J Am Acad Audiol 29:389–404 (2018)

fMRI as a Preimplant Objective Tool to Predict Children's Postimplant Auditory and Language Outcomes as Measured by Parental Observations

DOI: 10.3766/jaaa.16149

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Abstract

Background: The trends in cochlear implantation candidacy and benefit have changed rapidly in the last two decades. It is now widely accepted that early implantation leads to better postimplant outcomes. Although some generalizations can be made about postimplant auditory and language performance, neural mechanisms need to be studied to predict individual prognosis.

Purpose: The aim of this study was to use functional magnetic resonance imaging (fMRI) to identify preimplant neuroimaging biomarkers that predict children's postimplant auditory and language outcomes as measured by parental observation/reports.

Research Design: This is a pre–post correlational measures study.

Study Sample: Twelve possible cochlear implant candidates with bilateral severe to profound hearing loss were recruited via referrals for a clinical magnetic resonance imaging to ensure structural integrity of the auditory nerve for implantation.

Intervention: Participants underwent cochlear implantation at a mean age of 19.4 mo. All children used the advanced combination encoder strategy (ACE, Cochlear Corporation™, Nucleus® Freedom cochlear implants). Three participants received an implant in the right ear; one in the left ear whereas eight participants received bilateral implants. Participants' preimplant neuronal activation in response to two auditory stimuli was studied using an event-related fMRI method.

Data Collection and Analysis: Blood oxygen level dependent contrast maps were calculated for speech and noise stimuli. The general linear model was used to create z-maps. The Auditory Skills Checklist (ASC) and the SKI-HI Language Development Scale (SKI-HI LDS) were administered to the parents 2 yr after implantation. A nonparametric correlation analysis was implemented between preimplant fMRI activation and postimplant auditory and language outcomes based on ASC and SKI-HI LDS. Statistical Parametric Mapping software was used to create regression maps between fMRI activation and scores on the aforementioned tests. Regression maps were overlaid on the Imaging Research Center infant template and visualized in MRIcro.

Results: Regression maps revealed two clusters of brain activation for the speech versus silence contrast and five clusters for the noise versus silence contrast that were significantly correlated with the

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This study was funded in part by a grant from the National Institute of Deafness and other Communication Disorders, R01-DC07186 (P.I. S. K. Holland). The authors would also like to acknowledge the following funding source: National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program, grant 5UL1TR001425-03. Portions of this article were presented orally at the annual American Speech Language Hearing Association (ASHA) convention at Orlando, FL, in November 2014.

parental reports. These clusters included auditory and extra-auditory regions such as the middle temporal gyrus, supramarginal gyrus, precuneus, cingulate gyrus, middle frontal gyrus, subgyral, and middle occipital gyrus. Both positive and negative correlations were observed. Correlation values for the different clusters ranged from -0.90 to 0.95 and were significant at a corrected p value of <0.05. Correlations suggest that postimplant performance may be predicted by activation in specific brain regions.

Conclusions: The results of the present study suggest that (1) fMRI can be used to identify neuroimaging biomarkers of auditory and language performance before implantation and (2) activation in certain brain regions may be predictive of postimplant auditory and language performance as measured by parental observation/reports.

Key Words: cochlear implants, functional magnetic resonance imaging, hearing, infants, language, observation, parents

Abbreviations: ASC = Auditory Skills Checklist; BOLD = blood oxygen level dependent; CCHMC = Cincinnati Children's Hospital Medical Center; CI = cochlear implant; CID = Central Institute for the Deaf; fMRI = functional magnetic resonance imaging; HUSH = Hemodynamics Unrelated to Sounds of Hardware; MRI = magnetic resonance imaging; MRLs = minimum response levels; MNI = Montreal Neurological Institute; SD = standard deviation; SKI-HI LDS = SKI-HI Language Development Scale

INTRODUCTION

Benefits of cochlear implantation during the critical period are evident in terms of speech recognition and language performance of children fitted with a cochlear implant (CI) (e.g., McConkey Robbins et al, 2004; Nikolopoulos et al, 2004; Svirsky et al, 2004; Sharma and Dorman, 2006; Geers and Nicholas, 2013; Tobey et al, 2013; Castellanos et al, 2014). Although studies show a general trend of improved auditory and speech-language performance after implantation, there is considerable variability in individual outcomes (Zeng, 2004; Zaidman-Zait and Most, 2005; Kirk et al, 2006; Geers et al, 2008; Pisoni et al, 2008; Lazard et al, 2010; Niparko et al, 2010; Geers et al, 2011). "Despite significant research effort, there is no reliable and accurate presurgical predictor of postsurgical performance in cochlear implants" (Zeng, 2004, p. T5). Although various factors such as age at onset of hearing loss, preimplant auditory status, age at implantation and stimulation, surgical and postsurgical procedures, postimplant intervention, and family involvement contribute to this variability (McKay, 2005; Tomblin et al, 2005; Wake et al, 2005; Finley et al, 2008; Geers et al, 2008; Gilley et al, 2008; Green et al, 2012; Tobey et al, 2013), a single factor that will be able to explain a significant portion of the variability has not yet been identified conclusively (Zeng, 2004). Understanding the neural mechanisms that support hearing, speech and language functions in successful CI users could facilitate accurate individual prognosis (Lazard et al, 2010). Preimplant neuroimaging techniques may have the potential to improve prediction accuracy of postimplant performance outcomes (Zeng, 2004; Petersen et al, 2013; Smalt et al, 2013). Activation of certain regions in the brain has been found to correlate with behavioral measures of auditory and speech-language performance (Patel et al, 2007; Eisner et al, 2010; Morillon et al, 2010; Horowitz-Kraus et al, 2013; Nagels et al, 2013). For instance, Eisner et al (2010) used functional magnetic resonance imaging (fMRI) to study brain regions responsible for analyzing CI-simulated speech stimuli in normal hearing individuals. The fMRI technique utilizes differences in magnetic properties of oxygenated blood, deoxygenated blood, and tissue to acquire images of "the brain in action." Participants in the Eisner et al (2010) study listened to noise-vocoded speech stimuli spectrally shifted either upward (from low to high frequencies) or downward (from high to low frequencies) during fMRI. Participants displayed greater activation in the left superior temporal sulcus and inferior frontal gyrus in response to the upward, more learnable condition; thus, implicating these regions in speech perception and comprehension of CI-simulated speech. Other auditory stimuli have also been used in fMRI studies of brain activation. Tan et al (2013) used a combination of structural and functional magnetic resonance imaging (MRI) data to delineate regions that effectively classified between the brains of infants with normal hearing and those with severe to profound hearing loss. The functional imaging portion of their experiment used a passive story listening task. They highlighted several brain regions that maximally differentiated between the two groups including regions in the parietal, frontal, and limbic lobes. Other fMRI experiments have also used the story listening task because of the feasibility and relevance of its use with young children (Ahmad et al, 2003; Schmithorst et al, 2006, 2007; Vannest et al, 2009; Szaflarski et al, 2012; Horowitz-Kraus et al, 2013; Deshpande et al, 2016).

A recent study by our group (Deshpande et al, 2016) identified neuroimaging biomarkers of postimplant oral language performance in young CI recipients. Eleven children with severe to profound hearing loss passively listened to narratives while inside the scanner. They obtained CI(s) after the fMRI task. Participants' speech-language performance was measured 2 yr postimplant using standardized clinician-administered tests.

A correlation analysis (controlled for preimplant hearing levels and age at implantation) performed between preimplant fMRI activation and postimplant oral language performance as measured by the Clinical Evaluation of Language Fundamentals-Preschool, Second Edition (CELF-P2; Wiig et al, 2004) revealed brain regions including the angular gyrus, medial frontal gyrus, and the cingulate gyrus. The results of this study indicate that (a) greater activation in certain brain regions may suggest better postimplant outcomes and (b) fMRI can possibly be used as a predictor of postimplant oral language outcomes.

Measures in the Deshpande et al (2016) study were clinician-administered. Yoshinaga-Itano et al (1998) have succinctly summarized the need and appropriateness of using parental reports in studying child language. They stated three distinct advantages of using parental observations/reports: In a home-based setting—(a) parents have a greater understanding of their child's language abilities, (b) familiarity with people and surroundings elicits better responses from children, and (c) children's speech/language performance is not unfairly affected by fatigue. In an extensive review of studies on pediatric cochlear implantation, Thoutenhoofd et al (2005) emphasized the need to observe children "in their day-to-day lives, after implantation, rather than in clinical tests" (p. 243). Parents have the unique opportunity to observe their children's auditory and language performance every day. This rich dataset must be tapped into to better understand children's auditory and speech-language status (Hyde et al, 2011). Other researchers have also suggested the use of parental observations and reports to supplement clinician-administered tests (e.g., Knoors et al, 2003; Lin et al, 2008). Ching et al (2010) found significant positive correlations between language performance as measured by parental reports and that measured by clinician-administered tests suggesting the validity of the use of parent reports/observations in children with hearing loss. Parental observations/reports like the Auditory Skills Checklist (ASC; Meinzen-Derr et al, 2007) and the SKI-HI Language Development Scale (SKI-HI LDS, 2nd edition; Watkins and Tonelson, 2004) have been used to study auditory and language performance of children with normal hearing, hearing loss, and developmental delays (e.g., Meinzen-Derr et al, 2007; Wiley et al, 2008; Nowakowski et al, 2009; Ruggirello and Mayer, 2010; Meinzen-Derr et al, 2011).

Because information obtained from parental observations of children's auditory and language performance is vital, neuroimaging biomarkers predicting such information may prove to be useful in guiding postimplant rehabilitation plans. The aim of this study was to identify preimplant neuroimaging biomarkers that predict children's postimplant auditory and language outcomes as measured by parental observations. ASC and SKI-HI LDS were specifically chosen for this investigation as they are well-suited to study auditory hierarchy and language performance in young CI recipients as witnessed by their primary caregiver.

