

Early Unilateral Cochlear Implantation Promotes Mature Cortical Asymmetries in Adolescents Who Are Deaf

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Abstract: Unilateral cochlear implant (CI) stimulation establishes hearing to children who are deaf but compromises bilateral auditory development if a second implant is not provided within ~1.5 years. In this study we asked: 1) What are the cortical consequences of missing this early sensitive period once children reach adolescence? 2) What are the effects of unilateral deprivation on the pathways from the opposite ear? Cortical responses were recorded from 64-cephalic electrodes within the first week of bilateral CI activation in 34 adolescents who had over 10 years of unilateral right CI experience and in 16 normal hearing peers. Cortical activation underlying the evoked peaks was localized to areas of the brain using beamformer imaging. The first CI evoked activity which was more strongly lateralized to the contralateral left hemisphere than normal, with abnormal recruitment of the left prefrontal cortex (involved in cognition/attention), left temporo-parietal-occipital junction (multi-modal integration), and right precuneus (visual processing) region. CI stimulation in the opposite deprived ear evoked atypical cortical responses with abnormally large and widespread dipole activity across the cortex. Thus, using a unilateral CI to hear beyond the period of cortical maturation causes lasting asymmetries in the auditory system, requires recruitment of additional cortical areas to support hearing, and does little to protect the unstimulated pathways from effects of auditory deprivation. The persistence of this reorganization into maturity could signal a closing of a sensitive period for promoting auditory development on the deprived side. *Hum Brain Mapp* 37:135–152, 2016. © 2015 Wiley Periodicals, Inc.

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INTRODUCTION

Cochlear implants (CI) are surgically implanted auditory prostheses which provide hearing to individuals who are deaf. While CIs allow children to develop remarkable oral speech and language abilities, their hearing is significantly poorer than normal because the CI delivers only a crude representation of acoustic sounds and eliminates important cochlear processing. Prior to cochlear implantation, the absence of sound in early life leaves the auditory brain vulnerable to cross-modal recruitment [Bavelier et al., 2006; Bavelier and Neville, 2002; Finney et al., 2001] by the visual [Lomber et al., 2010] and somatosensory systems [Lomber et al., 2010; Meredith and Lomber, 2011]. If hearing is not established during sensitive periods in development, this reorganization will impair hearing with a CI [Lee et al., 2001]. CIs have thus been provided to children within limited durations of bilateral deafness with aims to halt, and perhaps reverse, any such effects of deafness on the brain.

Traditionally, CIs have been provided to children in only one ear, which put them at risk for language delays and educational difficulties [Bess and Tharpe, 1984, 1986; Lieu et al., 2010]. While unilateral stimulation with an implant promotes auditory maturation in the brainstem [Gordon et al., 2013a, 2006; Thai-Van et al., 2007], midbrain [Gordon et al., 2005] and cortex [Jiwani et al., 2013; Ponton and Eggermont, 2001; Sharma et al., 2005] of young children, depriving the opposite pathways of auditory input might leave the auditory system susceptible to deafness-induced reorganization. Although we have already shown that delays of >1.5 years between the first and second implants distort bilateral auditory development [Gordon et al., 2011a, 2013a,b], it is also possible that there is an upper age after which it is too late to re-establish function in the deprived pathways following long term unilateral CI use.

Graham and colleagues suggested that the mid-teenage years could mark the end of a critical period for implanting the non-implanted side in adolescents who used a unilateral CI to hear for most of their lives [Graham and Vickers, 2011; Graham et al., 2009]. Even in younger children, outcomes of bilateral implant decline as the delay between implants increases; speech comprehension in the second implanted ear is poorer [Gordon et al., 2011a; Gordon and Papsin, 2009; Graham and Vickers, 2011; Graham et al., 2009; Illg et al., 2013; Peters et al., 2007] and binaural hearing abilities are reduced [Chadha et al., 2011; Gordon et al., 2011a; Gordon and Papsin, 2009; Grieco-Calub and Litovsky, 2010; Salloum et al., 2010; Van Deun et al., 2009] when the second

implant is delayed. Moreover, the new implant may not be worn consistently in children implanted sequentially [Fitzgerald et al., 2013]. Poor performance of older children receiving a second implant may be attributed to increased dependency on the first and earlier implanted ear for hearing [Kral et al., 2013b], decreased motivation or emotional resistance to change in teenagers [Fitzpatrick and Irannejad, 2008], and/or decreased auditory plasticity with maturation [Lohmann and Kessels, 2014].

Limits in human auditory plasticity can be explored using electrophysiological measures. Unilateral CI stimulation/deprivation exceeding 1.5 years resulted in faster response latencies in the brainstem [Gordon et al., 2012] and abnormally strong activity driven by the first CI to both auditory cortices [Gordon et al., 2013b; Kral et al., 2013b], reflecting a strengthening of the immature auditory pathways from the more experienced implanted right ear. This was consistent with effects of unilateral deafness in an animal model of congenital deafness [Kral et al., 2013b] and might be explained by a disruption in the normal balance of inhibitory-excitatory activity occurring with binaural hearing [Byrne and Byrne, 1993; Grothe et al., 2010; Kotak et al., 2005; Takesian et al., 2009]. Because the cortical changes observed in the children using unilateral CIs occurred over approximately the same time-course of CI-driven brainstem maturation (~1.5 year) [Gordon et al., 2006], there appears to be an important early developmental period for bilateral input in the human auditory system [Gordon et al., 2013b].

Adolescence normally marks the maturation of the auditory cortex [Eggermont, 1988; Jiwani et al., 2013; Moore and Linthicum, 2007; Ponton et al., 2000] and could signal the end of another important developmental period. Much of the brain is maturing during this time. There is a slowing of white matter increase and a sharp decline in gray matter during adolescence [Lebel and Beaulieu, 2011] which likely reflects synaptic elimination [Blakemore, 2012; Giedd et al., 1999; Sowell et al., 2001] as existing connections in the mature brain are refined [Blakemore and Choudhury, 2006; Lohmann and Kessels, 2014] and as each cortical hemisphere becomes specialized [Davidson, 1984; Gotts et al., 2013; Le Grand et al., 2003; Rivera et al., 2005; Toga and Thompson, 2003; Zatorre and Belin, 2001]. Maturation driven by CI stimulation, particularly when only from one ear, could be very different from normal. Some children have been using unilateral CIs for many years and have developed age-appropriate speech and language [Geers et al., 2008; Geers and Sedey, 2011] yet they still face challenges including increased effort/attention needed to hear [Gordon et al., 2013a; Hopyan-Misakyan et al., 2009; Kronenberger et al., 2014; Lee et al., 2007; Pisoni et al., 2010; Powell, 1974; Steel et al., 2015]. Perhaps it is because of these challenges that adolescents using one CI seek a second implant for their long-deprived ear. Whatever the motivation, this unique cohort provides a opportunity to stimulate the deaf ear for the first time and study the effects of long-

Abbreviations

BEM	Boundary element model
CI	Cochlear implant
MNI	Montreal Neurologic Institute;
MRI	Magnetic resonance imaging
PBK	Phonemic Balanced Kindergarten;
SD	Standard deviations

term unilateral implant stimulation in the adolescent brain, both in the experienced and deprived pathways.

In this study, we explored the underlying consequences of driving auditory maturation in the brainstem and cortex with CI stimulation from one ear. We hypothesized that maturation of the auditory cortex with over a decade of unilateral CI use drives lasting asymmetries in the auditory system but does not protect the opposite pathways from deprivation. Results supported these hypotheses suggesting that establishing binaural hearing may be challenging after unilaterally driven maturation of the auditory cortex.

MATERIALS AND METHODS

Participants

Thirty-four adolescents who received one CI in their right ear by 3.2 ± 1.3 years of age after a limited period of bilateral auditory deprivation (1.8 ± 1.3 years) participated in this study. They had 12.4 ± 1.7 years of unilateral CI experience at the time of the test. All were successful implant users and had never received auditory stimulation in their opposite ear. Twenty-one of these adolescents later received a second implant in their opposite-left ear after 12.0 ± 2.1 years of unilateral deprivation on that side. Age at implantation on this second implanted side was 15.9 ± 2.0 years. Responses were recorded from the 21 bilateral CI recipients on the first day of activation of the second implant to study the long-term cortical effects of single-sided deafness on the deprived pathways in the mature auditory system. Etiology of deafness varied. All adolescents were implanted with a Cochlear Nucleus device from Cochlear Corporation Limited in both ears. All but two adolescents were right handed. Cortical responses evoked in CI users were compared with the same responses recorded from 16 adolescents with normal hearing (six boys: 10 girls) who were 15.9 ± 6.4 years and matched for chronological age and duration of hearing experience. All but three adolescents with normal hearing were right handed.

Recording Cortical Responses

Cortical responses were evoked by each ear/implant separately using 62-cephalic electrodes and referenced to the right earlobe. In the CI group, responses were generated using biphasic electrical pulse trains of 250 pulses per second, lasting 36 ms and delivered by a single electrode (# 20) at the apex of the electrode array. These electrical pulse trains were presented at a rate of 1 Hz. Current levels were determined for each CI as in previous studies [e.g. Gordon et al., 2013b] by recording auditory brainstem responses at increasing intensities from the experienced and newly implanted sides separately. Brainstem responses were evoked by single biphasic pulses from electrode # 20 presented at 11 pulses per second and recorded using a

NeuroScan-4.3 system with a Synamps-II amplifier from a mid-line cephalic electrode referenced to the ipsilateral earlobe and filtered from 10 to 3000 Hz. Sweeps of $\pm 30\text{--}40 \mu\text{V}$ were rejected from the average. Current levels were increased within a comfortable range of intensities for the participant. The maximum levels at which wave eV amplitudes on each side were equal were used to evoke cortical responses. Levels measured with single pulses were reduced by 10 Current Units on each side so that pulse train stimulation would not exceed tolerance levels.

