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The Effects of Asymmetric Hearing on Bilateral Brainstem Function: Findings in Children with Bimodal (Electric and Acoustic) Hearing

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Key Words

Asymmetric hearing loss · Auditory evoked brainstem responses · Bimodal hearing · Cochlear implants · EEG · Electroacoustic stimulation · Hearing loss · Single-sided deafness

Abstract

As implantation criteria are broadening to include children with asymmetric hearing loss, it is important to determine the degree of residual hearing needed to protect the bilateral auditory pathways for binaural hearing and whether there is a sensitive period in development for implantation in these children. We have been studying these questions in a growing cohort of children. In the present study, auditory brainstem responses were recorded in 21 children who had 2.2 ± 2.2 years of bimodal hearing. Responses were evoked by 11-Hz acoustic clicks presented to the non-implanted ear and with biphasic electric pulses presented to the implanted ear. Twelve of these children also completed a behavioural task in which they were asked to which side of their heads bilaterally presented clicks/pulses that varied in interaural level or timing lateralized. All children experienced a delay in the non-implanted ear that resulted in 2.0 ± 0.35 ms longer peak latencies. These were further prolonged in 7 children as measured by longer interwave latencies from this ear than from the implanted ear. Despite large asymmetries in timing of brainstem activity between the two ears, all children perceived changes in interaural level differences. They were unable to detect differences in interaural timing cues. Symmetric brainstem function suggests bilateral development was preserved in some children. Future work will explore whether these children have better potential for developing binaural hearing using bimodal input.

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Introduction

Children with significant and permanent hearing loss were traditionally provided with only one cochlear implant (CI) to promote speech and language development [Gordon and Papsin, 2009], as

well as development of the auditory brainstem [Gordon et al., 2003, 2006, 2007a] and cortex [Gordon et al., 2005a, b]. Although there are benefits to using one CI, it has become clear that the immature auditory system requires input from both ears. Lack of stimulation from the non-implanted ear not only restricts access to the binaural cues necessary for navigating and interpreting complex acoustic environments, but also drives abnormal reorganisation in the developing auditory system [Gordon et al., 2013; Kral et al., 2013a, b]. In recent work, a sensitive period of 1.5 years was defined as a time window within which to provide two CI in order to promote symmetric brainstem development and avoid reorganisation of the cortex toward an abnormal 'aural preference' for the hearing ear [Gordon et al., 2013]. A second CI provided beyond this sensitive period was unable to change the unilaterally driven cortical reorganisation; both auditory cortices remained preferential to the first implanted ear [Gordon et al., 2013; Kral et al., 2013a, b]. The degree of persistently abnormal reorganisation significantly correlated with poorer speech perception in the second implanted side relative to the first.

Because the previous studies focused on children who were bilaterally deaf and became unilaterally hearing through a CI, we are presently asking whether children who are unilaterally deaf with various degrees of residual hearing in the other ear will experience the same developmental effects within the same sensitive period. We hypothesized that bimodal hearing (electric hearing with a CI in one ear and acoustic hearing in the other ear) will protect the bilateral auditory pathways from developing asymmetric function at young ages.

Methods

Subjects. The Cochlear Implant Program at The Hospital for Sick Children currently follows 73 children who use one CI and a hearing aid in the non-implanted ear, called bimodal hearing. Twenty-one of these children who have worn both devices for at least 9 months participated in this study. Most children had early-onset hearing loss, with the exception of 2 children: 1 child had recurrent middle ear infections and subsequent mastoiditis, and the 2nd child had a sudden-onset single-sided deafness of unknown origin. Right CI were provided to 38% of the children and 48% of the children were male. Biographical details of each child, as well as the group mean and standard deviation are listed in table 1. Hearing aid settings were verified to be appropriate using the DSL (Desired Sensation Level) Method and targets prescribed by DSL v5.0a [Scollie et al., 2005]. Written consent was obtained from the caregivers and assent from the children before participation in the study, according to protocols approved by Research Ethics at The Hospital for Sick Children (approved study No. 2954).

