

# Bilateral input protects the cortex from unilaterally-driven reorganization in children who are deaf

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Unilateral hearing in childhood restricts input along the bilateral auditory pathways, possibly causing permanent reorganization. In this study we asked: (i) do the auditory pathways develop abnormally in children who are bilaterally deaf and hear with a unilateral cochlear implant? and (ii) can such differences be reversed by restoring input to the deprived ear? We measured multichannel electroencephalography in 34 children using cochlear implants and seven normal hearing peers. Dipole moments of activity became abnormally high in the auditory cortex contralateral to the first implant as unilateral cochlear implant use exceeded 1.5 years. This resulted in increased lateralization of activity to the auditory cortex contralateral to the stimulated ear and a decline in normal contralateral activity in response to stimulation from the newly implanted ear, corresponding to poorer speech perception. These results reflect an abnormal strengthening of pathways from the stimulated ear in consequence to the loss of contralateral activity including inhibitory processes normally involved in bilateral hearing. Although this reorganization occurred within a fairly short period (~1.5 years of unilateral hearing), it was not reversed by long-term (3–4 years) bilateral cochlear implant stimulation. In bilateral listeners, effects of side of stimulation were assessed; children with long periods of unilateral cochlear implant use prior to bilateral implantation showed a reduction in normal dominance of contralateral input in the auditory cortex ipsilateral to the stimulated ear, further confirming an abnormal strengthening of pathways from the stimulated ear. By contrast, cortical activity in children using bilateral cochlear implants after limited or no unilateral cochlear implant exposure normally lateralized to the hemisphere contralateral to side of stimulation and retained normal contralateral dominance of auditory input in both hemispheres. Results demonstrate that the immature human auditory cortex reorganizes, potentially permanently, with unilateral stimulation and that bilateral auditory input provided with limited delay can protect the brain from such changes. These results indicate for the first time that there is a sensitive period for bilateral auditory input in human development with implications for functional hearing.

**Keywords:** hearing loss; cochlear implantation; auditory brain; EEG dipole source localization; beamformer

**Abbreviations:** CI-1 = first cochlear implant; CI-2 = second cochlear implant

## Introduction

Cochlear implants stimulate the auditory nerve with electrical pulses allowing users who are deaf to hear (Papsin and Gordon, 2007). Prior to implantation, the deaf auditory cortex can be taken over by other sensory inputs (cross-modal reorganization) during important sensitive periods in development (Lee, 2001; Bavelier and Neville, 2002; Lomber *et al.*, 2010) and even in adulthood (Lazard *et al.*, 2011; Sandmann *et al.*, 2012). The developmental changes may be impossible to reverse if the cochlear implant is provided too late (Lee *et al.*, 2001; Kral and O'Donoghue, 2010). A single cochlear implant promotes auditory development (Sharma *et al.*, 2002; Gordon *et al.*, 2005, 2006) but may distort the normal bilateral auditory pathways. Having found that unilateral cochlear implant stimulation results in abnormally large asymmetry in auditory brainstem activity (Gordon *et al.*, 2007b, 2008), we asked whether there are any cortical effects.

We hypothesize that unilateral input through a single cochlear implant (and no intervention for severe to profound deafness in the opposite ear) strengthens pathways from the stimulated side, leaving developing pathways from the deprived ear immature or subject to degenerative changes or reorganization. There is evidence for this in animal models at the level of brainstem and cortex where connections from the hearing ear increase and those from the impaired ear decrease (Nordeen *et al.*, 1983; Moore and Kowalchuk, 1988; Kitzes *et al.*, 1995; Popescu and Polley, 2010). The strengthening of inputs from the hearing ear to the ipsilateral cortex are age-dependent, occurring only if the deafness occurs in early life (Moore, 1994; Popescu and Polley, 2010; Kral *et al.*, 2013). In humans, unilateral hearing loss has been studied primarily in adults who lose hearing in one ear after maturation of bilateral auditory pathways. In general, the normal lateralization of activity to contralateral auditory centres in the brainstem (inferior colliculus) and thalamus (medial geniculate body) is unaffected (Langers *et al.*, 2005; Schonwiesner *et al.*, 2007) but there is an increase in symmetrical activation of both auditory cortices (Ponton *et al.*, 2001; Langers *et al.*, 2005). This is particularly true when the hearing loss occurs in the left ear (Khosla *et al.*, 2003; Burton *et al.*, 2012), perhaps reflecting hemispheric specialization of auditory processing (Zatorre and Belin, 2001). Reorganization may be different in children who develop hearing from only one ear. Although not much data are available from this population, one group has shown that contralateral dominance of activity from the hearing ear remains (Vasama and Makela, 1997) and another reports increases in cortical areas supporting auditory processing (Tibbetts *et al.*, 2011).

The potential to reverse abnormal changes caused by unilateral hearing is not known but can be studied in children who are bilaterally deaf, develop hearing through one cochlear implant, and then receive a second device in the opposite ear. In the present study, these children were compared with children who continued

to use one cochlear implant and with children who received bilateral cochlear implants at the same time, as well as to children with normal hearing. Children using one cochlear implant have similar hearing problems as children with unilateral hearing loss; both groups have difficulties listening to speech in noise (Bess *et al.*, 1986; Beijen *et al.*, 2008; Gordon and Papsin, 2009) and localizing sound (Bess *et al.*, 1986; Litovsky *et al.*, 2006). The aim of bilateral implantation is to reduce these deficits but outcomes appear to depend on the timing of this procedure. Children receiving bilateral cochlear implants sequentially have poorer abilities to detect speech in noise than children implanted with two devices simultaneously (Chadha *et al.*, 2011) and their ability to localize sound declines as the delay between implants increases (Van Deun *et al.*, 2009). Moreover, these children often cannot recognize speech from their newly implanted ear as accurately as with their first device and this asymmetry increases with the period of unilateral implant use (Gordon and Papsin, 2009).

The poorer functional outcomes of sequential compared with simultaneous bilateral cochlear implantation could reflect abnormalities along the bilateral auditory pathways. Unilateral cochlear implant use followed by implantation of the second ear sets up asymmetric development and function in the auditory brainstem of children (Gordon *et al.*, 2007a; Sparreboom *et al.*, 2010). Remarkably, interaction of bilateral input is retained in their auditory brainstem although abnormal timing remains (Gordon *et al.*, 2008, 2012). This provides some hope of restoring binaural function to children who are deaf but further cortical processing will be needed. Evidence for this includes impaired sound localization with experimental cooling of bilateral primary (A1 and the dorsal zone) and non-primary (posterior auditory field, anterior ectosylvian sulcus) auditory cortices (Malhotra and Lomber, 2007; Malhotra *et al.*, 2008). A balance of activity between the two hemispheres in the auditory brainstem is important for coding binaural cues (Grothe *et al.*, 2010) and similar processing appears to be retained in the cortex as shown by lateralization of activity to the hemisphere contralateral to the leading ear when interaural timing differences are introduced (Palomaki *et al.*, 2000, 2005; Thompson *et al.*, 2006; Krumbholz *et al.*, 2007). The degree of contralaterality is greater for left than right ear stimulation (Hine and Debener, 2007), particularly when unilateral stimuli are presented in context with binaural input (Schonwiesner *et al.*, 2007). This reflects a bias for processing spatial information in the right auditory hemisphere (Zatorre and Penhune, 2001; Krumbholz *et al.*, 2007; Schonwiesner *et al.*, 2007; Johnson and Hautus, 2010) as compared with a specialization for temporal information in the left auditory hemisphere (Zatorre and Belin, 2001; Lazard *et al.*, 2012). Thus, reorganization of either or both auditory cortices could impair both speech perception and binaural hearing.

The present study examines whether unilateral auditory input from a cochlear implant promotes reorganization of the developing human auditory system and whether a sensitive period exists

for the restoration of the bilateral pathways. We present evidence confirming abnormal patterns of cortical activity in response to unilateral stimulation in children who are deaf, which are associated with decreasing accuracy of speech perception. We also show that this reorganization can be limited by providing bilateral auditory input in early stages of development.

## Materials and methods

This study was approved by the Hospital for Sick Children's Research Ethics Board, which adheres to the 2nd Edition of Tri-council Policy Statement: Ethical Conduct for Research Involving Humans.

Multi-channel EEG was recorded in response to right or left stimulation in seven children with normal hearing in both ears and 34 children using cochlear implants either in the right ear only ( $n = 8$ , unilateral cochlear implant) or bilaterally ( $n = 26$ , bilateral cochlear implant). The bilateral cochlear implant group was divided into the children who had first used a right unilateral cochlear implant (CI-1) prior to receiving the second device (CI-2) ( $n = 16$ , sequential bilateral cochlear implant), and children receiving bilateral cochlear implants in the same surgery ( $n = 10$ , simultaneous bilateral cochlear implant).

