Cortical Representation of Interaural Time Difference Is Impaired by Deafness in Development: Evidence from Children with Early Long-term Access to Sound through Bilateral Cochlear Implants Provided Simultaneously

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Accurate use of interaural time differences (ITDs) for spatial hearing may require access to bilateral auditory input during sensitive periods in human development. Providing bilateral cochlear implants (CIs) simultaneously promotes symmetrical development of bilateral auditory pathways but does not support normal ITD sensitivity. Thus, although binaural interactions are established by bilateral CIs in the auditory brainstem, potential deficits in cortical processing of ITDs remain. Cortical ITD processing in children with simultaneous bilateral CIs and normal hearing with similar time-in-sound was explored in the present study. Cortical activity evoked by bilateral stimuli with varying ITDs (0, ± 0.4 , ± 1 ms) was recorded using multichannel electroencephalography. Source analyses indicated dominant activity in the right auditory cortex in both groups but limited ITD processing in children with bilateral CIs. In normal-hearing children, adult-like processing patterns were found underlying the immature P1 (~ 100 ms) response peak with reduced activity in the auditory cortex ipsilateral to the leading ITD. Further, the left cortex showed a stronger preference than the right cortex for stimuli leading from the contralateral hemifield. By contrast, children with CIs demonstrated reduced ITD-related changes in both auditory cortices. Decreased parieto-occipital activity, possibly involved in spatial processing, was also revealed in children with CIs. Thus, simultaneous bilateral implantation in young children maintains right cortical dominance during binaural processing but does not fully overcome effects of deafness using present CI devices. Protection of bilateral pathways through simultaneous implantation might be capitalized for ITD processing with signal processing advances, which more consistently represent binaural timing cues.

Key words: beamformer; hearing loss; right dominance; simultaneous bilateral cochlear implant; source localization; spatial processing

Significance Statement

Multichannel electroencephalography demonstrated impairment of binaural processing in children who are deaf despite early access to bilateral auditory input by first finding that foundations for binaural hearing are normally established during early stages of cortical development. Although 4- to 7-year-old children with normal hearing had immature cortical responses, adult patterns in cortical coding of binaural timing cues were measured. Second, children receiving two cochlear implants in the same surgery maintained normal-like input from both ears, but this did not support significant effects of binaural timing cues in either auditory cortex. Deficits in parieto-occipital areas further suggested impairment in spatial processing. Results indicate that cochlear implants working independently in each ear do not fully overcome deafness-related binaural processing deficits, even after long-term experience.

Introduction

Detecting differences in the time of arrival of sound in both ears helps locate a sound source and understand speech in noise. Sen-

sitivity to interaural time differences (ITDs) on the order of 50–70 μ s is observed in typically developing 4- to 7-month-old infants (Ashmead et al., 1991) and improves with age (median 12.5 μ s in adults) (Van Deun et al., 2009). Changes in both sen-

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sory (neural encoding) and nonsensory (e.g., attention) components could contribute to development of ITD sensitivity and/or its evaluation (Van Deun et al., 2009; Litovsky, 2012); thus, we aimed to identify cortical (sensory) representation of ITDs in normal-hearing children and determine whether that was promoted in children with deafness who had access to sound through bilateral cochlear implants (CIs) from young ages.

Cortical processing of ITDs is supported by near-field data in animals (Werner-Reiss and Groh, 2008; Lee and Middlebrooks, 2011) and imaging in human adults demonstrating contralateral processing of leading ITDs (McEvoy et al., 1993; Krumbholz et al., 2005; Johnson and Hautus, 2010). Some human studies also report hemispheric asymmetry in contralaterality with similar sensitivity of the right hemisphere to spatial cues in both hemifields as opposed to more restricted right hemifield preference of the left hemisphere (Krumbholz et al., 2005; Magezi and Krumbholz, 2010; Briley et al., 2013). Because children show mature ITD perception by 5 years of age (Litovsky, 1997; Van Deun et al., 2009), we hypothesized that adult patterns of ITD coding in the cortex are present in normal-hearing children and that access to these cues could be established in children with deafness through early bilateral cochlear implantation.

Early-onset deafness impairs ITD sensitivity in the inferior colliculus (IC) (Hancock et al., 2010, 2013) and reduces the number of cortical neurons coding ITDs (Tillein et al., 2010, 2016), but the basic pathways remain preserved. Although longer duration of deafness leads to poorer ITD tuning, the effects of early-onset deafness on ITD sensitivity are more detrimental than late-onset deafness (Hancock et al., 2013). Symmetrical development of bilateral pathways can be promoted through early (<3 years of age) and bilateral implantation with limited interimplant delay (Papsin and Gordon, 2008). Binaural brainstem interactions in children with bilateral CIs confirm tonotopic registration of bilateral input (Gordon et al., 2012); however, representations of binaural activity more centrally have not been explored in these children. Behavioral findings suggest that abnormalities in binaural perception may be present. ITD perception was initially considered to be deficient in children using bilateral CIs (Salloum et al., 2010); however, detection of these cues in a lateralization task emerged in cohorts with long-term bilateral CI use (Gordon et al., 2014). The inability by a similar cohort to perceive these bilateral stimuli as a fused image (Steel et al., 2015) might reflect compensatory mechanisms to perform the lateralization task with a diffused image. This altered mechanism may be in response to the deficits in passive sensory processing of binaural timing cues. Moreover, whereas children who received CIs simultaneously demonstrated equal sensitivity to right and left leading stimuli, children who received CIs sequentially demonstrated a bias toward the first implanted CI, potentially reflecting abnormal aural preference consequent to prolonged unilateral CI stimulation (Gordon et al., 2015).

Using multichannel electroencephalogram (EEG) in the present study, normal-hearing children were found to exhibit mature cortical ITD patterns from an early age of 4 years, consistent with adult behavioral performance at this age. This was supported by right hemispheric dominance during binaural processing, higher activity for contralateral leading ITDs in each hemisphere, and

Table 1. Demographic data^a

	Etiology/risk factor	Age at test (yr)	Age at implant (yr)	Time-in-sound (yr)	Bilateral CI experience (yr)
CI participant					
CI1	Unknown	5.84	2.70	3.15	3.15
CI2	Family history	5.29	3.26	2.04	2.04
CI3	Enlarged vestibular aqueduct	6.58	2.85	3.73	3.73
CI4	Incomplete partition Type II	5.25	3.16	3.52	2.09
CI5	Unknown	5.88	2.36	3.52	3.52
CI6	Unknown	5.44	1.20	5.04	4.24
CI7	Unknown	6.90	2.83	4.07	4.07
CI8	Premature birth	5.77	1.12	4.65	4.65
CI9	Unknown	5.17	1.04	4.12	4.12
CI10	Congenital cytomegalovirus infection	5.17	1.06	4.11	4.11
CI11	Unknown	7.36	3.49	5.13	3.87
CI12	Low birth weight/NICU stay	6.09	1.09	4.99	4.99
CI13	Family history	6.85	1.82	5.03	5.03
CI14	Unknown	7.40	3.12	4.95	4.33
CI15	Connexin26	7.08	1.05	6.03	6.03
CI16	Unknown	5.98	1.38	4.61	4.61
Group					
Normal hearing	N = 16	5.24 (0.95)	NA	5.24 (0.95)	NA
Bilateral CIs	N = 16	6.13 (0.79)	2.10 (0.95)	4.29 (0.97)	4.04 (1.02)

^aNA, Not applicable.

hemispheric asymmetry for right versus left leading ITDs. We also demonstrate that normal-like right dominance during binaural processing can be established in children with deafness through the recommended clinical standard of early and simultaneous provision of two CIs (Ramsden et al., 2012). Nonetheless, this was accompanied by poor ITD sensitivity and limited hemispheric differences, suggesting that sensory coding of ITDs continues to be impaired even with long-term bilateral CI use.

