Hearing Thresholds and fMRI of Auditory Cortex Following Eighth Cranial Nerve Surgery

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. Determine whether auditory cortex (AC) organization changed following eighth cranial nerve surgery in adults with vestibular-cochlear nerve pathologies. We examined whether hearing thresholds before and after surgery correlated with increased ipsilateral activation of AC from the intact ear.

Study Design. During magnetic resonance imaging sessions before and 3 and 6 months after surgery, subjects listened with the intact ear to noise-like random spectrogram sounds.

Setting. Departments of Radiology and Otolaryngology of Washington University School of Medicine.

Subjects and Methods. Three patients with acoustic neuromas received Gamma Knife radiosurgery (GK); 1 patient with Meniere’s disease and 5 with acoustic neuromas had surgical resections (SR); 2 of the latter also had GK. Hearing thresholds in each ear were for pure tone stimuli from 250 to 8000 Hz before and after surgery (3 and 6 months). At the same intervals, we imaged blood oxygen level–dependent responses to auditory stimulation of the intact ear using an interrupted single-event design.

Results. Hearing thresholds in 2 of 3 individuals treated with GK did not change. Five of 6 individuals became unilaterally deaf after SRs. Ipsilateral AC activity was present before surgery in 6 of 9 individuals with ipsilateral spatial extents greater than contralateral in 3 of 9. Greater contralateral predominance was significant especially in left compared to right ear affected individuals, including those treated by GK.

Conclusion. Lateralization of auditory-evoked responses in AC did not change significantly after surgery possibly due to preexisting sensory loss before surgery, indicating that less than profound loss may prompt cortical reorganization.

Keywords

auditory cortex, acoustic neuroma, unilateral deafness, neuroplasticity, Gamma Knife radiosurgery, functional imaging

Introduction

Monaural acoustic stimulation evokes larger responses contralateral to the stimulated ear with normal hearing. This results in hemispheric asymmetry in auditory cortex (AC), characterized by greater contralateral compared to ipsilateral response magnitudes and spatial extents to the stimulated ear. According to 1 study, contralateral dominant responses only occur with left ear stimulation, but others reported contralateral asymmetry with auditory inputs to either ear. In contrast, with unilateral hearing loss, stimulation of the intact ear evokes greater ipsilateral than contralateral activity, especially notable in core and adjacent belt AC fields. Neural changes occur immediately, from periphery to cortex, following deafferentation in many sensory systems. For example, in adult guinea pigs, enhanced ipsilateral auditory-evoked responses occurred in AC within 2 to 3 weeks after unilateral cochlea hair cell damage. Sudden unilateral hearing loss in humans similarly reduced asymmetrical AC activity within days. After surgical resection (SR) of a left acoustic neuroma, 1 study reported symmetrical bilateral responses to 1 kHz tone bursts at 5 weeks and expanded ipsilateral activation at 1 year post SR. Comparably, auditory-evoked field potentials (AEF) were larger and had shorter latencies for ipsilateral compared to contralateral ear inputs at 1 month after SRs. However, 1 study reported near normal contralateral asymmetrical AEF response magnitudes and shorter latencies to hearing speech and non-speech sounds with an intact left ear and right ear deafness. For

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those with an intact right ear and left ear deafness, significant ipsilateral activation occurred. These differences among studies warrant additional investigation of altered asymmetrical activation to monaural stimulation in auditory cortex.

We evoked responses in AC with random spectrogram sounds (RSS) before and at 3 and 6 months after surgical treatment for unilateral eighth cranial nerve pathology. Only 1 of 6 individuals treated with SR had preserved hearing on the affected side. In 3 individuals treated with Gamma Knife radiosurgery (GK), preoperative hearing persisted in 2; in 1, hearing decreased but did not reach a profound level. These results are consistent with individuals receiving GK treatments in multi-institution meta-analyses24,25 where 60% had hearing preservation. Given hearing differences with treatment modalities, we also determined whether individuals treated with GK showed less lateralization reorganization in AC.

**Methods**

We measured blood oxygen level–dependent (BOLD) responses using echo-planar imaging (EPI) sequences in 9 individuals before and after surgery. The study was reviewed and approved by the Human Studies Institutional Review Board of Washington University and was in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All enrolled individuals gave informed consent.