Because bilateral deafness in early development allows competitive takeover by other sensory systems over time (Lee, 2001; Lomber *et al.*, 2010), study participants who were deaf were implanted at young ages and soon after the onset of profound hearing loss [mean  $\pm$  standard deviation (SD) =  $1.74 \pm 0.90$  years]. None of these children used a hearing aid in the unimplanted ear during the inter-implant period. All children with cochlear implants were using Nucleus 24 devices consistently and successfully as measured by speech perception testing (detailed below). Table 1 provides additional demographic information. As indicated, simultaneous bilateral users had  $3.26 \pm 0.44$  years of bilateral experience and sequential bilateral users had  $3.57 \pm 0.74$  years at the time of testing. This meant that children who had prior experience hearing with a unilateral cochlear implant had, overall, longer periods of time in sound than the children who received bilateral cochlear implants simultaneously [ $t(26) = 4.45$ ,  $P < 0.0001$ ] and were older when they received the second cochlear implant [ $t(20) = 3.74$ ,  $P < 0.005$ ] and at the time of testing [ $t(23) = 3.51$ ,  $P < 0.005$ ]. Children using right unilateral implants had, on average, the longest duration of unilateral hearing [ $F(2,33) = 50.77$ ,  $P < 0.0001$ ] but their overall time in sound was not significantly different from the sequential group [ $t(22) = 1.55$ ,  $P > 0.05$ ]. Of all the groups, children with normal hearing had the most time in sound ( $11.02 \pm 2.22$  years), which was defined as equivalent to their chronological age [ $F(3,39) = 27.30$ ,  $P < 0.0001$ ]. The simultaneous group was the youngest at time of testing [ $F(3,29) = 12.83$ ,  $P < 0.0001$ ].

## Cortical source localization using multi-channel electroencephalography

Evoked potential multichannel EEG was used to measure cortical activation in response to auditory stimuli delivered to the left and right ears/cochlear implants. This modality was selected over functional MRI because the magnet of the implant in the receiver–stimulator (Fig. 1A) causes an artefact over the temporal lobe and could become dislodged in scanners with stronger than 1.5 T magnets (Majdani *et al.*, 2009; Crane *et al.*, 2010). Instead, the distribution of electric potentials, measured at multiple places across the entire head, was used to determine the location of cortical activity using a beamformer analysis (Wong and Gordon, 2009). Further details of this method are provided below and in the Supplementary material.

### Recording set-up

Children sat in a soundproof booth watching a movie with captioning and no sound. They wore an electrode cap with 64 electrodes (reference electrode positioned on the right earlobe) that were each filled with conducting gel. A reference electrode was positioned on the right earlobe; this set-up is often used in auditory evoked potential recordings and thus allowed us to recognize responses at the CZ recording site during testing. Further analyses were conducted on responses that were referenced to an average of all sensors. The children with normal hearing listened to 500 Hz tones (36 ms duration enveloped with Tukey window over the first and last eighths to minimize high frequency onset and offset effects). The tones were presented at 1 Hz through EAR-3 earphones to one ear at a time at 40 dB over their behavioural threshold in that ear (measured with a behavioural bracketing approach) (Leijon, 1992).

For children using cochlear implants, biphasic electrical pulses (25  $\mu$ s/phase) were delivered from an electrode at the apical end of the array (#20) at 250 pulses/s in trains lasting 36 ms. An X-ray from the head of one user with bilateral cochlear implant is shown in Fig. 1A. The large components visibly fixed to the skull are the two independent receiver–stimulators that receive instructions from externally worn equipment about the frequency and intensity of the acoustic environment. This information dictates which of the electrodes along each of the implanted arrays will deliver electrical pulses to stimulate the ipsilateral auditory nerve. The implanted arrays within the two cochleae are highlighted by the black boxes. As shown in Fig. 1B, one of the electrodes at the apical end of the array was instructed to deliver a train of biphasic electrical pulses (using the SPEAR system in collaboration with Richard van Hoesel at CRC-HEAR, Melbourne, Australia). Pulse trains were delivered at 1 Hz. Because differences in amplitude of brainstem responses are associated with perception of bilateral implant stimulation toward one side of the head (i.e. unbalanced) (Salloum *et al.*, 2010), we determined current levels of single electrical pulses

**Table 1** Demographic data for children in each group

	Normal hearing	Simultaneous bilateral CI	Sequential bilateral CI	Unilateral CI
Age of first implant	-	$1.74 \pm 0.95$	$1.87 \pm 1.25$	$2.31 \pm 1.44$
Age of second implant	-	$1.74 \pm 0.95$	$4.22 \pm 2.50$	-
Age at test	$11.02 \pm 2.22$	$5.01 \pm 1.11$	$7.79 \pm 2.46$	$9.52 \pm 2.27$
Duration of unilateral hearing	0	0	$2.32 \pm 1.61$	$7.21 \pm 2.48$
Duration of bilateral hearing	$11.02 \pm 2.22$	$3.26 \pm 0.44$	$3.57 \pm 0.74$	0
Time in sound	$11.02 \pm 2.22$	$3.26 \pm 0.44$	$5.90 \pm 1.64$	$7.21 \pm 2.48$

Values are mean  $\pm$  SD. CI = cochlear implant.

required to evoke clear auditory brainstem responses of similar amplitude on each side. These levels were reduced by 12.2  $\mu\text{A}$  (10 manufacturer defined current units) in order to account for possible temporal integration/increased loudness of the 36 ms pulse train stimulus relative to single pulses. The EEG was recorded for each of  $\geq 300$  stimulus presentations at 64 cephalic locations. Epochs from 200 ms before the onset of the stimulus to 600 ms afterward and within  $\pm 100 \mu\text{V}$  were averaged. A typical response from a cochlear implant user (average referenced), shown in Fig. 1C, demonstrates that the electrical pulse from the implant was measured as large peaks in the early time period of the recording (typically largest at temporal recording electrodes on the side of the implant). Later in the recording period, two main amplitude peaks of activity were identified (labelled P1ci and N1ci). The Global Mean Field Power across all recording electrodes is shown for this example in Fig. 1D. The stimulus artefact is clear but does not obscure the two amplitude response peaks. The topography of activity recorded on the head is shown above for the peak at 117 ms.

### Recording analyses for location of cortical sources

We located and measured the neural generators of the P1ci activity in both auditory cortices using the TRACS (Time-Restricted, Artefact and Coherent source Suppression) beamformer (Wong and Gordon, 2009) while suppressing the cochlear implant artefact. In brief, the beamformer is an adaptive spatial filter that examines the brain voxel by voxel and measures the contribution of each voxel to the measured field, thereby producing a tomographic image. Lead potentials were computed for dipoles located at the centre of each  $3 \times 3 \times 3 \text{ mm}$  voxel with a given orientation. These potentials are affected by changing conductivities through the brain, skull and scalp and age-related changes in head geometry. To account for these factors, a three layer boundary element mesh was constructed from an adult head template MRI and adjusted for age using the template-o-matic toolbox (Wilke *et al.*, 2008). Further details about this procedure are included in the Supplementary material. Figure 1E shows an example of the generators of the P1ci (Fig. 1C and D) in the left and right temporal lobes. The coloured areas in these plots represent voxels in which the evoked activity (signal) is greater than activity in the prestimulus recording interval (noise). The signal at each voxel is normalized into a pseudo-Z statistic which divides the sample signal mean by the standard deviation of the sample noise (Vrba and Robinson, 2001). This signal to noise measure is displayed as a colour from red to light yellow. The strength of the activity at the identified locations was measured in dipole moments (nAm) and measured in the left and right cortical hemispheres separately, as shown in Fig. 1F.

A K-medoid cluster analysis was performed for all detected sources in each child by group (normal hearing, simultaneous bilateral, sequential bilateral, unilateral). A Dunn's alternative index analysis of cluster validity revealed the presence of two clusters in all four groups. The cluster medoids were located in the left and right auditory areas within the superior temporal gyrii, respectively. Only the closest point to the cluster medoids in each child was included in the analysis of hemispheric lateralization. Locations of accepted sources by group are shown in a template glass brain in Fig. 2 (axes are MNI co-ordinates in mm).

### Speech perception testing

Children using bilateral cochlear implants performed age-appropriate speech perception tests after  $37.8 \pm 8.8$  months of bilateral implant use. All but two children completed open-set tests in which they were asked to repeat back a word without any visual cues or pictures

provided. These tests included the Phonemically Balanced Kindergarten Test (nine of sixteen children tested in the sequential bilateral group and 1 of 10 children tested in the simultaneous group); the Lexical Neighbourhood Test (one child in the sequential bilateral group); the Multisyllabic Lexical Neighbourhood Test (three in the sequential bilateral group and six children in the simultaneous group); and the Glendonald Auditory Speech Perception Test (one in the sequential bilateral group and three in the simultaneous group). Two children in the sequential bilateral group completed closed-set tests in which they pointed to one picture in a set of six (Word Identification by Picture Index or 12 Early Speech Perception Test) that best represented the word spoken. Words were delivered through a loudspeaker at 0 degrees azimuth to the child at 65 dB sound pressure level. The test was completed twice using different word lists; once while wearing the left implant and once while wearing the right in random order.

### Statistics

The effect of demographic variables on cortical lateralization was assessed using a factor analysis that describes the variability of a correlated set of variables in terms of a potentially lower number of latent variables called factors. The formula for this analysis is:

$$X_i = C_{i1}F_1 + C_{i2}F_2 + C_{i3}F_3 + e_i$$

Where  $X_i$  is the  $i$ th variable (e.g. age at CI-1 implantation),  $C_{ij}$  is the  $j$ th factor loading corresponding to the  $i$ th variable,  $F_j$  is the  $j$ th factor, and  $e_i$  is the error term. By plotting the factor loadings along their own axes, the relationship between the demographic variables of interest and the calculated factors was analysed.

