Functional Magnetic Resonance Imaging of Hearing-Impaired Children Under Sedation Before Cochlear Implantation

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Objective: To investigate functional magnetic resonance imaging (fMRI) in pediatric cochlear implantation candidates with residual hearing who are under sedation for evaluation of auditory function.

Design: During fMRI, subjects heard a random sequence of tones (250-4000 Hz) presented 10 dB above hearing thresholds. Tones were interleaved with silence in a block-periodic fMRI design with 30-second on-off intervals. Twenty-four axial sections (5 mm thick) covering most of the brain were obtained every 3 seconds for a total acquisition time of 5.5 minutes.

Setting: Single tertiary academic medical institution.

Patients: Severely to profoundly hearing-impaired children (n=10; mean age, 49.1 months). During fMRI, subjects were awake (n=2) or sedated with pentobarbital sodium if their weight was 10 kg or greater (n=4) or chloral hydrate if their weight was less than 10 kg (n=4).

Main Outcome Measures: Detection of brain activation by fMRI in the primary auditory cortex (A1) in hearing-impaired patients under sedation, and correlation of A1 activation with hearing levels measured after cochlear implantation.

Results: In most subjects, fMRI detected significant levels of activation in the A1 region before cochlear implantation. The improvement in hearing threshold after cochlear implantation correlated strongly (linear regression coefficient, $R=0.88$) with the amount of activation in the A1 region detected by fMRI before cochlear implantation.

Conclusions: Functional MRI can be considered a means of assessing residual function in the A1 region in sedated hearing-impaired toddlers. With improvements in acquisition, processing, and sedation methods, fMRI may be translated into a prognostic indicator for outcome after cochlear implantation in infants.

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It has been estimated that approximately 60 infants are born each day in the United States with significant hearing loss (1 to 6 infants per 1000). The effects of early hearing loss on communication development, as well as social and educational development, are well documented. A growing body of evidence now supports the benefit of early detection of congenital hearing loss and the concomitant implementation of early intervention strategies.

Current research suggests that the development of language-relevant areas in the brain may be significantly altered in hearing-impaired (HI) children compared with normal-hearing children. As with other neurocognitive systems, early language experience and biological circuitry interact to stimulate and support mutual development of structure and function. With the advent of universal newborn hearing screening in nearly all areas of the United States, the average age of diagnosis of congenital hearing impairment has now decreased to 3 to 6 months, thereby increasing the likelihood for appropriate early intervention in these infants.

Cochlear implantation is an effective way of restoring hearing in children with severe to profound sensorineural hearing loss. The application of cochlear implants has extended to include children with pure-tone averages ranging from an 80- to 100-dB hearing level. An impetus for consideration of children with significant residual hearing for implantation arose from the sizable proportion of such children not experiencing progress with their hearing aids at the same rate as those with implants. Outcome studies and comparisons with hearing aid users have established that cochlear implantation can produce communication benefits, particularly improved speech understanding, even in children with significant residual hearing.
The clinical dilemma is predicting the likelihood of substantial communication benefits from cochlear implantation in infants and children with residual hearing. Several highly sensitive diagnostic instruments are available that reliably evaluate various aspects of peripheral hearing acuity and sensory function using nonbehavioral methods, such as the auditory brainstem response, otoacoustic emissions, and auditory steady-state response. However, the nature of higher auditory cortical processing and perception in the HI neurosystem is not well characterized by the battery of instrumentation traditionally used. An objective and minimally invasive tool that assists in describing central auditory system function and ultimately in determining the potential speech perception benefit from cochlear implantation is highly desirable.

Functional magnetic resonance imaging (fMRI) has been used previously to examine brain activation in response to auditory and language stimulation in children and infants. Cortical activation results in localized increases in blood flow that in turn cause a change in signal intensity in MRIs constructed using methods that are sensitive to small changes in magnetization associated with blood oxygenation. In these MRIs, the activated and nonactivated cortices have measurably different signal intensities, and brain activation maps can be constructed from the contrast between brain images of the activated and nonactivated states. This MRI method is termed blood oxygenation level–dependent (BOLD) contrast and is the technique used for fMRI.