Electrophysiological Recordings. EEG data of obligatory evoked activity in the auditory brainstem were recorded from a midline cephalic recording electrode (CZ) referenced to the ipsilateral earlobe while children sat in a soundproof booth and watched a movie with captioning but no sound. Responses were evoked using

Table 1. Biographical information for each child and the group mean $\pm$ SD

Subject code	Gender	CI		Aetiology of hearing loss	Age, years		Bimodal experience, years	Deprivation, years		PTA, dB HL	
		ear	type		at test	at CI		bilateral	unilateral	non-CI	CI
16028	Female	Left	CI24RE (CA)	Mondini m., EVA, Pendred syndrome	8.9	7.8	1.1	0.2	0.1	78	95
22691	Female	Right	CI24RE (CA)	Mild right EVA	3.1	1.3	1.8	0.3	0.2	73	118
26308	Female	Right	CI422	Mondini m., EVA	15.3	13.7	1.4	0.3	0.2	73	85
26570	Male	Right	CI24 (CA)	Mondini m., EVA	11.0	2.5	8.3	1.5	0.3	82	103
40745	Male	Right	CI24RE (CA)	Unknown	10.7	9.7	0.8	0.0	0.4	70	73
41522	Female	Left	CI24RE (CA)	GJB2 mutation	3.1	1.9	0.8	0.7	0.6	63	123
42607	Female	Left	CI422	Mondini m., EVA	13.0	12.3	0.6	0.0	0.1	70	93
44907	Male	Right	CI513	Mondini m., EVA, Pendred syndrome	6.2	4.1	2.0	0.3	0.1	83	90
49137	Male	Left	CI422	Unknown	7.4	6.6	0.8	0.0	0.1	38	48
58171	Female	Left	CI24RE (CA)	Unknown	15.2	14.2	0.9	0.0	0.1	2	92
62848	Female	Right	CI422	Right mastoiditis	14.0	12.5	1.5	0.0	0.1	43	130
62882	Female	Left	CI24RE (CA)	Waardenburg syndrome	6.8	4.1	2.5	0.3	0.2	88	98
63763	Male	Left	CI24RE (CA)	Mondini m., EVA	8.5	7.2	1.3	0.0	0.1	83	95
64711	Male	Left	CI24RE (CA)	GJB2 mutation	6.0	4.3	1.7	0.1	0.1	63	110
67574	Female	Right	CI24RE (CA)	Mondini m., EVA	11.1	3.0	7.7	1.2	0.5	85	130
71183	Male	Left	CI24RE (CA)	Left EVA	17.2	15.9	1.1	0.8	0.3	75	80
72949	Male	Left	CI24RE (CA)	Mondini m., EVA	5.1	2.8	2.0	0.6	0.4	72	120
80770	Female	Left	CI24RE (CA)	Unknown	11.0	2.4	4.9	1.4	3.8	93	103
81119	Female	Left	CI24RE (CA)	Unknown	6.2	5.2	1.0	0.0	0.1	78	77
88069	Male	Left	CI24RE (CA)	Meningitis	9.5	3.2	3.5	0.0	2.9	78	88
94129	Male	Right	CI24RE (CA)	Meningitis	4.1	2.4	1.6	0.0	0.2	75	100
Mean $\pm$ SD					9.2 $\pm$ 4.1	6.5 $\pm$ 4.7	2.2 $\pm$ 2.2	0.4 $\pm$ 0.5	0.5 $\pm$ 1.0	79 $\pm$ 20	98 $\pm$ 20
PTA = Pure-tone average at the non-CI or CI ear; (CA) = with Contour Advance; EVA = enlarged vestibular aqueduct; m. = malformation.											