Eight individuals had unilateral acoustic neuromas, and 1 had Meniere’s disease (Table 1). The acoustic neuromas mostly were at the cerebellopontine angle but with varied sizes including several extending intracanalicular (Table 2). Cases 1, 3, 5, and 6 had surgical resections; cases 2 and 4 had SR followed by GK; and cases 7, 8, and 9 had GK exclusively (Table 2).

We measured monaural audiometric hearing thresholds for each preoperative and postoperative session with insert phones and pure tone stimuli from 250 to 8000 Hz, presented in a double-walled sound booth while using a standard Hughson-Westlake procedure.

During imaging, individuals heard noise-like random spectrogram sounds (RSS) presented monaurally to the intact ear through magnetic resonance compatible circumaural, cushion sealed headphones. These previously described stimuli result from manipulation and combination of temporal and spectral parameters for 1638 pure tones spanning a 6-octave bandwidth (250-16000 Hz). RSS stimuli have matching average intensities across spectral regions and temporal ranges, thereby avoiding confounds of differing bandwidth, intensity, or duration as specifying variables common to speech. Additionally, there is independent control of spectral and temporal sound complexity. The complexity of RSS was low or high, based on temporal rates (8 for low and 30 Hz for high) or number of spectral bands (3 for low and 16 for high). Participants pressed an optical key to signal detection of an oddball trial in which the complexity of the RSS differed from that during most other trials in an imaging run. Stimulus intensity in the intact ear was 70 dB SPL. The stimuli were predictably below audibility for the opposite ear, which was plugged and muffled with an expected mean interaural bone conduction attenuation of 64 dB for the RSS bandwidth. The sound system bandwidth was approximately 160 to 5 kHz with a 10dB/octave falloff at >5 kHz.

RSS presentations of 2-second durations occurred during 9 seconds silent intervals in 11-second volume acquisitions (TRs) of an interrupted single event design. EPI at the beginning of an immediately following TR had delays of 2 to 9 seconds from the onset of a RSS during silence in the preceding TR, which allowed reconstruction of a hemodynamic response.

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**Table 1.** Patient demographics and hearing thresholds in the affected ear.

<table>
<thead>
<tr>
<th>Case</th>
<th>Affected Ear</th>
<th>Gender</th>
<th>Age</th>
<th>3fPTA Pre</th>
<th>FFPTA Pre</th>
<th>3fPTA 3 mo</th>
<th>FFPTA 3 mo</th>
<th>3fPTA 6 mo</th>
<th>FFPTA 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>F</td>
<td>28</td>
<td>70.0</td>
<td>73.1</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>M</td>
<td>50</td>
<td>50.0</td>
<td>55.7</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>F</td>
<td>43</td>
<td>46.7</td>
<td>54.4</td>
<td>120.0</td>
<td>120.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>M</td>
<td>45</td>
<td>15.0</td>
<td>33.1</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>F</td>
<td>47</td>
<td>30.0</td>
<td>48.1</td>
<td>33.3</td>
<td>48.8</td>
<td>35.0</td>
<td>49.4</td>
</tr>
<tr>
<td>6</td>
<td>L</td>
<td>M</td>
<td>39</td>
<td>48.3</td>
<td>46.7</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
</tr>
<tr>
<td>7</td>
<td>L</td>
<td>M</td>
<td>52</td>
<td>43.3</td>
<td>61.3</td>
<td>50.0</td>
<td>63.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>L</td>
<td>F</td>
<td>56</td>
<td>35.0</td>
<td>38.3</td>
<td>36.7</td>
<td>50.0</td>
<td>38.3</td>
<td>40.8</td>
</tr>
<tr>
<td>9</td>
<td>L</td>
<td>F</td>
<td>53</td>
<td>18.3</td>
<td>28.1</td>
<td>61.7</td>
<td>65.8</td>
<td>61.7</td>
<td>61.1</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>45.9</td>
<td>39.6</td>
<td>48.8</td>
<td>86.9</td>
<td>92.0</td>
<td>87.9</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td></td>
<td></td>
<td>2.9</td>
<td>5.7</td>
<td>4.7</td>
<td>13.4</td>
<td>11.2</td>
<td>15.5</td>
</tr>
</tbody>
</table>

