causes for ITD insensitivity in CI patients. One possibility which we believe has not been given enough attention is that an innate ITD sensitivity could

conceivably degrade over the course of prolonged exposure to the entirely inconsistent and uninformative ITDs delivered by current standard clinical CI processors. This possibility is consistent with the observations by Zheng et al. (2015) and by Litovsky and Gordon (2016) who note that, even after binaural CI listening experience extending for >4 years or >6 years respectively, the ITD sensitivity of bilateral CI users still lags well behind that of age matched controls with normal hearing. If the clinical processors supplied to these bilateral CI users do not supply high quality ITD cues, then no amount of experience will make these patients experts in the use of ITDs. Contrast this with our NDCI-B rats, which received only highly precise and informative ITDs right from the start with no additional auditory cues, and were able to lateralize ITDs as well as their NH litter mates after only two weeks of training. This is admittedly a somewhat unfair comaprison. Clincal CI processors are, for good reason, designed first and foremost for the purpose of delivering all important speech formant information in real life settings, and optimizing ITD coding was not a priority in their original design. Nevertheless, our results raise the possibility that incorporating better ITD encoding in clinical processors might lead to better binaural outcomes for future generations of CI patients.

Current CI processors produce pulsatile stimulation based on fixed rate interleaved sampling (Wilson et al. 1991; Stupak et al. 2018), which is neither synchronized to stimulus fine structure nor synchronized between ears. Furthermore at typical clinical stimulation rates (>900 pps) CI users are not sensitive to speech envelope ITDs, as envelope ITD sensitivity requires peak shaped envelopes (Laback et al. 2004; Grantham et al. 2008; van Hoesel et al. 2009; Noel and Eddington 2013; Laback et al. 2015). Consequently, the carrier pulses are too fast, and the envelope shapes in everyday sounds are not peaked enough, so that speech processors only ever provide uninformative envelope ITDs to the children using them (Laback et al. 2004; Grantham et al. 2008; Laback et al. 2015). Perhaps brainstem circuits of children fitted with

conventional bilateral CIs simply “learn” to ignore the unhelpful ITDs that are contained in the inputs they receive. This would mean that these circuits are adaptive to uninformative ITDs. In contrast, precise ITD cues at low pulse rates were essentially the only form of useful auditory input that our NDCI-B rats experienced, and they quickly learned to use these precise ITD cues. Thus, our data raise the possibility that the mammalian auditory system may develop ITD sensitivity in the absence of early sensory input, and that this sensitivity may then either be refined or lost, depending on how informative the binaural inputs turn out to be.

The inability of early deaf CI patients to use ITDs may thus be somewhat similar to conditions such as amblyopia or failures of stereoscopic depth vision development, pathologies which are caused more by unbalanced or inappropriate inputs than by a lack of sensory experience (Levi et al. 2015). For the visual system, it has been shown that orientation selective neuronal responses exist at eye-opening and thus are established without visual input (Ko et al. 2013). If this hypothesis is correct, then it may be possible to “protect” ITD sensitivity in young bilateral CI users by exposing them to regular periods of precise ITD information from the beginning of binaural stimulation. Whether CI patients are able to recover normal ITD sensitivity much later if rehabilitated with useful ITDs for prolonged periods, or whether their ability to process microsecond ITDs atrophies irreversibly, is unknown and will require further investigation.

While these interpretations of our findings would lead us to argue that bilateral CI processing strategies may need to change to make microsecond ITD information available to CI patients, one must nevertheless acknowledge the difficulty in changing established CI processing strategies. The continuous interleaved sampling (CIS) paradigm (Wilson et al. 1991) from which most processor algorithms are derived, times the stimulus pulses so that only one electrode channel delivers a pulse at any one time. This has been shown to minimize cross-channel interactions due to “current spread” which might compromise the

already quite limited tonotopic place coding of CIs. Additionally, CI processors run at high pulse rates (≥900 Hz), which may be necessary to encode sufficient amplitude modulations (AM) for speech recognition (Loizou et al. 2000). However, ITD discrimination has been shown to deteriorate when pulse rates exceeded a few hundred Hz in humans (van Hoesel 2007; Laback et al. 2007) and animals (Joris and Yin 1998; Chung et al. 2016). Our own behavioral experiments described here were conducted with low pulse rates (50 Hz), and future work will need to determine whether ITD discrimination performance declines at higher pulse rates which would make pulse rate an important factor for the development of good ITD sensitivity under this stimulation conditions. Thus, designers of novel bilateral CI speech processors may face conflicting demands: They must invent devices which fire each of 20 or more electrode channels in turn, at rates that are both fast, so as to encode the speech envelope in fine detail, but also slow, so as not to overtax the brainstem's ITD extraction mechanisms, and they must make the timing of at least some of these pulses encode stimulus fine structure and ITDs. While difficult, this may not be impossible, and promising research is underway which either provides fine structure information on up to four apical electrodes while running CIS strategy on the remaining electrodes (MED-EL CIs; (Riss et al. 2014)), uses a mixture of different pulse rates for different electrode channels (Thakkar et al. 2018), presents redundant temporal fine structure information to multiple electrode channels (Churchill et al. 2014), or aims to "reset" the brain's ITD extraction mechanisms by introducing occasional "double pulses" into the stimulus (Srinivasan et al. 2018). A detailed discussion is beyond the scope of this paper. Our results underscore the need to pursue this work with urgency as we have provided evidence that the absence of auditory input during a critical period does not necessarily mean that early deafened CI users show poor or no ITD sensitivity.

On a final note, we would be remiss if we did not acknowledge that, while the "maladaptive plasticity hypothesis" that we have elaborated over the last few paragraphs is "compatible"

with the experimental data we have presented, it would be wrong to assert that our data so far prove that this hypothesis is correct. At present we have merely managed to shed serious doubts on the popular critical period hypothesis, but at present the maladaptive plasticity hypothesis is still, apart from others including different etiologies of deafness, just one possible alternative explanation for the observed poor ITD sensitivity of human bilateral CI users. It still needs to be put to the test by measuring the effect of deliberately degrading the quality of ITD cues to varying extent and over various periods. However, the animal model introduced in this study now makes this important task experimentally feasible.

Material and Methods

All procedures involving experimental animals reported here were approved by the Department of Health of Hong Kong (#16-52 DH/HA&P/8/2/5) and/or the Regierungspräsidium Freiburg (#35-9185.81/G-17/124), as well as by the appropriate local ethical review committee. A total of 14 rats were obtained for this study from the breeding facilities of the Chinese University of Hong Kong or from Janvier Labs (Le Genest-Saint-Isle, France), and these were allocated randomly to the deafened and hearing experienced cohorts described in Figure 1.

Deafening

Rats were neonatally deafened by daily intraperitoneal (i.p.) injections of 400 mg/kg kanamycin from postnatal day 9 to 20 inclusively (Osako et al. 1979; Rosskothen-Kuhl and Illing 2012). This is known to cause widespread death of inner and outer hair cells (Osako et al. 1979; Matsuda et al. 1999; Argence et al. 2008) while keeping the number of spiral ganglion cells comparable to that in untreated control rats (Osako et al. 1979; Argence et al. 2008). Osako et al. (1979) have shown that rat pups treated with this method achieve hearing thresholds around 70 dB for only a short period (~p14-16) and are severely to profoundly hearing impaired thereafter, resulting in widespread disturbances in the histological development of their central auditory pathways, including a nearly complete loss of tonotopic organisation (Rosskothen-Kuhl and Illing 2012; Rauch et al. 2016; Rosskothen-Kuhl et al. 2018). We verified that this procedure provoked profound hearing loss (> 90 dB) by the loss of Preyer's reflex (Jero et al. 2001), the absence of auditory brainstem responses (ABRs) to broadband click stimuli (Fig. 5b) as well as pure tones (at 500, 1000, 2000 and 8000 Hz), and by performing histological assesment on cochlea sections of 11 weeks old, neonatally deafened rats (data not shown). ABRs were measured as described in Rosskothen-Kuhl et al. (2018) under ketamine (80mg/kg) and xylazine (12 mg/kg) anesthesia each ear was stimulated separately through hollow ear bars with 0.5 ms broadband clicks with peak amplitudes up to 130 dB SPL delivered at a

rate of 43 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. 5a), deafened rats had very high click thresholds of ≥130 dB SPL; Fig. 5b).

CI implantation, stimulation and testing

All animals were implanted in early adulthood (between 10-14 weeks postnatally) for both behavioral training and electrophysiology recordings (Fig. 1). All surgical procedures, including CI implantation and craniotomy, were performed under anesthesia induced with i.p. injection of ketamine (80mg/kg) and xylazine (12 mg/kg). For maintenance of anesthesia during electrophysiological recordings, a pump delivered an i.p. infusion of 0.9% saline solution of ketamine (17.8 mg/kg/h) and xylazine (2.7 mg/kg/h) at a rate of 3.1 ml/h. During surgical and experimental procedures the body temperature was maintained at 38°C using a feedback-controlled heating pad (RWD Life Sciences, Shenzhen, China). Further detailed descriptions of our cochlear implantation methods can be found in previous studies (Rosskothen et al. 2008; Rosskothen-Kuhl and Illing 2010; Rosskothen-Kuhl and Illing 2012; Rosskothen-Kuhl and Illing 2014; Rosskothen-Kuhl and Illing 2015).

In short, two to four rings of an eight channel electrode carrier (Cochlear Ltd. animal array 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 with a duty cycle of 61.44 µs positive, 40.96 µs at zero, and 61.44 µs negative (Fig. 5c). 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 NDCI-B rats 6 dB above these thresholds.

Calibration measurements for electric ITD stimuli 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. 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. Measured calibration pulses such as those shown in Figure S1c 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 Figure S1d. 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; (van Hoesel and Tyler 2003)), they also do not covary with ITD. We can therefore be certain that sensitivity to ILDs cannot account for our behavior data. Acoustic stimuli used to measure behavioral ITD sensitivity in NH-B rats consisted of a single

sample pulse (generated as a digital delta function ‘click’) at a sample rate of 48,000 Hz. Acoustic stimuli were presented 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. The single sample pulse stimuli resonated in the tube phones to produce acoustic clicks which decayed exponentially over a couple of ms (see Figure S2d). Stimuli were delivered at sound intensities of ≈ 80 dB SPL. A 3D printed “rat acoustical manikin” with miniature microphones in each ear canal was used for validating that the acoustic setup delivered the desired ITDs and no usable intensity cues (see supplementary Figure S2 and Li et al. (2019). Note that the residual ILDs are much smaller than the reported behavioral thresholds for ferrets (~ 1.3 dB (Keating et al. 2014)) or rats (~3 dB (Wesolek et al. 2010)). We can therefore be certain that sensitivity to ILDs cannot account for our behavior data.

To produce electric or acoustic stimuli of varying ITDs spanning the rat’s physiological range of ± 130 µs (Koka et al. 2008), 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.

Animal psychoacoustic testing

We trained our rats on 2AFC sound lateralization tasks using methods similar to those described in (Walker et al. 2009; Bizley et al. 2013; Keating et al. 2013a; Li et al. 2019). 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 (Figs. S1a-b; S2a-c). 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-B rats. Given that CI stimulation can be experienced as effortful by human patients (Perreau et al. 2017), and to avoid potential discomfort from prolonged negative feedback stimuli, the NDCI-B rats received a flashing LED as an alternative negative feedback stimulus. The LED was housed in a sheet of aluminum foil both to direct the light forwards and to ground the light to the setup. 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 (Walker et al. 2009; Keating et al. 2014), 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-B 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. S2a). The

pulses resonated in the tubes, producing pulse-resonant sounds, resembling single-formant artificial vowels with a fundamental frequency corresponding to the 50 Hz 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. (Wightman and Kistler 1992; Keating et al. 2013a). We used a 3D printed “rat acoustical manikin” with miniature microphones in the ear canals (Fig. S2c). It produced a channel separation between ears of ≥ 20dB at the lowest, fundamental frequency and around 40 dB overall. Further details on the acoustic setup and procedure are described in Li et al. (2019). The NDCI-B 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 Rosskothen-Kuhl and Illing (2014).

Multi-unit recording from IC

Immediately following bilateral CI implantation, anesthetized NDCI-E rats were head fixed in a stereotactic frame (RWD Life Sciences), craniotomies were performed bilaterally just anterior to lambda. 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 kHz with a TDT RZ2 with a NeuroDigitizer head-stage 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 (≈ 20 ms; Syka et al. (2000)).

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 contralateral ear leading to 163.84 μs ipsilateral ear leading in 20.48 μs steps. Each ITD value was presented 30 times at each recording site. The inter-stimulus interval was 500 ms. At the end of the recording session the animals were overdosed with pentobarbitone.

Data analysis

To quantify the extracellular multi-unit responses we calculated the average activity for each stimulus over a response period (3-80 ms post stimulus onset) as well as baseline activity (300-500 ms after stimulus onset) at each electrode position. The first 2.5 ms post stimulus onset were dominated by electrical stimulus artifacts and were discarded. For display purposes of the raster plots in Figure 3 we extracted multi-unit spikes by simple threshold crossings of the band-passed (300 Hz - 6 kHz) electrode signal with a threshold set at four standard deviation of the signal amplitude. To quantify responses for tuning curves, instead of counting spikes by threshold crossings we instead computed an analog measure of multi-unit activity (AMUA) amplitudes as described in Schnupp et al. (2015). The mean AMUA amplitude during the response and baseline periods was computed by band-passing (300 Hz - 6 kHz), rectifying (taking the absolute value) and low-passing (6 kHz) the electrode signal. This AMUA value thus measures the mean signal amplitude in the frequency range in which spikes have energy. As illustrated in Figure 1 of Schnupp et al. (2015), this gives a less noisy measure of multi-unit neural activity than counting spikes by conventional threshold crossing measures because the latter are subject to errors due to spike collisions, noise events, or small spikes sometimes reach threshold and sometimes not. The tuning curves shown in the panels of Figure 3 are the normalized responses from this AMUA measure averaged across 30 trials for each ITD seen by each

of the dots per vertical panel in the raster plots where each panel is an ITD and each dot is a spike. Changes in the AMUA amplitudes tracked changes in spike density.

Signal-to-total variance ratio (STVR) calculation

STVR values are a measure of the strength of tuning of neural responses to ITD which we adopted from Hancock et al. (2010) to facilitate quantitative comparisons. The STVR is defined in Hancock et al. (2010) as the proportion of trial-to-trial variance in response amplitude explained by changes in ITD. The STVR is calculated by computing a one-way ANOVA of responses grouped by ITD value and dividing the total sum of squares by the group sum of squares. This yields values between 0 (no effect of ITD) and 1 (response amplitudes completely determined by ITD). P-values were also computed from the one-way ANOVA and $p < 0.01$ served as a criterion to determine whether the ITD tuning of a given multi-unit was deemed statistically significant. The number of responses for each ITD value was 30, yielding with a degree of freedom (df) for the ANOVA of 29.

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 (Wickens 2002; Schnupp et al. 2005). 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 the “right” spout (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 $(1-\gamma)$. 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 equation (2) to the following psychometric model:

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

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 2a-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 2k. That slope is easily calculated using the equation (4)

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

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

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

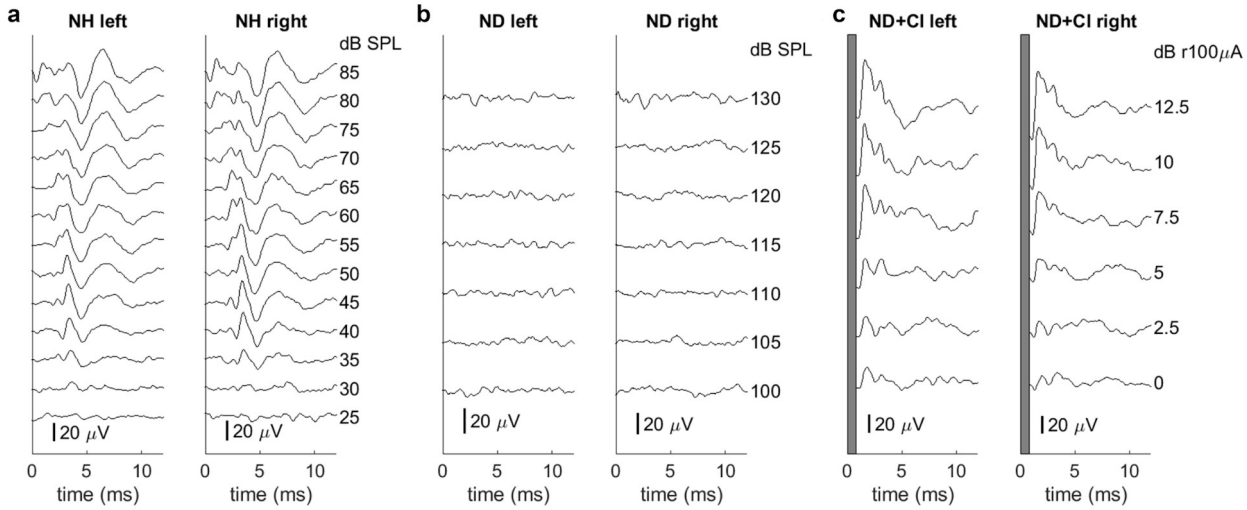

Figure 5: Examples of brainstem recordings to verify normal hearing or loss of hearing function as well as the symmetrical placement of CIs. Each recording is from a single animal. Panel (**b**) and (**c**) come from the same animal pre- and post CI implantation. **a** Auditory brainstem responses of an acoustically stimulated normal hearing (NH) rat. ABRs are symmetric 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.

Supplementary Materials

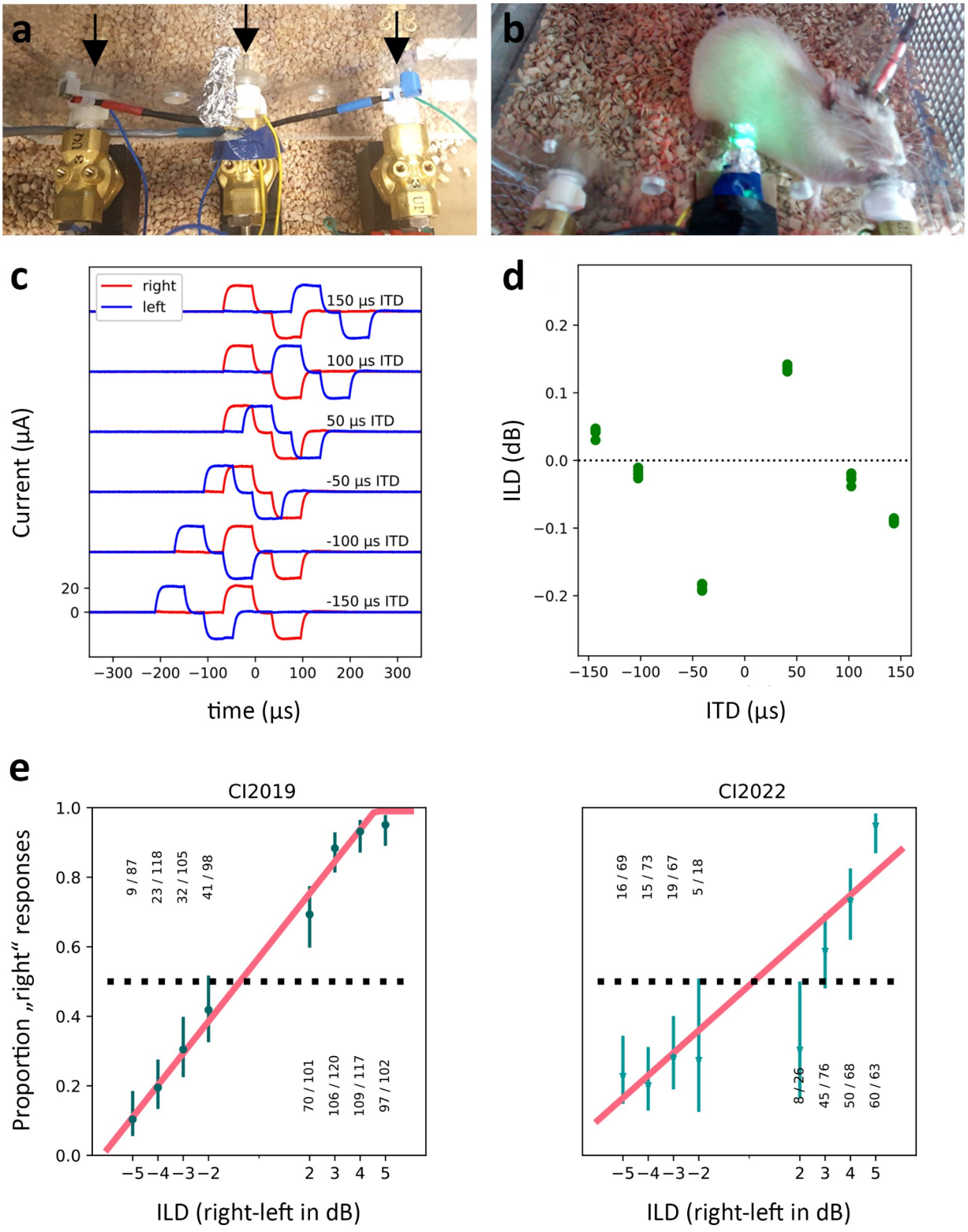

Figure 2 - figure supplement 1 (S1): Bilateral electrical intracochlear stimulation of CI rats. **a** Close-up of the training setup for CI rats. The central “start” and lateral “response” spouts deliver the water reward and are indicated by arrows. **b** CI rat during a testing session, making a response to the left by making contact with the left reward spout. **c** Calibration measurements of stimulus pulses recorded by connecting the stimulator cable to 10 kOhm resistors instead of the in-vivo electrodes and recording voltages using a Tektronix MSO 4034B oscilloscope. Recordings of stimulus pulses are shown with +/- 50, 100 and 150 µs ITDs as indicated. Pulses delivered to the right ear channel are shown in red, those delivered in the left ear in blue. **d** to measure the size of artifactual, unintended ILDs that our system generates, the root mean square (RMS) amplitudes of the stimulus traces shown in (**c**) were compared. The resulting ILDs for five repeat presentations are shown. One observes very small, artefactual ILDs which are attributable to a tiny amount of capacitive/inductive channel crosstalk in the wires leading from the programmable stimulator to the implants. A current pushed through one wire will induce a tiny current in the wire running parallel to it by magnetic induction. On careful inspection of the traces in Fig 2c, one can see tiny little red bumps coinciding with big blue rising or falling phases and vice versa, which correspond to these induced currents (Magnetic induction of currents is proportional to rate of change in field strength and hence occurs during rising and falling phases of the current pulses). The currents measured by the oscilloscope and used here for stimulus calibration are thus a superposition of the direct stimulus current injected into a given channel by the stimulator, plus the very much smaller induced current from the cross-talk from the neighboring channel. The direct current pulses and the cross talk current pulses can be either in phase or out of phase with each other depending on the ITD, which will lead to either constructive or destructive interference. This creates the small ILDs and accounts for their dependence on ITD. Note that these very small artifactual ILDs cannot account for our behavioral results because they are an order of

magnitude below the animals' typical ILD thresholds (see panel panel **e**) and they lack the required systematic relationship with ITD that would be needed if one tried to account for the ITD psychometric function in terms of sensitivity to the tiny artifactual ILDs. The largest ITD-induced ILD is 0.18 dB, or equivalently 2.17%. At 100 μs ITD, where our rats routinely achieve 80% correct or better (compare Figure 2) the ILD is as low as 0.018 dB and does not change sign with the ITD, and would therefore have to be completely uninformative. **e** behavioral ILD psychometric curves obtained from two additional ND-CI rats (not part of the cohorts introduced in Figure 1). Two rats were neonatally deafened, fitted with CIs as young adults and trained in sound lateralization tasks exactly as described in the methods, except that for these tests, the ITD of the pulses was kept constant at 0 and the relative amplitude of the left and right ear pulses was varied from trial to trial to introduce ILDs. The pyschometrics are plotted using the same conventions as in Figure 2, with the blue error bars showing Wilson confidence intervals for the proportion of right responses at each ILD and the red lines showing bounded linear psychometric functions fit to the data. Note that, to reach levels of performance > 75% correct, both animals need ILDs of >2 dB, at least an order of magnitude larger than the largest 0.18 dB artifactual ILD observed.

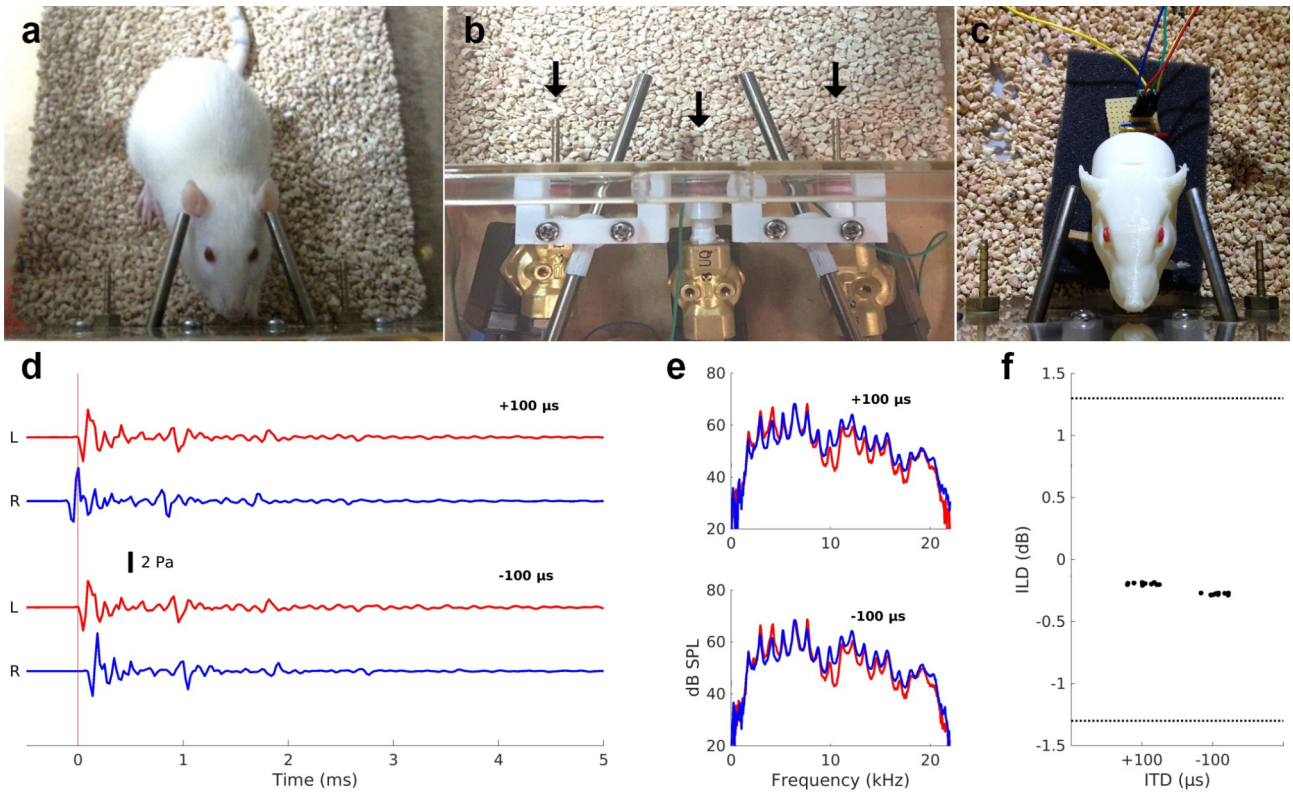

Figure 2 - figure supplement 2 (S2): Bilateral psychoacoustics near-field setup for NH rats. Note that the setup is identical to that described in Li et al. (2019) and this supplementary figure is similar to Figure 1 of that paper. **a** NH rat during a testing session, initiating a trial by making contact with the central “start” spout. Steel tube phones are positioned close to each ear, effectively implementing a pair of open stereo headphones. **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 interaural level differences (ILDs, y-axes) measured through the “rat

acoustical manikin" microphones for the +/- 100 µs ITD conditions. ILDs were computed as the difference in root mean square (RMS) power of the signals in panel (**d**). Data were recorded from 10 presentations of each ITD stimulus, and each dot represents one trial (a random amount of scatter along the x-axis was added for ease of visualization). Dotted lines show the reported behavioral thresholds for ferrets (~ +/-1.3 dB Keating et al. 2013b)).

Video Legend

Video 1: Neonatally deafened CI-rat performing a two-alternative forced choice ITD lateralization task in custom made behavior setup. The animal initiates trials by licking the center "start spout" and responds to binaural pulse trains by licking either the left or right "response spout" to receive drinking water as positive reinforcement if the response is correct or a time out with the flashing light as negative reinforcement if the response is incorrect. Which response was correct was indicated by the ITD stimulus presented on that trial when the animal licks the center spout.

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Chapter 3: Sensitivity to Interaural Time Differences in the Inferior Colliculus of Cochlear Implanted Rats With or Without Hearing Experience

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The authors declare that they have no competing interests.

Abstract:

For deaf patients cochlear implants (CIs) can restore substantial amounts of functional hearing. However, binaural hearing, and in particular, the perception of interaural time differences (ITDs) with current CIs has been found to be notoriously poor, especially in the event of early hearing loss. One popular hypothesis for these deficits posits that a lack of early binaural experience may be a principal cause of poor ITD perception in pre-lingually deaf CI patients. This is supported by previous electrophysiological studies done in neonatally deafened, bilateral CI-stimulated animals showing reduced ITD sensitivity. However, we have recently demonstrated that neonatally deafened CI rats can quickly learn to discriminate microsecond ITDs under optimized stimulation conditions which suggests that the inability of human CI users to make use of ITDs is not due to lack of binaural hearing experience during development. In the study presented here, we characterized ITD sensitivity and tuning of inferior colliculus neurons under bilateral CI stimulation of neonatally deafened and hearing experienced rats. The hearing experienced rats were not deafened prior to implantation. Both cohorts were implanted bilaterally between postnatal days 64-77 and recorded immediately following surgery. Both groups showed comparably large proportions of ITD sensitive multi-units in the inferior colliculus (Deaf: 82.5%, Hearing: 84.8%), and the strength of ITD tuning, quantified as mutual information between response and stimulus ITD, was independent of hearing experience. However, the shapes of tuning curves differed substantially between both groups. We observed four main clusters of tuning curves – trough, contralateral, central, and ipsilateral tuning. Interestingly, while over 90% of multi-units for hearing experienced rats showed predominantly contralateral tuning, as many as 50% of multi-units in neonatally deafened rats were centrally tuned. However, when we computed neural d' scores to predict likely limits on performance in sound lateralization tasks, we did not find that these differences in tuning shapes predicted worse psychoacoustic performance for the neonatally deafened animals. We conclude that, at least in rats, substantial amounts of highly precise, "innate" ITD sensitivity can be found even after profound hearing loss throughout infancy. However, ITD tuning curve shapes appear to be strongly

influenced by auditory experience although substantial lateralization encoding is present even in its absence.