single 100- μ s acoustic clicks or 25- μ s pulse width biphasic electric pulses presented at 11 Hz. Matlab (MathWorks) and Nucleus Implant Communicator (NIC; Cochlear Ltd., Melbourne, Vic., Australia) software programmes were created to deliver both the electric pulses to an apical electrode (No. 20) through the L34 processor and acoustic clicks through Etymotic Research (ER-3A) insert earphones. A standard 0.9-ms correction factor to account for the additional propagation delay of the earphone tubing [Picton, 2011] was subtracted from the acoustically evoked response latencies. The 0.9-ms correction was further verified by measuring the delay through an oscilloscope. Applying this correction was done so that latencies would be reported in reference to stimulus presentation to the auditory system (i.e. acoustic click to the ear canal and electric pulse to the internal electrode array). The level of stimulation was increased until the amplitude of wave V saturated, a myogenic response was obtained, or the child expressed discomfort. Established recording parameters were used that minimize the CI artefact [Gordon et al., 2003]. At least two replications were recorded to ensure response repeatability. Although other peaks were sometimes present beyond the stimulus artefact, the criteria for analysing peaks were focused to include waves III/eIII and V/eV when they were: (1) visually detectable; (2) replicable over the noise floor, and (3) occurring at expected wave latencies. These waves were chosen as prominent auditory brainstem responses (ABR), which are standardly used to evaluate brainstem function [Jiang et al., 1991]. Earlier waves II and eII are small and wave II has variable morphology, which significantly affects peak latency during all stages of maturation [Jiang et al., 1991].

Behavioural Lateralisation Measure. Twelve of the 21 children were also tested for their ability to detect binaural cues using a previously established task of perceived lateralisation to interaural timing differences (ITD) and interaural level differences (ILD) [Salloum et al., 2010]. During the forced-choice task, children indicated from which side of their head they heard the sound by raising the respective hand or pointing to that side of the head. Trial runs were completed to ensure that the children understood the task. A child's responses were considered valid if at least 8 out of the 10 unilaterally presented stimuli were accurate. Stimuli were presented using the same equipment as in the electrophysiological testing. Acoustic clicks and electric pulses were delivered at 250 Hz in 36-ms trains presented at 1 Hz. Levels used for the ABR –10% of the dynamic range (level for maximum activity – level for threshold activity) were used to account for temporal integration of the click/pulse trains. The stimuli were presented bilaterally with varying ILD ($\pm$ 10, $\pm$ 5 and 0 current units, CU) and ITD ($\pm$ 1, $\pm$ 0.4 and 0 ms). Each condition was repeated ten times in order to calculate the proportion of responses the child indicated hearing the sound to the non-implanted and implanted sides. During ILD conditions, the acoustic level was held constant while the electric level varied around the level determined by the ABR, in order to maintain similar units (CU of current) of stimulation for all ILD conditions and to ensure that balanced levels were used during the ITD testing (i.e. the closest level of electric stimulation that resulted in 50% lateralisation to either side, considered '0 CU of ILD'). In most cases, this level was equal to that set by the ABR.

Fig. 1. Example recordings from two bimodal users: 1 child with asymmetric hearing loss (a) and 1 child with symmetric, bilateral, severe hearing loss (b). Peak ABR to acoustic stimulation were delayed compared to electrically evoked responses in both children

(c, d). However, once responses to each mode of stimulation were normalised to begin at the peak of wave III/eIII, the latency to wave V/eV was either symmetric (e) or asymmetric (f) within a child.