*aAge at time of study enrollment.

bOne hundred twenty assigned to all thresholds with no response to test equipment limits.

cCase 1 had Meniere’s syndrome.
dPatient not available for threshold testing or imaging scans, NA.
Image acquisition, preprocessing procedures, and analyses of BOLD responses were as previously described. Briefly, following a general linear model (GLM) analysis, an F test per voxel assessed whether the BOLD response variance associated with presentation of a RSS stimulus was greater than that due to baseline noise. This test of significance involved no assumptions regarding the hemodynamic response function. Additionally, we transformed F statistics to equally probable z scores (F-Z stats) that were multiple comparisons corrected based on Monte Carlo simulations. The correction threshold for \( P = 0.05 \) was \( z \) scores of \( z = 4.0 \) over 12 face-connected voxels.

Each individual’s brain was rendered into the PALS-B12 CARET surface-based atlas by using Surefit software. The vertex mesh approximated the midcortical thickness of each hemisphere in the native brain. We registered volume-based data (VBD) of corrected F-Zstats to vertices based on nearest coordinate neighbors. Next, deformation of each native brain surface to the vertices for the left and right hemispheres of the PALS-B12 atlas normalized the brains. These procedures also registered VBD to the atlas coordinate surface space. The deformation maps created for each brain when applied to the native anatomy retained original brain structure but in the atlas coordinate space of vertices. Thus, surface maps for registered F-Zstats were viewable with respect to participant brain anatomy, but with all distribution distinctions between individuals based on a standard number of vertices.

The analyses focused on AC areas Te1, Te2, and Te3 as previously described. The combined Te areas occupied the posterior superior temporal plane (Figure 1). Te1 encompasses Heschl’s gyrus and adjoining caudal rostral areas as part of a core primary auditory cortical field; Te2 is caudal to Te1 within planum temporale and is within the caudal belt cortical field; and Te3 is lateral to Te1 along the superior temporal gyral crown within planum polare and is a component of the lateral belt cortical field.

Spatial extents reflected area measurement within the combined surface of the 3 Te areas whose uncorrected F-Zstats had a threshold value of \( \geq 2.57 \) (ie, \( P \leq 0.005 \)). The boundaries of these areas reflected brain anatomy in each individual brain. We computed a lateralization index (LI) across the Te combined surface area for preoperative and each postoperative imaging session and for the measurements of surface area that was ipsilateral and contralateral to stimulation of the intact ear.

### Results

#### Hearing Loss

The audiograms in 5 individuals showed profound hearing loss across all frequencies at 3 months after surgery (Figure 2, 1-4, 6). These losses at 120 dB hearing level were in the right ear for 1-4 and left ear in 6. Four other individuals had a moderate to severe sloping high frequency loss. Three had losses before surgery, and thresholds were unchanged at 3 months after surgery (Figure 2, 5, 7, and 8).

One individual showed a hearing loss at 3 months after surgery (Figure 2, 9). Three of the 4 with minimal or no change in hearing threshold following surgery had GK treatments (Table 2, Figure 2, 7-9).

#### Table 2. Tumor size and location per case.

<table>
<thead>
<tr>
<th>Case</th>
<th>Size (cm)</th>
<th>Volume (mm³)</th>
<th>Location</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
<td>SR vestibular nerve</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.4 × 3.2 × 3</td>
<td>3.2 × 3.3</td>
<td>CPA, residual tumor in IAC</td>
<td>Radical subtotal SR followed with GK</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2.2 × 2.9</td>
<td>CPA, extending in IAC</td>
<td>SR</td>
</tr>
<tr>
<td>4</td>
<td>0.5 × 1</td>
<td>1.9</td>
<td>CPA, extending in IAC</td>
<td>SR followed with GK</td>
</tr>
<tr>
<td>5</td>
<td>1.6 × 2.1 × 1.9</td>
<td>683.4</td>
<td>CPA, extending in IAC</td>
<td>Middle fossa craniotomy</td>
</tr>
<tr>
<td>6</td>
<td>1.2 × 1</td>
<td>217</td>
<td>CPA, extending in IAC</td>
<td>GK</td>
</tr>
<tr>
<td>7</td>
<td>0.6</td>
<td>1,700</td>
<td>IAC mid canal</td>
<td>GK</td>
</tr>
<tr>
<td>8</td>
<td>1700</td>
<td></td>
<td>CPA, extending in IAC</td>
<td>GK</td>
</tr>
</tbody>
</table>