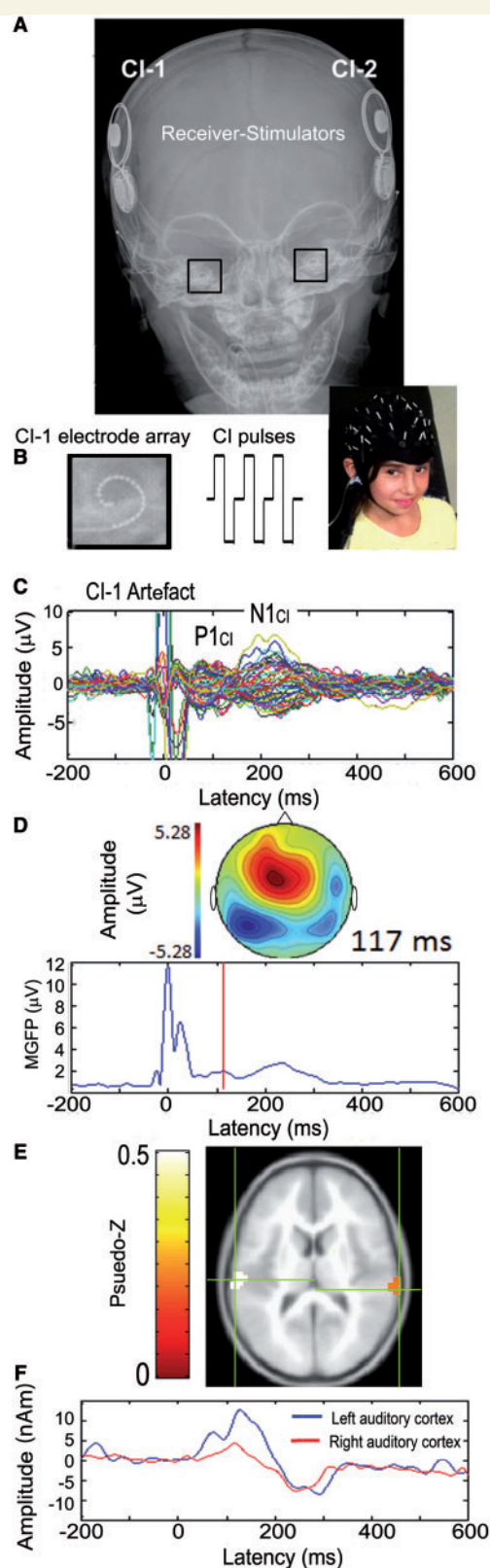
In order to more specifically determine the effect of unilateral implant use on the lateralization variables, a logarithmic regression analysis was performed using  $Y = B_0 + B_1 \log(X)$ , where  $Y$  was the lateralization value and  $X$  was the duration of unilateral implant use. This two coefficient regression line best fit the data ( $R^2 = 0.38$  for right/CI-1 ear lateralization and 0.44 for left/CI-2 ear lateralization). The values of cortical lateralization predicted by the regression line were normally distributed (Lilliefors test  $P > 0.05$ ) and were compared with lateralization values from the simultaneous group using a  $t$ -test. Significant difference between the predicted values and data from the simultaneous group was defined as  $P \leq 0.05$ . Two way repeated measures ANOVAs were used to assess effects of ear stimulated (CI-1/right versus CI-2/left) and group (normal, unilateral, short delay, long delay, simultaneous) on lateralization values and on dipole moments. Pearson correlations were calculated to evaluate associations between speech perception scores and both cortical lateralization (%) and stimulus preference (%).

## Results

### Lateralization of activity in the auditory cortex is variable in children using cochlear implants

Repeated presentations of auditory stimuli (electrical pulses for cochlear implant users and 500 Hz pure tones for normal hearing children) resulted in clear peaks of activity in the averaged EEG response. Grand mean responses plotted as Global Mean Field Power for each group are shown in Fig. 3. The first response





**Figure 1** (A) An X-ray of the head of a child with bilateral cochlear implants. The first implant (CI-1) was provided in the right ear and the second (CI-2) was implanted later in the left ear. The receiver-stimulators embedded into the skull can be seen. The intra-cochlear electrode arrays appear within the black squares. (B) The CI-1 electrode array has been increased in size

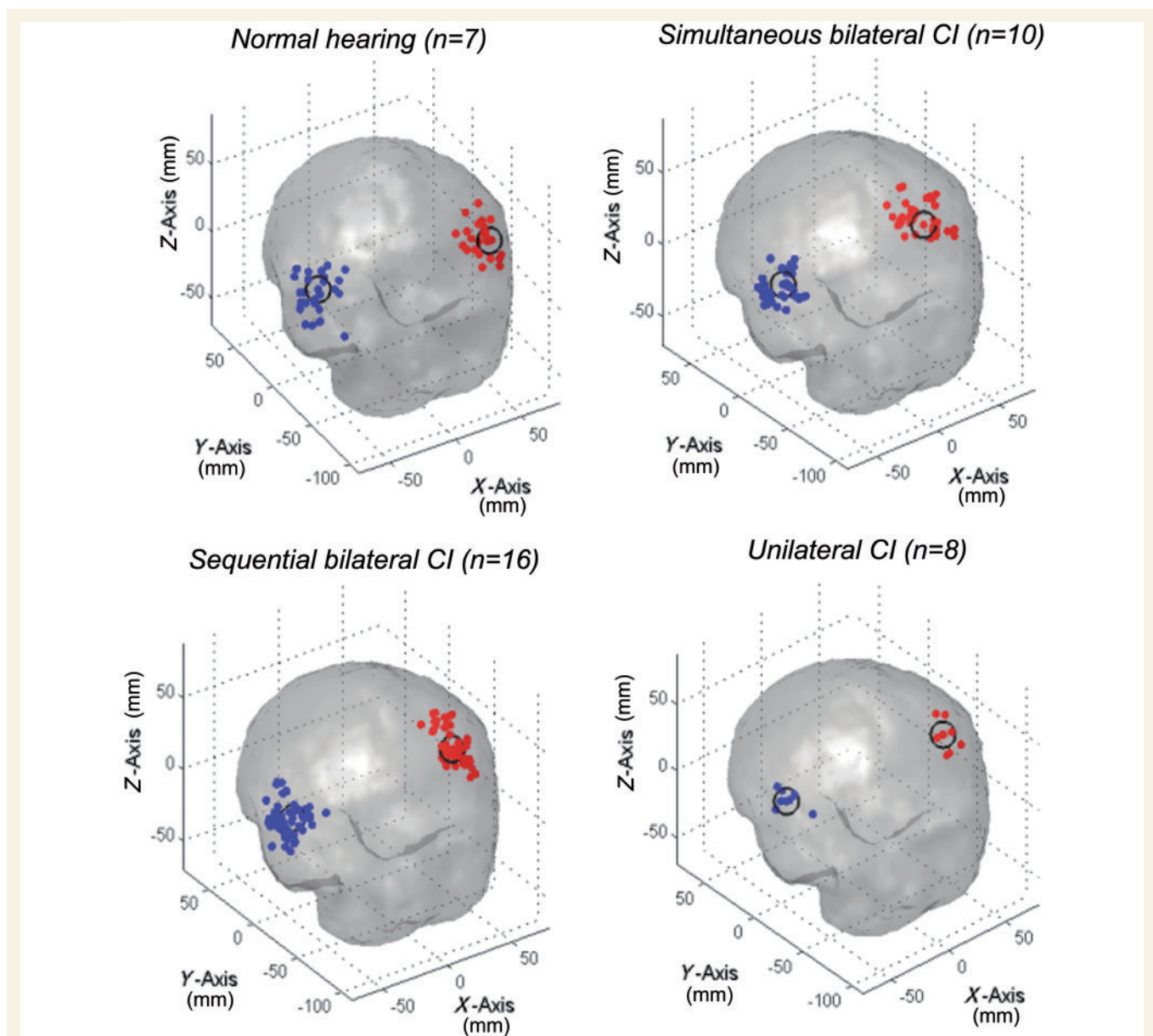
peaks at ~100 ms are shown, along with the respective topological maps of activity across the head at that latency. Responses in cochlear implant users are characterized by a large stimulus artefact in early latencies but this does not obscure the cortical response of interest (P1 or P1ci). Topological maps reveal that this peak was similarly distributed over the head across groups. We calculated the per cent of total activation in the right versus left auditory cortex as the measure of degree of lateralization of cortical activity toward one hemisphere, as previously described for unilateral hearing loss (Fujiki *et al.*, 1998; Ponton *et al.*, 2001; Khosla *et al.*, 2003; Hine *et al.*, 2008; Burton *et al.*, 2012). The per cent to which activity lateralized to one side was calculated as:

$$\text{Cortical lateralization (\%)} = \frac{(\text{right dipole moment} - \text{left dipole moment})}{(\text{right} + \text{left dipole moments})} \times 100$$

The cortical lateralization for each child is plotted in Fig. 4. Examples of source localization in the four groups of children are shown in Fig. 4A and, in Fig. 4B, the cortical lateralization (%) is plotted for each child by group; the left graph shows data evoked by CI-1/right stimulation and the right graph shows data evoked by stimulation of CI-2/left ear. As expected, cortical activity lateralized to the contralateral hemisphere in children with normal hearing (with one exception for left stimulation). Although some of the children using cochlear implants (unilateral, sequential bilateral and simultaneous bilateral) showed normal contralateral lateralization, there was high variability in the cochlear implant group. A large range of values was found in cochlear implant users (CI-1/right stimulation: –56 to 56% and CI-2/left stimulation: –68 to 57%) compared with the normal hearing group (CI-1/right: –28 to –8% and CI-2/left: –12 to 29%). Moreover, 7 of the 16 children in the sequential group showed lateralization of activity to the ipsilateral cortex in response to CI-2/left stimulation whereas this only occurred for one of the children in the normal hearing group.