Materials and Methods

The study protocol (#100000294) was approved by the Research Ethics Board at the Hospital for Sick Children and conforms to the Tri-Council Policy on the Ethical Conduct for Research Innovation. Written parent consent was obtained before data collection.

Participants. Children who received their two CIs (Cochlear's Nucleus 24 devices) in the same surgery at <3.5 years of age with >2 years of CI experience were invited to participate in the study. Participants were 16 children (12 boys). Etiology/risk factor of deafness, age at test, age at implant, and hearing experience for each child as well as group mean demographic information are provided in Table 1. All 16 children had prelingual hearing loss, which was additionally progressive in CI4. On average, children had 4.04 ± 1.02 years of bilateral CI experience at the time of data collection. Most children wore hearing aids before implantation and, together with minimal useable residual hearing with hearing aids (aided threshold of ≤ 40 dB HL at a minimum of one frequency between 0.5–4 kHz), had an average of 4.29 ± 0.97 years of time-in-sound (length of hearing experience). To evaluate cortical coding of ITD cues in children with normal hearing and to compare the development of cortical processing in children with bilateral CIs, 16 children (9 boys) with normal hearing with similar time-in-sound (assumed equivalent to their chronological age) were recruited (Fig. 1). Parents reported no complaints of ear, hearing, or neurological disorders/symptoms. Because children with normal hearing were matched for time-in-sound, their average chronological age was lower than the CI group by 0.89 years ($t_{(29)} = -2.88$, $p = 0.007$). Although the range of time-in-sound overlapped

Figure 1. Children in both groups had similar time-in-sound (in years) at the time of data collection.

almost entirely between the two groups (Fig. 1), children with CIs had a small yet significantly shorter time-in-sound experience by an average of <1 year (Table 1; $t_{(29)} = 2.78$, $p = 0.009$). Younger children with normal hearing could not be tested due to reduced compliance with testing, and older children with CIs with longer time-in-sound were not included as they tended to show more mature cortical responses (emerging P1-N1-P2 morphology) rather than an immature response (characterized by P1-N2; see Fig. 3A). The evolution from the immature to mature waveform has been clearly described, beginning as early as 8 years of age (Moore and Guan, 2001; Ponton and Eggermont, 2007). Any deviation from an immature response was excluded to avoid potential confounds in interpretation.

Stimuli. In children with CIs, biphasic electrical pulses with a width of 25 μ s/phase were delivered bilaterally to the electrode #20 pair (apical end) at 250 pulses/s using SPEAR3 (Hearworks). In children with normal hearing, clicks with a duration of 100 μ s were delivered bilaterally using Etymotic ER-3A coupled with a foam tip at 250 clicks/s. Stimulus trains were 36 ms long presented at a constant rate of 1 train/s. Similar to previous studies (Gordon et al., 2013; Jiواني et al., 2016; Easwar et al., 2017), in children with CIs, stimulus levels were set at 10 manufacturer-defined clinical units (CU; 10 CU = 20.96 μ A; 6.79 dB re 100 μ A) below those necessary to elicit equal amplitude brainstem responses when either CI was individually stimulated. Levels were further adjusted to perceptually matched levels (Gordon et al., 2016) if levels based on brainstem responses were not balanced. In children with normal hearing, click trains were presented at 50 dB above behavioral threshold in each ear. This was perceptually balanced between the ears. At constant stimulus levels, five conditions with varying ITDs were evaluated (Fig. 2). The onset of stimulus trains was delayed by 0.4 and 1 ms in either the left or the right ear/CI creating an interaural time difference. A condition with synchronized onset (Bil-0, 0 ITD) was also evaluated (Fig. 2). The ITD conditions chosen are similar to those used in a previous study (Gordon et al., 2014) which evaluated behavioral responses of lateralization in a similar cohort of children who received their CIs simultaneously with ~4 years of bilateral CI experience on average. As in that study, the normal-hearing control group in the present study listened to click trains. Clicks closely resemble onset characteristics of electric pulses (e.g., Khosla et al., 2003) and have more consistent contralaterally increased cortical activity from left or right monaural stimulation than tonebursts in young children with normal hearing (Yamazaki et al., unpublished observation). Thus, clicks were used to maximize chances of measuring changes in lateralization with ITDs. Throughout this study, the leading side is indicated either by the side in which the stimulus arrived earlier (right [R-1 ms, R-0.4 ms] and left [L-1 ms, L-0.4 ms]; Fig. 2) or described in terms of

Figure 2. Five bilateral conditions evaluated. Red bars represent the onset (magnified) of 36 ms pulse/click trains presented to the right ear/CI (length truncated). Blue bars represent the onset (magnified) of 36 ms pulse/click trains presented to the left ear/CI (length truncated). R, right leading ITDs; L, left leading ITDs. Position around schematic head is arbitrary for illustrative purposes.

leading side with reference to each hemisphere (ipsilateral [I-1 ms, I-0.4 ms] and contralateral [C-1 ms, C-0.4 ms]).

Response recording. EEG activity in response to the five bilateral conditions was recorded using a 64-channel electrode cap worn by the child. During the recording, children sat in a sound booth and watched a silent movie with subtitles, read a book, or engaged in games/visual distractions requiring minimal movement. EEG, referenced to the right ear lobe, was recorded using a Synamps-II amplifier and the Scan version 4.5 software (Compumedics). EEG was sampled at 1000 Hz and bandpass filtered (0.15–100 Hz) during recording. Each 1000 ms epoch included a pre-stimulus baseline of 200 ms. Epochs with EEG exceeding ± 100 μ V at the vertex electrode were removed before source localization. Two replicated averages with a minimum of 100 epochs each were obtained per condition.