**Note:**
- aCerebellopontine angle (CPA); intracanalicular (IAC).
- bTreatments included Gamma Knife radiosurgery (GK) and surgical resection (SR).
- cNot applicable (n/a); other dimensions as noted by surgeons in the patient records.
Individuals (Patches of contralateral activity with red painted patches) and in contralateral AC in 5 individuals. Some bilateral activity (present in all but individual 7 at 3 months after surgery). All individuals with intact left or right ears showed reversals from contralateral LIs at 3 months after surgery to ipsilateral LIs.

The right ear–affected individuals, who had increased ipsilateral activated surface areas prior to surgery (Figure 4, 1, 2, and 4), possibly showed this lateralization due to prior small elevations in hearing thresholds (Figure 2). Of the 4 individuals with affected right ears and total hearing loss after surgery, 2 had persistent ipsilateral predominance (1 and 4), 1 gained ipsilateral activation (3), and 1 switched to contralateral (2). The right ear–affected individual 5 with no postoperative change in the hearing threshold showed a switch from contralateral to nearly symmetrical lateralization.

All left ear–affected individuals (6-9) showed LIs favoring contralateral AC extents through all imaging sessions even though some ipsilateral activity was present in all but individual 7. Only individual 6 sustained total hearing loss whereas the other 3 received GK treatment and showed no alteration in preoperative hearing thresholds.

In summary, prior to any treatments, 8 individuals showed some ipsilateral activation but only 3 with intact left ears showed a higher ipsilateral than contralateral lateralization index. LIs indicating a contralateral bias occurred in 6 individuals, and 3 of them had GK treatments. Lateralization distinctions for significant activity in AC did not vary with the stimulated ear.

The regression of hearing thresholds with surface areas ipsilateral to the intact ear was not significant prior to surgery but reached significance at 3 months postoperative (Figure 5A1 and A2). The lowest spatial extents ipsilateral to stimulating the intact ear occurred in individuals treated with GK and whose hearing thresholds in the affected ear changed the least. There was no significant regression for contralateral surface areas (Figure 5B1 and B2).

**Discussion**

Most individuals showed bilateral activation of auditory cortex before and after eighth cranial nerve surgery, indicating little evidence for treatment-induced reorganization of lateralization in auditory cortex. These results are at variance with a study of 1 individual with an affected right ear who had predominant contralateral activation before and a shift toward more symmetrical activation following a surgical resection of an acoustic neuroma. This individual had matching normal binaural hearing thresholds before and total right hearing loss after surgical resection of the neuroma. In contrast, hearing thresholds before surgery of 9 individuals in the current study were above the 15 to 25 dB hearing level of age-matched normal hearing individuals tested by us and the preoperative hearing threshold reported previously. Elevated hearing thresholds in the affected ear before surgery were prevalent in those with...
acoustic neuromas even without a hearing loss perceived by the individual.\textsuperscript{25,41} Consequently, the single individual described by Bilecen and colleagues might have been exceptional rather than representative.

Auditory cortex lateralization varies in different auditory cortical fields and also differs with unilateral deafness in left and right ears. In chronic left ear deafness, right ear stimulation evoked greater left hemisphere (contralateral)

