Preoperative differences of cerebral metabolism relate to the outcome of cochlear implants in congenitally deaf children

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Received 10 March 2004; accepted 15 November 2004
Available online 22 December 2004

Abstract

In congenitally deaf children, chronological age is generally accepted as a critical factor that affects successful rehabilitation following cochlear implantation (CI). However, a wide variance among patients is known to exist regardless of the age at CI [Sarant, J.Z., Blamey, P.J., Dowell, R.C., Clark, G.M., Gibson, W.P., 2001. Variation in speech perception scores among children with cochlear implants. Ear Hear. 22, 18–28]. In a previous study, we reported that prelingually deaf children in the age range 5–7 years at implantation showed greatest outcome variability [Oh S.H., Kim C.S., Kang E.J., Lee D.S., Lee H.J., Chang S.O., Ahn S.H., Hwang C.H., Park H.J., Koo J.W., 2003. Speech perception after cochlear implantation over a 4-year time period. Acta Otolaryngol. 123, 148–153]. Eleven children who underwent CI between the age of 5 and 7 1/2 years were subdivided into a good (above 65%: GOOD) and a poor (below 45%: POOR) group based on the performance in a speech perception test given 2 years after CI. The preoperative 18F-FDG-PET (F-18 fluorodeoxyglucose positron emission tomography) images were compared between the two groups in order to examine if regional glucose metabolic difference preexisted before the CI surgery. In the GOOD group, metabolic activity was greater in diverse fronto-parietal regions compared to the POOR group. In the POOR group, the regions related to the ventral visual pathway showed greater metabolic activity relative to the GOOD group. These findings suggest that the deaf children who had developed greater executive and visuospatial functions subserved by the prefrontal and parietal cortices might be successful in auditory language learning after CI. On the contrary, greater dependency on the visual function subserved by the occipito-temporal region due to auditory deprivation may interfere with acquisition of auditory language after CI.

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Keywords: Cochlear implants; Brain imaging; PET; Deafness

1. Introduction

Previous literature on the outcome of cochlear implantation (CI) has consistently reported large individual variations among implant users. Some prelingually deafened children show outstanding outcome following the CI, rapidly acquiring spoken language and producing intelligible speech. Other children, however, develop awareness of sounds but never reach the age-appropriate level of auditory language.

Several traditional demographic factors explained 35–51% of the observed variance of the outcome among implanted children. These factors included duration of deafness, age at implantation, mode of communication, duration of device use and coding...
strategy (O'Donoghue et al., 2000; Miyamoto et al., 1994; Sarant et al., 2001; Hammes et al., 2002). Of these, the age at implantation has been reported to be the major determinant of pediatric cochlear implant candidacy (Nikolopoulos et al., 1999). Other previous work has demonstrated that children who undergo implantation at a younger age achieve a significantly better communication outcome and develop spoken language faster than those who undergo implantation at an older age (Fryauf-Bertschy et al., 1997; Hammes et al., 2002; Kirk et al., 2000; Waltzman and Cohen, 1998). Almost all the deaf children who receive CI surgery at a very young age such as before 2 or 3 years old do very well with the device unless the children have any other disadvantage (Waltzman and Cohen, 1998; Hammes et al., 2002). On the other hand, congenitally deaf patients implanted in later childhood show a widely variable outcome. They are likely to have poorer outcome than those implanted earlier but some adult congenitally deaf were reported to show considerable open set speech understanding (Waltzman et al., 2002). It needs to investigate what determines this wide variability in the older children besides the well-known demographic factors.

In fact, the pediatric cochlear implant candidates are widely heterogeneous with respect to several characteristics, e.g., audiologic status, language ability and cognitive function. These factors may account for CI outcome but they have not been fully investigated because of the lack of valid and reliable measuring tools.

Biological factors have also been investigated in past. For example, a histopathological study (Nadol et al., 2001) examined the relationship between the residual spiral ganglion cell populations in the temporal bones of CI patients with their speech perception ability during life. However, the unexpected negative correlation between them suggested that certain processes in the central auditory pathway are at least as important as peripheral factors.

Further research using a new approach is needed to understand the large individual variance observed in the CI performance outcome. Several neuroimaging studies have shown brain activity differences in various brain regions between cochlear implant users and normal hearing individuals (Naito et al., 1997, 2000; Roland et al., 2001; Giraud et al., 2000). However, few neuroimaging studies have been undertaken to identify those differences in the central auditory pathway that predict the functional outcome of implantation. Our past work (Lee et al., 2001) showed an association between better speech perception after CI and a greater extent of presurgical hypometabolism (decreased glucose metabolism) in superior temporal regions, including primary auditory area. However, the deaf patients with various duration of implant use and various age at implantation (i.e., duration of deafness in case of the congenitally deaf) were included in the past study although those factors were corrected statistically.