Results

ABR to both electric and acoustic stimulation were present in all 21 children. Example recordings from 2 children are shown in figure 1. These examples illustrate that regardless of whether the child had considerable residual hearing (fig. 1a) or poor residual hearing (fig. 1b) in the non-implanted ear, large differences existed in wave latencies when evoked by electric versus acoustic stimulation (fig. 1c, d). Some differences were expected since the two types of stimulation deliver sound to the auditory system in different modalities (electric current vs. acoustic sound pressure) and at different places in the auditory system (acoustic nerve vs. outer ear canal). Timing differences to the brainstem can be accounted for by measuring the latency of wave V relative to the peak latency of wave III (fig. 1e, f). In the first example, these normalised waveforms now overlap, indicating similar neural conduction through the brainstem for electric and acoustic stimulation (fig. 1e). But for some children, as in the second example (fig. 1f), the acoustically evoked waveform continued to be delayed relative to the electrically evoked

response despite normalisation to wave-III peak latencies, indicating slower neural conduction on that side from the brainstem to the midbrain and, thus, asymmetric bilateral brainstem function.

Brainstem Latencies Are Asymmetric in Bimodal Users. Since hearing loss is one factor known to affect ABR [Rosenhamer et al., 1981], wave-eIII/III and -eV/V latencies were compared across unaided hearing levels (pure-tone averages) in the non-implanted ear and preoperative unaided hearing levels for the implanted ear (fig. 2a). A wide range of asymmetric hearing loss was represented in this group of bimodal users, with most of the children having a severe or profound hearing loss in the implanted ear, and anywhere from normal hearing to a profound hearing loss in the non-implanted ear (table 1; fig. 2a). Across all degrees of hearing loss, the acoustically evoked wave latencies were shifted later than the electrically evoked wave latencies (fig. 2a). Linear regression analysis indicated that poorer hearing levels did not affect latencies of electrically evoked waves eIII ($R = 0.10$, $p = 0.66$) and eV ($R = 0.003$, $p = 0.99$) or the acoustically evoked wave III ($R = 0.18$, $p = 0.43$).

Fig. 2. Differences in ABR to electric versus acoustic stimulation. **a** ABR wave-III (solid symbols) and wave-V (open symbols) latencies to electric (triangles) and acoustic (circles) stimulation were not similarly affected by hearing loss. Poorer preoperative hearing does not impact electric stimulation of the brainstem, whereas hearing loss differentially affects acoustic stimulation of the brainstem. **b** Mean wave latencies were significantly shorter to electric than acoustic stimulation, but were comparable to normative values [Gordon et al., 2006] with electric stimulation, but not with acoustic stimulation [Campbell et al., 1981; Beiser et al., 1985; Eggermont and Salamy, 1988; Jiang et al., 1991, 2009]. **c** Interwave latencies were similar for electric and acoustic stimulation except for 7 children with severe-to-profound hearing loss in the non-implanted ear. **d** Children with asymmetric interwave intervals (IWI) had normal acoustically evoked wave-III latencies but prolonged wave-V latencies. * $p = 0.000$.

Acoustically evoked wave-V latencies became more variable with greater hearing loss, but non-linear regression indicated that the exponential relationship was not significant ($R = 0.55$, slope 95% confidence interval: -0.03 to 0.10). Overall, mean latencies of waves eIII and eV were within 2 SD of previously reported normative values in children using unilateral CI [Gordon et al., 2006], whereas the latencies of III and V were prolonged [Campbell et al., 1981; Beiser et al., 1985; Eggermont and Salamy, 1988; Jiang et al., 2009], especially for wave V (fig. 2b). Some wave-V latency delays were expected given the hearing loss in that ear [Rosenhamer et al., 1981]. Repeated-measures analysis of variance was conducted using wave (III/eIII or V/eV) and mode of stimulation (electric or acoustic) as within-subject factors, and sex and implanted ear as between-subject factors. Brainstem latencies were significantly different in response to electric and acoustic stimulation in the 21 bimodal users [$F(1, 17) = 179.8$, $p < 0.0001$; fig. 2b], and there was a significant interaction between mode and wave [$F(1, 17) = 3.4$,

