

Functional Magnetic Resonance Imaging Study of Brain Activation by Sound Localization in Artificial Unilateral Hearing Loss

Tsuyoshi MATSUSHITA^{1)*}, Takayuki MITSUI²⁾, Tomoki KANEKO¹⁾
Hitoshi UEDA³⁾ and Masumi KADOYA¹⁾

1) *Department of Radiology, Shinshu University School of Medicine*

2) *Department of Diagnostic Radiology, Nagano Municipal Hospital*

3) *Radiology Division, Shinshu University Hospital*

Purpose: We aimed to identify brain activation on functional magnetic resonance imaging after a sound localization task in artificial unilateral hearing loss using an earplug.

Materials and Methods: Subjects were 16 healthy volunteers who were divided equally into the right hearing loss group (R group) and the left hearing loss group (L group). Sound stimuli were stereo and pure tone of 2000 Hz with varying right and left amplitude ratios. Using a block design, sound stimuli were randomly presented to the subjects every 2 sec into the task. We investigated the activation areas under conditions of normal hearing (NH) and artificial unilateral hearing loss (UHL). The analysis region was focused on the combined Heschl's and superior temporal gyri. In addition, the % signal change was calculated to examine hemispheric laterality of the hemisphere.

Results: In artificial unilateral hearing loss, significant activation in response to the sound localization task was observed in the hemisphere ipsilateral to the ear with hearing loss. The % signal change of the right hemisphere was significantly higher in the R group under UHL conditions and that of the left hemisphere was significantly higher in the L group under NH conditions. In the analysis of laterality index (LI) and LI of each individual after wearing the earplug, the shift of laterality was right predominance.

Conclusion: In an artificial acute-phase UHL, the ipsilateral combined Heschl's and superior temporal gyri showed significant activation in a sound localization task. The right hemisphere was suggested to be the dominant brain region associated with sound localization. *Shinshu Med J 64 : 123–133, 2016*

(Received for publication December 7, 2015; accepted in revised form January 13, 2016)

Key words: functional MRI, sound localization, unilateral hearing loss, auditory cortex, laterality

I Introduction

Sound localization identifies the location of a sound source based on interaural intensity difference (IID) and interaural time difference (ITD)¹⁾. Therefore, in patients with unilateral hearing loss (UHL), sound localization is impaired²⁾³⁾. UHL is not uncommon and can be congenital or acquired. The

auditory cortex (temporal lobe), premotor cortex, and parietal lobe have been previously reported to be the brain regions associated with sound localization^{4)–7)}, but this conclusion cannot be confirmed for the laterality of the cerebral hemisphere. In healthy individuals, contralateral auditory cortex activation of the stimulated ear becomes dominant⁸⁾⁹⁾. However, there were reports of bilateral activation in chronic UHLs¹⁰⁾¹¹⁾. This is likely due to the plasticity of the central nervous system for recovery and adaptation. Scheffler et al. reported that plasticity or reorganization occurred in the auditory pathway of UHL patients¹²⁾.

* Corresponding author: Tsuyoshi Matsushita
Department of Radiology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail: matusita@shinshu-u.ac.jp

In patients recovering from hemiplegia due to cerebral infarction, some have reported brain activation on the contralateral hemisphere or around the area of cerebral infarction¹³⁾¹⁴⁾. To increase brain plasticity, rehabilitation should focus on training the affected extremities, rather than the normal extremities for compensation¹⁵⁾¹⁶⁾. Similarly, in UHL, there is a possibility that plasticity of the brain may lead to a certain degree of improvement in the ability to localize sound. In order to achieve better recovery, more extensive rehabilitation would be needed to effectively activate the diseased area. By identifying the brain regions associated with impaired function (sound localization), it may become possible to select the method of rehabilitation to activate the associated brain regions more effectively.

In addition, Okamoto et al.¹⁷⁾ performed sound therapy for patients with sudden sensorineural hearing loss and determined the therapeutic effects using the audiogram and magnetoencephalography. Using functional magnetic resonance imaging (fMRI), there is a possibility to verify more detailed therapeutic effects of hearing loss. Therefore, in UHL cases in the acute phase, it may be useful to identify the main brain activation region as the basis of the pre-treatment.

As a preliminary study, we aimed to identify brain activation on fMRI after a sound localization task in artificial unilateral hearing loss conditions using an earplug.