Localization of cortical activity. The Time Restricted, Artifact and Coherence source Suppression (TRACS) beamformer (details described by Wong and Gordon, 2009; Gordon et al., 2013; Jiواني et al., 2016) was used to localize cortical activity in each condition for each response peak (P1/Pc1 and N2; see Fig. 3A,B). In brief, the TRACS uses an adaptive spatial filter (linearly constrained minimum variance type) on the average-referenced EEG bandpass filtered between 1 and 30 Hz to estimate dipole activity in ~64,000 voxels of dimensions $3 \times 3 \times 3$ mm. Dipole activity was computed using an age-appropriate MNI head model template created using the Template-O-matic toolbox (Wilke et al., 2008). Head model templates were used because the surgically placed magnet in children with CIs is a contraindication for MRI. A 3-layer boundary element model mesh was created based on the head model template to simulate geometry of the brain volume, skull and scalp, and their respective conductivities. Source activity in each hemisphere underlying each response peak was evaluated by suppressing the other hemisphere (Dalal et al., 2006). In children with CIs, an artifact suppression algorithm was used to suppress the CI-generated artifact (Wong and Gordon, 2009). This validated algorithm estimates the artifact space based on activity between -80 and 10 ms (re stimulus onset) in an epoch and suppresses up to 97% of the CI artifact without distorting the response beyond the stimulus duration (Wong and Gordon, 2009). A pseudo-Z statistic, computed as the ratio of sample signal mean and SD of the prestimulus baseline (-200 to -80 ms re stimulus onset), was used to normalize activity in each voxel. A threshold pseudo-Z was determined based on a one-tailed omnibus test (Petersson et al., 1999) using a $\pm$ average that cancelled out time-locked signals (Gordon et al., 2013). The threshold pseudo-Z represented baseline activity and therefore enabled isolation of voxels with activity above baseline (Jiواني et al., 2016; Easwar et al., 2017; Yamazaki et al., unpublished observation). A pseudo-Z map, which plotted the threshold-corrected pseudo-Z per voxel on MNI head model templates, was generated to localize cortical activity within each hemisphere. Axial views are shown in Figure 5. The lower end of the scale in blue represents below-baseline activity, whereas the higher end in warmer colors represents hotspots of stimulus-evoked above-baseline activity. The time window surrounding each peak was individually

chosen for each condition based on the Cz waveforms (see Fig. 3A) and global field power (GFP) (see Fig. 3B).

Peak dipole activity and latency. Consistently activated cortical areas in each condition were identified using group averages of threshold-corrected pseudo-Z maps (see Fig. 5A,D). Signals were clearest in left and right temporal lobes as expected in response to sound and consistent with sound-evoked regions measured in other cohorts of children and adolescents using the TRACS beamformer (Gordon et al., 2013; Jiwani et al., 2016; Easwar et al., 2017; Yamazaki et al., unpublished observation) as well as in adults using other imaging technologies (e.g., Krumbholz et al., 2005, 2007; Johnson and Hautus, 2010; McLaughlin et al., 2016). Left and right auditory cortices were defined by MNI coordinates ($x \leq -55$, $-35 \leq y \leq 5$ and $-10 \leq z \leq 20$ mm for the left auditory cortex and $x \geq 55$, $-35 \leq y \leq 5$ and $-10 \leq z \leq 20$ mm for the right auditory cortex as in previous studies) (Jiwani et al., 2016; Easwar et al., 2017; Yamazaki et al., unpublished observation). The voxel with the highest pseudo-Z in the defined region of interest within each hemisphere was identified as the peak dipole for each condition. The source locations of P1/Pci peak dipoles across all conditions are shown in Fig. 4. Variance in source location around the mean was 10.21 ± 4.64 mm for P1/Pci and 10.69 ± 5.03 mm for N2. The dipole moment and associated latency of the peak dipole were used for statistical analysis and calculation of cortical lateralization and lead-side weighting indices. Consistency of the peak dipole moment and latency values were verified in voxels with the top 10 threshold-corrected pseudo-Z values.

For each condition, a cortical lateralization index was calculated to measure the change in balance between right and left hemispheric activity. A normalized difference in hemisphere-specific peak dipole moment was obtained using the formula: $(\text{right hemisphere} - \text{left hemisphere}) / (\text{right hemisphere} + \text{left hemisphere}) \times 100$ (Gordon et al., 2013; Jiwani et al., 2016). Values can range from -100% to 100% , the scale limits representing completely left to completely right lateralized activity with 0% representing balanced activity between the hemispheres. There were rare cases ($n = 4$ of 320 P1/Pci peak dipoles and 7 of 320 N2 peak dipoles) in which the pseudo-Z of the identified peak dipole in one auditory cortex was not above the threshold-pseudo-Z, but this was never observed in both auditory cortices for the same condition. The small dipole moment (<4 nAm; mean $\pm$ SD, 2.01 ± 0.92 nAm) of below-baseline peak dipoles indicated low activity in one hemisphere and therefore a high degree of cortical lateralization. The associated peak dipole moment was included for statistical analyses; however, the associated peak latencies were not, as this may vary more randomly.

A normalized lead-side weighting index was computed for each hemisphere to evaluate the degree of left versus right hemifield preference accounting for the possible bias of hemispheric dominance (i.e., larger dipole moments in one hemisphere) (Briley et al., 2013). At each ITD (see Fig. 7A), the degree of right-lead weighting was obtained using peak dipole moment elicited in right leading conditions $([\text{right leading} / (\text{right leading} + \text{left leading})] \times 100)$ and the degree of left-lead weighting was obtained using the peak dipole moment elicited in the left leading conditions $([\text{left leading} / (\text{right} + \text{left leading})] \times 100)$.

Permutation analyses. Because auditory spatial processing involves nonauditory areas (Griffiths et al., 1998; Weeks et al., 1999; Ducommun et al., 2002; Brunetti et al., 2005), activity in all voxels was compared using a between-group permutation analysis. Two-sided unpaired comparisons were used to compare differences in peak dipole moment voxel-by-voxel between normal-hearing children and children with CIs in each condition using 10,000 permutations (Blair and Karniski, 1993; Chau et al., 2004). A Bonferroni correction ($p = 0.05/62$ recording electrodes = 0.0008) was applied to counteract inflation of the false-positive rate due to multiple comparisons (Jiwani et al., 2016).

Statistical analyses. GFP peak amplitude and latency for P1/Pci and N2 were compared using two-way (condition, group) mixed ANOVA. Three-way (condition, hemisphere, and group) mixed ANOVAs were performed on dipole moment and latency of P1/Pci and N2 response peaks to evaluate the effects of ITD in each group. A two-way mixed ANOVA, with condition as the within-subject factor and group as the between-subject factor, was conducted to evaluate differences in cortical lateralization. A four-way mixed ANOVA with hemifield, ITD, and

hemisphere as within-subject factors and group as the between-subject factor was performed to evaluate hemispheric differences in lead-side weighting. Greenhouse-Geisser corrected degrees of freedom were used when sphericity was violated. *Post hoc* analyses included two-tailed paired *t* tests. False discovery rate was used to counteract multiple comparison bias on false-positive rates (Benjamini and Hochberg, 1995). Corrected *p* values are reported in this manuscript; values <0.05 were considered significant. Statistical analyses were performed using R (version 3.1.3 R core Team, 2013).