$p = 0.006$]. Post hoc paired t tests using Bonferroni's correction for multiple comparisons indicated a mean $\pm$ SD acoustic delay of 2.1 ± 0.37 ms for wave III/eIII [$t(20) = 26.0$, $p < 0.0001$] and 2.9 ± 1.3 ms for wave V/eV [$t(20) = 10.1$, $p < 0.0001$]. There were no significant effects of gender [$F(1, 17) = 0.38$, $p = 0.55$] or implanted ear [$F(1, 17) = 0.34$, $p = 0.46$], or interactions with mode of stimulation [gender: $F(1, 17) = 0.42$, $p = 0.44$; implanted ear: $F(1, 17) = 0.16$, $p = 0.63$] or wave [gender: $F(1, 17) = 0.21$, $p = 0.41$; implanted ear: $F(1, 17) = 0.007$, $p = 0.88$].

Symmetric Brainstem Function Is Preserved in Only a Portion of Bimodal Users. Given the large asymmetry in timing of neural conduction into the brainstem between electric and acoustic stimulation (wave eIII/III), latencies were normalised to reflect transmission of auditory information through the brainstem by calculating the wave III–V interwave latency (fig. 2c). Again, there were no significant effects of hearing loss on electrically ($R = 0.08$, $p = 0.73$) or acoustically ($R = 0.43$, $p = 0.05$) evoked interwave latencies, al-

Fig. 3. Group and individual behavioural responses to ITD (**a**) and ILD (**b**). The proportion of responses that children indicated they heard the sound towards the CI (electric) side is plotted against changes in each binaural cue, with positive cue values representing when CI electric stimulation led in time (ITD) or was greater in level (ILD). Children were not able to lateralise bilaterally presented sounds when timing cues were changed, regardless of whether

the child had symmetric (solid lines and closed symbols) or asymmetric interwave latencies (dashed lines and open symbols; **a**). On the other hand, all children were able to significantly detect level cues (**b**). Only the overall group mean is shown for ILD since there were only 3 children in the asymmetric group that completed this task.

though variability increased with hearing loss with acoustic stimulation. Interwave latencies were compared with previously reported normative values for electric [Gordon et al., 2006] and acoustic stimulation [Campbell et al., 1981; Beiser et al., 1985; Eggermont and Salamy, 1988; Jiang et al., 2009]. All 21 children had electrically evoked interwave latencies within the normative range [$+2$ SD = 2.48 ms; Gordon et al., 2006]; however, only 14 of the 21 children had interwave latencies that were within the normative range for acoustic stimulation when compared to the largest (most conservative) normative estimate [$+2$ SD = 2.31 ms; Eggermont and Salamy, 1988]. Seven children had abnormally prolonged (>2.31 ms) acoustically evoked interwave latencies (fig. 2c, upper dashed box) and, therefore, did not have bilaterally normative or symmetric brainstem function. Although symmetric brainstem function was evoked in the majority of the bimodal users, the proportion was not significant [$\chi^2(1) = 2.3$, $p = 0.13$]. On average, the interaural interwave difference was 0.11 ± 0.08 ms for the children with both acoustic and electric interwave latencies within the normative range for each mode of stimulation, and 2.23 ± 0.28 ms for the children with abnormally long acoustic III–V intervals. Of particular note was the group of 16 children with severe to profound hearing loss (fig. 2c, dashed boxes) in which a similar number of children had symmetric ($n = 9$, lower dashed box in fig. 2c) and asymmetric ($n = 7$, upper dashed box in fig. 2c) interwave latencies [$\chi^2(1) = 0.25$, $p = 0.62$]. Independent t tests with Bonferroni's correction for multiple comparisons indicated similar wave-III latencies between these two groups of children [$t(14) = -0.85$, $p = 0.82$], but significantly different wave-V latencies [$t(14) = -6.53$, $p < 0.0001$], which primarily contributed to the prolonged interwave latencies in these children (fig. 2d). Additionally, acoustically evoked wave-III and -V latencies were more similar to the norma-

tive values for children in the symmetric group. There were no significant differences in the number of right CI (Fisher's exact $p = 1.00$) or females (Fisher's exact $p = 1.00$) between the symmetric and asymmetric groups of children.