Although sedation is typically required in pediatric populations to obtain a complete evaluation, several investigations have shown that subjects given passive auditory stimulation under various types of sedation have exhibited a positive BOLD signal response. Functional neuroimaging techniques may be useful in evaluation of central auditory function in children who are candidates for cochlear implantation. Specifically, fMRI may permit differentiation of brain responses corresponding to auditory detection, speech perception, and language processing in normal-hearing and HI infants. The ability of fMRI to demonstrate neural representation of auditory perception may provide important information regarding various aspects of auditory and language processing in infants and toddlers.

In the present study, we examined the relationship between preimplantation cortical activation and improvement in pure-tone audiometry thresholds after cochlear implantation in HI children. We hypothesized that children with severe to profound sensorineural hearing loss with residual auditory cortical activity as shown by IMRI would also have greater improvement in pure-tone auditory thresholds after cochlear implantation.

### METHODS

#### SUBJECTS

Ten HI children (median age, 26 months; mean age, 49.1 months; 4 boys and 6 girls) were recruited for this feasibility study through the Departments of Otolaryngology and Radiology, according to an institutional review board–approved protocol, and informed consent was obtained from the parents or the guardian. The HI subjects all had at least minimal residual hearing levels, with pure-tone audiometry ranging from 75 to 115 dB, placing them in the classification of severe to profound hearing loss. None of the subjects in this study had a conductive hearing loss, as indicated on their clinical audiograms before and after cochlear implantation. Four patients had small internal auditory canals, as shown by preoperative computed tomography. To rule out a cochlear nerve aplasia, MRI studies were obtained. In 3 patients, a cochlear nerve was definitively observed within the internal auditory canal. In the last patient, interpretation of computed tomographic scans and MRI by a neuroradiologist was equivocal for the anatomic presence of a cochlear nerve. However, physiologically, the patient demonstrated consistent auditory responses on serial audiologic testing. Accordingly, the presence of a (poorly) functioning cochlear nerve was assumed. Patients demonstrating no audiological responses and lacking definitive anatomic evidence of a cochlear nerve on high-resolution imaging studies are not considered candidates for cochlear implantation at our institution.

Owing to the loudness of the MRI scanner gradients during IMRI, no auditory tone testing was performed during the imaging procedure. Audiological testing was performed in all subjects as part of the standard referral pathway for cochlear implantation at our institution. Pure-tone audiometry was performed on these subjects by a credentialed pediatric audiologist before implantation using sound field audiometry. These tests were repeated after cochlear implantation. The improvement in hearing threshold for each subject was calculated from the difference in pure-tone average hearing thresholds before and after cochlear implantations. This difference was based on the most recent preimplantation and postimplantation audiograms, with the most improved hearing level reported in the patient’s medical chart, up to 18 months after implantation.

All sedation procedures were performed by the Department of Pediatric Radiology to obtain a clinically indicated MRI requested by the patients’ referring physician. Children weighing less than 10 kg (typical age, 0-24 months) were sedated using orally administered chloral hydrate at a dose of 75 to 100 mg/kg. Children younger than 7 years but weighing 10 kg or greater were sedated using intravenous pentobarbital sodium (Nembutal; Baxter International Inc, Deerfield, Illinois) administered at a dose of 3 to 5 mg/kg. Subjects were excluded for any standard contraindications to an MRI, such as metal implants, orthopedic pins or plates above the waist, and orthodontic braces.

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### MRI SETTINGS

Following sedation for MRI, subjects were placed on the table in the scanner. Magnetic resonance–compatible headphones (Avotec Inc) were placed over the subject’s ears, and the head was restrained within a padded head holder with additional foam...
pads to minimize head motion. Prescribed clinical MRIs were completed first, and the fMRIs were added at the end of the clinical routine. Eight of 10 subjects underwent MRI on a 1.5-T scanning system with echo-speed gradients (GE Signa Horizon; General Electric Medical Systems, Milwaukee, Wisconsin); 2 subjects, on 3-T systems (Bruker Biospec 30/60 MRI system [Bruker Medizintechnik, Karlsruhe, Germany] for the nonanesthetized subject and a Siemens MRI system [Siemens Medical Solutions, Erlangen, Germany] for the other subject). Functional MRI was performed on these systems using a gradient-echo, echo planar imaging method. A time series of 110 echo planar imaging gradient-echo images (repetition/echo times, 3000/50 milliseconds) was acquired during each fMRI paradigm. The raw echo planar imaging data was Hamming windowed before reconstruction to reduce the truncation artifacts at the edges of k-space and to reduce high-frequency noise in the images. The data were corrected for motion using a pyramid iterative coregistration algorithm. After collection, the fMRI data were processed using the general linear model. A set of cosine basis functions was used as covariates to account for possible signal drift and aliased respiratory and cardiac signals. The z-score maps were computed and smoothed in 3 dimensions with a Gaussian filter of 4-mm width. Activated pixels were detected during the tone task in a region of interest (ROI) defined bilaterally in the auditory cortex at a threshold of $P<.05$ with a spatial extent threshold of 5 voxels. To create the individual activation maps displayed in Figure 1, a fixed-effects analysis was performed to find regions of significant activation as defined in the second sentence of this paragraph. Specificity was further improved using the clustering method proposed by Xiong et al.