Results

Children with normal hearing, as well as bilateral CIs, demonstrated similar cortical development evidenced by comparable immature response morphology (Fig. 3A), consistent with the same range of time-in-sound between groups. The biphasic response, characterized by a dominant positive peak (P1 in children with normal hearing and Pci in children with CIs) followed by a negative peak N2 (grand average Cz waveforms shown in Fig. 3A), is consistent with previous studies in young children (Ponton et al., 2000, 2002; Gordon et al., 2013). The mean GFP consisted of two corresponding peaks in both groups (Fig. 3B). GFP peak amplitude and latency of P1/Pci and N2 are provided in Table 2. Two-way mixed ANOVA (condition $\times$ group) revealed a significant main effect of group for P1 ($F_{(1,30)} = 15.92$, $p < 0.001$) and N2 ($F_{(1,30)} = 25.50$, $p < 0.001$) GFP peak amplitude, with higher amplitudes in children with CIs. GFP peak latencies were similar between groups (P1/Pci: $F_{(1,30)} = 0.89$, $p = 0.35$; N2: $F_{(1,30)} = 0.58$, $p = 0.45$). No main or interaction effects of condition were found for GFP amplitude and latency ($p > 0.05$). Topographical plots illustrating the spatial distribution of average-referenced surface EEG at peak GFPs are shown in Figure 3C. The effects of ITD during P1/Pci and N2 are quantified and interpreted based on the following source data from each hemisphere.

The accuracy of source localization using the TRACS beamformer relative to MEG has been measured as 15.3 mm in a small sample of individuals with normal hearing listening to pure tones (Wong, 2012) but can vary across individuals depending on deviations from template head models. In the present study, auditory evoked activity localized to the same left and right temporal areas as in previous studies in children (Gordon et al., 2013; Jiwani et al., 2016) and adults (Krumbholz et al., 2005, 2007; Johnson and Hautus, 2010; McLaughlin et al., 2016). Peak dipoles were chosen within two defined regions of interest (Fig. 4) that varied by an average ($\pm$ SD) of 10.21 ± 4.64 mm for P1/Pci and 10.69 ± 5.03 mm for N2 within subjects across the 5 ITD conditions.

Right hemispheric dominance of cortical activity is evident in both groups, but sensitivity to ITD changes is impaired in children with CIs

Mean peak dipole moment values in Figure 5A illustrate higher activity in the right relative to the left hemisphere in both groups. This similarity between groups in right hemispheric dominance, when averaged across all bilateral conditions, is evident in Figure 5B. The difference in overall activity between hemispheres was confirmed by a significant main effect of hemisphere ($F_{(1,30)} = 9.29$, $p = 0.005$) in the three-way ANOVA (hemisphere, condition, group). Pooled across groups and conditions (nonsignificant group $\times$ hemisphere interaction, $F_{(1,30)} = 1.43$, $p = 0.24$; nonsignificant group $\times$ condition $\times$ hemisphere interaction, $F_{(4,120)} = 0.08$, $p = 0.99$), activity in the right auditory cortex (mean $\pm$ SD, 13.01 ± 7.67 nAm) was significantly higher than in the left (10.14 ± 7.47 nAm). The overall activity was similar

Figure 3. Similar response morphology in both groups confirms similar length of hearing experience. Grand mean waveforms at Cz (ear lobe reference; **A**) and GFP (**B**) illustrate immature biphasic cortical response in both groups. L, left leading ITDs; R, right leading ITDs; Bil-0, 0 ITD (simultaneous onset of bilateral stimuli); 0.4 and 1 ms, ITDs at onset used. 0 ms on the x-axis indicates stimulus onset. **C**, Topographical distribution of the average-reference surface EEG at peak GFP latencies indicated for each condition.

between groups ($F_{(1,30)} = 0.55$, $p = 0.47$), although GFP peak amplitude was higher in children with CIs (Table 2). Normal-like right dominance during bilateral stimulation confirms protection of bilateral pathways achieved through simultaneous bilateral implantation in children with deafness.

Although normal-like dominance of the right auditory cortex in response to bilateral input was evident in children with CIs, ITD-dependent changes in cortical activity were limited. Mean peak dipole moment values in Figure 5A illustrate lower activity for ITD conditions leading from the ipsilateral side (relative to Bil-0 and ITDs leading from the contralateral side) in normal-hearing children, but not in children with bilateral CIs. The pattern appears similar for both hemispheres in normal-hearing children. The difference in the effect of ITD on cortical activity

between the two groups was confirmed by a significant group $\times$ condition interaction ($F_{(2,84,85,20)} = 4.27$, $p = 0.008$). As evident in Figure 5C, averaged across the two hemispheres, children with normal hearing had significantly weaker cortical activity for ITDs leading from the ipsilateral side. *Post hoc* pairwise comparisons confirmed that ipsilateral leading ITDs elicited significantly lower activity than the Bil-0 condition with no ITD (I-1 ms: $t_{(15)} = -3.45$, $p = 0.018$; I-0.4 ms: $t_{(15)} = -3.86$, $p = 0.016$) and the 0.4 ms contralateral leading condition (I-1 ms: $t_{(15)} = -2.65$, $p = 0.048$, I-0.4 ms: $t_{(15)} = -2.63$, $p = 0.048$). The difference between ipsilateral and the 1 ms contralateral leading ITD, which was significant before correction for multiple comparisons, approached significance after correction (I-1 ms: $t_{(15)} = -2.35$, $p = 0.065$, I-0.4 ms: $t_{(15)} = -2.14$, $p = 0.079$). Peak dipole moment did not vary with the length of ITD (0.4 vs 1 ms) within ipsilateral ($t_{(15)} = 0.46$, $p = 0.73$) and within contralateral leading conditions ($t_{(15)} = -0.34$, $p = 0.74$). In children with CIs, no differences were found between any of the five conditions ($p > 0.05$; Fig. 5C). One child with CI (CI9) had abnormally high dipole activity in the left hemisphere during Pci (>28 nAm in all conditions). We did not exclude data from this child as an outlier because bilateral stimulation levels remained constant. Exclusion of data from this child did not change the analysis outcome. In summary, both groups of children demonstrated similar right dominance during binaural processing. Children with normal hearing demonstrated significantly lower activity to ITDs leading from the ipsilateral side as expected, whereas children with CIs lacked this differentiation.

