



Review

Binaural hearing with electrical stimulation

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ABSTRACT

Bilateral cochlear implantation is becoming a standard of care in many clinics. While much benefit has been shown through bilateral implantation, patients who have bilateral cochlear implants (CIs) still do not perform as well as normal hearing listeners in sound localization and understanding speech in noisy environments. This difference in performance can arise from a number of different factors, including the areas of hardware and engineering, surgical precision and pathology of the auditory system in deaf persons. While surgical precision and individual pathology are factors that are beyond careful control, improvements can be made in the areas of clinical practice and the engineering of binaural speech processors. These improvements should be grounded in a good understanding of the sensitivities of bilateral CI patients to the acoustic binaural cues that are important to normal hearing listeners for sound localization and speech in noise understanding. To this end, we review the current state-of-the-art in the understanding of the sensitivities of bilateral CI patients to binaural cues in electric hearing, and highlight the important issues and challenges as they relate to clinical practice and the development of new binaural processing strategies.

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1. Introduction

The trend for bilateral implantation of cochlear implants (CIs) is growing. As of 2010, it is estimated that 5% of CI patients worldwide are bilateral (Peters et al., 2010). One of the motivations for bilateral implantation has been to restore spatial hearing abilities, which include segregation of speech from background noise or competing sounds, and improved sound localization ability. In normal hearing (NH) people, sound localization abilities in the horizontal plane depend primarily on acoustic cues arising from differences in arrival time and level of stimuli at the two ears. Localization of unmodulated signals up to approximately 1500 Hz is known to depend on the interaural time difference (ITD) arising from disparities in the fine-structure of the waveform. The prominent cue for localization of high-frequency signals is the inter-aural level difference (ILD) cue (Blauert, 1997). However, it has also been well established that, for higher frequency signals, ITD information can be transmitted by imposing a slow modulation, or envelope, on the carrier (Bernstein, 2001). The use of modulated signals with high-

frequency carriers is particularly relevant to stimulus coding by CI processors that utilize envelope cues and relatively high stimulation rates (Seligman et al., 1984; Skinner et al., 1994; Vandali et al., 2000; Wilson and Dorman, 2007; Wilson et al., 1991). The studies reviewed in this paper have deliberately manipulated these cues to various extents, in an effort to understand whether bilateral CI users are sensitive to the cues that NH listeners rely on and use almost effortlessly.

When tested in the sound field, CI users using two implants have demonstrated improved sound localization ability compared to using one (e.g., see: Litovsky et al., 2009, 2004; Tyler et al., 2007; Van Hoesel and Tyler, 2003); however, they still do not perform as well as NH listeners, even after many years of experience (Chang et al., 2010; Kerber and Seeber, 2012; Litovsky, 2011a,b; Loizou et al., 2009). Factors limiting performance in bilateral CI users fall into numerous categories and include those in the areas of hardware and engineering, surgical precision, and pathology of the auditory system in deaf persons. While other factors, such as the speech processing strategies used, and microphone characteristics, are also thought to be important, these will not be discussed here.

1.1. Hardware- and software-based limitations

Bilateral CI users are essentially fit with two separate monaural systems. Speech processing strategies in clinical processors utilize

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pulsatile, non-simultaneous multi-channel stimulation, whereby a bank of bandpass filters is used to filter the incoming signal into a number of frequency bands (ranging from 12 to 22), and sends specific frequency ranges to individual electrodes. The envelope of the signal is extracted from the output of each band and is used to set stimulation levels for each frequency band, thus fine-structure is discarded. Although ITDs in the envelopes may be present, because the processors have independent sampling clocks, the ITD can vary dynamically and unreliably (Litovsky et al., 2012; Van Hoesel, 2004). In addition, the microphones are not placed in the ear in a manner that maximizes the capture of directional cues such as spectrum and level cues. Microphone characteristics, independent automatic gain control and compressions settings distort the monaural and interaural level directional cues that would otherwise be present in the horizontal plane.

1.2. Surgical-based limitations

The anatomical positioning of the electrode array in the cochlea is such that the most apical placement is typically near the place of stimulation on the basilar membrane with best frequencies of 1000 Hz or higher (e.g., Stakhovskaya et al., 2007). Furthermore, surgical insertion of the electrode array is not precise enough to guarantee that the electrode arrays in the two ears are physically matched for insertion depth. This is likely to cause imprecise matching of inputs at the two ears because current clinical programming is likely to deliver stimuli bearing different frequency ranges to electrodes that are anatomically placed at comparable places in the two cochleae (Kan et al., 2013). Bilateral fitting strategies have been suggested and recent developments have shown promising results for improving ILD discrimination ability (Parkinson and Smith, 2013).

1.3. Limitations due to pathology in the auditory system

There is likely to be both a peripheral and central degeneration due to lack of stimulation (Shepherd and McCreery, 2006). At fairly peripheral levels in the auditory system there is known to be degradation in size and function of neural ganglion cells following a prolonged period of auditory deprivation (Leake et al., 1999). Profound deafness in the early developmental period seems to result in loss of normal tonotopic organization of the primary auditory cortex, although there is some reversal following reactivation of afferent input (e.g., Kral et al., 2009). We are interested in this potential reactivation and possible regaining of perceptual sensitivity to sensory input. While plasticity of sensory systems is most pronounced during infancy, when the establishment of neural architecture first occurs, plasticity is known to continue into adulthood such that neural systems remain capable of undergoing substantial reorganization in response to altered inputs due to trauma or an adaptive byproduct known as perceptual learning (see Irvine and Wright, 2005 for review).

Ideally, binaural speech processors that provide bilateral CI users with similar cues used by NH listeners would be available; however such devices do not exist in forms other than research platforms. Development of such devices would depend on knowledge about the extent to which bilateral CI users are sensitive to, and able to utilize, binaural cues. In order to examine these issues in more detail, a growing number of studies have been performed using bilaterally-synchronized research devices allowing precise stimulus control at the electrode level, in order to understand the potential and limitations of electrical stimulation for restoring binaural hearing in CI patients. In this article, we will review this literature and the potential clinical applications of this research. A thorough understanding of the sensitivities of bilateral

CI users to different acoustic cues that can be presented through electrical stimulation will help inform the engineering of binaural CI speech processors and focus development efforts on the aspects of the acoustic signals that will be important to preserve in the conversion between acoustic and electric signals. In this paper, we will first review the body of work that has been conducted to investigate the binaural sensitivities of bilateral CI users at a single electrode pair level, followed by more recent work where multiple electrode pairs are stimulated together, which is closer to real-world listening. We will also discuss some general implications of these results and highlight their significance on future engineering efforts.