Repeated-measure analysis of variance was conducted again in only the 14 children with symmetric interwave latencies, using wave (III/V) and mode of stimulation (electric/acoustic) as within-subject factors. As expected, brainstem latencies were significantly different in response to electric and acoustic stimulation [$F(1, 13) = 402.6$, $p < 0.0001$], but there was no longer a significant interaction between mode and wave [$F(1, 13) = 1.8$, $p = 0.20$], indicating that neural conduction from the caudal to rostral auditory brainstem was similar regardless of stimulus modality in these children. Post hoc paired t tests using Bonferroni's correction for multiple comparisons indicated a mean $\pm$ SD acoustic delay of 2.0 ± 0.35 ms for wave eIII/III [$t(13) = 21.3$, $p < 0.0001$] and 2.1 ± 0.47 ms for wave eV/V [$t(13) = 1.3$, $p < 0.0001$]. On the other hand, paired t tests with Bonferroni's correction completed for wave asymmetries in the 7 children with prolonged interwave latencies had a mean $\pm$ SD acoustic delay of 2.22 ± 0.14 ms for wave eIII/III [$t(6) = 15.6$, $p < 0.0001$] and 4.45 ± 0.39 ms for wave eV/V [$t(6) = 11.4$, $p < 0.0001$].

Asymmetric Brainstem Function Is Difficult to Predict in Bimodal Users. To determine which demographic features differentiated whether a child with severe to profound hearing loss would develop symmetric brainstem function with bimodal stimulation, independent-sample Mann-Whitney U tests were used, since most demographic variables were not normally distributed (one-sample Kolmogorov-Smirnov tests $p > 0.05$). Only total deprivation was significantly differently distributed between symmetric and asymmetric interwave latency groups ($p = 0.02$). All other factors were not significant ($p > 0.05$), including uni- and bilateral deprivation,

auditory experience, age at implantation, acoustic pure-tone average and pure-tone average asymmetry.

Bimodal Users Were Able to Detect Level Cues but Not Timing Cues. All 12 children completed behavioural testing with ITD cues (interwave ABR latency groups: symmetric $n = 8$ and asymmetric $n = 4$), and 8 of these children also listened for ILD cues (symmetric group $n = 6$ and asymmetric group $n = 2$). Detection of these binaural cues was measured as the proportion of responses that children indicated that they heard the sound on the CI (or electric) side. Positive values of binaural conditions indicated when the electric stimulation led in time (ITD; fig. 3a) or was at a greater level (ILD; fig. 3b) than the acoustic stimulation, and vice versa for negative ITD and ILD values. A generalised linear, mixed model with random intercept and slope effects was used to fit binary logistic functions to each child for ITD and ILD lateralisation and compare ITD slopes in the symmetric versus asymmetric groups, using the symmetric group as the reference. The symmetric group ITD slope did not significantly differ from zero ($p = 0.86$) and was not significantly different from the asymmetric group ITD slope ($p = 0.11$). A similar model was used to determine that the group slope for ILD lateralisation was significantly positive ($p < 0.0001$). The average ILD that generated a predicted response rate of 0.5 (i.e. the ILD at which bilateral input was perceived as balanced or neither coming from left or right), using the binary logit equations, was -0.14 ± 0.70 CU and ranged from -2.9 to $+3.7$ CU.