Similar to P1/Pci (Fig. 5A,B), mean N2 peak dipole moment in Figure 5D illustrates generally higher peak activity in the right hemisphere compared with the left; however, no ITD-sensitive changes were found for this response peak. The main effect of hemisphere approached significance ($F_{(1,30)} = 3.60$, $p = 0.067$) in the three-way ANOVA (hemisphere, condition, group). Pooled across both groups and five conditions (nonsignificant group $\times$ hemisphere interaction, $F_{(1,30)} = 0.45$, $p = 0.51$; nonsignificant group $\times$ condition $\times$ hemisphere interaction, $F_{(4,120)} = 0.86$, $p = 0.49$), activity in the right hemisphere (10.82 ± 5.19 nAm) tended to be higher than activity in the left hemisphere (8.79 ± 7.38 nAm). The main effect of condition was nonsignificant demonstrating limited ITD sensitivity ($F_{(4,120)} = 2.00$, $p = 0.09$), and the overall dipole activity was similar between groups ($F_{(1,30)} = 0.065$, $p = 0.80$), although peak GFP amplitudes were higher in children with CIs (Table 2). The same child (CI9) had high activity in the left hemisphere also during N2 (>26 nAm in all conditions). Exclusion of data from this child

Table 2. GFP peak amplitude and latencies^a

	Group	L-1 ms	L-0.4 ms	Bil-0	R-0.4 ms	R-1 ms
Amplitude (μ V)						
P1/Pci	Normal hearing	2.90 $\pm$ 0.26	2.94 $\pm$ 0.22	3.31 $\pm$ 0.21	2.87 $\pm$ 0.19	2.94 $\pm$ 0.21
	Bilateral CIs	4.29 $\pm$ 0.39	4.29 $\pm$ 0.37	4.07 $\pm$ 0.28	4.33 $\pm$ 0.28	3.92 $\pm$ 0.25
N2	Normal hearing	4.03 $\pm$ 0.24	3.99 $\pm$ 0.36	4.21 $\pm$ 0.37	3.98 $\pm$ 0.36	3.88 $\pm$ 0.25
	Bilateral CIs	6.76 $\pm$ 0.43	6.71 $\pm$ 0.54	6.50 $\pm$ 0.59	6.54 $\pm$ 0.52	6.92 $\pm$ 0.49
Latency (ms)						
P1/Pci	Normal hearing	98.00 $\pm$ 3.02	95.00 $\pm$ 2.37	96.50 $\pm$ 3.37	96.81 $\pm$ 2.21	99.19 $\pm$ 2.40
	Bilateral CIs	99.63 $\pm$ 3.31	101.63 $\pm$ 3.01	100.13 $\pm$ 3.68	99.00 $\pm$ 3.25	102.44 $\pm$ 4.12
N2	Normal hearing	233.19 $\pm$ 13.92	219.75 $\pm$ 10.87	226.88 $\pm$ 12.81	233.69 $\pm$ 15.67	216.06 $\pm$ 9.32
	Bilateral CIs	216.44 $\pm$ 6.28	222.19 $\pm$ 8.88	212.25 $\pm$ 6.31	219.13 $\pm$ 5.76	217.00 $\pm$ 4.90

^aData are mean $\pm$ SE. Children with CIs had significantly higher GFP amplitude for Pci and N2 peaks compared with children with normal hearing ($p < 0.001$). Peak latencies did not differ by group ($p > 0.05$). R, right leading conditions; L, left leading conditions; Bil-0, simultaneous onset of bilateral stimuli; 0.4 and 1 ms, ITDs at stimulus onset.

Figure 4. Peak dipoles (illustrated for P1/Pci only) were identified in similar locations across conditions in both groups of children.

rendered the main effect of hemisphere significant ($F_{(1,29)} = 11.31$, $p = 0.002$). On average, right hemisphere activity (10.59 ± 5.11 nAm) was higher than left hemisphere activity (7.86 ± 5.17 nAm). No other main or interaction effects were found. In summary, cortical activity underlying N2, like the P1/Pci, had a right hemispheric bias in both groups.

Latency (P1/Pci) of peak dipole varied by group but not by condition (Table 3). A significant main effect of group on P1/Pci latency ($F_{(1,28)} = 4.20$, $p = 0.049$) was found in the three-way ANOVA (hemisphere, condition, group). Averaged across ITD conditions and hemispheres, Pci peak dipole latency in children with bilateral CIs (95.99 ± 17.39 ms) was significantly shorter than children with normal hearing (103.81 ± 10.77 ms) despite the lack of latency differences in the GFP (Table 2). No other main or interaction effects of condition were significant. No significant main or interaction effects were found for N2 peak dipole latency in the three-way ANOVA (hemisphere, condition, group). Peak dipole latencies are provided in Table 3.

Children with bilateral CIs do not show expected changes in cortical lateralization with ITD

Cortical lateralization was computed only for P1/Pci given that no ITD-sensitive changes were found for N2 (Fig. 5D). A main

effect of condition (Bil-0, R/L-0.4, R/L-1 ms) was found on the cortical lateralization measure ($F_{(4,120)} = 2.49$, $p = 0.047$); however, none of the conditions differed significantly in *post hoc* analyses after false discovery rate correction. This may be due to the relatively small changes in far-field/surface-based lateralization measures from a population of neurons (Werner-Reiss and Groh, 2008) and/or individual variability. Further analyses probed two questions about ITD-sensitive changes in cortical lateralization: (1) Does cortical lateralization vary by hemifield and ITDs within the same hemifield (Bil-0 condition excluded)? (2) Does cortical lateralization reflect a change between the presence and absence of an ITD (ITD conditions vs Bil-0)?

As plotted in Figure 6A, lateralization indices varied between hemifields more than within each hemifield. In normal-hearing children, cortical lateralization of left leading stimuli was more right hemisphere weighted relative to right leading stimuli, changing from a right lateralized pattern to bilaterally distributed activity. This is consistent with both the dominance of activity in the right auditory cortex and the reduction of dipole moment ipsilateral to the side of the leading ITD (Fig. 5). Relatively, smaller differences were evident between 0.4 and 1 ms ITDs leading from the same hemifield. In comparison, children with CIs showed similar lateralization for left and right leading ITDs.

Figure 5. Both children with normal hearing and bilateral CIs demonstrated dominance of the right auditory cortex during binaural listening; however, cortical activity in children using CIs was less sensitive to changes in ITD. **A**, Average pseudo-Z maps (top row), mean peak dipole moment (bottom row) across ITDs for P1 in normal-hearing children and Pci in children with bilateral CIs. I, ipsilateral leading ITD conditions; C, contralateral leading ITD conditions. The pseudo-Z maps from each condition were split by hemisphere to correspond to the conditions in the bottom graph. Axes are in MNI coordinates (millimeters). **B**, Increased peak dipole moment in the right relative to left hemisphere, averaged across all ITD conditions, is evident in both groups. **C**, Averaged across hemispheres, children with normal hearing exhibited reduced activity for ITDs leading from the ipsilateral side during P1, whereas this was unclear in children with bilateral CIs. Horizontal bracketed lines indicate significant differences between conditions. **D**, Average pseudo-Z maps (top row), mean peak dipole moment (bottom row) across ITDs for N2 in normal-hearing children and children with bilateral CIs. A tendency for increased activity in the right rather than left auditory cortex ($p = 0.067$) was evident in both groups, but N2 peak activity did not vary by condition. Error bars indicate SE.