Recently, we reported the CI outcomes based on a 4-year follow-up (Oh et al., 2003) where a statistically significant negative correlation was found between the age at implantation and speech perception ability in the prelingually deaf child group, which was in accord with the findings of other researchers (Nikolopoulos et al., 1999; O'Donoghue et al., 2000). In addition, it was brought to our attention that there was an apparent age transition zone between 5 and 7 years old, where the most variable outcomes were found even though subjects were in a narrow age range.

In the present study, we were interested in identifying preoperative brain regional differences which were associated with the variable degree of CI outcome in the congenitally deaf children at this transitional age period (5–7 years old). Resting cortical metabolic activity was assessed using 18F-FDG-PET in these patients before CI. We included only a group of patients who were similar in the known prognostic factors such as duration of deafness, age at implantation, cause of deafness, developmental history, and educational setting. These children, nevertheless, showed a wide range of outcomes following CI. We removed the age factor as a potential variable of CI outcome by including the pediatric patients only in this age group. We compared two groups of deaf children (one with a ‘good’ and the other with ‘poor’ outcome) who were comparable in implantation age (5–7.5 years old) and in the length of rehabilitation (about two years after implantation) in order to find if there were differences in preoperative brain metabolic status.

2. Materials and methods

2.1. Subjects

From November 1988 to April 2001, 111 profoundly hearing impaired children received cochlear implants at Seoul National University Hospital, and 61 children with congenital deafness were followed for 2 years after implantation. Of these, 26 children, between the ages 5 and 7.5, have had cochlear implants since we started an ongoing 18F-FDG-PET study in 1997. Ten children with a history of medical illness known to affect neurological development (meningitis, neonatal jaundice, congenital rubella), or any known psychological illness (autism), or any evidence of inner ear anomaly proven by high resolution computed tomography of the temporal bone were excluded. Five children were excluded because their parents did not agree to the PET scan. Finally, 11 children (7 boys and 4 girls) aged from 5 to 71/2 years at implantation were included and their
preoperative $^{18}$F-FDG-PET images were analyzed retrospectively.

Two patients received Nucleus 22M system, 5 Nucleus 24M, 1 Nucleus 24 contour, and 3 Clarion devices. All 11 received auditory training in an auditory-oral educational setting, and all 11 were implanted and followed up at the same hospital. Subjects’ demographic findings are summarized in Table 1. This study was carried out under the guidelines established by the institutional review board of Seoul National University Hospital for research involving human subjects, and written informed consent was obtained from all subject’s parents before $^{18}$F-FDG-PET.

### 2.2. Preoperative PET image acquisition

At the time of the preoperative work-up, PET scans were acquired using an ECAT EXACT47 (Siemens-CTI, Knoxville, USA) PET scanner (BGO crystal detector, spatial resolution 6.1 mm, axial resolution 4.3 mm, sensitivity 214 kcps/microCi/mi) in two-dimensional mode with an 16.2 cm axial field of view. An intravenous injection of 370 MBq or less of F-18-FDG, according to the subject body weight was administrated 30–40 min before PET scanning. During and after the FDG injection, all patients stayed in a waiting room with ambient lighting and noise. A transmission scan was performed using a Ge-68 rod source to yield attenuation maps immediately before an emission PET scan. During the emission scan, 47 slices of brain emission images were acquired over a 20-min period and no particular stimulation was given to the patients, who were at rest. Emission images were reconstructed in a $128 \times 128 \times 47$ matrix with a pixel size of $2.1 \times 2.1 \times 3.4$ mm using a filtered back projection method with a Shepp filter with a cutoff value of 0.35 cycles/pixel. All reconstructed images were corrected for attenuation, and the transaxial images were realigned to yield sagittal and coronal images.

### 2.3. Speech perception ability and subject grouping

Speech perception was measured using the Korean version of the CID (Central Institute for the Deaf) sentence test for children, without visual cues (auditory cues only). All subjects were tested in the same institute. The test results obtained at approximately 2 years after implantation were analyzed. Fig. 1 shows speech perception ability as measured about 2 years after implantation. Though all 11 children were in a similar age group, their speech perception abilities showed a wide variation, ranging from 23% to 100% after constant auroral oral speech training. Children were divided into two groups, a GOOD group (K-CID $>$65%) and POOR group (K-CID $<$45%).