The fMRI activation was parameterized by counting the number of pixels that exceeded the $P<.05$ threshold within an ROI defined bilaterally in the auditory cortex of each subject. The ROI was defined manually by consensus of 2 neuroimaging experts (A.M.P. and S.H.I.) to encompass the full extent of the primary auditory cortex (A1) located within the transverse temporal gyrus (the Heschl gyrus and Brodmann area 41), identified in each subject’s anatomic images. The A1 ROI typically spanned 3 to 5 fMRI sections (nominal section thickness, 5 mm) for the subjects and images included in this study. Within this A1 ROI, the total number of suprathreshold pixels was tallied and then used in the graph of Figure 2 and in the linear regression of pixel count vs improvement in hearing threshold.

These data are from children undergoing MRI on a 3-T MRI system (Bruker Biospec 30/60) without sedation ($n=1$), on a 1.5-T MRI system scanner (GE Signa Horizon) without sedation ($n=2$) and with sedation ($n=6$),

### RESULTS

The 3-dimensional anatomic and fMRI data were processed using Cincinnati Children’s Hospital Image Processing Soft-

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**Figure 1.** General linear model z-score map showing positive (yellow) and negative (blue) activation ($P<.05$), overlaid on an anatomic image with the primary auditory cortex region of interest outlined in white. The patient is a 2-year-old hearing-impaired child, sedated with pentobarbital sodium (Nembutal) for scanning on a 1.5-T magnetic resonance imaging system.

**Figure 2.** Improvement in hearing level vs brain activation. The graph shows the strong correlation (linear regression coefficient, $R=0.88$) between the improvement in hearing threshold after cochlear implantation and the amount of activation in the primary auditory cortex (A1) detected by functional magnetic resonance imaging before surgery.
and on a 3-T MRI system (Siemens Medical Solutions) with sedation (n = 1). The Table shows a list of subjects, which MRI system was used, their age in months, and what type of sedation was administered (none, chloral hydrate, or pentobarbital), the improvement in hearing threshold (ΔHL), and the number of activated voxels identified in the ROI.

Table. Subject Age, MRI System, and Type of Sedation Used

<table>
<thead>
<tr>
<th>Subject No./Age, mo</th>
<th>MRI System (T)</th>
<th>Sedation</th>
<th>ΔHL, dB</th>
<th>A1 Pixels</th>
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<tr>
<td>1/149</td>
<td>GE (1.5)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>31</td>
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<td>4/15</td>
<td>GE (1.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pentobarbital&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>0</td>
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<td>Pentobarbital&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>116</td>
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<td>6/33</td>
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<td>Pentobarbital&lt;sup&gt;d&lt;/sup&gt;</td>
<td>52</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations: A1, primary auditory cortex; ΔHL, improvement in hearing threshold; MRI, magnetic resonance imaging.

<sup>a</sup>Indicates GE Signa Horizon (General Electric Medical Systems, Milwaukee, Wisconsin).
<sup>b</sup>Indicates Siemens (Siemens Medical Solutions, Erlangen, Germany).
<sup>c</sup>Indicates Bruker Biospec 30/60 (Bruker Medizintechnik, Karlsruhe, Germany).
<sup>d</sup>Administered as pentobarbital sodium (Nembutal).