Discussion

In the present study, we examined whether bimodal stimulation protects the bilateral auditory brainstem from developing asymmetric function. Overall differences were expected in the absolute latency of evoked activity in the brainstem due to delayed stimulus conduction time and reduced neural synchrony evoked by acoustic rather than electric stimuli. Indeed, latency asymmetries for both waves eIII/III and eV/V in these bimodal users were even longer than previously recorded in bilateral CI users [Gordon et al., 2007b, c, 2008] and bilateral hearing aid users who had an asymmetric hearing loss [Selters and Brackmann, 1977; Bauch and Olsen, 1988, 1989]. Asymmetries were three times longer in the bimodal users with symmetric interwave latencies, and seven times longer in those children with asymmetric interwave latencies. Furthermore, asymmetries in both these bimodal groups were even larger than interaural timing differences experienced in the environment [Grothe et al., 2010]. In some bimodal users, these large asymmetries likely represented a peripheral delay; once the information reached the caudal brainstem, the information transfer through the brainstem to the midbrain was symmetric (fig. 1e, 2c, d). Even some children with severe to profound hearing loss in the non-implanted ear had interwave latencies within normative ranges for both electric and acoustic stimulation. However, in other children, the acoustic delay was further prolonged through the brainstem, as indicated by the longer acoustically evoked interwave latencies (fig. 1f, 2c, d). In this subgroup of bimodal users, the evoked activity was not a simple difference in peripheral timing between the two types of stimulation, but also neural conduction in the brainstem. Transmission through the brainstem remained within the normative electric range but was significantly abnormal when evoked by acoustic stimulation, creating asymmetric bilateral brainstem function. Although both groups of bimodal children had larger interaural differences in interwave latency (III–V

– eIII–eV) than previously reported for bilateral acoustic hearing in neonates [Eldredge and Salamy, 1996; Sininger and Cone-Wesson, 2006], on average, the children with bilaterally normative interwave latencies (symmetric group) had similar interaural interwave differences to children who received two CI either simultaneously or with a short delay between surgeries [Gordon et al., 2008]. On the other hand, interaural interwave differences were about twenty times larger in the bimodal users with abnormally prolonged acoustic interwave latencies than even the children who received a second CI after a long duration of unilateral CI use [Gordon et al., 2008]. It is important to note, however, that previously reported values for interaural interwave differences to bilateral acoustic or bilateral electric stimulation may not directly apply to bimodal stimulation; there will likely remain a larger range of acceptable interaural difference due to different stimulation modalities, particularly because the normative ranges for electric and acoustic interwave latencies differ. Testing of more bimodal children is required to further understand functional implications of the bimodal interaural interwave difference. Regardless, it is clear that bimodal children with prolonged interwave latencies on their acoustic side have significantly larger interaural asymmetries than previously reported for any peak latency or interwave latency, including I–V [Rosenhamer et al., 1981; Eldredge and Salamy, 1996; Sininger and Cone-Wesson, 2006; Gordon et al., 2008]. Therefore, despite introducing larger absolute brainstem asymmetries than previously reported in children and adults with hearing loss, bimodal stimulation can provide some protection of bilateral auditory brainstem function in a portion of children.

Preservation of normative brainstem function in only a portion of children using bimodal stimulation raises the question of whether there was some factor or sensitive period that affected brainstem development in these bimodal users. Unfortunately, this is not an easy question to answer, as it is extremely difficult to quantify what differentiates these two groups of bimodal users due to the large variations in hearing history. Several factors likely contribute to the differences in evoked activity with acoustic and electric stimulation, and bimodal users with asymmetric hearing loss are inherently more variable (table 1) than traditional paediatric bilateral CI users, who had restricted access to acoustic sound in both ears from an early age. How bilateral auditory brainstem function could be protected in some bimodal users is unclear, but input to the auditory system likely plays a significant role. The type of input could be spontaneous and/or evoked, and could have occurred any time during development, including the prenatal period of hearing. Even children with congenital deafness could have experienced spontaneous activity before birth, depending on their aetiology of hearing loss. In addition, many children in our cohort of bimodal users had progressive and/or fluctuating hearing loss due to enlarged vestibular aqueducts (10 cases). Questions about this input remain due to unclear and variable histories around the deterioration of hearing and consistency of hearing aid use. Our best estimate of total auditory deprivation indicated differences between the two groups of bimodal users (as indicated in the results), highlighting the importance of minimising auditory deprivation in children with asymmetric hearing loss.