2. Single electrode stimulation

The modern multi-channel cochlear implant was designed to take advantage of the tonotopic organization of the cochlea in order to present stimuli from broadband sound sources with some degree of spectral resolution. Electrode arrays inserted into the cochlea have a number of electrode contacts (typically 12–22) designed to stimulate the auditory nerves in a limited region of the cochlea, and thereby allowing for different pitches to be perceived. When studies involve binaural stimulation, there has to be an understanding as to how stimulation in the two ears is combined.

Much of the earliest work was undertaken to determine whether electrical stimulation at the two ears would be combined into a single fused auditory percept, and how this percept could be altered by varying the interaural time, amplitude and place of stimulation. The ability to fuse the electrical stimulation at the two ears into a single auditory percept is particularly important for studying binaural sensitivity, because non-fusion indicates an inability to combine interaural information which may lead to an inability to compare interaural disparities such as ITDs and ILDs. Studies have been typically conducted using synchronized research processors that allow direct stimulation of single interaural electrode pairs with electrical stimuli that had precise ITDs and ILDs. Some of the earliest studies (Lawson et al., 1998; Van Hoesel et al., 1993; Van Hoesel and Clark, 1997) demonstrated that electrical stimulation at the two ears could be fused into a single percept, and that the auditory image could be lateralized with changes in interaural amplitude. However, the ability to use ITDs for lateralization was typically much poorer and heavily dependent on the place of stimulation in each ear.

2.1. Interaural place matching

The early work highlighted the importance of carefully selecting the electrode stimulated in each ear for maximizing ITD sensitivity. This is largely because neural survival and the interaural insertion depths of electrodes may differ across the ears. The difference in interaural insertion depth would lead to differences in the anatomical place of stimulation in each ear for electrodes of the same number. A schematic of the type of interaural place of stimulation mismatch is illustrated in Fig. 1. If we consider the tonotopic organization of the cochlea and models of binaural sound localization, which assume ITDs are interaurally compared at each frequency (e.g., Colburn, 1977; Jeffress, 1948), a mismatch in the interaural place of stimulation will cause a mismatch in the frequencies being compared by the brain, likely leading to a decrease in ITD sensitivity. Prior work (Van Hoesel et al., 1993; Van Hoesel and Tyler, 2003; Van Hoesel, 2008) has shown that when studying ITD sensitivity, selecting interaurally pitch-matched electrodes typically yields the smallest ITD just noticeable differences (JNDs). However, when the stimulating electrodes on one side was held constant and the stimulating

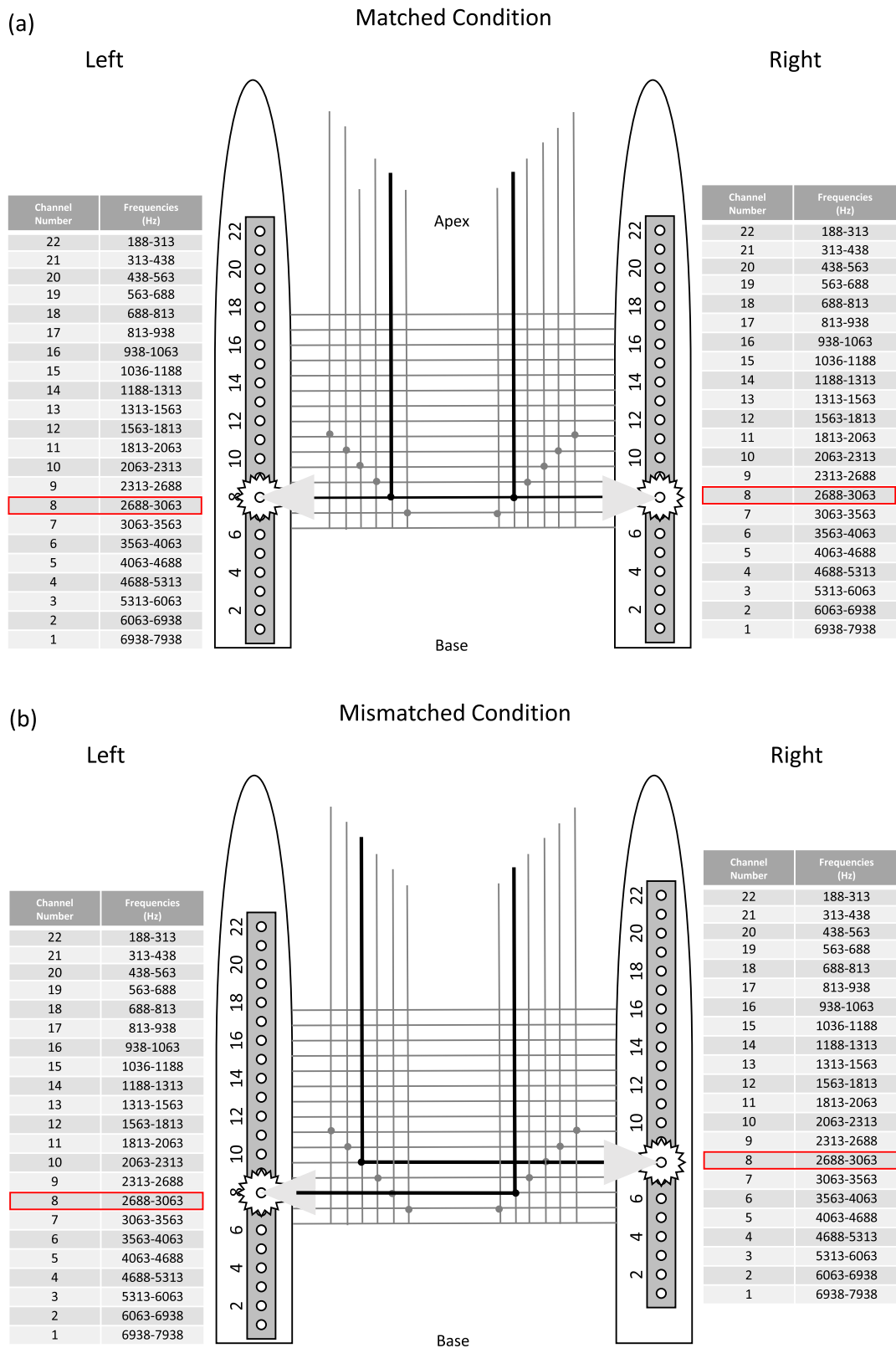


Fig. 1. A schematic of the anatomical placement of electrode arrays in the left and right unrolled cochlea is shown for the condition where interaural place of stimulation is: (a) matched and (b) mismatched. The frequency allocation tables to the right and left of the cochlea show the range of frequencies assigned to each electrode, as per standard mapping procedures in a Cochlear Nucleus device. The array of lines connecting the left and right cochlea symbolizes the neural network that compares interaural disparities for calculation of interaural time and level differences. In (a), the matched interaural stimulation condition, electrical stimulation of the auditory nerve fibers activate the same delay lines on both sides, leading to a coherent calculation of interaural disparity. However, in (b), the mismatched interaural stimulation condition, the electrodes carrying frequencies of 2688–3063 Hz are mismatched by 3 electrode locations (approximately $3 \times 0.75 \text{ mm} = 2.25 \text{ mm}$). Thus, for this frequency range, the auditory fibers that are tuned to different frequencies are stimulated, leading to an incoherent calculation of interaural disparity by the neural network.