### 2.4. Data processing and group comparison

All PET data were analyzed by Statistical Parametric Mapping (SPM99, University College of London, UK), implemented in Matlab (Mathworks Inc., Natick, MA, USA). Head movement correction, transformation into stereotaxic space (Montreal Neurological Institute coordinates (MNI) as provided by SPM99), and smoothing (Gaussian filter of 16 mm FWHM) were performed. Using SPM99, a two-sample $t$-test was performed in a voxel wise manner on preprocessed PET images following global normalization for FDG-uptake. Comparison was made between the GOOD group and the POOR group. The statistical parametric

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### Table 1

Demographic characteristics of the GOOD and POOR groups

<table>
<thead>
<tr>
<th>Group</th>
<th>GOOD</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>G1</td>
<td>G2</td>
<td>G3</td>
<td>G4</td>
<td>G5</td>
<td>G6</td>
<td>P1</td>
<td>P2</td>
<td>P3</td>
<td>P4</td>
<td>P5</td>
<td>CI age (months)</td>
<td>82</td>
<td>60</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>K-CID score (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before CI</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>After CI</td>
<td>96.7</td>
<td>66.7</td>
<td>83</td>
<td>100</td>
<td>83.3</td>
<td>73</td>
<td>83.8 (12.9)</td>
<td>36.7</td>
<td>33</td>
<td>43</td>
<td>37</td>
<td>23</td>
<td>34.5 (7.4)</td>
<td>&lt;0.007</td>
<td></td>
</tr>
<tr>
<td>Duration of CI use at time of K-CID test (months)</td>
<td></td>
<td>22</td>
<td>18</td>
<td>24</td>
<td>20</td>
<td>25</td>
<td>18</td>
<td>21.2 (3.0)</td>
<td>12</td>
<td>25</td>
<td>19</td>
<td>18</td>
<td>25</td>
<td>19.8 (5.4)</td>
<td>&gt;0.10</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
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<td>M</td>
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</tbody>
</table>

* Mann–Whitney U test using SPSS 11.5 (SPSS Inc., Chicago, IL) for Windows.
maps were thresholded at an uncorrected $p < 0.005$ ($T = 3.25$). A significant cluster was deemed to be composed of a contiguous 25 voxels (each voxel represented an 8 mm cube). The local maximum of each significant cluster is reported in Talairach coordinates in Table 2 of this study (Talairach and Tournoux, 1988). A slightly lenient statistical parametric threshold ($p < 0.01$) was used for illustrative purpose in Fig. 2.

### Table 2
Regions showing significant glucose metabolism differences in the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Region</th>
<th>BA$^a$</th>
<th>Talairach coordinates$^b$</th>
<th>T score</th>
<th>Cluster size</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$ $y$ $z$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOOD $&gt;$ POOR</td>
<td>L dorsolateral prefrontal region</td>
<td>9</td>
<td>$-38$ $0$ $39$</td>
<td>6.07</td>
<td>523</td>
</tr>
<tr>
<td></td>
<td>R Precuneus</td>
<td>7</td>
<td>$20$ $-54$ $45$</td>
<td>5.71</td>
<td>406</td>
</tr>
<tr>
<td></td>
<td>R frontopolar region</td>
<td>10</td>
<td>$26$ $55$ $16$</td>
<td>4.35</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>L medial frontal region</td>
<td>6</td>
<td>$-12$ $36$ $29$</td>
<td>3.96</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>L inferior parietal region</td>
<td>40</td>
<td>$-59$ $-29$ $38$</td>
<td>3.76</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>R medial frontal region</td>
<td>6</td>
<td>$18$ $-13$ $49$</td>
<td>3.75</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>L middle frontal region</td>
<td>9</td>
<td>$-34$ $33$ $35$</td>
<td>3.47</td>
<td>59</td>
</tr>
<tr>
<td>POOR $&gt;$ GOOD</td>
<td>R inferior occipital region</td>
<td>18</td>
<td>$34$ $-94$ $-10$</td>
<td>6.25</td>
<td>497</td>
</tr>
<tr>
<td></td>
<td>L fusiform gyrus</td>
<td>20, 36</td>
<td>$-46$ $-22$ $-17$</td>
<td>6.15</td>
<td>1281</td>
</tr>
<tr>
<td></td>
<td>L orbitofrontal region</td>
<td>11</td>
<td>$-10$ $53$ $-23$</td>
<td>4.58</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>R fusiform gyrus</td>
<td>37</td>
<td>$42$ $-38$ $-13$</td>
<td>3.68</td>
<td>74</td>
</tr>
</tbody>
</table>

$^a$ Brodmann’s area.
$^b$ Local maxima of clusters composed of 25 contiguous significant ($p < 0.005$) voxels.
Results are displayed as a rendered brain or as high-resolution T1-weighted MR reference images.