#### Figure 1 Continued

to display the individual contacts that produce electrical pulses. Cortical responses to pulses delivered by an electrode at the apical end of the array were recorded at 64 locations over the head in children. (C) Responses from all channels were recorded and averaged, referenced as shown in this example. A large stimulus artefact is present at early latencies followed by two peak amplitude responses (P1ci and N1ci). (D) The Mean Global Field Power (MGFP) across recording electrodes in this child is shown over latency. The topography of activity for the maxima of the P1ci peak (at 117 ms) is shown above. (E) Pseudo-Z activity in the left and right superior temporal gyri in an axial tomographic beamformer image for the time window of the P1ci. The image is split down the middle to show left and right activation centres independently. (F) Virtual sensor data across latency at the cortical locations (E) identified. CI = cochlear implant.

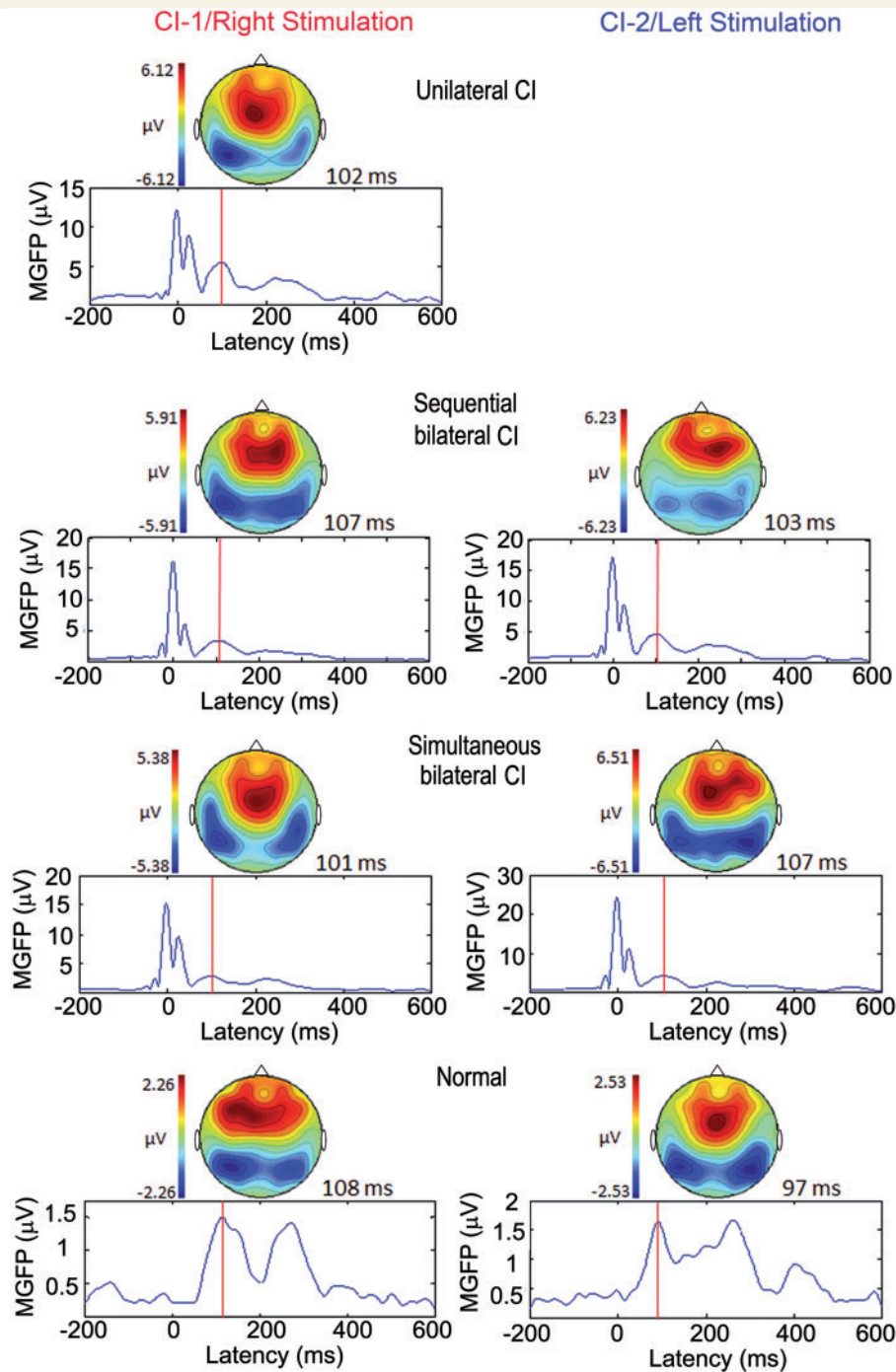


**Figure 2** Dipole locations for each subject group formed two clusters using K-medoid cluster analyses. Axes are MNI co-ordinates in millimetres. The medoids of the clusters, shown by the black circles, lie in the left and right superior temporal gyri. CI = cochlear implant.

## Abnormal cortical lateralization occurs with unilateral cochlear implant exposure

The variability in cortical lateralization in cochlear implant users might be explained by a number of variables that are time-based (age at the time of testing, age at CI-1, age at CI-2, total duration of cochlear implant experience i.e. unilateral cochlear implant use + bilateral cochlear implant use, duration of unilateral cochlear implant use, and/or duration of bilateral cochlear implant use). Because these variables were all highly correlated (with the exception of duration of bilateral use which was similar in all cochlear implant groups), it was inappropriate to use a multiple regression

model to identify which of these time-based variables best explained the distribution of cortical lateralization measured. Instead, a factor analysis was completed to elucidate interrelationships between cortical lateralization and confounding variables. A three-factor model was chosen based on a hypothesis test of the existence of factors greater than three [ $\chi^2(7) = 8.67$ ,  $P = 0.28$ ]. Three main factors were identified: (i) duration of unilateral cochlear implant use; (ii) age at CI-1; and (iii) duration of bilateral cochlear implant use. In Fig. 5, these factors are plotted in red in three different dimensions, illustrating their independence from one another. Cortical lateralization in response to CI-1/right and CI-2/left sided stimulation are plotted in green; both coincide with duration of unilateral cochlear implant use. The additional variables (age at test, age at CI-2, time in sound), plotted in blue, have



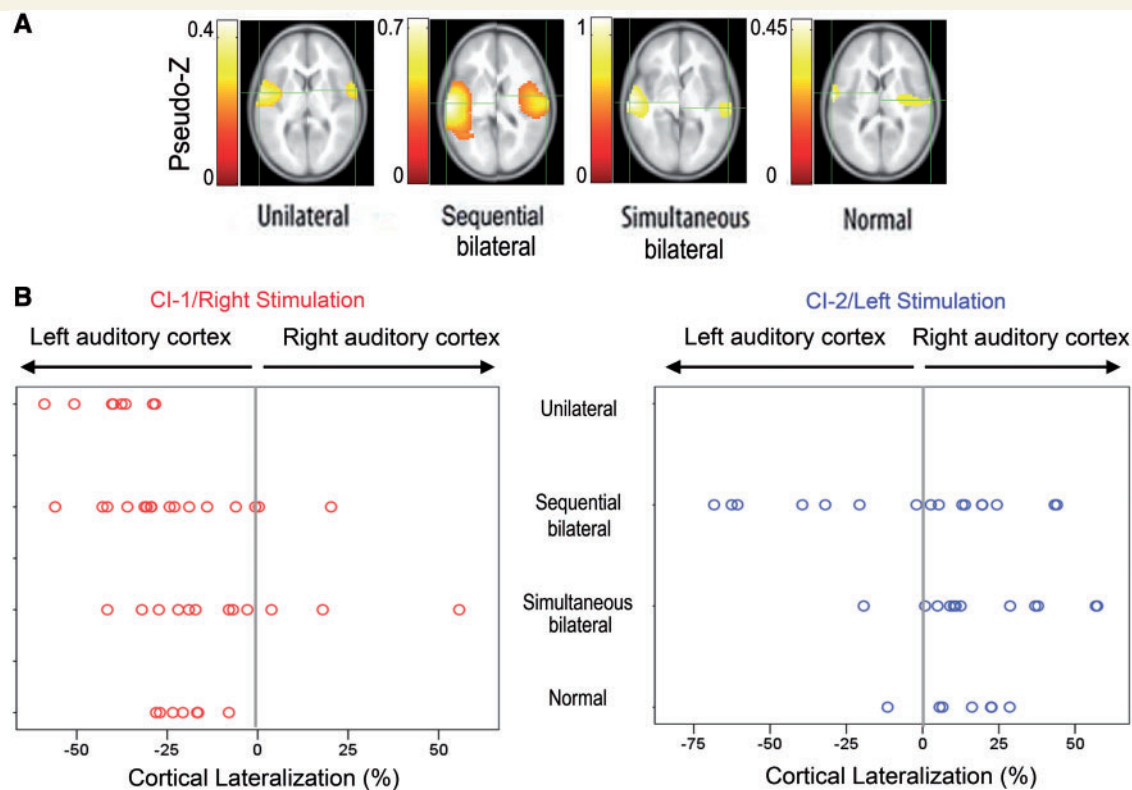
**Figure 3** Mean Global Field Power (MGFP) is plotted for responses from each group of children studied. Early latencies show the large stimulus artefact in the cochlear implant groups. The duration of the artefact is sufficiently short to allow identification of the P1ci peak in implant users and P1 in children with normal hearing. The topological maps for the P1 and P1ci peaks are shown above indicating the distribution of amplitudes of responses recorded over the surface of the head.

contributions from all three main factors. Any correlation between these variables and cortical lateralization thus exist because they are also correlated with the duration of unilateral cochlear implant hearing.

