fMRI as a Preimplant Objective Tool to Predict Postimplant Oral Language Outcomes in Children with Cochlear Implants

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Objectives: Despite the positive effects of cochlear implantation, postimplant variability in speech perception and oral language outcomes is still difficult to predict. The aim of this study was to identify neuroimaging biomarkers of postimplant speech perception and oral language performance in children with hearing loss who receive a cochlear implant. The authors hypothesized positive correlations between blood oxygen level-dependent functional magnetic resonance imaging (fMRI) activation in brain regions related to auditory language processing and attention and scores on the Clinical Evaluation of Language Fundamentals-Preschool, Second Edition (CELF-P2) and the Early Speech Perception Test for Profoundly Hearing-Impaired Children (ESP), in children with congenital hearing loss.

Design: Eleven children with congenital hearing loss were recruited for the present study based on referral for clinical MRI and other inclusion criteria. All participants were <24 months at fMRI scanning and <36 months at first implantation. A silent background fMRI acquisition method was performed to acquire fMRI during auditory stimulation. A voxel-based analysis technique was utilized to generate z maps showing significant contrast in brain activation between auditory stimulation conditions (spoken narratives and narrow band noise). CELF-P2 and ESP were administered 2 years after implantation. Because most participants reached a ceiling on ESP, a voxel-wise regression analysis was performed between preimplant fMRI activation and postimplant CELF-P2 scores alone. Age at implantation and preimplant hearing thresholds were controlled in this regression analysis.

Results: Four brain regions were found to be significantly correlated with CELF-P2 scores. These clusters of positive correlation encompassed the temporo-parieto-occipital junction, areas in the prefrontal cortex and the cingulate gyrus. For the story versus silence contrast, CELF-P2 core language score demonstrated significant positive correlation with activation in the right angular gyrus ($r = 0.95$), left medial frontal gyrus ($r = 0.94$), and left cingulate gyrus ($r = 0.96$). For the narrow band noise versus silence contrast, the CELF-P2 core language score exhibited significant positive correlation with activation in the left angular gyrus ($r = 0.89$; for all clusters, corrected $p < 0.05$).

Conclusions: Four brain regions related to language function and attention were identified that correlated with CELF-P2. Children with better oral language performance postimplant displayed greater activation in these regions preimplant. The results suggest that despite auditory deprivation, these regions are more receptive to gains in oral language development performance of children with hearing loss who receive early intervention via cochlear implantation. The present study suggests that oral language outcome following cochlear implant may be predicted by preimplant fMRI with auditory stimulation using natural speech.

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Key words: Children, Cochlear implants, Functional magnetic resonance imaging, Infants, Language, Preschool, Speech perception.

(Ear & Hearing 2016;37;e263–e272)

INTRODUCTION

Currently, more than 324,200 individuals with hearing loss worldwide have received a cochlear implant (CI; National Institute on Deafness and Other Communication Disorders 2014). As an increasing number of infants with hearing loss are detected at an earlier age, the CI team faces a challenging task of providing parents and teachers with appropriate expectations for oral language outcomes with the implant. Various behavioral tests are administered postimplantation to measure speech, language, and hearing performance of infants and toddlers. However, an objective tool that accurately predicts postimplant oral language performance before CI in infants is still lacking (Zeng 2004).

Multiple factors such as duration of deafness, age at implantation, and duration of implant use play a crucial role in understanding the benefits of cochlear implantation (Tomblin et al. 2005; Wake et al. 2005; Geers et al. 2008; Gilley et al. 2008; Tobey et al. 2013). Children with hearing loss who are identified before 6 months of age and provided with intervention before 8 months of age have better receptive and expressive language skills than those identified later (Yoshinaga-Itano et al. 1998). Research has indicated the importance of early intervention, especially during the critical period for speech-language development (Geers 2006; Kennedy et al. 2006; Sharma & Dorman 2006; Niparko et al. 2010; Colletti et al. 2011; Cardon & Sharma 2013; Tobey et al. 2013; Yoshinaga-Itano 2013). Children who are implanted at an earlier age and who continue to use a CI have better language and speech recognition skills (e.g., McConkey Robbins et al. 2004; Nikolopoulos et al. 2004; Svirsky et al. 2004; Geers & Nicholas 2013; Tobey et al. 2013; Castellanos et al. 2014) due to brain plasticity (Niparko et al. 2010). This body of work influences the clinical decision to identify hearing loss during infancy and to remediate it with hearing aid trials and ultimately, cochlear implantation, as early as 12 months of life. While a number of factors are known to influence the success of post-CI speech and language outcomes, individual postimplant oral language outcomes remain somewhat variable. This is particularly problematic in children with congenital hearing loss, implanted during infancy (Svirsky et al. 2000; Sarant et al. 2001; McKay 2005; Tomblin et al. 2005; Finley & Skinner 2008; Eisner et al. 2010; Green et al. 2012; Tobey et al. 2013). The need exists for better prognostic indicators to provide clinicians and parents with calibrated expectations for speech and language outcomes in such cases. Here, we explore

0196/0202/2016/374-e263/0 • Ear & Hearing • Printed in the U.S.A.