electrode on the contralateral side was varied, there was a systematic change in ITD sensitivity such that best sensitivity occurred usually nearest the pitch-matched pair (Long et al., 2003) and that there is approximately a 3.4 mm interaural range along the cochlea whereby ITD sensitivity is within a factor of 2 of the smallest JND (Poon et al., 2009).

Approaches to finding a pitch-matched pair across the ears vary. In Long et al. (2003) and Van Hoesel (2004), a two-interval, two alternative forced choice task was used, in which subjects were sequentially stimulated on a pair of electrode across the ears and responded by indicating which electrode was higher in pitch. X-ray scans of the implant in the two cochleae were used as a guide for choosing which electrodes to test. In the absence of available X-ray scans, Litovsky et al. (2012) describes a two-staged approach to identifying interaural pitch matched pairs using a pitch magnitude estimation task and a direct left-right pitch comparison task. In pitch magnitude estimation, subjects rate the pitch of the stimulus on a scale from 1 (low pitch) to 100 (high pitch) after being presented a single stimulus on a single electrode either in the left or right ear. Subjects are encouraged to use the same rating scale for pitch in both ears and to use the full range of numbers as much as possible. Pitch rating results for electrodes typically have large variability and hence the results obtained from this stage only give reasonable estimates of possible pitch-matched pairs across the ears. Therefore, a second direct left-right comparison task is used to improve the quality of the pitch matching. The left-right comparison task is a two-interval, five-alternative forced choice task. In each trial, the subject is sequentially presented a stimulus in each and the subject responded with whether the second sound was “much higher,” “higher,” “same,” “lower” or “much lower” in pitch compared to the first sound. These categories were assigned values of 2, 1, 0, –1 and –2, respectively, and a metric, μ , was calculated by summing the enumerated responses. The pair with a total μ closest to zero was chosen as the “matched” pair.

In Kan et al. (2013), the effect of interaural place of stimulation mismatch on binaural auditory image fusion and lateralization of ITDs and ILDs was systematically investigated. Mismatch in the interaural place of stimulation was simulated by firstly identifying an interaural pitch-matched pair of electrodes (interaural mismatch = 0) using the methods described in Litovsky et al. (2012), and then systematically introducing a mismatch by varying the stimulating electrode on one side while the contralateral side was held constant. Fig. 2a shows the proportion of fused auditory images and their perceived lateral locations when both ITD and ILD were set to zero. The highest proportion of centered and fused auditory images was seen at zero interaural mismatch. With increasing amounts of mismatch, there was a decrease in the proportion of fused auditory images and a systematic increase in the number of off-centered auditory images being perceived. When an ITD was introduced into the stimuli, the range of perceived lateral locations of the auditory image within the head was typically greatest around the pitch-matched pair and steadily decreased with increasing mismatch. In contrast, the range of lateral locations with ILDs was not significantly different as a function of interaural mismatch (Fig. 2b). However, in both cases, the spatial map of lateral locations was distorted at large interaural mismatches such that a centered auditory image was not perceived when either ITD or ILD was set to zero.

These results highlight the importance of assigning appropriate acoustic frequency information to electrode contacts along the array in each ear, in order for the electrical stimulation at the two ears to be fused into a single auditory percept and for maximizing sensitivity to binaural cues, especially ITDs.

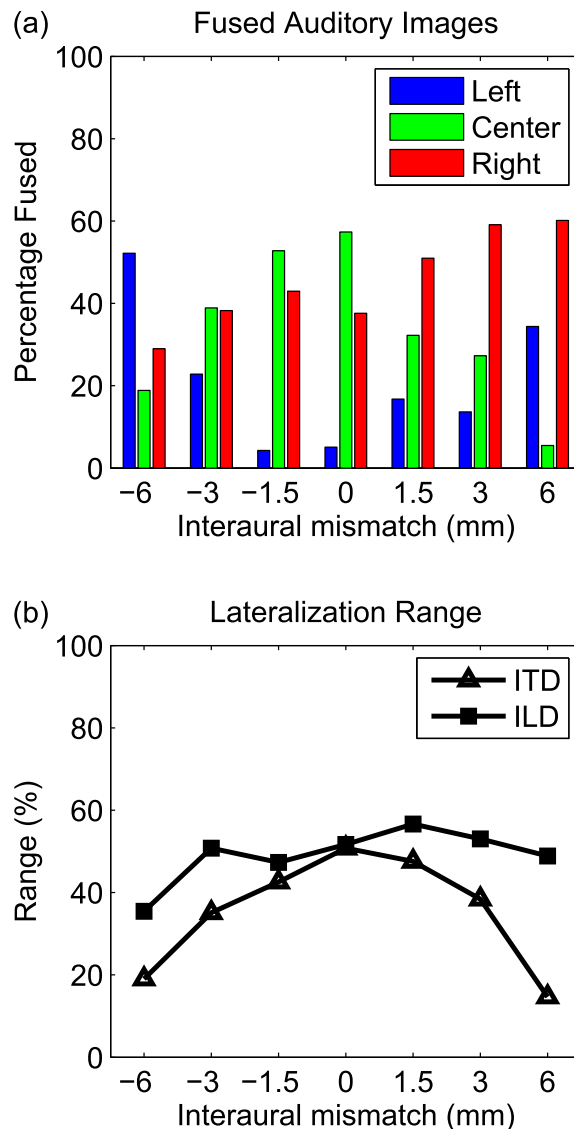


Fig. 2. Panel (a) shows the percentage of fused auditory images and their perceived intercranial locations as a function of interaural place of stimulation mismatch, for simultaneous stimulation at equal loudness at the two ears. Negative interaural mismatch indicates that the left electrode being stimulated is more basal in place than that of the right and positive interaural mismatch indicates the reverse. Panel (b) shows the change in the range of perceived intercranial locations as a function of interaural place of stimulation mismatch.