Keywords:

cochlear implants, binaural hearing, interaural time differences, early onset deafness, electrophysiology, inferior colliculus

1. Introduction:

Cochlear implants (CIs) have greatly improved the quality of life of more than half a million deaf patients, often restoring the ability to take part in spoken conversations. However, patients vary greatly in how much benefit their CIs give them. Here, hearing experience is an important factor, both prior to hearing loss as well as following implantation. One major challenge for CI patients is spatial hearing, and in particular, the use of interaural time differences (ITDs). In particular pre-lingually deafened subjects, even those who have received bilateral implants within the first 18 months of life, are usually unable to detect ITDs (Wickens 2002; van Hoesel 2004; Grieco-Calub and Litovsky 2010; Litovsky 2010; Litovsky et al. 2010; Litovsky 2011a; van Hoesel 2012; Kerber and Seeber 2012; Laback et al. 2015; Ehlers et al. 2017). In many cases, ITD thresholds of theses\ patients are, if at all measurable, orders of magnitude above their acoustic normal hearing peers who can resolve ITDs of a few tens of μs (Zwislocki and Feldman 1956). Post-lingually deafened CI users often perform significantly better than pre-lingually deafened peers, but even their thresholds are many times higher than those of their normal hearing experienced peers (Litovsky et al. 2010; Litovsky 2011b; Brughera et al. 2013). Furthermore, sound localization performance does not improve much with long-term CI exposure (Loizou et al. 2009; Chang et al. 2010; Litovsky 2011b; Kerber and Seeber 2012).

It is widely believed that lack of binaural exposure during an early “critical” period of the binaural auditory pathway development is a major factor contributing to the ITD insensitivity of human CI users (Harper and McAlpine 2004; Kral and Sharma 2012; Kral 2013; Litovsky and Gordon 2016; Yusuf et al. 2017). However, we recently demonstrated that neonatally deafened rats fitted with bilaterally synchronized CIs in young adulthood were capable of learning to lateralize ITDs with thresholds as low as 50 μs, comparable with their normal hearing peers (Rosskothen-Kuhl et al. 2021). Thus, in spite of having no early hearing experience, these animals were able to make use of these cues that have been elusive to human CI listeners. This raises the possibility that reasons other than lack of early auditory experience may limit CI users’ ability to develop normal ITD

sensitivity. These may include technology limitations of current clinical CIs such as the lack of synchronization between the left and right speech processors and the spread of electric fields resulting in blurring (Carlyon et al. 2007; Oxenham and Kreft 2014) across frequency bands. In addition, there may be prolonged periods without auditory input, either bilaterally or unilaterally, which has been shown to alter binaural processes under both acoustic and electric hearing (King et al. 1988; King et al. 2000; Gordon et al. 2014). However, the underlying mechanisms for these plastic changes, particularly for electric hearing, are not fully understood. Thus, a better understanding of how innate binaural processing mechanisms and experience dependent plasticity interact in a brain that receives stimulation only after prolonged early deafness could inform improved CI treatment strategies.

Several physiological studies have reported ITD sensitivity in the inferior colliculus under CI stimulation (Hancock et al. 2010; Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2019). However, these studies only sparsely sampled ITDs within the respective animals' physiologically relevant range. In addition ITDs well beyond the physiological range were used. This greatly reduces the translatability of these studies in predicting behavioral performance limitations for physiologically relevant ITDs. Furthermore, earlier reports by Hancock et al. (2010); Hancock et al. (2012); Hancock et al. (2013) excluded onset responses from the analysis, as they were investigatimg sustained ITD responses rather than the onset response which are known to dominate ITD perception (Brown and Stecker 2010; Stecker 2013), and it has been demonstrated that the early response would encode the early stimulus (Heil 1998) which is often weighted the most heavily in perceptual lateralization judgments. We hypothesized that these methodological choices made in previous studies may have led to underestimates of "intrinsic" ITD sensitivity present in the auditory pathway under electric stimulation in the absence of early hearing experience. Thus, in this study we revisited the question of physiological ITD sensitivity under CI stimulation in a new animal model of neonatally deafened rats and compared these to hearing experienced rats. Stimuli were designed to sample the physiologically relevant ITD range for this

species at a resolution fine enough to resolve the animals' known behavioral ITD thresholds and the analysis methods included onset responses, thought to be the most salient. In addition, we have concluded our analysis in a manner that facilitates comparison to behavioral thresholds.

2. Methods and Materials

All procedures involving experimental animals reported here were performed under license issued by the Department of Health of Hong Kong (#16-52 DH/HA&P/8/2/5) and approved by the City University of Hong Kong Animal Research Ethics Sub-Committee.

2.1. Subjects & Deafening

A total of twelve wild type female Wistar rats were used in this study to investigate ITD sensitivity in the inferior colliculus under bilateral CI stimulation. Four animals grew up with normal hearing experience, the other eight rats were deafened using kanamycin injection protocols to induce cochlear hair cell loss prior to the onset of hearing, as described previously (Rosskothen-Kuhl and Illing 2010; Rosskothen-Kuhl and Illing 2012; Rauch et al. 2016; Rosskothen-Kuhl et al. 2018) Each of these eight animals had kanamycin sulfate (Sigma, 400 mg/kg body weight) intraperitoneally injected daily from postnatal day 9 to day 20, inclusively. This method results in widespread death of inner and outer hair cells (Matsuda et al. 1999). Osako et al. (1979) have shown that rat pups treated with this method never achieve hearing thresholds below 70 dB SPL during very early infancy (~p14-16), after which they are severely to profoundly hearing impaired with thresholds above 95 dB SPL. This early deafening results in widespread modifications in the development of the central auditory pathways histologically. These modifications include: changes in molecular, cellular, and morphological properties, including a massive increase and broadening of neuronal activation patterns which indicates a degraded tonotopic organization (Rosskothen-Kuhl and Illing 2012; Rauch et al. 2016; Jakob et al. 2019). In the inferior colliculus, this neuronal response was accompanied by a massive hypertrophy of astrocytes and microglia and an augmentation of the GABAergic neuronal network (Rosskothen-Kuhl and Illing 2012;

Rauch et al. 2016; Rosskothen-Kuhl et al. 2018). The Preyer's reflex, motor reflexes to a loud hand-claps, was checked daily with each kanamycin injection and was onlypresent between ~p14-16 (Jero et al. 2001). In addition, hearing loss was confirmed by measuring auditory brainstem response (ABR) thresholds to broadband click stimuli up to 90 dB SPL or higher prior to implantation in early adulthood.

2.2. Cochlear Implantation & Craniotomy

All animals in this study were implanted with bilateral CIs in early adulthood (~p64-77) and recorded the same day. All surgeries and recordings were conducted under anesthesia, which was induced by intraperitoneal (i.p.) injection of ketamine (Alfasan International B.V, 80mg/kg) and xylazine (Alfasan International B.V, 12 mg/kg), and maintained with an infusion pump delivering 17.8 mg/kg/h ketamine and 2.7 mg/kg/h xylazine in 0.9 % saline i.p. at a rate of 3.1 ml/h. Body temperature was kept constant at 38°C using a feedback-controlled heating pad (RWD Life Sciences, Shenzhen, China). A midline scalp incision was made to expose the skull, and craniotomies were performed just anterior to lambda and just lateral to the midline suture to expose the occipital cortex that covers the dorsal surface of the inferior colliculus. All neonatally deafened animals had bilateral craniotomies over both inferior colliculi while hearing experienced animals had only one craniotomy over the right inferior colliculus. All animals then received binaural cochlear implants. Detailed descriptions of our cochlear implantation methods can be found in (Rosskothen-Kuhl and Illing 2010; Rosskothen-Kuhl and Illing 2014; Rosskothen-Kuhl and Illing 2015; Rauch et al. 2016; Rosskothen-Kuhl et al. 2021). In short, four rings of an eight channel intracochlear electrode array (ST08.45, Peira, Beerse, Belgium) were fully inserted through a cochleostomy window into the middle turn of each cochlea. The arrays were directed towards the apical cochlear so that the tip electrode, used for intracochlear stimulation, sits approximately in the 4-8 kHz region. This CI insertion method is highly reproducible, and places the electrodes in a

range that would normally also be covered by clinical electrode arrays inserted in human CI patients and does not specifically target apical regions of the cochlea. Although ITD sensitivity is traditionally thought to be a spatial cue for low-frequency signals, recent psychoacoustic studies in human CI users did not in general find lower ITD thresholds when more apical regions of the cochlea were stimulated (Kan et al. 2015). In our animal model we target a part of the cochlea which would routinely be covered by clinical implants for better translation to human CI users.

Our cohort of normal hearing animals was not chemically deafened prior to implantation and recording, although their tympanic membrane and middle ear ossicle chain were removed in the process of exposing the inner ear for cochleostomy. This would lead to substantial conductive hearing loss, and no acoustic stimuli were presented during the experiments. Nevertheless, this leaves open the possibility that these animals therefore received some "electrophonic" stimulation through surviving hair-cells, so the nature of the CI stimulation of their auditory nerves will likely have differed in subtle ways from that of the neonatally deafened cohort. However, our practice here is in keeping with current clinical practice in human patients, where one tries to encourage post-implantation hair cell survival where possible (von Ilberg et al. 1999; Gstoettner et al. 2006; Turner et al. 2010). Animal studies on electro-acoustic hearing suggest that, if anything, electrophonic responses would result in mild suppression and minimal distortion of the auditory nerve fiber responses (Tillein et al. 2015). Moreover, no hair cell excitation occurs when presenting electrical stimulation in the context of electro-acoustic masking (Imsiecke et al. 2020). In any event, it is unlikely that electrophonic hearing could have any major effects on ITD encoding in our study. Any physiological delays or changes in the temporal pattern of nerve fiber discharges induced by electrophonic stimulation would be expected to be symmetric in both ears and therefore independent of interaural delays. Even if there was some left-right asymmetry in the evoked responses, such an asymmetry could only add a constant offset to the ITDs, but would not change the way changes in stimulus ITD are reflected in changes in auditory nerve firing patterns. It is

therefore very hard to see how the amount of ITD tuning observed, that is, the extent to which changes in stimulus ITD are reflected in changes in IC neuron response amplitudes, could be affected by or be due to the presence of electrophonic stimulation.

2.3. ABR and eABR recording

To verify that hearing experienced animals did in fact have normal hearing thresholds and neonatally deafened animals had threshold above 90 dB SPL, ABRs were measured prior to implantation in all animals. The recording procedure is described in Rosskothen-Kuhl et al. (2018): 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 43 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. Examples for each cohort are shown in Figure 1A and B. Following CI surgery, electrically evoked ABRs (eABRs) were measured for each ear individually to verify that both CIs were symmetrically implanted and operated at acceptably low electrical stimulation thresholds, usually around 100 µA. eABRs were recorded before and after inferior colliculus recordings as described in (Rosskothen-Kuhl et al. 2021). eABR thresholds are shown in Table 1 and an example recording in Figure 1C.

Animals	Left eABR threshold (dB re 100 µA)	Right eABR threshold (dB re 100 µA)
Neonatally Deafened 1	5	2.5
Neonatally Deafened 2	2	0
Neonatally Deafened 3	2.5	2.5
Neonatally Deafened 4	5	0
Neonatally Deafened 5	7.5	7.5

Neonatally Deafened 6	4	8
Neonatally Deafened 7	7.5	7.5
Neonatally Deafened 8	5	2.5
Hearing Experienced 1	0	0
Hearing Experienced 2	2.5	2.5
Hearing Experienced 3	2.5	2.5
Hearing Experienced 4	5	0

Table 1: Overview of the left and the right eABR thresholds of all CI animals.

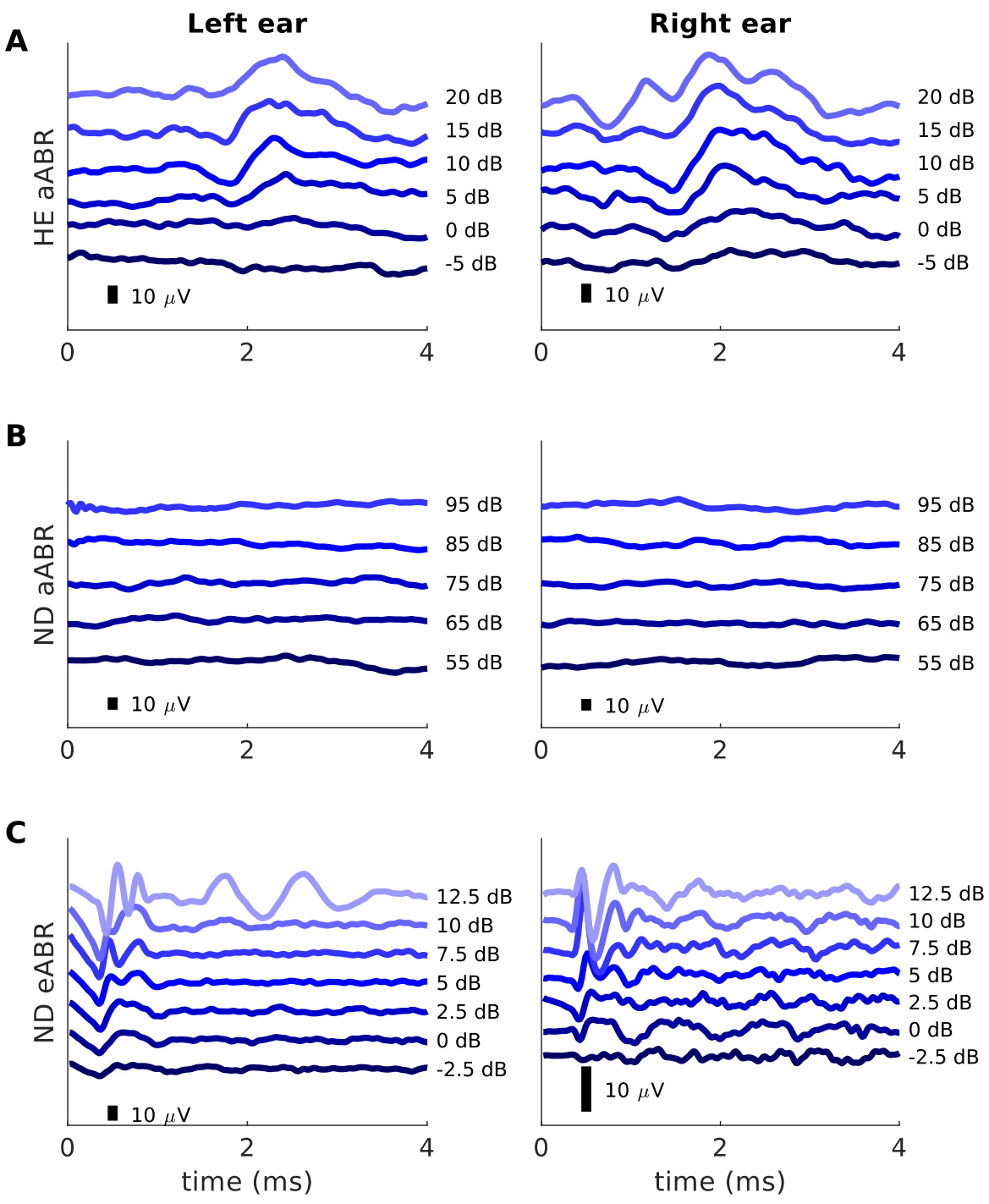

Figure 1: Examples of auditory brainstem responses (ABRs) of hearing experienced (HE) and neonatally deafened (ND) animals. Responses are shown in left and right columns for the left and right ears, respectively. Sound intensities are shown to the right of each plot. A and B show acoustic ABRs (aABRs) with broadband click presentation at the respective SPL levels. A: aABR for hearing experienced animal prior to implantation. B: aABRs for neonatally deafened animal prior to implantation. C: electric ABRs (eABRs) for a neonatally deafened animal post implantation with stimulation levels in relation to 100 µA (see method 2.4 for details).

2.4. Electric intracochlear stimulation and multi-unit recordings

All stimuli were presented using a Tucker Davis Technology (TDT, Alachua, Florida, US) IZ2MH programmable constant current stimulator at a sample rate of 48,828.125 Hz thus allowing for a minimum sample duration of 20.48 μs. The most apical ring of each CI electrode array served as the stimulating electrode and the second ring as the ground electrode. The remaining rings on the array were not used in these experiments. All electrical intracochlear stimuli consisted of single, binaural, biphasic, anode leading current pulses similar to those used in clinical devices (duty cycle: 61.44 μs positive, 40.96 μs at zero, 61.44 μs negative). Stimulus amplitude in each ear was held constant at a value of 5-10 dB above eABR thresholds, corresponding to typical amplitudes in the order of ~200-600 μA. We report CI stimulus dB values as $20 \cdot \log_{10}(A/A_{ref})$ where A and A_{ref} are peak amplitudes of the biphasic pulses, and A_{ref} is either the threshold amplitude, or a reference amplitude of 100 μA or as indicated.

To deliver ITDs on the binaural stimuli, the pulses were delayed in one ear relative to the other by an integer number of samples, enabling us to vary ITDs in steps of 20.48 μs. Stimuli consisted of a single pulse in each ear. In four neonatally deafened rats, we recorded responses with ITDs in single sample steps, covering the values ± {0, 20.48, 40.96, 61.44, 81.92, 102.40, 122.88, 143.36, 163.48 } μs. For simplicity, and given that ITD changes of less than 4 μs are well below any physiological or psychoacoustic threshold ever reported, we report ITDs below rounded to the nearest 10 μs, i.e. as ± 0, 20, 40, 60, 80, 100, 120, 140, or 160 μs. Each ITD value was presented 30 times at each recording site, in a pseudo randomly interleaved order. Inter-trial intervals were approximately 500 ms, with some variability given that the software controlling the stimulus delivery was not a real time system. In this manner we collected ITD responses in steps fine enough to resolve the animal's known behavioral threshold of ~50 μs (Li et al. 2019; Rosskothen-Kuhl et al. 2021). The chosen range of ITDs was slightly wider than the rats' physiological ITD range (~± 120 μs, Koka et al. (2008)), and by sampling with fine-grained ~20 μs steps we placed 13 ITD values within the rat's physiological ITD range. The remaining four neonatally deafened animals were subsequently tested with a larger ITD range (±300 μs) and with wider steps of ~75 μs, similarly to what had been done

in previous studies by other authors who mostly used steps of 100 µs or greater and typically only included a minority of sample points (between 1 and 7) within the physiological ITD range of the respective model species (~±400 µs for cats and ~±300 µs for rabbits) (Day et al. 2012). For details on the calibration which confirmed that our CI setup delivered the desired ITDs and no usable intensity cues, see Rosskothen-Kuhl et al. (2021). In this paper we reported ITD values as negative if the ITD is leading in the ear contralateral to the inferior colliculus from which recordings were taken, and as positive where the ear ipsilateral to the recording site is leading. In doing so we follow a long established and common convention in the sound localization literature to use negative values to denote contralateral space (Yin and Chan 1990; Middlebrooks et al. 1998; Mrsic-Flogel et al. 2003; Campbell et al. 2006; Tollin and Yin 2009), but we acknowledge that the opposite convention is also common.

Multi-units were recorded using a single-shaft, 32-channel silicon electrode array (ATLAS Neuroengineering, E32-50-S1-L6/L10), which was inserted into the inferior colliculus through a craniotomy exposing the overlying occipital cortex while the anesthetized animal was fixed in a stereotaxic frame within a sound attenuating chamber. Both, the left and right, inferior colliculi were targeted using stereotaxic coordinates and anatomical landmarks around the sagittal sinus. Penetration locations were chosen so as to sample the stereotactic area of interest extensively and fairly evenly while avoiding blood vessels or other potential obstacles, and observing a minimum distance of 0.5 mm from previous penetration sites. For each penetration, the tip of our electrode was initially advanced to a depth of 4.5 mm from the brain surface, and then slowly advanced further while monitoring the electrodes for responses to isolated “search stimulus” CI pulses delivered at ~ 1 Hz. Extracellular recordings were made using TDT equipment at a sampling rate of 25 kHz. Brainware software with custom stimulus scripts was used to deliver the stimuli and acquire the electrophysiological data. All experiments were terminal.

2.5. Analysis

All data processing and analysis was performed using custom code written in Matlab R2018b. Analog multi-unit activity (AMUA) was computed from the recorded extracellular voltage traces as described in (Kayser et al. 2007; Schnupp et al. 2015). This method quantifies neural activity based on the amplitude envelope of the electrode signal in the frequency band occupied by action potentials. To compute the AMUA, electrode signals were bandpass filtered using a 4th order butterworth filter (0.3-6 kHz), the absolute value was taken, followed by further lowpass filtering (6 kHz). The resulting AMUA trace served as a measure of local multi-unit firing rates that is usually less noisy than multi-unit activity measures based on threshold crossings (see Fig. 1 in Schnupp et al. (2015)). This is due to the fact that thresholding itself can introduce quantization noise. For this reason, we used threshold crossings (three standard deviations below the mean of the 0.3-6 kHz band-passed signal) only for the raster plot visualizations and the comparison of spike count and AMUA amplitude based tuning curves shown in Figure 2. Statistical analyses were all performed on AMUA amplitudes. Responses to stimuli were then quantified by computing the mean amplitude of the AMUA signal during a response period set to be 2.8-40 ms post stimulus onset, and subtracting mean baseline amplitudes computed over a period of 300 to 500 ms after stimulus onset. For brevity we shall refer to this baseline corrected mean AMUA response amplitude as “AMUA response” below. No evoked neuronal responses were expected or observed at latencies shorter than about 3 ms in the inferior colliculus. Note that our analysis quantifies “onset” ITD responses, which are known to be the most salient in behavior (Brown and Stecker 2010) and in physiological measures (Greenberg et al. 2017). This differs from previous studies which focused on steady-state and sustained ITD responses (Hancock et al. 2010; Hancock et al. 2012; Hancock et al. 2013), and in which onset ITDs were intentionally excluded. Our electric intracochlear stimuli were single binaural pulses of less than one ms duration (see above) and their electrical artifacts had died down completely before the start of our analysis time window, so we were able to remove electrical

stimulus artifacts simply by “blanking” the recordings over the period of 0-2.8 ms post stimulus onset.

To quantify the ITD sensitivity of neurons in the inferior colliculus, we computed the mutual information (Mrsic-Flogel et al. 2003; Nelken et al. 2005; Gordon et al. 2008) between AMUA responses and stimulus ITD. Mutual information quantifies the statistical interdependence between neural response and stimulus parameter in bits per response. AMUA responses were discretized into seven levels, and the adaptive-direct method described by Nelken et al. (2005) was used to estimate mutual information values from neural response distributions, as well as to determine whether mutual information values (after bias correction) were significantly greater than zero. The statistical significance was assessed, and values were bias corrected, by the commonly used method of performing a permutation test, in which responses were randomly reassigned to different ITD values, allowing us to quantify the amount of mutual information we would expect to see by chance. This random shuffling of responses was repeated 100 times, and the mean mutual information value from the shuffled responses then served as an estimate of the bias of the raw mutual information value, and the 99^{th} centile served as critical value for the permutation test with $\alpha=0.01$. Only multi-units with mutual information values significantly above zero were deemed ITD sensitive and included in further analysis. In addition, a linear mixed effects model was used to determine if the difference between groups was statistically significant. We have included penetration identity as a random effect to account for the non-independent sampling of neighboring electrodes.

To determine the tuning of these ITD sensitive multi-units we used a principal component analysis in which four statistically independent clusters were identified in the pooled normal hearing experienced and neonatally deafened cohorts according to Euclidean distances (Fig. 5 A-C). Prior to principal component analysis, the responses for each tuning curve were “centered” by subtracting their mean and normalized by their standard deviation effectively calculating z-scores. This

normalization step makes the analysis insensitive to possible confounding effects of differences in overall response amplitudes, rather than tuning curve shape. Principal components were then subjected to hierarchical clustering and distributions of clusters per cohort and animals were then determined.

Finally, in an attempt to quantify how observed differences in ITD tuning curve shapes between the different cohorts might influence the ability to perform a left-right two-alternative forced choice ITD discrimination task, we calculated neural d-prime (*d'*) values. Our approach is inspired by (Shackleton et al. 2003), who computed ROC values from neural response data in order to make these more directly comparable to psychophysical performance measures. The approach is equivalent since, in psychophysical signal detection theory, ROC and *d*' are linked via the relationship $d' = \sqrt{2}\,Z(ROC)$ where Z() is the inverse cumulative normal distribution. In essence, *d'* quantifies how far apart the means of two distributions are in multiples of their standard deviations. It thereby quantifies the discriminability of responses drawn from the distributions as an inverse relation to the overlap between the distributions. Here, we considered the contralateral and ipsilateral AMUA response distributions for paired ITD values in order to measure the discriminability of neural responses across the 30 trials for each ITD. Following a convention established by Hancock et al. (2010), we treat cases as a "hit" where the response to the contralateral stimulus was strongest and as a "false alarm" where the ipsilateral response was strongest, irrespective of the tuning curve shape. The mean values and variances for the contra- and ipsilateral segments of the AMUA responses for symmetric ITD values in each trial are taken in order to calculate the *d'* value so that:

$$d' = \frac{mean(ipsi) - mean(contra)}{\sqrt{(0.5\,(var(ipsi) + var(contra)))}} \qquad (1)$$

≥1, are equivalent to performances in a two alternative forced choice task that exceeds 75% correct, and can serve as a useful “performance threshold” (see Fig 6). Note that the use of Eqn 1 for computing *d’* is highly computationally efficient, but may not be suitable for signals with a highly non-normal distribution, in which case the ROC method introduced by Shackleton et al. (2003)may be preferable. We verified that, for our data, Eqn 1 gives very similar results to those obtained when computing ROC values using the Shackleton et al. (2003) method and then converting them to *d'*.

2.6. Code accessibility

All data and custom code will be made available upon request.

3. Results

Using the methods just described, we recorded responses from a total of 12 animals, four hearing experienced finely sampled, four neonatally deafened finely sampled, and four neonatally deafened coarsely sampled animals. The breakdown of how many penetrations were sampled from each animal is given in Table 2. In total, we recorded from 106 penetrations with a 32 multi-channel electrode, and our total dataset therefore comprises 3392 recording sites. One-way ANOVA on response amplitudes during the response window (2.8-40 ms post stimulus onset) against baseline (alpha=0.01) confirmed that all 3392 recording sites exhibited evoked responses to the CI stimulation, and AMUA response amplitudes were therefore computed as described for all recording sites.

Animal ID	# Penetrations in right IC	# Penetrations in left IC	Sampling of ITD tuning curves (fine or coarse)
Hearing Experienced 1	13	0	fine
Hearing Experienced 2	8	0	fine
Hearing Experienced 3	9	0	fine
Hearing Experienced 4	11	0	fine
Neonatally Deafened 1	6	8	fine
Neonatally Deafened 2	4	5	fine
Neonatally Deafened 3	3	6	fine
Neonatally Deafened 4	3	3	fine
Neonatally Deafened 5	3	0	coarse
Neonatally Deafened 6	10	0	coarse
Neonatally Deafened 7	9	0	coarse
Neonatally Deafened 8	5	0	coarse

Table 2: Overview of number of penetrations in the left or right inferior colliculus of both cohorts. Also shown is whether ”fine grained” ITD tuning curves from -160 to +160 µs in 20 µs steps or “coarse grained” tuning curves with ITDs ranging from -300 to +300 µs in 75 µs steps were sampled.

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3.1. ITD sensitivity exists in both n*eonatally deafened* and *hearing experienced* animals, but with differing patterns

Figure 2 shows representative examples of individual multi-unit raster plots and corresponding tuning curves of bilaterally CI stimulated, neonatally deafened animals (left) and hearing experienced animals (right). In each raster plot, alternating horizontal bands of shading separate each of the 17 ITDs tested. Each band of ITD consists of 30 repeated presentations stacked vertically. The response window shown excludes the first 2.8 ms to blank the electric artifact. Most multi-units showed initial onset responses at around 5 ms after stimulus onset, as well as secondary responses peaking at around 10-20 ms post stimulus onset. The tuning curves shown have been normalized relative to their maxima for ease of comparison. As previously described for other animal models (Hancock et al. 2010; Tillein et al. 2010; Hancock et al. 2013; Tillein et al. 2016; Vollmer 2018; Chung et al. 2019), we observed various neuronal ITD tuning shapes such as “peak”, “trough”, “multi-peak”, all within the physiological range of rats.

The illustrative examples shown in Figure 2 were selected to show a range of responses varying in the “strength” of ITD tuning as quantified by the mutual information between single trial AMUA response amplitudes and stimulus ITD, as well as to illustrate some of the variation in tuning curve shapes observed. The mutual information values increase from top to bottom, and multi-units were selected to give examples of comparable mutual information values between the neonatally deafened and hearing experienced datasets. Also shown for comparison are tuning strengths computed as signal-to-total-variance-ratios (STVRs, also sometimes referred to as signal-to-noise-ratios SNRs), a metric favored by some other authors (Hancock et al. 2010; Hancock et al. 2012). We show two versions of the computed tuning curves for each multi-unit in Figure 2: one computed with traditional spike counting after spike detection by thresholding (light colored lines) and one computed using our preferred AMUA method described above (darker lines). It is readily apparent that the general shape of the tuning curves is very similar for both metrics. In some of the examples,

the AMUA method gives tuning curves that may seem a little more shallow, with less pronounced dips for less effective ITDs, but it makes up for that with much smaller error bars, indicating substantially lower trial-to-trial variablility in the responses.