Table 3. P1/Pci and N2 peak dipole latencies across conditions^a

	Group	Hemisphere	I-1 ms	I-0.4 ms	Bil-0	C-0.4 ms	C-1 ms
P1/Pci	Normal hearing	Left	104.50 ± 3.50	103.73 ± 2.05	107.69 ± 2.17	103.75 ± 2.75	107.12 ± 2.22
		Right	104.75 ± 2.66	102.69 ± 2.50	101.69 ± 2.32	100.69 ± 2.95	101.50 ± 3.53
	Bilateral CIs	Left	96.06 ± 5.60	95.80 ± 4.96	98.40 ± 4.22	95.88 ± 4.27	97.88 ± 4.03
		Right	94.56 ± 3.94	92.73 ± 3.37	93.12 ± 3.60	100.88 ± 6.04	94.50 ± 3.47
N2	Normal hearing	Left	207.87 ± 4.51	201.88 ± 8.20	207.81 ± 6.55	203.81 ± 10.93	216.56 ± 10.82
		Right	210.56 ± 9.54	207.88 ± 10.56	210.31 ± 10.60	206.88 ± 9.79	210.19 ± 11.95
	Bilateral CIs	Left	208.44 ± 4.36	200.00 ± 4.97	206.73 ± 7.44	205.71 ± 4.43	212.62 ± 5.02
		Right	203.69 ± 6.56	206.12 ± 7.03	197.62 ± 7.89	203.75 ± 5.80	205.31 ± 7.68

^aData are mean ± SE in milliseconds. Children with bilateral CIs had significantly shorter Pci latencies compared with P1 in normal-hearing children ($p = 0.049$). No significant group or condition effects were found for N2 latencies. I, ipsilateral leading conditions; C, contralateral leading conditions; Bil-0, simultaneous onset of bilateral stimuli.

Sensitivity of the lateralization measure to between-hemifield changes in children with normal hearing and the lack thereof in children with CIs was confirmed by a significant two-way interaction (group × hemifield, $F_{(1,30)} = 4.75$, $p = 0.037$) in the three-way ANOVA (hemifield [left/right], ITD [0.4 ms, 1 ms], group). In children with normal hearing, left leading ITDs ($19.96 \pm 20.50\%$) were significantly more right lateralized than right leading ITDs ($7.04 \pm 21.78\%$, $t_{(15)} = 4.27$, $p < 0.001$). This change was nonsignificant in children with bilateral CIs (left leading ITDs: $13.68 \pm 25.12\%$; right leading ITDs: $12.17 \pm 26.41\%$; $t_{(15)} = 0.35$, $p = 0.73$). The limited within-hemifield sensitivity of lateralization index was confirmed by nonsignificant main ($F_{(1,30)} = 0.02$, $p = 0.89$) and interaction effects of ITD (ITD × group, $F_{(1,30)} = 0.04$, $p = 0.84$; ITD × hemifield, $F_{(1,30)} = 0.05$, $p = 0.83$). The lack of differences in cortical lateralization between the two large ITDs leading from the same hemifield parallels similar behavioral lateralization performance for these same stimuli in children with normal hearing (Gordon et al., 2014). The smaller within-hemifield than between-hemifield differences are consistent with broadly tuned opponent channels with shallow rate-azimuth slopes for location changes away from the midline (Stecker et al., 2005).

To evaluate if lateralization could indicate detection of ITD from the Bil-0 condition, (1) a two-way ANOVA (condition [L-/R-lead/Bil-0], group) was performed on lateralization indices averaged over 0.4 and 1 ms ITDs in each hemifield given that lateralization did not vary by within-hemifield ITDs (Fig. 6A); and (2) lateralization slope (computed as the linear rate of change in lateralization index between left leading, Bil-0 and right leading ITD conditions) was compared between the groups using an independent t test. We speculated that slope measures may be more sensitive because the detection of ITD would likely depend on the change from Bil-0, rather than the absolute lateralization index, and that the absolute lateralization index at Bil-0 may vary across individuals.

Post hoc analyses following the significant main effect of condition ($F_{(2,60)} = 4.02$, $p = 0.022$) revealed greater right lateralized activity for left ($16.82 \pm 22.78\%$) than right leading stimuli ($9.60 \pm 23.96\%$; $t_{(31)} = 2.60$, $p = 0.042$; Fig. 6B), as expected from Figure 6A. The degree of right lateralized activity was similar for the Bil-0 condition ($16.43 \pm 24.98\%$) and left leading stimuli ($16.81 \pm 22.78\%$, $t_{(31)} = -0.13$, $p = 0.89$). The difference between Bil-0 ($16.43 \pm 24.98\%$) and right leading stimuli ($9.60 \pm 23.96\%$) approached significance ($t_{(31)} = 2.23$, $p = 0.05$). The main effect of group ($F_{(1,30)} = 0.03$, $p = 0.87$) and interaction between group and condition ($F_{(2,60)} = 2.08$, $p = 0.13$) were nonsignificant. Although group differences with absolute lateralization indices were nonsignificant, the slopes (shown in Fig. 6C) were significantly lower in children with bilateral CIs (-0.75 ± 8.56) relative to children with normal hearing (-6.46 ± 6.05 ;

$t_{(27,0)} = -2.18$, $p = 0.038$). The shallower slope in children with CIs is consistent with impaired change in behavioral lateralization with ITDs (Gordon et al., 2014, their Figs. 2, 3). This suggests that the overall slope, as opposed to the absolute lateralization indices, more likely reflects poorer-than-normal behavioral ITD detection in children with bilateral CIs.

In summary, cortical lateralization measures corroborate findings of right hemispheric dominance to bilateral click/pulse trains with decreasing ipsilateral activity to ITDs leading from the same side (Fig. 5). The shift in right lateralized activity for left leading ITDs to more bilateral activity for right leading ITDs was not found in children with bilateral CIs (Fig. 6A). Moreover, the change in cortical lateralization was reduced in children with bilateral CIs compared with normal-hearing children (Fig. 6C). This parallels poorer behavioral detection of ITDs (Gordon et al., 2014). The significant group effects shown by slope of lateralization and not by absolute lateralization suggest a limitation of using absolute lateralization measures across ITD conditions and/or individual variability in ITD impairment among children with bilateral CIs. Either issue would reduce the detectable differences in absolute lateralization between groups.

Children with bilateral CIs do not show expected hemispheric differences for ITD processing

Similar to cortical lateralization scores, right and left leading ITD weighting was computed only for P1/Pci given that no ITD-sensitive changes were found for N2 (Fig. 5D). Individual and mean weighting indices in Figure 7B indicate a difference in preference for right and left leading stimuli between the two hemispheres in normal-hearing children but not in children with CIs. This was confirmed by a significant three-way interaction (group, hemisphere, hemifield; $F_{(1,30)} = 4.89$, $p = 0.035$) in the four-way ANOVA (group, hemisphere, hemifield, ITD). Collapsed across ITDs (no significant main effects or interactions), in normal-hearing children (Fig. 7B), the left hemisphere showed a significantly higher weighting for right leading stimuli ($54.88 \pm 4.54\%$) relative to left leading stimuli ($45.12 \pm 4.54\%$; $t_{(15)} = 4.30$, $p = 0.001$), whereas the right hemisphere showed no significant difference (left-lead weighting: $51.90 \pm 5.18\%$, right-lead weighting: $48.09 \pm 5.19\%$; $t_{(15)} = -1.47$, $p = 0.16$). In children with bilateral CIs, no hemispheric differences were found (right hemisphere: $t_{(15)} = 0.47$, $p = 0.64$, left hemisphere: $t_{(15)} = 1.11$, $p = 0.58$). The lack of a significant effect of ITD (0.4 vs 1 ms) is consistent with the similarities in peak dipole moment (Fig. 5C) and cortical lateralization index (Fig. 6A) for these stimuli.