2.2. Interaural loudness balancing and centering

An important consideration in maximizing sensitivity to binaural cues is that when ITDs and ILDs are both set to zero, a centered auditory image is perceived. In current clinical practice, it is often the case that unilateral loudness balancing across the electrodes is performed, but there is rarely any consideration of whether a centered auditory image is perceived when both CIs are activated in a bilateral CI user. Fitzgerald et al. (2013) showed that following current clinical procedures, unilateral loudness balancing does not usually lead to a centered auditory image, which implies that current bilateral CIs are not mapped to maximize binaural sensitivity. Even with careful bilateral loudness balance and centering at a maximum comfortable level, the location of the centered auditory image can vary along the dynamic range of the bilateral CI user (Goupell et al., 2013). This implies that careful

engineering considerations are needed in CI processing strategies to ensure that as the input loudness changes, the conversion of the acoustic signal to electrical stimulation is done in such a way that maintains a centered auditory image when the interaural differences are the same.

2.3. Place of stimulation

Considering the tonotopic organization of the cochlea and that ITD sensitivity is typically best at lower frequencies, one may assume that more apical cochlea locations will produce best binaural sensitivity with ITDs. In the NH system, ITD sensitivity is best at low frequencies, or at high frequencies with low frequency amplitude modulation. In bilateral CI users, it appears that sensitivity to ITDs does not systematically change with place of stimulation, but rather, varies between subjects. Fig. 3 shows the ITD JNDs measured at different places along the cochlea (apex, middle, base) from a number of different studies using 100 pulse per second, constant amplitude, electrical pulse trains (Litovsky et al., 2012; Van Hoesel et al., 2002, 2009; Van Hoesel and Clark, 1997). For these three places, ITD sensitivity is, on average, about the same. Although the group data appear to indicate that general ITD sensitivity is similar at all places along the cochlea, individual differences exist. This can be seen in Fig. 4, where ITD JNDs measured at the apex are plotted against ITD JNDs measured in the middle (4a) and basal (4b) places along the cochlear array. These data show that JNDs are somewhat higher when stimulation occurs at the apical portion of the array (more data points fall below the dashed line). Anecdotal evidence suggests that pitch-matching was more difficult at apical locations, and if we consider that with interaural mismatch there is a decrease in ITD sensitivity, it may mean that the most “optimal” interaural pair of electrode may not have been chosen for testing, leading to higher ITD JNDs being obtained. In addition, ITD JNDs also appear less variable in the mid locations along the cochlear and may reflect better neural survival in these areas in general, leading to better ITD sensitivity. These results suggest that careful consideration should be taken when engineering binaural signal processing strategies for CIs, because choice of interaural electrodes for presenting binaural cues may need to be made on an individual basis in order to maximize binaural sensitivity. A general assumption that ITD information should be provided in the apical channels because ITD information is pertinent at low-frequency for NH listeners may not necessarily be the best for providing binaural cues for a patient who cannot discriminate ITDs at this cochlea location.

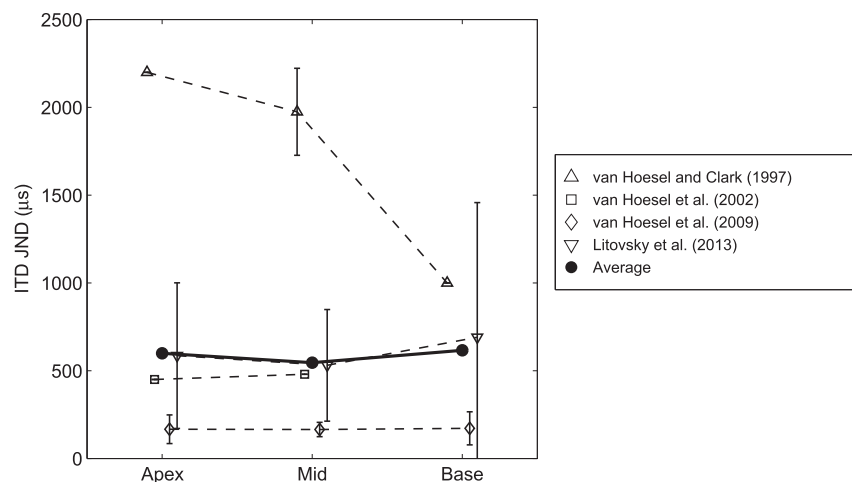


Fig. 3. ITD JNDs are compared from a number of different studies; values are plotted as a function of place of stimulation. The solid black circle shows the average ITD JND from all these studies.

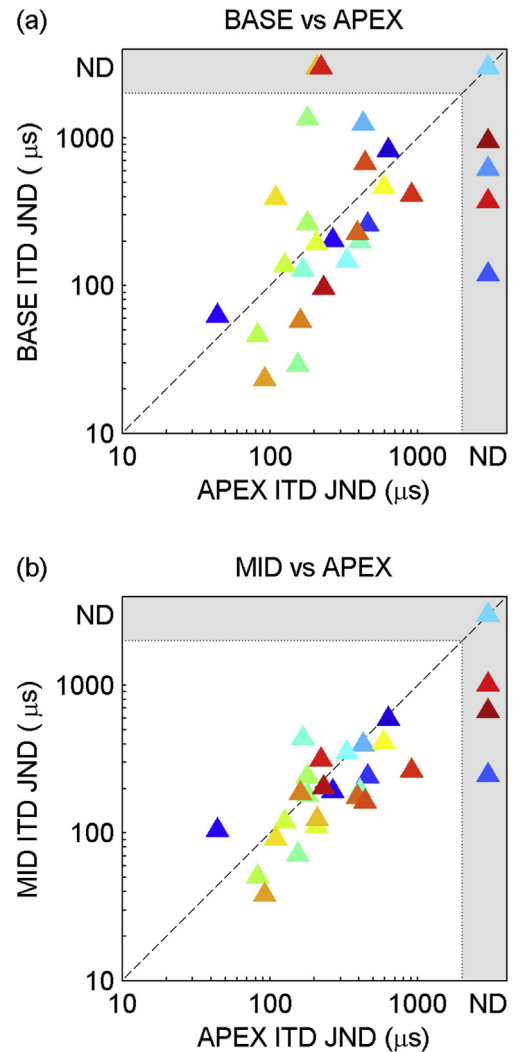


Fig. 4. Panel (a) ITD JNDs obtained from stimulation at the apical region are plotted vs. ITD JNDs obtained with basal stimulation. Panel (b) shows ITD JNDs obtained from stimulation at the apical region vs. ITD JNDs obtained with stimulation in the middle of the electrode array. In each panel, data are shown for 33 bilateral CI subjects.