II Materials and Methods

A Subjects

Sixteen right-handed volunteers, 10 men and 6 women with ages ranging from 22 to 58 years (mean, 29.9 years), participated in this study. All subjects were healthy individuals with no history of neurologic diseases. They were randomly divided into two equal halves, based on the location of the earplug (E.A.R. Classic): the right UHL group (R group, n=8) and the left UHL group (L group, n=8).

This study was approved by the institutional review board of Shinshu University, Matsumoto,

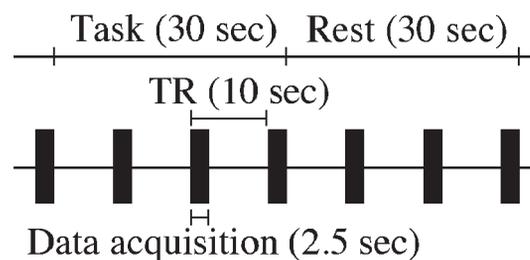


Fig. 1 Diagram of fMRI scan and acoustic stimulation timing

For silent auditory fMRI studies, the duration of data acquisitions is 2.5 sec in TR (10 sec).

fMRI, functional magnetic resonance imaging ;
TR, repetition time

Japan (No. 2163). All participants gave written informed consent to the experimental protocol.

B Data acquisition

The experiment was conducted using a 3-T whole-body MRI scanner (Magnetom Trio; Siemens, Erlangen, Germany) with a 32-channel head coil system. For BOLD-based imaging¹⁸⁾, spin-echo planar images of the entire brain were acquired in the transverse orientation (repetition time (TR)=10 s; echo time (TE)=30 msec; flip angle 90°; field of view (FOV)=192×192 mm; 64×64 matrix; 40 interleaved slices 3-mm thick and with slice gaps of 0.75 mm). In auditory studies using fMRI, there is a possibility that the acoustic scanner noise affects the experiment. In order to reduce this effect, Scheffler et al. performed an experiment in which the duration of data acquisition was 1.8 sec in TR (15 sec)¹²⁾. Based on their settings, the duration of data acquisition during silent auditory fMRI studies was 2.5 sec in TR (10 sec) in our study (Fig. 1). In addition, high-resolution T1-weighted anatomical images were acquired using an MP-RAGE sequence (TR=2.3 s; TE=2.98 msec; TI=900 msec; flip angle 9°; FOV=256×240 mm; 256×230 matrix, 160 sagittal slices 1.1-mm thick).

C Stimuli and tasks

In this study, we used sound stimuli generated by IID in MatLab 8.2 (The MathWorks Inc., Natick, MA, USA) because UHL was considered to have more adverse effects on IID than on ITD. Eleven sound stimuli on the right ear and left ear were

stereo and pure tone with varying amplitude ratios. The frequency of these sounds was 2000 Hz, because cues of sound localization at a frequency of more than 1500 Hz are mainly from IID¹⁹). To achieve constant energy for each sound stimulus, the cumulative squared amplitude on the right and left was made constant. Sound stimuli had a duration of 1 sec and were gated on and off with 40 msec of raised-cosine ramps.

Auditory stimuli were presented to the subjects through fMRI-compatible headphones (VisuaStim; Resonance Technologies, Inc.). Sound volume was adjusted so that each subject could hear the stimuli properly, but not at excessive and painful volumes. Consequently, volume was constant for all subjects. Stimulus presentation and synchronization with the MR system were controlled by presentation software (Neurobehavioral Systems, Albany, NY, USA).

Response devices with four buttons on the front were placed on both hands (under the thumb) of the subjects and were optically connected to a computer outside the scanner room. In our experiment one button was used of the four buttons of the devices on both sides. Subjects were instructed to indicate the location of the presented sound by pressing the right and left buttons accordingly. They pressed the right side button if the sound source was identified on the right side, the button with both hands if it was identified in the center, and the left side button if it was identified on the left side.

Using a block design, sound stimuli in a pseudorandom order were presented every 2 sec into the task; silence was maintained during the remainder of the task. One set was composed of the task (30 sec) and the rest (30 sec), and 1 section (8 min) was composed of the 8 sets. Subjects performed 1 section under normal hearing (NH) conditions, and then 1 section under artificial UHL conditions using an earplug. All subjects received the same training in task performance prior to fMRI.