Figure 1 depicts an activation map for a typical sedated, 2-year-old HI subject undergoing MRI on a 1.5-T MRI system. This patient was sedated with pentobarbital and had a preimplantation hearing threshold of 115 dB in both ears. The general linear model z-score map shows both positive and negative fMRI activation with a significance threshold of P < .05 in a single section through the A1 ROI during auditory stimulation with the tone task. Pixels labeled in yellow indicate positive BOLD activation, whereas pixels labeled in blue indicate negative BOLD activation. The ROI covering A1 in this section is also displayed on this image. One hundred sixteen activated pixels were counted within the A1 ROI over 3 sections of the brain activation map for this subject. Typically, the Heschl gyrus spans 3 to 4 sections (each 5 mm thick) in these images, but only 1 of these sections is displayed in Figure 1. This image further demonstrates that fMRI can indeed detect central auditory activation in children with severe to profound hearing loss. Furthermore, we observed that central auditory activation is both positive and negative under the influence of sedation during fMRI. This effect has been observed in many of the infants and toddlers in our studies, as well as in reports from other studies involving fMRI in infants and toddlers. Negative activation in fMRI corresponds to a decrease in blood oxygenation that follows increased cortical activity in a localized group of neurons. This effect will occur if neuronal metabolism increases to meet demand but is not accompanied by a concomitant increase in blood flow to deliver the additional oxygen required to support the increased cerebral metabolic rate.

Figure 2 shows the improvement in the pure-tone audiometry hearing threshold in the 10 patients before and after cochlear implantation. The differences are plotted so that the y-axis represents the improvement in hearing threshold after implantation (these values reflect the change in hearing threshold from before to after implantation). The x-axis plots the number of activated pixels detected during the tone task in an ROI defined bilaterally in the A1 ROI, located in the transverse temporal gyrus (Heschl gyrus). When charted in this way, 2 observations become apparent. First, in this limited sample of 10 subjects, IMRI effectively detects significant levels of A1 activation in most of the subjects, before cochlear implantation. Second, the improvement in hearing threshold after implantation correlates strongly (linear regression coefficient, R²=0.88) with the amount of activation in A1 detected by IMRI before implantation.

Severe to profoundly HI children who showed auditory cortical activation with IMRI before cochlear implantation had statistically greater improved pure-tone audiometry thresholds after implantation compared with children who did not show activation. Future research is focused on developing more stringent exclusion criteria for the HI group and on gathering a control group of normal-hearing children. Nevertheless, the present results indicate that, for children with residual hearing under sedation, it is possible to obtain meaningful fMRI responses to auditory stimuli that appear to be related to potential benefit from cochlear implants.

In constructing the typical activation map shown in Figure 1, we avoided the use of the Talairach reference frame and linear spatial normalization. Affine transformation of pediatric brain image data to standardized dimensions defined for an adult brain is not optimal for use with infant brain data. Distortions are particularly noticeable in the anterior temporal lobe region of the images. In earlier studies of language development in normal children, we have found that construction of our own brain image templates for a nonlinear spatial normalization is the best approach for spatial normalization of...
pediatric brain image data.44 We will consider such an approach in future studies of this young population as additional data accrued.

A number of factors affect the success of fMRI for detecting auditory brain stimulation, including those mentioned already as well as acoustic noise presented by the scanner itself. Consequently, we have developed a method in which auditory stimuli can be presented during a silent interval of the MRI gradients, producing hemodynamics unrelated to sounds of hardware (HUSH).45 Unlike previous implementations of behavior interleaved gradient fMRI,46 the HUSH method does not require long acquisition times. Non-equilibrium acquisitions require modified postprocessing methods. However, the auditory activation produced by this method shows promise for further investigations of the developing neural substrates for auditory and language processing in HI infants and children. This technique should improve the specificity of fMRI for evaluating candidates for cochlear implantation in the future.

It is well established that prolonged lack of auditory stimulation will result in irreversible auditory cortical loss that is nonresponsive to cochlear implantation.45,46 Conversely, early implantation (before age 18 months in cases of congenital hearing impairment) is known to facilitate language development.47,48 The mean age of the subject cohort reported herein was 49 months. If we exclude the two 12-year-old children, the mean age of the remaining 8 children was 25 months. This younger subset is more typical of the age of implantation in many programs at present. At our institution, we begin the cochlear implant staging process between ages 6 and 9 months, with an average age range for implantation of 12 to 18 months. It is possible that the duration of deafness in the 2 older children could account for some of the variability in our data. However, for both of these children, the improvement in hearing level after cochlear implantation was greater than in the children who underwent implantation at younger ages. This trend runs counter to what might be expected from the literature,31 suggesting that earlier implantation results in better language performance during the school age years. However, it is important to note that pure-tone average hearing levels as reported in the Table and Figure 2 may not be the best indicator of language performance after implantation. Language measures were not available on the subjects included in this preliminary fMRI feasibility study, but one might expect that children with a longer duration of deafness might not demonstrate as great an improvement in standardized language measures as children undergoing implantation earlier in the developmental period for language. This demonstrates the critical importance of timely clinical decision making in the provision of a surgical implant and implementation of intervention for communication development.