Based on the factor analysis, we investigated the change in cortical lateralization in children who had used unilateral cochlear

implants (unilateral cochlear implant and sequential bilateral groups). These children were compared with similar children who had no prior unilateral cochlear implant use (simultaneous group). As shown in Fig. 6A, cortical lateralization in the simultaneous group was not significantly different from the normal group [Right:  $t(14) = 1.02$ ,  $P > 0.05$ ; Left:  $t(14) = 0.89$ ,  $P > 0.05$ ] despite





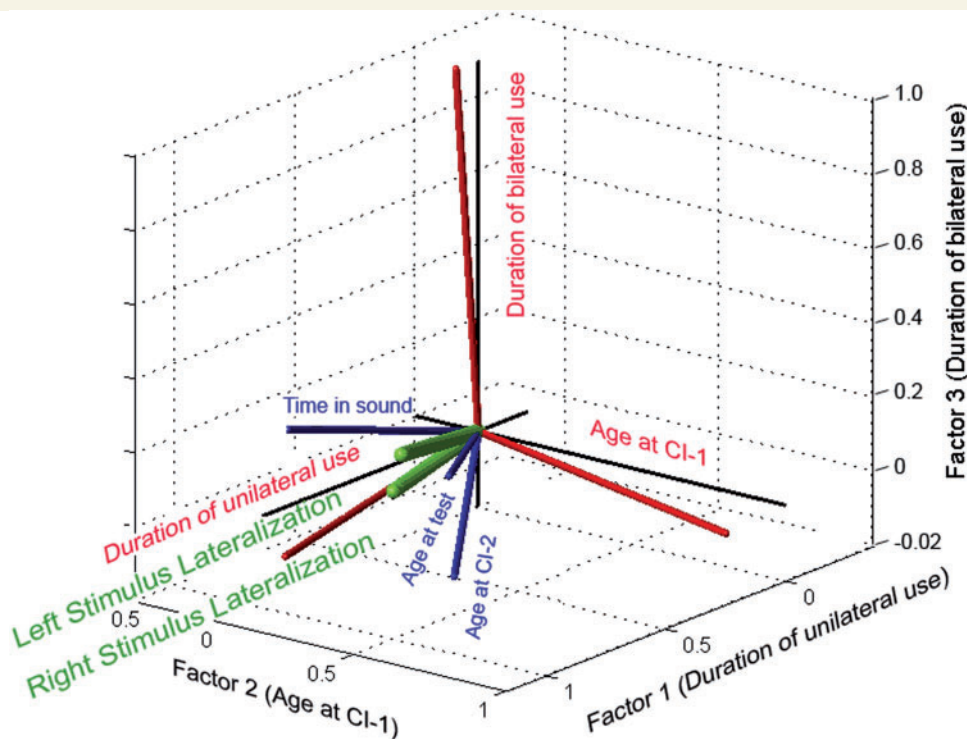
**Figure 4** (A) Axial tomographic beamformer images are shown for a child with normal hearing, two using bilateral cochlear implants (one implanted sequentially and the other simultaneously) and another using a unilateral cochlear implant. (B) Cortical lateralization [(left hemisphere dipole – right hemisphere dipole) / (left + right hemisphere dipoles) × 100] values are plotted for left and right stimuli for each of the children in four groups: children with normal hearing; right sided unilateral cochlear implant users (unilateral cochlear implant); bilateral cochlear implant users who had had an initial period of right sided unilateral cochlear implant use prior to receiving the second device (sequential bilateral cochlear implant); and children receiving bilateral cochlear implants in the same surgery (simultaneous bilateral cochlear implant). Values are more variable in cochlear implant users than in the group with normal hearing with increased ipsilateral activation in response to CI-2/left stimulation.

these being the youngest and oldest groups at test time, respectively. Data from the other cochlear implant users are shown in the scatterplot in Fig. 6B. In the left plot, responses evoked by CI-1 (in unilateral cochlear implant and sequential bilateral groups) show increasing cortical lateralization to the contralateral (left) cortex with increasing duration of unilateral cochlear implant use. These values became significantly larger than in the simultaneous group by 1.48 years [ $t(11.9) = 1.79$ ,  $P = 0.05$ ]. On the right, responses evoked by CI-2 in the sequential bilateral group show a decrease in cortical lateralization from the contralateral side, moving toward the ipsilateral auditory cortex. This change became significantly different from the simultaneous group by 1.37 years of unilateral cochlear implant use [ $t(17.8) = 1.74$ ,  $P = 0.05$ ] with the curve indicating a change to ipsilateral lateralization at this time point. Changes found in CI-2 responses were significantly related to the degree of change in cortical lateralization with CI-1 ( $R = 0.60$ ,  $P < 0.05$ , mean regression slope  $\pm$  SD =  $0.87 \pm 0.22$ ). This indicates that, as left hemisphere cortical lateralization increased with right sided stimulation, input from the other (left) ear increasingly shifted away from right auditory cortex toward the same left hemisphere.

## Abnormal cortical lateralization is restricted when bilateral input is available in early auditory development

Given the abnormal changes occurring with over 1.5 years of unilateral cochlear implant exposure, we hypothesized that normal cortical symmetry could be achieved by restricting the delay for bilateral cochlear implantation. To answer this, the sequential group was divided into a group with short inter-implant delays [ $< 1.5$  years, mean  $\pm$  SD =  $0.86 \pm 0.10$  years, short delay group ( $n = 7$ )] and another with long inter-implant delays [ $> 2$  years, mean  $\pm$  SD =  $3.44 \pm 1.27$ , long delay group ( $n = 9$ )] as indicated in Fig. 6B. Mean cortical lateralization data plotted in Fig. 7A indicate no significant differences in lateralization values between normal, simultaneous and short delay groups for either side of stimulation [repeated measures ANOVA: effect of subject group  $F(2,20) = 0.57$ ,  $P > 0.05$ , interaction between subject group and side of stimulus  $F(2,20) = 0.63$ ,  $P > 0.05$ ], confirming the hypothesis. On the other hand, CI-1/right evoked stimuli resulted in significantly larger cortical lateralization in the long delay and unilateral groups compared with the normal group [ANOVA:





**Figure 5** A factor analysis of demographic variables and lateralization percentage evoked by CI-1/right and CI-2/left stimuli was conducted to examine how each variable relates to the others. Each axis (black lines) represents a factor that contributes to the variance of one of the variables. The end co-ordinate of each variable (red, green and blue lines) indicates how much of that variable's variance is explained by each factor. A dominant contribution for each of three factors was found (red lines). Factor 1: duration of unilateral use; Factor 2: age at CI-1; and Factor 3: duration of bilateral cochlear implant use. Factor 1 (duration of unilateral use) contributes almost entirely to both CI-1/right and CI-2/left lateralization percentage, which are shown in green. As such, any correlation between lateralization and one of the variables highlighted in blue is a result of correlations between these variables and duration of unilateral implant use.

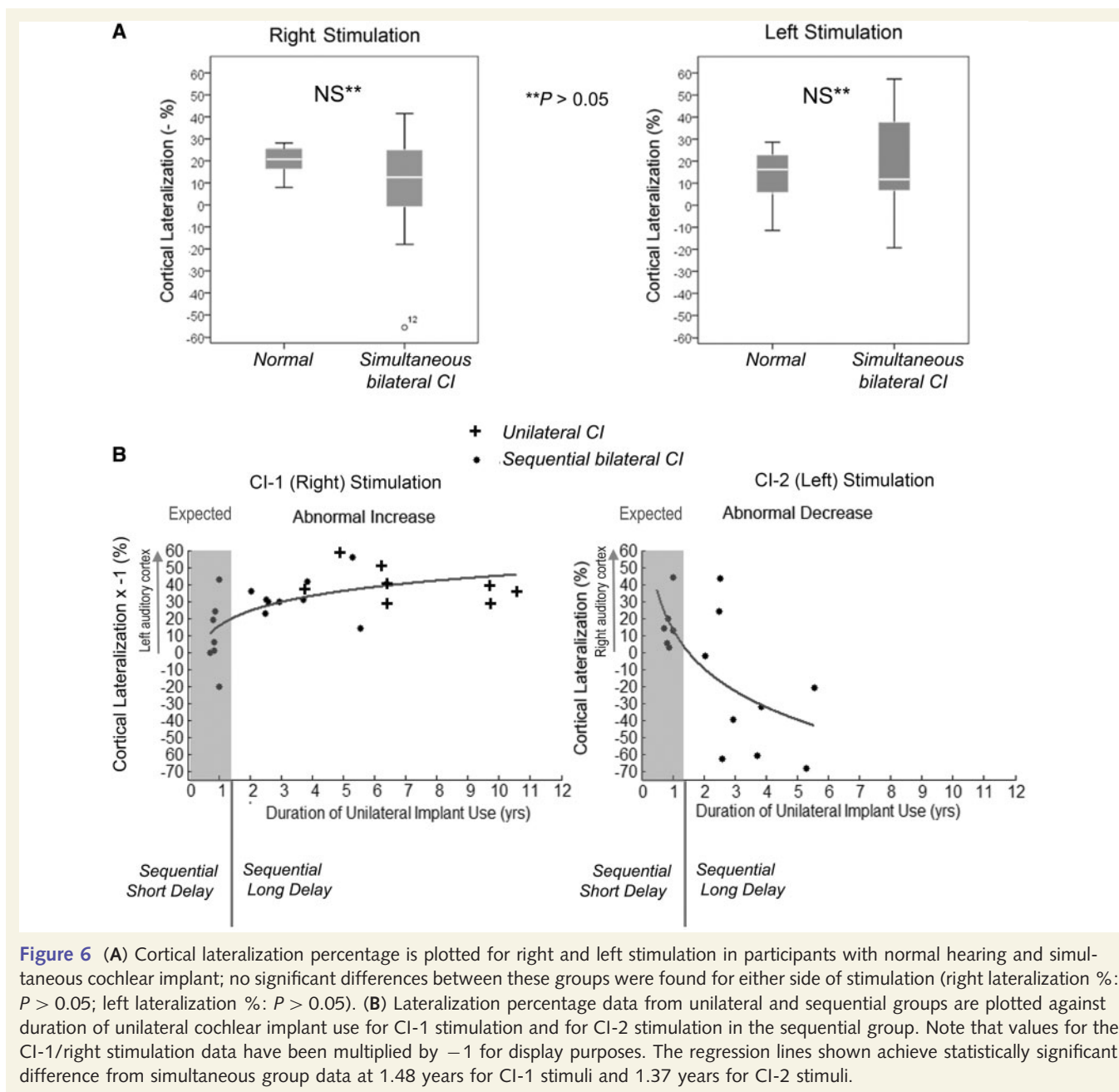
$F(3,28) = 3.62$ ,  $P < 0.05$ ; long delay versus normal:  $t(14) = 2.45$ ,  $P < 0.05$ ; unilateral versus normal:  $t(13) = 4.33$ ,  $P < 0.001$  and significantly reduced cortical lateralization relative to the normal group in response to CI-2/left stimulation [ANOVA:  $F(3,28) = 5.5$ ,  $P < 0.005$ ; long delay versus normal:  $t(14) = 2.36$ ,  $P < 0.05$ ].