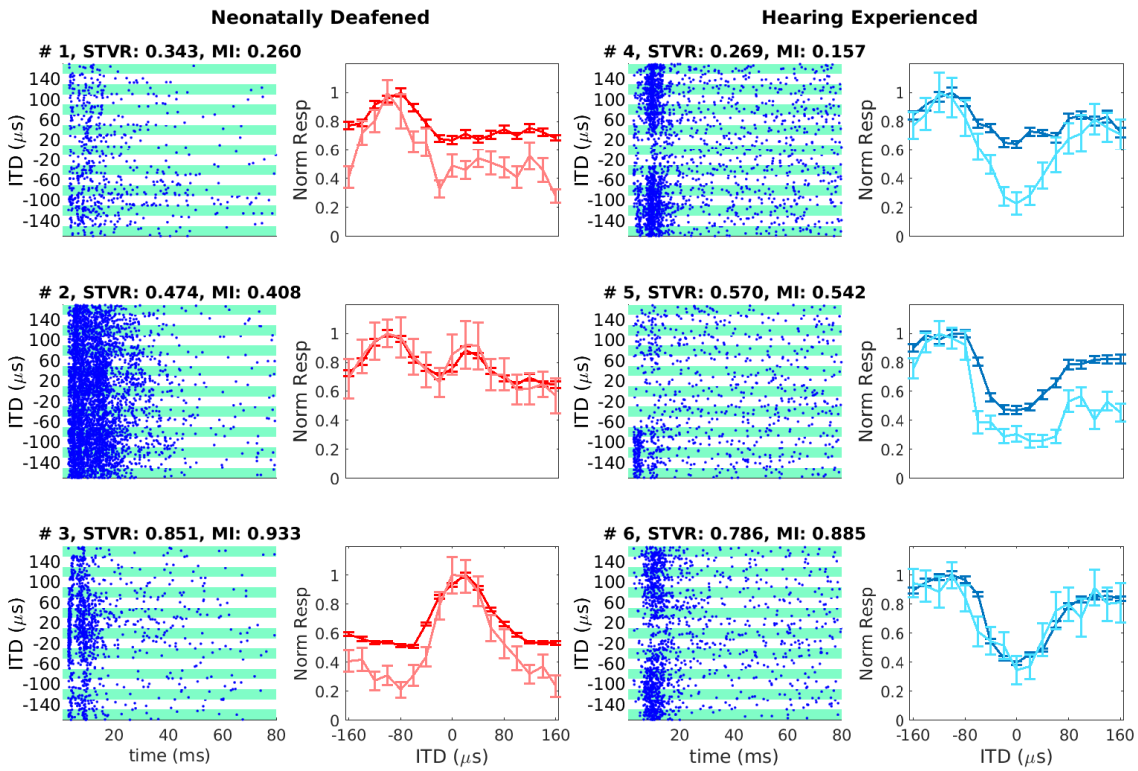

Figure 2: Spike raster plots and tuning curves for representative example multi-units for neonatally deafened (left columns) and hearing experienced (right columns) animals. Each blue dot represents a spike, successive rows of dots show responses to repeated presentations of stimuli. Responses for different ITD values are indicated by the alternating white and light green backgrounds. Multi-units are arranged from top to bottom in order of increasing ITD sensitivity, as quantified by higher mutual information (MI). The "signal-to-total-variance-ratio" (STVR) and corresponding MI value, in bits/response, are shown above each panel for each multi-unit. The tuning curves for these same units (red for neonatally deafened rats, blue for hearing experienced rats) are plotted with error bars showing the standard error of the mean response amplitude calculated across repeated presentations for each ITD value. Tuning curves in red and dark blue are computed from AMUA response amplitudes, those in pink or light blue are from multi-unit spike counts determined by simple thresholding. For these tuning curve plots, responses were baseline corrected and normalized relative to the maximal response. Negative ITD values indicate that pulses are earlier in the ear contralateral to the recording site.

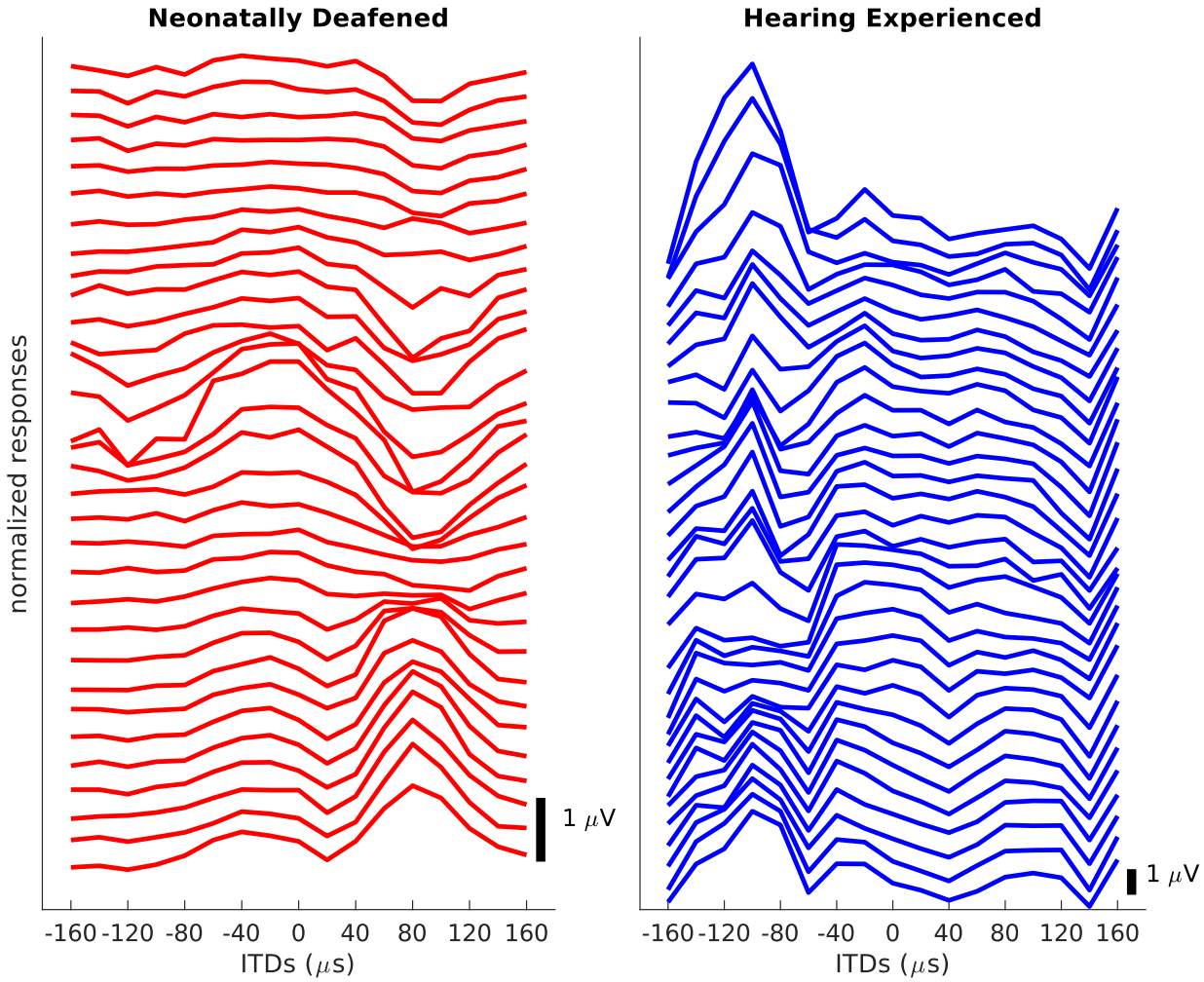

Figure 3: AMUA ITD tuning curves recorded along the 32 recording sites of a single vertical multi-electrode penetration into the inferior colliculus of a neonatally deafened (left) and a hearing experienced (right) animal. Scale bars for 1 μV are shown to the right of each subplot.

Tuning properties for neurons in inferior colliculus (as well as many other sensory structures) tended to "cluster" in the sense that anatomically neighboring neurons are expected to have more similar tuning curves than two neurons chosen at random (Schnupp et al. 2015; Li et al. 2019). Consequently, neighboring multi-units that were simultaneously recorded along a single multi-channel electrode may not safely be considered "independent observations" for the purposes of statistical testing. To illustrate that this is a relevant factor in our dataset, and to give some examples of how similar or dissimilar tuning-curves along a single multi-channel electrode penetration may be, we give in Figure 3 examples of two 32-channel electrode penetrations, one from each cohort,

showing tuning curves recorded at 0.05 mm intervals along the dorso-ventral axis. As we will see below, these examples are somewhat “typical”, in that the tuning curves seen in hearing experienced recordings (Fig. 3, right plot) were predominantly contralaterally peaked, while those in the neonatally deafened animal were more diverse and were more likely to exhibit high levels of activity for central or ipsilateral ITDs.

3.2. Multi-units in n*eonatally deafened* rats were on average no less ITD sensitive than those in h*earing experienced* rats

To compare the strength of ITD tuning in hearing experienced and neonatally deafened animals, we examined the distributions of mutual information values between AMUA response and ITD for both cohorts tested with finely sampled ITDs. These distributions are shown in Figure 4A and B, respectively. Different shading is used to indicate whether the mutual information value for a given multi-unit was significantly greater than zero (dark green bars), as determined by the permutation test described in methods. In total, 82.5% (1081/1311) of the inferior colliculus multi-units from neonatally deafened animals and 84.8% (966/1139) from hearing experienced animals showed statistically significant (α=0.01) amounts of mutual information between ITD value and neural response. We observed a higher number of units with relatively large MI values in the neonatally deafened rats (Fig. 4A) than in the hearing experienced animals (Fig. 4B), but the two distributions substantially overlapped, and the overall number of units showing significant ITD sensitivity was comparable between the two groups. It is noteworthy that mutual information is calculated as a log-base -2. Thus, with 17 ITD values a mutual information value of 4.0875 would allow us with 100% certainty be able to predict the ITD value we presented based on the neural response.

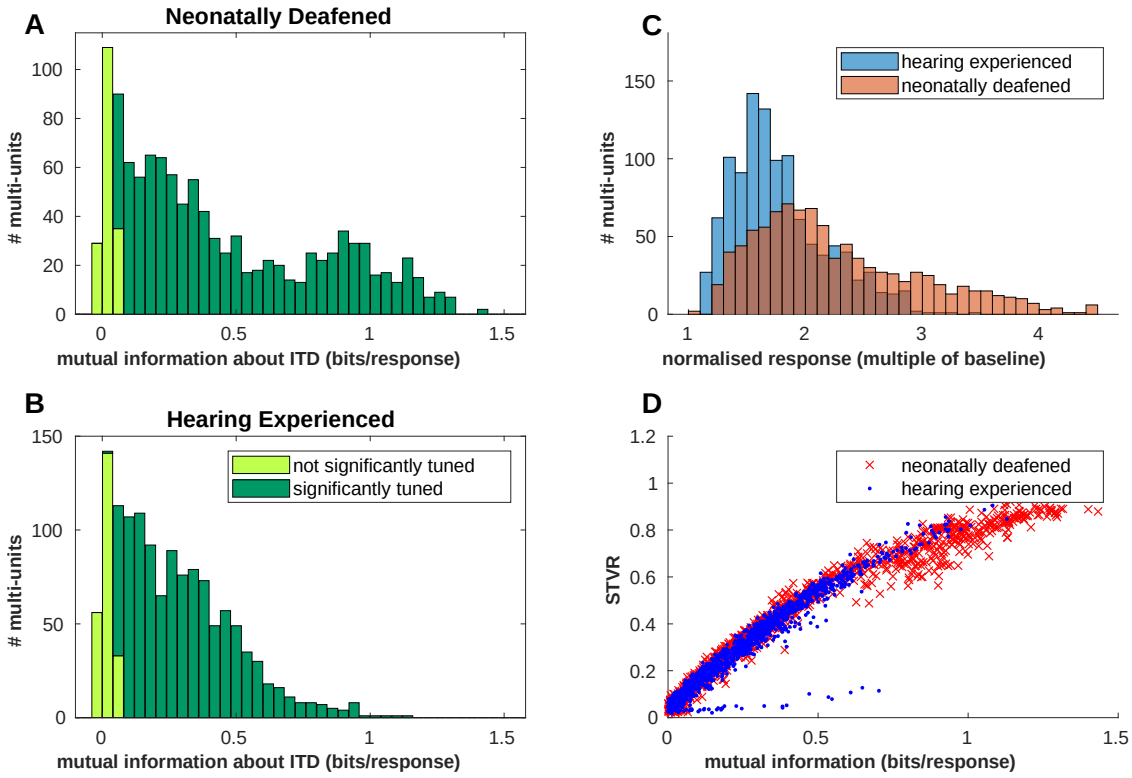

Figure 4: Mutual information between ITD and responses of inferior colliculus multi-units. A, B: Stacked bar charts showing the distribution of mutual information values between ITD and neural response in bits/response for multi-units recorded in neonatally deafened (A), and hearing experienced (B) rats. Multi-units with mutual information values significantly above zero are shown in dark green, those failing to reach significance in light green. C: Histograms of peak response amplitudes, quantified as multiples of baseline activity, for multi-units with significant ITD tuning based on mutual information values for neonatally deafened rats (red) and hearing experienced rats (blue). D: Mutual information values correlated highly with signal-to-total-variance-ratio (STVR) values for our multi-unit data.

In order to determine whether the apparent differences in the distributions of the mutual information values for the two cohorts (Fig. 4A, B) were statistically significant, we log transformed the mutual information values for all units to obtain a more normally distributed outcome variable, and used a linear mixed-effects model factor to test whether hearing experience had a significant effect on the average log(mutual information). The mixed-effects model took into account that simultaneously recorded multi-units from a single 32 multichannel electrode penetration cannot be considered independent observations, by treating the 79 multi-channel electrode penetrations performed with fine sampling in this study as a random effect. The model formula was therefore:

$$log(mutual\ information) \sim 1 + hearing\ experienced + (1 \mid penId) \quad (2)$$

where *hearing experienced* is an index variable giving hearing experience status (0 for neonatally deafened rats or 1 for hearing experienced rats), and *penId* is an index variable for penetration number, which groups all multi-units from the same penetration and removes systematic differences from one penetration to another. The model confirmed that *hearing experience* had a significant effect on mutual information values with $p = 0.017$. This can also be appreciated with the different shapes of the mutual information histograms shown in Figure 4A and B. However, note that the mixed-effects model does not take into account the possibility of "nested" dependencies of penetrations within individual animals and it may therefore overestimate significance levels. At the time of writing, we were unable to find a statistical library that offers nested mixed-effect linear model fits to continuous valued data. Ultimately, we are not too concerned about whether the neonatally deafened cohort had significantly higher mutual information than the hearing experienced one. What we can say with certainty though, is that the mutual information in the deafened animals was not lower, which in itself is an interesting and perhaps surprising result given numerous other studies mentioned in the introduction which have documented difficulties with ITD sensitivity in deafened patients or animals.

We also examined whether there were any trends for mutual information values to increase or decrease systematically over the course of each recording experiment, as that might have indicated an instability or gradual deterioration in the physiological condition of the animals. No systematic relationship was found between mutual information values and time of recording relative to the start of the experiment.

Figure 4C compares response amplitudes in the two cohorts, showing histograms of maximum response values expressed as multiples of the baseline amplitudes. For this Figure, expressing peak

response amplitudes as multiples of the baseline activity observed at each recording site was done in order to make this comparison less sensitive to changes in electrode impedances that are to be expected from site to site and from animal to animal, and which would affect the recorded voltages, but should not change the factor by which they increase following stimulation. It is clear that responses to CI stimulation are on average stronger in the inferior colliculus of the neonatally deafened cohort as compared to the hearing experienced group. In Figure 4C we see that almost a quarter of multi-units of the neonatally deafened cohort exhibited peak responses more than three times that of the baseline activity, while in the CI-stimulated hearing experienced cohort peak responses greater than three times that of the baseline were very rare. The median peak response for multi-units in the inferior colliculus of neonatally deafened rats was 2.2 times greater than baseline responses, compared to 1.7 times seen in multi-units of hearing experienced animals. These differences were statistically significant ($p < 10e-6$), as determined by a linear mixed-effects model equivalent to that used above to test for differences in mutual information between cohorts. Note that the amplitudes of stimulus pulses used, as well as eABR thresholds, were comparable between cohorts, suggesting these differences cannot be explained by simple, systematic differences in stimulation intensities.

From these data we conclude that ITD tuning in our neonatally deafened cohort was comparable to that in the hearing experienced cohort. This is a surprising result in light of several studies which have documented reduced ITD sensitivity in deafened animals. One set of studies which described reduced ITD sensitivity in deafened cats (Hancock et al. 2010; Hancock et al. 2012) uses a metric known as "signal to noise ratio" or later, perhaps more accurately, as "signal-to-total-variance-ratio". We have compared this signal-to-total-variance-ratio to our measure of ITD sensitivity, mutual information, in Figure 4D. From this we can clearly see that the two measures correlated closely for both cohorts and thus our results are not a consequence of our choice of ITD senstivity measure.

3.3. Distributions of ITD tuning curve shapes differed between h*earing experienced* and *neonatally deafened* animals

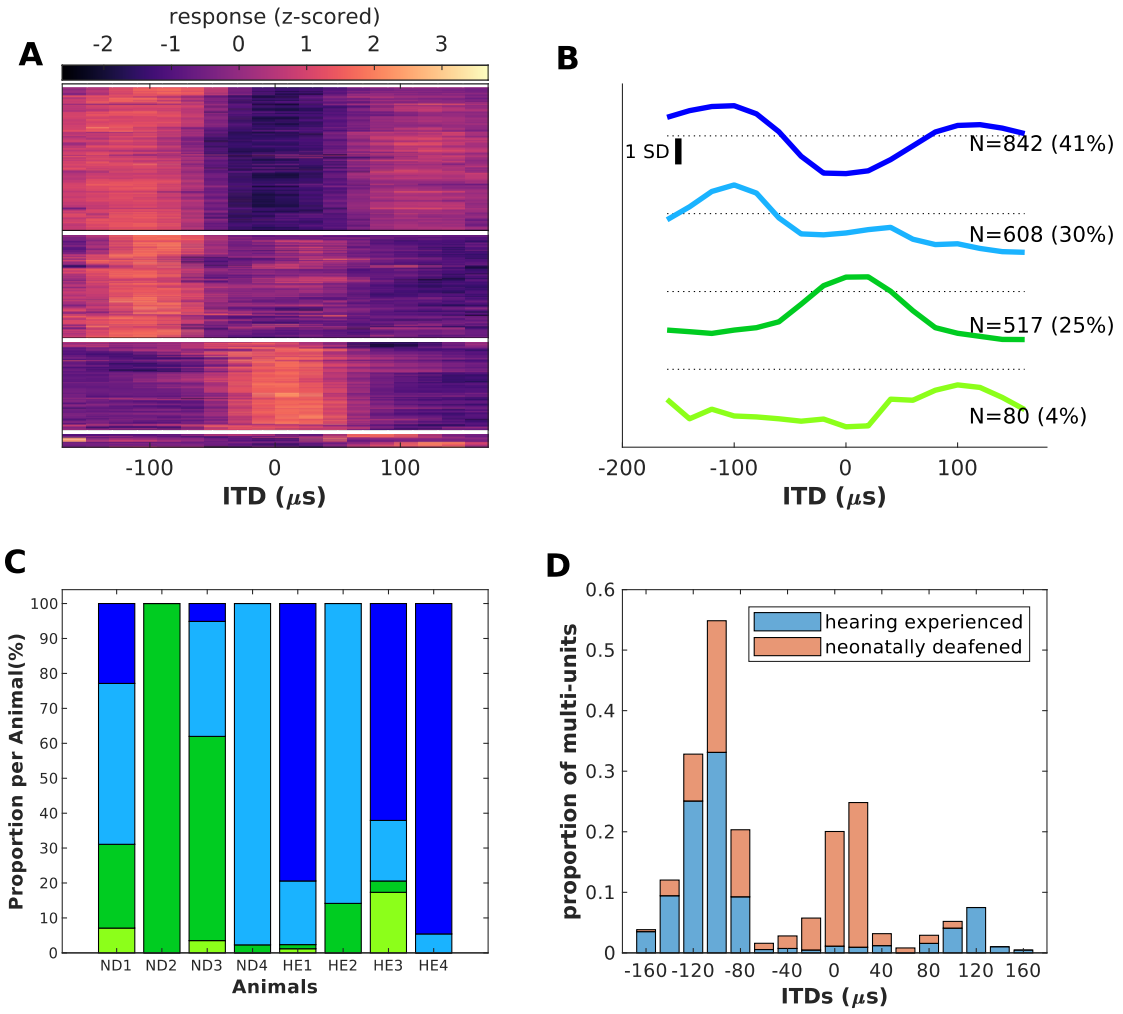

Figure 5: Distribution of ITD tuning curve shapes differ systematically between normal hearing experienced (HE) and neonatally deafened (ND) rats. A: Tuning curves of all multi-units with significant ITD tuning, shown as a heat map, with tuning curves sorted into four clusters determined by a hierarchical clustering algorithm (see methods). B: Mean tuning curve for each of the four clusters shown in A. Responses in the tuning curves were normalized to unit standard deviation. Scale bar shows 1 standard deviation (SD). The total number of multi-units, and its percentage, are shown next to each curve. C: Stacked bars showing the distribution of tuning curve types (clusters) for the four neonatally deafened animals (ND1-ND4) and the four hearing experienced (HE1-HE4) animals with finely sampled ITDs. Colors match those of the mean tuning curves for the clusters shown in B. D: Stacked histograms of peak ITD values for all multi-units from neonatally deafened (salmon-pink) and hearing experienced (blue) animals.

The data in Figure 4 show that the strength of tuning to ITD, as quantified by the mutual information between neural responses and stimulus ITD, was on average, no worse in our neonatally deafened rats compared to their hearing experienced peers. However, similar proportions of ITD sensitive units do not imply that ITD tuning curve shapes are also similar btween the two cohorts. The examples from Figures 2 and 3 show that ITD tuning curve shapes in the inferior colliculus in response to electrical stimulation can be quite diverse, a fact that has also been reported previously (Hancock et al. 2010; Tillein et al. 2010; Chung et al. 2019; Rosskothen-Kuhl et al. 2021). In order to impose an order on the diverse tuning curve shapes in a data-driven manner, we subjected them to a cluster analysis. The tuning curves for all significantly tuned multi-units were pooled across both cohorts (n=2047), with their mean subtracted and normalized by their standard deviation resulting in z-scores, and subjected to principal component analysis followed by hierarchical clustering. The first five principal components were found to account for 90.36% of the variance in tuning curve shapes. We therefore represented each tuning curve by the first five principal components, and subjected these vectors to hierarchical clustering using the Matlab function “cluster()” with Euclidean distance metrics and complete linkage. This categorized the tuning curves into four distinct clusters shown in Figure 5A which accounts for 66.7% of the variability from the first five principal components. The heatmap in Figure 5A shows all normalized tuning curves of all significantly tuned multi-units in our database, arranged by cluster membership. It illustrates the variety of tuning curves in each cluster. Figure 5B shows the mean tuning curve for each cluster. The first and second clusters contained two varieties of contralateral dominant tuning, with peaks near -100 µs, and accounted for 41%(n=842/2047) and 30% (n=608/2047) of all multi-units, respectively. Together these two contralaterally tuned clusters comprise the large majority of ITD multi-units, as would be expected in light of previous findings (Hancock et al. 2013; Tillein et al. 2016). The primary difference between these two clusters is that the tuning curves in the cluster 1 (dark blue in Fig. 5B and C) exhibit a second, slightly smaller peak for ipsilateral ITDs at +120 µs, and they may therefore be described as “trough” shaped, unlike tuning curves in cluster 2 (light blue

in Fig. 5B and C) which exhibit only a single substantial peak for contralateral ITDs at -100 µs and are thus considered “contralateral” in shape. However, both clusters 1 and 2 are clearly predominantly contralaterally tuned. The third largest cluster contained mostly multi-units which gave strongest responses for ITDs near zero, “central” tuning and comprised 25% (n=517/2047) of the significantly tuned multi-units. The fourth cluster comprised only 4% (n=80/2047) of multi-units, and these peaked for ipsilateral ITDs at 100 µs ”ipislateral” tuning.

Next, we asked whether each of the four clusters of tuning curves (“trough”, “contralateral”, “central”, and “ipsilateral”) was equally represented in the neonatally deafened and hearing experienced cohorts. Figure 5C shows the distribution for each of the four clusters found in 5A and B for each animal. Here we see a fair amount of individual variability. However, we can still appreciate some general trends. In the hearing experienced rats, the majority of units belonged to either the “trough” shaped cluster 1 (71%) or the “contralateral” cluster 2 (21%), giving a total of 95% of multi-units with predominantly contralateral tuning. Central or ipsilateral tuning were rare in multi-units from hearing experienced animals, representing only 3% and 5% of our sample, respectively. In contrast, the neonatally deafened animals were found to have far fewer contralateral peak type units, at only 47% (8% from “trough” cluster 1 and 39% from “contralateral” cluster 2) with the exception of ND4. Instead, in neonatally deafened rats far more multi-units (50% of the total) were found with peak tuning near the midline (“central” cluster 3). Ipsilateral tuning (cluster 4) was rare in the neonatally deafened samples, at 3%, similar to that in the hearing experienced cohort.

One may of course wonder whether the just described differences in the proportions of contralaterally tuned multi-units seen in the two cohorts could have arisen by chance from random “sampling bias”, if one were to assume that every inferior colliculus might have both contralaterally and centrally tuned units, and that these just happened to be sampled differently in the two cohorts. However, given that the number of independent electrode penetrations used to sample the inferior colliculus in both cohorts was quite large (see Tab. 2), one can use critical values of the binomial

distribution to estimate the likelihood of observing differences of such magnitude by chance. The probability of observing 95% predominantly contralateral tuning in a sample of 41 penetrations in the inferior colliculus of the hearing experienced animals if the expected probability is only 71% would be as small as p=0.000014 suggesting that this chance likelihood is negligibly small.

To further confirm that the trends seen in Figure 5C are robust, we determined the "best ITD" (that is, the ITD value giving the largest response) for each multi-unit, and plotted the distributions in Figure 5D for both the hearing experienced (blue) and the neonatally deafened (salmon-pink) cohorts. Overall, the distributions shows two clear peaks, corresponding to units with maximal responses for contralateral (-80 to -120 μs), or just off-centre (0 to +20 μs) ITDs, corresponding to contralaterally (clusters 1 and 2) and centrally (cluster 3) tuned units, respectively. There is also a much smaller peak at +120 μs showing ipsilateral preference. Again we note differences between cohorts: the majority of multi-units recorded in the hearing experienced animals (blue bars) have their maximum responses at contralateral ITDs, with a much smaller peak for ipsilateral ITDs (near +120 μs). Tuning curves of multi-units recorded from neonatally deafened animals (salmon-pink bars) also often have their maxima at contralateral ITDs with a large portion showing peak response at -100 μs. However, in contrast to the hearing experienced data, these multi-units commonly exhibit maxima just ipsilateral to the midline, with best ITD between 0 and +20 μs. This best ITD distribution arises because the "centrally" tuned responses that form cluster 3 in Figure 5B are not exactly at the midline, but slightly offset toward the ipsilateral ITDs. Overall, we observed hearing experienced animals showed a clear contralateral dominance for best ITD, while the neonatally deafened cohort showed equal proportions of units with central, or just ipsilateral,and contralateral peak ITDs.

The differences in the distributions of tuning curve types and best ITD illustrated in Figure 5C and D are pronounced. However, assessing the statistical significance of these differences is again complicated by the fact that tuning curves of neighboring multi-units cannot be considered independent observations. We therefore opted to perform a highly conservative Kruskal-Wallis test,

comparing best ITD averaged over all tuning curves from each of the 79 multi-electrode penetrations in our fine-sampled animals. Thus, each multi-channel electrode penetration contributed only a single best ITD value to this test. The null hypothesis was that the median best ITD would be the same in both the hearing experienced and the neonatally deafened cohort, but the data in Figure 5D suggest that they may be different. Hearing experienced animal tuning curves had a median best ITD at a firmly contralateral -100 μs, while the median best ITD for the neonatally deafened animal tuning curves was just contralateral off the midline, at -20 μs. The Kruskal-Wallis test confirmed that these differences in median were significant with p = 0.00004. Note that this test does not allow for "nesting" of penetrations within individual animals, and may therefore overestimate the true level of statistical significance. To the best of our knowledge there is no routinely accepted or widely available method for dealing with nested non-parametric data.

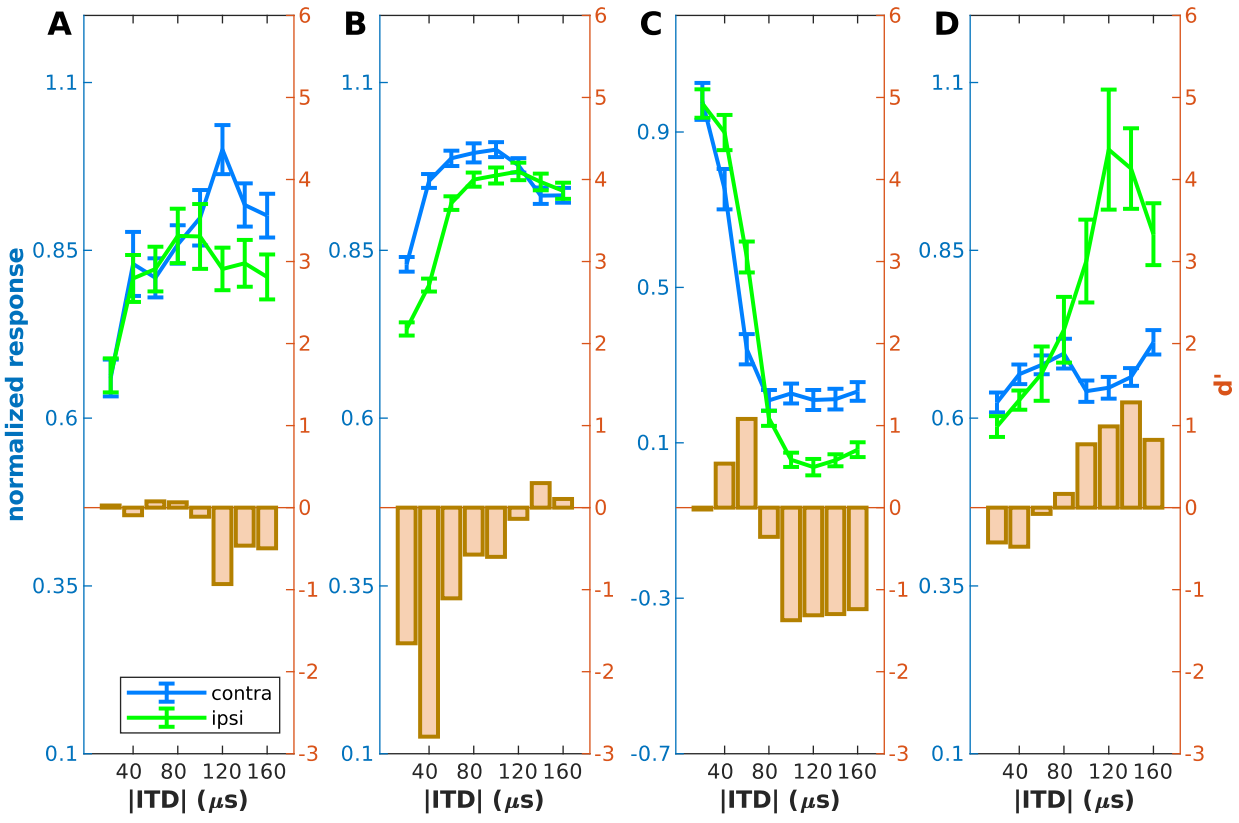

Figure 6: Four examples of multi-units with different tuning curve shapes, plotted alongside their respective *d'* values. Blue y-axis on the left shows the normalized

responses, with both the contralateral tuning curve segment (blue) and the ipsilateral segment (green) plotted against increasing absolute ITD. Error bars show the standard error of the mean. The orange y-axis on the right gives the *d'* values plotted as bronze bars below the tuning curves for each of the four examples. Note how absolute *d'* values are large when the distance between the ipsi- and contralateral tuning curve is large relative to the standard error of the mean. *d'* values are positive when the response to the ipsilateral ITD is larger than that to the contralateral ITD and negative for the reverse case.