Cortical responses were evoked by 500 Hz tone-bursts in children with normal hearing. This stimulus was chosen because this frequency was allocated to the same apical electrode (# 20) of the CI device used to evoke responses in all CI participants. The same stimulus duration (36 ms) and rate of presentation (1 Hz) was used as in the CI users. The tone was enveloped with a Tukey window over the first and last eighths to minimize effects of high frequency onset and offset. Tone-bursts were delivered at 40 dB above behavioural threshold and presented to the right and left ears separately using ER3-14A insert earphones. Responses for all participants were recorded using the NeuroScan-4.3 system with a Synamps-II amplifier. They were sampled at a rate of 1,000 Hz and an online band-pass filter between 0.15 to 100 Hz was applied. A minimum of 400 sweeps with at least two visually replicable cortical responses were obtained. Epochs which were greater than $\pm 100 \mu\text{V}$ between the 100 and 800 ms latencies were rejected.

Localization of Cortical Evoked Peaks

The Time Restricted, Artefact and Coherence Source suppression (TRACS) linearly constrained minimum variance beamformer (adaptive spatial filter) [Wong and Gordon, 2009] was used to localize dipole activity underlying the evoked peaks in the cortex in response to stimulation from the experienced and naïve CIs, and right and left ears in normal hearing peers. Neuroanatomical data is unavailable for adolescents with long-term CI experience because the internal portion of the CI device contains a magnet that renders it incompatible with magnetic resonance imaging (MRI). Dipole activity was thus reconstructed for each adolescent using age-appropriate head model templates derived from the Montreal Neurologic Institute (MNI) MRI library. The Template-O-Matic toolbox was used to generate the age-specific template head models and account for physiological changes occurring with maturation [Wilke et al., 2008]. Because all the participants in this study were adolescents, the same template head model was used.

A three-layer boundary element model (BEM) mesh was constructed using the derived age-appropriate head model templates. This was used to represent age-appropriate head geometry and tissue conductivities of the brain, meninges, skull and scalp to account for spatial smearing

TABLE I. Measures of response peaks at C_z electrode

	P_1 (Mean \pm SD)	$N_1/N_{(ci)}$ (Mean \pm SD)	$P_2/P_{(ci)}$ (Mean \pm SD)
<i>Latency (ms)</i>			
Normal hearing right	78.87 \pm 9.20	108.83 \pm 9.53	164.22 \pm 17.94
Normal hearing Left	77.63 \pm 4.46	111.64 \pm 7.16	163.87 \pm 19.19
Experienced-right CI	79.59 \pm 6.22	105.43 \pm 9.57	162.20 \pm 18.24
Naïve-left CI	–	114.10 \pm 8.34	184.58 \pm 19.01
<i>Amplitude (μV)</i>			
Normal hearing right	0.92 \pm 1.46	–1.56 \pm 1.72	2.83 \pm 1.96
Normal hearing left	1.06 \pm 1.41	–2.27 \pm 1.95	2.61 \pm 1.73
Experienced-right CI	0.63 \pm 2.92	–1.92 \pm 3.18	5.30 \pm 3.61
Naïve-left CI	–	–12.27 \pm 5.94	8.77 \pm 5.86

of electric potentials at the surface of the head. A thin plate spline warp method [Darvas et al., 2006] was used to warp the 3-layered triangular BEM mesh to the template MRI image of the human head and match the 3-dimensional coordinates of the generic human scalp to the 10–20 electrode coordinate system used in the study [Acar and Makeig, 2013; Darvas et al., 2006]. The BEM model assumes that the head is a sphere of evenly distributed spaces (voxels) of $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$ (3 mm^3).

Source activity in the left hemisphere was assessed using region suppression of activity in the right hemisphere, and vice versa, as bilaterally correlated activity is known to pose a particular problem for source localization in auditory cortices [Dalal et al., 2006]. In adolescents using CIs, a time restricted artefact suppression algorithm was applied to suppress the implant-generated electrical artefact, corresponding to the four largest singular vector values over the -80 to 10 ms latency range. This ensures that singular vectors representing up to 97% of the CI artefact are suppressed while maintaining responses beyond the stimulus [Wong and Gordon, 2009].

Peaks in the cortical response were visually identified at latencies corresponding to those previously reported from normal hearing peers and CI users [Gordon et al., 2008; Jiwani et al., 2013]. Peak latencies and amplitudes recorded at C_z were marked for responses evoked by stimulation of the right and left ears in the normal hearing group and the experienced-right and naïve-left sides in the CI group (i.e., P_1 , N_1 and P_2 for normal hearing responses and experienced CI stimulation; and $N_{(ci)}$ and $P_{(ci)}$ for responses evoked by stimulation of the naïve CI). Mean \pm standard deviations (SD) are shown in Table I for each group.

Covariance was estimated over latency windows encompassing each peak of the cortical response for each individual [Van Veen et al., 1997]. A pseudo-Z statistic was calculated relative to baseline activity in the pre-stimulus interval (-200 to -80 ms) to normalize the signal-to-noise ratio of each voxel. Once sources were localized using this lead normalization process, the strength of source activity, measured in dipole moments (nAm), was computed for the peaks of the cortical waveform. A one-tailed omnibus-noise T-test [Pettersson et al., 1999] was used to calculate a statisti-

cal threshold pseudo-Z value ($P \leq 0.0005$) reflecting baseline brain activity. Only voxels with pseudo-Z activity greater than this omnibus value were accepted and used in the analyses. Figure 1 provides an example of a response recorded from an adolescent with long-term CI experience (Fig. 1A) with corresponding head topographies of potential distribution (Fig. 1B) and the activity underlying the mature peaks (P_1 , N_1 and P_2) in 63,646 brain voxels (Fig. 1C). Source locations of the voxels with the strongest signal to noise ratio (pseudo-Z value) in the red hotspots (in each temporal lobe) are marked in by the green cross hairs in the left and right hemispheres separately. The waveforms show the corresponding virtual channels of the marked voxel. As shown, the CI artefact has been suppressed leaving the peak dipole in the latency range of the P_1 , N_1 or P_2 peak.

Analyses of Dipole Activity

Dipole activity was visualized topographically on age-appropriate MNI head model templates by plotting pseudo-Z values in the 63,646 three-dimensional voxels in brain space from highest (top) to lowest (bottom). It should be noted that significant dipole activity can exist in underlying layers. Mean beamformer brain images were created to assess areas of cortical activity which were consistently evoked by sound for each ear/implant. The dipole peak from the voxel with the strongest pseudo-Z within the left and right auditory areas were measured from each participant. The location of the auditory cortex were identified within MNI coordinates ($X = < -55$, $Y = > -35$ to < -5 , $Z = > -10$ to < 20) mm in the left hemisphere and ($X = > 55$, $Y = > -35$ to < -5 , $Z = > -10$ to < 20) mm in the right hemisphere in both the normal hearing and the CI group, consistent with other reports [Wong and Gordon, 2009; Gordon, Wong et al., 2010; Gordon, Wong et al., 2013b]. Two-sided paired permutation tests were used to compare voxel-by-voxel dipole activity in 2,048 permutations [Blair and Karniski, 1993; Chau et al., 2004] to assess differences between the left and right hemispheres and permutation tests were also used to assess significant differences in activity for each voxel-pair between each group. Although permutation tests provide strong control for family-wise-error rates [Groppe et al., 2011], further corrections were applied to account for the 62 recording channels used (Bonferroni correction $P = 0.05/62 = 0.0008$).

Repeated measures ANOVA with Bonferroni corrections were used to identify differences in peak dipole moment and latencies between activity evoked in each auditory cortex and in each group. These analyses were based on voxels with the strongest dipoles in the left and right auditory cortices for each cortical wavepeak in each individual. Percent cortical lateralization [(right hemisphere dipole – left hemisphere dipole)/(right hemisphere dipole + left hemisphere dipole) $\times 100$] were calculated from these extracted peak dipoles.