## Unilateral cochlear implant use increases activity in contralateral and ipsilateral auditory cortices

We hypothesized that increased lateralization of activity to the left auditory cortex in unilateral cochlear implant users reflects increased activity in the left auditory cortex rather than reduced activity in the right auditory cortex. Data shown in Fig. 7B and C confirm this hypothesis. Grand mean virtual sensor data for sources in the right and left auditory cortices in each group are shown in Fig. 7B and the mean dipoles at the P1 and P1ci peaks are shown in Fig. 7C. Marked increases in P1 and P1ci dipole moments are evident in the left auditory cortex in the two groups with  $>2$  years of unilateral cochlear implant use (long delay and unilateral groups) both when stimulated with CI-1 [ $F(4,36) = 3.52$ ,  $P < 0.05$ ; long delay versus normal:  $t(14) = 2.71$ ,  $P < 0.05$ , unilateral versus normal:  $t(13) = 2.28$ ,  $P < 0.05$ ; long delay versus unilateral:  $t(15) = 0.55$ ,  $P > 0.05$ ] and in response to CI-2 [ $F(3,29) = 5.31$ ,  $P < 0.01$ ; long

delay versus normal  $t(14) = 3.82$ ,  $P < 0.005$ ]. P1 and P1ci activity in the right auditory cortex was not significantly different between groups for either CI-1/right [ $F(3,29) = 1.93$ ,  $P > 0.05$ ] or CI-2/left stimulation [ $F(3,29) = 2.44$ ,  $P > 0.05$ ].

Effects of the side of stimulation were further analysed at each cortical hemisphere in all children with bilateral hearing. In each hemisphere, activity evoked by contralateral versus ipsilateral ears was calculated [stimulus preference (%) = (dipole evoked by contralateral stimulation – dipole evoked by ipsilateral stimulation) / (ipsilateral + contralaterally evoked dipoles)  $\times 100$ ]. The mean ( $\pm 1$  SE) of these data are shown for each group of bilateral listeners in Fig. 8. The left auditory cortex shows an increase in activity stimulated by the contralateral side (CI-1/right) (positive values) in all groups with no significant difference between the per cent of contralateral preference [ANOVA:  $F(3,31) = 0.64$ ,  $P > 0.05$ ]. In the right auditory cortex, contralateral preference (for left stimulation) was found in all groups but not in the long delay group. This difference approached significance [ANOVA:  $F(3,31) = 2.89$ ,  $P = 0.05$ ]. Further analyses of the proportions of contralateral preference in the right auditory cortex were conducted. There were no differences between the proportion of children in the normal, simultaneous and short delay groups with contralateral preference [normal: six of seven (86%); simultaneous: 9 of 12 (75%); short delay: five of seven (71%)]

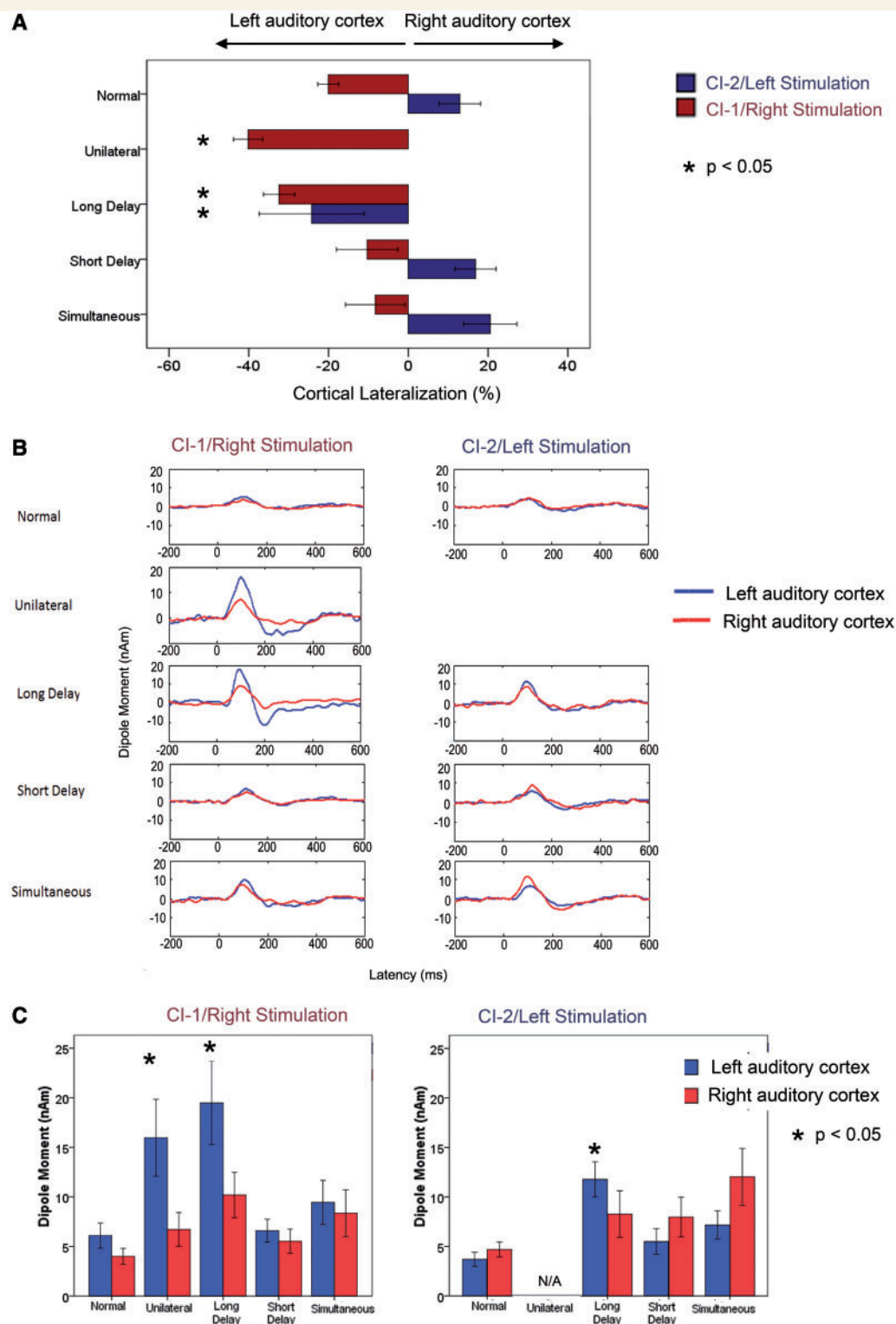


$[X^2(1) < 0.45, P > 0.05]$ . By contrast, many of the children in the long delay group [six of nine (67%)] showed a reversal of the normal contralateral pattern toward ipsilateral preference  $[X^2(1) = 4.39, P < 0.05]$ . This reflects an abnormal increase in activity promoted by the first implanted ear in children with long periods of unilateral hearing prior to bilateral implantation.