2.4. Rate of stimulation

Effects of stimulation rate could be important for binaural sensitivity because higher rates have been found to relate to better speech understanding (Loizou et al., 2000); however, for bilateral CI users, lower rates have been shown to yield better ITD sensitivity. For stimuli presented at a low rate of 100 Hz, ITD JNDs can be excellent, as low as 50 μ s in some bilateral CI users; however, they can be an order of magnitude larger in other bilateral CI users (Lawson et al., 1998; Litovsky et al., 2012; Majdak et al., 2006; Van Hoesel et al., 1993; Van Hoesel, 2007). JNDs from best-performers in the bilateral CI population are comparable to moderately-trained NH listeners (~ 40 – 70 μ s) presented with low-frequency tones carrying ITD information (Blauert, 1997). As electrical stimulation rates increase, performance of bilateral CI users typically deteriorates, such that at rates of 500 pulses per second or higher, ITD sensitivity is often poor or unmeasurable. Fig. 5 shows the increase in ITD JNDs with increasing rates of stimulation from a number of studies (Laback et al., 2007; Van Hoesel et al., 2002, 2009; Van Hoesel and Tyler, 2003; Van Hoesel, 2007). This trend in decreased performance with increase in rate is similar to what is seen in NH listeners tested using unmodulated high frequency tones (Haft et al. and Dye, 1983). However, bilateral CI users have shown sensitivity to ITDs in slow-varying modulation envelopes applied to high-rate electrical pulse trains (Majdak et al., 2006; Van Hoesel and Tyler, 2003; Van Hoesel, 2007; Van Hoesel et al., 2009). This is similar to results in NH listeners with modulated high-rate carriers with ITDs imposed on the envelopes (e.g., Haft et al. and Dye, 1983) and with “transposed tones” (Van de Par and Kohlrausch, 1997). There is also some evidence to suggest that non-uniform pulse rates can also provide ITD cues (Laback and Majdak, 2008).

The differential sensitivity to ITDs as a function of rate needs to be carefully considered when choosing an optimal rate for electrical stimulation. While high rate stimulation has been shown to provide good speech understanding, lower rates of stimulation appear to be necessary for good ITD sensitivity. Hence, it is likely that strategies with a mix of rates of stimulation may be necessary as a compromise between good speech understanding and binaural sensitivity.

2.5. Age at onset of deafness

Typically, previous studies have deliberately recruited patients who are known to have good binaural sensitivity. Other studies deliberately focus on comparing performance across patients with

varying abilities, in particular those that might relate to the age at onset of deafness, duration of deafness and auditory experience following implantation. Litovsky and colleagues have primarily used the latter approach. To some extent there are overall findings in adult patients, such that ITD sensitivity is generally better when patients have had access to acoustic cues early in life. Poorer performance on the other hand is observed in patients with earlier onset of deafness. Additionally, ILD sensitivity is less susceptible to disruption by auditory deprivation early in life (Litovsky et al., 2010). However, these statements do have some exceptions, with some early-deafened adults showing fairly good ITD sensitivity.

Related findings have been reported in young children who are bilaterally implanted, whereby spatial hearing abilities have been shown to be related to the amount of bilateral experience. Toddlers aged 2.5 years generally have better spatial hearing acuity as measured with a minimum audible angle task once they have had 12 months or more of bilateral experience. Interestingly, not all toddlers with 12 months of experience show excellent performance, but the better performers have had more experience (Grieco-Calub and Litovsky, 2012). Those findings suggest that experience-dependent emergence of spatial hearing abilities is one of the factors that can be taken into account when considering patient outcomes; however, other factors that were not manipulated in that study are clearly important. Some of those have been considered in this paper, including factors such as interaural matching between the ears, rate of stimulation and loudness balancing. It must also be noted that the aforementioned study with toddlers did not utilize electrical stimulation with direct control over the binaural cues. Hence, the extent to which the young children relied on each of the binaural cues known to be important for spatial hearing is unclear. Studies with direct electrical stimulation are very difficult to perform with young children, thus very few data are available regarding the development of binaural sensitivity in children who use bilateral CIs. Salloum et al. (2010) measured perception of lateralization in a 4-alternative forced choice (left side, right side, middle of the head, or from both sides simultaneously), and concluded that children who use bilateral CIs could use ILDs, but most could not use ITDs, to perceived changes in lateralization of sound images. Recent findings by Litovsky and colleagues (Ehlers et al., 2013; Litovsky, 2011a,b) have addressed this issue as well, in particular by recruiting children who either had access to acoustic input early in life, or who were congenitally deaf. Results to date suggest that children with early onset of deafness perform worse with ITDs than children with onset of deafness during mid-childhood; however as

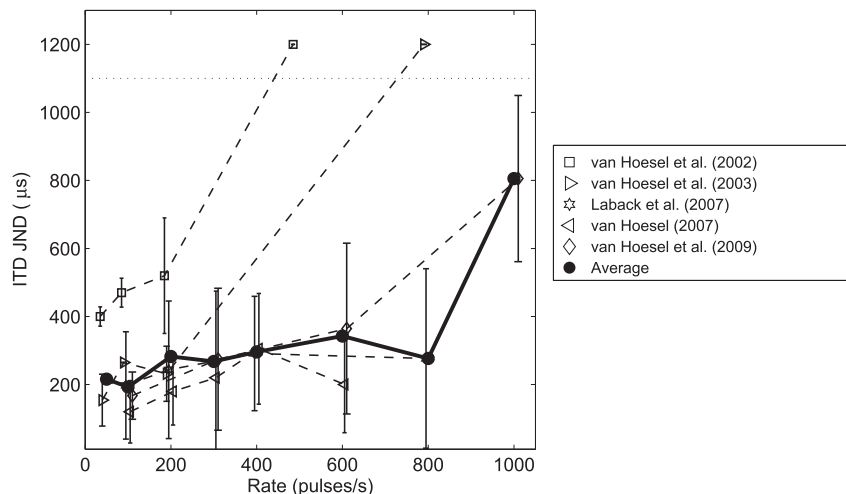


Fig. 5. ITD JNDs reported in a number of different studies are shown as a function of rate of stimulation. The solid black circle shows the average ITD JND from all these studies.

was also observed in adults, ILD sensitivity was less vulnerable to disruption.