The substantial differences in tuning curve distributions between neonatally deafened and hearing experienced animals which we have just described raises the question of how these differences might affect an animal's performance in particular types of sound localization tasks. For example, midline tuned multi-units have tuning curves that are fairly symmetric around the midline, and might therefore be expected to be less suitable for signaling whether sound came from the left or right than either ipsi- or contralaterally tuned units. At present, our understanding of how the activity of inferior colliculus neurons is read out by thalamic, and ultimately, cortical neurons to control sound localization tasks is very incomplete, and any assessment of the neural coding at the level of the inferior colliculus in order to predict limits of behavioral performance will depend on a numerous assumptions. Nevertheless, it is possible to analyze neural responses using the tools of signal detection theory to compute receiver operating characteristics and sensitivity *d'* indices, which can serve as theoretical upper bounds of the discriminability of pairs of stimuli (Geissler 2003). Here, we opted to evaluate how well the observed neural tuning of each multi-unit might support the performance in an ITD lateralization task by computing *d'* values for the observed distributions of neuronal responses to pairs of contralateral and ipsilateral stimuli for a given ITD. Figure 6 shows responses and derived *d'* values (computed as described in the methods) for four example units, one contralaterally tuned (A), one trough shape (B), one centrally tuned (C), and one ipsilaterally tuned (D). To put the values plotted along the right y-axes in Figure 6 into perspective, remember that *d'* values relate to the percent correct scores that an ideal observer should be able to achieve in a two-alternative forced choice task according to the relationship $percent\ correct = \Phi(d'/\sqrt{2})$, where Φ is the cumulative normal distribution. Also remember that the sign of the *d'*

reflects only whether a unit fires more strongly for contra- or ipsilateral stimuli. Normally inferior colliculus units exhibit predominantly contralateral tuning, which our analysis maps on to negative *d'* values, but units with reliable ipsilateral tuning and therefore strongly positive *d'* values could in principal also guide successful lateralization behavior. Some of the analysis below will therefore consider absolute *d'* values (|*d'*|). We remind the reader that a |*d'*| of 1 is equivalent to an upper limit of performance of ~75% correct, while a |*d'*| of 3 is equivalent to an upper limit of ~98% correct. With these values in mind, we note that all of the multi-units shown in Figure 6 should be capable of supporting behavioral performance much above chance level in a two-alternative forced choice ITD lateralization task, but the four multi-units shown differ in the range of ITDs for which they can facilitate lateralization at 75% correct performance, in other words where they have an |*d'*| value of 1 or above. Note also that the trough or central peak tuned units shown in Figure 6B and C, which due to the relative symmetry of their tuning curves might be considered less suitable for lateralization tasks, nevertheless are sufficiently left-right asymmetric to yield quite sizable |*d'*| values for certain ITDs.

In Figure 7A we show the distributions of *d'* by the multi-units recorded for each pair of left and right leading ITDs. The distributions for both the neonatally deafened (pink bars) and the hearing experienced (blue bars) cohorts are plotted as overlapping histograms. The distribution of *d'* values for the neonatally deafened group appears to be wider at all ITDs. Additionally, the neonatally deafened group has more positive *d'* values, particularly for ITDs of +/-40 and +/-60 μs and more negative *d'* values for ITDs ≥ +/-80 μs. One question we can address with the data in Figure 7A is: how many multi-units would support "suprathreshold" performance, which we define here as |*d'*|>1, and would therefore be capable of facilitating an above ~75% correct performance by an optimal observer in a two-alternative forced choice lateralization task for a given ITD? These multi-units lie outside the range of $d' \in [-1, 1]$ indicated by the broken lines in Figure 7A. The proportion of these

multi-units for each ITD value in each cohort are summarized in Figure 7B (neonatally deafened) and C (hearing experienced).

Figure 7B and C show the proportion of units with an ITD sensitivity large enough to be theoretically capable of supporting an ITD lateralization performance of up to 75%, where d' values were either below -1 (dashed lines) or above +1 (solid lines). Hearing experienced animals showed almost no units with a d' > +1 which would indicate a strong ipsilateral lateralization (Fig. 7C, solid line). However, the number of units with good contralateral encoding (d' < -1) increased sharply after +/-40 μs with a maximum between 100 to 120 μs (Fig. 7C, dashed line). The proportion of multi-units with absolute d' > 1 for neonatally deafened animals (Fig. 7B) is slightly higher than that for hearing experienced animals, both for negative (dashed line) and positive (solid line) d' values. As in the hearing experienced cohort, the neural responses from the neonatally deafened animals also showed a sharp increase in the proportion of units with d' < -1 as ITDs increased above +/-40 μs. These increases in multi-unit proportions with sizable d' values for increasing ITD qualitatively match similar increases in behavioral ITD discrimination abilities previously demonstrated (Li et al. 2019; Rosskothen-Kuhl et al. 2021).

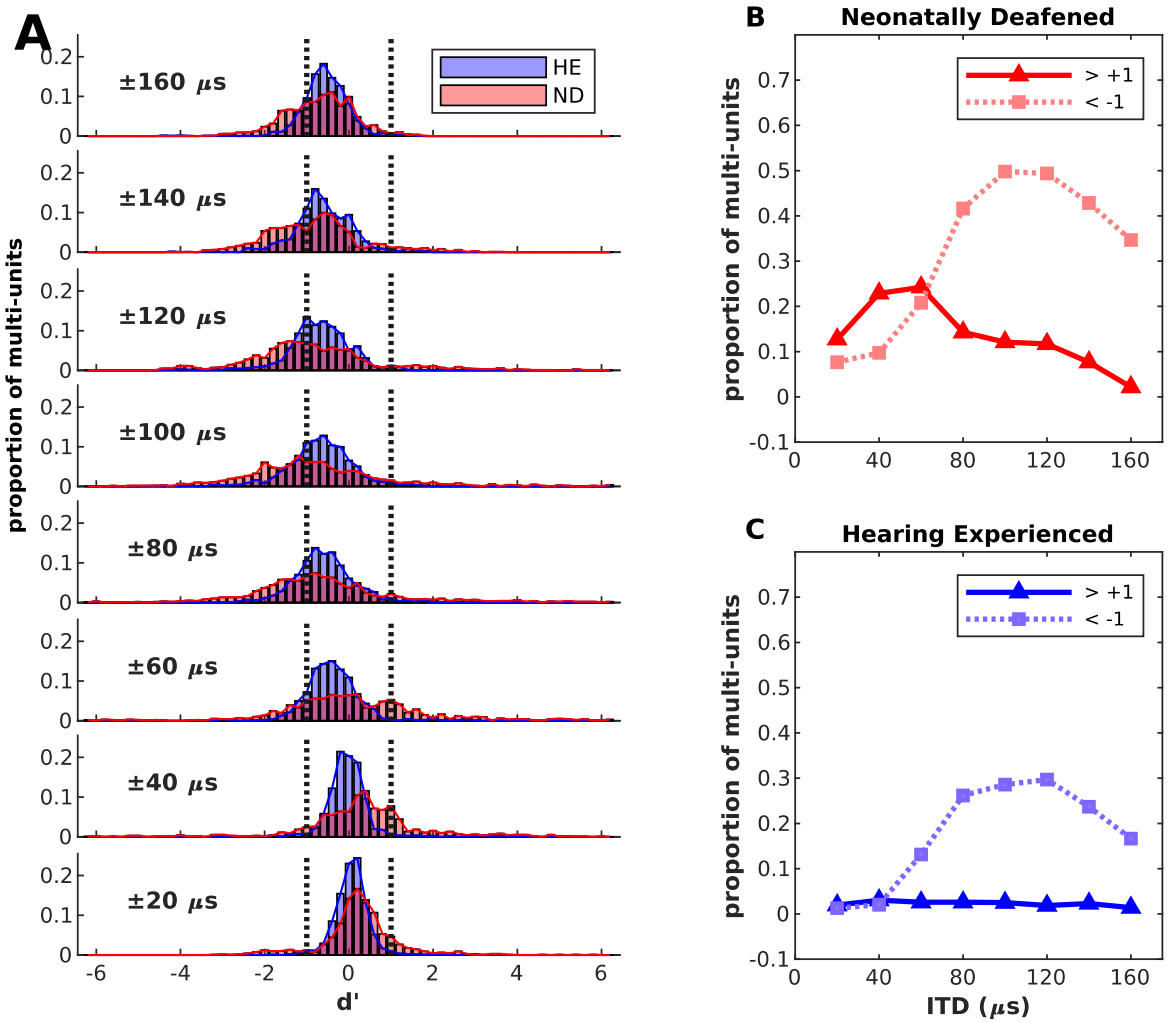

Figure 7: A: Distributions of *d'* values for pairs of ITD values shown on the left. Negative *d'* values indicate stronger contralateral responses, positive *d'* values indicate stronger ipsilateral responses. Distributions for hearing experienced animals are shown in blue, those for neonatally deafened animals in pink. Broken vertical lines highlight d' values of +/-1, equivalent to a discrimination performance of ~75%. B: Proportions of multi-units with *d'* either > +1 (solid lines) or < -1 (dashed lines), as a function of ITD, for the neonatally deafened cohort. C: as in B, but for the hearing experienced cohort. HE: hearing experienced animals, ND: neonatally deafened animals.

3.4. Sampling ITDs predominantly outside the physiological range and excluding onset responses resulted in sizable reductions in measured ITD sensitivity

As mentioned above, most previous studies of ITD tuning have sampled a very wide range of ITD values, often several times larger than the animal's physiological range, at fairly coarse intervals.

Our results here are unusual in that we found ITD tuning in neonatally deafened CI animals which was no less robust than that seen in hearing experienced controls. Importantly, the +/-160 μs range of ITDs we tested barely extends beyond the animals' physiological range of +/-120 μs (Koka et al. 2008). Within this range, we sampled with a 20 μs step size, which is small enough to resolve behavioral just noticeable differences, which are in the order of ~50 μs (Rosskothen-Kuhl et al. 2021). It seems possible that previous reports of impaired ITD tuning in CI animals could be adversely affected by sub-optimal sampling of ITD values, for example if the range of ITDs sampled is unnaturally large, several times larger than the range of values that the system would have evolved to process, or if the sampling resolution is too coarse relative to known or expected behavioral thresholds.

To investigate that possibility, we recorded inferior colliculus ITD tuning curves from additional four neonatally deafened rats, using the same procedures, but sampling a wider ITD range, from -300 to +300 μs, in coarser, 75 μs step sizes. This "wide and coarse sampling" spans a range of ITDs that corresponds to 250% of the normal physiological range in our animal model, and is more similar to ranges adopted by other authors in previous studies. Figure 8A shows the distribution of mutual information values for the 406 ITD tuning curves recorded with wide and coarse sampling during 27 multi-channel electrode penetrations into the inferior colliculi of the second batch of four neonatally deafened animals. For easy comparison, the mutual information values for the neonatally deafened animals sampled with our tight sampling which was already shown in Figure 4A is also reproduced in Figure 8B. The differences in these distributions are pronounced. Of the coarsely sampled units, only 52.7% (n=214/406) had mutual information values that were significantly above zero, in contrast to the finely sampled units, where 82.5% (1081/1311) were significantly ITD sensitive. When including both significant and non-significant mutual information values we found that the median mutual information value for the coarsely sampled data was 0.06 bits/response compared to 0.3 bits/response for the fine sampled cohort. Based on a Kruskal-Wallis test, this difference was significant ($p < 0.001$).

If we were to additionally exclude at least the first 15 ms of the response in our dataset, as has been done in a few previous published studies (Hancock et al. 2010; Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2019), then the proportion of multi-units with significant mutual information values, drops from 52.7% to as low as 5% with coarse sampling and from 82.5% to 61% with fine sampling ITDs (data not shown). However, it should be noted that the absence of sustained responses is not too surprising given that these were single pulse stimuli.

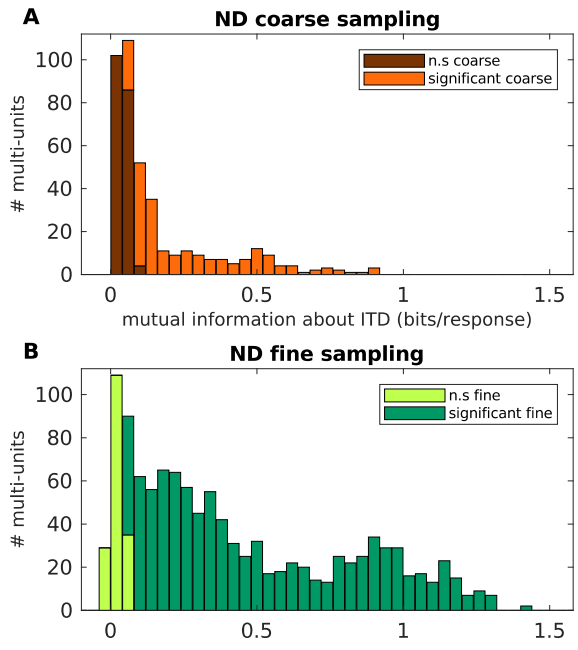

Figure 8: Coarsely and broadly sampled ITD tuning curves recorded in neonatally deafened CI rats yielded lower sensitivity values than ITD tuning curves which finely sample the physiological range. A: Mutual information values for coarsely sampled ITDs (from -300 µs to +300 µs in 75 µs steps). B: Histogram of mutual information values from the cohort with finely sampled ITDs (from -160 µs to +160 µs in 20 µs steps) reproduced from Figure 4A for comparison. Mutual information values which are significantly above zero are shown in orange (A) or dark green (B). ND: neonatally deafened animals, n.s.: non-significant.

4. Discussion

4.1. I*nferior colliculus* neurons showed prominent ITD sensitivity even in the absence of hearing experience

In this study we have documented an abundance of ITD tuning in the inferior colliculus of cochlear implanted rats immediately after bilateral cochlear implantation, even in the absence of early auditory experience. ITD sensitivity has been previously reported in early deaf animal models, both in inferior colliculus and in auditory cortex, although it was found in fewer units than in hearing experienced controls (Hancock et al. 2010; Tillein et al. 2010; Hancock et al. 2013; Chung et al. 2016; Tillein et al. 2016; Vollmer 2018; Chung et al. 2019). Before we turn our attention to the differences between our findings and those reported by others, we must note that there is an important agreement among all studies of ITD sensitivity in early deaf CI animals to date: none of these studies has yet observed a reduction in ITD sensitivity compared to normal which would be large enough to adequately explain the severe lack of behavioral ITD sensitivity observed in early deaf human patients with bilateral CIs (van Hoesel 2004; Grieco-Calub and Litovsky 2010; Litovsky 2010; van Hoesel 2012; Kerber and Seeber 2012; Laback et al. 2015; Ehlers et al. 2017).

Our results are unusual in that we did not find any marked decrease in the quality of ITD tuning in our neonatally deafened animals compared to hearing experienced controls. Indeed, the ITD sensitivity in neonatally deafened CI animals was comparable to hearing experienced CI animals (Fig. 4A, B). There are many possible reasons for this possible discrepancy. One of course, is species differences, given that we used rats while other previous studies have used predominantly cats or rabbits. However, as shown in the context of Figure 8, the very robust ITD tuning in neonatally deafened animals is only apparent if the ITDs sampled focus on the physiological range, and if onset responses are included in the analysis. Other previous studies (e.g. Hancock et al. (2012); Hancock et al. (2013)) may therefore have missed some of the ITD sensitivity in their early deaf CI animals due to their use of coarse and wide ITD sampling and exclusion of onset

responses. So what may have motivated the wide and coarse ITD sampling choices made in previous studies of ITD sensitivity in CI animals? Unfortunately, the articles do not describe how the authors chose the ITD values they tested, but it seems very likely that they simply followed the example set by classic studies on ITD sensitivity in the brainstem and midbrain in response to acoustic, often pure tone stimulation. Indeed, most previous studies of ITD coding under acoustic stimulation have used ranges of ITD values that extend far beyond the physiological range (Yin and Chan 1990; McAlpine et al. 1998; Brand et al. 2002; Yin 2002). With acoustic stimuli, such a wide range of ITDs can be useful, for example because it can reveal periodic ITD tuning curve shapes at periods which reflect a unit's characteristic frequency. This, in turn can hint at the nature of ITD detection circuits in the brainstem, revealing a "cross-correlator-like" operation, in which periodic inputs from the cochlear filters produce periodic outputs (Schnupp and Carr 2009). In addition in echoic environments optimal encoding of ITDs beyond the physiological ITD ranges is thought to exist (Harper and McAlpine 2004). Thus, in the context of studies with acoustic stimuli which are interested in possible underlying neural mechanisms, sampling unnaturally large ITD ranges can be revealing. However, CI stimulation bypasses the cochlea's mechanical filters. There is no filter ringing which would induce periodic auditory nerve responses, and obvious periodicities in midbrain ITD tuning curves, which are so common with acoustic stimuli, are neither expected nor observed under CI stimulation. Furthermore, in studies of prosthetic hearing, the focus is often more on likely capabilities rather than underlying mechanisms. Our objective here was to assess the likely capabilities of the binaural system after neonatal deafening. Our exclusion of unnaturally large ITDs in favor of a fine-grained focus on the physiological range is well motivated, even if it makes it difficult to compare our results directly with those of other previous studies which did not prioritize the use of ITDs within the physiological range and step sizes which are small enough to resolve behavioral just noticeable differences,

Another important difference is that our quantification of response strength included onset responses, while several other studies (Smith and Delgutte 2007; Hancock et al. 2010; Hancock et

al. 2012; Hancock et al. 2013; Chung et al. 2019) excluded them. In our analysis we used a response window from 2.8 – 40 ms post-stimulus onset. Our study focused on optimizing the delivery of ITDs and as such we looked at the most salient aspect of the ITD cue response namely the onset ITD responses (Brown and Stecker 2010; Greenberg et al. 2017). To us, including onsets in the analysis seems well motivated, given that Brown and Stecker (2010) and others have shown that the onset of stimuli dominates the perception of both ITDs and ILDs in normal hearing human listeners, and that physiological studies have ascertained that stimuli with sharp onsets yield better ITD sensitivity (Greenberg et al. 2017). Indeed, many studies of the so-called "precedence effect" have documented the dominance of sound onset in spatial hearing, and highlighted the usefulness of strong onset weighting in reverberant acoustic environments, where only the earliest part of a sound stimulus can be expected to be uncontaminated by confounds generated by strong echoes created by indirect sound reflected off nearby surfaces (Litovsky et al. 1999; Brown et al. 2015a,b). Studies which analyzed exclusively or predominantly the sustained part of neural responses to ongoing stimuli therefore exclude a very important portion of the neural response, and are bound to underestimate the "true" ITD sensitivity of the neurons studied. In fact, when we excluded onsets from our analysis, the proportion of multi-units exhibiting statistically significant ITD sensitivity in the group of neonatally deafened animals tested with the "wide and coarse" stimulus set dropped dramatically from 52.7% to only 5% and with fine sampling from 82.5% to 61%. These results indicate that details in the choice of stimulus parameters range as well as whether analysis time windows focus on onset or sustained responses can have dramatic effects on the quality of the ITD tuning observed. In our study, we chose parameters which we believe to be well motivated from a perspective of ecological validity, with ITDs mostly confined to the physiological range, and onset responses included in the analysis, given the well known onset-bias of binaural processing. In summary, we believe that methodological differences may be chiefly responsible for the fact that we did not observe the reduction of ITD sensitivity in neonatally deafened animals that has been previously described by others.

4.2. Increased neuronal excitability in the absence of hearing experience

Multi-units from our neonatally deafened rats showed appreciably stronger responses, as well as higher mutual information values for ITD tuning, compared to the multi-units from hearing experienced rats (Fig. 4). eABR thresholds and stimulus amplitudes were similar in the two groups, so the increased activity is likely due to biological factors. This is reminiscent of observations by (Hancock et al. 2010; Hancock et al. 2013) that spontaneous activity is increased in long-term deafened or congenitally deaf cats when compared to acutely deafened animals. Homeostatic plasticity may limit the strength of responses to sensory inputs in hearing experienced animals, but not in neonatally deafened animals. Neonatally deafened animals would then exhibit a form of hypersensitivity when they are supplied with CI stimulation for the first time in these experiments. Support for this hypothesis comes from reports showing that inhibitory interactions weaken and inhibitory synaptic strengths decrease in the deafened auditory system (Bledsoe et al. 1995; Abbott et al. 1999). Similarly, Tirko and Ryugo (2012) have shown that numbers of inhibitory axosomatic terminals in the medial superior olive (MSO) were substantially reduced in deafened animals, and Vale et al. (2003) and Vale and Sanes (2002) found that the inhibitory synaptic strength in the central inferior colliculus of gerbils declines after deafening, while excitatory post-synaptic currents increase. Auditory cortical excitability too becomes stronger following hearing loss, with increased excitatory post-synaptic potential amplitudes as well as substantially less GABAergic inhibitory activity (Kotak 2005). In a similar vein, some of our earlier studies have observed significantly larger numbers of activated inferior colliculus neurons in neonatally deafened rats compared to hearing experienced controls after identical schedules of CI stimulation (Rosskothen-Kuhl and Illing 2012; Rauch et al. 2016; Rosskothen-Kuhl et al. 2018). In addition, CI stimulation of neonatally deafened, but not hearing experienced rats has been shown to modulate the inhibitory network at the site of activation resulting in an up-regulation of inhibitory markers, such as glutamic acid decarboxylase (GAD) GAD65 and GAD67 (Rosskothen-Kuhl et al. 2018).We therefore expect

increased excitation and reduced inhibition following deafness, as this should lead to stronger responses and perhaps also to a higher “signal-to-noise-ratio” or “signal-to-total-variance-ratio” in the encoding of stimulus parameters, which may explain the high levels of mutual information between stimulus parameter and response we observed in our neonatally deafened animals (Fig. 4). However, although increased excitation can lead to higher mutual information values it is still stimulus-dependent such such that a statistically significant mutual information value would still require variability in response with respect to ITD values and it is only that these stimulus-dependent variation have a larger amplitude fluctuation from baseline that affects the magnitude of the mutual information. These findings of hyperexcitability following a period of auditory deprivation corroborate additionally with the findings of Bernstein and Trahiotis (2020) where internal noise was found to be higher even in the presence of ‘slight’ hearing loss which could account for the higher magnitude of response amplitudes above baseline as shown in figure 4.

4.3. Substantial differences in tuning curve shapes between hearing experienced and inexperienced animals

In Figure 5 we documented apparent differences in tuning curve shape distributions between neonatally deafened and hearing experienced cohorts. These differences were large and appear to be statistically robust as suggested by a highly significant Kruskal-Wallis test. However, the cohort sizes were relatively small, individual differences were quite marked (see Figure 5C), and one cannot completely exclude the possibility of electrophonic responses in the hearing experienced animals generating some sort of confound, even if it is hard to see how that would work. We therefore do not wish to exaggerate the statistical reliability of the observed differences in tuning curve distributions. However, differences in tuning curve shapes between early deafened and hearing experienced cohorts have been reported in previous studies (Hancock et al. 2012; Hancock et al. 2013). Additionally, these studies point to experience dependent mechanisms that appear capable of altering ITD tuning curve shapes in the auditory brainstem. These facts make it plausible to assume that there may be systematic differences in the distributions of ITD tuning curves

observed in hearing experienced or inexperienced animals, respectively, and thus the group differences we reported here are likely robust in spite of individual variability or a sampling bias.

Much previous work has classified ITD tuning curves into four main types: sigmoid, biphasic, trough, and peak/multi-peak shaped, based on how well the tuning curves correlated with predefined canonical shapes, such as “peak”, “trough”, “biphasic” or “sigmoid” (Smith and Delgutte 2007; Hancock et al. 2010; Tillein et al. 2010; Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2016; Tillein et al. 2016; Vollmer 2018; Chung et al. 2019). Some of these studies have documented differences in the proportions of tuning curves in each of these classes between early deafened and hearing experienced animals. We decided not to assume predefined tuning curve shapes, in part because we sampled a narrower, physiologically relevant range of ITDs much more densely, which is bound to affect the range of shapes observed, and in part because we generally favor data-driven approaches with minimal prior assumptions. Nevertheless, the clusters we observed do resemble the “peak”, “trough” and “biphasic” shapes used by others. A direct comparison of proportions of observed tuning curve “types” between studies is hindered by numerous methodological details, including the very different sets of ITDs tested. Nevertheless, we can observe clear parallels. For example, several studies have reported greatest slopes near ITDs of zero (McAlpine et al. 2001; Brand et al. 2002; Shackleton et al. 2003; Hancock and Delgutte 2004). Our best ITD distributions, for trough or central clusters (Fig. 5B andD) are in line with these previous observations, and are comparable to those seen in Figure 4A of Hancock et al. (2013). Thus, even if we cannot make precise quantitative comparisons, we nevertheless note clear qualitative agreement in the types of tuning shapes seen, and in the fact that proportions of shapes seen may differ depending on hearing experience status.

So what might drive such experience dependent differences in ITD tuning curve shapes? ITD sensitivity observed in the inferior colliculus is usually thought to arise first in the superior olivary complex, particularly the MSO, but particularly in animals with relatively high frequency

hearing, such as rats, envelope ITD coding through the lateral superior olive (LSO) is also likely to make important contributions (Joris and Yin 1995). The development of ITD sensitivity in the MSO has so far been studied in much greater detail. A number of studies have demonstrated that inhibitory inputs to the MSO play a major role in shaping ITD tuning curves (Brand et al. 2002; Pecka et al. 2008; Leibold 2010; Myoga et al. 2014; Beiderbeck et al. 2018), and Kapfer et al. (2002) have shown that inhibitory glycinergic inputs to the MSO undergo postnatal developmental refinement. Beiderbeck et al. (2018) used models to explore how the timing of the inhibition can suppress or facilitate neural spiking and confirmed their simulated findings *in vitro.* Pecka et al. (2008) used glycinergic antagonists to demonstrate the importance of inhibitory inputs to the MSO in shaping ITD tuning curves, and a modeling study by Leibold (2010) illustrated how ITD tuning curves can be shaped by the balance of inhibitory and excitatory inputs, and these in turn appear to be amenable to modification through experience dependent plasticity (Seidl and Grothe 2005). Similar mechanisms may well occur in ITD processing pathways of the LSO, but they have not yet been investigated. Nevertheless, ITD processing pathways can clearly be refined by experience, but that does not imply that binaural neurons lacking early experience cannot be highly ITD sensitive. We therefore think it likely that the differences in tuning curve shapes observed between our hearing experienced and neonatally deafened animals reflect differences in the amount and nature of experience dependent plasticity. It would be interesting to know whether hearing experience in adulthood, through CIs, can change tuning curve shapes in neonatally deafened animals, or whether it is developmentally regulated. This may be possible, given that there is some evidence of adult plasticity in binaural pathways, for example in response to a loss of stimulation (Vale and Sanes 2002) or a supply of stimulation through CIs (Rosskothen-Kuhl et al. 2018).

5. Conclusions

Our multi-unit recordings from the inferior colliculus of four neonatally deafened and four hearing experienced rats, all of which were acutely implanted with bilateral CIs as young adults, pointed to the presence of large amounts of innate ITD sensitivity even in the absence of early auditory

experience when sampled appropriately. Even though the ITD tuning appeared somewhat abnormal, with fewer contralaterally tuned multi-units in the neonatally deafened compared with the hearing experienced animals. However, our mutual information and *d'* analyses showed that the ITD tuning in neonatally deafened animals is nevertheless highly informative about ITD values in the physiological range, and they should therefore be able to support accurate ITD discrimination in spatial hearing tasks. To what extent these findings translate to human patients remains to be seen, but they do suggest that early deaf CI patients fitted with binaural CIs may not be fundamentally ITD insensitive, poor psychometric results in previous studies notwithstanding. Perhaps good functional ITD sensitivity could be elicited in early deaf humans if they are supplied with adequate stimulation and training following CI insertion.

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Chapter 4: Interaural time difference sensitivity is invariant to stimulation frequency

Abstract

Current cochlear implant (CI) design requires rates fast enough for speech envelope sampling but slow enough for interaural time difference encoding. In the previous two chapters we showed significant ITD sensitivity, even in the absence of early auditory experience at least at low pulse rates. Here, to follow on we investigated how pulse rates and fast or slow rising envelopes affect ITD sensitivity of early deafened CI users. In addition, we investigated the effects of training on ITD sensitivity under ideal conditions.

Rats were deafened neonatally by kanamycin injection as in chapter 2. Profound hearing loss was confirmed by measuring auditory brainstem responses while presenting click stimuli. In young adulthood (~p60), CI electrodes were chronically implanted bilaterally. Sensitivity to ITDs of binaural, biphasic pulse trains at pulse rates of 50, 300, 900, and 1800 pps with either rectangular or Hanning windows were studied by training CI rats on a two-alternative forced choice lateralisation task.

All neonatally deafened CI rats showed significant sensitivity to ITDs for pulse rates up to 900 pps for both rectangular and Hanning windowed stimuli, with a steep drop-off in performance at 1800 pps for both envelope types. Peak performance was found to be at 300 pps and at 50 pps for rectangular and Hanning windows respectively. Envelope shape showed a significant effect, with better ITD sensitivity for rectangular windowed pulse trains, presumably because they afford sharp “onset ITDs”.

In conclusion, stimulation rates of 900 pps alone should not prevent the development of ITD discrimination, although significantly higher ITD sensitivity was found at lower pulse rates. This suggests that CI design is not constrained by the rate limiting parody such that high rates are required for speech envelope sampling but lower rates are need for ITD perception. Furthermore, CI pulse trains with gentle rising slopes, similar to those found in speech, can provide usable ITD information even up to 900 pps, although these performances could be improved with sharper onset and offset cues in general. In addition, minimal training produces significant improvements in ITD sensitivity measures.

Introduction

Cochlear implants (CIs) have been provided to over 500,000 people across the globe (Ear Foundation, UK, 2016) and have hugely improved the quality of life of these people. However, limitations remain. Current CI processors generally run at a fixed rate between 900 and 1200 Hz (pulses per second; pps). The rationale here is that better temporal sampling of the speech envelopes should improve speech recognition thresholds. However, Shannon et al. (2011) demonstrate that between 600 and 2400 pps there was little to no benefit for phoneme, word, and sentence recognition in quiet or noise at these pulse rates. In addition, high pulse rates prevent CI users from making use of temporal spatial cues, namely interaural time differences (ITDs).

In a review by Laback et al. (2015), ITD performance of bilateral CI users plummeted with pulse rates above 300 pps. Thus, CI designs face conflicting demands: they must be fast enough to encode speech and slow enough to allow ITD stimulation. One proposed strategy around this is to combine both high and low pulse rates together. Srinivasan et al. (2018) shows that the introduction of an additional slower pulse train overlying the faster pulse train, but with a small offset, improves ITD sensitivity beyond an equivalent increase in the amplitude. Alternatively, both ITD localisation and speech performance improve with increasing the number of electrodes stimulated (Shannon et al. 2011; Thakkar et al. 2018). Whether this is due to the increased amplitude and energy spread, thus increasing the chance of stimulating surviving spiral ganglion cells, or a result of wider frequency activation, is purely speculation. It could also be that wider activation increases the energy reaching the apex of the cochlea, and thus the low frequency region, as ITDs are considered a low frequency cue according to the duplex theory (Lord Rayleigh, 1907). However, surgical limitation prevents most electrode arrays from reaching the apical-most, low-frequency, pathways (Stakhovskaya et al. 2007). A monoaural penetrating auditory nerve electrode directly stimulating the low frequency pathways results in better temporal acuity compared to the same electrodes stimulating higher frequency fibres in an animal model (Middlebrooks and Snyder 2007; Middlebrooks and Snyder 2010). While there is some evidence that temporal acuity and ITD processing may have similar mechanics (Snyder et al. 1995; Vollmer et al. 1999) there is also evidence that temporal encoding is only improved under higher electric pulse rates (Vollmer et al. 1999; Sunwoo et al. 2019) compared to the lower pulse rates expected to improve ITD sensitivity.