MATERIALS AND METHODS

Participants

All study procedures were carried out following approval from Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board. Twelve children with bilateral severe to profound hearing loss were recruited for the present study (from a larger dataset recruited for an NIH study—R01-DC07186). Preimplant minimum response levels (MRLs) were calculated for all participants as a four-frequency average (500, 1000, 2000, and 4000 Hz) using sound field audiometry. The mean preimplant MRL of participants was 104.42 dB HL. All participants received fMRI scanning before 24 mo of age, under sedation with propofol. After the fMRI procedure, all participants received CI(s) before 36 mo of age. Two years postimplant, ASC and SKI-HI scores were obtained at a follow-up visit to the hospital. ASC scores were available on all 12 children whereas SKI-HI LDS scores were available on 11 of the 12 participants. Children with metallic or electronic implants; gestational age $<$ 36 weeks; birth weight less than the 25th percentile; head circumference less than the 5th percentile or greater than the 95th percentile; neurological disorders and/or anatomical malformations; or cognitive impairments were excluded. Participants underwent cochlear implantation at a mean age of 19.4 mo (range: 12–36 mo). All children received Cochlear's™ Nucleus® Freedom implants and used the advanced combination encoder (ACE) strategy for their everyday implant maps. The demographic data of participants is presented in Table 1. The group consisted of an equal number of male and female participants. They received the implant either in the right ear (n = 3), or the left ear (n = 1), or both ears (n = 8). Additional information about the side of first implant for children who received bilateral sequential implants is noted under the "ear of implant" column. "R-L" denotes acquisition of right implant before the left implant and vice versa.

PreImaging Procedures

Per CCHMC protocol, after initial identification of hearing loss, all children received a re-evaluation of hearing status via auditory brainstem response and otoacoustic emission testing. Next, possible CI candidates were referred for a clinical MRI of the auditory nerve to ensure structural integrity and to rule out other abnormality affecting hearing. At this point, parents of these children were informed about the current fMRI study by their attending otolaryngologist. Interested parents were explained the entire protocol in

Table 1. Demographic Data of CI Participants

Participant	Gender	Preimplant MRLs (dB HL)	Ear of Implant	Age at First Implant (mo)	ASC Score	SKI-HI LDS RLA (mo)	SKI-HI LDS ELA (mo)
P1	Female	117	Bilateral sequential R-L	20	65	38	34
P2	Male	73	Bilateral sequential R-L	20	60	38	38
P3	Female	105	Right	20	59	38	38
P4	Male	115	Bilateral sequential R-L	13	59	34	30
P5	Male	106	Bilateral simultaneous	12	58	34	30
P6	Female	106	Bilateral sequential L-R	18	28	23	21
P7	Male	90	Right	25	21	—	—
P8	Female	113	Bilateral simultaneous	13	60	30	30
P9	Female	95	Bilateral simultaneous	36	64	42	38
P10	Male	98	Bilateral sequential L-R	20	65	46	46
P11	Male	117	Left	14	26	5	3
P12	Female	118	Right	22	37	26	21

Note: ELA = Expressive Language Age; RLA = Receptive Language Age.

detail and their questions were answered by one of the investigators. Although the clinical MRI procedure requires sedation (propofol: 200–300 μg/kg/min with an 8% sevofluorane induction), children cannot be sedated for research purposes at our institution. However, the Institutional Review Board does permit the addition of an fMRI study at the end of the clinical MRI procedure provided that not >15 min of additional sedation is required. The fMRI procedures, including additional sedation, were described to parents as part of the informed consent process. If parents agreed to participate in the study, written informed consent was obtained before the clinical MRI. The fMRI experiment was conducted at the end of the clinical MRI after the magnetic resonance images were reviewed by the neuroradiologists and determined to have no abnormalities in auditory or language areas of the brain. Note that the use of propofol for sedation during fMRI with auditory stimulation has previously been reported by our group (Patel et al, 2007; DiFrancesco et al, 2013; Deshpande et al, 2016).

Imaging Procedures

fMRI was performed on a Siemens 3T Trio scanner. All participants were between 9 and 23 mo during fMRI scanning. Blood oxygen level dependent (BOLD) hemodynamic response was obtained in response to three auditory conditions: speech, noise, and silence. The speech condition consisted of stories read in a female voice (36 sentences; 18 segments of two sentences each) whereas the noise condition consisted of narrowband noise presented randomly at octave frequencies from 250 to 4000 Hz. Three comparisons (or contrasts) were possible with the presentation of the three-condition paradigm: speech versus silence, noise versus silence, and speech versus noise. During fMRI, stimuli were presented binaurally via high fidelity magnetic resonance-compatible headphones (Avotec Inc.). The headphones were a part of the Avotec Silent Scan Audio System (SS3100). The intensity of stimulus presentation was set at 10–15 dB SL with respect to MRLs of each participant (Tan et al, 2013; Deshpande et al, 2016). The duration of each "stimulus" condition (when speech, noise, or silence was presented) was 5 sec while the "no stimulus" condition (when the scanner was active) lasted for 6 sec. Each stimulus condition was preceded by 1 sec of silence for acoustic demarcation (Tan et al, 2013; Deshpande et al, 2016).

During MRI, rapid switching of magnetic gradients within the scanner creates a loud noise up to 110 dBA (Hall, 2006; Gaab et al, 2007). We used a silent acquisition method called Hemodynamics Unrelated to Sounds of Hardware (HUSH; Schmithorst and Holland, 2004) which utilizes the delay in hemodynamic response (Frahm et al, 1996; Krüger et al, 1996; Buxton et al, 1998; Logothetis et al, 1999) to facilitate evaluation of neuronal activity in auditory research by minimizing the confounding effects of scanner noise. Figure 1 depicts representation of six sequential time points (1 through 6) during fMRI acquisition using the HUSH technique. At time point 1, noise was presented for 5 sec; hemodynamic response was initiated in the brain; image acquisition stayed off; the scanner was silent and hence did not interfere with stimulus presentation. No stimulus was presented during the next 6 sec (time point 2); the hemodynamic response reached its peak approximately 5 sec after initiation of the auditory stimulus; and the scanner captured this activity with three sequential brain image volumes (2 sec each). In Figure 1,

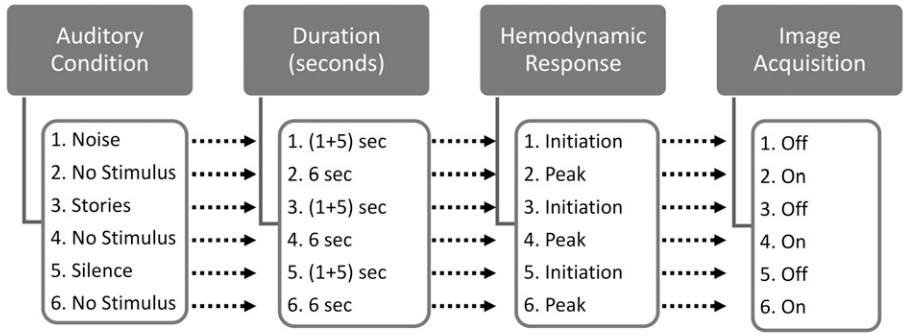

Figure 1. Block diagram of HUSH story listening paradigm showing the duration and order of presentation of auditory stimuli with the corresponding hemodynamic changes and image acquisition parameters at six different time points.

(1 + 5) seconds during time points 1, 3, and 5 represents an additional 1 sec of silence for acoustic demarcation and to allow for hemodynamic response to return to equilibrium. The total fMRI scan time for each participant was limited to <11 min.

Cochlear Implantation and Postimplant Procedures

Participants received CI(s) after the fMRI scanning (see Table 1 for age at implantation). Auditory and language tests—including SKI-HI LDS and ASC—were administered 2 yr after implantation. All participants enrolled in this study used verbal language as the primary mode of communication, and test scores were obtained based on parental participation/observation.

The ASC is a criterion-referenced tool administered to assess the functional auditory skills of young children with hearing loss. It consists of 35 questions on a continuum of detection–discrimination–identification–comprehension. Each domain has different number of questions: detection (nine questions), discrimination (seven questions), identification (seven questions), and comprehension (12 questions). Examples of questions in each domain are as follows: "Does your child localize correct sound source?" (detection), "Does your child discriminate minimal-pair words?" (discrimination), "Does your child identify his/her name when called?" (identification), and "Does your child follow two-step directions?" (comprehension). Both parent responses and clinician observations are combined to arrive at the answers to the above questions. Finally, the tester assigns a rating based on the answers as either 0 (does not have the skill); 1 (emerging skill development); or 2 (consistently demonstrates the skill). Thus, the score for a given child can range from 0 to 70 with each domain contributing to the total maximum possible score as follows: detection (18), discrimination (14), identification (14), and comprehension (24). It takes approximately 10 min to administer the complete test. A high correlation ($r = 0.90$, $p < 0.0001$) between ASC and the Infant Toddler-Meaningful Auditory Integration Scale (Zimmerman-Phillips et al, 2001) validated the ASC as a tool for early evaluation of functional auditory skills. A high internal consistency between questions and between domains was also observed (Cronbach's alpha >0.91).