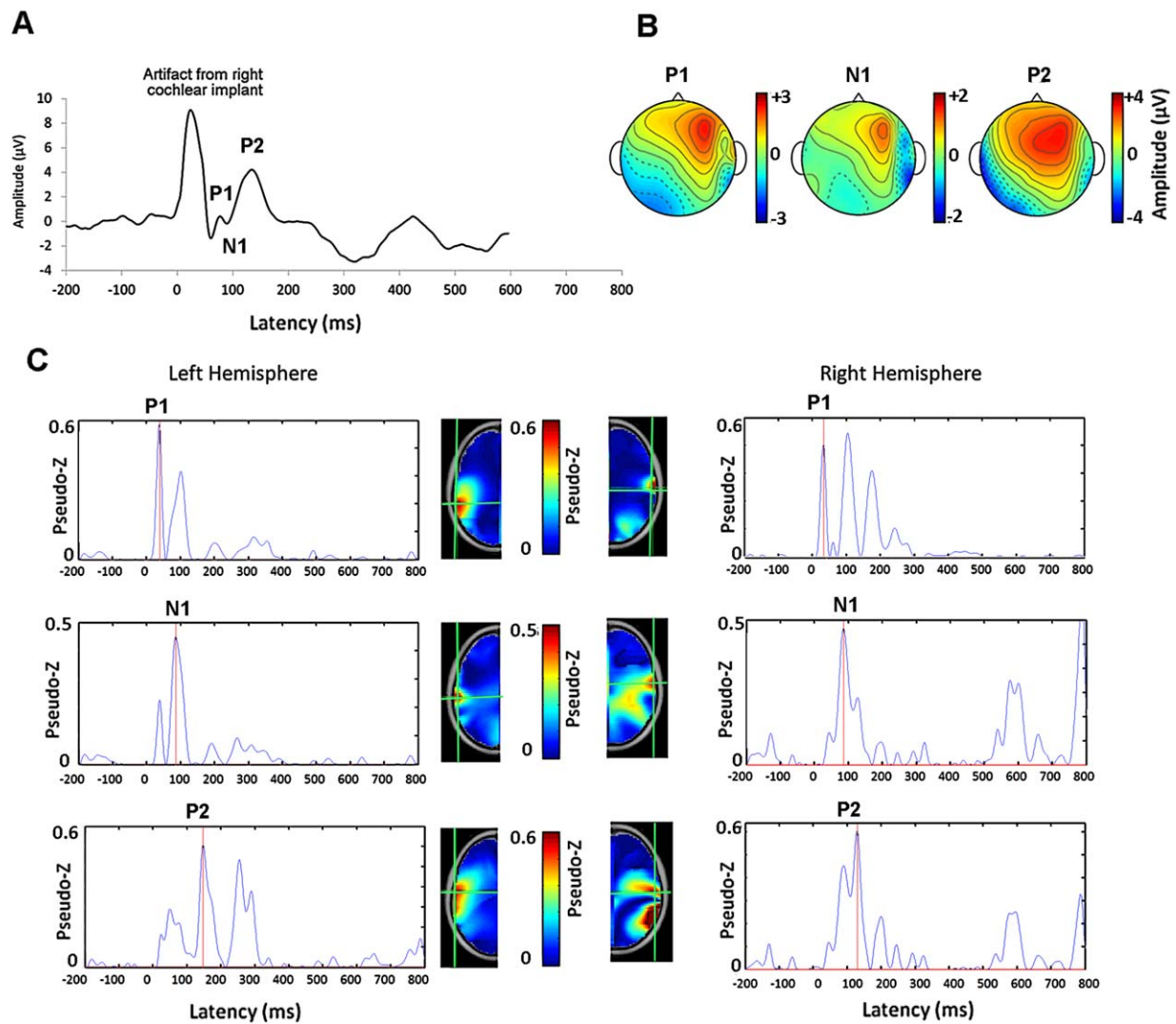


Figure 1.

A. Example of a cortical evoked waveform at C_z recorded from one adolescent with 15.95 years of CI experience in the right ear indicates a mature response with peaks P_1 , N_1 and P_2 . The electrical artifact from the right CI preceding this response is clear. **B.** Head topographies of potential distribution for each peak (common averaged reference) of the mature cortical response are shown. **C.** The activity underlying the mature peaks in 63,646 brain voxels are shown relative to the noise floor using the pseudo-Z. The virtual channel waveforms corresponding to the voxel with the strongest activity (red hotspots)

are shown for the left and right hemispheres for each peak. Source locations are marked by the green cross hairs on the axial view of the age-appropriate topographic head model derived from the MNI MRI Library. The virtual channel data reveals that the CI artifact has been suppressed in early latencies by the beamforming procedure and that the strongest dipole underlying each peak of the mature response occurs in areas of the left and right auditory cortices, in line with the latency of the cortical wave peaks.

Speech Perception Tests to Assess Outcomes with CIs

Functional outcomes with CIs were assessed using the age-appropriate Phonemic Balanced Kindergarten (PBK) monosyllabic words open-set speech perception test. This

test assesses speech recognition abilities using a list of twenty-five words. Words were presented at 0-degree azimuth in a double-walled sound-proof booth, through a GSI-61 Grason-Stadler audiometer, using monitored-live voice at 65 dB sound pressure level. Words were presented

in quiet to the first and second implants separately and scored as a percentage of words repeated correctly. Given the focus on effects of unilateral stimulation/deprivation, testing occurred at initial stages of bilateral CI use (8.0 ± 2.1 months (range: 5.8–15.0 months). This was considered appropriate relative to the long duration of bilateral implant use required for binaural hearing to emerge even in children implanted at younger ages [Gordon et al., 2014]. Pearson correlations were used to assess associations between speech perception scores, duration of bilateral CI use, dipole moment and cortical lateralization.

RESULTS

Tone-Bursts Preferentially Stimulate the Right Auditory Cortex in Adolescents With Normal Hearing

Cortical responses recorded at a midline-cephalic location (C_z) with corresponding head topographies of potential distribution are shown in Figure 2A for the normal hearing group. Cortical responses with peaks P_1 , N_1 and P_2 , characteristic of the mature response were recorded in adolescents with normal hearing [Albrecht et al., 2000; Ponton et al., 2000; Wunderlich et al., 2006] when either the right ($n = 13$) or left ears ($n = 12$) were stimulated by 500 Hz tone-bursts. The mean latencies and amplitudes for all the recorded responses appear in Table I. The responses were similarly distributed over the scalp between the right and left ears. However, dipole moments underlying the mature cortical peaks were stronger in the right hemisphere. This is shown by the dark red hotspots in the right hemisphere mean brain plots of Figure 2B (axial view only) and by the larger right (red bars) than left cortex (blue bars) peak dipole magnitudes in Figure 2C. Dipoles in auditory cortex showed effects of side of stimulation [$F_{(1,10)} = 5.976$, $P = 0.035$], hemisphere [$F_{(1,10)} = 8.018$, $P = 0.015$] and an interaction of these factors [$F_{(1,10)} = 10.308$, $P = 0.009$] but no differences between the different cortical peaks [$F_{(2,20)} = 8.018$, $P > 0.05$]. This means that as mature cortical responses emerge, the right hemisphere preferentially responds to tone-bursts, particularly when they are presented to the left ear.

Long Periods of Unilateral CI Use Drive Abnormal Patterns of Auditory Activity

Auditory stimulation with a CI for over 10 years appears to promote normal-like maturation of cortical responses. The cortical waveform from electrode C_z , shown in Figure 3A sometimes contained stimulus artefact in early latencies from the short 36 ms CI pulse train. Because the stimulus was short, a polyphasic response was seen thereafter consisting of peaks with similar latencies to the normal hearing group (P_1 : $t_{(10)} = -0.88$, $P > 0.05$; N_1 : $t_{(10,18)} = -1.3$, $P > 0.05$; P_2 : $t_{(10,77)} = 1.43$, $P > 0.05$) and similar peak-to-peak amplitudes for the P_1 - N_1 complex [$t_{(6,87)} = 1.75$, $P > 0.05$]. None-

theless, differences from normal remained. The amplitude of peak P_2 was significantly larger in CI users [$t_{(14,51)} = 2.49$, $P < 0.05$]. In the topological maps, a peripheral negativity corresponding to the implant on either side was seen and the current distribution of the N_1 revealed little clear negativity across the scalp (Fig. 3A). Furthermore, even though cortical activity evoked by the experienced CI was generated predominantly in areas of the temporal cortex, the auditory input in these adolescents activated the left and right auditory cortices differently from their normal hearing peers. Following artifact suppression and source localization with the TRACS beamformer, measured dipole activity underlying the mature cortical response was stronger in the left as compared to the right auditory cortex, as shown by the red hotspots in the brain images in Figure 3B (axial view only) and the extracted peak dipoles plotted in Figure 3C [$F_{(2,24)} = 10.978$, $P < 0.001$; post hoc: P_1 : $t_{(26)} = 2.4$, $P < 0.05$, P_2 : $t_{(26)} = 3.9$, $P < 0.01$]. This reflects cortical activation in an opposite direction compared to the rightward hemispheric bias shown in Figure 2. There were no significant differences in these dipoles from normal across or within each of the three peaks [$F_{(2,40)} = 1.016$, $P > 0.05$].

Activity evoked by stimulation of the naïve pathways on the first day of activation of that left side was significantly different from the experienced side. As shown in Figure 3D, the morphology of these cortical waveforms was atypical and different from the response evoked by the experienced ear. At electrode C_z , the waveforms were characterized by a large negative amplitude peak, labeled $N_{(ci)}$, followed by a large positive peak [$P_{(ci)}$]. While the latency of these peaks were similar to that of N_1 and P_2 of the experienced side [$N_{(ci)}/N_1$: $t_{(11)} = 1.85$, $P > 0.05$; $P_{(ci)}/P_2$: $t_{(11)} = 2.71$, $P > 0.05$], the absolute amplitudes [$N_{(ci)}/N_1$: $t_{(11)} = 3.45$, $P < 0.01$; $P_{(ci)}/P_2$: $t_{(11)} = 3.31$, $P < 0.01$], and peak-to-peak amplitudes [$N_{(ci)} - P_{(ci)}/N_1 - P_2$: $t_{(11)} = -3.37$, $P < 0.01$] were significantly larger than responses from the experienced and normal hearing ears [$F_{(3,70)} = 5.4$, $P < 0.05$]. Dipole activity was more widespread and symmetric across both auditory cortices [$N_{(ci)}$: $t_{(20)} = -0.56$, $P > 0.05$; $P_{(ci)}$: $t_{(20)} = 1.6$, $P > 0.05$] as shown in the brain plots in Figure 3E (axial view only). Dipole moments for both peaks were abnormally large in both hemispheres compared to the experienced side [$F_{(1,42)} = 29.589$, $P < 0.01$] and both the right and left normal hearing ears [$F_{(2,39)} = 20.582$, $P < 0.01$] (Figure 3F).