D Preprocessing

Data were pre-processed and analyzed using Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, London, UK)

implemented in MatLab 8.2 (The MathWorks Inc., Natick, MA, USA). The first image of each run was discarded to allow the MRI signal to reach a steady state. The remaining scans were adjusted according to slice timing and were realigned to the mean image to correct for head movements. Images were co-registered to the individual anatomical T1-weighted images and were normalized to the MNI space by applying a unified segmentation normalization procedure. Finally, images were smoothed using an 8-mm Gaussian kernel.

E Data analysis

We investigated the brain activation areas under NH and UHL conditions. The auditory cortex (temporal lobe), premotor cortex, and parietal lobe have been previously reported to be the brain regions associated with sound localization^{4)–7)}. We also examined these areas as the evaluation target. In our study, because it was suspected that movement of the subject's fingers to operate the button devices influenced the motor and sensory areas, the frontal lobe and the parietal lobe were excluded from evaluation. The analysis region was focused on the combined Heschl's and superior temporal gyri, including the auditory cortex. The activation areas under NH and UHL conditions were identified for the R and L groups. Group analysis was performed on a fixed effect model to detect areas of significant changes in brain activity under the four task conditions (NH in the R group, UHL in the R group, NH in the L group, and UHL in the L group). The threshold was set at $p < 0.05$ for multiple comparisons using FWE (family wise error). Individual analysis was conducted at a threshold value of uncorrected $p < 0.001$.

In addition, the % signal change in the region of interest (ROI) was calculated and analyzed to examine for laterality of the hemisphere. Because the cluster size in the contralateral hemisphere was about 0 under the UHL conditions, evaluation using cluster size was estimated to be difficult and in this study we therefore used the % signal change. Using MarsBaR AAL ROI package, the combined bilateral Heschl's and superior temporal gyri, including

the auditory cortex, were defined as ROIs²⁰). Using SPM Anatomy toolbox, the combined bilateral Brodmann's area 41 (BA41) and Brodmann's area 42 (BA42), which corresponded to the auditory cortex, were defined as ROIs²¹⁾²²). ROI analysis was conducted using MarsBaR toolbox for SPM (<http://marsbar.sourceforge.net>)²³). The clusters were separated individually to derive the % signal change for NH and UHL.

Wilcoxon signed rank test was performed between the values on each side. In order to examine whether there was a shift in laterality due to UHL, the laterality index (LI) was calculated from the % signal change. The LI was calculated based on the previous report as the following formula²⁴):

$$LI = (LH - RH) / (|LH| + |RH|)$$

where LH represents the % signal change of the left hemisphere ROI and RH represents the % signal change of the right hemisphere ROI. If the LI was a negative value, the right hemisphere was dominant; if the LI was a positive value, the left hemisphere was dominant. Wilcoxon signed rank test was performed to compare values between NH and UHL conditions.

In addition, we examined the changes in laterality for each subject after wearing the earplug. The threshold LI value was set at 0.2, according to a previously reported rule²⁴). In each subject, laterality was classified as left hemispheric dominance ($LI > 0.2$), bilateral dominance ($LI \leq 0.2$), or right hemispheric dominance ($LI < -0.2$).

III Results

Brain activations were observed bilaterally in the R and L groups under NH conditions (**Fig. 2A**, **Table 1**). The cluster size of the left hemisphere was greater than that of the right hemisphere. Under UHL conditions, brain activations were observed in the ipsilateral hemisphere. The main significant activation was observed in the ipsilateral BA41 and BA42 areas (**Fig. 2B**).

The % signal changes in the combined Heschl's and superior temporal gyri of each hemisphere and under both NH and UHL conditions are shown in **Fig. 3**. In the R group, the % signal changes were 0.6455 ± 0.2972 on the left hemisphere and 0.5651 ± 0.3263 on the right hemisphere under NH conditions; and 0.2286 ± 0.2312 on the left hemisphere and

Table 1 Functional magnetic resonance imaging data on brain regions activated during sound localization task
Threshold was set at $p < 0.05$ for multiple comparisons using FWE.