The SKI-HI LDS was primarily developed for caregivers as a tool to evaluate and monitor their children's language skills. It assesses receptive and expressive language skills of children with hearing loss from birth to 5 yr of age. It gives an age-related norm based on the LDS score. Language performance is given credit irrespective of the modality used (e.g., sign language). The test consists of 20 units which delineate language skills at 2 mo intervals from 0 to 2 yr of age; 4 mo intervals from 2 to 4 yr of age; and 6 mo intervals from 4 to 5 yr of age. Each unit is divided into receptive and expressive skills. Intertester and intratester reliability measures have been performed during test development of the LDS. Internal consistency measures ensure unit-level and item-level reliability. Concurrent and construct validity were rated high based on comparisons with Receptive-Expressive Emergent Language Scale (Bzoch and League, 1994) and coefficient of reproducibility, respectively. Caregivers administer this test every 6 mo while observing their child for 1 week. Caregivers/parents are expected to get familiarized with the test items—a parent advisor can help them reach this goal—before marking an observed behavior. It is advised that the parents mark the language behavior as a plus (+) as soon as it is observed. If the child obtains pluses for >50% of the items on a unit, the child receives credit for the entire unit, and parents can proceed to the next unit. Caregivers are blind to the age range that each unit represents, and thus eliminating observer's bias and ensuring validity of observations. Guidelines on identifying units relevant to the child's language ability are provided to the caregivers.

For the present study, the total score on the ASC (maximum possible score: 70) and the receptive and expressive language age on the SKI-HI LDS (maximum receptive and expressive language age: 54–60 mo) were considered as outcomes of interest. The age range obtained for SKI-HI LDS receptive and expressive language skills was converted into a mean age for data analysis.

Data Analysis

Raw functional data from each participant were obtained along with time-series information to ensure validity of observations (Szaflarski et al, 2006). A pyramid iterative coregistration algorithm (Thévenaz et al, 1998) was used to realign fMRI data because of subject motion. Following motion correction, fMRI time series data were transformed to the Anterior-Posterior Commissure alignment plane. Preprocessing also included correction for global intensity variation. The general linear model implemented in an in-house software developed at Cincinnati Children's Hospital (Schmithorst and Dardzinski, 2000) was used to create unthresholded z-maps for each contrast (Worsley et al, 2002). Because there were three auditory conditions, three contrasts were obtained: speech versus silence, noise versus silence, and speech versus noise. No significant activation was detected in regions of interest related to hearing or language for the contrast of speech versus noise, so this contrast was not considered for further analysis. The subjects' functional and anatomical images were normalized to the CCHMC Imaging Research Center infant template (available as a free download at https://irc.cchmc.org/software/infant.php) in the Statistical Parametric Mapping (Wellcome Trust Centre for Neuroimaging, London, UK) software. It has been shown that pediatric or adult templates may not be suitable for normalization of infant functional data (Altaye et al, 2008). Hence the infant template, which includes brain image data from 76 infants in the age range of 9–15 mo, was used for the existing data. The Pick Atlas (Maldjian et al, 2003), developed at the fMRI Laboratory of the Wake Forest University School of Medicine (available as a free download at http://fmri.wfubmc.edu/software/PickAtlas), was also normalized to the infant template. Finally, data were transformed into the Montreal Neurological Institute (MNI) space (Friston et al, 1995). Both positive and negative activated voxels from the first-level general linear model analysis were included in subsequent analyses (Schmithorst and Holland, 2004; Patel et al, 2007; Deshpande et al, 2016). In the second-level analysis, participants' functional contrast maps were correlated with postimplant scores on parental observation reports in MATLAB (MathWorks, Natick, MA). Initially, a linear regression was performed with the contrast maps and test scores as formulated in Equation (1) to control for effects of MRLs and age at implantation (Wake et al, 2005; Gilley et al, 2008).

$$
\begin{aligned}
y &= \beta_1 * \text{MRLs} + \beta_2 * \text{Age} + b \\
\hat{y} &= y - \beta_1 * \text{MRLs} - \beta_2 * \text{Age}
\end{aligned}
\tag{1}
$$

where y is the original language test score, β_1, β_2, and b are the parameters in the regression model, $\hat{y}$ is the score on either parental observation reports (ASC and SKI-HI LDS) after regressing out MRLs and age at implantation. $\hat{y}$ was used for subsequent correlation analysis instead of the original language test scores as it reflected the corrected test score after controlling for the two variables (MRLs and age at implantation). A nonparametric correlation analysis was performed and the Spearman's correlation coefficient was calculated in addition to the p-value for each voxel. Regression maps were corrected for multiple correlations by controlling for the family-wise error rate using the AlphaSim program (Ward, 2000). Default parametric values were used during the AlphaSim p-value correction method (as described in Deshpande et al, 2016). The regression maps were overlaid on the infant template (Altaye et al, 2008) and visualized in MRIcro (http://www.mricro.com) (Rorden, 2005). For each significantly correlated cluster, Brodmann areas and co-ordinates of the center of the cluster have been reported in the MNI framework.

RESULTS

Table 2 summarizes means and standard deviations (SDs) of scores and language ages obtained by participants on ASC and SKI-HI LDS, respectively. The mean ASC score was 50.17 (SD = 16.90, range = 21–65, maximum possible score = 70). A mean ASC score of 50.17/70 on the detection–discrimination–identification–comprehension continuum indicates that participants in the present study achieved most of the skills required for auditory detection, discrimination, and identification. Auditory comprehension skills of most participants were emergent (see ASC subscale scores in Table 3 for details). On the SKI-HI LDS, participants obtained a mean receptive language age of 32.18 mo (SD = 11.23, range = 5–46 mo, maximum possible age range = 54–60 mo) and a mean expressive language age of 29.91 mo (SD = 11.64, range = 3–46 mo, maximum possible age range = 54–60 mo). The mean age of participants at the time of SKI-HI LDS test administration was 45.91 mo (SD = 6.94, range = 37–61 mo). These data indicate that as a group, participants in the present study lagged by 13.73 mo in their receptive language skills and by 16 mo in their expressive language skills 2 yr after implantation as compared with the normative data.

Results from the correlation of the BOLD contrasts with parent-reported language skill measures, and the fMRI contrast maps are described next.

Table 2. Descriptive Data of Participants on ASC and SKI-HI LDS

	Mean	SD	N
ASC	50.17	16.90	12
SKI-HI LDS receptive language age (mo)	32.18	11.23	11
SKI-HI LDS expressive language age (mo)	29.91	11.64	11

Comparison of Speech and Silence

Figure 2 and Table 4 depict brain regions graphically and in tabular format, where significant correlations were found between the fMRI contrast of speech versus silence and the two behavioral measures. Correlation coefficients, corresponding Brodmann areas, and laterality of the clusters are reported in Table 4. The cluster size and the MNI co-ordinates of the center of the cluster are also listed. The MNI co-ordinates represent the location of a centroid in three dimensions: Lateral–Medial, Anterior–Posterior, and Superior–Inferior (x, y, and z, respectively). A positive "x" value indicates that the centroid is located in the right hemisphere whereas a negative "x" value indicates that the centroid is located in the left hemisphere. Similarly, positive "y" indicates anterior and negative "y" indicates posterior location with respect to the anterior commissure (AC, a white matter tract connecting the two hemispheres). Finally, a centroid with positive "z" value is located superior to the AC and a negative "z" value is located inferior to the AC. The speech versus silence contrast did not reveal significant correlations between preimplant fMRI activation and the ASC or the receptive language subtest of SKI-HI LDS. However, two clusters with significant positive correlation with postimplant SKI-HI LDS expressive language age were identified—supramarginal gyrus in the parietal lobe (Spearman's correlation coefficient $r = 0.89$, corrected p via AlphaSim = 0.0008) and cingulate gyrus in the limbic lobe ($r = 0.83$, corrected $p = 0.0014$). Figure 2 displays maps of Spearman's correlation between preimplant fMRI activation and postimplant scores on SKI-HI LDS (expressive language subtest) for the speech versus silence BOLD contrast. For all figures, the identified clusters can be visualized in three separate sections: coronal, sagittal, and transverse. The coronal and transverse sections are presented in the radiological orientation, that is, the left side of the image represents the right side of the brain and vice versa. The color bar at the bottom of the figure represents correlation values from –1 to 0 (bottom half) and 0 to 1 (top half). For Figure 2, bright colors (e.g., yellow) of the identified clusters depict a positive correlation value closer to 1.

Comparison of Noise and Silence

Figures 3 and 4 represent maps of the Spearman's correlations between the preimplant fMRI activation and postimplant scores on ASC and SKI-HI LDS for the noise versus silence BOLD contrast. Table 5 lists the regions of high correlation between preimplant activation for the noise versus silence contrast and parents' responses for these measures of auditory and language behaviors postimplant. Corresponding Brodmann areas, cluster sizes, laterality, MNI coordinates of the centroid of the cluster, and Spearman's correlation coefficients are also tabulated here. A total of five clusters were identified to correlate significantly with the postimplant behavioral measures after the corrections for multiple comparisons. The left precuneus, an area in the parietal lobe, was the only brain region that correlated ($r = 0.95$, corrected $p = 0.0011$) with postimplant ASC scores. Four clusters correlated with the SKI-HI LDS, of which two correlated with the receptive subtest (right middle frontal gyrus, $r = -0.90$, corrected $p = 0.0140$; and right sub gyral, $r = -0.88$, corrected $p = 0.0001$) and two with

Table 3. ASC Subscale Scores for All Participants (The Number in Parenthesis in the Top Row Indicates the Maximum Possible Score on Each Subscale)

Participants	ASC Detection (18)	ASC Discrimination (14)	ASC Identification (14)	ASC Comprehension (24)	ASC Total (70)
P1	18	14	14	19	65
P2	18	12	14	16	60
P3	18	14	14	13	59
P4	18	14	14	13	59
P5	18	13	14	13	58
P6	16	10	2	0	28
P7	13	4	4	0	21
P8	18	11	14	17	60
P9	18	13	14	19	64
P10	18	14	14	19	65
P11	14	6	5	1	26
P12	16	10	9	2	37