We are intrigued by the differential effect of age of onset of deafness on ILD and ITD sensitivity, and thus consider possible ways in which disruptions to these circuits during development would have a reversible effect on ILD processing but not on ITD processing. First, disruption of these inputs is thought to compromise the extent to which information arriving from the two ears can ultimately be processed and integrated with fidelity. Because projections to the MSO are refined with auditory experience during development, normal acoustic experience plays an important role in the elimination of extraneous synapses, a process that is thought to ultimately facilitate synchronous bilateral input to the MSO (Kapfer et al., 2002). Furthermore, there is a critical period in development during which neurons mature into having adult-like tuning to ITDs, which can be disrupted with abnormal auditory exposure (Seidl and Grothe, 2005). LSO neurons, however, also require normal levels of activity in order to undergo the natural course of rearrangement and of inhibition-dependent selectivity for sound source direction that occurs during postnatal maturation (Kotak and Sanes, 2000). Thus, the dependence on appropriate input during development does not sufficiently account for these effects.

There may be another explanation for the differential effects on ITD and ILD sensitivity that are rooted in the various mechanisms through which ITD and ILD can each be produced and preserved in the auditory system. ITD is processed by a small number of nuclei and is limited to a more predetermined circuitry (Joris et al., 2006), whereas, there are a number of ways in which ILD processing can be achieved and several brainstem nuclei respond to level differences (e.g., Green and Sanes, 2005; Pollak et al., 2003; Shore et al., 2003).

One might also look to synaptic transmission processes to glean some reasons for ITD coding being more vulnerable to hearing loss than ILD coding. It has been suggested that the sensitivity to ITD at the level of the MSO comes from the neurons' exceedingly short temporal integration window, created at least in part by a low-threshold potassium channel which is activated rapidly following depolarization of MSO neurons, thus requiring timing of interaural coincidence to be rather precise (Svirskis et al., 2004, 2002). Expression of this potassium channel has been shown to depend on activity during development, without which resolution of ITD coding is likely to be degraded (Leao et al., 2004). The same is not known to be true, however, for ILD thus we consider the possibility that the ILD-generating mechanism is not thought to be susceptible to degradation by lack of activation (e.g., hearing loss) in the same manner.

At higher levels of the system, such as the auditory cortex, sensory experience involving learning and attention is known to have a profound effect on the plasticity that is observed in the structure and function of the auditory system (Dahmen and King, 2007), and top-down influences arising from perceptual learning seem to affect reorganization of cortical maps (Polley et al., 2006). It is worth considering whether plasticity following altered sensory experience is particular to the binaural system, or represents a more general predisposition of auditory system functionality following deprivation and subsequent activation. There is ample evidence from research with cochlear implant users to suggest that in other areas, including speech and language abilities, adults whose deafness occurred during adult life experience better outcomes than adults whose onset of deafness was early in life (Busby et al., 1993; Friesen et al., 2001; Skinner et al., 1994). This evidence, supporting the general predisposition of neural systems to function best with early exposure, has long-standing roots in other sensory systems (Blakemore and Cooper, 1970; Kaas et al., 1983; Rakic and Goldman-Rakic, 1982) and there is little reason to suspect that the

findings with regard to effect of age at onset of deafness on performance is unique to audition. What remains unclear is why ILD sensitivity seems to be less susceptible to being abolished by early deprivation, whereas ITD sensitivity is absent in pre-lingually deafened persons. A possible parallel of this finding can be found in perceptual learning studies in which human adults with normal hearing were trained to discriminate changes in stimuli bearing either ITD or ILD information. With training and experience there appears to be greater malleability for sensitivity to ILDs than to ITDs (e.g., Zhang and Wright, 2007). From that work, one might expect that adults in our study who had undergone early auditory deprivation would be able to undergo recalibration of sensitivity to ILD cues following onset of auditory stimulation, but perhaps not of ITD cues.

There may be some insights to be gained from the auditory deprivation literature in which animals underwent periods of monaural occlusion during various stages in development. It appears that neural circuits involved in binaural hearing can be recalibrated throughout life (Kacelnik et al., 2006). What is not clear from that literature is the extent to which the remapping involves alterations in sensitivity to specific binaural cues. Hence, the extent to which the circuits that mediate ITD and ILD, respectively, are affected by experience remains to be studied with greater precision. When plasticity and recalibration of sensitivity to auditory cues are considered, however, in particular at the level of the auditory cortex, there appears to be a protracted period of plasticity in the adult animal. A factor that is most clearly potent in driving plasticity of neural circuits involved in spatial hearing is the shaping that takes place by training and experience (Kacelnik et al., 2006; Keuroghlian and Knudsen, 2007). These findings from the animal literature can be viewed as potentially encouraging with regard to the role of training and rehabilitation of cochlear implant and hearing aid users and the possibility that, with experience, their spatial maps may be altered in ways that will lead to functional improvement in performance. Also noteworthy is the potential role of cues provided in clinical sound processors. If ITDs are not well coded by sound processors, but ILDs are, then listeners are being trained in their everyday situations with ILDs, but not ITDs.

Our results also speak to the long-term potency of functional connections in the binaural auditory pathway, which are particularly notable in the individuals who became deaf as young adults, spent numerous years, even decades, being deprived of hearing, and subsequently had their auditory pathways reactivated with electric hearing. Although, relative to binaural sensitivity of normal-hearing people, which can be as good as 1–2 dB, thresholds observed in some bilateral CI users are more than an order of magnitude worse. Nonetheless, such cues are still potentially usable in real life. For instance, if ILD cues are absent then segregation of sources that are widely separated across the right and left hemifields, then source location identification could be achieved with such ITDs. The long-term potency of connections maintaining localization ability after reactivation of auditory input has been reported in the non-human animal literature (Dahmen and King, 2007). However, this potency may not be well supported without early stimulation. Recent studies in children who are born deaf and receive bilateral CIs as their first mode of auditory stimulation suggest the important role of early activation in the emergence of binaural interaction components at the level of the brainstem (Gordon et al., 2007) and cortex (Bauer et al., 2006). Behavioral results also suggest that children who receive bilateral CIs at a young age are more likely to reach age-appropriate spatial hearing resolution (Grieco-Calub et al., 2008) than children who are stimulated bilaterally at a later age (Litovsky et al., 2006a, 2006b).