R group, right unilateral hearing loss group; L group, left unilateral hearing loss group; MNI, Montreal Neurological Institute; FWE, family wise error

Group	Condition	Region	Cluster size	T-value	MNI coordinates		
					x	y	z
R group							
	Normal hearing	L Superior Temporal Gyrus	1079	11.73	-48	-30	12
		L Superior Temporal Gyrus		7.15	-52	-2	-2
		L Superior Temporal Gyrus		6.23	-64	-14	12
		R Superior Temporal Gyrus	772	9.1	66	-2	2
		R Superior Temporal Gyrus		8.66	64	-10	6
		R Superior Temporal Gyrus		8.63	54	-24	12
	Unilateral hearing loss	R Superior Temporal Gyrus	82	5.7	56	-20	10
L group							
	Normal hearing	L Superior Temporal Gyrus	251	7.31	-48	-34	12
		L Heschl's Gyrus		5.11	-34	-32	14
		R Superior Temporal Gyrus	100	5.84	54	-20	10
		R Superior Temporal Gyrus		4.87	44	-32	14
		L Superior Temporal Gyrus		56	5.46	-50	-6
	Unilateral hearing loss	L Superior Temporal Gyrus	115	6.39	-46	-36	12

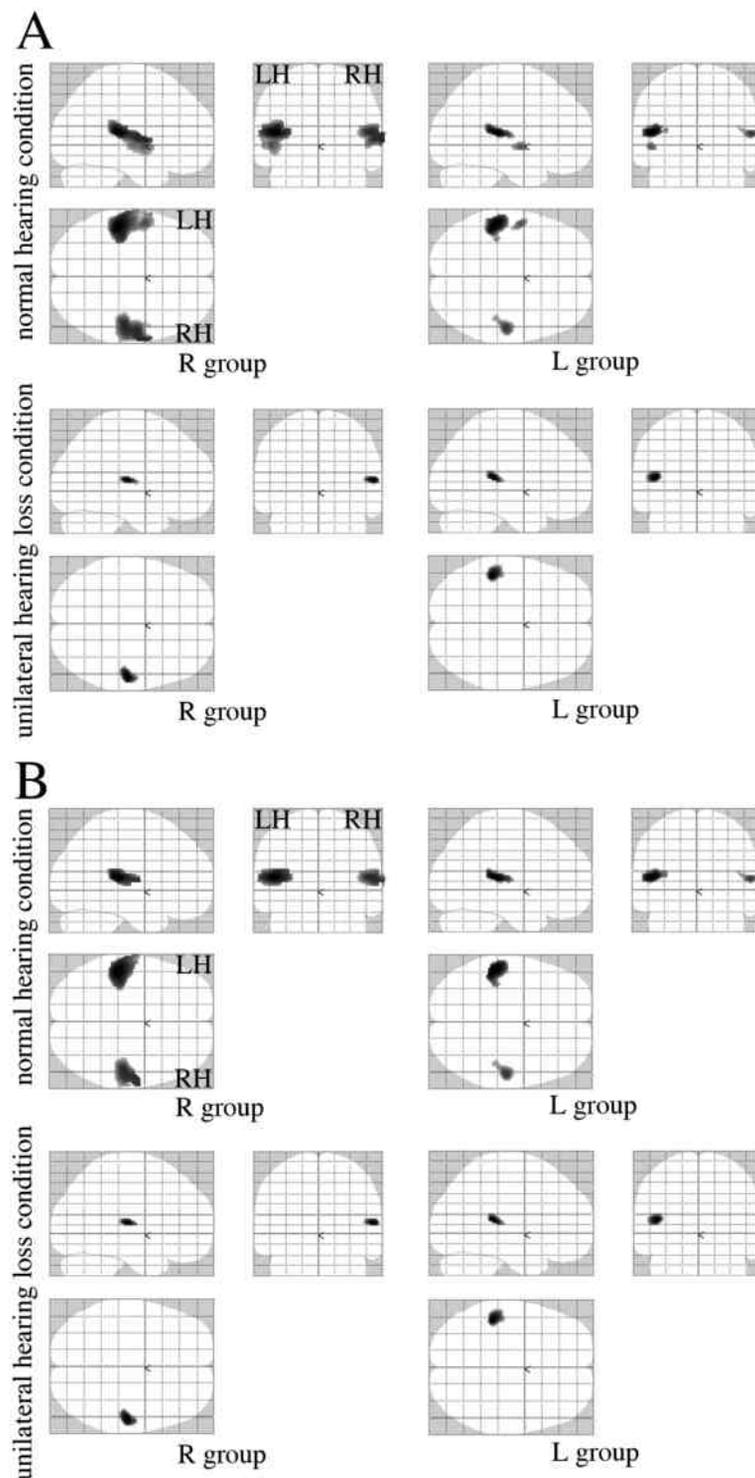


Fig. 2 Images of brain activation to sound stimuli under NH and UHL conditions

A. The analysis region was focused on the combined Heschl's and superior temporal gyri, including the auditory cortex. B. The analysis region was focused on combined BA41 and BA42, which corresponds to the auditory cortex. In A and B respectively, the upper row shows the set of the R group and the set of the L group under NH conditions and the lower row shows the set of the R group and the set of the L group under UHL conditions. One set presents three orthogonal projections. The RH and LH letters on the images indicate the right and left hemispheres, respectively.