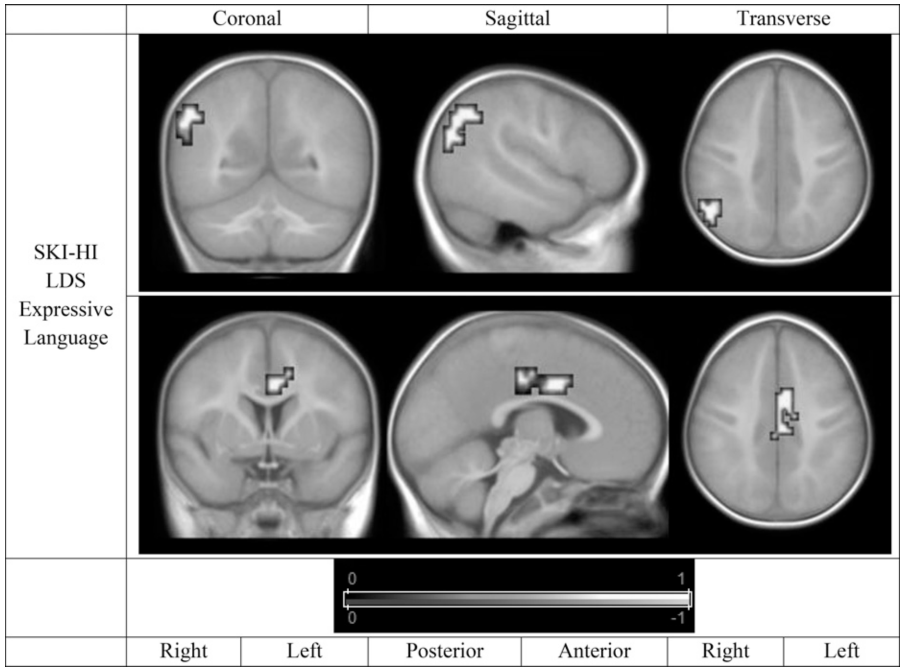

Figure 2. Spearman's correlation map depicting clusters of significant correlation (corrected $p < 0.05$) between the SKI-HI expressive language age and brain activation to the speech versus silence BOLD contrast in n = 11 CI participants.

the expressive subtest (left middle temporal gyrus, $r = -0.86$, corrected $p = 0.0016$; and right middle occipital gyrus, $r = -0.86$, corrected $p = 0.0005$). Note that for the noise versus silence contrast, brain regions that correlated with the SKI-HI LDS displayed a negative correlation value (Figure 4). For Figure 4, the reader is directed to the bottom half of the color bar which indicates negative values of correlation. A dark blue color indicates correlation coefficient values closer to zero whereas light blue and green colors indicate correlation coefficient values closer to -1. The actual correlation coefficient values are reported in Table 5.

DISCUSSION

Use of Parent Reports

Structured parent questionnaires have been used to assess various linguistic and nonlinguistic behaviors in young children (e.g., Coplan et al, 1982; Glascoe, 2000; Rescorla and Alley, 2001; Wolraich et al, 2003; Meinzen-Derr et al, 2007). Use of parental reports is recommended in very young children or children with additional disabilities (Kim et al, 2010). Yoshinaga-Itano et al (1998) have emphasized the need for home-based parental observation to obtain holistic information

Table 4. Clusters Revealed by Correlation between Preimplant BOLD Activation and Postimplant Scores on SKI-HI LDS Reveals the Two Clusters Listed Previously

	BOLD Contrast: Speech vs. Silence						
Assessment Tool	Brodmann Areas	Predictive Regions	Cluster Size	Laterality	MNI Co-ordinates (*x*, *y*, *z*)	Correlation Coefficient (*r*)	Corrected *p* Value
ASC	—	—	—	—	—	—	—
SKI-HI LDS receptive language	—	—	—	—	—	—	—
SKI-HI LDS expressive language	BA 40	Parietal lobe, supramarginal gyrus	45	Right	62, −58, 33	0.89	0.0008
	BA 24	Limbic lobe, cingulate gyrus	42	Right	2, -2, 28	0.83	0.0014

Note: Preimplant MRLs and age at implantation were controlled for. AlphaSim was implemented post hoc to correct for multiple correlations. Significant Brodmann areas and cluster sizes are listed along with the MNI coordinates of peak correlation in the identified hemisphere for the speech vs. silence BOLD contrast.

about children's speech-language abilities. Responses may be obtained in a more natural environment and are not limited by physical or temporal constraints. Sharma et al (2009) reported the clinical profile of a young girl who received a CI at 7.4 yr of age. Her cortical auditory evoked potential responses 6 mo postimplant revealed an abnormal polyphasic waveform. Her scores on Infant Toddler-Meaningful Auditory Integration Scale, a parental report of auditory behavior, correlated with CAEP responses and were also poor. On the other hand, Kang et al (2010) found that despite absent electric compound action potential or poor auditory steady state responses, CI recipients in their study received acceptable scores on parent observation reports. This variability indicates the need for identifying additional neuroimaging biomarkers (e.g., as identified by fMRI) to predict auditory/language behaviors based on parent observations.

The aim of the present study was to use fMRI to identify preimplant neuroimaging biomarkers that predict children's postimplant auditory and language outcomes as measured by parental observation/reports, specifically the ASC and the SKI-HI LDS. Voxel clusters that correlated significantly with either ASC or SKI-HI LDS were identified in the vicinity of the temporal, parietal, and occipital junction. The different regions in this area are responsible for, among other functions, auditory processing of language, attention to sounds, extraction of meaning, and higher level processing and integration of information (Stoeckel et al, 2009; Regev et al, 2013; Seghier, 2013). This junction has been implicated in the processing of speech and nonspeech auditory stimuli (Belin et al, 2000). In addition, clusters in "extra-auditory" regions were also identified and are discussed in greater detail in the next section.

Neuroimaging Biomarkers

Given the auditory nature of the stimuli, temporoparietal lobe involvement was expected in the present study. The supramarginal gyrus (BA 40) in the right parietal lobe exhibited a strong positive correlation with SKI-HI LDS expressive language age (r = 0.89, corrected p = 0.0008) for the speech versus silence contrast. The left middle temporal gyrus (BA 21) also correlated with postimplant SKI-HI LDS expressive language age (Spearman's r = −0.86, corrected p = 0.0016) for the noise versus silence contrast. The middle temporal and supramarginal gyri have been identified previously in neuroimaging studies of various language measures (Ahmad et al, 2003; Schmithorst et al, 2006; Catani et al, 2007; Binder et al, 2009; Turkeltaub and Coslett, 2010; Horowitz-Kraus et al, 2013; Li et al, 2013; Regev et al, 2013; Seghier, 2013; Smalt et al, 2013; Tan et al, 2013; Specht, 2014). Notably, Tan et al (2013) identified multiple brain regions that differentiated between normal and impaired hearing using a combined structural and functional image analysis approach. Implementing this approach on MRI/fMRI image data from 39 infants/toddlers with normal and impaired hearing, the authors identified 16 regions of interest (ROIs) that effectively classified between the two groups. These ROIs included the supramarginal and middle temporal gyri. In the present study, the correlation of these regions with ASC and SKI-HI LDS underlines the role of these regions in predicting postimplant auditory and language performance of young CI recipients as observed by the primary caregiver.

Brain regions other than the primary and associative auditory cortices such as the precuneus, the cingulate gyrus, and areas of the visual cortex have been identified in comparisons of brain activations between normal hearing individuals and those with hearing loss/CI (Naito et al, 2000; Giraud et al, 2001a,b; Kang et al, 2004; Green et al, 2008; Smalt et al, 2013; Tan et al, 2013). The cingulate cortex has been implicated in processing of speech (Xu et al, 2005; Obleser et al, 2007), comprehension of narratives (Schmithorst et al,

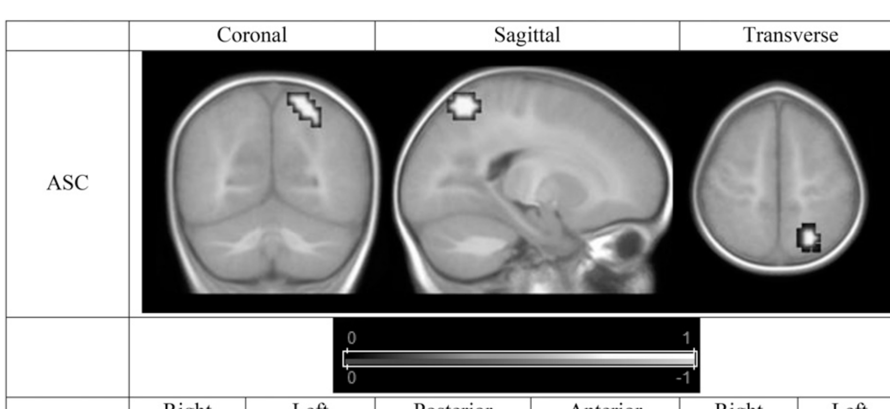

Figure 3. Regression maps depicting clusters of strong correlation (corrected $p < 0.05$) between fMRI activation and ASC scores for the noise versus silence BOLD contrast. The color bar denotes the correlation coefficient value (from −1 to +1). Image views and their orientations are indicated at the top and bottom of the figure, respectively.