### Long periods of unilateral cochlear implant use result in asymmetric speech perception abilities

Effects of cortical reorganization measured by abnormalities in cortical lateralization and stimulus dominance were compared to scores of speech perception accuracy in the 26 bilateral cochlear

implant users. As shown in Table 2, there was a tendency for increases in cortical lateralization toward the left hemisphere with CI-1/right stimulation to occur with decreases in speech perception in both CI-1/right and CI-2/left ( $R = -0.37, P = 0.06$  and  $R = -0.034, P = 0.09$ , respectively). The decrease in contralateral cortical lateralization from CI-2/left ear tended to occur with decreases in speech perception when using CI-1/right ( $R = 0.36, P = 0.07$ ) and significantly correlated with decreases in speech perception using CI-2/left ( $R = 0.47, P = 0.02$ ). There was also a tendency for increases in asymmetry of speech perception between the ears (poorer CI-2 than CI-1 scores) as the lateralization decreased from the contralateral to ipsilateral cortex ( $R = -0.38, P = 0.05$ ). The change in stimulus preference from contralateral to ipsilateral in the right hemisphere tended to correlate with



**Figure 7** (A) Per cent cortical lateralization (mean  $\pm$  1 SE) is plotted for each participant group. Greater than normal contralateral lateralization to right/CI-1 stimuli was found in long delay and unilateral cochlear implant users ( $P < 0.05$  and  $< 0.0001$ , respectively) but not in short delay and simultaneous groups ( $P > 0.05$ ). The long delay group showed a decrease in contralateral lateralization/increase in ipsilateral lateralization relative to those with normal hearing in response to left/CI-2 stimulation. This did not occur in the short delay and simultaneous groups. (B) Grand mean virtual sensor data for left and right hemispheric sources of P1 (normal hearing) and P1ci (cochlear implant users) for stimulation from right/CI-1 and left/CI-2. Large peaks in responses to CI-1 (right) stimulation can be seen in the long delay and unilateral group data. (C) Left and right hemispheric dipole moments (mean  $\pm$  1 SE) for P1/P1ci in each group in response to right/CI-1 and left/CI-2 stimulation. In response to CI-1 (right) stimulation, there is a marked increase in left hemispheric dipole moments in participant groups with  $> 2$  years of unilateral hearing experience (long delay and unilateral;  $P > 0.05$ ). Dipole moment in the ipsilateral left cortex is also increased in the long delay group compared to normal in response to CI-2 (left) stimulation.



decreases in CI-2 speech perception ( $R = 0.36$ ,  $P = 0.07$ ) and an increase in asymmetry (poorer CI-2 scores) ( $R = -0.38$ ,  $P = 0.05$ ). There were no correlations between the degree of contralateral stimulus preference in the left hemisphere and speech perception scores ( $R < |0.12|$ ,  $P > 0.50$ ).

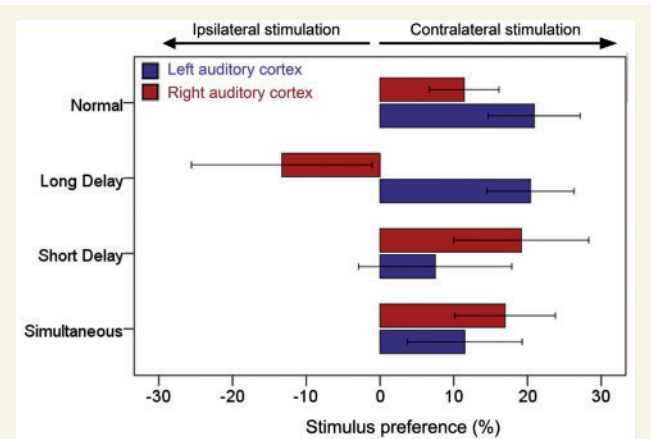
# Discussion

Our results indicate that extended periods of right-sided unilateral cochlear implant use ( $>2$  years) give rise to a greater than normal increase in auditory cortex lateralization toward the contralateral (left) hemisphere (Figs 6, 7A and 8) reflecting an increase in activity evoked by the CI-1 to the contralateral (left) auditory cortex

(Fig. 7B and C). Moreover, these children show a reversal of normal right auditory cortex activity; responses are no longer larger when evoked by the contralateral (CI-2/left) than ipsilateral (CI-1/right) ear (Fig. 8), which significantly correlates with decreasing speech perception in the second implant (Table 2). This reorganization persists even after several years of bilateral cochlear implant stimulation; however it can be significantly lessened by providing bilateral cochlear implants with shorter delays. Bilateral implantation thus protects the auditory cortices from unilaterally-driven changes to sustain normal cortical lateralization and stimulus preference.

# Unilateral cochlear implant stimulation increases activity in contralateral auditory cortex

Abnormally large contralateral lateralization of activity would result if there was over-strengthening of the crossing neural projections between the right ear and the left auditory cortex during unilateral stimulation and/or an under-development of the ipsilateral projections. Analysis of the dipole moments stimulated by input to the right ear (Fig. 7B and C) indicates no apparent difference in activation of the right cortical hemisphere between the groups of children with unilateral implants. By contrast, there was increased activity in the left hemisphere in the groups who had used their first (right) implant for  $>2$  years (long delay and unilateral) compared with children with normal hearing or children who received bilateral cochlear implants with short or no delays (short delay and simultaneous) both when stimulated from the first cochlear implant and from the second cochlear implant. There were also important changes in the side of stimulus preference; the long delay group showed a reversal of normal patterns in the right auditory cortex with stronger responses from the ipsilateral (CI-1) ear (Fig. 8). Thus, unilateral cochlear implantation promotes an abnormally high degree of synchronous activity in the contralateral auditory cortex and disrupts normal patterns in the ipsilateral auditory cortex.



**Figure 8** Mean ( $\pm 1$  SE) stimulus preference [(dipole evoked by contralateral stimulus – dipole evoked by ipsilateral stimulus / contralateral + ipsilaterally evoked dipoles)  $\times 100$ ] for the right and left auditory cortices are shown. Normal contralateral preference was found in all groups in the left auditory cortex but the long delay group showed a reversal of this pattern in the right hemisphere. This reflected larger dipoles from the first implanted ear in the ipsilateral auditory cortex in this group.

**Table 2** Pearson correlations between evoked cortical activity and speech perception

		Speech Perception		
		CI-1	CI-2	Asymmetry (CI-1–CI-2)
Cortical lateralization (%) CI-1/right stimulation	Pearson correlation	-0.37	-0.34	0.19
	Sig. (two-tailed)	0.06	0.09	0.35
	<i>n</i>	26	26	26
Cortical lateralization (%) CI-2/left stimulation	Pearson correlation	0.36	0.47	-0.39
	Sig. (two-tailed)	0.07	0.01	0.05
	<i>n</i>	26	26	26
Stimulus preference (%) Right hemisphere	Pearson correlation	0.15	0.36	-0.38
	Sig. (two-tailed)	0.47	0.07	0.05
	<i>n</i>	26	26	26
Stimulus preference (%) Left hemisphere	Pearson correlation	-0.03	-0.10	0.12
	Sig. (two-tailed)	0.90	0.62	0.56
	<i>n</i>	26	26	26

The increased activation of the left auditory cortex in the children who received a unilateral cochlear implant is consistent with a larger than normal area of contralateral cortical activity reported in congenitally deaf white cats who were implanted unilaterally (Kral *et al.*, 2002) and large areas of neural activation in inferior colliculus after unilateral cochlear implant stimulation (Snyder *et al.*, 1990). These observations could be explained by the rapid onset of the electrical pulses from the cochlear implant and the wide spread of delivered current that promote more synchronous and larger responses from the auditory pathways (Moore, 1991; Gordon *et al.*, 2003, 2007c). Although this explanation is well-founded, the increase in cortical lateralization occurs in children with considerable unilateral cochlear implant experience and not in children whose bilateral implants were provided with minimal delay. Thus, we cannot attribute abnormal cortical lateralization, which reflects increases in activity in the auditory cortex, to cochlear implant stimulation. Our results indicate, rather, that expansions of activity in the auditory cortex contralateral to a unilateral cochlear implant in the developing human auditory system are due to the lack of significant input from the unimplanted side.

The increase in activation of the right auditory cortex with long term unilateral hearing in the ipsilateral ear bears out the predictions of animal studies of unilateral deafness. Kral and colleagues (2013) recently reported a reversal of normal patterns of activity in the auditory cortex ipsilateral to the stimulated/hearing ear (i.e. contralateral to the deaf ear) in congenitally deaf white cats when unilateral hearing was initiated at young ages. Specifically, ipsilaterally evoked responses were of greater amplitude and reduced latency relative to responses from contralateral ear input whereas the opposite was found in normally hearing cats. Similar to the cats with early onset unilateral hearing, the children participating in the present study were deaf from young ages and exposed to unilateral stimulation early in life; they too showed a loss of normal patterns of activity in the right auditory cortex when right unilateral cochlear implant use exceeded 2 years. Consistencies between the two species confirm that pathways from the deprived ear retain connections to both sides of the auditory brain but also indicate that there is an abnormal expansion of connections from the stimulated ear when the other ear is left without hearing for extended periods. Thus, bilateral input appears to be important in development of the bilateral auditory pathways.