There are schools of thought that believe ITD envelope cues, ITDs resulting from slower rate sound envelopes, are perceptible under CI stimulation. However, this is only possible when the shape of the envelope is peaked (Laback et al. 2004; van Hoesel et al. 2009; Laback et al. 2011; Noel and Eddington 2013). In fact when presented with speech envelope stimuli, CI users show no envelope ITD sensitivity (Laback et al. 2004; Grantham et al. 2008). This would strongly suggest that a speech envelope, or any slow rising envelope (such as a Hanning windowed pulse train) does not exhibit temporal features needed for the effective encoding of ITD information by current CI processors. That ITD sensitivity falls off at higher frequencies is not unlike that seen in normal hearing listeners

(Zwislocki and Feldman 1956; Wightman and Kistler 1992). However, the peripheral auditory mechanics demonstrated by Bernstein and Trahiotis (1996); Bernstein et al. (1999) behind these frequency differences in terms of envelope compression simply do not apply to Ci stimulation which entirely bypasses the cochlea filter mechanics directly stimulating the auditory nerve. Thus that ITD sensitivity appears to be limited to carrier rates below 300 pps in CI users is likely to have more to do with mechanism shared with rate discrimination as previously proposed (Ihlefeld et al. 2015).

Differences in ITD sensitivity are apparent in users with different auditory experience. CI users who are deafened pre-lingually generally show ITD thresholds that are orders of magnitude worse than those post-lingually deafened CI users,and they are often too poor to be measurable (Litovsky et al. 2010; Litovsky et al. 2012; Ellinger et al. 2017; Thakkar et al. 2020). This poor sensitivity is often thought to be a result of the absence of auditory experience during a critical period, as outlined by Kral (2013), for ITD sensitivity. However, we have demonstrated (Rosskothen-Kuhl et al. 2021) (see chapter 2) that the absence of ITD sensitivity is not a result of the lack of auditory input itself. In fact, it appears that there is no strong critical period for ITD sensitivity, at least in terms of absent input. Additionally, several aspects of audition including speech recognition thresholds are improved with electric hearing experience and training. Fu et al. (2004), for example, demonstrate significant improvements in speech perception performance with only two weeks of home-based training. Stacey et al. (2010) additionally showed significant improvements in consonant recognition at only an hour per day, five days per week for a period of three weeks. The effects of experience are also evident in the development of aural preference syndrome, where a period of prolonged unilateral auditory deprivation occurs prior to the second implantation (Gordon et al. 2015). However, little evidence exists on the effects of training specifically to ITD sensitivity.

The majority of CI subjects recruited in human studies have a multitude of uncontrollable variables, including diverse aetiology of deafness, age of deafness onset, period of unilateral auditory deprivation, CI strategy and years of experience under CI stimulation, to name a few. Thus we use our animal model presented in Chapter 2 to test the effects of ITD sensitivity on pulse rate without these confounding variables, and explore the effects of envelopes using rectangular (sharp onset and offset) or Hanning windowed pulse trains.

In this study we used our binaural behavioural CI animal model (Rosskothen-Kuhl et al. 2021) to investigate the impact of pulse rate and envelope shape on ITD sensitivity controlling for variables in the patient population such as age at deafness, synchronicity of bilateral implantation, and stimulation synchronicity between bilateral CI processors. Based on previous studies in CI patients (Litovsky et al. 2012; Ehlers et al. 2017; Thakkar et al. 2020) and electrophysiology studies in bilateral CI-stimulated animals (Tillein et al. 2009; Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2014; Chung et al. 2016; Tillein et al. 2016) we expected to see the better ITD sensitivities for pulse rates slower than the typical clinical rates (~900-1200 pps). In addition, from our previous finding on the importance of onset ITDs in electrophysiology (see chapter 3) and the observations of Brown and Stecker (2010), as well as the general presence of the precedence effect, we

anticipated reduced ITD localisation performances when presenting pulse trains with gently rising slopes (Hanning windowed) as compared to sharp onset rectangle windowed pulse trains.

Methods

12 neonatally deafened (ND) adult female Wistar rats were implanted with CIs in early adulthood and underwent behavioural training as described in Chapter 2. As before, animals were implanted bilaterally simultaneously receiving binaurally synchronised stimulation from the first stimulation.

Testing for the 12 animals was done in a pseudo random order following implantation (see Figure 3.1). Animals were tested on four pulse rates, 50, 300, 900 and 1800 pps, for rectangular windowed pulse trains (n=12), followed by Hanning windowed (n=8). For this experiment, both individual pulses and envelopes carried the same ITD information by keeping the fine structure and envelope ITDs equal for all trials. As in Chapter 2, the ITDs were presented between -150 and +150 µs, where negative represents a left leading and positive a right leading ITD. This range covers 125% of the animal's physiological range, which is between -120 and +120 µs (Koka et al. 2008). Each pulse train had a duration of 200 ms, and animals were stimulated in the order of 2-6 dB (re to 100 µA peak pulse amplitude) above their electric auditory brainstem response (eABR) thresholds (see Chapter 2 for details), an example of which is shown in Figure S1. Behavioural comfort levels were tested for each subsequently tested carrier rate to finely adjust level differences. In this way stimulus intensity decreased as a function of increasing carrier rate. The starting frequency was assigned pseudo randomly to rule out any effects from the order in which they were tested. Hanning windows consisted of a raised -cosine waveform with a 100 ms rising and falling phase respectively (see Figure 3.2).

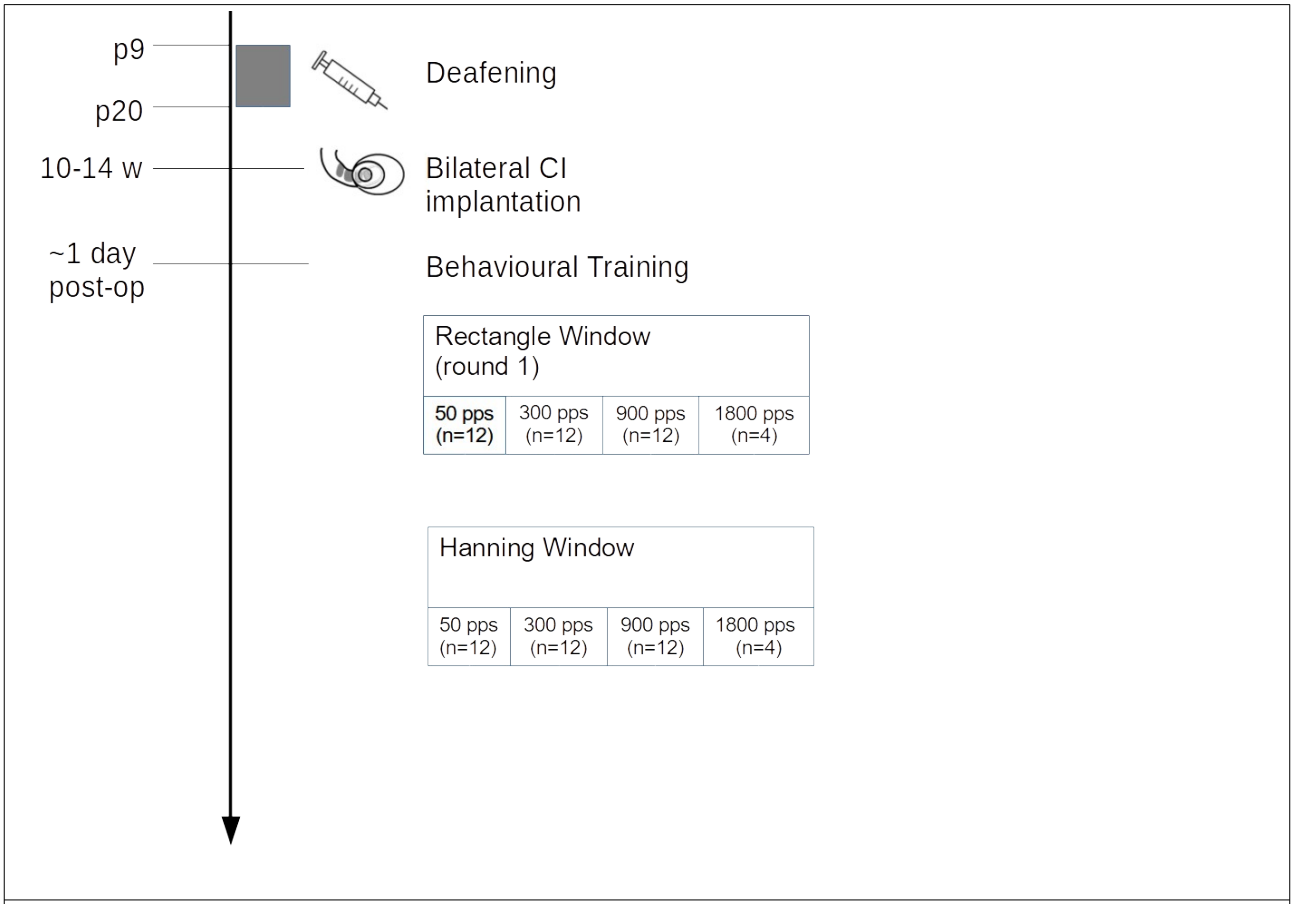


Fig 3.1 Experimental pipeline with timeline running from top to bottom. Abbreviations: p =

postnatal day, w = week, post-op = post-operation.

If animals struggled with the higher frequencies (particularly 1800 pps) in training sessions, these rates were interleaved with trials at easier pulse rates in order to keep the animals motivated and to allow them to obtain sufficient water rewards for both rectangular and Hanning envelopes. All 12 animals were tested at 50, 300 and 900 Hz and four of them were additionally tested at 1800 pps. (last column in Figure 3.3).

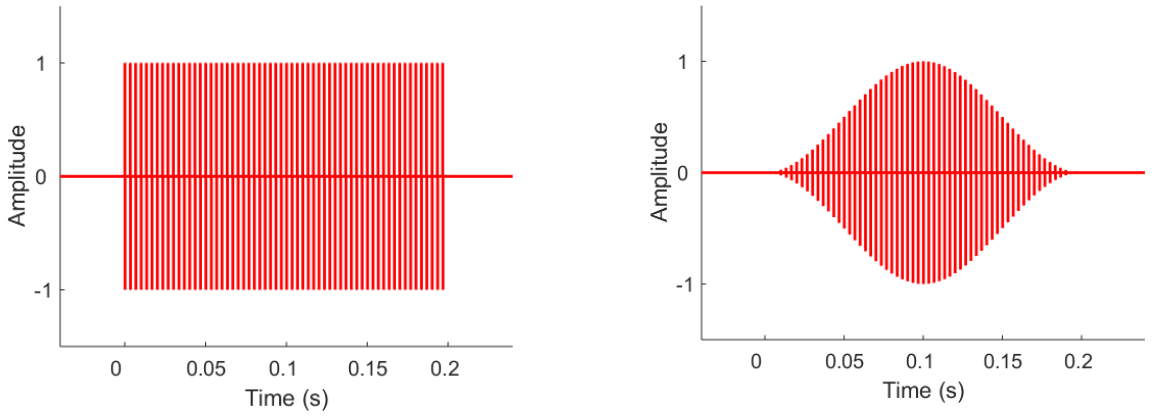


Figure 3.2 Representative electrical stimuli for rectangular windowed stimulation (left) and Hanning windowed stimulation (right). Example waveforms of 200 ms duration are shown for a pulse rate of 300 pps.

Analysis

Psychometric curve fits were estimated as described in (Rosskothen-Kuhl et al. 2021) as well as Chapter 2. To determine behavioural ITD sensitivity, slopes of ITD performance psychometrics fitted using null, linear or sigmoid functions (see Chapter 2) were used. A measure in percentage correct per µs ITD was determined from the linear components for these fits. This value gives a quantitative indication of how much performance can improve with increasing ITD value.

To determine statistical significance of the overall affect of pulse rate in rectangular and Hanning window data as well as a comparison between the two, a permutation method was used. For each animal at each pulse rate for each window trials across all training sessions were randomly sampled with replacement and a slope, as a measure of ITD sensitivity, was calculated as described in Rosskothen-Kuhl and Buck et al(2021). This process of resampling was repeated 1000 times. This provided 1000 simulated ITD sensitivities (slopes) for each animal for each condition. A second permutation was then done by randomly pulling one slope per animal per condition, with replacement, and calculating an average across animals for each condition 1000 times providing a group mean. Statistical comparisons were then possible to determine a group effect across pulse

rates for each window and between the same pulse rate across windows by calculating how many of the group statistics were higher for a given comparison and thus determining a p value.

Results

Effect of pulse rate on ITD sensitivity

All 12 ND rats were successfully trained to localise ITD cues within 3-5 days, 8 sessions on average, of behavioural training regardless of the starting pulse rate (50, 300 or 900 pps). The results of these training sessions are shown in Figure 3.3. It is apparent from figure 3.3 and S2 that all animals were able to localise ITDs with magnitudes of 0.75 to 0.15 ms with a success rate between ~70-95% across all frequencies except 1800 pps, where the tested animals performed almost at chance level ~50% (last column in Figure 3.3), and with one animal having a null model fit just below this. Ten of the 12 animals were able to perform successful ITD localisation even at 900 pps, whereas human CI users reportedly usually start to fail at pulse rates above 300 pps (Laback et al. 2015) if they show any ITD sensitivity at all.

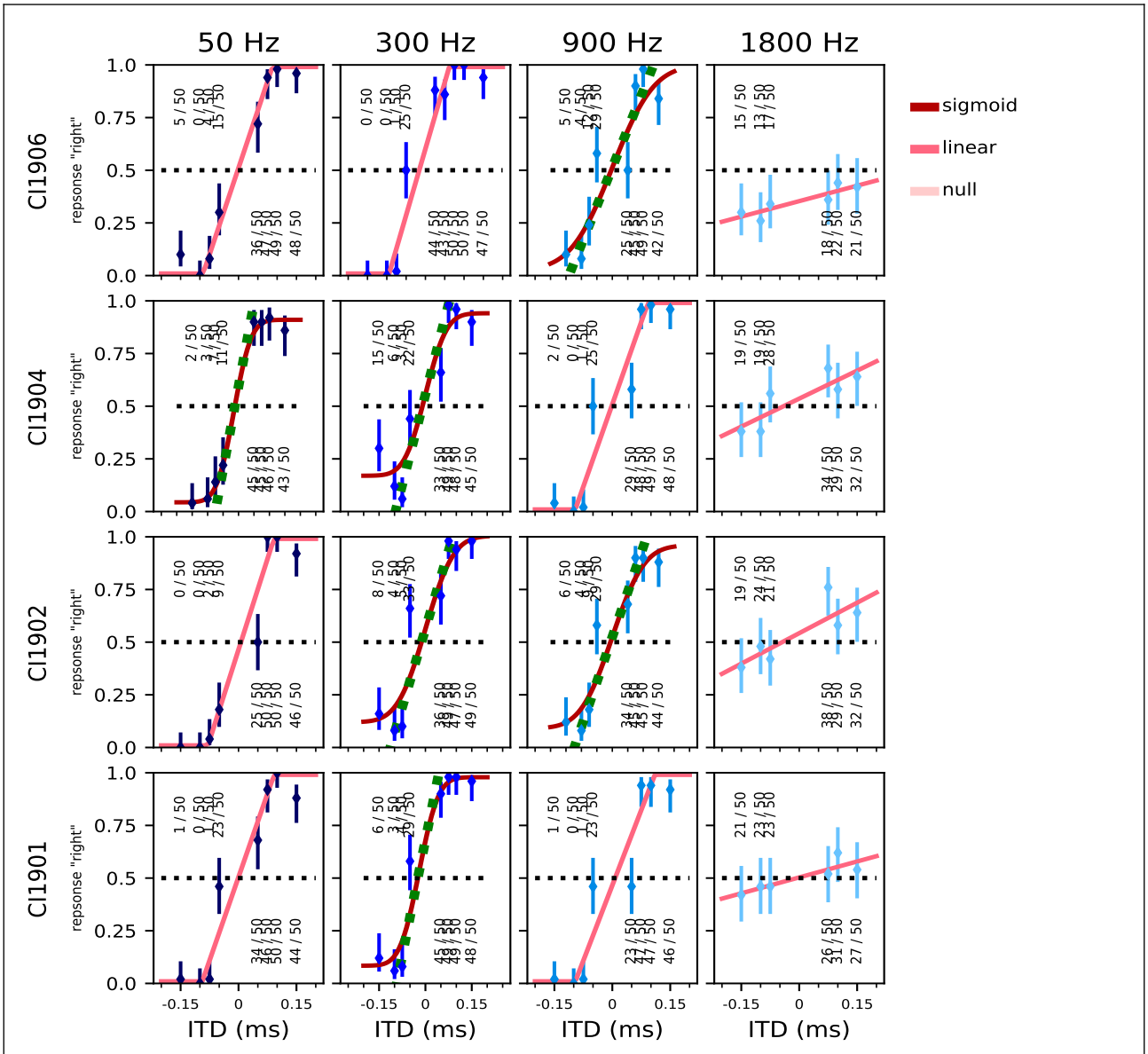


Figure 3.3 Rectangular psychometric functions for each pulse rate for four example animals. Each column represents a different pulse rate from left to right 50, 300, 900 and 1800 Hz, each indicated with a different shade of blue and different marker shape. Each row shows the

responses for a given animal. The y-coordinates reflect the proportion of trials during which the animal responded on the right hand spout. The x-axis shows the tested ITD values from – 0.15 to + 0.15 ms. Negative ITD values indicate left leading ITDs. Annotations above or below each marker indicate number of trials the animal chose the right hand side spout over the total number of presentation for the ITD value given by the x-coordinate. The legend shows the colour code indicating whether the best fit psychometric was sigmoid, linear with bounds, or null. Dashed green lines for sigmoid best fit slopes (dark red) show the linear components of the sigmoids. Psychometrics for the remaining animals are shown in Figure S2.

The 8 ND rats were then additionally tested on stimuli with the same pulse rates but instead of a rectangular window, the pulse rates were amplitude modulated with a slow rising and falling Hanning window as shown in Figure 3.2. Again, animals successfully managed to use ITD cues for localisation at all pulse rates with the exception of 1800 pps which in this dataset is almost completely flat for all animals tested (n = 4) as shown in the last column of Figure 3.4 and S2. It is visually apparent from this figure that the slopes of the Hanning windowed psychometric functions are more shallow compared to the sharp onset rectangular windowed stimuli shown in figure 3.3 and S2. In addition, the variability between animals appears to be greater under Hanning windowed stimulation (see Figure S2) compared to rectangle windowed stimuli (Figure S2).

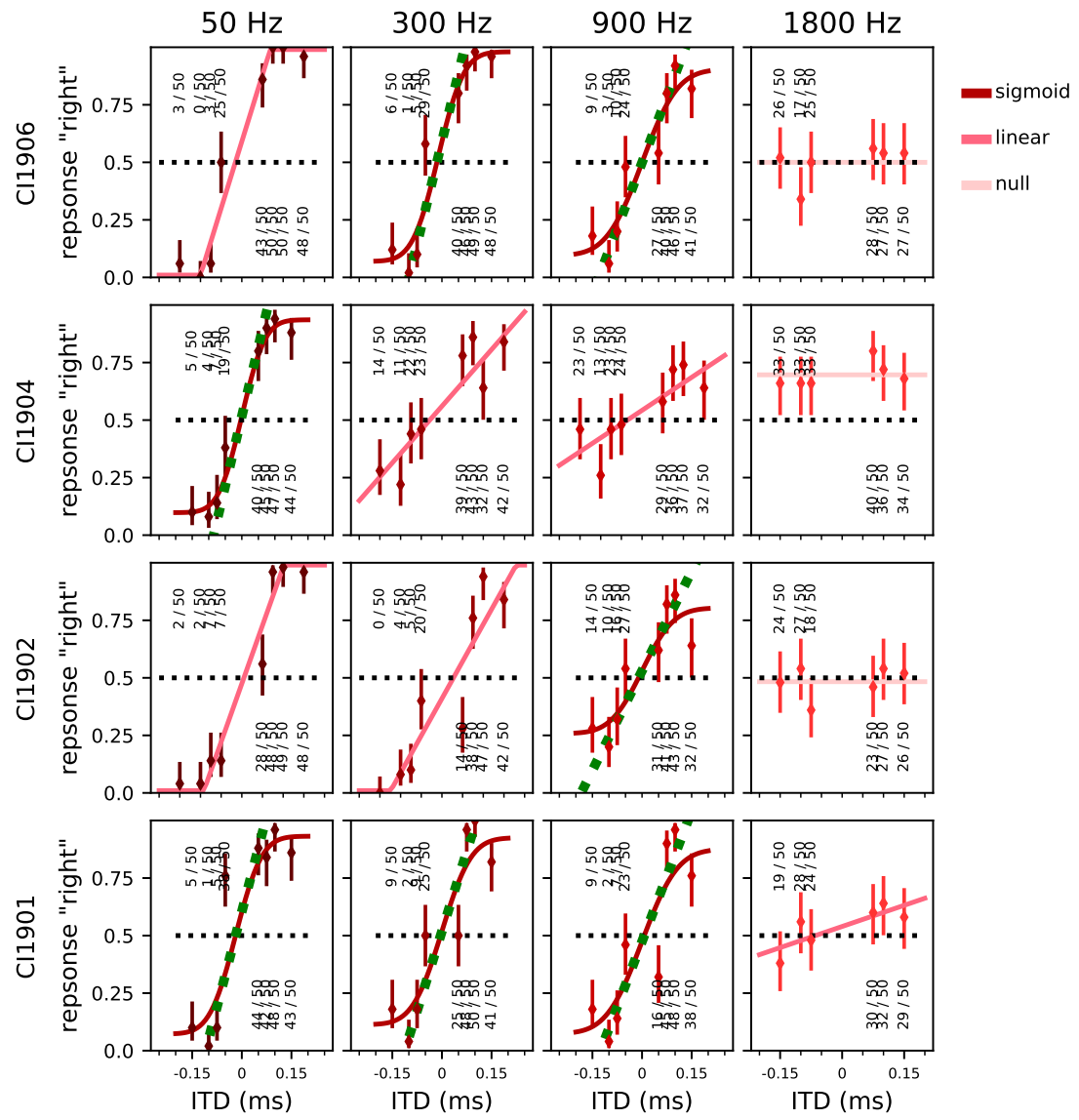


Figure 3.4 Psychometrics for Hanning windowed pulse trains with varying ITDs as in Figure 3.3 for the same animals. Details are as for 3.3. Psychometrics for all animals are shown in figure S3.

Effects of envelope onset and/or offset

If we take the fitted slopes from the psychometrics shown in Figures S2 and S3 as a measure of ITD sensitivity, we have a measure of percentage correct per µs ITD. The permuted group ITD sensitivities, a function of the simulated psychometric slopes (see methods) are shown in Figure 3.5, for both rectangle (blue) and Hanning (red) windowed stimuli at each pulse rate. For rectangle windowed stimuli at 1800 pps resulted in significantly less ITD sensitivity than all other pulse rates ($p < 0.001$). In addition 50 and 300 pps resulted in significantly higher sensitivity than at 900 pps ($p = 0.0039$ and $p < 0.001$ respectively). No significant difference in ITD sensitivity was found between 50 and 300 pps.

For Hanning windowed stimuli ITD sensitivity was found to be significantly different for all pulse rate comparissons. Stimuli presented at 1800 pps results in signifacntly flatter slopes, reduced ITD sensitivity, when compared to all other pulse rates ($p<0.001$). In addition stimuli at 50 pps resulted in greater ITD sensitivity than when 300 ($p = 0.00047$) or 900 ($p<0.001$) pps were presented and likewise sensitivity at 300 pps was significantly higher than at 900 pps ($p = 0.0083$).

Comparisons were additionally made to determine the effects of enevelope on ITD sensitivity. Ractangular windowed data showed significantly higher ITD sensitivity at 300 ($p<0.001$) and 900 ($p = 0.0027$). ITD sensitivity did not differ signifcantly between the two pulse rates at 50 pps 9 $p= 0.467$) or at 1800 pps ($p = 1$). These trends can further be appreciated from the violin plots shown in Figure 3.5 where no overlap between the main body of the violins would suggest statistically different permuted distributions.

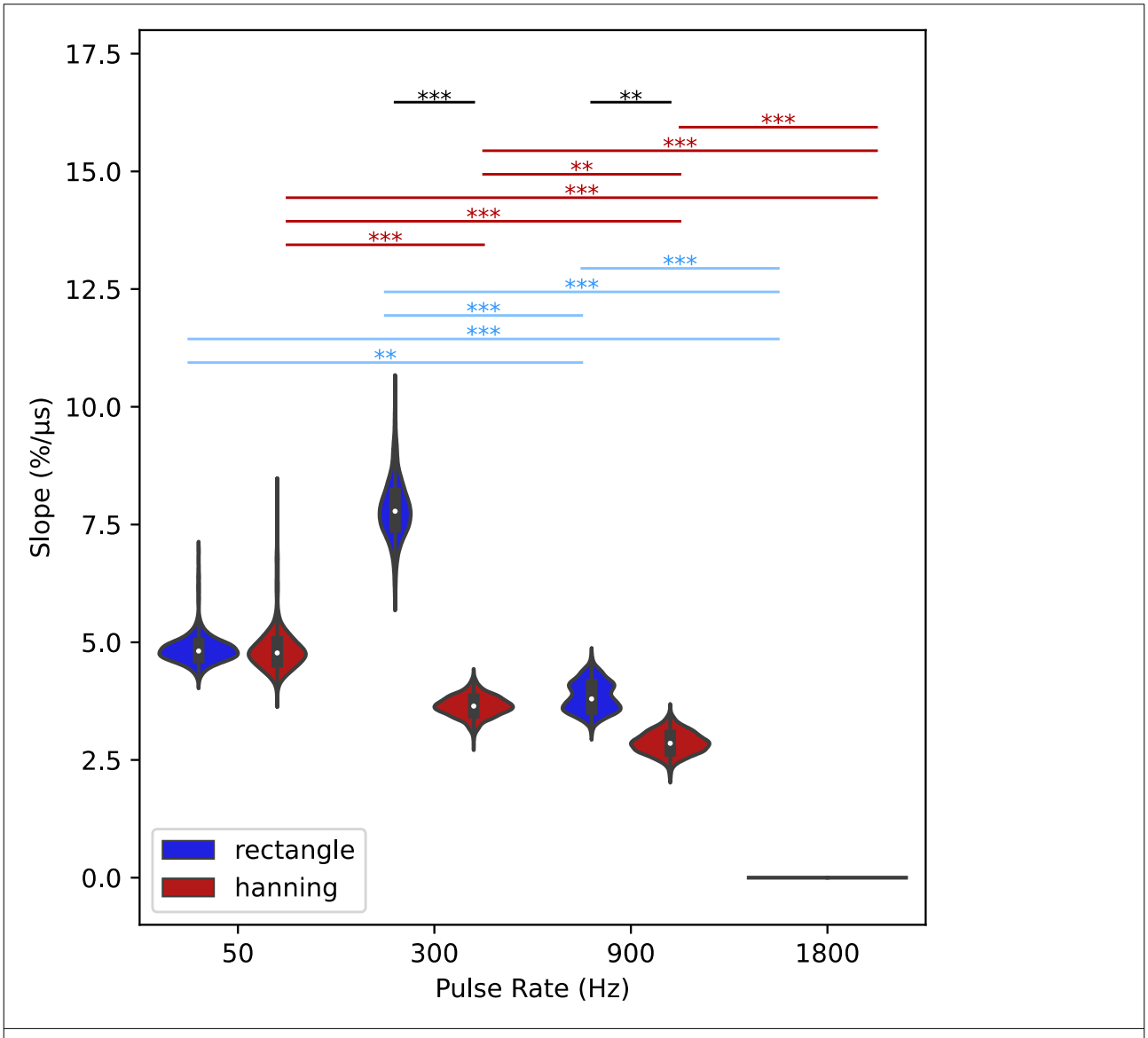


Figure 3.5 Violin plots showing the distribution of the mean group effects for each pulse rate following permutation for rectangular (blue) and Hanning (red) windowed stimuli. The overall

means for each violin are shown by the white centroid and the black rectangles indicate the interquartile range. Significant group statistics are shown above violin plots for rectangle (blue), Hanning (red) and the comparison between the two envelopes (black). *** = $p < 0.001$; **= $0.001 > p < 0.01$; * $0.01 < p < 0.05$.

Discussion

Early deafened subjects show good ITD localisation for pulse rates as high as 900 pps

In this study, we have demonstrated remarkably good ITD sensitivity even at pulse rates as high as 900 pps. This is in contrast to early deafened human CI users who, even when ITD sensitivity is present at all, show a rapid drop-off in performance with pulse rates higher than 300-500 pps (Laback et al. 2015).

That our neonatally deafened animals can perform ITD localisation at all at 900 pps after a substantial period of hearing deprivation is surprising, given that the absence of early hearing experience has largely been thought to be the reason ITD sensitivity is poor in CI patients (Litovsky 2010; Gordon et al. 2014). However, as illustrated in Chapter 2 and Rosskothen-Kuhl et al. (2021), in our animal model, rats experience a long period of hearing deprivation until early adulthood development and this does not affect ITD capabilities providing evidence that ITD sensitivity does in fact not have a critical period at least in terms of symmetric sensory stimulation. This provides evidence that the nature of auditory input, rather than its presence or absence, may play the key role in the differences between our animal model and human CI listeners. For example, rectangular windowed pulses provided strong onset cues which are thought to be the most salient for ITD perception (Brown and Stecker 2010) and auditory input in general as per the precedence effect.

The fact that our CI animals are able to perform well even at clinical pulse rates points towards a possible new avenue in approaching the paradox in CI design. Rather than finding a balance with a pulse rate that is both fast enough for speech envelope encoding and slow enough for ITD encoding, the performance of our animals suggest it may not only be a question of fast and slow pulse rates. The fact that our animals are able to perform well at rates as high as 900 pps while human CI listeners fail highlights the need for alternative possible explanations, as high pulse rates alone cannot account for the poor performance in human CI users. However, one can not ignofre the significant decline in ITD sensitivity with increasing pulse rate particularly for Hanning windowed data.