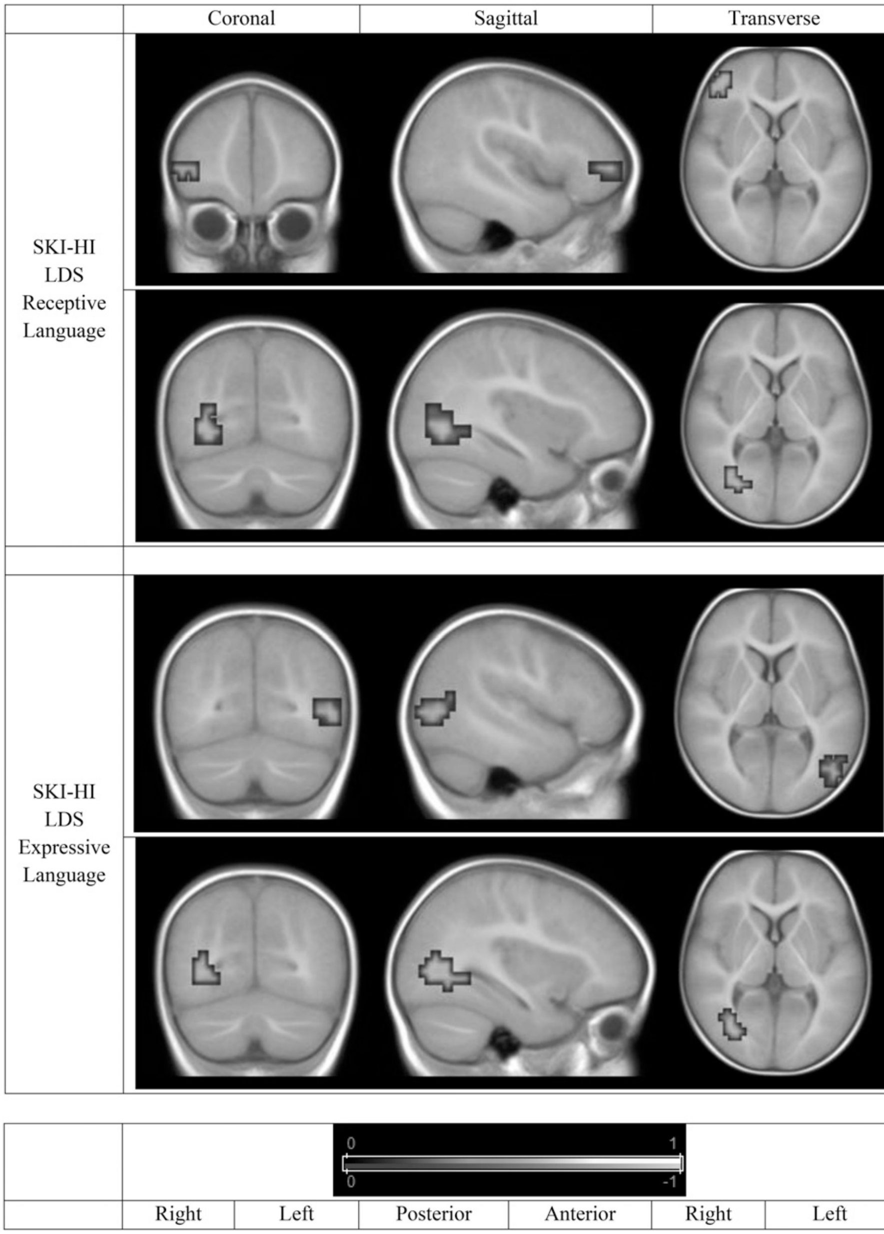

Figure 4. Correlation maps depicting clusters of strong correlation (corrected $p < 0.05$) between fMRI activation and SKI-HI LDS subtests for the noise versus silence BOLD contrast. The color bar denotes the correlation coefficient value (from -1 to $+1$). Image views and their orientations are indicated at the top and bottom of the figure, respectively.

2006), attending to relevant stimuli, and conflict resolution (Weissman et al, 2005). Blood flow changes in the precuneus in response to speech stimuli have been noted in normal hearing individuals as well as CI recipients (Wong et al, 1999; Giraud et al, 2001a; Moteki et al, 2014). Also, visual association areas (e.g., subgyral; BA 19) have been implicated in response to passive narratives (Karunanayaka et al, 2007) and "may be relevant to the future use of functional neuroimaging to guide predictions about speech and language outcomes in HI infants who receive a cochlear implant" (Tan et al, 2013, p. 427).

Lee et al (2005) retrospectively studied the preimplant F-18 fluorodeoxyglucose positron emission tomography images of 11 congenitally hearing impaired children in the age range of 5–7 1/2 yr at cochlear implantation. They divided their participants in two groups based on the Korean version of the Central Institute for the Deaf (CID) sentence test: those with 2-yr postimplant K-CID score of >65% (the better performing group) and those with 2-yr postimplant K-CID score of <45% (the poorer performing group). They found greater metabolic activity in the frontoparietal regions of the good group and greater metabolic activity in the

Table 5. Correlation between Preimplant BOLD Activation and Postimplant Scores on ASC and SKI-HI LDS Reveals the Previously Mentioned Clusters

BOLD Contrast: Noise vs. Silence							
Assessment Tool	Brodmann Areas	Predictive Regions	Cluster Size	Laterality	MNI Co-ordinates (*x, y, z*)	Correlation Coefficient (*r*)	Corrected *p* Value
ASC	BA 7	Parietal lobe, Precuneus	44	Left	−14, −62, 58	0.95	0.0011
SKI-HI LDS receptive language	BA 10, 11	Frontal lobe, middle frontal gyrus	31	Right	46, 46, −2	−0.90	0.0140
	BA 19	Occipital lobe, subgyral	52	Right	38, −66, −7	−0.88	0.0001
SKI-HI LDS expressive language	BA 21	Temporal lobe, middle temporal gyrus	40	Left	−50, −66, 8	−0.86	0.0016
	BA 19	Occipital lobe, middle occipital gyrus	46	Right	38, −78, −2	−0.86	0.0005

Note: Preimplant MRLs and age at implantation were controlled for in the second-level regressions. AlphaSim was implemented post hoc to adjust the significance threshold for multiple correlations. MNI coordinates and cluster sizes are listed along with Brodmann areas associated with the coordinates and hemisphere activated for the noise vs. silence BOLD contrast.

visual occipital regions of the poor group. Although the limited sample size prevented further subdivision of the group based on postimplant behavioral measures, the areas of significant correlation found in the current study are consistent with the Lee et al (2005) study. Five of the seven clusters identified as having strong correlations with the postimplant ASC score and SKI-HI LDS language age, were localized to the frontal, parietal, or occipital lobes. The correlation of extra-auditory regions with postimplant behavioral measures in the present study is further evidence of the predictive value of these regions in auditory and language performance.

Hemispheric Laterality

In this study, observation of significantly correlated clusters revealed no consistent pattern of laterality in response to the different auditory stimuli. Previously, leftward activation of temporo-parieto-occipital areas for speech stimuli has been noted (e.g., Vigneau et al, 2006; Turkeltaub and Coslett, 2010; Seghier, 2013). Fewer studies have found a rightward activation of speech-language areas in response to speech stimuli (Belin et al, 2000; van Ettinger-Veenstra et al, 2010; Lazard et al, 2010; Smith et al, 2011). However, a finding of mixed laterality (bilateral activation) especially in children predominates the fMRI literature (Schmithorst et al, 2006; Holland et al, 2007; Yeatman et al, 2010; Moteki et al, 2014). The results of a study by our group (Deshpande et al, 2016) displayed clusters of significant correlation in the temporo-parieto-occipital junction bilaterally in response to similar speech and noise stimuli as used in the present study. Split test-wise, current results show one cluster in the left precuneus that was predictive of the ASC score whereas five clusters in the right hemisphere (supramarginal gyrus, cingulate gyrus, middle frontal gyrus, subgyral, and middle occipital gyrus) which were predictive of the SKI-HI LDS language age. Only one cluster was identified in the left hemisphere that was predictive of postimplant SKI-HI LDS language age. This cluster correlated with the SKI-HI LDS expressive language age and was found in the middle temporal gyrus (BA 21). These results suggest that different brain regions in both hemispheres of the central auditory system of children with hearing loss may be predictive of auditory and language performance 2 yr after implantation.

Differences between "Speech versus Silence" and "Noise versus Silence" Contrasts

In the present study, comparison of the regression maps across different contrasts revealed that some clusters that correlated with ASC and SKI-HI LDS for the noise versus silence contrast failed to correlate with the behavioral measures for the speech versus silence contrast. For instance, a group of voxels in the parietal lobe that correlated strongly with ASC scores for the noise versus silence contrast did not present itself on the speech versus silence contrast for the same test (Figures 2 and 3). Only two clusters were identified on the speech versus silence contrast whereas five were identified on the noise versus silence contrast. In one of the landmark neuroimaging studies of CI users and normal hearing listeners in response to speech and noise, Wong et al (1999) found that the noise-like stimulus used in their study (multitalker babble) activated bilateral temporal regions in the CI group only. They attributed this finding to the lack of habituation to noise by the CI group. In the present study, the presence of bilateral clusters for the noise versus silence contrast may indicate a different coding strategy employed by young CI users in response to noise. The lack of habituation and the employment of a "coarse" coding strategy in response to noise may explain the presence of multiple clusters of significant correlation for the noise versus silence contrast (Wong et al, 1999). Another explanation may be related to the parameters of data analysis. Evaluation of the group composite maps revealed that although some clusters did not appear on the correlation maps, they were activated on the composite maps. This finding suggests that the minimum cluster size restriction in AlphaSim may have prevented some clusters from appearing on the correlation maps. Several studies in the fMRI literature have used a smaller cluster size (e.g., Shomstein and Yantis, 2004; 2006; Napadow et al, 2005; Phan et al, 2006).

Positive and Negative Correlations

In the present study, positive correlations were found between two brain regions (right supramarginal gyrus and right cingulate gyrus) and the SKI-HI LDS expressive language age for the speech versus silence contrast. Similarly, one cluster (left precuneus) was identified that correlated positively with postimplant ASC scores for the noise versus silence contrast. These positive correlations suggest that a greater preimplant activation in specific brain regions may predict improved auditory and language performance in young CI recipients as measured by parental observations/reports.