Children with CIs show deficits in nonauditory areas when listening bilaterally

Between-group comparisons indicated lower than normal activity in children with CIs in nonauditory areas. The lack of condition-specific differences in auditory areas likely reflects the

Figure 6. No significant ITD-dependent changes in cortical lateralization were evident in children with bilateral CIs. **A**, Cortical lateralization of P1 activity varied significantly for ITDs leading from opposite hemifields but not from within the same hemifield in children with normal hearing. Cortical lateralization did not vary between hemifields for children with bilateral CIs. $*p < 0.05$. **B**, Cortical lateralization of P1 activity was more right-weighted in left leading (L-lead) and Bil-0 conditions relative to right leading (R-lead) conditions. Lateralization indices in the 0.4 and 1 ms ITD conditions were averaged to represent L-lead and R-lead conditions. Error bars indicate SE. Significant differences in **B** represent change in lateralization indices collapsed across both groups. $^{\dagger}p = 0.05$. **C**, Cortical lateralization slope (computed as the linear rate of change in lateralization between left leading, Bil-0 and right leading ITD conditions) was significantly lower in children with bilateral CIs compared with children with normal hearing.

reduced power of the between-group comparisons and slightly variable locations of peak dipoles within the defined auditory cortex chosen for each condition (Fig. 4) in comparison to repeated-measures analyses of peak dipole moment (Fig. 5). Figure 8 illustrates that decreased activity in children with bilateral CIs occurs in fairly consistent cortical locations across all conditions and both response peaks, suggesting that these deficits

were not specific to conditions with an ITD. Regions of lower activity in children with CIs included the precuneus and cuneus, inferior and middle occipital lobe, inferior parietal lobe, fusiform gyrus, and posterior cingulate gyrus. The inferior and middle occipital gyrus, inferior parietal lobe, fusiform gyrus, cuneus, and precuneus were also identified with significantly reduced activity from normal in bilateral and unilateral conditions in a subset of children in the present cohort (Easwar et al., 2017). One focused region of higher activity in the CI group was evident in the right inferior frontal gyrus during N2 while processing the 1 ms right leading condition, but this included only one voxel and thus was not considered further. In summary, regions in the right hemisphere, associated with spatial hearing, showed deficits in activity in children using bilateral CIs.

Discussion

The present study evaluated cortical representation of ITDs in young normal-hearing children and children with long-term experience using simultaneously implanted bilateral CIs. Our findings are: (1) dominant right cortical activity during bilateral stimulation in both groups, (2) reduction of P1 activity to ipsilaterally leading ITDs and hemispheric asymmetry for weighting contralateral leading ITDs in normal-hearing children, (3) limited cortical ITD sensitivity in children with CIs, and (4) lower than normal activity in nonauditory areas in CI users.

Cortical representation of ITD in young normal-hearing children resembles mature patterns

Dominant right cortical activity in young children with normal hearing (Fig. 4A–C) is consistent with findings in adults for spatially informative stimuli (Palomäki et al., 2002; Brunetti et al., 2005; Johnson and Hautus, 2010). Stronger activity for contralateral leading ITDs (Fig. 5C) also resembles patterns in adults (McEvoy et al., 1993; Palomäki et al., 2005; Johnson and Hautus, 2010) and concurs with the distribution of best ITDs in mammalian brainstem (Hancock et al., 2010, 2013) and cortex (Werner-Reiss and Groh, 2008; Tillein et al., 2010, 2016). Although contralaterally biased responses

are dominant, prevalence of ipsilateral ITD preferring neurons and neurons with complex preference patterns (Werner-Reiss and Groh, 2008; Tillein et al., 2016), along with wide receptive areas of cortical neurons (Middlebrooks et al., 1994; Chadderton et al., 2009), reduce the cumulative contralaterality assessed by imaging (Werner-Reiss and Groh, 2008). Although right domi-

Figure 7. The left auditory cortex uniquely weighs leading ITDs in children with normal hearing. This specialized processing of ITDs is not found in children with CIs. **A**, Computation of normalized weighting (%) for processing ITDs leading from right and left hemifields. Right-lead weighting (right leading/[right leading + left leading] $\times$ 100) and left-lead weighting (left leading/[right leading + left leading] $\times$ 100) (Briley et al., 2013) was computed using peak dipole moment for each hemisphere at the same ITD. **B**, Group mean (black) and individual (gray) lead-side weighting for left and right hemispheres. *Significantly higher right-lead than left-lead weighting for the left hemisphere in normal-hearing children. The tendency for higher left-lead than right-lead weighting for the right hemisphere was nonsignificant in normal-hearing children. No such differences were found in children with bilateral CIs. Data represent weighting indices averaged between 0.4 and 1 ms ITDs leading from the same side. Error bars indicate SE.

nance was also evident during N2, the lack of ITD sensitivity is contradictory to one report in adults measured in an active task (Johnson et al., 2007). It is possible that insensitivity of N2 to ITDs reflects top-down processes that can alter spatial tuning (Lee and Middlebrooks, 2010).

Normal-hearing children also demonstrated a panoramic role of the right hemisphere in ITD processing in contrast to the stronger weighting of the left hemisphere for right leading ITDs (Fig. 7B). This may reflect differences in the balance of neuronal populations tuned to ipsilateral and contralateral leading ITDs in each hemisphere, and supports a 3-channel model consisting of a contralateral channel in each hemisphere and an additional ipsilateral channel in the right hemisphere (Krumbholz et al., 2005, 2007; Magezi and Krumbholz, 2010; Briley et al., 2013; McLaughlin et al., 2016; however, see Salminen et al., 2010). This hemispheric asymmetry is also supported by lesion studies in which right hemispheric lesions cause spatial deficits in both hemifields while left hemispheric lesions lead to deficits restricted to the right hemifield (Zatorre and Penhune, 2001; Spierer et al., 2009).