The threshold was set at $p < 0.05$ and corrected with FWE.

NH, normal hearing ; UHL, unilateral hearing loss ; R group, right unilateral hearing loss group ; L group, left unilateral hearing loss group ; FWE, family wise error

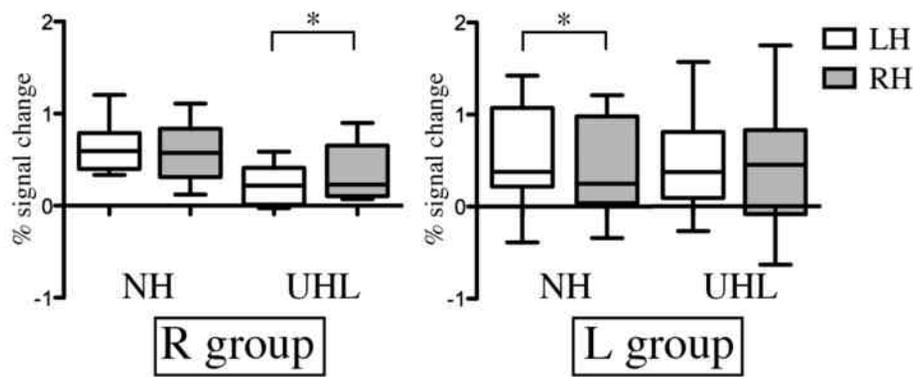


Fig. 3 % signal change of the combined Heschl's and superior temporal gyri

The % signal change of the right hemisphere was significantly higher than that of the left hemisphere in UHL conditions in the R group. The % signal change of the left hemisphere was significantly higher than that of the right hemisphere in NH conditions in the L group.

The boundary of the box closest to 0 represents the 25th percentile, whereas that farthest from zero corresponds to the 75th percentile. Lines in boxes represent the median. Error bars show minimum and maximum values.

* $p < 0.05$

NH, normal hearing ; UHL, unilateral hearing loss ; LH, left hemisphere ; RH, right hemisphere ; R group, right unilateral hearing loss group ; L group, left unilateral hearing loss group

0.3270 ± 0.3166 on the right hemisphere under UHL conditions. In the L group, the % signal changes were 0.5104 ± 0.6065 on the left hemisphere and 0.3825 ± 0.5514 on the right hemisphere under NH conditions ; and 0.4936 ± 0.5791 on the left hemisphere and 0.4366 ± 0.7511 on the right hemisphere under UHL conditions. In the right hemisphere, % signal change was significantly higher in the R group under UHL conditions ($p = 0.0234$). In the left hemisphere, % signal change was significantly higher in the L group under NH conditions ($p = 0.0234$). A significant difference was not observed under NH conditions in the R group and under UHL conditions in the L group.

The LI of the combined Heschl's gyrus and superior temporal gyrus are shown in Fig. 4. In the R group, the LI of the UHL was significantly lower than that of the NH (-0.3974 ± 0.4171 vs. 0.1021 ± 0.1883 , $p = 0.0078$). In the L group, LI was 0.2116 ± 0.3049 under NH conditions and 0.2796 ± 0.4750 under UHL conditions.

The % signal change of the combined BA41 and BA42 are shown in Fig. 5. In the R group, the % signal changes were 1.098 ± 0.1777 on the left hemisphere and 1.183 ± 0.1883 on the right hemisphere

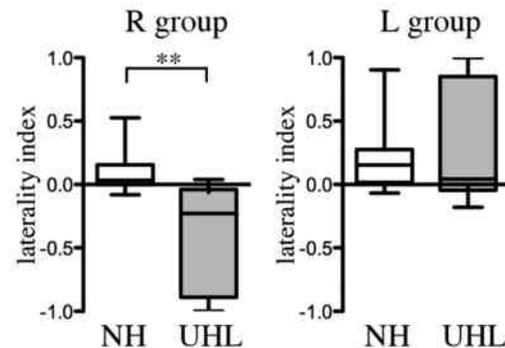


Fig. 4 The laterality index in the combined Heschl's and superior temporal gyri

The laterality index of the NH condition was significantly higher than that of the UHL condition in the R group.