Normalized lateralization values of the peak dipoles indicated that, while tonal stimuli lateralized to the right auditory cortex regardless of ear of stimulation in adolescents with normal hearing, long-term right CI use promoted leftward lateralization in adolescents (Fig. 4). Despite developing mature-like cortical responses with over a decade of CI experience, significantly strong left hemisphere lateralization was found for all peaks recorded in CI users [P_1 : $t_{(10)} = -2.460$, $P = 0.034$, N_1 : $t_{(14)} = -2.260$, $P = 0.04$, P_2 : $t_{(15)} = -6.912$, $P < 0.001$]. This pattern was significantly different from the responses of either ear in normal hearing peers [$F_{(4,92)} = 3.286$, $P = 0.015$, post-hoc: right stimulation:

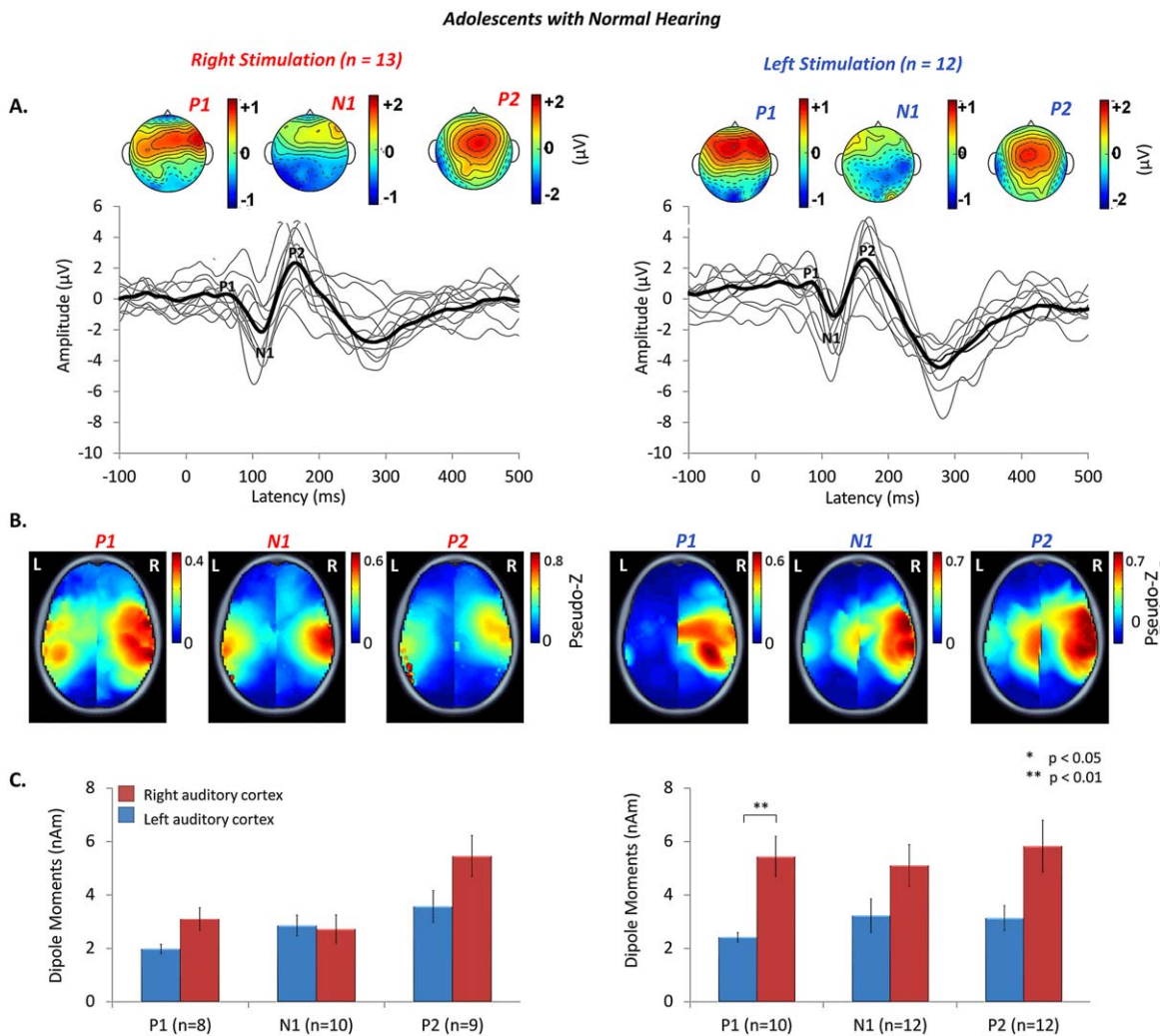


Figure 2.

A. Auditory evoked cortical responses were stimulated from the right ($n = 13$) and left ($n = 12$) ears of adolescents with normal hearing, aged 15.9 ± 6.4 years. Individual responses from a midline cephalic electrode (C_z) (thin grey lines), and grand mean responses (thick black lines) show three peaks (P_1 , N_1 , P_2), characteristic of mature responses. Topographic maps indicate similarly distributed scalp potentials (red = positive potentials, blue = negative potentials) for the mature peaks in both ears

P_1 : $P = 0.03$, P_2 : $P = 0.003$; left stimulation: P_1 : $P = 0.002$, N_1 : $P = 0.001$, P_2 : $P < 0.001$. Dipole activity evoked by stimulation in the newly implanted ear was more symmetrical as shown by a reduction in lateralization for peaks $N_{(ci)}$ and $P_{(ci)}$ [$N_{(ci)}$: $t_{(15)} = -0.726$, $P = 0.479$ $P_{(ci)}$ = 2.238: $t_{(12)}$, $P = 0.816$]. This was significantly different from the right lateralized responses stimulated by tones in normal left ears [$F_{(1,7)} = 6.674$, $P = 0.036$, post-hoc: N_1 : $P = 0.03$, P_2 : $P = 0.006$].

Permutation analyses were used to identify significant differences in activity between left and right auditory cor-

(common averaged reference). **B.** Mean peak dipole activity reveals stronger activity, shown by hotspots of dark red, in the right hemisphere, particularly for left ear stimulation. **C.** Mean [± 1 standard error (SE)] dipole moment strength is plotted for the left (blue bars) and right (red bars) auditory cortices for all cortical peaks. Consistent with the topographic plots in **B.** peak dipole activity is stronger in the right than left auditory cortex for stimulation of both ears, particularly for left ear stimulation.

tices in the normal hearing and CI groups. Unlike the peak dipole measures, which were specific to defined auditory areas, these analyses assessed whether every voxel in one hemisphere was significantly different from its corresponding voxel in the opposite hemisphere. This analysis revealed significant differences in activation between left and right temporo-frontal and temporo-parietal regions in both groups with unique patterns in the CI users relative to their normal hearing peers (Fig. 5A–D) (axial views only). Minimal differences in activity between