Some correlation maps also displayed a negative correlation between the preimplant fMRI activation and postimplant test scores. For instance, both the SKI-HI LDS receptive and expressive subtest language ages correlated negatively with fMRI activation for the noise versus silence contrast. In other words, greater fMRI activation in response to noise indicated a lower language age 2 yr postimplant. This phenomenon was observed across different brain regions including the occipital lobe, the temporal lobe, and the frontal lobe.

Previous studies have found both structural and functional changes in the occipital region of children with hearing loss (e.g., Lee et al, 2005; Smith et al, 2011). In an F-18 fluorodeoxyglucose positron emission tomography imaging study of 11 CI candidates between 5 and 7 1/2 yr of age, Lee et al (2005) observed greater metabolic activity in the occipital regions of children who performed poorly on speech perception measures after implantation. In the current study, a simple explanation for the observed negative correlations may be that greater activation in certain extra-auditory areas may be detrimental to future auditory/language development and indicate that these regions are engaging in auditory processes that are not augmentative to recognition and processing of speech stimuli.

A negative correlation was also observed between fMRI activation in the middle temporal gyrus and SKI-HI LDS expressive language age for the noise versus silence contrast. Previous studies (e.g., Chou et al, 2006a,b) have found a negative correlation between the middle temporal gyrus and semantic association in children. The negative correlation between activation in the middle temporal gyrus and relatively low semantic auditory stimuli may arise from "more extensive access to semantic representations in order to identify overlapping features" (Booth et al, 2007, p. 775). The low semantic quality inherent to the narrow band noise stimuli used in the present study may have resulted in the negative correlations observed in the noise versus silence contrast.

Finally, a negative correlation was observed between fMRI activation in the right middle frontal gyrus (BA 10) and SKI-HI LDS receptive language age for the noise versus silence contrast. This observation is consistent with previous findings wherein activation in the right middle frontal gyrus was negatively correlated with reading, writing, phonological, and decoding skills in children (Hoeft et al, 2007). Decreased performance accuracy on semantic judgment and picture naming has also been identified with increased activation in the middle frontal gyrus (Blumenfeld et al, 2006).

Limitations and Future Directions

In the present study, a sample size of 12 may be perceived as a limitation. Desmond and Glover (2002) reported that fMRI studies with a sample size of 12 yielded adequate power to detect a significant differences in populations in fMRI studies. Although the present study had 12 participants, a post hoc power analysis was conducted using nQuery Advisor (nQuery Advisor 6.0, Statistical Solutions, Cork, Ireland) to investigate if the results could be extended to the general population. Power was calculated for each cluster and each contrast based on the mean voxel value of clusters that correlated significantly with ASC and SKI-HI LDS. Such analysis based on estimated slope and variance yielded power of up to 68% in certain clusters. The above results indicate that the present study had moderate power to detect a significant correlation between fMRI activation in relevant clusters and behavioral measures (scores/language ages on ASC and SKI-HI LDS).

In the present study, two major variables that affect postimplant auditory/language performance were controlled viz. preimplant auditory status and age at implantation. These variables directly affect auditory/language development and account for a large proportion of variance in postimplant outcomes (Wake et al, 2005; Gilley et al, 2008). However, because of the limited sample size, additional variables that may have affected postimplant behavioral outcomes (e.g., hearing aid use before implantation, duration or frequency of postimplant speech-language intervention) could not be controlled. Future studies may consider evaluating contribution of multiple variables affecting postimplant speech-language and auditory outcomes in a structural equation model (SEM).

One variable that could not be controlled for because of the limited sample size was side of CI and bilateral versus unilateral CI. Literature is still emerging on the benefits of early bilateral implantation for long-term speech and language outcomes (van Hoesel, 2004; Litovsky et al, 2006; Brown and Balkany, 2007). Therefore, we might expect bilateral CI patients in our cohort to experience better outcomes 2 yr after CI than unilateral implant patients. However, the parent report measures are not likely to be sensitive to the specific benefits of bilateral implantation such as better perception of speech in noise or better localization. We did not investigate unilateral, bilateral, or side of implant as covariates in this study because of the sample size limitation.

As early as the 1990s, Kampfe et al, (1993) emphasized the importance of education, guidance, and counseling in a successful rehabilitation program before, during, and after implantation. According to them, listing the benefits and limitations of the CI, discussing other possible alternatives, and providing opportunities for dialogue with other parents of CI recipients will help parents make an informed decision about cochlear implantation. If parents are provided evidence-based counseling about postimplant outcomes before implantation, it helps them set realistic expectations from the implant and prepare for the rigorous rehabilitation process. Parents with a greater understanding of the realistic benefits of CI report higher satisfaction with the CI (e.g., Meadow-Orlans et al, 2003). Both measures used in the present study (SKI-HI LDS and ASC) may be viewed as indirect measures of parental expectations in that they do not include questions such as "What is your expectation out of the CI?" Instead, these measures of behavioral observation include items that parents attribute to the children's auditory/language performance. Results of the present study suggest that direct measures of parental expectation/satisfaction (e.g., Zaidman-Zait and Most, 2005) may be used in conjunction with fMRI in the future to help establish realistic expectations for parents considering a CI for their child.

CONCLUSIONS

The aim of the present study was to use fMRI to identify preimplant neuroimaging biomarkers that predict children's postimplant auditory and language outcomes as measured by parental observation/reports, specifically the ASC and the SKI-HI LDS. A regression analysis was implemented between preimplant fMRI activation (in response to speech and noise) and postimplant scores on ASC and SKI-HI LDS. Clusters of significant correlation were identified in auditory as well as extra-auditory brain regions. The results of this study indicate that (a) it is possible to identify neuroimaging biomarkers of auditory and language performance before implantation and (b) brain activation in specific regions correlates with postimplant auditory and language outcomes as measured by parental observation/reports. These results may be helpful in directing efforts toward validating fMRI as an objective predictor of postimplant auditory/language performance of young CI recipients.

Acknowledgments. The authors would like to thank Thomas Maloney and Robert Keith for their inputs and guidance throughout the project.

REFERENCES

Ahmad Z, Balsamo LM, Sachs BC, Xu B, Gaillard WD. (2003) Auditory comprehension of language in young children: neural networks identified with fMRI. *Neurology* 60(10):1598–1605.

Altaye M, Holland SK, Wilke M, Gaser C. (2008) Infant brain probability templates for MRI segmentation and normalization. *Neuroimage* 43(4):721–730.

Belin P, Zatorre RJ, Lafaille P, Ahad P, Pike B. (2000) Voice-selective areas in human auditory cortex. *Nature* 403(6767):309–312.

Binder JR, Desai RH, Graves WW, Conant LL. (2009) Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex* 19(12):2767–2796.

Blumenfeld HK, Booth JR, Burman DD. (2006) Differential prefrontal-temporal neural correlates of semantic processing in children. *Brain Lang* 99(3):226–235.

Booth JR, Bebko G, Burman DD, Bitan T. (2007) Children with reading disorder show modality independent brain abnormalities during semantic tasks. *Neuropsychologia* 45(4):775–783.

Brown KD, Balkany TJ. (2007) Benefits of bilateral cochlear implantation: a review. *Curr Opin Otolaryngol Head Neck Surg* 15(5):315–318.

Buxton RB, Wong EC, Frank LR. (1998) Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. *Magn Reson Med* 39(6):855–864.

Bzoch KR, League R. (1994) *Receptive-Expressive Emergent Language Scale*. 2nd ed. Austin, TX: Pro-Ed.

Castellanos I, Kronenberger WG, Beer J, Henning SC, Colson BG, Pisoni DB. (2014) Preschool speech intelligibility and vocabulary skills predict long-term speech and language outcomes following cochlear implantation in early childhood. *Cochlear Implants Int* 15(4):200–210.

Catani M, Allin MP, Husain M, Pugliese L, Mesulam MM, Murray RM, Jones DK. (2007) Symmetries in human brain language pathways correlate with verbal recall. *Proc Natl Acad Sci USA* 104(43):17163–17168.

Ching TY, Crowe K, Martin V, Day J, Mahler N, Youn S, Street L, Cook C, Orsini J. (2010) Language development and everyday functioning of children with hearing loss assessed at 3 years of age. *Int J Speech-Language Pathol* 12(2):124–131.

Chou TL, Booth JR, Bitan T, Burman DD, Bigio JD, Cone NE, Lu D, Cao F. (2006b) Developmental and skill effects on the neural correlates of semantic processing to visually presented words. *Hum Brain Mapp* 27(11):915–924.

Chou TL, Booth JR, Burman DD, Bitan T, Bigio JD, Lu D, Cone NE. (2006a) Developmental changes in the neural correlates of semantic processing. *Neuroimage* 29(4):1141–1149.

Coplan J, Gleason JR, Ryan R, Burke MG, Williams ML. (1982) Validation of an early language milestone scale in a high-risk population. *Pediatrics* 70(5):677–683.

Deshpande AK, Tan L, Lu LJ, Altaye M, Holland SK. (2016) fMRI as a preimplant objective tool to predict postimplant oral language outcomes in children with cochlear implants. *Ear Hear* 37(4): e263–e272.

Desmond JE, Glover GH. (2002) Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods* 118(2):115–128.

DiFrancesco MW, Robertson SA, Karunanayaka P, Holland SK. (2013) BOLD fMRI in infants under sedation: comparing the impact of pentobarbital and propofol on auditory and language activation. *J Magn Reson Imaging* 38(5):1184–1195.