**Figure 3.** Z score maps for individuals with (A) and without (B) hearing loss. View as shown in Figure 1. White arrows A and S indicate anterior and superior directions in each hemisphere. LH indicates left hemisphere; RH, right hemisphere.
response magnitudes only in primary auditory cortex, greater right hemisphere (ipsilateral) responses in belt area Te3, and equal magnitudes in bilateral parabelt areas in comparison to activation from monaural right ear stimulation in normal hearing individuals. In the current study, a contralateral spatial activation asymmetry occurred in the left hemisphere (contralateral) of the 3 left ear–affected cases receiving GK treatments. However, this asymmetry was present even before surgery. Auditory cortex lateralization in right ear–affected individuals did not confirm prior findings that right ear deafness leads to fewer examples of changes in contralateral (right hemisphere) asymmetry according to AEF measures. As noted previously in comparing individuals with chronic right ear deafness to those with normal hearing, left ear stimulation evoked larger left hemisphere (ipsilateral) response magnitudes in primary-core auditory cortex, larger responses in right hemisphere (contralateral) belt auditory fields (Te2 and Te3), and equivalent response magnitudes in bilateral parabelt areas. These prior findings were consistent with the current finding of larger left hemisphere (ipsilateral) spatial activation extents even prior to surgery in 3 of 5 right ear–affected patients. Thus, contrary to prior speculations, there was no evidence that functional plastic changes were more prevalent in the right than in the left auditory cortex. More important, the presence of auditory cortex lateralization changes in the studied cases prior to surgery and the larger sample data set of previously studied chronic cases did not support the speculation that the right temporal lobe has a greater potential for structural reorganization possibly involving remyelination. However, our data relied on activation evoked by RSS stimulation and might not reflect auditory cortex lateralization evoked by speech inputs in different intact ears of individuals with unilateral deafness.

A clinically important and unexpected finding was minimal, nonsignificant changes in auditory cortex lateralization from preoperative to postoperative imaging sessions with monaural stimulation. A practical implication of this finding is that the studied individuals already sustained some deafferentation prior to surgery. Others have previously found audiograms with elevated thresholds in some patients who were unaware of hearing loss. Despite preservation of preoperative hearing levels after Gamma Knife surgeries, the current findings realistically indicate little likelihood of reversing altered auditory cortex lateralization changes that resulted from preoperative hearing losses. These observations suggest that neuroplasticity in preoperative auditory cortex reflected the effects of possibly less than complete.
unilateral hearing loss. Reversible lateralization shifts can also occur without material deafferentation as shown by such changes following sudden short-term functional yet reversible deafness.19,21,22 Several studies in animals have shown that partial damage to isolated portions of the cochlea can provoke auditory cortex reorganization of tonotopic maps.13,15,42 Similarly, cortical reorganization with minimal sensory deficits is not an exclusive property of the auditory cortex as shown by changes in the somatosensory system of adult animals and humans experiencing sensory deafferentation.11,43,44

Another clinically significant finding was confirmation of prior reports that Gamma Knife surgeries better maintained preoperative hearing levels.24,25 Additionally, however, GK, in better preserving the eighth nerve, functionally supported the lateralization pattern in auditory cortex, especially a more normal contralateral asymmetry despite enhanced ipsilateral activity not normally present in most normal hearing individuals. Thus, lateralization patterns found before surgery persisted in postoperative imaging sessions because GK possibly did no or minimal further nerve damage. The observed lateralization reflected what preexisting nerve injury had alreadyinstigated. An important notion, however, was that even optimal tumor excision did not reestablish a normal auditory cortex organization because the preexisting tumor already induced nerve pathology.

Alterations in crossed inhibitory connections normally present with ipsilateral inputs possibly provide the underlying mechanism responsible for the effects of partial unilateral deafferentation before surgery. Altered inhibition probably arises from changes in the auditory brainstem and also interhemispheric cortical connections that influence local inhibitory synapses.14,16 The observed increase in ipsilateral spatial extents to auditory stimulation of an intact ear might have indicated prior deafferentation and reduced inhibition of crossed inhibition even without severely affecting hearing levels. A relevant future clinical objective might involve direct attempts to affect crossed inhibition through micro-stimulation of interhemispheric auditory connections or the auditory brainstem, above the damaged eighth nerve.

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Author Contributions

Harold Burton, conceived and designed study; acquired, analyzed, and interpreted data; drafted and critically revised the intellectual content of the article; approved the final version to be published; Jill B. Firszt, conceived and designed study; acquired, analyzed, and interpreted data; critically revised the intellectual content of the article; approved the final version to be published; Timothy Holden, acquired, analyzed, and interpreted data; critically revised the intellectual content of the article; approved the final version to be published.

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