2.6. The precedence effect

Humans spend much of their time in complex acoustic environments, where multiple sounds arise from many locations simultaneously. A fundamental feature of acoustic environments is the barrage of echoes that are dynamically propagated. When a sound is emitted in a reverberant setting it arrives at the listener's ears through a direct path, which is the most rapid and least disturbed path. In addition, reflections of the sound from nearby surfaces, including walls and various objects, reach the ears, subsequently creating a cacophony of stimuli, each with their own set of localization cues. The auditory system of mammals appears to be remarkably adept at sorting and prioritizing amongst potentially competing signals. In NH auditory systems, localization cues carried by the echoes are de-emphasized relative to the cues carried by the leading sound, such that localization errors are minimized. This phenomenon is commonly known as the *precedence effect* (PE) because the auditory system assigns greater weight to the localization cues belonging to the preceding, or first-arriving sound. The PE has been studied by measuring (1) the delay between the leading sound and lagging sound (simulated echo) at which listeners hear two sounds (i.e., PE is weak or absent) vs. 1 sound (i.e., the PE is operative); and (2) the extent to which listeners can extract ITD and/or ILD cues from the leading sound vs. from the lagging sound. It appears that when the time delay between the lead and lag are short, ITD JNDs for the leading sound are small, suggesting that the PE acts in a manner that suppresses directional cues from the echoes (Litovsky et al., 1999).

Agrawal, Litovsky and colleagues (Agrawal, 2008; Agrawal et al., 2008) studied the PE in bilateral CI users in order to understand whether these listeners were able to perceptually weight the binaural cues in the leading sound more heavily than in the lagging sound, similarly to what has been reported in NH listeners (e.g., Litovsky and Shinn-Cunningham, 2001). In one experiment, sounds were presented in free field from loudspeakers, and in a second experiment, lead-lag pairs of binaural stimuli were generated with electrically pulsed signals and presented to listeners through the direct stimulation interface described above for the ITD and ILD experiments. In free field, bilateral CI users performed significantly worse than NH listeners, and were seemingly unable to extract directional cues from the leading source in an effective manner. In contrast, when using the direct electrical stimulation, there was robust evidence for the PE. That is, similar to NH listeners, bilateral CI users were able to discriminate between ITDs carried by the leading sound, and were unable to extract ITD cues from the lagging sound. The exact reason for failure of the PE in the free field is not known. Future studies can consider examining numerous issues related to the multi-electrode stimulation causing peripheral interactions, as well as potential temporal degradation of the binaural cues as the stimuli are processed through the microphones. These findings suggest that, although localization and speech understanding in noise in bilateral CI users is overall better than that seen with unilateral CIs, the fact that bilateral CI users are fitted with two independent processors may undermine the binaural system's ability to utilize mechanisms such as the PE.

2.7. Binaural masking level differences (BMLDs) and interaural decorrelation

BMLDs refer to a phenomenon that is thought to be at the heart of the detection and perception of signals under complex listening situations. The ability to understand speech in noisy listening conditions is at least partly dependent on binaural hearing. Binaural unmasking was first described by J.C.R. Licklider and Ira Hirsh in 1948. In its most common form, the BMLD is considered to

be the difference in masked threshold for an in-phase signal (zero interaural phase difference between the ears) and an anti-phase signal (180° , or π , interaural phase difference between the ears) when the masker consists of identical noise tokens at the two ears. This configuration, referred to as NOS0 vs. NOS π is one of a number of possible configurations for the target and masker that have been used to study BMLDs in the 60+ years since its discovery. In listeners with NH, BMLD experiments have been used to address fundamental questions concerning the nature of binaural processing per se. Models of binaural unmasking propose neural elements that bear striking resemblance to patterns of neural activation known to exist in the auditory brain. Some models are based on the equalization-cancellation (E-C) hypothesis (Durlach, 1963), whereby binaural unmasking is thought to arise through operations that compute differences between the signals at each ear; neural elements that are excited by one ear and inhibited by the other are included in these models. In contrast, modern correlation-based models employ purely excitatory neural elements that focus on Jeffress' (1948) model of coincidence detection. These models propose arrays of binaural neurons that are maximally responsive when inputs from the two ears are timed in such a way that compensates for differences between the ears in axonal conduction delays.

In listeners with bilateral CIs, studies that measure BMLDs have been used to evaluate binaural sensitivity through the evaluation of perceptual mechanisms that enable unmasking of targets from maskers when binaural cues are applied (Long et al., 2006; Lu et al., 2011, 2010). Long et al. (2006) and Lu et al. (2010) showed that, when electrically pulsed signals are presented at a single electrode pair, and a "realistic" amplitude compression function that is typical of clinical processing strategy, BMLDs can be around 9 dB, which is within the range of effects seen in listeners with acoustic hearing (e.g., Van de Par and Kohlrausch, 1997a,b). BMLDs in electrical hearing with single pairs of electrodes have also been measured in a group of children between the ages of 6–15 years (Van Deun et al., 2009). Six of the children showed some amount of BMLD, with a group average of 6.4 dB. This finding raises interesting questions about the extent to which early exposure to binaural cues may be relevant to BMLD, given that the children were deafened early in life, and that they did not receive binaural cues with fidelity during their everyday listening experiences.

3. Multi-electrode stimulation with same or different ITDs

As described above, psychophysical studies on binaural sensitivity in bilateral CI users have focused on an idealized stimulation approach, whereby one pair of electrodes that are carefully matched by perceived pitch and/or anatomical placement within the cochlear arrays are stimulated. This is akin to studying binaural sensitivity in NH listeners using filtered clicks or narrow-band noise bursts and exploring parameters that enhance or reduce performance for this limited stimulus type. Such studies have been extremely informative regarding sensitivity of bilateral CI users to binaural cues, and binaural mechanisms in the normal system, respectively. However, this mode of stimulation is not representative of real-life stimuli which are typically more spectrally complex, dynamic and stimulate multiple places along the basilar membrane. It is unlikely that single electrode stimulation strategies will ever be implemented due to their inability to provide good speech intelligibility. Hence, studying the effects of multi-electrode stimulation on ITD sensitivity is an important next step towards restoring binaural sensitivity to bilaterally implanted users.

Multi-electrode stimulation leads to a few intersecting issues that need to be considered for the engineering of binaural processors. First, there are known "channel interaction effects" in the

unilateral CI literature, which refer to psychophysical and physiological effects on sensitivity to single-electrode stimuli when one or more additional electrodes on the same cochlear array are activated (e.g., Chatterjee and Shannon, 1998; Cohen et al., 2003). One source of interaction is spread of current. Pulsatile stimulation of one channel can affect responses to a channel that follows it in time either by changing the membrane potential of neurons that are stimulated by both channels or by eliciting action potentials, thus putting some part of the target neuron population into a refractory state. This may reduce sensitivity to important binaural cues on adjacent electrode channels.