<zdoi; 10.1097/AUD.0000000000000259>

the potential of functional magnetic resonance imaging (fMRI) as one such technique.

Functional MRI makes use of blood oxygen level-dependent (BOLD) contrast to measure brain activity indirectly through changes in blood oxygenation that accompany neuronal activity. MRI is noninvasive and according to the US Food and Drug Administration guidelines (Zaremba 2003) and recent longitudinal pediatric exposure data (Holland et al. 2014), poses no known risks if operated within specified limits. The high spatial and relatively high temporal resolution that fMRI provides can be used to study the central auditory nervous system in response to various auditory tasks.

Differences in central auditory response to stimulation has been identified between groups of deaf and normal-hearing individuals using fMRI (Scheffler et al. 1998; Bilecen et al. 2000; Tschopp et al. 2000; Patel et al. 2007; Propst et al. 2010). Patel et al. used linear regression analysis to investigate the relationship between preimplant fMRI activation in the primary auditory cortex and postimplant hearing thresholds of young CI recipients, revealing positive correlation between the two variables. That work demonstrated the potential of fMRI as a prognostic indicator of postimplant auditory outcomes. Recently, Tan et al. (2013) used a machine learning approach to classify infants with and without hearing loss based on their structural and functional neuroimaging data. They used the support vector machine algorithm (e.g., Orrù et al. 2012) to identify key regions such as the angular gyrus, the cingulate gyrus, and regions in the prefrontal cortex that effectively distinguished between the brains of the two groups. These findings provide some guidance on brain regions that we might examine in the present study in attempting to predict post-CI language outcomes based on preimplant fMRI results.

While evaluating the results of fMRI studies, it is important to consider the auditory paradigm used to elicit activation and its relevance in spoken language performance (Leach & Holland 2010). Narrative comprehension, a crucial skill for normal language development, refers to the understanding of the content of spoken narrative discourse. Brain regions responsible for this skill have been extensively mapped in children with normal hearing (Ahmad et al. 2003; Schmithorst et al. 2006, 2007; Vannest et al. 2009; Horowitz-Kraus et al. 2013). However, there is a dearth of such studies in children with hearing loss, especially those who receive a CI.

The aim of this study was to identify objective, neuroimaging biomarkers that might predict speech perception and oral language performance in young candidates for cochlear implantation. Specifically, this study was designed to test the hypothesis that positive correlations should exist between the fMRI signal in brain regions related to auditory language processing and attention in infants with congenital severe to profound hearing loss before cochlear implantation and their scores on tests of speech perception and oral language ability 2 years after cochlear implantation. Postimplant speech perception and oral language performance of CI users was evaluated using the Clinical Evaluation of Language Fundamentals-Preschool, Second Edition (CELF-P2; Wiig et al. 2004) and the Early Speech Perception Test for Profoundly Hearing-Impaired Children (ESP; Moog & Geers 1990). These tests are administered, scored, and interpreted by trained clinical professionals. In the present study, the regression analysis of ESP and fMRI was not considered due to lack of variability in postimplant ESP scores.

MATERIALS AND METHODS

Participants

The study was conducted following approval by the Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board. For the present study, a subset of children from a larger neuroimaging study of hearing loss were selected who fit the following criteria:

- Congenital bilateral severe to profound hearing loss as determined by sound field testing, auditory brainstem responses and otoacoustic emission testing
- Age < 24 months at the time of scanning
- Sedated with propofol (DiFrancesco et al. 2013)
- Received CI(s)
- Completed CELF-P2 and ESP testing 2 years postimplantation

This resulted in a sample size of n = 11. Ten participants completed the ESP and 10 completed the CELF-P2; however, 1 participant for each test did not complete the other test. So the sample size for each behavioral measure was 10. All participants were between the ages of 9 to 23 months at fMRI scanning and 12 to 36 months at first implantation.

The following exclusion criteria for fMRI were enforced for all participants:

- Presence of metallic or electronic devices in the body, such as artificial heart valves, drug infusion ports, metal pins, plates, screws, shunts, stents, or surgical staples
- Gestational age less than 36 weeks and/or a birth weight less than the 25th percentile
- Head circumference <5th or >95th percentile
- Neurological disorders and/or anatomical malformations
- Additional major cognitive impairments restricting participation in the evaluations

The demographic data of all participants are presented in Table 1. As all participants had congenital hearing loss, duration of hearing loss was defined as the age at first implantation (e.g., Green et al. 2005; Kelly et al. 2005). Preimplant sound field minimum response levels (MRLs) were calculated based on a four-frequency average (500, 1000, 2000, and 4000 Hz). All participants received Cochlear's Nucleus Freedom Implant with Contour Advance electrode array (CI24RE CA) and used the Advanced Combination Encoder (ACE) stimulation strategy.

Data Collection

Neuroimaging Procedures • Potential CI candidates were referred to the radiology department for MRI of the auditory nerve to ensure structural integrity and to rule out any other brain abnormality (clinical MRI). They received general anesthesia for the clinical MRI using intravenous Propofol (200 to 300 μg/kg/min with an 8% sevofluorane induction). After appropriate consent procedures, the fMRI experiment was conducted using a Siemens 3T Trio scanner at the end of the clinical MRI after the MR images were reviewed by a pediatric neuroradiologist, to ensure that there was no brain pathology affecting hearing. No infant was exposed to the risks of anesthesia solely for research purposes.