3. Results

Significant glucose metabolism differences were found between the two groups. Table 2 summarizes the coordinates of brain regions showing group FDG-uptake differences in the GOOD and POOR groups ($p < 0.001$, extent threshold = 25 voxels). The brain regions showing different metabolic activities between the two groups are displayed in Fig. 2. The regions with greater metabolism in the GOOD group relative to the POOR group are marked in red and the regions with lower metabolism, in green.

3.1. GOOD group > POOR group

The GOOD group showed significantly greater metabolic activity in various regions in the dorsal portion of the brain than the POOR group. These included the left dorsolateral prefrontal (BA 9), the right frontopolar (BA 10), the bilateral medial frontal cortices (BA 6), the right precuneus (BA 7), and the left inferior parietal cortex (BA 40) (Fig. 2).

3.2. GOOD group < POOR group

Metabolic activity in the GOOD group was lower in the ventral part of the cerebral cortex than the POOR group, in such areas as the right inferior occipital cortex (BA 18), the bilateral fusiform gyri (left BA 20/36, right BA 37) and the left orbitofrontal region (BA 11) (Fig. 2).

4. Discussion

4.1. Congenitally deaf children aged from 5 to 7 years old

We examined the differences in the brain of congenitally deaf children in this particular transitional age zone, age 5–7 years old in order to observe any possible preoperative cerebral metabolic differences in auditory language learning. Confining the study to pediatric patients only within this narrow age range was advantageous in two aspects. First, it gave us an opportunity to delineate the brain regions associated with CI outcome by removing the confounding effect of developmental age. Second, more importantly, this particular age group provided us the most sufficiently wide range of variability of CI outcome to investigate within a narrow age range. This age range happened to coincide with the developmental period when important transition occurred in terms of regaining auditory responses after CI in the deaf brain (Sharma et al., 2002; Eggermont and Ponton, 2003). Deaf children aged from 3.5 to 6.5 years at implantation (the ‘middle age group’ in Sharma et al. study) showed apparent age-independent variation in P1 latency, unlike the younger or the older children who showed restored age-appropriate P1 cortical latency or delayed P1 cortical responses, respectively, after years of auditory stimulation. Important cytoarchitectonic development also occurred in auditory cortex in this age range in normal hearing children (Moore and Guan, 2001).

4.2. Higher metabolic areas in the GOOD group

Cortical metabolism of diverse areas in frontal regions was increased in the GOOD group, including left posterior dorsolateral prefrontal gyrus (BA 9) and right frontal pole (BA 10). The dorsolateral prefrontal cortex has been known to be involved in working memory or executive function (Owen et al., 1996; Kammer et al., 1997). The frontopolar region (BA 10) has also been suggested to play a role in the monitoring information within working memory (Petrides et al., 1993) or in problem-solving/reasoning (Koechlin et al., 1999). This region was found to be involved in executive processing when early-stage multiple sclerosis patients showed compensatory cortical activation during a cognitive task (Audolin et al., 2003).

The GOOD group also showed greater metabolic activity in the right precuneus (BA 7) in comparison to the POOR group. In previous functional imaging studies using memory-related tasks, right lateralized activation of the precuneus was noted during visual imagery occurring in episodic memory retrieval (Fletcher et al., 1995; Krause et al., 1999) or during memory-related imagery (Fletcher et al., 1995; Herath et al., 2001).

Recent evidence suggest that working memory might be an important patient factor, and that this could explain individual differences in spoken word recognition ability after CI (Pisoni and Geers, 2000; Pisoni and Cleary, 2003; Surowiecki et al., 2002; Dawson et al., 2002). These findings are also in agreement with the group difference found in the present study concerning the metabolic activities of the dorsolateral prefrontal or inferior parietal cortices, which were greater in the GOOD group than in the POOR group even before CI. However in these studies, working memory was measured postoperatively after years of speech rehabilitation. Thus, it cannot be ruled out that improved working memory resulted from successful speech training. Unlike these previous studies, our data suggest that group differences exist in the metabolic rate of dorsolateral prefrontal region in the left hemisphere before CI. Therefore, we considered the possibility that in patients of the GOOD group might have had better working memory capacity, which in turn could have yielded
better rehabilitation of speech perception/speech learning following CI. This notion is also supported by recent fMRI data (Crottaz-Herbette et al., 2004) where the dorsolateral prefrontal cortex was activated bilaterally during verbal working memory tasks along with the ventrolateral prefrontal, intraparietal, supramarginal, and basal ganglia. However, the left dorsolateral prefrontal cortex was found to be involved more in auditory than visual working memory.