Sharp onset/offset cues permit significantly better ITD sensitivity at clinically relevant pulse rates

The drop in performance with the slow rising envelope cue, which was chosen as a simplified approximation for speech, was found to be significant only at 300 and 900 pps.The reduced ability to use slow rising ITD cues corroborates with evidence for ITD envelope insensitivity for speech waveforms which also have a slow rising envelope (Laback et al. 2004; Grantham et al. 2008). These findings should not come as a surprise given that we know, at least for normal hearing subjects, that onset ITDs are the most salient (Brown and Stecker 2010) which pertains to the precedence effect (see Chapter 5). Additionally increased ITD sensitivity has been shown for sharp onset envelopes or ‘damped’ rather than ‘ramped’ waveforms acoustically(Greenberg et al. 2017).

One might expect the decrease in performance with a slow rising cue to be more prevalent at faster pulse rates, given the higher sampling of the envelope shape. This is indeed what we see at

pulse rates capable of delivering adequate ITD cues while also being of clinically used for speech reception. However, interestingly the reduced ITD sensivitiy is most evident at 300 pps and not at 900 pps as would be expected from the carrier rate relationship with onset responses (Brown and Stecker (2010); Chapter 5). In addition, unlike for rectangle windowed data which seems to show a peak ITD sensitivity at 300 pps, for Hanning windowed pulse trains, there appears to be a more steady decline in performance from 50 pps (Figure 3.5). Whether the shape of the envelope changes the nature of ITD sensitivity and pulse rate would require a wider range of pulse rates to be tested and is therefore beyond the scope of this study. However, in relation to our temporal weighting findings in neonatally deafened CI stimulated animals the relationship between carrier rate and onset dominance is altered either as an effect of electric stimulation or due to the absence of hearing experience (see Chapter 5).

Importantly, while there is a significant difference in ITD performance between Hanning and rectangle windowed pulse trains, a substantial amount of ITD sensitivity is present even up to a stimulation rates of 900 pps for both windows. This suggests that relatively slow pulse rates of 300 pps or lower may not always be required to deliver ITD cues, as suggested by the proposal of such new strategies to deliver slower pulse rates without decreasing speech envelope sampling by Srinivasan et al. (2018) and Thakkar et al. (2018). That is of course not to say that using lower pulse rates can not improve ITD sensitivity, as has been shown in previous studies (Smith and Delgutte 2007; van Hoesel et al. 2009; Hancock et al. 2012; Kan and Litovsky 2015; Laback et al. 2015; Chung et al. 2016), but it may not be absolutely necessary given that our animals were able to perform quite well at pulse rates as fast as 900 pps even with slow rising envelopes. Nevertheless, we see a significant declline in ITD sensitivity with increasing pulse rate for both Hanning and rectangular envelope data and importantly there appears to be an upper bound with a sudden drop at 1800 pps(see Figure 3.5). However, our data strongly suggests that lower pulse rates are not essential to encode ITD sensitivity even for slow rising envelope cues, such as speech. This then begs the question of how can we improve ITD sensitivity?

Conclusion

Under synchronized bilateral stimulation, we have shown that, at least in rats, clinical pulse rates of 900 pps should not prevent the development of good ITD sensitivity although lower pulse rates may help to improve it. In addition, we have found that onset and/or offset cues can improve ITD sensitivity, although this was only significant for clinically relevant pulse rates. However, importantly, good ITD sensitivity was still found with a simplistic and more ‘speech-like’ waveform even at 900 pps. Thus, we demonstrate that ITDs do not require slower rates in order to be usable and that envelope shape, particularly sharpness of onset and/or offset, influence the saliency, but not the presence, of ITD cues. This is an important finding for speech processor algorithm designs and in tackling the ongoing problems of temporal spatial perception in CI users.

Supplementary Materials:

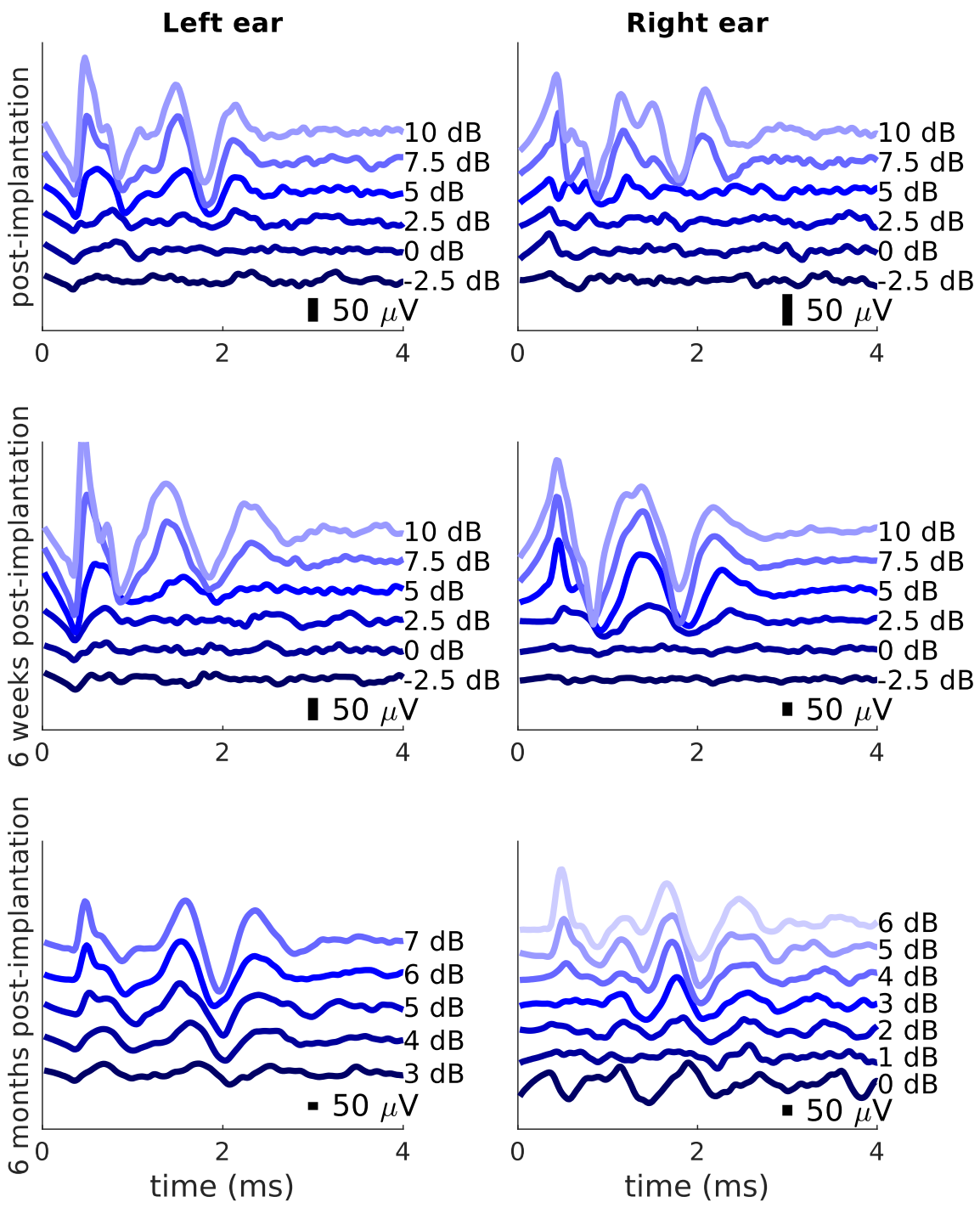


Figure S1: Example EABR showing immediately, 6 weeks and 6 months after implantation thresholds for left and right ears. Scale bars are shown in each plot with reference to 50 µV. Color represents a different SPL with dark to light colors going from softest to loudest. Electric artifacts have been removed using interpolation over the duration of the stimulus. For details on the stimulus and presentation, see Rosskothen-Kuhl et al. (2021).

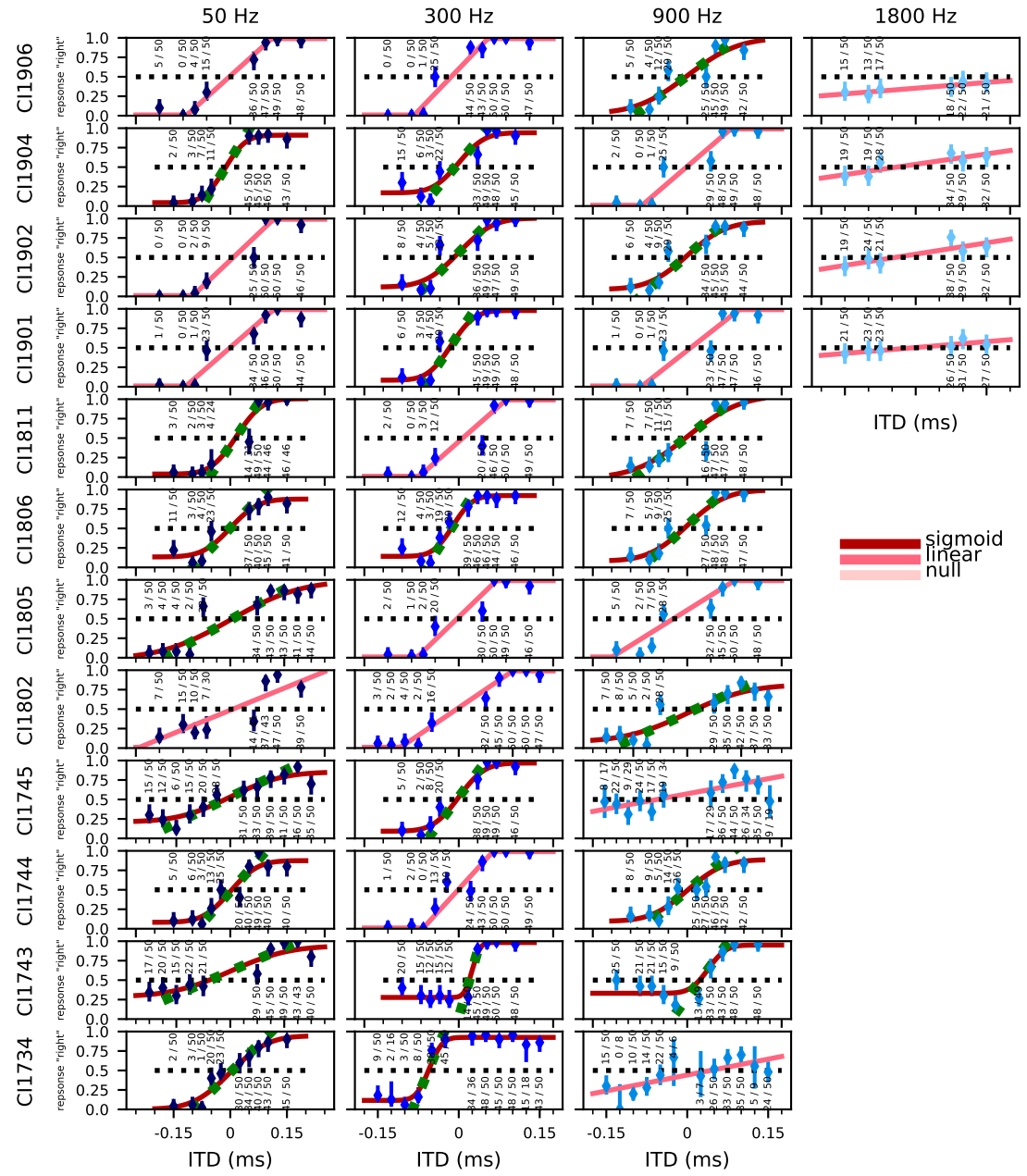
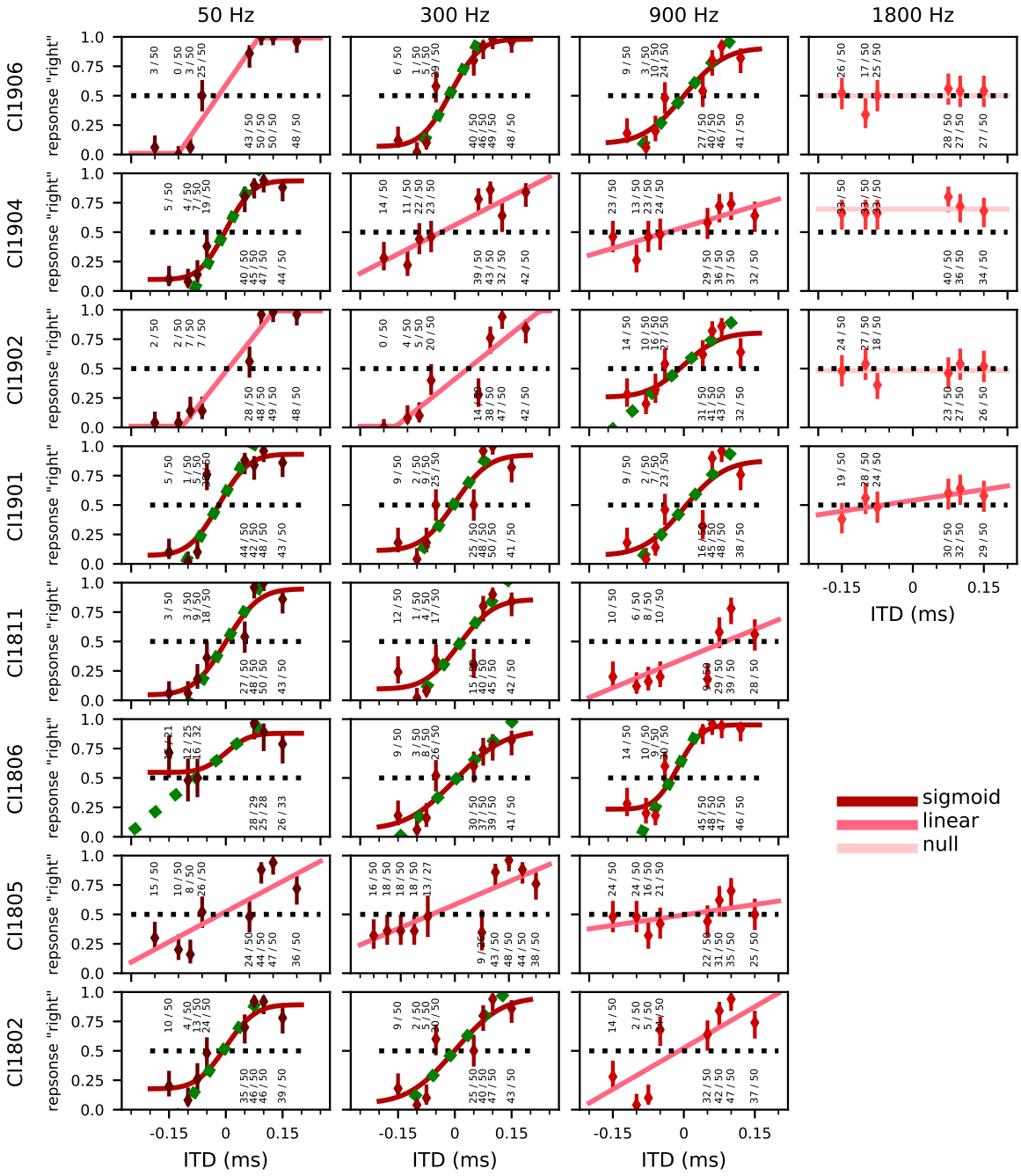


Figure S2: Rectangular psychometric functions for each pulse rate. Each column represents a different pulse rate from 50, 300, 900 and 1800 Hz (left to right). Each row shows the responses for a given animal with the top 4 animals being those shown in Figure 3.4. The y-axis reflects 'right' responses where 'right' refers to the right hand spout. The x-axis shows the tested ITD values from – 0.15 to + 0.15 ms. Negative ITD values indicate left leading ITDs. Annotations above or below each marker indicate number of trials the animal chose the right hand side spout over the total number of presentation for a given ITD value. Only the first 50 presentations were included. Legend indicates results for the estimated best fit either sigmoid, linear or null.



S3: Psychometrics for Hanning windowed pulse trains with varying ITDs as in figure S2. Details are as for S2. Top 4 animals are the examples shown in Figure 3.4.

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Chapter 5: Onset Weighting and its relation to ITD sensitivity

Abstract:

Cochlear implants (CIs) have undeniably improved the quality of life of many deaf individuals, but the perceptual performance they permit in complex, real-life environments still falls short. One particular shortcoming is the inability to provide CI users with adequate temporal spatial cues, interaural time differences (ITDs). Early deaf users of current CIs are almost entirely insensitive to ITD cues across the physiological range (Litovsky et al. 2010). However, we have previously shown that neonatally deafened (ND) rats are capable of discriminating ITDs as small as 50 µs, no worse than normal hearing (NH) rats (Rosskothen-Kuhl et al. 2019). Better ITD sensitivity may therefore be achievable with better devices which could be explored most effectively with the use of a developed animal model in order to improve the technology. We therefore determined whether rats show similar onset weighting for ITDs as humans (Brown and Stecker 2010), and whether that onset weighting is similar in NH and CI-ND animals.

CI-ND rats were prepared by neonatal injection of kanamycin, followed by bilateral implantation as young adults. Age matched NH litter mates were also tested. Animals learned a two-alternative forced choice task to lateralize pulse trains consisting of eight binaural pulses (for ND rats: biphasic electric stimuli delivered via CIs; for NH rats: acoustic clicks delivered over tube phones). ITD values for individual pulses varied independently and uniformly across the rat's physiological range (+/- 130 µs). Pulse rates were 50, 300 or 900 Hz. Two types of trials were presented for each session: "Honesty trials" comprised either all left- or all right-ear leading pulses, while for "probe trials" pulse ITDs were unconstrained. Temporal Weighting Functions (TWFs) were calculated using probit analysis to determine the perceptual weight of each pulse in the train in shaping the behavioral response to probe trials.

Both CI-ND and NH animals showed onset dominance across all pulse rates that were comparable with the TWFs of human listeners. However, these weights were substantially lower for CI-ND animals, compared to NH litter mates, and the effects of increasing pulse rate were lost under electric hearing. Additionally, neither cohort showed convincing evidence of offset weighting.

Rat TWFs are fundamentally similar to those found in humans, further illustrating the suitability of rats as a model for human binaural hearing. The pulse rate dependence of onset ITD processing we observed in CI rats may also help explain the poor ITD perception of early deafened CI users, given that current clinical CI processors are running at ≥900 Hz.

Introduction

In our everyday environment, spatial cues not only allow us to locate sound sources, but also to understand the complex auditory scene around us. In the real world, we have natural sounds with competing sound sources occurring at the same time, as well as reverberation which can interfere with spatial cue perception. In spite of all these possible confounding elements, the auditory system is relatively robust in the face of these negative interferences, in part because it has evolved to be adept at strongly weighting the first wavefront, the least distorted by reverberations, and paying less attention to later lessreliable cues (Brown and Stecker 2010). This phenomenon was first described by Wallach et al. (1949) and was coined the precedence effect.

In the classic precedence paradigm, a pair of clicks, which are intended to mimic a direct sound source and a single echo (lead and lag click), are presented from loudspeakers positioned at each side of a listener in the free field (Wallach et al. 1949). The time delay between lead and lag click is decreased up to a point where the listener only perceives a single auditory event, also termed fusion. This delay, around 5-10 ms for clicks and 50 ms for speech (Litovsky et al. 1999), is called the echo threshold, below which lead and lag fuse and only one click is perceived. At delays shorter than that, the listeners localise the merged sound in the direction of the lead click, a phenomenon called localisation dominance. The listeners are not able to differentiate changes in the location of the lag click. This is true even if the lag consists of hundreds of clicks comprising contradicting interaural information (Freyman et al. 1997).

Thus, in rapid click trains, the first (“onset”) click dominates ITD perception, and this onset dominance has been quantified in normal hearing listeners in various studies (Stecker and Hafter 2002; Brown and Stecker 2010; Stecker 2013; Stecker 2014; Stecker 2018). Importantly, this onset dominance is more pronounced at higher click rates. Brown and Stecker (2010) demonstrate that onset dominance only occurs in normal hearing listeners with inter click intervals shorter than 5 ms (equivalent to a click rate greater than 200 Hz), while “temporal weighting functions” (TWFs) at slower click rates are relatively flat. Here, TWF refers to the relative perceptual weight given to each click in the train (Stecker and Hafter 2002; Brown and Stecker 2010; Stecker 2014). In addition to onset weighting at higher click rates, slower click rates show an upweighting towards the end of the click train regardless of the number of clicks (Stecker and Hafter 2002; Stecker 2010).

To date, not much is known about the precedence effect under electric stimulation,nor has the physiological basis been clearly elucidated under any form of stimulation. Two hypotheses exist: The first suggests that the precedence effect is mediated by peripheral mechanisms. Bianchi et al. (2013) argue that the precedence effect arises from mechanical interaction on the basement membrane as a results of cochlea ringing. Given that the pathway from basement membrane to auditory nerve is bypassed under CI stimulation, this would suggest that electric hearing precludes any precedence effects. However, Brown et al. (2015) demonstrate that, although the precedence effect was weaker in CI subjects compared with normal hearing peers, it was definitely present with both fusion and localisation dominance being present under electric stimulation. The second hypothesis suggests a central mechanism for the precedence effect. Pecka et al. (2007) argue that the dorsal nucleus lateral lemniscus (DNLL) inhibition of the inferior colliculus and opposite DNLL would lead to impaired lag spatial sensitivity. Central mechanisms would partially explain previous findings on some elements of the binarual precedence effect, at least in post-linguilly deafened CI users (van Hoesel 2007; Agrawal 2008; Brown et al. 2013). Notably, none of these studies systematically investigated the effects of carrier rate on the precedence effects measured under electric stimulation.

The importance of successful streaming and reverb suppression in our daily auditory scenes is readily apparent. However, it is well appreciated that cochlear implant (CI) listeners are notoriously bad at complex auditory scene analysis (the so-called ‘cocktail party effect’) although the underlying reasons are less clear. Under electric hearing, separating multiple competing talkers is very difficult. In normal hearing, ITD sensitivity and “binaural unmasking” are likely to help with such scene analysis tasks, but many CI users have ITD thresholds orders of magnitude above their normal hearing peers, if they are measurable at all (Litovsky et al. 2010). In addition, it is unknown how much of the resilience to competing sound sources and reverberations seen in the normal auditory system is innate and would therefore exist in an auditory deprived system when provided with cochlear implants. This is the first study to asses whether onset dominance still exists in these circumstances, using our established neonatally deafened animal model fitted with bilateral Cis. In addition we have assessed the effects of varying pulse rates. ITDs were presented on electric pulse trains to determine temporal weighting functions and establish 1) if onset dominance is present and if so, 2) if the effects of pulse rate remain and 3) if offset upweighting are present under

electric stimulation in an auditory naive system and 4) how these compare to acoustic normal hearing.

Methods

Subjects

Eight neonatally deafened adult female Wistar rats were implanted with CIs in early adulthood as described in Chapter 2 (CI-ND). Animals were implanted bilaterally simultaneously, receiving binaurally synchronised stimulation from the first stimulation. These animals were compared to 4 normal hearing (NH), acoustically stimulated animals. Electric or acoustic auditory brainstem responses (ABRs) were assessed to ensure normal hearing and successful CI insertion, as well as to determine thresholds for stimulation parameters as described in the methods of Chapter 2 (also see Figure 5).

Behavioural Training Setup

Animals were trained on a two-alternative forced choice task as described in Chapter 2, using the same behavioural setup, administering water rewards from three spouts. The stimulus is initiated when the animal licks the centre spout, and the animal then needs to respond by licking either the left or right spout depending on the stimulus presented. CI and acoustic stimulation were as described in Chapter 2, with acoustic click trains delivered through speakers (GQ-30783-000, Knowles, Itasca, Illinois, US) attached to the end of ear bars receiving input from a Rasberry Pi 3 via a USB sound card and amplifier. The CI stimuli were presented as biphasic, electric pulses generated with a TDT IZ2MH programmable constant current stimulator.

Stimulus Design

The stimuli were designed to evaluate temporal weighting of ITD cues as inspired by Brown and Stecker's study in normal hearing humans (Brown and Stecker 2010). As in previous chapters, ITDs within the animals physiological range were used (-120 to +120 µs; (Koka et al. 2008)). Negative ITDs represent left leading cues. Each trial consisted of 8 clicks/pulses presented at 50, 300 or 900 Hz. Each click or pulse was randomly assigned an ITD value within the given range. Higher pulse rates were not tested, as the data in Chapter 4 had shown that animals are not sensitive to ITDs at pulse rates much above 900 Hz (see Chapter 4).

Training sessions randomly interleaved "honesty" and "probe" trials, with both consisting of 8 clicks or pulses for acoustic and electric stimulation respectively. In honesty trials, the ITDs for each pulse were drawn from either {-120, -80, -40} or {+40, +80, +120} µs. In honesty trials, all ITDs

pointed to the same side. This was achieved by randomly using an initial offset ITD of -100 µs or + 100 µs, thus providing a definitive localisation cue so that animals had to respond correctly to obtain a reward. In contrast, in probe trials, the animal was rewarded for licking on either side – in other words both spouts would be considered 'correct'. In probe trials, the ITDs for each click are drawn independently and uniformly from -120 µs to +120 µs in 40 µs steps, such that a given trial may contain ITDs pointing both left and right. Examples of the two trial types are shown in Figure 4.1. Honesty trials outnumbered probe trials at the ratio of 4:1 to ensure the animals were paying attention, and honesty trial performance needed to be maintained at >75% correct in order for training sessions to be included in the temporal weighting function analysis. Importantly, there was no way for the animals to know whether a given trial was an honesty or probe trial.

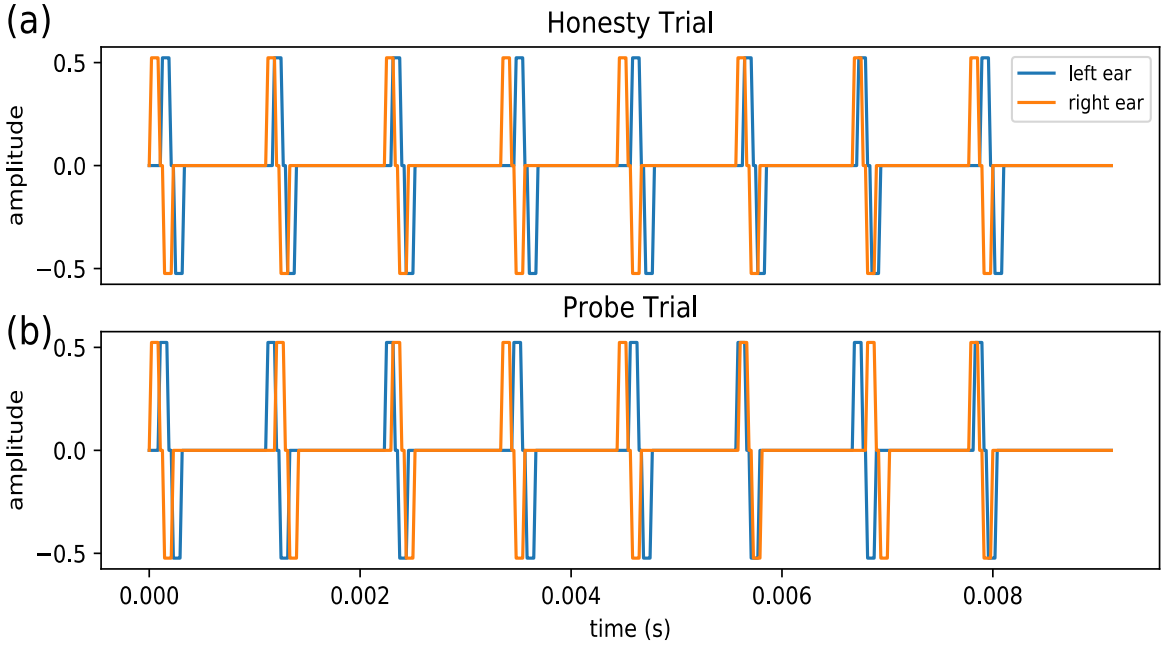

Figure 4.1 CI jittered ITD stimulus example. Right ear stimuli are shown in orange and blue indicates left pulse trains. (a) Example of honesty trial with all pulses consisting of ITDs pointing towards the right (orange pulses). (b) Example of probe trial with ITDs point both left (blue) and right (orange).

Analysis

TWFs were computed from the behavioural responses to determine the whether the three aspects of ITD temporal weighting found in normal hearing listeners (Brown and Stecker 2010) were also present in our early deafness onset bilateral CI supplied animal model, particularly if onset

dominance persisted under electric hearing. We modified the ROC estimate of TWFs from Brown and Stecker(2010) by using a probit analysis which yielded a better fit to the data. The equation for the probit analysis is given by:

$$P(\text{“right”response}) = \varphi(\beta_0 + \beta_1 ITD_1 + \beta_2 ITD_2 + \beta_3 ITD_3 + \beta_4 ITD_4 + \beta_5 ITD_5 + \beta_6 ITD_6 + \beta_7 ITD_7 + \beta_8 ITD_8)$$

(eq. 4.1)

where P is the probability of an animal choosing the “right” side spout, and β0 is a constant offset that can capture a possible bias, or idiosyncratic preference, that an animal may have for one of the spouts.. ITD_1, ITD_2... ITD_N correspond to the ITDs on each of the N=8 pulses presented during each trial, and are set as the exogenous parameters. Probit regression analysis was performed for each animal at each pulse rate independently.

The reader is reminded that, during probe trials the animals received a reward regardless of their choice, such that a good performance on honesty trials was needed to ensure that the animals’ choices were a reasonably accurate reflection of their lateralisation judgements and not just random guesses. Therefore, only testing sessions where honesty trials reached at least 75% correct were included in the probit analysis. Only probe trials for each of the included testing sessions were used in the probit analysis. The probit coefficients (β_1, β_2.. β_8, from eq 4.1) quantify the relative contribution, or “weight”, of each of the 8 pulses towards the animal’s behaviour decision.

To determine if the onset responses were significantly different between groups we used a bootstrap permutation method: we resampled trials for each animal at each pulse rate 1000 times with replacement, and recalculated the probit coefficients each time. The 1st and 99th percentile of the thus obtained coefficients served to estimate the 99% confidence intervals of the probit coefficients. By comparing the confidence intervals for the first pulse we then determined if the strength of onset weighting was comparable in different conditions.

Results

All animals were able to perform the task with at least 75% accuracy for honesty trials in most conditions, with the exception of 2 CI-ND animals failing to reach the 75% criterion at 900 Hz. This performance is shown in the third column of figure 4.2, with the 75% cut-off shown with the dashed grey line. NH animals were trained for fewer session on average, with blue crosses clustering on the left of the honesty trial performance plots (third column figure 4.2). This makes it look like more CI-ND animals failed to reach 75%, but in fact CI_ND animals simply had more training sessions resulting in more training sessions occurring below 75%. The performances for both groups tended to improve with time, with fewer training session below the 75% cut-off across time along the x-axis. The number of training session below the cut-off was higher for 900 Hz for both cohorts.