While in the scanner, participants heard a three-condition auditory paradigm consisting of narrow band noise (NBN),

TABLE 1. Demographic data of CI participants

Participant	Gender	Age at fMRI (Months)	Preimplant MRLs (dB HL)	Duration of Hearing Loss (Months)	Ear of Implant	CELF-P2 Core Language Score	ESP Score
S1	Female	16	117	20	Bilateral sequential R–L	81	4
S2	Male	14	73	20	Bilateral sequential R–L	69	4
S3	Male	9	115	13	Bilateral sequential R–L	65	4
S4	Male	11	106	12	Bilateral simultaneous	69	4
S5	Female	15	106	18	Bilateral sequential L–R	50	2
S6	Female	13	113	13	Bilateral simultaneous	73	4
S7	Female	23	95	36	Bilateral simultaneous	77	4
S8	Male	19	98	20	Bilateral sequential L–R	79	4
S9	Male	10	117	14	Left	45	-
S10	Female	9	118	22	Right	53	2
S11	Female	11	113	20	Right	-	4
Mean						66.10 ± 12.69	3.67 ± 0.84
Median						69	4
Mode						69	4

"R–L" indicates that participants received the right ear implant before the left ear implant. Similarly, "L–R" indicates that they received the left ear implant before the right ear implant. Descriptive statistics for both CELF-P2 and ESP are also included.

CELF-P2, Clinical Evaluation of Language Fundamentals-Preschool, Second Edition; CI, cochlear implant; fMRI, functional magnetic resonance imaging; MRL, minimum response level; ESP, Early Speech Perception Test for Profoundly Hearing-Impaired Children.

speech, and silence. The speech consisted of a narrated story in a female voice—18 segments of 2 sentences each; a total of 36 sentences. Each segment lasted for 5 seconds. This natural and ecologically plausible stimulus is one that we have used extensively in fMRI studies, including young children (Holland et al. 2007; Sroka et al. 2015) and infants (DiFrancesco et al. 2013; Tan et al. 2013) and consistently demonstrates robust bilateral auditory and language activation, even under the influence of sleep (Wilke et al. 2003) and anesthesia (DiFrancesco et al. 2013). Given its demonstrated utility in producing strong brain activation in auditory language circuitry in the brain, we chose to use it in this study. In contrast to the narrative speech stimulus, segments of either NBN or silence were used. NBN stimuli were presented for 1 second each in random order at octave frequencies from 250 to 4000 Hz with noise bandwidth of 50%. The three auditory conditions were of equal duration and were presented binaurally through MR-compatible headphones (Avotec Silent Scan Audio System SS3100) at an intensity of 10 to 15 dB SL (ref: MRLs of each participant). The Avotec audio system was connected to a computer outside the MR chamber and provided a flat frequency response (±5 dB) across the nominal bandwidth of the Avotec Audio System (150 to 4500 Hz). Use of three auditory stimuli led to three contrasts—story versus silence, NBN versus silence, and story versus NBN.

fMRI was performed using a silent background method to acquire BOLD images (Schmithorst & Holland 2004). Auditory stimuli were presented during silent periods of sparse echo planar imaging (EPI-BOLD) acquisition for a period of 5 seconds and the scanner acquired images between the auditory stimulus conditions for a period of 6 seconds. Each auditory condition was preceded by an additional 1 second of silence to allow for decay of the hemodynamic BOLD response to the scanner noise (e.g., Tan et al. 2013). One block of stimulus acquisition is outlined in Figure 1. Eighteen such blocks were presented to each participant for a total scan time of approximately 11 min.

Postimplantation Audiological Procedures • A follow-up audiological test battery was performed on participants 2 years after they received the CI. The follow-up test battery included the CELF-P2 and the ESP. These tests were selected as relevant outcome measures in the present study because they examine some of the more important outcomes expected after implantation such as receptive and expressive language skills, speech pattern acquisition, and verbal interaction ability. They assess different aspects of speech perception and oral language performance and together cover a wide range of skills critical for successful verbal communication by the age of kindergarten. These measures are norm/criterion referenced and have high reliability because they are administered by clinical professionals with audiological training.

The CELF-P2 has been developed to assess language skills of preschoolers between the ages of 3 years to 6 years 11 months. The following three subtests were administered as a part of the present study: Sentence Structure (analysis of spoken sentences), Word Structure (morphological abilities), and Expressive Vocabulary (use of appropriate subject/object/verb labels). The raw score obtained on each subtest was converted into a norm-referenced scaled score with 95% confidence intervals. The sum of scaled scores was then converted into the standard core language score (mean: 100; SD: 15; range: 45 to 155 corresponding to percentile rank of <0.1 to >99.9, respectively). The core language score was used in the second level correlation analysis with fMRI activation.