Cortical processing of ITDs in the normal-hearing children here is consistent with adult-like spatial hearing abilities in 4- to 5-year-olds (Litovsky, 1997; Van Deun et al., 2009). Early development of spatial processing is likely possible due to functional binaural circuits evident at birth. Although monaural response characteristics are immature, adult-like processing of binaural

Figure 8. Between-group differences in cortical activity (peak dipole moment) in all voxels evaluated using unpaired two-sided permutation tests (Bonferroni-corrected; adjusted p value = 0.05/62 recording electrodes = 0.0008). Hotter colors represent higher activity in children with CIs. Cooler colors represent higher activity in children with normal hearing. Children with CIs exhibited lower cortical activity most commonly in right cerebral regions, including cuneus, precuneus, inferior and middle occipital lobe, inferior parietal lobe, and postcingulate cortex during P1/Pc1 and N2.

cues is evident in kitten IC (Blatchley and Brugge, 1990) and auditory cortex (Brugge et al., 1988), likely mediated through matched monaural afferent pathways (Blatchley and Brugge, 1990). Adult-like brainstem interactions for binaural processing are also evident in newborn infants (McPherson et al., 1989; Cone-Wesson et al., 1997). Although delayed and harder to detect, binaural interactions are evident even for ITDs up to 1 ms (Furst et al., 2004). Infant cortical activity is sensitive to spatial cues but lack adult-like contralaterality for lateralized stimuli (Németh et al., 2015). Evidence of adult-like patterns in the present study demonstrates developmental advances molded by hearing experience with age.

Development of cortical ITD processing is impaired in children who are deaf and have limited access to reliable binaural timing cues

Normal-like right cortical dominance during binaural listening in children with CIs (Fig. 5B) indicates that bilateral auditory pathways have been protected from unilaterally driven reorganization (Jiwani et al., 2016). These data reinforce the recommendation for bilateral implantation in children without delay (Gordon et al., 2013, 2015). We cannot speculate on the effects of late but bilateral simultaneous implantation on right hemispheric dominance. However, the lack of contralaterally biased ITD processing (Fig. 5C), reduced change in cortical lateralization with ITD (Fig. 6A,C), and limited asymmetry in hemispheric preference for leading ITDs (Fig. 7B) in current study CI cohort suggest that early symmetrical input is essential but insufficient for normal development of ITD coding. This is true despite controlling for length of hearing experience. Similar cohorts log ~9.5 h of average device use/d (Easwar et al., 2016), making inconsistent use an unlikely contributor. It is also unlikely that stimulus disparities contributed to group differences because normal-hearing children detect ITDs even with limited temporal fine structure cues, simulating CI stimulation (Ehlers et al., 2016). ITD processing deficits therefore reflect early-onset deafness and/or the nature of hearing experience.

Deaf animals show changes in auditory pathways involved in ITD processing, including the following: reduced cochlear nucleus volume (Hardie and Shepherd, 1999); reduced branching and density in endbulbs of Held (Ryugo et al., 1997); lower temporal firing precision in the medial nucleus of trapezoid body (Leao et al., 2004); lower excitatory and inhibitory medial superior olive input (Kandler and Gillespie, 2005; Tirko and Ryugo, 2012); fewer ITD-sensitive IC neurons with limited contralateral bias (Hancock et al., 2010, 2013); and high prevalence of nonresponsive cortical sites with reduced firing rates (Tillein et al., 2010, 2016). Although bilateral CI stimulation can revert function in binaural nuclei (Tirko and Ryugo, 2012), the extent of recovery in humans is unknown. Earlier (relative to late/postlingual deafness) and longer deprivation worsens ITD sensitivity (Litovsky et al., 2010; Hancock et al., 2013), suggesting that early (pre-CI) years of deprivation could contribute to ITD processing deficits in behavioral (Gordon et al., 2014) and cortical measures in children with CIs.

Refinement of binaural networks subcortically is experience- and use-dependent. Guinea pigs reared in omnidirectional noise lack collicular spatial maps (Withington-Wray et al., 1990), and similarly raised gerbils fail selective pruning of inhibitory inputs to medial superior olive (Kapfer et al., 2002). Although simultaneous provision of two CIs provides the best clinical option for developing spatial hearing through symmetrical sensitivity to both hemifields, reliable ITDs may be unavailable with two independently functioning CIs. Each CI convolves the input envelope with a constant-rate pulse train; their independent clocks therefore introduce unintended ITDs unrelated to the fine structure (van Hoesel, 2004). This compromises consistency of ITD cues for reliable use and increases reliance on level cues for spatial hearing in CI users (e.g., Seeber and Fastl, 2008).

Electrical pulses may also impede normal development of ITD processing by evoking higher than acoustically driven neural synchrony (Hartmann et al., 1984), leading to saturation in binaural neurons and, consequently, poorer ITD sensitivity (Colburn et al., 2009; Laback et al., 2015). Lack of frequency-specific cochlear delay may also affect brainstem ITD coding (Colburn et al., 2009). Children with bilateral CIs do not show expected decre-

ases in ipsilateral auditory cortex activity during unilateral stimulation (Easwar et al., 2017), which is consistent with the compressed differences for lateralized stimuli found here. In summary, ITD processing deficits may be due to the effects of deafness, current CI signal processing, and/or nature of electric hearing. The relative contributions of early-onset deafness and electric hearing could be investigated in future studies by comparing ITD processing in early- and late-onset deafness in CI users with matched CI experience.

In light of impaired cortical ITD processing in children using CIs, their improved ITD perception with long-term use (Gordon et al., 2014) could: (1) reflect reliance on alternate consistent cues similar to increased reliance on undistorted monaural spectral cues after unilateral ear plugging in ferrets (King et al., 2000); (2) indicate partial reliance on cortical processing for locating sounds in the correct target hemifield as in cats with bilateral cortical deactivation (Malhotra and Lomber, 2007); and (3) suggest subcortical mechanisms supporting localization as in hemispherectomized patients (Zatorre et al., 1995). Although one or more of these speculations may underlie compensatory mechanisms, significant abnormalities remain (Gordon et al., 2014).

Deficits in binaural processing persist in nonauditory areas in children with CIs

Children with CIs had lower than normal cortical activity mostly in right parieto-occipital regions across all bilateral conditions but similar activity in auditory/temporal areas (Fig. 8), indicating smaller abnormalities in auditory areas in children with CIs. Lower parieto-occipital activity may indicate spatial coding deficits (inferior parietal lobe: Griffiths et al., 1998; Weeks et al., 1999; Brunetti et al., 2005 and extrastriate visual cortex: Poirier et al., 2005; Collignon et al., 2008) and/or sensory integration (precuneus: Cavanna and Trimble, 2006). Because similar deficits were also evident during unilateral listening (Easwar et al., 2017), these results could reflect a generic processing deficit in children with deafness, or differences in default mode networks that entail the posterior cingulate cortex and precuneus (Utevsky et al., 2014). Alternatively, this may reflect visual attention deficits in children with CIs (Quittner et al., 2009) and consequently, differences in visual activity during data collection.

In conclusion, results indicate that (1) adult-like ITD processing is evident in young normal-hearing children with immature sound-evoked cortical activity and (2) early and simultaneous provision of two independently functioning CIs protects bilateral pathways from unilaterally driven reorganization but appears to be insufficient to fully reverse deafness-related deficits and promote normal ITD processing.

Notes

Supplemental material for this article is available at <https://sickkids.box.com/s/x8q6gh1zt1i6m2z0fahgel7xnqjfxm0v>. This material has not been peer reviewed.

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