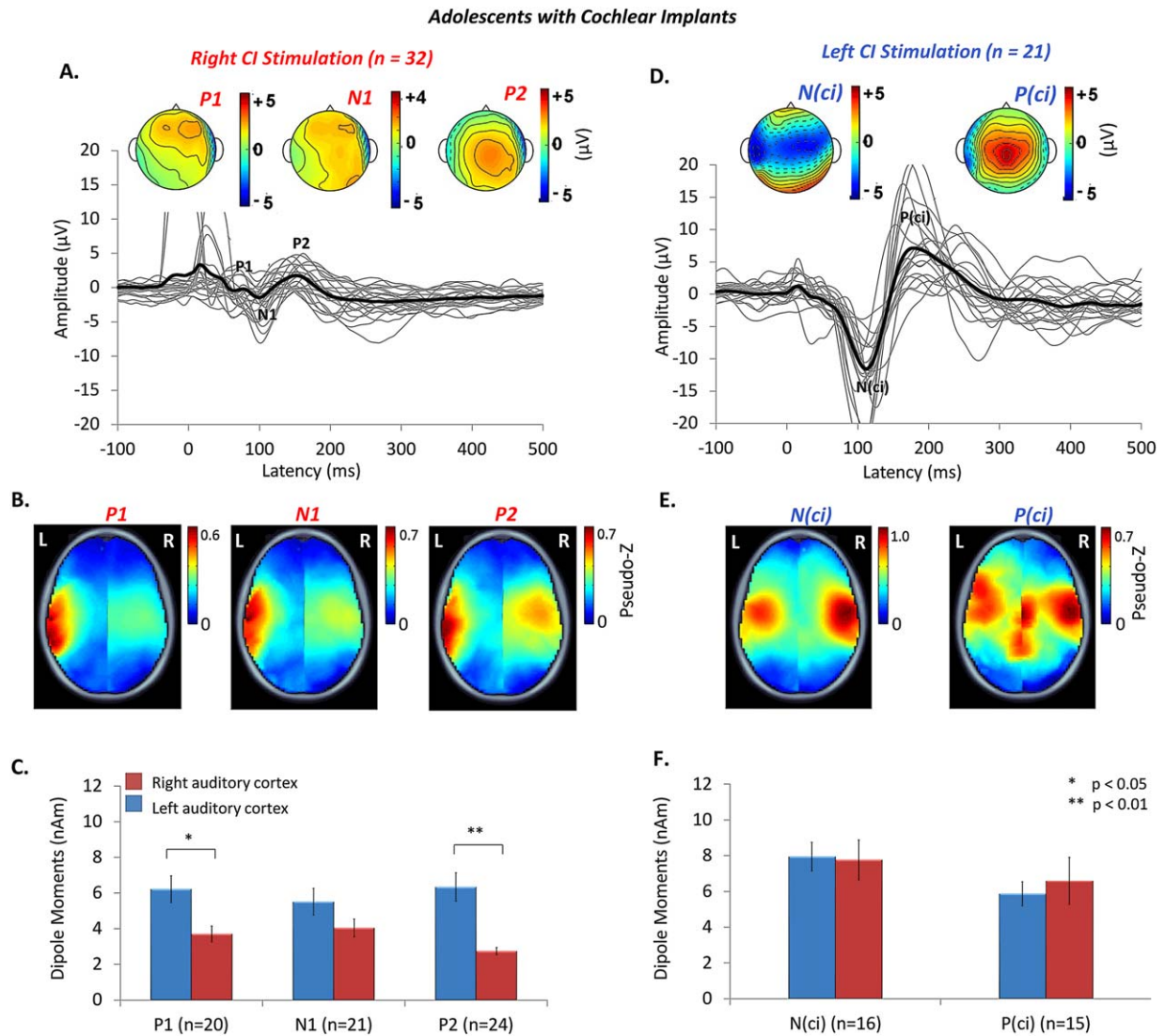


Figure 3.

Auditory evoked cortical responses were stimulated from the experienced-right ($n = 32$) and naïve-left ($n = 21$) ears of adolescents with CIs, aged 15.9 ± 2.0 years. Cortical activity evoked by stimulation of the right ear after 12.4 ± 1.7 years of unilateral CI experience is shown in **A**. – **C**. Left ear had 12.0 ± 2.1 years of unilateral deprivation. Responses recorded within the first week of CI activation on that side are shown in **D**. – **F**. Individual responses from a midline cephalic electrode (C_z) (thin grey lines), and grand mean responses (thick black lines) show three peaks (P_1 , N_1 , P_2), characteristic of mature responses, evoked by stimulation of the experienced-right CI in **A**., but an abnormal biphasic peaked response [$N_{(ci)}$, $P_{(ci)}$] of abnormally large amplitudes was evoked by the naïve-left side ($n = 21$), shown in **D**. Topographic maps (common averaged reference) indicate unusually similarly distributed scalp potentials for the three peaks of the mature response on the experienced side but a clearly

opposite distribution for $N_{(ci)}$ (widely negative) than $P_{(ci)}$ (widely positive) from the naïve-left side. **B**. A strong contralateral bias in the left hemisphere, shown by hotspots of dark red in the mean peak dipole activity plots, occurs with stimulation of the experienced-right CI. By contrast, dipole activity evoked by stimulation of the naïve-left ear in **E**. is symmetrically distributed in both hemispheres and is stronger compared to right ear dipoles for both peaks of the response. **C**. Mean (± 1 SE) dipole moment strength is plotted for the left (blue bars) and right (red bars) auditory cortices for all cortical peaks on the experienced side. Consistent with the topographic plots in **B**., peak dipole activity is significantly stronger in the left than right auditory cortex for the mature peaks P_1 ($P < 0.05$) and P_2 ($P < 0.01$). **F**. The same responses are plotted for the naïve side and shows dipole activity consistent with the data in **E**.

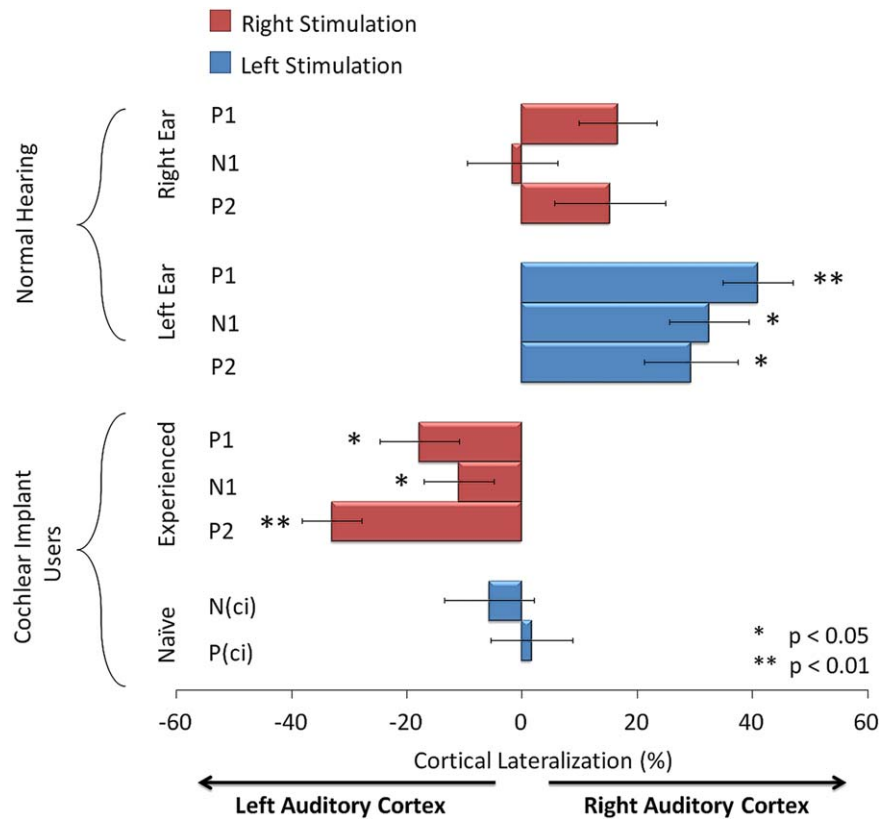


Figure 4.

Mean (\pm 1 SE) percent cortical lateralization of peak dipoles was calculated using the formula: [(right hemisphere peak dipole moment – left hemisphere peak dipole moment)/(right hemisphere peak dipole moment + left hemisphere peak dipole moment) \times

100]. Red bars indicate dipoles evoked from stimulation of the right ear/experienced CI and blue bars indicate activity from the left ear/naïve CI. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the cortical hemispheres were evident when tone-bursts were presented to normal right ears using this analysis (Fig. 5A). Significant differences were clearer in the auditory cortices as well as temporo-frontal and temporo-parietal regions for normal left ear stimulation (Fig. 5B). These differences were larger in the right (contralateral) than left cortical hemisphere. The CI group also showed strong contralateral temporo-parietal activation from both ears underlying all response peaks (Fig. 5C). The ipsilateral temporo-parietal junction was strongly activated in the later latency ranges (i.e. P_2 for right experienced ear stimulation and $P_{(ci)}$ for naïve left stimulation) (Fig. 5C).

Additional Cortical Areas Are Recruited by Cochlear Implant Stimulation Relative to Normal

We hypothesized that long-term unilateral CI use would drive abnormal underlying cortical activity in the stimulated pathways compared to normal and

leave the opposite deprived pathways vulnerable to significant change. To test this hypothesis, we compared dipoles in all 63,646 voxels between CI and normal hearing groups using permutation analyses. As shown in Figure 6A (axial view only), significantly larger dipoles were identified in the left frontal cortex underlying peak P_1 , in a small left parietal area underlying N_1 , and the right precuneus region underlying peak P_2 for the experienced CI side compared to responses from the right ear in the normal hearing group. This indicates that CI users recruit additional cortical areas to process sound. At the same time, depriving auditory input on the opposite side for over a decade led to significantly different activation in those pathways relative to responses from the normal hearing left ear. Dipole activity in the naïve-left ear was significantly larger across most of the cortex, particularly for peak $N_{(ci)}$, compared to normal left ear evoked activity (Fig. 6B) (axial view only). This might indicate aberrant cortical organization as a result of long-term deafness, in line with our hypothesis.

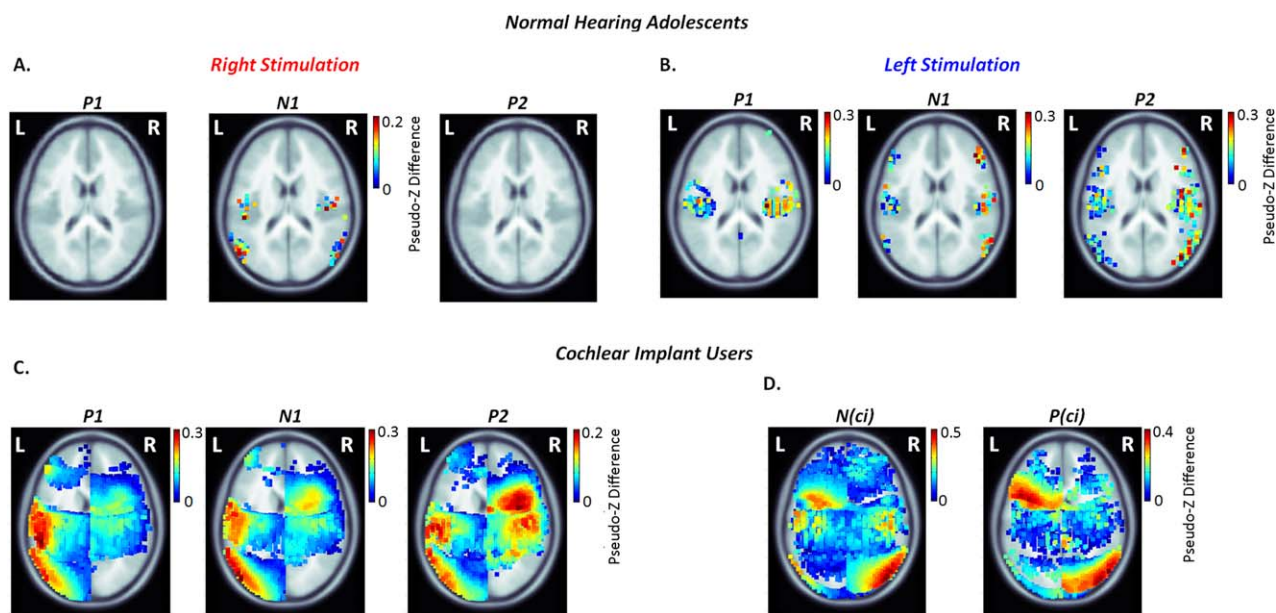


Figure 5.