Other functional differences, aside from working memory difference, could be related to the relatively greater metabolic rate in the dorsolateral prefrontal region in the GOOD group. The precentral ‘face’ area seemed to be involved during speech even without auditory input in normal hearing subjects (Paus et al., 1996), though the exact location of our study was again slightly rostral to the reported location of peak activation in the left precentral ‘face’ area \([x, y, z = -2, -9, 41]\). The greater activity observed in the dorsolateral region in our study might indicate the possibility that deaf patients in the GOOD group had a greater use of mouth movement, either as means of speech perception or simultaneous communication (Caccamise and Newell, 1984).

### 4.3. Higher metabolic areas in the POOR group

The POOR group showed relatively higher metabolic activity in the bilateral fusiform and right inferior occipital regions. These regions are known to be part of the ventral visual pathway (Ungerleider and Haxby, 1994; Boussaoud et al., 1995; Haxby et al., 1991). This pathway, called ‘what’ pathway, is known to carry out form discrimination and object identification in visual processing (Ishai et al., 1999; Ptito et al., 2003; Gerlach et al., 1999). The enhancement of visual performance in the prelingual deaf has been suggested to be the consequence of auditory deprivation from birth, leading to compensatory changes within the visual system. Several studies have reported enhanced attentional processing of the congenitally deaf versus normal-hearing controls (Proksch and Bavelier, 2002; Bavelier et al., 2000). According to our metabolic data, the POOR group may have developed a greater demand for visual function before implantation, subserved by the ventral visual ‘what’ system.

Our finding is consistent with one of our past work (Lee et al., 2001) in that the extent of cerebral hypometabolic areas, particularly in the ventral part of brain, was reported to be associated with better CI outcome. However, we did not directly compare our results with the past study where a correlation was reported between the extent of presurgical hypometabolism in selected cortical areas (BA 41, 42 and 22) and CI outcome in the deaf patients with a wide age range (2.2–20.3 years old). A few methodological differences between the past study (analysis of only the superior temporal region, and comparison between a wide age range deaf and the normal hearing adults) and the current study (analysis of whole brain region and comparison between two limited age patient groups) should be considered. When the older congenital deaf patients were not included in analysis as in the current study, the findings are unlikely to include the effects of long term deaf-induced brain plasticity (Giraud et al., 2001a). Only further investigation of a large scale pediatric patient will be able to answer these important questions.

Given the empirical limitations of this kind of study, without data from a third comparison/control group of age-matched normal hearing children, we can only consider two different hypothetical possibilities that explain the observed group differences. First, the POOR group might show greater metabolic activity in the ventral visual pathway than ‘normal children’, due to compensatory visual processing in the absence of auditory sensation. Second, the metabolic activities of higher visual areas in the ventral visual pathway may have been reduced in the GOOD group relative to ‘normal hearing children’, due to some inexplicable result of deafness, even though this seems unlikely.

Caution should be exercised when two groups are directly contrasted, since the observed difference could be related with artifacts resulted from a global normalization procedure. With this procedure, the FDG uptake of each image is normalized based on the FDG uptake of the whole gray matter. However, the remedy of this artifact (measuring absolute global FDG-uptake) is too invasive and unpractical, and the effect of this artifact is negligible when the analysis is performed between two groups which are assumed to be similar in global brain activity.

### 4.4. Application of functional brain imaging to cochlear implants

Several functional imaging studies have suggested that the success of the postlingual adult CI users is related to distinctive features of a larger cortical network, which includes use of visual areas during speech processing (Giraud et al., 2000, 2001b; Naito et al., 2000; Wong et al., 1999). However, our knowledge which requires to use functional brain imaging to predict CI outcome has been primitive. According to our findings, a lower metabolic activity in the fusiform area along with a higher metabolic activity in the fronto-parietal region seem to yield a better CI outcome in the patients with this developmental age (5 to 7 1/2 years old). The results of our study suggest that functional brain imaging may serve as a clinically powerful tool for predicting CI outcome. Further studies on the central features of the pre-CI brain may provide us with more opportunity to explain...
the high outcome variance following CI in addition to a number of demographic characteristics known to affect CI outcome.

Acknowledgements

This work was supported by Grant No. R01-2002-000-00346-0 from the Basic Research Program of the Korea Science & Engineering Foundation.

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