Brain activity in patients with unilateral sensorineural hearing loss during auditory perception in noisy environments

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Patients with unilateral sensorineural hearing loss (UHL) often complain of hearing difficulties in noisy environments. To clarify this, we compared brain activation in patients with UHL with that of healthy participants during speech perception in a noisy environment, using functional magnetic resonance imaging (fMRI). A pure tone of 1 kHz, or 14 monosyllabic speech sounds at 65–70 dB accompanied by MRI scan noise at 75 dB, were presented to both ears for 1 second each and participants were instructed to press a button when they could hear the pure tone or speech sound. Based on the activation areas of healthy participants, the primary auditory cortex, the anterior auditory association areas, and the posterior auditory association areas were set as regions of interest (ROI). In each of these regions, we compared brain activity between healthy participants and patients with UHL. The results revealed that patients with right-side UHL showed different brain activity in the right posterior auditory area during perception of pure tones versus monosyllables. Clinically, left-side and right-side UHL are not presently differentiated and are similarly diagnosed and treated; however, the results of this study suggest that a laterality-specific treatment should be chosen.

Key Words: Unilateral hearing loss, sensorineural hearing loss, functional magnetic resonance imaging, acoustic stimulation

Introduction

Patients with acquired unilateral sensorineural hearing loss (UHL) often complain that noise in the healthy ear makes the perception of speech difficulties in noisy environments. Importantly, difficulties in hearing speech affect patients’ quality of life. A study by the Japanese Ministry of Health, Labor, and Welfare used the Short-Form Health Survey Version 2 to demonstrate that many patients with UHL experience psychological hardship. This can result from and intensify difficulties in conversation and unpleasant sensations caused by noisy environments. Furthermore, Colletti and co-workers compared psychosocial and social disorders and handicaps between healthy participants and patients with UHL, and reported that the latter faced problems in understanding language and in locating sound sources in noisy environments. Accordingly, we need a better understanding of the mechanisms of and potential therapeutic strategies for difficulties in speech perception in noisy environments in patients with acquired UHL.

Welsh and co-workers examined the ability of patients with UHL to hear monosyllables spoken at 50 dB in noisy environments and found that the mishearing rate in patients with one deaf ear and one healthy ear ranged...
from 4 to 40%, compared with a range of 4 to 72% in
patients with one deaf ear and one ear with hearing
loss. These results indicate that among the deaf, the
functioning ear does not necessarily compensate for
the deaf ear in a noisy environment. Further, we have
to differentiate hearing difficulties in patients with left-
or right-side UHL, because auditory evoked potentials
have been reported to vary among left- or right-side UHL
and in healthy participants4.

Surveys and audiometry are useful tools for evaluating
hearing difficulties in these patients, but these tools
contain multiple subjective elements and therefore do
not permit objective evaluations. Thus, we see a need
for objective indicators of hearing difficulty.

The development of neuroimaging techniques in recent
years has allowed real-time visualization of brain regions
involved in sound processing5,6. Propst and co-workers5
examined brain activity in children with UHL using both
narrowband noise and speech with noise. They found
that the secondary auditory cortex was not activated
by narrowband noise, but was activated by speech
with noise. This contrasts with the results of Suzuki
and co-workers6, who examined patients with UHL for
cortical activation areas that responded to unilateral
auditory stimulation by syllables, the latter consisting
of syllables used in clinical otolaryngologic speech
differentiation tests. They showed that the primary and
secondary cortices responded to stimulation given not
only to the healthy ear but also to the impaired ear. This
study indicated that cortical activation in patients with
UHL is similar to that of healthy participants. However,
unilateral sound stimulation was used, precluding study
of hearing difficulties involving interactions between
ears. The study also included data from patients with
both congenital and acquired hearing loss, complicating
interpretation.

In the present study, we used neuroimaging techniques
to analyze brain activity. We employed as stimuli
monosyllables frequently used in speech differentiation
tests and the pure tones most commonly used to assess
hearing in clinical settings. We stimulated both ears
simultaneously with each of the two types of sound
in turn, to compare the resultant brain activity among
patients with UHL and healthy participants.