The question remains whether those children with symmetric brainstem development were potentially better able to benefit from spatial hearing than those with asymmetric brainstem function. Despite significant peripheral acoustic delays (>2 ms), all 8 children were able to significantly detect level cues (fig. 3b), but only 1 of the

12 bimodal users were able to detect timing cues (fig. 3a). This poorer ability to detect ITD than ILD is not surprising given the significant peripheral delays, which would have a greater effect on the coincident detection mechanisms for processing ITD in the medial superior olive [Jeffress, 1948; Grothe and Sanes, 1994; Brand et al., 2002; Jercog et al., 2010] than the integrative mechanisms of processing ILD in the lateral superior olive [Finlayson and Caspary, 1991]. Furthermore, preferential use of ILD cues is consistent with previously documented lateralisation abilities of children and adults using bilateral CI [van Hoesel and Tyler, 2003; Laback et al., 2004; Grantham et al., 2007, 2008; Seeber and Fastl, 2008; Salloum et al., 2010]. Comparison across studies of binaural hearing suggests there are similar binaural advantages for children with bilateral CI and bimodal hearing [Ching et al., 2007], although several of our children had greater residual hearing than previously studied bimodal groups. Paediatric bimodal users also show highly variable sound localisation abilities [Ching et al., 2001, 2005; Litovsky et al., 2006], and the present findings suggest that bimodal users may be relying on ILD cues and perhaps other cues or strategies to locate a sound. Additionally, the bimodal asymmetries may be compounded when listening through their own devices, rather than the direct stimulation provided in the present study that was delivered through research equipment. CI processors and hearing aids are currently independent, and their automatic gain control processing would differentially affect sound reaching both ears, thereby reducing level differences and further skewing timing differences reaching the auditory brainstem. Regardless, in early stages of bimodal hearing (2.2 ± 2.2 years), integrating the information from both sides is challenging for these children, even with symmetric activation through the brainstem.

This study is part of a larger, ongoing investigation of bilateral auditory development in bimodal users, including measures of cortical activity and other behavioural outcomes. Future investigations focus on whether we can compensate for these large asymmetries in stimulation and neural conduction, and whether children using a CI and a hearing aid can develop a fused binaural image or obtain true binaural hearing. It may be that children require greater lengths of experience to use ITD and ILD cues, as we have seen in bilaterally deafened children with a long delay between receiving their two CI [Gordon et al., 2014]. These children were able to detect some ITD cues only after several years of using bilateral CI, although sensitivity remained abnormal. Perhaps bimodal users with symmetric brainstem function will be more likely to use the information after long durations of bimodal use. Even if we are not able to restore true binaural hearing to these children, we know that providing a longer period with acoustic hearing can have positive benefits on performance with bilateral CI for tasks such as identifying different characteristics of music [Hopyan et al., 2012]. We are, therefore, also asking whether bimodal use, even in those children with asymmetric brainstem function, primes the auditory system to function better with a second CI, thereby lengthening the critical period for bilateral implantation.

Conclusions

Results from this study demonstrated that bimodal stimulation can protect bilateral symmetry in auditory transmission through the brainstem in a portion of children, but this protection cannot be generalised to the whole population of bimodal users. Irrespective of whether this protection occurs, peripheral asymmetries

from electric versus acoustic stimuli still remain for all children. Regardless of whether symmetric brainstem function was preserved, children were able to detect level cues – but not timing cues – for lateralisation of sound. Given the variability in responses and hearing histories of bimodal users, a clear sensitive period within which to implant cannot be determined at this point in time.

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Disclosure Statement

Both the second and last authors are on Speaker's Bureau with Cochlear Limited.

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