Eisner F, McGettigan C, Faulkner A, Rosen S, Scott SK. (2010) Inferior frontal gyrus activation predicts individual differences in perceptual learning of cochlear-implant simulations. *J Neurosci* 30(21):7179–7186.

Finley CC, Holden TA, Holden LK, Whiting BR, Chole RA, Neely GJ, Hullar TE, Skinner MW. (2008) Role of electrode placement as a contributor to variability in cochlear implant outcomes. *Otol Neurotol* 29(7):920–928.

Frahm J, Krüger G, Merboldt KD, Kleinschmidt A. (1996) Dynamic uncoupling and recoupling of perfusion and oxidative metabolism during focal brain activation in man. *Magn Reson Med* 35(2):143–148.

Friston K, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ. (1995) Spatial registration and normalization of images. *Hum Brain Mapp* 3:165–189.

Gaab N, Gabrieli JD, Glover GH. (2007) Assessing the influence of scanner background noise on auditory processing. I. An fMRI study comparing three experimental designs with varying degrees of scanner noise. *Hum Brain Mapp* 28(8):703–720.

Geers AE, Nicholas JG. (2013) Enduring advantages of early cochlear implantation for spoken language development. *J Speech Lang Hear Res* 56(2):643–655.

Geers AE, Strube MJ, Tobey EA, Pisoni DB, Moog JS. (2011) Epilogue: factors contributing to long-term outcomes of cochlear implantation in early childhood. *Ear Hear* 32(1, Suppl): 84S–92S.

Geers A, Tobey E, Moog J, Brenner C. (2008) Long-term outcomes of cochlear implantation in the preschool years: from elementary grades to high school. *Int J Audiol* 47(Suppl 2):S21–S30.

Gilley PM, Sharma A, Dorman MF. (2008) Cortical reorganization in children with cochlear implants. *Brain Res* 1239:56–65.

Giraud AL, Price CJ, Graham JM, Frackowiak RS. (2001a) Functional plasticity of language-related brain areas after cochlear implantation. *Brain* 124(Pt 7):1307–1316.

Giraud AL, Price CJ, Graham JM, Truy E, Frackowiak RS. (2001b) Cross-modal plasticity underpins language recovery after cochlear implantation. *Neuron* 30(3):657–663.

Glascoe FP. (2000) Early detection of developmental and behavioral problems. *Pediatr Rev* 21(8):272–279, quiz 280.

Green KM, Ramsden RT, Julyan PJ, Hastings DL. (2008) Neural plasticity in blind cochlear implant users. *Cochlear Implants Int* 9(4):177–185.

Green T, Faulkner A, Rosen S. (2012) Frequency selectivity of contralateral residual acoustic hearing in bimodal cochlear implant users, and limitations on the ability to match the pitch of electric and acoustic stimuli. *Int J Audiol* 51(5):389–398.

Hall DA. (2006) fMRI of the auditory cortex. In: Faro SH, Mohamed FB, eds. *Functional MRI: Basic Principles and Clinical Applications*. New York, NY: Springer, 364–393.

Hoeft F, Ueno T, Reiss AL, Meyler A, Whitfield-Gabrieli S, Glover GH, Keller TA, Kobayashi N, Mazaika P, Jo B, Just MA, Gabrieli JD. (2007) Prediction of children's reading skills using behavioral, functional, and structural neuroimaging measures. *Behav Neurosci* 121(3):602–613.

Holland SK, Vannest J, Mecoli M, Jacola LM, Tillema JM, Karunanayaka PR, Schmithorst VJ, Yuan W, Plante E, Byars AW. (2007) Functional MRI of language lateralization during development in children. *Int J Audiol* 46(9):533–551.

Horowitz-Kraus T, Vannest JJ, Holland SK. (2013) Overlapping neural circuitry for narrative comprehension and proficient reading in children and adolescents. *Neuropsychologia* 51(13): 2651–2662.

Hyde M, Punch R, Grimbeek P. (2011) Factors predicting functional outcomes of cochlear implants in children. *Cochlear Implants Int* 12(2):94–104.

Kampfe CM, Harrison M, Oettinger T, Ludington J, McDonald-Bell C, Pillsbury HC 3rd. (1993) Parental expectations as a factor in evaluating children for the multichannel cochlear implant. *Am Ann Deaf* 138(3):297–303.

Kang E, Lee DS, Kang H, Lee JS, Oh SH, Lee MC, Kim CS. (2004) Neural changes associated with speech learning in deaf children following cochlear implantation. *Neuroimage* 22(3):1173–1181.

Kang WS, Lee JH, Lee HN, Lee KS. (2010) Cochlear implantations in young children with cochlear nerve deficiency diagnosed by MRI. *Otolaryngol Head Neck Surg* 143(1):101–108.

Karunanayaka PR, Holland SK, Schmithorst VJ, Solodkin A, Chen EE, Szaflarski JP, Plante E. (2007) Age-related connectivity changes in fMRI data from children listening to stories. *Neuroimage* 34(1):349–360.

Kim LS, Jeong SW, Lee YM, Kim JS. (2010) Cochlear implantation in children. *Auris Nasus Larynx* 37(1):6–17.

Kirk KI, Firszt JB, Hood LJ, Holt RF. (2006) New directions in pediatric cochlear implantation: effects on candidacy. *ASHA Lead* 11:6–15.

Knoors H, Meuleman J, Klatter-Folmer J. (2003) Parents' and teachers' evaluations of the communicative abilities of deaf children. *Am Ann Deaf* 148(4):287–294.

Krüger G, Kleinschmidt A, Frahm J. (1996) Dynamic MRI sensitized to cerebral blood oxygenation and flow during sustained activation of human visual cortex. *Magn Reson Med* 35(6): 797–800.

Lazard DS, Lee HJ, Gaebler M, Kell CA, Truy E, Giraud AL. (2010) Phonological processing in post-lingual deafness and cochlear implant outcome. *Neuroimage* 49(4):3443–3451.

Lee HJ, Kang E, Oh SH, Kang H, Lee DS, Lee MC, Kim CS. (2005) Preoperative differences of cerebral metabolism relate to the outcome of cochlear implants in congenitally deaf children. *Hear Res* 203(1-2):2–9.

Li J, Struzik Z, Zhang L, Zhang L, Cichocki A. (2013) Spectral power estimation for unevenly spaced motor imagery data. *Neural Information Processing*. Berlin, Heidelberg: Springer, 168–175.

Lin FR, Wang NY, Fink NE, Quittner AL, Eisenberg LS, Tobey EA, Niparko JK; CDaCI Investigative Team. (2008) Assessing the use of speech and language measures in relation to parental perceptions of development after early cochlear implantation. *Otol Neurotol* 29(2):208–213.

Litovsky RY, Johnstone PM, Godar SP. (2006) Benefits of bilateral cochlear implants and/or hearing aids in children. *Int J Audiol* 45(Suppl 1):S78–S91.

Logothetis NK, Guggenberger H, Peled S, Pauls J. (1999) Functional imaging of the monkey brain. *Nat Neurosci* 2(6):555–562.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. (2003) An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19: 1233–1239 (WFU Pickatlas, version 3.0.4).

McConkey Robbins A, Koch DB, Osberger MJ, Zimmerman-Phillips S, Kishon-Rabin L. (2004) Effect of age at cochlear implantation on auditory skill development in infants and toddlers. *Arch Otolaryngol Head Neck Surg* 130(5):570–574.

McKay CM. (2005) Spectral processing in cochlear implants. *Int Rev Neurobiol* 70:473–509.

Meadow-Orlans KP, Mertens DM, Sass-Lehrer MA. (2003) *Parents and Their Deaf Children*. Washington, DC: Galladuet University Press.

Meinzen-Derr J, Wiley S, Choo DI. (2011) Impact of early intervention on expressive and receptive language development among young children with permanent hearing loss. *Am Ann Deaf* 155(5):580–591.

Meinzen-Derr J, Wiley S, Creighton J, Choo D. (2007) Auditory skills checklist: clinical tool for monitoring functional auditory skill development in young children with cochlear implants. *Ann Otol Rhinol Laryngol* 116(11):812–818.

Morillon B, Lehongre K, Frackowiak RS, Ducorps A, Kleinschmidt A, Poeppel D, Giraud AL. (2010) Neurophysiological origin of human brain asymmetry for speech and language. *Proc Natl Acad Sci USA* 107(43):18688–18693.

Moteki H, Suzuki M, Naito Y, Fujiwara K, Oguchi K, Nishio SY, Iwasaki S, Usami S. (2014) Evaluation of cortical processing of language by use of positron emission tomography in hearing loss children with congenital cytomegalovirus infection. *Int J Pediatr Otorhinolaryngol* 78(2):285–289.

Nagels A, Kauschke C, Schrauf J, Whitney C, Straube B, Kircher T. (2013) Neural substrates of figurative language during natural speech perception: an fMRI study. *Front Behav Neurosci* 7:121–160.

Naito Y, Tateya I, Fujiki N, Hirano S, Ishizu K, Nagahama Y, Fukuyama H, Kojima H. (2000) Increased cortical activation during hearing of speech in cochlear implant users. *Hear Res* 143(1–2):139–146.

Napadow V, Makris N, Liu J, Kettner NW, Kwong KK, Hui KK. (2005) Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI. *Hum Brain Mapp* 24(3):193–205.

Nikolopoulos TP, Dyar D, Archbold S, O'Donoghue GM. (2004) Development of spoken language grammar following cochlear implantation in prelingually deaf children. *Arch Otolaryngol Head Neck Surg* 130(5):629–633.

Niparko JK, Tobey EA, Thal DJ, Eisenberg LS, Wang NY, Quittner AL, Fink NE; CDaCI Investigative Team. (2010) Spoken language development in children following cochlear implantation. *JAMA* 303(15):1498–1506.