### Materials and Methods

#### Participants

The present study was based on data from eight
healthy volunteers (3 men and 5 women; age range 30–
60 years; age 41.8 ± 12.8 years [mean ± SD]) and 12
patients with UHL (6 men and 6 women; age range 26–72
years; age 45.4 ± 15.7 years). No significant differences
with regard to age or sex were noted in either group. All
participants were native speakers of Japanese and right
handed. Edinburgh handedness scores were 91.9 ±
23.3. (If the score is positive, the person is right handed;
if the score is negative, the person is left handed.) The
details of the study were explained to all participants,
and written, informed consent was obtained from all
participants. All work was conducted in accordance
with the Declaration of Helsinki, and was approved by
the Institutional Review Board of Tokyo Medical and
Dental University (review no. 604).

#### Hearing Ability

The healthy volunteers had normal hearing, defined
as a pure tone audiometry result less than 25 dB HL
(hearing level) in both ears when tested between 125
Hz and 8 kHz. In contrast, patients with UHL had a pure
tone audiometry result of 90 dB HL (hearing level) or
higher when tested between 125 Hz and 8 kHz. The
average duration of UHL was 3.7 years (range 1–15
years). Of these patients, seven had right-side UHL
and five had left-side UHL. The causes of hearing loss
included sudden hearing loss (11 patients) and mumps-
related hearing loss (1 patient).

#### Auditory Stimulation

Because of the possibility that certain selected
monosyllables would be difficult to distinguish even
for participants with normal hearing, we selected a
subset of 14 monosyllables considered easy for healthy
volunteers to distinguish. These were a, ki, shi, ni, yo,
chi, u, ku, su, ne, o, te, mo, and to, selected from the 67-S
Japanese monosyllable word list (see Supplementary
Table). Additionally, a pure tone of 1000 Hz was used as
a stimulus in this study.

#### Experimental Design

In the present study, we used an event-related design
paradigm. Sound stimulation was presented every 8
seconds (65–70 dB; sound maintained for 1 second)
in combination with MRI scan noise (75 dB), both
delivered through headphones. The 14 monosyllables
and pure tones were grouped together and the order
of presentation was randomized in each group. Each
stimulus was presented ten times and participants were
presented a total of 150 sound stimuli during a single
session. Participants were instructed to push a button
with their index finger when they were able to perceive
a sound stimulus. In the present study, perception of the
sound stimulus itself was regarded as the task; accuracy in identification of the monosyllables was not of interest. Furthermore, participants were instructed to concentrate on remembering the monosyllables that were heard. To stabilize the gaze of the participants, a fixation point was displayed on the center of the screen.

**Acquisition of MRI Data**

All MRI data were collected using a 1.5-T MRI scanner (Siemens A.G., Erlangen, Germany, at Nihon University School of Medicine). Gradient-echo, echo-planar imaging was used for functional neuroimaging. Images were scans of the entire brain and each slice was acquired parallel to the anterior commissure-posterior commissure line. Imaging conditions were as follows: 32 slices, slice thickness = 4 mm, repetition time = 3000 ms, echo time = 50 ms, flip angle = 90°, field of view = 192 × 192 mm, imaging matrix = 64 × 64 pixels. For all analyses, the first five slices were discarded to allow for stabilization of magnetic susceptibility. After functional imaging, a T1-weighted image of each participant was obtained, with recording conditions as follows: 112 slices, slice thickness = 1 mm, repetition time = 2000 ms, echo time = 3.93 ms, flip angle = 15°, field of view = 256 × 224 mm, in-plane resolution = 1 × 1 mm.

**Analysis of MRI Data**

Echo-planar imaging data was preprocessed using Statistical Parametric Mapping (SPM) 5 software (Wellcome Department of Cognitive Neurology, London, UK). All images were realigned to the first volume and corrected for motion artifacts. Participants with translations in the left-right, anterior-posterior, or superior-inferior directions of 1 mm or greater were excluded from the study. Anatomical imaging of each participant was normalized and co-registered using the Montreal Neurological Institute template as the mean functional image. Functional images were then corrected to the normalized voxel size of 2 × 2 × 2 mm using the same conversion parameters. We subsequently smoothed the images by convolution with a Gaussian kernel of 6-mm full width at a half maximum. The coordinates of observed brain activity were reported using the Montreal Neurological Institute coordinate system. For group analysis, we studied individual imaging data using fixed-effect analysis, and calculated the data of healthy volunteers and patients with UHL based on statistical inferences at the \( p < 0.05 \) Family-wise error rate (FWE) level. We then examined specific activities in patients with UHL by comparing to those in healthy volunteers using a statistical threshold of \( p < 0.05 \) FWE level.