Cortical lateralization for each peak of the cortical waveform was assessed across 63,646 peak dipoles using permutation testing to compare activation of the left and right hemispheres. Significant absolute differences in dipole for right – left hemisphere (voxel-wise permutation, $P < 0.05$, corrected for 62 recording channels; Bonferroni correction $P = 0.05/62 = 0.0008$) are plotted on topographic plots for stimulation of the right ear in **A.** and the left ear in **B.** for adolescents with normal hearing; and the right-experienced CI in **C.** and naïve-left side in **D.** in the implant cohort. Auditory activity lateralized towards the right hemisphere in normal hearing individuals, particularly in response to left ear stimulation, as shown by the dark red hot-

spots indicating greater inter-hemispheric dipole differences. A significant shift in lateralization towards the contralateral left auditory cortex was observed in CI users with stimulation of the experienced-right side. Cortical asymmetries towards the auditory cortices in either hemisphere were not clear when stimulated from the naïve side. Lateralization of secondary sources in the left temporo-parietal junction and right temporo-frontal cortex was present for the experienced-right side, with stronger activity underlying P_2 . This activity was reversed on the naïve-left side and occurred with increased dipole strength in the right parietal-temporal-occipital association areas and left temporo-frontal cortex.

Abnormal Activity Evoked by the Naïve Side Predicts Poor Speech Perception Outcomes

We asked whether there was a relationship between cortical activity in CI users and their speech perception once they had used their bilateral CIs for at least 6 months. As shown in Figure 7A, speech perception performance with the experienced CI was high, with a mean ± 1 standard error score of $77.54 \pm 2.88\%$. By contrast, this was significantly worse ($14 \pm 4.92\%$) when adolescents listened with their newly implanted ear alone ($t_{(17)} = 5.70$, $P < 0.01$). All but 2 adolescents achieved less than 50% accuracy. There was no significant correlation between speech scores and duration of bilateral experience with either the experienced ($R = -0.12$, $P = 0.65$) or the newly implanted ear ($R = 0.44$, $P = 0.08$). An analysis of speech perception and dipole activity between both ears indicated a significant correlation between speech perception outcomes and left hemisphere lateralization for peak P_2 ($R = -0.55$, $P = 0.02$) (Fig. 7B). We hypothesized that this

relationship reflects a supportive role of increased activity in the contralateral pathways towards the left cortex for speech perception, rather than reduced activity in the right auditory cortex. In support, a significant positive correlation between dipole strength and speech perception scores was found in the left auditory cortex (P_1 : $R = 0.48$, $P = 0.05$, N_1 : $R = 0.51$, $P = 0.03$, P_2 : $R = 0.53$, $P = 0.02$) but not the right (P_1 : $R = -0.14$, $P = 0.62$, N_1 : $R = 0.43$, $P = 0.06$, P_2 : $R = 0.03$, $P = 0.92$) for the experienced-right CI. No significant correlations with speech outcomes were found for cortical activity evoked by the naïve CI. Further analyses confirmed that as the asymmetry in speech perception increased (better speech perception in the first implanted ear), the greater the asymmetry in left P_2 dipoles (larger left hemisphere dipoles when evoked by the first than second implanted ear) ($R = 0.70$, $P = 0.004$) and, consistently, the leftward cortical lateralization of P_2 increased (more leftward lateralization when stimulated by the first than second implant) ($R = 0.56$, $P < 0.03$). No other significant correlations were found ($P > 0.05$).

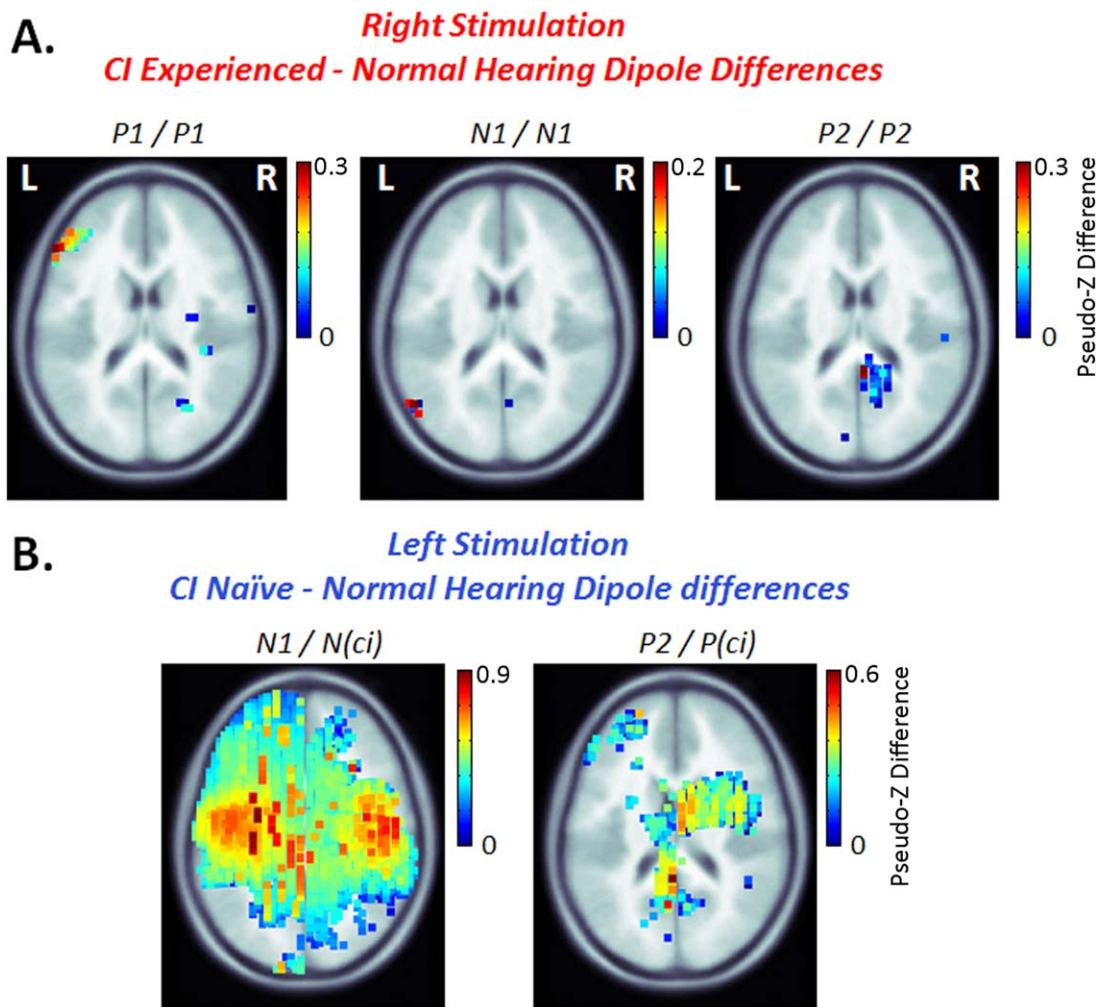


Figure 6.

Permutation analyses were used to compare dipole activation between the group of CI users and the group of normal hearing peers. Significant absolute dipole differences between the two groups (voxel-wise permutation, $P < 0.05$, corrected for 62 recording channels; Bonferroni correction $P = 0.05/62 = 0.0008$) are shown on topographic brain plots for experienced-right CI – normal hearing right ear stimulation in **A.**, and naïve-left CI – normal hearing left ear stimulation in **B.** Dipole magnitudes underlying the mature cortical peaks were generally similar

between adolescents with normal hearing and experienced CI users, but CI stimulation of the experienced side activated cortical regions in the left frontal cortex underlying peak P_1 , a small left parietal area underlying N_1 , and the right precuneus regions underlying P_2 which were not present in normal hearing peers, as shown by the dark red hotspots in **A.** By contrast, the naïve ear evoked abnormally large and diffuse cortical activity across the brain, with significantly stronger dipole activity compared to the left ear of the normal hearing cohort.