TWFs are shown for CI-ND animals in red on the left and NH animals in blue in the middle columns (figure 4.2). The average TWFs for all animals are shown in black for each cohort at each pulse rate, with standard biases of the probit anlaysis indicated by the shaded areas. Asterisks indicate average coefficients with $p < 0.005$. It is apparent from the average plots that our data set for both CI-ND and NH animals are comparable with the previous study (Brown and Stecker,2010) in that onset dominance is present at all pulse rates. Importantly, while this onset dominance is also present under electric stimulation, it is substantially reduced compared to NH coefficients at higher pulse rates. At 900 Hz, the average probit coefficient for the first pulse, the onset ITD, for CI-ND animals is almost one third as large as that for NH animals. Overall we see an increase in onset dominance with increasing pulse rate for the NH animals, while the effect of pulse rate does not seem to be present for the CI-ND animals, as the CI-ND probit coefficients of the onset ITD remain within the range of 3-4 irrespective of pulse rate, with no obvious trends.

In addition, pulses other than the first exhibit significantly non-zero probit coefficients ($p< 0.005$; computed by Python module statsmodel.api.Probit()) for the CI-ND group but not for the NH animals. For example, at both 50 and 900 Hz, pulse 2 and 3 have non-zero weights, meaning that, at least for a substantial number of trials, these pulses contributed to the animals' behavioural decision. This is in contrast to the finding of Stecker (2013), demonstrating that the 2nd and 3rd pulses had the lowest weights. Furthermore, the variability in TWFs between CI-ND rats is considerably higher than between NH rats, even with a larger sample size.

Interestingly, we do not see convincing evidence of an offset response. Only at 300 Hz for NH and at 900 Hz for CI-ND does pulse 8 have significant weighting ($p<0.05$) and thus contributes significantly to the animals' decisions (see asterisks in Figure 4.2).

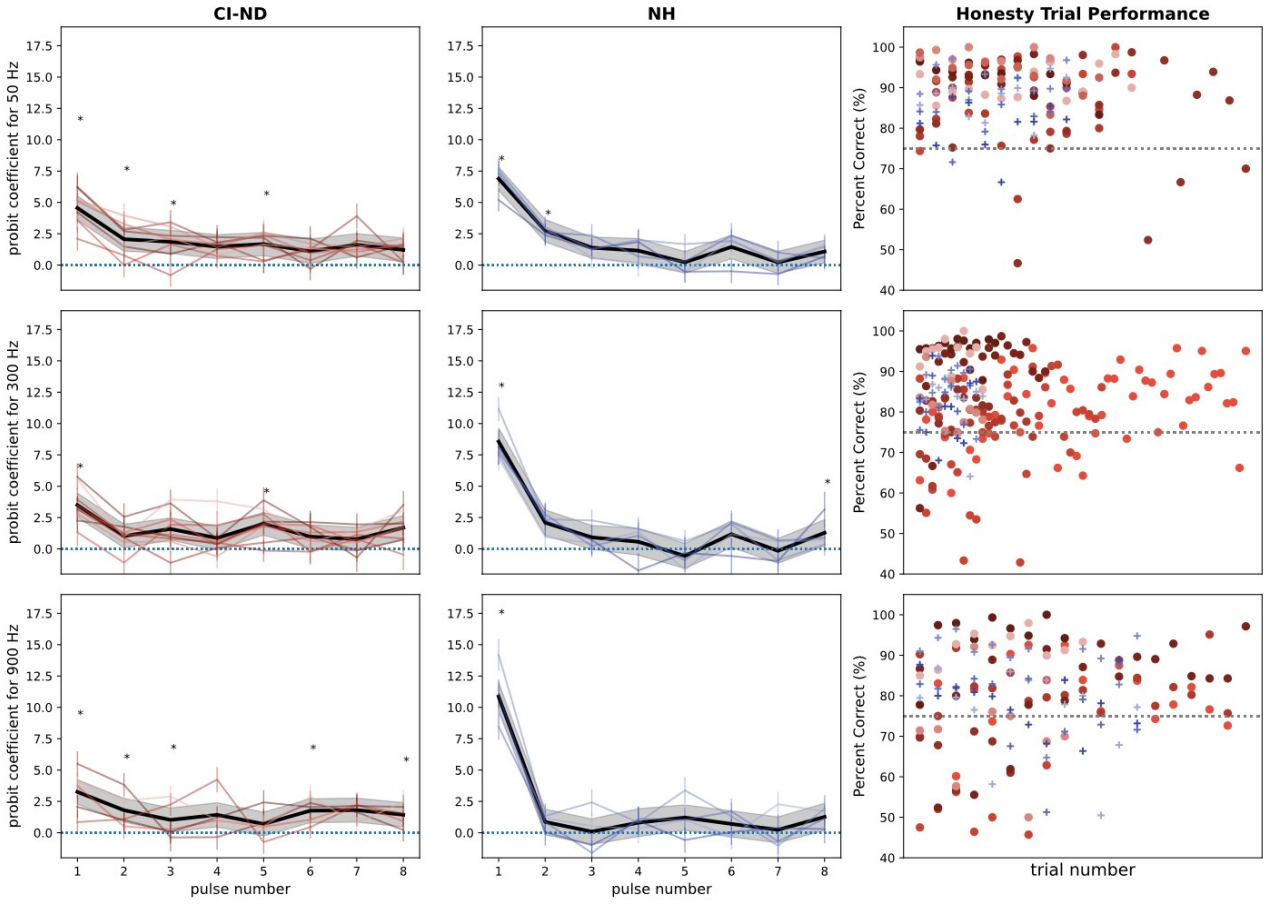

Figure 4.2 TWFs and performance levels for Honesty Trials. Top, middle and bottom rows show results for 50, 300 and 900 Hz respectively. Left (CI_ND; red) and middle (NH; blue) columns show temporal weighting for each of the eight pulses, calculated as a linear regression weight in 1/ms ITD. Each animal is shown in a different colour. Black lines are pooled results from all animals. Error bars and shading show SEM. The right column shows the performance for Honesty trials in each session. Only sessions > 75% correct (dashed line) were included in the TWF analysis. Each individual animal is a different marker shape, with CI animals in red and NH animals in blue.

Next, to determine if the difference in the onset weights in between cohorts was significant, we randomly sampled, with replacement, training sessions from each animal at each pulse rate and recalculated the probit weights for 1000 trials. 99 % confidence intervals were calculated from the bootstrapped data and are shown for the first pulse (onset response) in Figure 4.3. There is significant overlap for all animals at 50 Hz as well as at 300 Hz with the exception of 2 NH animals.

At 900 Hz, we see no overlap between confidence intervals of the two cohorts, illustrating that onset responses are significantly lower for CI-ND compared to NH animals. We also note that the confidence intervals for CI_ND rats are generally wider than those for NH rats, which indicates a higher inter-trial variability within an animal's training set, in addition to the larger inter-individual variability in CI_ND seen in Figure 4.2.

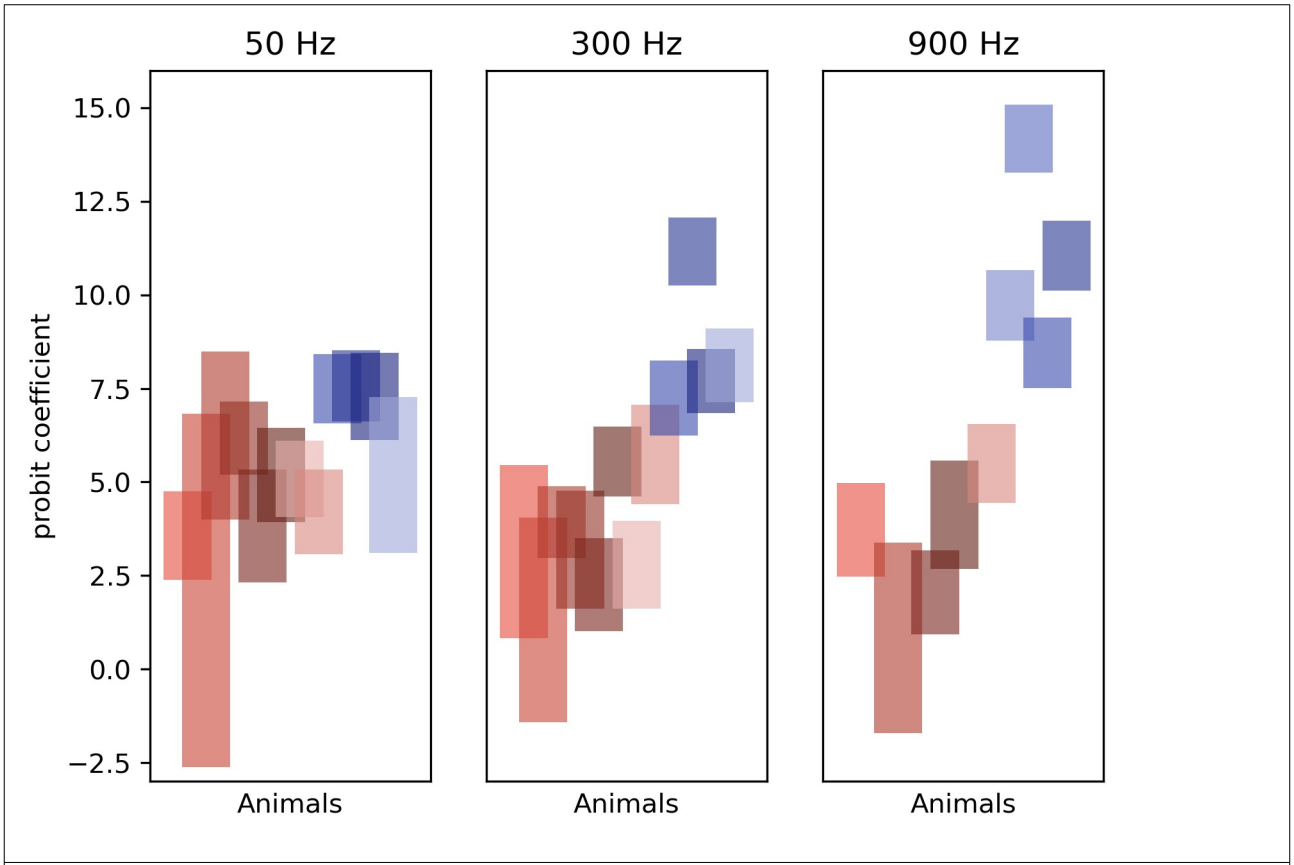

Figure 4.3 Confidence intervals for the probit coefficients on the bootstrapped trials for the first pulse at each pulse rate. Each animal is shown in a different colour, with CI_ND shown in shades of red and NH shown in shades of blue, as in Figure 4.2. The 99% confidence intervals are given by the length of each bar.

Discussion

To the best of our knowledge, this is the first study to look at the temporal weighting function for ITDs under CI stimulation in an early onset deafness animal model with direct comparison to normal hearing peers. Studies in humans are limited by elements such as poor spatial localisation in general (Litovsky et al. 2006; Grantham et al. 2008), and poor ITD sensitivity is further associated with worsening localisation in reverberant environments (Kerber and Seeber 2012). This would suggest that the precedence effect may operate less effectively under electric hearing. In addition, any peripheral mechanism of the precedence effect pertaining to cochlea ringing (Bianchi et al,2013) would not be possible. However, our results clearly show the presence of onset dominance across all tested pulse rates, as was also found by van Hoesel (2008).

It is important to note that our CI animals have only ever experienced bilaterally synchronised input, and have good ITD sensitivity (see Chapter 4). The bilaterally synchronised input enables the delivery of temporally precise and accurate ITDs, similar to research interfaces used in human CI studies (van Hoesel 2007; Agrawal 2008). This similarity in stimulus presentation, and that all subjects showed prior ITD sensitivity, suggest that neither the absence of hearing experience nor electric stimulation prevent onset dominance mechanisms from occurring. Nevertheless, our findings show the precedence effect to be weaker under CI stimulation compared to normal acoustic hearing subjects, suggesting that both innate and experience dependent mechanisms may be at play in the development of temporal onset weighting.

Another important stimulation element in our experiment is that our animals have only ever received pulse frm a single electrode stimulation in each ear. Thus they have never experienced a complex auditory environment which would include exposure to echoes and competing sound sources experienced by normal hearing listening, or even those with clinical speech processors. Our data do not allow us to discern whether it is this absence of experience or the absence of cochlea ringing mechanisms that account for the lack of increased onset weighting with increasing pulse rate that is seen in the normal hearing animals presented here and in humans (Brown and Stecker 2010). The data presented by van Hoesel (2008) for post-linguilly deafend CI users was normalised to the onset pulse, and therefore a post hoc comparison of onset weightings across carrier rates is not possible.

It should also be born in mind that, unlike human CI users, even those post-linguilly deafened, our CI animals are able to discriminate ITDs well even at 900 Hz (see Chapter 4). The good spatial localisation at these higher pulse rates shown in Chapter 4 could account for the constant onset weighting across pulse rates compared to the decrease seen from 100 to 300 Hz seen in the three patients tested by van Hoesel (2007). Interestingly, this would suggest that the effect of pulse rate on onset dominance depends either on basement membrane mechanics or is experience dependent. Further studies using normal hearing experienced animals under electric stimulation would be needed to distinguish these possibilities indisputably.

In this study, we have thus demonstrated that CI stimulated subjects with good ITD sensitivity with a prolonged period of deafness show clear evidence of the precedence effect. Furthermore, the increase in the onset weighting with increasing pulse rate is absent, and this could either be due to the modality of stimulation (electric vs acoustic), or the absence of normal hearing experience with exposure to complex and reverberant auditory scenes.

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Chapter 6: The importance of Envelope and Pulse Timing in carrying ITDs

Abstract

Noisy environments remain a particular challenge for cochlear implant (CI) users, given their very limited inability to make use of temporal spatial cues or interaural time differences (ITDs). Previous studies have suggested that ITD perception is possible when these cues are present on the amplitude modulating envelope under electric hearing. In this study we tested whether ITD perception relies more on ITDs created by differences in timing of the fixed rate pulses between ears (pulse-timing ITDs) or ITDs carried on the envelope (envelope ITDs). This study used an established animal model for early onset deafness with subjects implanted in early adulthood with CIs and receiving bilaterally synchronised stimulation. Carrier rates of 900 and 4500 Hz were tested at different modulation rates (5,20 and 100 Hz) and repetition rates (1, 5, 20, 100 Hz). In all animals (n=4) we find that ITD performance relies overwhelmingly on pulse timing ITDs, while envelope ITDs carry almost no weight in behavioural localisation decisions in a two-alternate forced choice task across all conditions. In addition, 900 Hz carrier rate resulted in a significantly better performance for pulse timing ITDs compared to 4500 Hz. Furthermore the higher modulation rate (100 Hz) facilitated significantly better performance compared to lower rates (5 and 20 Hz). This study provides evidence that synchronising the pulse timing, and not just the envelopes, of binaural CI input is likely to be crucial for delivering salient ITD cues under electric hearing.

Introduction

The ability to decorrelate target sounds against a backdrop of competing sound sources requires the use of interaural time differences (ITDs), as well as interaural level differences (ILDs). It is appreciated that most cochlear implant (CI) users have difficulties in identifying target sounds in complex auditory scenes, experiencing what has been coined the 'Cocktail Party Effect'. These difficulties are, at least in part, due to the inability of most CI users to perceive ITDs, particularly if they have early onset deafness. To some extent this has been attributed to the lower pulse rates required to deliver ITDs (Litovsky 2010; Laback et al. 2015).

Normal hearing listeners are sensitive to ITDs conveyed in the temporal fine structure of low frequency sounds (<1500; (Zwislocki and Feldman 1956; Wightman and Kistler 1992). At higher frequencies, normal listeners are still highly sensitive to ITDs when a slow modulated envelope is present (Henning 1974; McFadden and Pasanen 1976).For CI users with clinical speech processors, the temporal fine structure is discarded and replaced with pulses at a fixed rate, usually between 900 - 1200 pps. Importantly, in the large majority of clinical processors, these pulses are not synchronised to sub-milisecond temporal features of the binaural input, and their timing is thus unable to deliver ITDs on the individual pulses. However, Laback et al. (2004a) showed that just noticeable differences (JNDs) in ITD of 250 µs were nevertheless attainable, suggesting that CI users can make use of envelope ITDs. Even so, thresholds of 250 µs for envelope ITDs are still about ten times higher than thresholds obtainable by normal hearing listeners. Furthermore, these envelope ITD cues were found to be less reliable for speech or noise bursts compared to pulse trains (Laback et al. 2004a) which suggests that the envelope shape is of importance. This is also evidenced by the fact that, in order to test ITD sensitivity, even in the best CI users, the use of bilaterally synchronised input is generally adopted, and this is delivered with a research interface, bypassing the standard clinical processors (Litovsky et al. 2010). Overall, there is little evidence that CI users would be able to derive worthwhile benefits from envelope ITD sensitivity.

CI users tested on research interfaces, capable of synchronising pulses and therefore providing pulse timing ITDs, show reduced ITD sensitivity at carrier rates above 100 pps in pulse trains with no amplitude modulation (van Hoesel and Tyler 2003; Laback et al. 2005; Majdak et al. 2006). However, Smith and Delgutte (2008) show that pulse rates up to 5000 pps show ITD sensitivity with amplitude modulated stimuli in single unit physiology recordings. This study also shows that, at lower frequencies (≤ 1000 pps), pulse-timing ITD had both a lower JND and sharper tuning compared to envelope ITDs in the inferior colliculus of cats under modulated electric pulse trains. Furthermore, responses to waveform ITDs (ITD presented on the pulse and envelope) showed pulse timing ITDs to be the dominant response within the physiologically relevant range in adult deafened cats (Smith and Delgutte 2008). In addition at higher carrier rates, those that would be more clinically relevant for speech encoding, there is huge variability in ITD performance among CI users with some being able to use envelope ITDs even with shallow modulation depths suggesting that while some users would benefit from fine structure cues others are able to make use of envelope cues (Ihlefeld et al. 2014). Furthermore, even normal hearing listeners require consistent

ITD fine structure information as ILDs alone were not sufficient to provide spatial release from masking (Ihlefeld and Litovsky 2012).

Thus, in order to determine the extent to which the mammalian auditory system is capable of using pulse timing or pulse envelope ITDs respectively under electric hearing, we used our established, neonatally deafened animal model and behavioural setup to systematically evaluate CI users ITD performance while isolating whether pulse timing or envelope ITDs dominates the animals behavioural decision. Here pulses are bilaterally synchronised and thus able to carry reliable ITD information as well as appropriately sample the modulated envelope shape. Pulse rates of 900 and 4500 pps were assessed to determine if envelope ITDs becomes more important at higher pulse rates. In addition we assessed the effects of envelope shapes by using different modulation and repetition rates so that when the repetition rate was smaller than the modulation rate brief pauses were introduced between each sinusoid amplitude modulation. The envelopes were convolved to Hanning windows with a slow rise similar to those seen in chapter 4. This variety of envelope shapes was selected to cover a range of different and ecologically relevant auditory stimuli.

Methods

Four neonatally deafened adult female Wistar rats were implanted with bilateral cochlear implants in early adulthood (between 8-10 weeks post-natally). The kanamycin deafening and implantation were as described in Chapter 2 and Rosskothen-Kuhl et al. (2021). As before, deafness was confirmed prior to implantation using acoustic auditory brainstem responses (ABRs) and electrode position and function following implantation using electrical ABRs as previously described (Chapter 2 and 4).

Following implantation, animals were trained to use ITD cues as described in Chapter 2 and 4. We then needed to interdependently control ITD presentation on the envelope and individual pulses in order to determine their relative importance in the animal's ability to lateralize with these cues. Thus we interleaved four different trial types of namely non-zero ITDs presented only with the pulse timing and zero ITDs on the envelope, non-zero ITDs only on the envelope and zero ITDs presented with pulse timing, the ITD from the same side for both pulse timing and envelope and ITDs indicating opposite sides on the envelope and pulse timing. Note that the individual electric biphasic, bipolar pulses within a pulse train are referred to as the pulse-timing (ITD_{pulse}) in this chapter while the shape of the amplitude modulation is referred to as the pulse-envelope (ITD_{ENV}). All pulse trains were convolved with a Hanning window as described in Chapter 4. Only ITD values of +/- 100 µs were used, with the sign denoting right and left ear leading, respectively. We have seen in previous chapters that 100 µs ITD tend to permit good performance for all animals (> 75% correct lateralisation performance; see Chapter 4).

1) Congruent ITD

The value of the ITD applied to the individual pulses and the envelope ITD were identical. This is effectively the same type of stimulus as presented in Chapter 4 for Hanning windowed pulse trains, although the window duration here could be shorter. The corresponding pulses of right and left channels thus have the same amplitude, but were presented with a temporal shift (see Figure 5.1A).

2) Incongruent ITD

The same value of ITD was presented in both, pulse timing and envelope, but with opposite signs, in other words in opposite directions. The animal's decision of choosing either the side with leading pulse or the side with a leading envelope would thus determine whether the animal relies more on the sensitivity to pulse-timing or pulse-envelope ITD. This is demonstrated in Figure 5.1B. In order not to bias the animal's decision with any learning, the animal was rewarded regardless of which spout she chose, in other words whether she chose to follow pulse-timing or pulse-envelope ITDs.

3) Pulse -Envelope ITD

An ITD was applied only to the amplitude envelope while the ITD of the individual pulses was set to zero. Thus, only the amplitudes of corresponding pulses varied for the left and right channels. At the level of the individual pulses, this results in only an amplitude difference between to the two channels (left and right CIs), resulting in a very small, dynamic ILD during the rising phase, and an opposite ILD at the falling phase, but if the auditory system could perform and envelope

reconstruction from the pulse trained sampled waveform in a way similar to the way a digital music device reconstructs analog music from digital pulses then the envelope ITD should be fully available to it from that signal. Note that the magnitude of the dynamic ILDs at the rising and falling phases of the envelope are far below the animals' thresholds, as demonstrated in S1.3 in Rosskothen-Kuhl et al. (2021) and Chapter 2, and they are of course also a feature of any natural "acoustic" ITD, but they are never treated as "ILD cues" in the literature, with good reason. (Figure 5.1C).

4) Pulse-timing ITD

The ITD was presented only on the individual pulses shifting the pulse train between ears. The amplitude of the pulses was defined by the envelope shape condition which was the same for both ears. In other words, the onset of the left and right channel envelopes had no temporal shift with respect to each other. Therefore, the amplitude of pulses of the left and right ear were defined by the same envelope, effectively. This led to slightly higher amplitudes of pulses of the lagging channel compared to corresponding pulses of the leading channel, until the peak amplitude of the burst was reached. After that, the amplitudes of leading channel pulses were higher than the amplitudes of lagging channel pulses (see Figure 5.1D). However as shown in chapter 2, these ILDs are orders of magnitude below the animals' ILD behavioural thresholds (see Chapter 2 Figure S1.3).

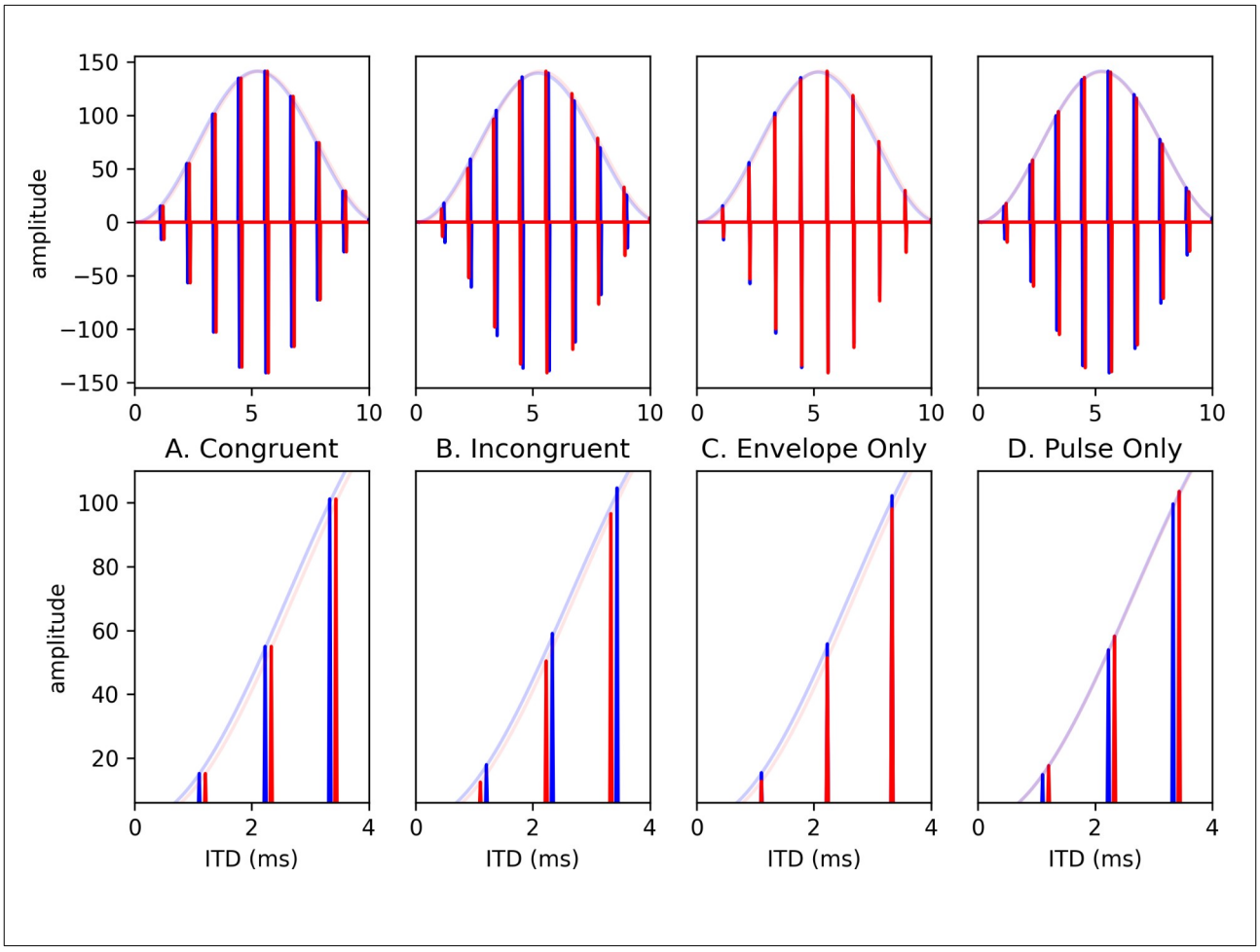

Figure 5.1 Four ITD presentation types. All examples are shown at 900 pps for a 10 ms duration. The top row shows one complete cycle. The bottom row shows as zoomed in segment on the rising Hanning window. Right ear stimuli are are shown in red and left in blue. A. Congruent trial type: left leading ITDs presented on the envelope and the pulses. B. Incongruent trials type: right leading pulse ITD and left leading envelope ITD. C: Envelope ITD only: pulses overlap in time with the ITD only on the envelope resulting in an earlier rise in amplitude of the leading ear(blue). D: Pulse ITD only: common envelope shared by time separated pulses so that the lagging ear receives a pulse with a slightly higher amplitude.

The four trial types shown in Figure 5.1 were interleaved randomly within a given training session. The carrier rate, burst width and repetition rates were varied. Pulse trains had carrier rates of 900 pps or 4500 pps; burst widths of 10, 20 or 200 ms; and repetition rates of 1, 5 20 or 100 Hz referring to repetition of the burst (see Figure 5.2). When the repetition rate was equal to the reciprocal of burst width, the stimulus shape could effectively be considered as sinusoidal amplitude modulated (SAM) stimulus with no pause between bursts. Repetition rates lower than the reciprocal of burst width resulted in a non-zero pause duration. Thus we could investigate the effects of these pauses. The stimulus duration was kept constant at 3 s for all variations. Note that Figure 5.2 shows only the envelope shapes for simplicity. All stimulus combinations (Figure 5.2) and trial types (Figure 5.1) were randomly interleaved for each training session and only sorted and the analysis phase.

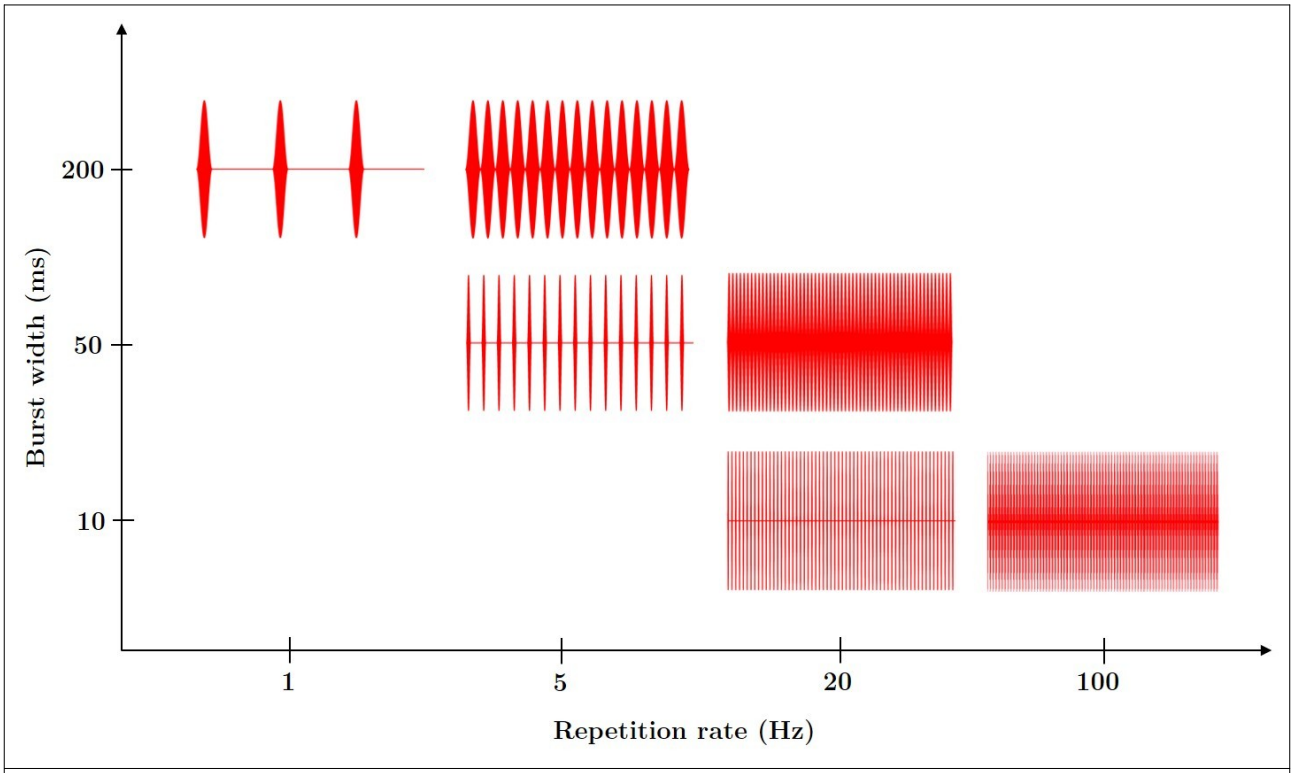

Figure 5.2: Stimulus envelope shapes. Burst width (y-axis) and repetition rate (x-axis) were both varied. Each stimulus has a duration of 3 s. Only the envelope shapes are shown, no individual pulses. The number of pulses in each burst depended on the carrier rate (900 or 4500 pps).