We defined spherical ROIs with a diameter of 1 cm in the six areas where activity specific to speech reception was observed in healthy participants (i.e., bilateral primary auditory cortices, bilateral anterior auditory association areas, and bilateral posterior auditory association areas; see Table 1). We defined spherical ROIs with a diameter of 1 cm in the six areas where activity specific to speech reception was observed in healthy participants (i.e., bilateral primary auditory cortices, bilateral anterior auditory association areas, and bilateral posterior auditory association areas; see Table 1). We used toolbox MarsBaR\(^7\) to calculate the percent signal change in each ROI of each participant. The number of the data in the present study was too small to determine whether it would be a normal distribution. Nevertheless, we assumed that the percent signal change followed a normal distribution because it represents brain activity that would be continuous variable. We then analyzed the changes with the paired t-test using EZR software\(^8\). Since we analyzed six times in each group, we corrected the significance level by the Bonferroni method (\( p < 0.008 \)).

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<th>Left/ Right</th>
<th>Brain region (Brodmann’s area)</th>
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Shown are the six regions of interest (ROIs) where maximal brain activity is observed among healthy participants during monosyllable perception. Voxel, number of voxels in ROI.
Results

Behavioral Data

The behavioral responses (i.e., button press) after the perception of sound stimuli indicated that participants perceived all the stimulus sounds (pure tone and 14 monosyllables) while in the MRI scanner, i.e., the rate of this responding in each trial was 100% for all participants.

Functional Neuroimaging Analyses

Figure 1A shows the mean brain activity across eight healthy participants while monosyllables (Fig. 1A; a–c) and the pure tone (Fig. 1A; d–f) were presented. Activity was observed in the primary auditory area in the superior and transverse gyri of both hemispheres (Fig. 1A; b, e). In the anterior auditory association area (Fig. 1A; a, d), activity was observed in bilateral superior temporal gyri. In the posterior auditory association area (Fig. 1A; c, f), activity was observed in the right middle temporal gyrus and in the left superior temporal gyrus. Fig. 1B shows the mean brain activity across the twelve patients with UHL. The areas of brain activity were similar to those of healthy volunteers. There was no significant difference of activation between healthy volunteers and patients with UHL. The t-test provided in SPM was used for this analysis.

Because we aimed to analyze the brain activity caused by hearing impairment in the present study, we selected ROIs (Table 1) based on the results from healthy volunteers. We calculated the percent signal change in each ROI for healthy participants and for patients with UHL during perception of monosyllables or pure tones. Among healthy participants and patients with left-side UHL, no significant differences in percent signal change upon perception of monosyllables versus pure tone were detected in any ROI (Figs. 2A, C). We show all p-scores in each ROI in each group in Table. 2. Importantly, in patients with right-side UHL, we found a statistically significant

<table>
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<th>Table 2. p scores of ROIs</th>
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<tr>
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<td>left UHL</td>
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Shown are p-scores for the monosyllable/tone contrast, by region of interest and by group. Only the right posterior association area in cases of right UHL has a significant score.
Brain activity in unilateral sensorineural hearing loss

A small significant difference (p = 0.047) was also found in the left posterior auditory association area in patients with right-side UHL. However, its neurophysiological significance remains uncertain.

**Discussion**

To investigate the neural mechanisms underlying difficulty in discerning speech under noisy conditions, we used fMRI to compare activity in auditory brain regions between patients with UHL and healthy participants during presentation of monosyllables and a pure tone. In both healthy subjects and patients with UHL, we observed bilateral activation of the primary and association auditory cortices during monosyllable and pure tone perception. However, direct subtraction in auditory area did not reveal differences between the groups. We therefore selected six ROIs based on auditory stimulus-induced activation patterns in healthy participants and conducted further comparative analyses.

Among healthy participants and patients with left-side UHL, we found no significant differences in activity in response to monosyllables and pure tones. However, in patients with right-side UHL, we observed a significant difference between monosyllable and pure tone conditions in the activation of the right secondary auditory cortex. Previous studies have suggested a superiority of left versus right hemisphere in the perception of speech sounds under noisy conditions. Shtyrov and co-workers compared mismatch negativities between the left and right auditory cortices in healthy participants listening to speech in both ears in a noisy environment. They found large potentials in the left hemisphere in a noiseless environment, but large potentials in the right hemisphere in a noisy environment. Kejala and co-workers have reviewed evidence for the superiority of the right hemisphere in speech discrimination in a noisy environment. Our findings in patients with right-side UHL are consistent with these studies: monosyllables entering the left ear were processed mainly in the right hemisphere; thus, differences in brain activity during the processing of monosyllables versus pure tones can be ascribed to a role of the right hemisphere in discriminating speech sounds in a noisy environment. Furthermore, our results in patients with right-side UHL might indicate that significant differences in activation by pure-tone stimuli vs. monosyllables are due to a relative enhancement of activity in response to a pure tone.