Nowakowski ME, Tasker SL, Schmidt LA. (2009) Establishment of joint attention in dyads involving hearing mothers of deaf and hearing children, and its relation to adaptive social behavior. *Am Ann Deaf* 154(1):15–29.

Obleser J, Wise RJS, Dresner MA, Scott SK. (2007) Functional integration across brain regions improves speech perception under adverse listening conditions. *J Neurosci* 27(9):2283–2289.

Patel AM, Cahill LD, Ret J, Schmithorst V, Choo D, Holland S. (2007) Functional magnetic resonance imaging of hearing-impaired children under sedation before cochlear implantation. *Arch Otolaryngol Head Neck Surg* 133(7):677–683.

Petersen B, Gjedde A, Wallentin M, Vuust P. (2013) Cortical plasticity after cochlear implantation. *Neural Plast* 2013:318521.

Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. (2006) Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry* 59(5):424–429.

Pisoni DB, Conway CM, Kronenberger WG, Horn DL, Karpicke J, Henning SC. (2008) Efficacy and effectiveness of cochlear implants in deaf children. In: Marschark M, Hauser PC, eds. *Deaf Cognition: Foundations and Outcomes*. New York, NY: Oxford University Press.

Regev M, Honey CJ, Simony E, Hasson U. (2013) Selective and invariant neural responses to spoken and written narratives. *J Neurosci* 33(40):15978–15988.

Rescorla L, Alley A. (2001) Validation of the language development survey (LDS): a parent report tool for identifying language delay in toddlers. *J Speech Lang Hear Res* 44(2):434–445.

Rorden C. (2005) MRIcro. University of South Carolina.

Ruggirello C, Mayer C. (2010) Language development in a hearing and a deaf twin with simultaneous bilateral cochlear implants. *J Deaf Stud Deaf Educ* 15(3):274–286.

Schmithorst VJ, Dardzinski BJ. (2000) CCHIPS/IDL enables detailed MRI analysis. http://www.researchsystems.com/AppProfile/idl_med_cchips.cfm.

Schmithorst VJ, Holland SK. (2004) Event-related fMRI technique for auditory processing with hemodynamics unrelated to acoustic gradient noise. *Magn Reson Med* 51(2): 399–402.

Schmithorst VJ, Holland SK, Plante E. (2006) Cognitive modules utilized for narrative comprehension in children: a functional magnetic resonance imaging study. *Neuroimage* 29(1):254–266.

Schmithorst VJ, Holland SK, Plante E. (2007) Development of effective connectivity for narrative comprehension in children. *Neuroreport* 18(14):1411–1415.

Seghier ML. (2013) The angular gyrus: multiple functions and multiple subdivisions. *Neuroscientist* 19(1):43–61.

Sharma A, Dorman MF. (2006) Central auditory development in children with cochlear implants: clinical implications. *Adv Otorhinolaryngol* 64:66–88.

Sharma A, Nash AA, Dorman M. (2009) Cortical development, plasticity and re-organization in children with cochlear implants. *J Commun Disord* 42(4):272–279.

Shomstein S, Yantis S. (2004) Control of attention shifts between vision and audition in human cortex. *J Neurosci* 24(47):10702–10706.

Shomstein S, Yantis S. (2006) Parietal cortex mediates voluntary control of spatial and nonspatial auditory attention. *J Neurosci* 26(2):435–439.

Smalt CJ, Gonzalez-Castillo J, Talavage TM, Pisoni DB, Svirsky MA. (2013) Neural correlates of adaptation in normal hearing subjects to free learning with cochlear implant acoustic simulations. *Neuroimage* 82:500–509.

Smith KM, Mecoli MD, Altaye M, Komlos M, Maitra R, Eaton KP, Egelhoff JC, Holland SK. (2011) Morphometric differences in the Heschl's gyrus of hearing impaired and normal hearing infants. *Cereb Cortex* 21(5):991–998.

Specht K. (2014) Neuronal basis of speech comprehension. *Hear Res* 307:121–135.

Stoeckel C, Gough PM, Watkins KE, Devlin JT. (2009) Supramarginal gyrus involvement in visual word recognition. *Cortex* 45(9): 1091–1096.

Svirsky MA, Teoh SW, Neuburger H. (2004) Development of language and speech perception in congenitally, profoundly deaf children as a function of age at cochlear implantation. *Audiol Neurootol* 9(4):224–233.

Szaflarski JP, Altaye M, Rajagopal A, Eaton K, Meng X, Plante E, Holland SK. (2012) A 10-year longitudinal fMRI study of narrative comprehension in children and adolescents. *Neuroimage* 63(3):1188–1195.

Szaflarski JP, Schmithorst VJ, Altaye M, Byars AW, Ret J, Plante E, Holland SK. (2006) A longitudinal functional magnetic resonance imaging study of language development in children 5 to 11 years old. *Ann Neurol* 59(5):796–807.

Tan L, Chen Y, Maloney TC, Caré MM, Holland SK, Lu LJ. (2013) Combined analysis of sMRI and fMRI imaging data provides accurate disease markers for hearing impairment. *Neuroimage Clin* 3:416–428.

Thévenaz P, Ruttimann UE, Unser M. (1998) A pyramid approach to subpixel registration based on intensity. *IEEE Trans Image Process* 7(1):27–41.

Thoutenhoofd ED, Archbold SM, Gregory S, Lutman ME, Nikolopoulos TP, Sach TH. (2005) *Paediatric Cochlear Implantations: Evaluating Outcomes*. London: Whurr.

Tobey EA, Thal D, Niparko JK, Eisenberg LS, Quittner AL, Wang NY; CDaCI Investigative Team. (2013) Influence of implantation age on school-age language performance in pediatric cochlear implant users. *Int J Audiol* 52(4):219–229.

Tomblin JB, Barker BA, Spencer LJ, Zhang X, Gantz BJ. (2005) The effect of age at cochlear implant initial stimulation on expressive language growth in infants and toddlers. *J Speech Lang Hear Res* 48(4):853–867.

Turkeltaub PE, Coslett HB. (2010) Localization of sublexical speech perception components. *Brain Lang* 114(1):1–15.

van Ettinger-Veenstra HM, Ragnehed M, Hällgren M, Karlsson T, Landtblom AM, Lundberg P, Engström M. (2010) Right-hemispheric brain activation correlates to language performance. *Neuroimage* 49(4):3481–3488.

van Hoesel RJ. (2004) Exploring the benefits of bilateral cochlear implants. *Audiol Neurootol* 9(4):234–246.

Vannest JJ, Karunanayaka PR, Altaye M, Schmithorst VJ, Plante EM, Eaton KJ, Rasmussen JM, Holland SK. (2009) Comparison of fMRI data from passive listening and active-response story processing tasks in children. *J Magn Reson Imaging* 29 (4):971–976.

Vigneau M, Beaucousin V, Hervé PY, Duffau H, Crivello F, Houdé O, Mazoyer B, Tzourio-Mazoyer N. (2006) Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *Neuroimage* 30(4):1414–1432.

Wake M, Poulakis Z, Hughes EK, Carey-Sargeant C, Rickards FW. (2005) Hearing impairment: a population study of age at diagnosis, severity, and language outcomes at 7-8 years. *Arch Dis Child* 90(3): 238–244.

Ward BD. (2000) Simultaneous inference for FMRI data. http://web.mit.edu/seven/doc/AFNI98/AlphaSim.ps 02/2012.

Watkins S, Tonelson S. (2004) *SKI-HI Language Development Scale: Assessment of Language Skills for Children Who are Deaf or Hard of Hearing from Infancy to Five Years of Age*. 2nd ed. Logan, UT: Utah State University, HOPE, Inc.

Weissman DH, Gopalakrishnan A, Hazlett CJ, Woldorff MG. (2005) Dorsal anterior cingulate cortex resolves conflict from distracting stimuli by boosting attention toward relevant events. *Cereb Cortex* 15(2):229–237.

Wiig EH, Secord WA, Semel E. (2004) *Clinical Evaluation of Language Fundamentals-Preschool*. 2nd ed. San Antonio, TX: The Psychological Corporation.

Wiley S, Meinzen-Derr J, Choo D. (2008) Auditory skills development among children with developmental delays and cochlear implants. *Ann Otol Rhinol Laryngol* 117(10):711–718.

Wolraich ML, Lambert W, Doffing MA, Bickman L, Simmons T, Worley K. (2003) Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. *J Pediatr Psychol* 28(8):559–567.

Wong D, Miyamoto RT, Pisoni DB, Sehgal M, Hutchins GD. (1999) PET imaging of cochlear-implant and normal-hearing subjects listening to speech and nonspeech. *Hear Res* 132(1–2): 34–42.

Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, Evans AC. (2002) A general statistical analysis for fMRI data. *Neuroimage* 15(1):1–15.

Xu J, Kemeny S, Park G, Frattali C, Braun A. (2005) Language in context: emergent features of word, sentence, and narrative comprehension. *Neuroimage* 25(3):1002–1015.

Yeatman JD, Ben-Shachar M, Glover GH, Feldman HM. (2010) Individual differences in auditory sentence comprehension in children: An exploratory event-related functional magnetic resonance imaging investigation. *Brain Lang* 114(2):72–79.

Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL. (1998) Language of early- and later-identified children with hearing loss. *Pediatrics* 102(5):1161–1171.

Zaidman-Zait A, Most T. (2005) Cochlear implants in children with hearing loss: maternal expectations and impact on the family. *Volta Review* 105:129–150.

Zeng FG. (2004) Trends in cochlear implants. *Trends Amplif* 8(1):1–34.

Zimmerman-Phillips S, Osberger MJ, Robbins AM. (2001) *Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS)*. Sylmar, CA: Advanced Bionics Corporation.