Analysis

To analyse data for each of the 4 trial types shown in Figure 5.1 separately, as a first step, we evaluated that each animal had obtained an average performance of at least 75% for all the congruent trial types (Figure 5.1A) across training sessions. The data was then sorted depending on the carrier rate, burst width and repetition rate (see Figure 5.2).. The behavioural data for each animal was then subjected to a probit regression analysis, where ITD_{pulse} and ITD_{ENV} were used as exogenous parameters to determine how much the animals weighed each cue for each of the 29 different conditions of carrier rate, burst width and repetition rate (see Figure 5.2). To determine whether carrier rate, burst width and/or pause between consecutive bursts affect the ITD sensitivity, we used a bootstrap permutation method to calculate confidence intervals and determine significant difference between condition where by non-overlapping confidence intervals indicate a significant difference for a given parameter. For example, given our results from Chapter 4 we expect carrier rate to have a significant effect on ITD performance and will thus we should see no-overlap in performances between carrier rates.

Probit model analysis

The probit analysis was performed using the same python statsmodel module as for Chapter 5 with the form:

$$P(\text{“right”response}) = \phi(\beta_0 + \beta_{pulse}ITD_{pulse} + \beta_{ENV}ITD_{ENV}) \qquad \text{(eq. 5.1)}$$

where P is the probability of animal choosing the “right” side spout and β_0 is the bias factor. ITD_{pulse} and ITD_{ENV} set are the exogenous parameters. Probit regression analysis was performed for each animal independently. Probit coefficients for envelope ITDs were near zero and thus these trials were excluded from further analysis.

Permutation analysis

To determine how the different stimulus parameters, namely carrier rate, burst width and repetition rate, affected the pulse time ITD performance we used a bootstrap permutation method to calculate confidence intervals per condition.

Any trial that included a pulse ITD was included (types A, B and D in Figure 5.1). For each animal at each condition these trials were randomly sampled with replacement 1000 times with a sample length equal to the total number of trials each time. A percentage correct for each sample was then calculated. Correct responses were determined based on the pulse ITD values. The average percentage correct across animals at each condition for the 1000 bootstrapped trials was then used to calculate the 99% confidence interval for this condition.

Results

Congruent trials for each animal were used as a measure of the animal's performance for each training session. Bearing in mind that these congruent trials would be a random mix of all stimulus conditions in a given training sessions we considered average performances of at least 75 % to indicate that the animals were paying adequate attention to the task. Figure 5.3 shows the variability in performance for each condition for 900 and 4500 Hz carrier rates for each animal. It is evident that the highest modulation rate seems to have the better performance at both carrier rates (purple shades in Figure 5.3), and that overall the performance at 900 pps appears to be better than at 4500 pps.

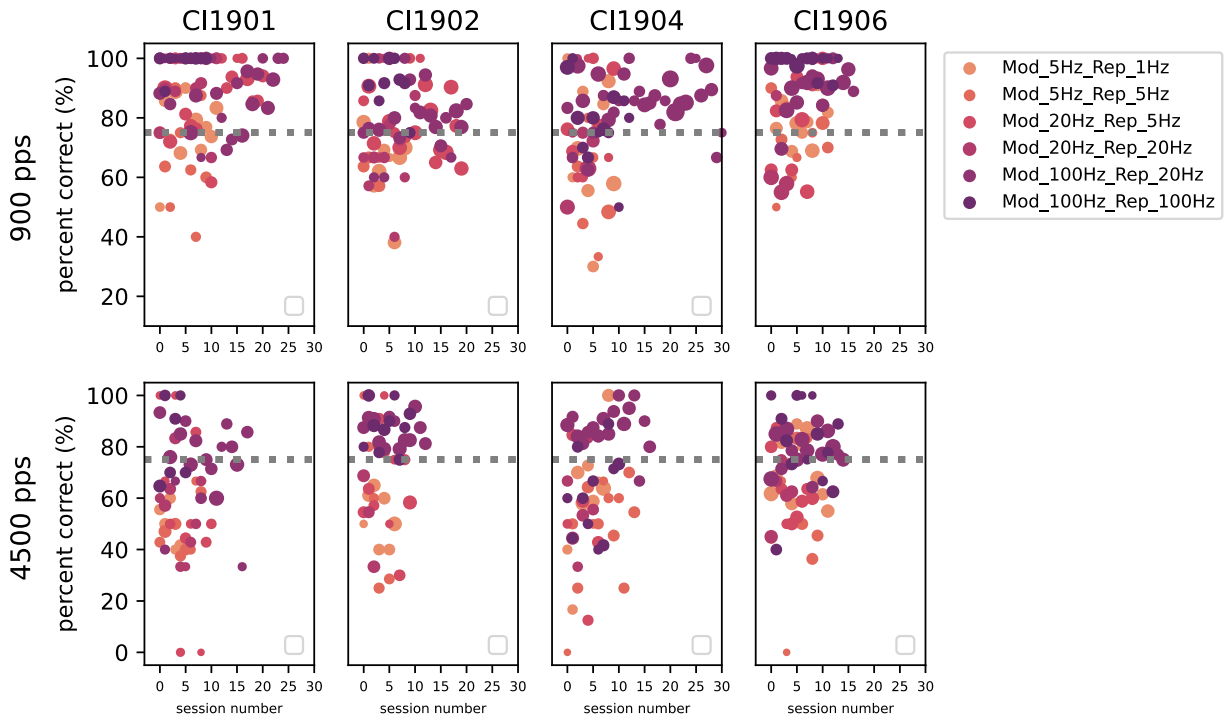

Figure 5.3 Congruent trial performance for each condition for each behavioural training session. Each column represents the performance for one animal. Top row shows the performance at 900 pps carrier rate and the bottom row at 4500 pps. The colour code represents the different modulation rates and repetition rates used. The area of each point reflects the square root of the number of trials of that parameter combination presented in that particular session, ranging from a minumum of 1 to a maximum of 83.

These trends are confirmed with the results of the probit analysis shown in Figure 5.4, with probit coefficients illustrating the influence each parameter has on each animal's lateralisation decision. Most notably, pulse-envelope ITDs are near zero at all conditions with only a single instance for one animal showing a significant weighting of these ITD cues (CI1902 at 100 Hz modulation and 20

Hz repetition). In addition, the probit coefficients at 4500 pps (green) are lower than those for 900 pps (blue) across all modulation and repetition rates, although pulse-timing ITDs are still significantly weighted at 4500 pps for most animals at most conditions with the exception of 5 Hz modulation and 5 Hz repetition.

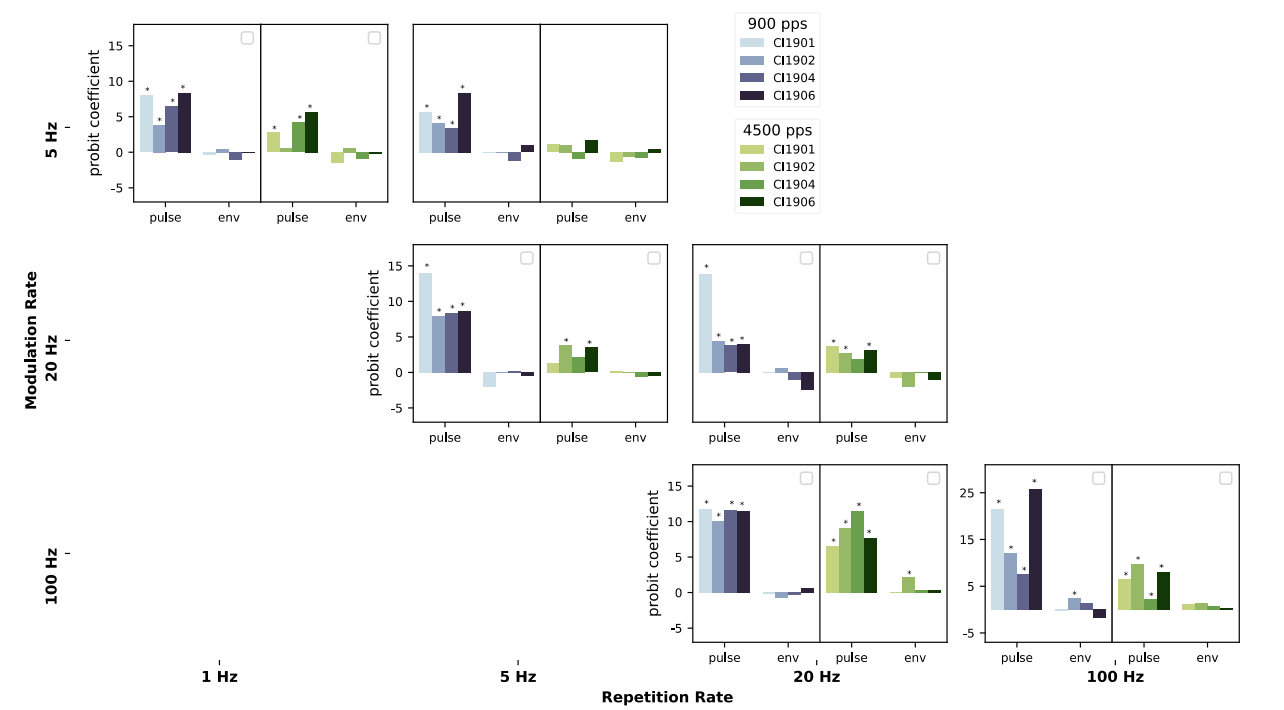

Figure 5.4 Probit coefficients for each animal at each condition. Columns indicate the repetition rate and rows the modulation rate as in the stimulus Figure 5.2. Shades of blue show the results at 900 pps and green at 4500 pps. The different shades reflect the different access. Pulse and envelope ITD conditions are shown on the x axis of each subplot. Asterisks indicate significant probit coefficients ($\boldsymbol{p} < 0.01$).

Envelope ITDs appear to affect the animal's behavioural decision very little across all parameters. To determine if envelope cues had an additive effect to pulse timing ITDs, we additionally looked at lateralisation performance comparing pulse timing ITDs with congruent ITDs (ITDs on both pulse and envelope). Wilcoxin rank sum tests showed no significant differences in ITD lateralisation performance with or without the presence of envelope ITDs.

To tease out which stimulus parameters affected ITD performance, only trials with non-zero pulse ITD information were included in the bootstrap permutation analysis. Figure 5.5 shows the percentage correct for each modulation rate at 900 pps (blue) and 4500 pps (green). This figure shows that , for both carrier rates, the performance at a modulation rate of 100 Hz is significantly larger than at other modulation rates ($p < 0.01$). This indicates that the modulation rate significantly influences the animals' performance of pulse timing ITDs. In addition, a significant effect of the carrier rate (900 pps and 4500 pps) across all modulation rates on pulse-timing ITD performance was found ($p < 0.01$), as seen by the absence of overlapping confidence intervals in Figure 5.5.

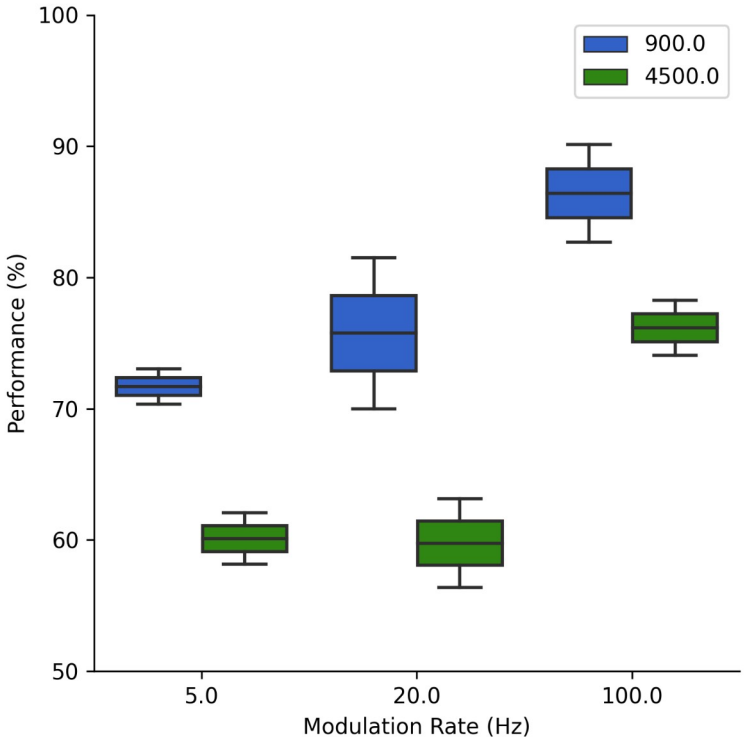

Figure 5.5 Pulse ITD performance for each modulation rate. Performance measured as percentage correct according to pulse ITD stimulus. Data for 900 pps shown in blue and for 4500 pps in green. Boxes indicate mean and interquartile range. Box whiskers indicate 99 % confidence intervals determine from bootstrap method. Repetition rates are pooled together.

Figure 5.6 shows the effect of repetition rate at each modulation rate. Here again we see the general trend of increasing performance with increasing modulation rate. We do not see a significant effect of repetition rate, either at each modulation rate or in the pooled data across all conditions. As shown in Figure 5.2, each modulation rate was tested at 2 repetition rates. One that was effectively a sinusoid amplitude modulated waveform (SAM) and one that results in gaps or pauses between each envelope rise (Figure 5.2). From Figure 5.6, we can see that at no one modulation rate does the pause appear to significantly affect the performance. Only at a repetition rate of 20 Hz do we see a significant difference between a modulation rate of 20 and 100 Hz where the former would have no pause and the latter would. To determine whether it was the pause or the modulation rate that was playing a role here we can look at Figure 5.7 which shows the bootsrapped permutation results comparing pause conditions across modulation rates. Here it is clear that the presence or absence of a pause has no significant effect on the performance based on the permutation tests ($p > 0.01$) whereas there is a significant difference in performance at 100 Hz modulation when compared to the lower modulation rates regardless of whether a pause was present or not($p < 0.01$).

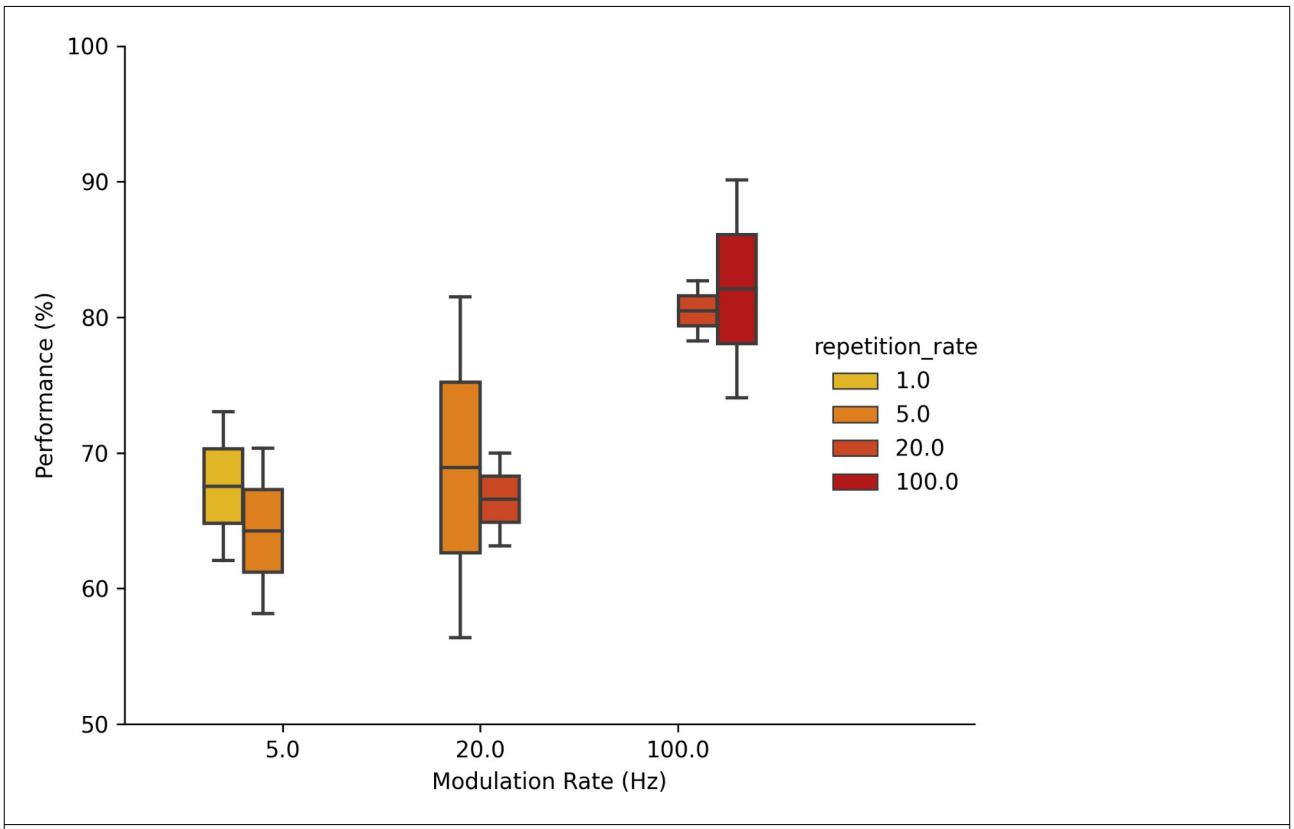

Figure 5.6 Performance for each repetition rate as a function of modulation rate. As for Figure 5.5, performance is a measure of percentage correct based on pulse ITD value. Legend indicates the different repetition rates at each modulation rate shown on the x-axis. Box whiskers indicate 99% confidence intervals. Data for 900 and 4500 pps is pooled.

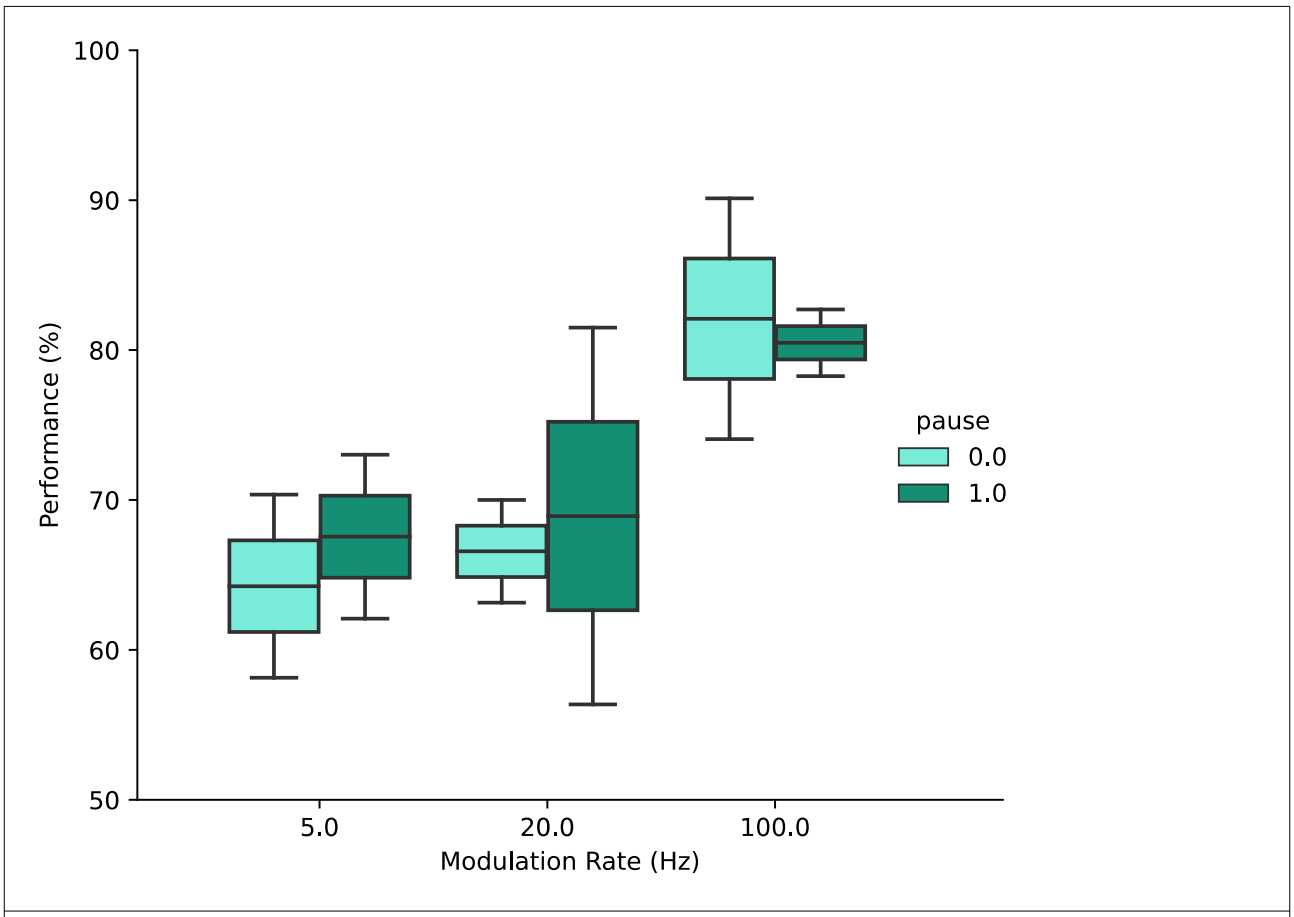

Figure 5.7 Performance at each modulation rate with and without pauses. Data is pooled for repetition rates and carrier rates. Different shades of teal indicate whether pause was present. Legend shows logical values. Box plots are as for Figure 5.5 and 5.6 with boxes showing the mean and interquartile range and whiskers indicating the 99 % confidence interval from the bootsrapped trials.

Discussion

This study has demonstrated the importance of pulse timing ITDs in an early onset deafness animal model. These findings corroborate with those of Smith and Delgutte (2008), who found physiological responses to pulse timing ITDs, although present in smaller number of units, to be significantly stronger compared to the responses for envelope ITDs. If one considers what non-zero envelope ITDs with pulse-timing ITDs of zero stimuli actually boil down to (see Figure 5.1) with only a very small ILD far below the animals behavioural capability (see supplementary materials Chapter 2), it is not all that surprising the animals weight their behavioural decision elsewhere. In this study, not only are envelope ITDs weighted close to zero across all parameters but envelope ITDs do not even significantly improve ITD performance when added on top of pulse timing ITDs.

Given that current clinical speech processors are not bilaterally synchronised on a day-to-day basis, CI users are not able to make use of pulse timing ITDs. It is thus possible that the absence of these cues results in desensitisation to them or, alternatively, increased sensitivity to envelope ITDs which can, at least in theory, still be delivered. This may account for the higher sensitivity to envelope ITDs found in previous studies on post-linguilly deafened CI users (Majdak et al. 2006; van Hoesel et al. 2009). However, one cannot rule out possible effects of auditory deprivation during development in our animal model which could also be held to account for these differences. Alternatively if we consider that previous studies have shown both physiologically (Smith and Delgutte 2008) and behaviourally (Majdak et al. 2006; van Hoesel 2008) sensitivity for pulse timing ITDs, as compared to envelope ITDs , it is possible that the animals in our study, who were always receiving bilaterally synchronised input, were simply relying on the more salient cue available to their auditory system.

The fact that these animals base their lateralisation decisions almost entirely on the pulse timing ITDs rather than the envelope ITDs at all modulation rates is of particular clinical relevance. Current clinical CI processors do not provide bilaterally temporally synchronised pulse trains and are thus discarding the most valuable component of ITD sensitivity. While it has been argued that the slow modulation of speech at around 5 Hz (Greenberg S. 2004) should allow envelope ITD perception to be possible post-linguilly deafened CI listeners, show a greater sensitivity for pulse timing ITDs when delivered over a research interface (Majdak et al. 2006). This together with the striking varibility we see in envelope ITD performance at high pulse rate in these subjects (Ihlefeld et al. 2014) strongly suggest that many of these users would indeed benefit from pulse timing ITDs and thus bilaterally synchronised processors.

It should be noted that the mechanisms at play under CI stimulation between pulse timing ITDs and envelope ITDs are not akin to those between fines structure and envelope ITDs in acoustic hearing. While analogously the fine structure of a waveform is replaced with the fixed rate pulse of the CI processors these pulses are essentially conveyed as first order envelopes with the amplitude

envelope ITDs being carried on the second order envelopes once they reach the auditory nerves. This is unlike the frequnecy-related differences bewteen fine structure and envelope ITDs in normal hearing listeners where by peripheral mechanisms of envelope compression result in differing transmission of these ITD cues which can be 'translated' artificially to imporve ITD sensitivity at higher frequencies (Bernstein and Trahiotis 1996; Bernstein et al. 1999).

The effects of amplitude modulation rate and carrier rate on pulse timing ITD sensitivity is not surprising. Several previous studies have demonstrated a reduction in ITD sensitivity with increasing carrier rate (van Hoesel and Tyler 2003; Laback et al. 2004b; Litovsky 2005; van Hoesel et al. 2009). van Hoesel et al. (2009) found a decrease in ITD sensitivity with increasing modulation rates but across a range of 100 – 1000 Hz in post-linguilly deafened CI users. In contrast, in this study we have modulation rates of 5, 20 and 100 Hz. Thus our highest modulation rate, which showed significantly higher ITD performance compared to two other lower rates, corresponds to the lowest, and best, modulation frequency tested by van Hoesel et al. (2009) . Our finding shows the best performance at 100 Hz modulation (Figure 5.4), confirmed by the probit coefficient on the performances for each animal (figure 5.3) and their corresponding confidence intervals from the permutation test (Figure 5.5).

Interestingly, we did not find a significant effect of pause or repetition rate. This suggests that the reseting of adaptation, or in other words restarting of the adapted binaural system proposed by previous studies (Laback and Majdak 2008; Goupell et al. 2009) does not seem to play a role in the pulse timing ITD sensitivity. It is of course possible that the pause at the highest modulation rate, where you would expect the greatest effect, is simply not long enough to allow a recovery over the refractory period given the nature of our stimulus design. The latter would be more in keeping with acoustic studies demonstrating reduced ITD thresholds with longer pauses in tone pips (Bernstein and Trahiotis 2009) as well as strongest ITD tuning with long pauses and steep attacks (Dietz et al. 2016). In addition Hancock et al (2017) demonstrated under CI stimulation that neurons were most responsive to short burst widths, or faster modulation rates, and lower reptition rates in acutely deafened cats. However, However, there was a high degree of indervidual variability adn these were temporal but not specific to ITDs. Other studies have also demonstrated reduced ITD thresholds with faster modulation but found no dependence on repetition rate in CI subjects (Noel and Eddington 2013).

In summary, we have provided clear evidence of pulse timing ITD sensitivity even in the absence of early hearing experience. In contrast envelope ITD sensitivity does not contribute significantly to ITD behavioural performance under CI stimulation. These results are of clinical relevance and should hopefully prompt CI manufactorers to reconsider the importance of bilateral synchronisation for the sake of ITD sensitivitiy for CI users and the resulting benefit to electric hearing in noisy environments.

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Retrospective

This thesis presents a validated early deafened animal model to investigate binaural CI stimulation, and emphasises the importance of appropriate stimulation strategies over biological limitations in temporal spatial perception. In the first instance does ITD sensitivity have a critical period?, I have demonstrated that, at least in our model system, ITD sensitivity does not depend on auditory input during development. Our neonatally deafened animal model, which experiences prolonged auditory deprivation into early adulthood, and only then receives bilateral CIs in the middle turn of the cochlear, shows ITD behavioural thresholds comparable to normal hearing litter mates ((Rosskothen-Kuhl et al. 2021); Chapter 2). Subsequently, what are the effects of hearing experience on ITD sensitivity? Further physiological recordings in these auditory naive animals under CI stimulation show ITD sensitivity in the inferior colliculus that is as good as that obtained in normal hearing experienced animals under the same electric stimulation (Chapter 3). Both studies contribute strong evidence towards the absence of a “hard critical period” for ITD sensitivity, at least in terms of deprivation. Previous studies in gerbils that are reared in omni-directional noise suggest the same is true for altered input at least in terms of a critical period (Maier et al. 2008).

Sufficiently high rate pulses in order to adequately sample speech envelopes is necessary for good speech recognition thresholds but does ITD sensitivity exist at clincially relevant pulse rates under appropriate stimulation? In contrast to human studies (van Hoesel 2007; Laback et al. 2007) we have demonstrated that, in fact, high pulse rates may not preclude ITD sensitivity, as our animal model with binaural electric stimulation has shown good ITD performance up to 900 pps – a clinically relevant pulse rate (see Chapter 4). Our findings suggest that, under appropriate stimulation, ITDs at these higher pulse rates can in fact be perceptible, and lower pulse rates which could perhaps compromise the integrity of speech delivery are not necessary. This together with studies from Shannon et al. (2011) demonstrating no benefit to speech reception at pulse rates greater than 600 pps strongly indicates that there are common pulse rates that can convey both speech and ITD cues and more importantly pulse rates are not the limiting factor for perceiving either speech in noise or ITDs suggesting other technical limitation need be explored.

The precedence effect and the saliency of onset cues has been demonstrated to play a role in ITD sensitivity (Brown and Stecker 2010). Here we asked if ITD sensitivity shows onset dominance in the absence of early hearing experience? Our studies confirm the presence of onset dominance for ITD sensitivity under electric stimulation, even after a period of prolonged auditory deprivation (see Chapter 5). However this dominance was not seen to increase in effect size with increasing pulse rate unlike that seen in normal hearing cohort (Chapter 5). This could allude to alternative mechanisms for onset dominance frequency dependence compared with simply ITD sensitivity frequency dependence.

Finally given that speech processors extract the envelope and discard the ITD fine structure the ability of CI users to make use of envelope ITDs was assessed in asking if ITD sensitivity was more reliably carried on the fixed rate pulses or the modulating amplitude? We have illustrated that in fact pulse timing ITD cues dominant lateralisation task performance decision making while envelope ITDs play almost no role in the animal's decision (Chapter 6). This hones down on a key shortcoming of current clinical speech processors – the asynchrony between fixed rate pulses delivered to the two ears, and thus the inability to deliver pulse timing ITDs which carry the most ITD sensitive information.

In summary, my research conducted in pursuance of this thesis has demonstrated that, even in the absence of early hearing experience, without necessarily stimulating the apical cochlear and while using high carrier rates, CI users are capable of developing good ITD sensitivity if stimulated appropriately. These results are of clinical importance as they prove that uncontrollable biological factors, such as age of deafness and length of period of deprivation, are most likely not the limiting factors for developing usable ITD sensitivity under CI stimulation which they have hitherto been suspected to be. Rather, better control of the stimulation strategy to improve pulse time delivery is what is needed. Determining the effects of asynchronous clock-times on ITD sensitivity are currently under way as follow on studies to the work presented here which together with the evidence herein will hopefully motivated CI manufacturers to reconsider strategies for stimulation delivery if ITDs are ever to be delivered perceivably to CI users.

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