Khosla and co-workers compared ipsilateral and contralateral auditory evoked potentials in patients with left- or right-side UHL and in healthy participants. In the latter, large potentials were recorded from the hemisphere contralateral to the ear that received a stimulus. Left-ear stimulation produced large potentials on the contralateral side (in the right hemisphere) in patients with right-side UHL, as in healthy participants.
while no left-right differences were observed in patients with left-side UHL during stimulation in the right ear. The authors speculated that patients with left-side UHL had developed changes in the inhibitory auditory pathways\textsuperscript{11-14} that resulted in a lack of contralateral dominance. In the present study, a similar mechanism may underlie the variations in brain activity between patients with right-side vs. left-side UHL. Specifically, we observed differences in the processing of monosyllables vs. pure tones in a noisy environment between patients with right-side, but not left-side, UHL. This may be due to differences in the mechanism of sound processing between left and right sides in patients with UHL. Khosla and co-workers stimulated the unilateral ear using clicks, while we stimulated both ears using a pure tone and monosyllables, which would explain the different results obtained by the present study and theirs. In our results, the brain activity of left-side UHL patients is similar to that of healthy volunteers. Thus, the mechanism of processing of binaural stimulation might be different from that of monaural stimulation.

Indeed, we did not identify regions of activity characteristic of patients with UHL compared with normal participants. Thus, our findings suggest differences in the neural mechanisms of speech-sound processing in patients with left- vs. right-side UHL, located in the right posterior auditory association area. The auditory association area, which is located in Wernicke’s area, is responsible for processing complex sounds, whether the sound would be recognized as speech or music. The functions of receiving sounds and recognizing sounds were found here to differ in that receiving the sounds was 100% accurate for both healthy volunteers and UHL patients. Thus, based on our results, the function of receiving sounds is not highly related to the posterior association area. Clinically, left-side and right-side UHL are not differentiated and are similarly diagnosed and treated; however, the results of this study suggest that, depending on which is the affected ear, characteristic symptoms may develop and warrant more specific treatment.

We conclude that in noisy environments, patients with right-side UHL exhibit different brain activity in the right secondary auditory cortex dependent on whether they are hearing monosyllables or a pure tone. This might be the cause of different symptoms between patients with right vs. left UHL. Our results may have implications for the clinical treatment of right-side versus left-side UHL.

Acknowledgments

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References

Supplementary Tables.

55 dB under white noise heard through both ears

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<td>ta</td>
<td>8/240 3.33%</td>
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<td>wa</td>
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55 dB under white noise heard through one ear

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75 dB under MRI scan noise heard through both ears

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65 dB under MRI scan noise heard through both ears

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<tr>
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85 dB under MRI scan noise heard through one ear

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65 dB under MRI scan noise heard through one ear

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Monosyllable tests were performed in 12 healthy participants (6 men and 6 women, age range 23–33 years, mean age 28 ± 3.4 years). One of these participants (a 30-year-old woman) also participated in the MRI experiments. Speech discrimination tests using 20 items from the 67-S Japanese monosyllable word list were performed in both ears of the participants under white noise or MRI scan noise. Speech sounds were presented at strengths of 55 dB, 65 dB, and 75 dB with white noise at a strength of 65 dB, or at strengths of 65 dB, 75 dB, and 85 dB with MRI scan noise at a strength of 75 dB. Shown is a table listing the positive error rates for each monosyllable. Based on these results, we calculate the mishearing rate at 95%. We define monosyllables with a lower limit of 1% or higher as the speech sounds that are difficult for healthy persons to hear. Furthermore, the rate for hearing the monosyllable “ha” is similar to the rate for hearing “ba”, similarly, the rate for hearing “wa” is similar to the rates for hearing “ri” and “gu”. Based on these data, we exclude the monosyllables “ha,” “ta,” “wa,” “ri,” “gu,” and “ba” and adopt the remaining 14 sounds as the speech sound stimuli to be used in the present study.