## Unilateral auditory stimulation restricts binaural inhibition

Without bilateral input, important inhibitory processes are missing, perhaps permitting an abnormal strengthening of contralateral pathways with ongoing stimulation from one ear. Normally, converging excitatory and inhibitory inputs to the superior olive of the brainstem provide the auditory pathways with information about interaural level differences, setting the foundation for binaural processing along the auditory pathways (Moore, 1991). It is clear that inhibition is an integral part of activation in the bilateral human auditory system; amplitudes of auditory brainstem responses and

middle latency responses from the thalamo-cortex decrease when evoked by binaural presentations of stimuli as compared with the sum of responses from monaural presentations (stimuli presented to left and right ears separately) (Riedel and Kollmeier, 2002; Smith and Delgutte, 2007; Gordon *et al.*, 2012). Auditory deprivation on one side may interfere with binaural inhibitory circuits (Takesian *et al.*, 2009), allowing stimulated activity in contralateral pathways to be projected without suppression. If so, there would be good opportunity for the immature pathways from the stimulated side to become abnormally strengthened with cochlear implant use. This is keeping with the Hebbian view of development, which indicates that successful and repeated communication between two neurons strengthens their synaptic efficiency (Hebb, 1949). Moreover, it is consistent with our previous findings of asymmetric brainstem response latencies in children with long delays between implants compared to children implanted simultaneously or with short delays (Gordon *et al.*, 2007a, 2008, 2012). The persistently slow latencies evoked by the newly implanted ear suggest a weakening of these pathways relative to those stimulated by the more experienced ear. Unimpeded strengthening of pathways during the period of unilateral hearing could also account for the increased ipsilateral dominance in the hemisphere ipsilateral to the stimulated ear.

## Developmental effects of bilateral input

Our results in children show two main differences from cortical responses to sound measured in adults: (i) the degree of contralateral activity in children with bilateral hearing early in development was similar in both ears; and (ii) there was an increase in activity contralateral to the hearing ear.

Both ears showed similar degrees of contralateral lateralization in children with little to no unilateral hearing (normal, simultaneous, short delay) whereas, in adults with normal hearing, the left ear evokes more contralateral activity than the right ear (Hine and Debener, 2007; Schonwiesner *et al.*, 2007). These asymmetries are associated with a bias for spatial processing to occur in the right auditory cortex (Palomaki *et al.*, 2000, 2005; Zatorre and Penhune, 2001; Krumbholz *et al.*, 2007). It is possible that this specialization is either immature and/or is not reflected by the P1 response measured here. Indeed, much of this processing likely occurs in association areas of the auditory brain (Krumbholz *et al.*, 2007) that are relatively late to mature (Moore and Guan, 2001; Moore, 2002). The P1 and P1ci responses, recorded and analysed in the children studied, attest to the immaturity of the auditory cortices even in children who were oldest and had normal hearing (normal group). The immature P1 response represents activity from excitatory thalamic inputs to the cortical pyramidal neurons in layers III/IV of the auditory cortex. As interhemispheric projections mature in the superficial layers, a characteristic negative amplitude peak at ~100 ms emerges (N1) (Ponton *et al.*, 2002). A period of unilateral cochlear implant use could compromise the development of specialized auditory cortices as measured by the N1. This is consistent with reduced N1 amplitudes and abnormal cortical lateralization of activity underlying this response in a group of adult implant users (Sandmann *et al.*, 2009). In that cohort, abnormally low contralateral activity was

associated with poor speech perception. Similarly, the children studied here showed a decrease in contralateral activity from the second implanted ear that was correlated with poorer speech perception in that ear (Table 2). Children with normal cortical lateralization (simultaneous and short delay groups) at early stages of bilateral cochlear implant thus appear to have better potential for developing normal bilateral auditory pathways; however, we will have to patiently wait for these children to grow older to determine whether this foundation supports maturation of auditory cortices with normal specialization of spatial cues on the right and temporal cues on the left.

The second difference evident in our data, relative to that in adults, is that the abnormalities in cortical activity measured in children with considerable unilateral stimulation appear to counter the changes in cortical function in adults who lost hearing on one side. Late onset unilateral deafness results in a loss of cortical lateralization as measured by a more symmetrical activation of the left and right auditory cortices (Fujiki *et al.*, 1998; Khosla *et al.*, 2003; Langers *et al.*, 2005; Firszt *et al.*, 2006; Li *et al.*, 2006; Hanss *et al.*, 2009; Burton *et al.*, 2012). By comparison, we found increased asymmetry in children using unilateral cochlear implants for almost 2 years or more in the cortex contralateral to the stimulated ear and a reversal of normal stimulus dominance in the ipsilateral cortex. This contrast with the adult findings might have been explained by use of cochlear implant electrical stimulation in the children but, as already discussed, normal lateralization patterns were maintained when bilateral cochlear implants were provided with minimal delays. Rather, the most obvious difference is that the response of a developed bilateral auditory system to a loss of unilateral input is different from that of the immature and deaf system that only receives input from one side. In the adult case, homeostatic plasticity would likely play a role in compensating for the loss of bilateral input whereas development of the immature and deaf pathways will be shaped by the unilateral input.

## Bilateral input provided later than the sensitive period does little to restore cortical symmetry

Data from the present study indicate that increases in cortical lateralization with unilateral cochlear implant use (~2 years or more) is not reversed by long term bilateral cochlear implant use (3–4 years). Indeed, there were no significant differences in cortical lateralization in response to CI-1 between the children using bilateral cochlear implants in the long delay group and the unilateral group. This cannot be explained by insufficient stimulation from the second side in the former group; stimulation from CI-2 resulted in cortical activity in both hemispheres. Moreover, dipole moments in the right (contralateral) auditory cortex to CI-2 were not significantly different in the long delay group relative to normal and other cochlear implant groups (Fig. 7C). A similar result was obtained in congenitally deaf white cats after several months of unilateral cochlear implant use (Kral *et al.*, 2002). Cochlear implants were placed in the opposite ears and acute stimulation from these naïve sides revealed activation in the contralateral auditory cortex (ipsilateral to the chronically stimulated side), which was similar to that evoked acutely in

auditory-deprived deaf white cats. The authors interpreted this to mean that unilateral cochlear implant use in the cats did not suppress responses from the ‘untrained’ ear. Unfortunately, they did not measure activity in the opposite hemisphere.

In the present study, we found that increases in cortical activity in the left (contralateral) auditory cortex with CI-1 use in children were also present when stimulus was delivered from CI-2. On the one hand this might be beneficial; the developmental change in the brain can be accessed by the second implant. This might explain to some degree why children are able to understand speech through CI-2 more quickly than they did when first implanted (albeit less accurately) (Wolfe *et al.*, 2007; Gordon and Papsin, 2009). On the other hand, this change was significantly correlated with decreasing speech perception in the second implanted ear with a trend toward decreasing abilities with the first cochlear implant and an increase in the asymmetry of speech perception between the two sides as shown in Table 2. Increased stimulation of the left auditory cortex evoked by CI-1 (in the right ear) and CI-2 (in the left ear) in the long delay group implies that the newly stimulated pathways do not successfully compete with the more established pathways from the first implanted ear and/or that there is limited sensory integration between the two pathways. If the latter is true, each pathway may be operating more independently than normal thereby limiting binaural processing and explaining the behavioural outcomes. By contrast, children who show more symmetric and normal degrees of cortical lateralization and stimulus dominances in both cortical hemispheres, such as those in the simultaneous and short delay groups, might have better potential to develop binaural hearing through their bilateral cochlear implants. In support are reports of improved use of spatial separation to detect speech in noise in these children (Chadha *et al.*, 2011) and advantages of early bilateral input for sound localization (Van Deun *et al.*, 2010). Future studies will need to compare current results to those evoked by binaural stimulation in order to isolate any binaural processing deficits in the auditory cortices of children using bilateral cochlear implants.

## Limitations of the head model for beamformer analyses

It must be kept in mind that the reliability of beamformer methods is influenced by how accurately the conduction of currents from dipole sources in the brain to recording electrodes on the scalp is calculated. A perfectly accurate calculation requires a head model that exactly represents the geometry and anisotropic conductivity of all the tissues in each participant's head as well the position of the electrodes on the scalp. Generating such a realistic head conductivity model is currently not practical; simplifying assumptions are thus made. In the present study, we did not have any individual MRI information and precise electrode position data were not collected. Instead, we used three-layer boundary element head models constructed from an adult head template MRI that was geometrically adjusted for age using the Template-O-Matic toolbox (Wilke *et al.*, 2008) as detailed in the Supplementary material. Tissue conductivities for the head models were taken from Roth *et al.* (1993) and electrode positions



were based on a 3D template representation of the electrode cap. These head models are geometrically representative of each age group but do not account for individual differences in head geometry, tissue conductivity or recording electrode position relative to the electric potential. Deviations created by the head conductivity model could increase errors in dipole location and amplitude and, because the tissue conductivity was based on adult data, there could be a systematic error with age-dependent changes in tissue conductivity (Wendel *et al.*, 2010). To ensure these errors were minimal, we compared sources measured by magnetoencephalography (MEG) and EEG in the same individuals and found that they were significantly correlated (Supplementary material). A direct comparison cannot be made, however, as MEG and EEG measure differently oriented dipoles. In addition, we only obtained MEG measures in adolescents with normal hearing so we cannot be sure that this correlation holds for all ages. Nonetheless, no age dependence of hemispheric lateralization was found in the factor analysis (Fig. 5), which suggests that any effect of age on the cortical lateralization (%) measure would be smaller than the effect of unilateral implant use.

## Conclusion

Results from the present study demonstrate that: (i) unilateral cochlear implant use during early childhood disrupts bilateral auditory pathways by allowing an abnormal expansion of activity from the stimulated ear in both auditory cortices but most dramatically in the contralateral hemisphere; and (ii) this reorganization can be avoided in children who are deaf when two cochlear implants are provided with minimal delay (<1.5 years) with improvements in speech perception. Thus, there is a sensitive period for binaural input in the human auditory system.

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## Supplementary material

Supplementary material is available at *Brain* online.

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