Second, in a NH listener, a broadband stimulus activates a wide region along the basilar membrane and produces a pattern of cross-correlations across the range of frequencies activated. A broadband stimulus can result in a coherent auditory image whose perceived intracranial spatial location is determined by a weighted linear combination of the “centroids” that arise from each of the frequency-based binaural stimuli, essentially integration of binaural information across channels (Stern et al., 1988). In a bilateral CI user, the effects of cross-channel integration on the perceived location of an auditory image are likely to be affected by factors that do not exist in NH listeners. For instance, the natural time that it takes for waves to physically travel along the basilar membrane is effectively bypassed in CI stimulation, which may affect binaural sensitivity that is thought to depend to some extent on these cochlear delays (De Cheveigné and Pressnitzer, 2006; Shamma et al., 1989). Lacking the natural cochlear delays can lead to imprecise binaural integration and thus broader ITD tuning curves, as has been recently modeled by Colburn et al. (2009). In addition, pathology at various places along the cochlea will result in differential sensitivity to stimulation in the base, middle and apex.

Third, stimulation at multiple places with the same binaural cue can have a number of effects, including both enhancement and degradation. Consider the following possibilities: (a) If a given subject has good sensitivity to ITDs at the base, middle and apex, there will be either no effects, or enhancement effects on binaural sensitivity, due to multiple “looks” at the auditory signal through multiple channels, or some other enhancement mechanism. (b) If a subject has some places with good ITD sensitivity and other places with poor sensitivity, then there will be either no effect, such that places with good ITD sensitivity simply dominate and are weighted more heavily, or there will be degradation relative to the good place, due to integration of binaural information across both good and poor channels. Ihlefeld et al. (2014) studied how bilateral CI users integrated binaural information when two widely spaced cochlea places were stimulated. When listening to high rate, amplitude modulated pulse trains, subjects showed that their overall ITD sensitivity did not appear to be affected by an electrode pair with poorer ITD sensitivity. Overall, subjects appeared to be optimally integrating ITD information from the two cochlear places or listening to the better electrode pair.

Conversely, when stimulation at multiple places are with different binaural cues, “binaural interference” may occur, which is when binaural judgments of a high-frequency target stimulus is affected by the presence of a simultaneous low-frequency interferer (Heller and Trahiotis, 1996; McFadden and Pasanen, 1976) and is considered to be related to auditory streaming abilities (Best et al., 2007). Best and colleagues showed that binaural interference can occur in electrical stimulation (Best et al., 2011) but that there can be individual differences in susceptibility to binaural interference. Of the six subjects they tested, only one subject showed no binaural interference. However, similar individual differences have been observed in NH listeners (Best et al., 2007) and have been ascribed to an individual's ability to selectively listen to stimuli in a narrow frequency region, and ignore information in the

other frequency region. For subjects inept at listening selectively, information across different frequencies are combined and thus exhibit interference.

Another situation in which stimulation at multiple places with different binaural cues can occur is in the measurement of the BMLD. Given that speech signals are generally presented on multiple electrodes, the question of whether BMLDs would be sustained across multiple electrodes is also of relevance. Since the interaural decorrelation in the dichotic stimulus is encoded solely in the instantaneous amplitudes of the envelope (Goupell and Litovsky, 2014), it is likely that stimulation from adjacent electrodes (either diotic or dichotic) would interfere with the envelope encoding due to the spread of current and channel interactions that are ubiquitous in CIs. Indeed, Lu et al. (2011) reported that BMLDs were greatly reduced from 9 dB to near zero after the inclusion of adjacent masking electrodes. The degree of channel interaction was estimated from auditory nerve evoked potentials in three subjects, and was found to be significantly and negatively correlated with BMLD. Findings from that study suggest that if the amount of channel interactions can be reduced, bilateral CI users may experience some performance improvements in perceptual phenomena that rely on binaural mechanisms.

4. Implications for clinicians and future directions

Studies using carefully controlled, direct electrical stimulation to selected pairs of electrodes, have demonstrated that bilateral CI users are generally sensitive to binaural cues. The current body of work has highlighted a number of important considerations when converting acoustic information into electrical stimulation in order to maximize binaural sensitivity. First, the allocation of frequency ranges to electrodes must be carefully considered, and similar places along the cochlea should be stimulated with information of the same acoustic frequency to ensure maximal binaural sensitivity. This is especially a concern for ITDs. In addition, this approach minimizes distortion to the auditory spatial map. In clinical settings, these approaches might lead to improved performance with processors operating in the free field. However, it might require clinician-friendly tools that enable binaural matching of frequency-to-electrode allocation during the mapping procedure. These tools would require a mechanism for rapid identification of electrode pairs that are matched in the place of stimulation, and an ability to quickly verify the efficacy of such allocations in the clinic.

Second, the choice of stimulation rate for speech processing strategies is important because it is likely that a trade-off needs to be made between high stimulation rates needed for good speech understanding and lower stimulation rates for good ITD sensitivity. To date, few mixed rate strategies have been investigated, but the benefit of such strategies have not been significant (Arnoldner et al., 2007; Schatzer et al., 2010; Van Hoesel, 2007). However, these strategies have not accounted for the mismatch in the interaural place of stimulation, or individual binaural sensitivity variations along the cochlear array. Mixed strategies have typically assumed that lower rates should be assigned to more apical locations, but current evidence suggests that for some individuals, this is probably not a good assumption. A more thorough understanding of how best to allocate stimulation rates and coding of binaural information on interaural pairs is needed in order to provide maximum binaural benefit for bilateral CI patients.

Third, the restoration of the precedence effect (PE) in clinical processors is important for everyday listening in rooms. It is unclear whether a specially-designed binaural speech processing strategy that is designed to maximize ITD and ILD sensitivity will automatically restore the PE in bilateral CI patients. Although PE has been demonstrated at a single electrode level, it is unclear whether

bilateral CI patients will exhibit PE when multiple electrodes are stimulated, and the role cochlea delays and channel interactions from spread of current will affect the manifestation of the PE.

Even with improved engineering considerations, individual etiology of the patient may play an important role in whether maximum benefit can be obtained with bilateral speech processors. Current evidence suggests that for patients with onset of hearing loss early in life, but are implanted later, it is important that considerations are made that will allow them to maximally benefit from ILDs, because it is likely that they will have limited sensitivity to ITDs.

The modern CI and associated signal processing were originally designed as a monaural processor to restore speech understanding. With the advent of bilateral implantation, there needs to be a re-assessment of how the signal processing within CI speech processors should be implemented. Much of the current research work with direct electrical stimulation has shown promising results that argue for more well-informed engineering of speech processors in order to maximize the benefit of bilateral implementation.

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