The ESP was developed to test pattern perception and word identification skills of children with hearing loss. The pattern perception, spondee identification, and monosyllable identification subtests of the standard version of ESP were used to classify participants into one of the following categories: category 1 = 0% to 20% (no pattern perception), category 2 = 21% to 49% (some pattern perception), category 3 = 50% to 69% (some word identification), and category 4 = 70% to 100% (consistent word identification). The ESP was not considered in the second level correlation analysis with fMRI activation due to limited variability in scores.

Data Analysis

fMRI datasets were preprocessed to calculate cortical activation maps for each contrast described above on a voxel-by-voxel

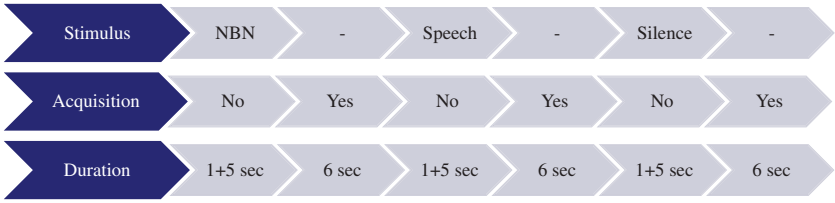

Fig. 1. The HUSH paradigm (Schmithorst & Holland 2004). Auditory stimuli are presented for a period of 5 seconds when the MRI scanner is silent, followed by MRI acquisition periods of 6 seconds. This alternation of stimuli and scanner noise reduced the effect of scanner noise on measured brain activity. (1 + 5 sec) denotes that each auditory condition is preceded by 1 second of silence for acoustic demarcation and to reduce fMRI contamination by gradient noise stimulation. fMRI indicates functional magnetic resonance imaging.

basis. Preprocessing was done using our own software written in the IDL software environment (Research Systems Inc., Boulder, CO). The program initially coregistered the fMRI time series data to the image volume that resulted in the smallest overall value of a cost-function based on variance from the reference frame (Szaflarski et al. 2006). Participants' movements were corrected using a pyramid iterative co-registration algorithm (Thevenaz et al. 1998). Functional MRI time series data were transformed to the anterior commissure (AC)–posterior commissure (PC) alignment plane. A final step in preprocessing corrected for global intensity variation through the fMRI time series using a set of cosine basis functions. Images from each stimulus condition were then separated by the software and grouped for construction of statistical parameter maps. A general linear model (Worsley et al. 2002) was used to create z maps for each contrast for each participant. Motion correction transformation parameters (linear terms only) and global intensity variation parameters were included in the general linear model at this stage to control for the influence of these variations in the final results. Then, individual z maps in the anterior commissure–posterior commissure space were normalized to the imaging research center infant template (Altaye et al. 2008) in the Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK) software. Data were then transformed from the infant brain template space into the Montreal Neurological Institute (MNI) space (Friston et al. 1995). Use of the infant template developed in our laboratory optimizes the transformation of the infant brain to the standard brain coordinate system and reduces coregistration errors across multiple subjects.

The z maps of all participants in the MNI framework were then concatenated (Schmithorst & Holland 2004; Patel et al. 2007). Both positive and negative voxels were considered for further analysis (Martin et al. 1999; Altman & Bernal 2001; Anderson et al. 2001; Patel et al. 2007). A voxel-wise regression between preimplant-activated voxels and postimplant CELF-P2 scores was performed in MATLAB (MathWorks, Natick, MA). Simulation of type I errors in the fMRI activation maps was performed using the AlphaSim (Ward 2000) program to compute the probability of occurrence of activated voxels and control for the family wise error rate and to select a corrected threshold for significant activations. The AlphaSim parameters used in this study were as follows: full width at half maximum noise smoothness = 8 mm, cluster connection radius (rmm) = 8 mm, p value for each voxel (uncorrected) < 0.01, number of Monte Carlo simulation iterations = 10,000, minimal cluster size = 26, p value for each cluster (corrected) < 0.05. The regression maps were projected back on the imaging research center infant T1 template (Altaye et al. 2008). The corresponding Brodmann areas and the coordinates of the cluster centroids in the MNI framework are reported in the results section.

Preimplant MRLs and duration of hearing loss before implantation were included as covariates in the multiple regression analysis as these factors are known to affect postimplant behavioral scores (Wake et al. 2005; Gilley et al. 2008).

RESULTS

Descriptive statistics of the two behavioral measures are displayed in Table 1. The participants' mean core language standard score on CELF-P2 was 66.10 (SD = 12.69, range = 45 to 81), >2 SD below the score achieved by typically developing children. Their mean ESP score was 3.67 (SD = 0.84, range = 2 to 4) while their modal and median values were 4 each, indicating that most participants achieved high speech perception scores as measured by ESP.

The composite map of the "story versus NBN" contrast did not reveal activation in temporal, frontal, or limbic lobes and hence not examined further in the present study. This lack of activation may be attributed to cancellation of activation in similar brain regions in response to two auditory stimuli (speech and noise). The contrasts with the silence condition yielded activation in auditory and language areas (Figs. 2 and 3). The regression maps of the participants for each of the contrast with the silence condition are described below.