The activation patterns observed in this cohort of children with severe to profound hearing impairment, as shown in Figure 1, appear to replicate the typical patterns observed in normal-hearing children under sedation.32 Similar rates of positive and negative activation in A1 are found in both groups, regardless of the form of sedation. Therefore we believe the incidence of negative activation is not due to the sedation or the hearing impairment in this study. Rather, we hypothesize that the mixture of positive and negative activation in this cohort is a consequence of the immature cerebrovascular system in subjects aged 1 to 3 years.

In addition, a similar pattern of A1 activation has been identified in a large cohort (n = 323) of normal-hearing children and adolescents aged 5 to 18 years who were not sedated.33 Although the activation in the sedated HI subjects in this report seems to be attenuated and to contain a mixture of positive and negative activation, the similarity of the distribution of activated pixels in the A1 ROI provides further assurance that the observed patterns correspond to the tone stimulus administered to these subjects.

A limitation of this study arises from the use of MRI systems operating at different field strengths (1.5 and 3.0 T) and different forms of sedation (chloral hydrate, pentobarbital, or none). This variability in methods might be expected to result in variability in the correlation of fMRI activation in the A1 ROI with post-implantation hearing thresholds as shown in Figure 2. Unfortunately, with the limited sample size in this preliminary study, we are unable to explore the effects of field strength on A1 activation in a statistical manner. However, despite the built-in variability in this pilot study, the correlation between A1 activation and improvement in hearing thresholds as shown in Figure 2 is convincing. In fact, this correlation seems to transcend the influences of sedation, field strength, duration of deafness, and other confounds. The robustness of this finding gives us confidence that fMRI is feasible in this context and, if administered under more carefully controlled conditions, it may offer potentially diagnostic information.

Noninvasive assessment of the cortical response to sound input in an infant who is unable to respond reliably to behavioral auditory system assessment is important for accurate decision making in the cochlear implantation staging process. Functional MRI has the potential to provide clinicians with an advanced, objective diagnostic tool with capabilities beyond peripheral auditory system assessment. This report demonstrates the feasibility of fMRI for assessment of auditory cortical function in severe to profoundly HI infants, even with sedation. More research will be required to demonstrate the utility of fMRI or other neuroimaging methods that highlight auditory cortical function as safe and effective approaches to predict cochlear implantation outcomes in prelingual HI infants and toddlers with residual hearing.

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Author Contributions: Dr Holland had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cahill, Choo, and Holland. Acquisition of data: Ret, Schmithorst, and Holland. Analysis and interpretation of data: Patel, Schmithorst, and Holland. Drafting of the manuscript: Patel, Cahill, and Holland. Critical revision of the manuscript for important intellectual content: Patel, Cahill, Ret, Schmithorst, Choo, and Holland. Statistical analysis: Schmithorst and Holland. Obtained funding: Holland. Administrative, technical, and material support: Patel, Cahill, Ret, Choo, and Holland. Study supervision: Choo and Holland. Financial Disclosure: None reported. Funding/Support: This study was supported in part by grants R21-DC05311 and RO1-HD38578 from the National Institutes of Health. Additional Contributions: The Department of Radiology at Cincinnati Children's Hospital Medical Center performed sedation procedures in pediatric subjects, and the Cochlear Implant Research Team identified appropriate subjects.

REFERENCES


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Correction

Error in Byline. In the Original Article titled “Graded Carbon Dioxide Laser–Induced Subglottic Injury in the Rabbit Model,” published in the April issue of the Archives (2007;133[4]:358-364), an error occurred in the presentation of the fifth author’s name in the byline on page 358. The byline should have appeared as follows: “J. Brett Chafin, MD; Vlad C. Sandulache, PhD; Joshua L. Dunklebarger, MD; Todd D. Otteson, MD; Paul J. Hoffmann, BS; Patricia A. Hebda, PhD; Joseph E. Dohar, MD, MS.”