DISCUSSION

Data from this study suggest that hemispheric specialization to tone-bursts in the right auditory hemisphere emerges with normal maturation of the auditory cortex. By contrast, adolescents who had over a decade of unilateral CI experience in the right ear developed cortical responses from the experienced ear which lateralized to the contralateral left auditory cortex despite developing mature normal-like cortical peaks. Increased response in the left auditory

cortex reflects abnormal strengthening from the unilaterally stimulated pathways and may support speech perception in CI users. On the other hand, bilateral cortical activation from the naïve-left ear at initial stimulation coupled with poorer speech understanding in that newly implanted ear could reflect undefined and perhaps compromised auditory processing. Evidence of alternate auditory processing was supported by the stimulation of additional cortical areas in adolescents using CIs relative to their normal hearing peers,

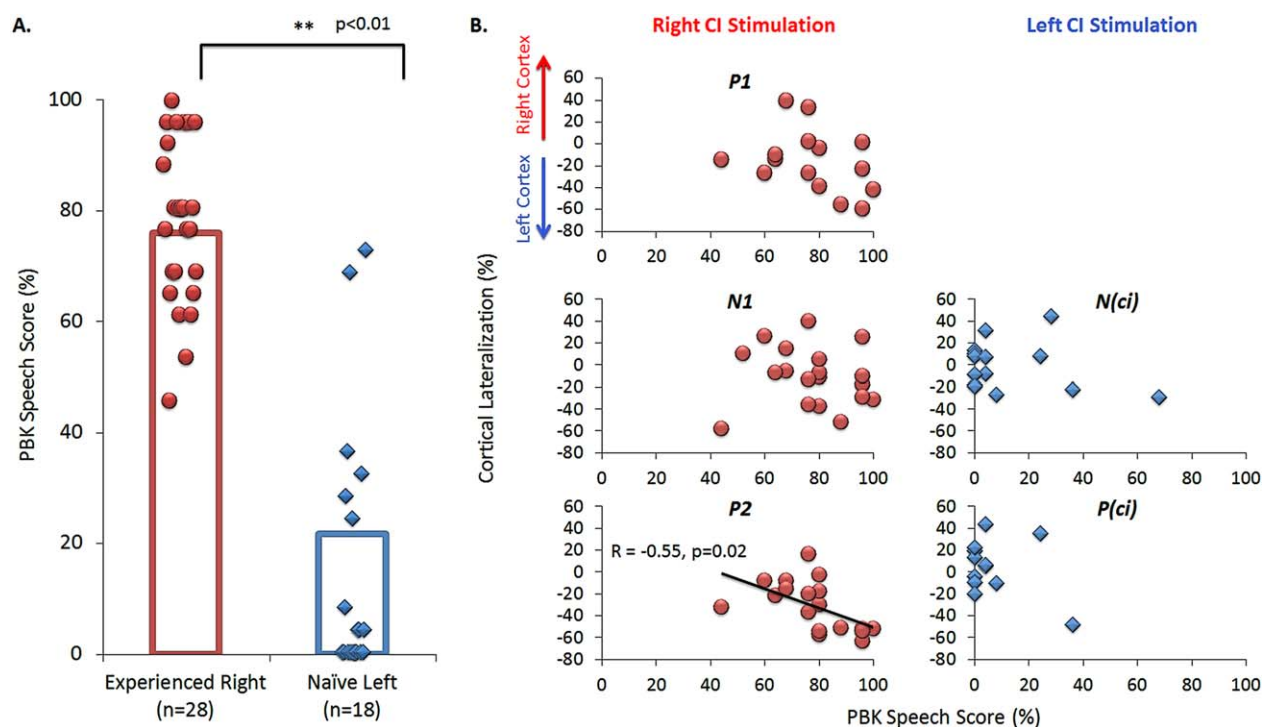


Figure 7.

A. Speech perception outcomes measured from the experienced side ($n = 28$) (red) and naïve ear ($n = 18$) (blue) of CI users was assessed using the PBK speech test after 6 to 18 months of bilateral CI experience. Individual responses are indicated by the round symbols for the experienced-right ear and diamonds for the naïve-left ear, with mean performance shown by the bar graph. Performance on the experienced side was significantly better than the naïve

side ($P < 0.01$). **B.** Analyses of cortical lateralization and performance on the PBK speech test indicated significant correlation between left hemisphere lateralization for peak P_2 ($P < 0.05$) and better speech scores on the experienced CI side. No significant correlations were found for dipole activity evoked by stimulation of the naïve side and speech perception. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

particularly when evoked by the newly implanted ear. These findings indicate that long-term stimulation of the auditory system with a unilateral CI promotes an asymmetric mature auditory cortex while, at the same time, leaving pathways from the opposite ear unprotected from abnormal effects of deafness. Because sensitive periods in development typically end once a period of maturation is reached [Blakemore, 2012; Lenroot and Giedd, 2006; Lohmann and Kessels, 2014], it may be challenging to promote further changes in these adolescents from the newly implanted side.

Hemispheric Specialization Requires Normal Bilateral Hearing

Data in Figure 2 indicate a normally mature response to a 500 Hz tone-burst with more activity in the right than left auditory cortex. Lateralization to the right hemisphere occurred for both left and right ear presentations (Figs. 4 and 5). A number of studies using electroencephalography (Picton et al., 1999; Hine and Debener, 2007; Hine et al.,

2008), as measured here, as well as magnetoencephalography (Kanno et al., 1996; Pantev et al., 1998; Fujioika et al., 2003) have shown similar findings in adults. This specialization of the right auditory cortex for pure tones appears to have emerged in development as the same stimulation resulted in contralateral lateralization in younger children with normal hearing regardless of ear of presentation [Gordon et al., 2013b]. Lateralization of auditory evoked activity to the contralateral cortex in the immature brain is consistent with the anatomy of the auditory system; most ascending auditory fibers cross contralaterally in the brainstem [Glendenning et al., 1981; Nordeen et al., 1983; Ponton et al., 2001]. The aural preference in each cortical hemisphere for the contralateral ear of younger peers can also be explained by this anatomical arrangement [Kral, 2013; Kral et al., 2013a,b].

Changes to cortical lateralization with age could occur as the structure and function of the brain becomes more specialized in each hemisphere. For example, cell columns become wider and more spaced with heavier axon myelination and increased inter-connectivity in left auditory

regions compared to right, providing specialized coding of temporal rather than spectral properties of sound [Penhune et al., 1996; Toga and Thompson, 2003; Zatorre and Belin, 2001; Zatorre et al., 2002]. The time course for many cortical changes are complete by late adolescence [Blakemore, 2012; Blakemore and Choudhury, 2006; Giedd et al., 1999; Giedd et al., 1996; Lebel and Beaulieu, 2011; Lenroot and Giedd, 2006; Lohmann and Kessels, 2014]. Auditory cortical responses are normally mature at this time [Eggermont and Ponton, 2003; Jiwani et al., 2013; Moore and Linthicum, 2007; Ponton et al., 2002; Ponton et al., 2000], corresponding with the emergence of better listening skills including perception of speech in noise and improved comprehension of degraded speech [Ponton et al., 2000].

Some of the same maturational processes likely occurred in adolescents using unilateral CIs, given that cortical peaks characteristic of adult responses were recorded in this group. The emergence of mature-like cortical response peaks in implant users is consistent with previous reports [Jiwani et al., 2013] and linked to the development of superficial cortical layers through thalamo-cortical and cortico-cortical connections [Ponton and Eggermont, 2001]. Good speech perception outcomes with the first implant, plotted in Figure 7, coupled with mature cortical responses provide a generally positive impression of auditory development with long-term CI stimulation. On the other hand, underlying dipole activity (Fig. 3) and cortical lateralization measures (Figs. 4 and 5) reveal abnormally strong dipoles of activity in the contralateral left auditory brain in response to stimulation of the experienced-right implant. Thus, adolescents with right CIs did not develop the normal right brain hemispheric bias associated with non-speech stimuli, despite having developed expected mature cortical waveforms.

Long Periods of Unilateral CI Use Strengthens Pathways From the Stimulated Ear

There are several reasons why adolescents using CIs may not have developed specialized auditory cortices similar to their normal hearing peers. They had been bilaterally deaf from early in life (typically from birth) and listened, often unilaterally, to a representation of sound missing much of its fine temporal information [Drennan and Rubinstein, 2008; Zeng et al., 2008].

It is possible that specialization has not yet emerged in these pathways, with contralateral afferent projections still dominating auditory input as in earlier development [Gordon et al., 2013a,b]. Effects of unilateral auditory deprivation/stimulation appear to occur early and persist into maturation. In younger children with CIs, abnormal strengthening of activity in the contralateral pathways from the experienced-right ear to the brainstem [Gordon et al., 2012] and cortex [Gordon et al., 2013b] was found when unilateral implant use exceeded 1.5 years. Stronger left than right hemisphere activation observed in Figures 3–5 are consistent with

these findings, indicating that increased activity in the left auditory cortex from the right implanted ear continues into maturation with longer periods of unilateral CI use. There was also strengthening of pathways to the ipsilateral cortex from the unilaterally right stimulated ear in the immature cortex, as measured by a reversal of stimulus preference from the contralateral ear to the ipsilateral first implanted ear [Gordon et al., 2013b]. Interestingly, there were no significant increases in the ipsilateral dipole strength in that study relative to normal, revealing the power of the aural preference measure to detect plasticity in the ipsilateral cortex [Kral et al., 2013a,b]. By contrast, the available data from adults with late onset unilateral deafness provide inconsistent EEG and MEG findings. Significant increases in responses recorded over the ipsilateral hemisphere were found in Ponton et al., 2001 and significant increases in dipoles located in both auditory cortices from EEG in Maslin et al., 2013. On the other hand, limited effects were found in several other studies [Vasama et al., 1995; Fujiki et al., 1998; Hine et al., 2008; Hanss et al., 2009]. One study of childhood unilateral deafness also showed minimal effects, perhaps for similar reasons [Vasama and Makela, 1994]. Although the aural preference could not be assessed in the present study because of the highly abnormal responses with very large underlying dipoles evoked in the newly implanted side, a significant increase in ipsilateral voxels in auditory areas was found underlying P_2 (Fig. 5C).