Story Versus Silence Contrast

Figure 2 displays regression maps of CELF-P2 for the story versus silence contrast. The color bar at the bottom of the figure depicts Spearman's correlation values ranging from −1 to 0 (lower half) and 0 to 1 (upper half). Since all correlations in the present study were positive, the reader is directed to the upper half of the color bar. Correlation coefficients closer to zero are depicted by dull colors (black, dark red), while correlation coefficients closer to one are depicted by bright colors (yellow, white). The predominantly yellow color of the clusters in the regression maps indicates that the correlation values obtained were closer to one. The results are presented in three views—coronal, axial, and sagittal—for ease of visualization and localization. The coronal and axial views are presented in the radiological orientation, that is, the left side of the image represents the right side of the brain and vice versa—as indicated by labels at the bottom of the figure.

The correlation coefficient for each cluster that exceeded a corrected (family wise error) p value of <0.05 threshold is listed in Table 2. It lists Brodmann areas for clusters in the story versus silence contrast (shown in Fig. 2) that correlated

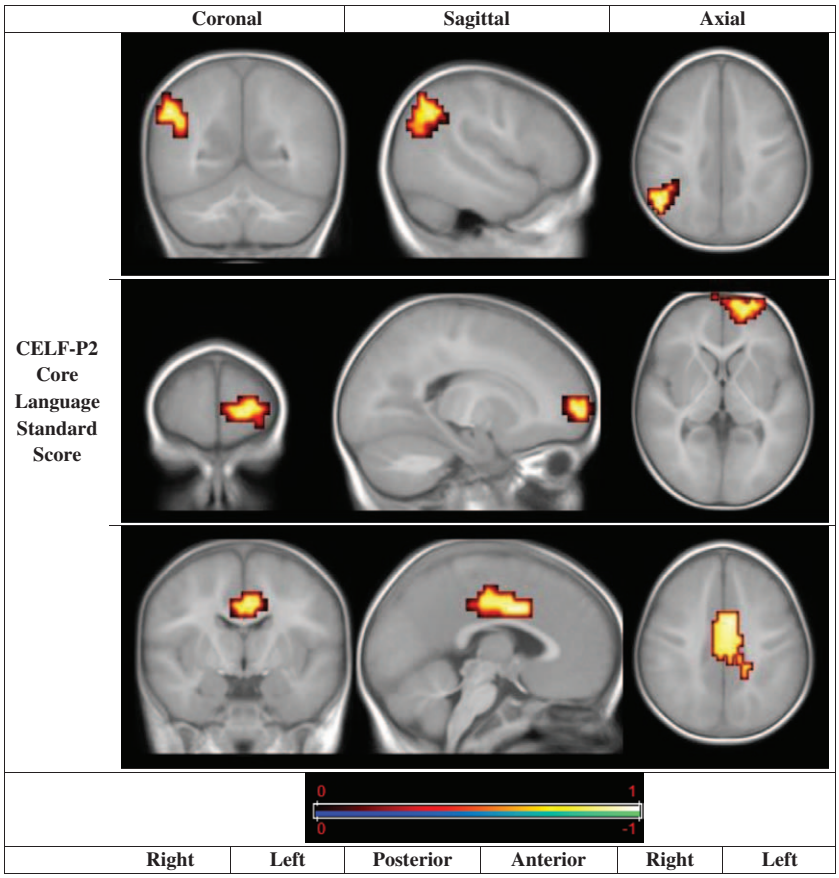

Fig. 2. CELF-P2 regression maps for the story versus silence contrast displayed in three views—coronal, sagittal, and axial (from *left* to *right*). CELF-P2 indicates Clinical Evaluation of Language Fundamentals-Preschool, Second Edition.

significantly with CELF-P2 scores after controlling for covariates. Table 2 also shows the cluster size, laterality of the clusters, and the MNI coordinates of the centroid of these clusters. The right angular gyrus, left medial frontal gyrus, and left cingulate gyrus correlated significantly with postimplant oral language abilities as measured by CELF-P2 (correlation coefficient $r = 0.95$ [$p < 0.0001$], 0.94 [$p = 0.0001$], and 0.96 [$p < 0.0001$], respectively). Each cluster had a substantial number of correlated voxels (68, 55, and 117, respectively).

NBN Versus Silence Contrast • Figure 3 displays regression map for the NBN versus silence contrast. The color bar at the bottom of the figure depicts similar Spearman's correlation values ranging from −1 to 1 and corresponding colors as in Figure 2. Predominantly, the left angular gyrus can be seen to correlate with CELF-P2 scores in response to NBN.

Table 3 lists areas of significant correlation between preimplant NBN-silence contrast and postimplant CELF-P2 scores after controlling for covariates. For the NBN versus silence contrast, only one cluster correlated significantly with postimplant CELF-P2 scores ($r = 0.89$, $p < 0.0001$). The centroid of this cluster fell in the angular gyrus in the left parietal lobe. The cluster size was substantial with 79 voxels.

TABLE 2. Clusters of significant correlation shown in Figure 2 between BOLD signal changes and CELF-P2 core language standard score after correction for multiple comparison using AlphaSim and covariation for pre-CI hearing threshold and age at implant

Story Vs. Silence Contrast							
Behavioral Test	Brodmann Areas	Activated Sites	Cluster Size	Hemisphere	MNI Coordinates	Correlation Coefficient (*r*)	*p* Value (Corrected)
CELF-P2 Core Language Standard Score	BA 39, 40, 7	Parietal lobe, angular gyrus	68	Right	58, –66, 33	0.95	<0.0001
	BA 10, 11	Frontal lobe, medial frontal gyrus	55	Left	–18, 58, –2	0.94	0.0001
	BA 23, 24, 31, 33	Limbic lobe, cingulate gyrus	117	Left	–2, –2, 28	0.96	<0.0001

BA, corresponding cluster sizes, and side of hemispheric activation for the story vs. silence contrast are listed.
BA, Brodmann areas; BOLD, blood oxygen level-dependent; CELF-P2, Clinical Evaluation of Language Fundamentals-Preschool, Second Edition; CI, cochlear implant; MNI, Montreal Neurological Institute.

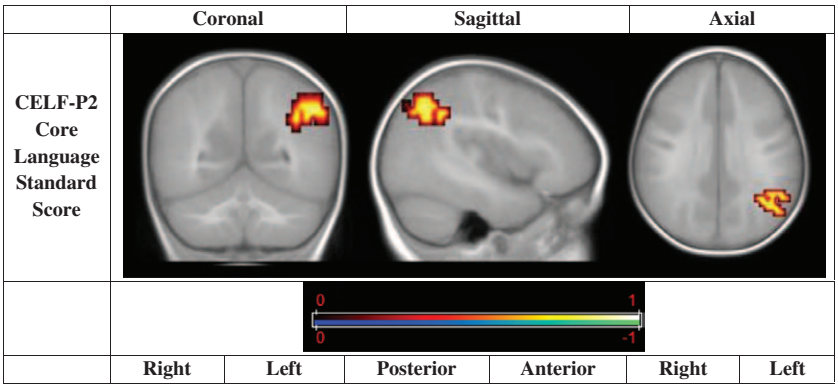

Fig. 3. CELF-P2 regression map for the NBN versus silence contrast displayed in three views—coronal, sagittal, and axial (from *left* to *right*). CELF-P2 indicates Clinical Evaluation of Language Fundamentals-Preschool, Second Edition; NBN, narrow band noise.

In addition to the clusters listed in Tables 2 and 3, some correlations were found in cerebellar and brainstem regions. However, due to high variability and limitations of image resolution to resolve brainstem nuclei, they were not included in further analyses and are not reported here.

DISCUSSION

The aims of this study were (a) to identify objective, neuroimaging biomarkers that might predict speech perception and oral language performance in young CI recipients and (b) to test our hypothesis that positive correlations should exist between the fMRI signal in brain regions related to auditory language processing and attention in infants with congenital severe to profound hearing loss before cochlear implantation and their scores on tests of speech perception and oral language ability 2 years after cochlear implantation. To that end, preimplant fMRI activation was correlated with 2-year postimplant oral language performance as measured by CELF-P2 (speech perception as measured by ESP was not included in the second level correlation analysis due to lack of variability). Two auditory stimuli were used to elicit fMRI activation. Several cortical regions were found to have significant clusters of positive correlation between the behavioral measure and brain activation contrasts as outlined in Tables 2 and 3, in part confirming our hypothesis.

Biomarkers of Significant Correlation

Angular gyrus, cingulate gyrus, and areas in the prefrontal cortex were some of the key regions identified in our analysis.

In a recent comprehensive review of the function of the angular gyrus, Seghier (2013) noted that the plasticity of the angular gyrus plays an important role in comprehension and storage of verbal stimuli. Its role in phonemic analysis (Turkeltaub & Coslett 2010) and semantic processing (Vigneau et al. 2006) has also been established via large-scale meta-analysis studies. Of greater relevance is the finding that the angular gyrus has been previously shown (e.g., Schmithorst et al. 2006; Karunanayaka et al. 2007) to be active in response to the passive narrative listening task similar to the one used in the present study. Participants in the present study who had greater activation in and around the angular gyrus preimplant showed improved oral language performance 2 years postimplant. The activation and subsequent correlation of the angular gyrus with postimplant CELF-P2 scores in CI recipients is consistent with its role as a key region for oral language development in children with hearing loss who receive early intervention.

In the present study, the cingulate gyrus and areas in the prefrontal cortex such as the medial frontal gyrus showed a strong positive correlation between activation in the story versus silence contrast and CELF-P2 scores. In a meta-analysis of 120 neuroimaging studies exploring brain regions responsible for semantic analysis, Binder et al. (2009) noted the cingulate gyrus and regions of the prefrontal cortex to be part of the speech processing stream. The prefrontal cortex—along with the angular gyrus and supramarginal gyrus—have been hypothesized to be part of the "ventral stream" responsible for comprehension of complex stimuli like speech in the proposed modification of Hickok and Poeppel's (2004, 2007) Dual Stream Model by Specht (2014). The presence of the aforementioned clusters is consistent with the early engagement of this "ventral stream" before 24 months old in infants with hearing loss.