The clear finding of asymmetric strengthening of the contralateral pathways from the stimulated ear might be explained by increased excitability of auditory neurons from this side. Early unilateral auditory deprivation leads to a loss of cochlear nucleus neurons and reduced synaptic inhibition in pathways from the affected side [Blumenthal et al., 1999; Byrne and Byrne, 1993; Hashisaki and Rubel, 1989; Sanes and Kotak, 2011; Takesian et al., 2009], and enhanced excitatory glutamatergic conductance from the superior olive [Kotak and Sanes, 1996], to the inferior colliculus [Blumenthal et al., 1999; Byrne and Byrne, 1993; Kitzes, 1984; Lang et al., 2010; Popescu and Polley, 2010; Takesian et al., 2009] and primary auditory cortex of the stimulated pathways [Kotak et al., 2005; Kral et al., 2013a,b; Moore et al., 2005; Popescu and Polley, 2010]. Importantly, effects are found only when the loss is present in early life [Blumenthal et al., 1999; Moore and Kowalchuk, 1988; Nordeen et al., 1983; Reale et al., 1987] and when it is unilateral [Moore, 1990]. Such deafness-induced disruptions to the delicate balance of excitatory-inhibitory inputs influence and shape the development of binaural hearing in the brainstem [Grothe et al., 2010] and neuronal circuits in the auditory cortex [King, 2010; Turrigiano and Nelson, 2004]. The coupling of excitatory-inhibitory synaptic inputs in the auditory system is influenced by experience during development [King, 2010]. Maturation of inhibitory tuning occurs more slowly than that of excitation [Dorm et al., 2010] and inhibitory synapses are more vulnerable to deafness-induced perturbation [Sanes and Kotak, 2011]. Thus, the abnormal strengthening of pathways from the unilaterally stimulated CI

ear could reflect a disrupted balance of excitatory-inhibitory transmission during early development.

An alternate explanation for the abnormally increased dipoles in the left auditory cortex of CI users is the possibility of compensation for inadequate input from the unilateral CI. The left auditory cortex normally codes temporal information including speech. Although no speech sounds were provided to evoke the cortical responses in this study, speech perception in the experienced ear increased with stronger dipoles in the left auditory cortex (Fig. 7B). This is consistent with a previous report showing better language outcomes in children with right CIs who lateralized auditory input in the contralateral left hemisphere [Chilosi et al., 2014]. Strong left cortical activity in individuals with normal hearing has been associated with better language skills [Kadis et al., 2011], more precise auditory processing [Schönwiesner et al., 2005; Zatorre and Belin, 2001; Zatorre et al., 2002] and increased reading and spelling skills [Abrams et al., 2006]. Enhanced activity in the left cortex of adolescents using CIs could thus mark plastic changes in the brain to compensate for the abnormal electrical input provided by the implant device and/or stimulation of the auditory pathways from only one side.

No significant increases in peak dipoles were found from the experienced CI side relative to normal across the three peak latency ranges ($P > 0.05$) despite a significant increase in P_2 amplitude measured at electrode C_z as previously reported [Jiwani et al., 2013]. However, permutation analyses of each voxel in the P_2 latency range revealed significantly increased activity in the precuneus region (Fig. 6) and, in a within group analysis, increased activity in right ipsilateral auditory cortex relative to corresponding voxels in the opposite hemisphere (Fig. 5). Other areas were also recruited more strongly in CI users; larger contralateral activity in temporo-parietal-occipital areas across the three latency ranges (Fig. 5C), significantly increased activity in the left contralateral prefrontal cortex underlying P_1 (Fig. 6A) and a small area of left contralateral parietal activity underlying N_1 (Fig. 6A). The prefrontal and precuneus regions are areas involved in attention and effort [Fletcher et al., 1995; Kane and Engle, 2002] and the temporo-parietal-occipital junction integrates multimodal information [von Stein et al., 1999]. Overall, evidence of additional recruitment of these non-auditory cortical areas suggests that even good CI users require increased cortical processing to support CI listening. Similar findings in successful CI users include increased activation of the left dorso-lateral pre-frontal, frontal, and parietal networks that include the precuneus region and are involved with higher cognitive functions [Giraud and Lee, 2007; Giraud et al., 2001; Lee and Winer, 2005]. It is clear that individuals compensate for CI listening by using increased multi-sensory information [Doucet et al., 2006; Giraud and Lee, 2007; Giraud et al., 2001; Lee et al., 2007; Powell, 1974] and increased effort/attention [Gordon et al., 2013a; Hopyan-Misakyan et al., 2009; Kronenberger et al., 2014; Pisoni et al., 2010]. This study provides further evidence that these networks are recruited

in adolescents with CIs even in a passive response evoked by non-speech stimulation from the ear they listened with for most of their lives. This suggests a developmental reorganization of normal cortical networks to support CI hearing.

Activity Evoked by Stimulation of the Newly Implanted Ear Is Abnormal

It is difficult to separate the effects of stimulation from one ear from the simultaneous effects of deprivation in the other ear in adolescents using unilateral CIs. We suggest, however, that leaving the opposite pathways deprived of input beyond the period of brainstem [Gordon et al., 2013a, 2006] and cortical [Jiwani et al., 2013] maturation further disrupts organization of activity in the auditory pathways. Cortical responses at initial stimulation of that side were atypical and dominated by an abnormally large biphasic waveform (Fig. 3), despite equal amplitudes of brainstem responses on each side. This may reflect cortical immaturity, as a similar response has been observed in normal hearing pre-term infants [Wunderlich and Cone-Wesson, 2006] and children with little auditory input due to GJB-2 deafness [Gordon et al., 2011b]. This could also reflect abnormal cortical activity, as the same response was recorded from children with congenital deafness implanted late [Sharma et al., 2002] and in children who had poor speech perception with their implants [Gordon et al., 2008].

Cortical activity underlying the abnormal response in the newly implanted ear occurred with abnormally large peak dipole moments in auditory regions compared to the activity evoked by the opposite experience side and the normal hearing group (Fig. 3). Moreover, activity was more widespread (Fig. 6) with a loss of cortical lateralization (Fig. 5). Reduced cortical lateralization has been associated with poor auditory processing skills, decreased academic performance and increased difficulty with reading and spelling [Abrams et al., 2006]. Poor speech perception outcomes when adolescents were listening with the new implant after ~8 months of experience (Fig. 7) is consistent with these reports, suggesting altered cortical processing in the deprived pathways. If changes are to occur with bilateral stimulation, considerably longer term follow-up will be required as binaural hearing has been reported to take several years to emerge even in children implanted at younger ages [Gordon et al., 2014].

The long period of deprivation in this ear could have left it vulnerable to many structural and functional changes [Gordon et al., 2013b; Kral et al., 2013a,b; Popescu and Polley, 2010], which allowed a reorganization of the auditory brain in favour of the hearing ear while reducing responsiveness of the deprived side to activate the cortex but not eliminating it [Kral et al., 2013a; Popescu and Polley, 2010]. Indeed, as shown in Figure 3, the deprived ear retains the ability to activate the cortex, albeit abnormally, even after over a decade unilateral deafness.

Similar cortical consequences of imbalanced input occur in the visual system, with prolonged monocular deprivation. Findings of reduced visual acuity from a deprived eye has been attributed to uneven competition between the two pathways [Blakemore, 1988; Hubel and Wiesel, 1970; Hubel et al., 1977; Le Vay et al., 1980; Lewis and Maurer, 2005], resulting in arrested [Antonini et al., 1999] or retracted [Antonini and Stryker, 1993; Antonini and Stryker, 1996] growth of axonal arbors in ocular dominance columns of the deprived eye [Hubel et al., 1977; Le Vay et al., 1980]. This in turn, resulted in jittered representation of visual input and a competitive disadvantage of this eye in the cortex [Antonini et al., 1999; Blakemore and Van Sluylters, 1974; Jeffrey et al., 2004]. In this study, the widespread dipole activity observed from the naïve CI, could similarly reflect undefined cortical activity across both hemispheres, and suggests that similar aberrant processes may underlie auditory cortical activity in these pathways. This might reflect an immaturity or disintegration of auditory areas in the cortex [Kral and Sharma, 2012] and would explain the inferior auditory outcome observed from this side (Fig. 7), thereby highlighting the deleterious effects of unilateral deprivation on the brain. The similarly large stimulation of contralateral temporo-parietal-occipital areas in response to this new implant may reflect recruitment of multi-modal areas for auditory input.

CONCLUSION

Maturation of the auditory brain is an experience-dependent process which promotes specialization of each cortical hemisphere in adolescents with normal hearing. By contrast, cortical organization in the auditory pathways differs from normal in adolescents who used a unilateral CI to hear for most of their lives. Present findings indicate that driving maturation of the auditory cortex with only one implant for over a decade leads to lasting asymmetries in the auditory system and leaves the deprived pathways unprotected from effects of unilateral auditory deprivation. Because sensitive periods typically end when maturation is reached, maturation of the cortex from the experienced CI may mark the closing of an important developmental period in the adolescent brain for gaining improved auditory function in the deprived pathways.

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