TABLE 3. Clusters of significant correlation between BOLD signal changes and CELF-P2 core language standard score after correction for multiple comparison using AlphaSim and covariation for pre-CI hearing threshold and age at implant

NBN Vs. Silence Contrast							
Behavioral Test	Brodmann Areas	Activated Sites	Cluster Size	Hemisphere	MNI Coordinates	Correlation Coefficient (*r*)	*p* Value (Corrected)
CELF-P2 Core Language Standard Score	BA 39, 40, 7, 19	Parietal lobe, angular gyrus	79	Left	–42, –58, 33	0.89	<0.0001

Brodmann areas, corresponding cluster sizes, and side of hemispheric activation for the NBN vs. silence contrast are listed.
BA, Brodmann areas; BOLD, blood oxygen level-dependent; CELF-P2, Clinical Evaluation of Language Fundamentals-Preschool, Second Edition; CI, cochlear implant; MNI, Montreal Neurological Institute.

Using the same auditory stimulation paradigm as in the present study, the angular gyrus, the cingulate gyrus, and regions in the prefrontal cortex were identified to be effective classifiers of normal versus impaired hearing in 39 children using a machine learning technique (Tan et al. 2013). The present study takes this finding one step further by investigating the role of these regions in postimplant oral language performance in CI recipients. The significant positive correlation between fMRI activation in the above brain regions and CELF-P2 scores postimplant shows that a higher activation in these regions is associated with higher CELF-P2 scores and suggests that these brain regions may be neuroimaging biomarkers of oral language abilities after implantation.

Differential Representation of Auditory Stimuli

An interesting observation was that in the present study, oral language performance correlated with the right temporo-parieto-occipital junction for the story versus silence contrast and the left temporo-parieto-occipital junction for the NBN versus silence contrast. Recently, Turkeltaub and Coslett (2010), in an activation likelihood estimation meta-analysis of 23 fMRI experiments studying sublexical speech perception, found a leftward activation of temporo-parietal brain regions. However, the authors attributed this leftward activation to explicit attention to phonology of the verbal stimuli. The lack of correlation of the left angular gyrus with CELF-P2 in response to the speech stimuli in the present study may be due to the structure of the auditory paradigm which did not demand explicit attention to the stimuli. An alternative explanation can be found in the recently proposed modification of the dual stream model by Specht (2014). Based on neuroimaging evidence, Specht proposed an addition of the angular gyrus and supramarginal gyrus to the existing dual stream model, thus creating two functionally different ventral streams on either side of the brain. In this proposed model, the right ventral stream is responsible for voice processing and prosody, while the left ventral stream is responsible for sublexical processing. The brief duration NBN stimuli used in the present study may have been perceived as short sublexical units (Whitney & Berndt 1999) and hence represented in the left hemisphere, in accordance with the Specht model. This explanation might be even more plausible in infants with hearing loss who have an untrained auditory and speech processing neural circuitry (Smith et al. 2011). Thus, the results of the present study present evidence of differential involvement of the hemispheres in children with hearing loss depending on the type of stimulus used. Other clusters found in the present study such as the posterior cingulate cortex had a bilateral representation, consistent with previous neuroimaging experiments using auditory stimuli (Maddock & Buonocore 1997; Maddock et al. 2003).

It is worthwhile to note that the significant cluster in the regression map for the NBN versus silence contrast was restricted to the angular gyrus (Fig. 3, Table 3). A comprehensive review of neuroimaging studies on auditory speech comprehension led Specht (2014) to conclude that "speech comprehension processes rely on a hierarchical network involving the temporal, parietal, and frontal lobes" (p. 121). Processing of complex stimuli like speech requires contribution from frontal and limbic lobes in addition to temporo-parietal regions (e.g., angular gyrus; Hickok & Poeppel 2004, 2007; Davis & Johnsrude 2007; Binder et al. 2009). In the present study, processing of noise may have been relatively less complex than stories and hence the activation and subsequent correlation was limited to the angular gyrus as seen in the NBN versus silence contrast. On the other hand, the speech stimuli required involvement of a widespread network of brain regions as seen in the story versus silence contrast.

Although participants in this fMRI study were anesthetized and had prelingual severe to profound hearing loss, the brain activation results indicate that the auditory language network still responded to supra-threshold auditory stimuli. In previous studies of normal-hearing children passively listening to stories during fMRI, we have found strong correlations between the activation in response to the story stimulus and language comprehension measures (Horowitz-Kraus et al. 2013). Increased brain activity in the right parietal lobe for children with better language comprehension was also found to correspond with greater white matter integrity in adjoining regions using diffusion tensor imaging (DTI) in the same children (Horowitz-Kraus et al. 2014). We suggest that the correlations between neural activity in the right parietal regions (BA 39 & 40) and CELF-P2 scores in CI recipients before implantation could be a reflection of a more well-developed neural circuitry for auditory language comprehension in those candidates who will have the best language outcomes following CI.

Brainstem and/or Cerebro-Cerebellar Interactions

Although brainstem and cerebellar activations were not studied in the current project, contributions from these centers cannot be ruled out. Inputs from the cerebellum have been observed in neuroimaging studies of speech comprehension (Papathanassiou et al. 2000) and listening to intelligible (Wong et al. 2008) and degraded acoustic stimuli (Strelnikov et al. 2011). Redcay et al. (2008) studied speech versus silence contrast in children with normal hearing using an event-related fMRI task and found right cerebellar activation in response to natural speech. Some of the correlations between cortical activation and postimplant outcomes in the present study might be due to differences in inputs from brainstem and/or cerebellar nuclei, rather than cortical differences in responsiveness alone, and need to be studied further.

Fidelity of Stimuli

Previous studies (Patel et al. 2007; Smith et al. 2011; Tan et al. 2013) have established feasibility of using the current auditory stimulation protocol in children with hearing loss. Nonetheless, the effects of acoustic distortion resulting due to presentation of high-intensity auditory stimuli through headphones cannot be ruled out. Some speech stimuli may comprise harmonics beyond 4500 Hz (the upper limit of the Avotec Audio System) raising the possibility of loss of fidelity in the high-frequency components of the speech stimuli. The possibility that the presentation level was less than 10 to 15 dB SL for some participants (e.g., for S10: MRL = 118 dB) cannot be ruled out either. It is not known how these limitations might impact brain activation in auditory-language circuitry in children with hearing loss and further investigation is needed.

Limitations and Future Directions

Since age at implantation is known to affect postimplant auditory, speech, and language performance (Gilley et al.

2008), the present analyses were restricted to children implanted before 36 months old. Furthermore, it is known that there is a rapid change in the anatomical microstructure of brains of young children up to 36 months old. Hence, the infant template (Altaye et al. 2008) was used and only those infants who were scanned before 24 months old were included. Finally, different anesthetic protocols used during scanning are known to affect imaging results variably (DiFrancesco et al. 2013). Hence, only those participants who were sedated with Propofol were included. This further decreased the sample size of the present study. A sample size of n = 12 has been previously found to provide adequate power for fMRI study designs (Desmond & Glover 2002). A posthoc power analysis conducted using nQuery Advisor (nQuery Advisor 6.0, Statistical Solutions, Cork, Ireland) revealed that the present study was able to detect an effect size of 0.7 to 1.1 at $\alpha = 0.05$ with reasonable power. Nonetheless, certain inherent limitations due to the small sample size must be addressed. Only two major factors known to affect postimplant outcomes—duration of hearing loss and preimplant hearing thresholds—could be controlled as nuisance covariates in our regression models (e.g., Venker et al. 2013). Additional influencing factors such as socioeconomic status, parental education level, and language enrichment at home can be considered in future studies. Although the type of implant and the stimulation strategy was kept consistent across participants, variability in results due to differences in programmable settings cannot be ruled out. In addition, the participants in the present study include children who received unilateral and bilateral CI on different time lines. This introduces additional variation in the post-CI language abilities. Due to the small sample size, we used Spearman's rank correlation analysis instead of the Pearson's product-moment correlation, further weakening our power to detect correlations.

Another weakness of the study is the lack of availability of preimplant-aided benefit or cause of hearing loss. We were unable to record this information in our database. Future studies can include aided thresholds as an additional control variable.

Additional studies will be required to ascertain whether the areas of correlation observed in this study hold true for different age groups and anesthetics. In recent years, the study of neuronal connectivity patterns using DTI and tractography analysis has revealed strong connections in humans between the angular gyrus and the precuneus (Makris et al. 2007), the supramarginal gyrus (Lee et al. 2007), the superior occipital gyrus (Seghier 2013), and the prefrontal cortex (Makris et al. 2005) and in nonhuman primates between the angular gyrus and the cingulate gyrus (Petrides & Pandya 2009). Some of these clusters were identified in the present study and further DTI investigation is needed to establish these regions as a part of the neural network responsible for oral language performance in children with hearing loss who receive early intervention via cochlear implantation.

CONCLUSIONS

The present study explored the relationship between preimplant fMRI activation and postimplant oral language development. Brain regions that correlated significantly with CELF-P2 scores 2 years after cochlear implantation in infants were identified as fMRI biomarkers that may be predictive of these outcomes in CI recipients with prelingual hearing loss. Positive correlations suggest that greater preimplant activation in these regions will be indicative of better postimplant oral language development in infants and toddlers receiving CIs.

Using the conventional voxel-wise regression analysis presented here, we are only able to make predictions on a group level. Future work should aim to extend the predictive value of fMRI in infants with hearing loss to individual patients before cochlear implantation. Machine learning methods such as support vector machine might allow fMRI biomarkers to extend predictions to the individual subject level (Tan et al. 2013). Although young children with severe to profound hearing loss will continue to receive CIs irrespective of their cortical activation levels, an effective neuroimaging biomarker could help guide clinical decisions for the CI team including audiologists, speech therapists, and aural rehabilitation specialists in the future.

ACKNOWLEDGMENTS

The authors would like to thank Thomas Maloney, Robert Keith, and Fawen Zhang for their input and guidance throughout the project.

This study was supported by National Institutes of Health Grant (NIH 1R01DC007186) awarded to PI: Scott K. Holland, Ph.D.

Portions of this article were presented at the Organization for Human Brain Mapping (OHBM), Seattle, Washington, June 18, 2013.

This research was conducted when AKD was at the Department of Communication Sciences and Disorders, University of Cincinnati.

The authors have no conflict of interest to disclose.

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Received September 15, 2014; accepted October 24, 2015.

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