The boundary of the box closest to 0 represents the 25th percentile, whereas that farthest from zero corresponds to the 75th percentile. Lines in boxes represent the median. Error bars show minimum and maximum values.

** $p < 0.01$

NH, normal hearing ; UHL, unilateral hearing loss ; R group, right unilateral hearing loss group ; L group, left unilateral hearing loss group

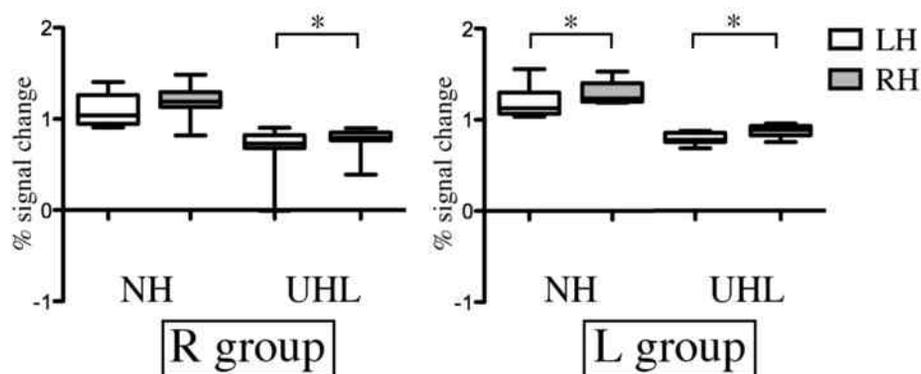


Fig. 5 % signal change of combined BA41 and BA42

The % signal change of the right hemisphere was significantly higher in UHL conditions in the R group. The % signal change of the right hemisphere was significantly higher in the NH condition and the UHL condition of the L group. The boundary of the box closest to 0 represents the 25th percentile, whereas that farthest from zero corresponds to the 75th percentile. Lines in boxes represent the median. Error bars show minimum and maximum values.

* $p < 0.05$

NH, normal hearing ; UHL, unilateral hearing loss ; LH, left hemisphere ; RH, right hemisphere ; R group, right unilateral hearing loss group ; L group, left unilateral hearing loss group

under NH conditions ; and 0.6663 ± 0.2822 on the left hemisphere and 0.7616 ± 0.1578 on the right hemisphere under UHL conditions. In the L group, the % signal changes were 1.189 ± 0.1767 on the left hemisphere and 1.290 ± 0.1262 on the right hemisphere under NH conditions ; and 0.7909 ± 0.06297 on the left hemisphere and 0.8764 ± 0.06773 on the right hemisphere under UHL conditions. In the R group, % signal change in the right hemisphere was significantly higher under conditions of UHL ($p = 0.0156$) than that in the left hemisphere. In the L group, % signal change in the right hemisphere was significantly higher under conditions of NH ($p = 0.0156$) and UHL ($p = 0.0142$) than that in the left hemisphere.

The LI of the combined BA41 and BA42 are shown in **Fig. 6**. In the R group, LI was -0.03728 ± 0.1078 under NH conditions and -0.1557 ± 0.3421 under UHL conditions. In the L group, LI was -0.04280 ± 0.02633 under NH conditions and -0.05179 ± 0.02498 under UHL conditions. LI was not significantly different between NH and UHL conditions in both groups.

Table 2 shows the LI and shift in laterality of the hemisphere in each subject after wearing earplugs.

In terms of laterality shift of the combined Hes-

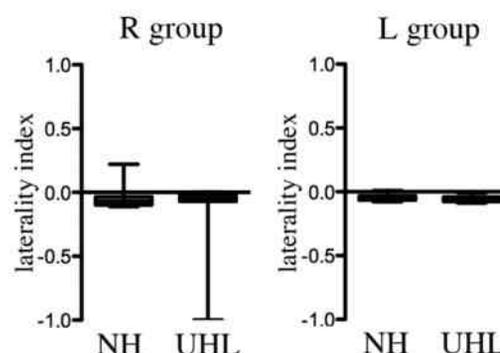


Fig. 6 The laterality index in the combined BA41 and BA42

There is no significant difference between NH and UHL conditions in both groups. The boundary of the box closest to 0 represents the 25th percentile, whereas that farthest from zero corresponds to the 75th percentile. Lines in boxes represent the median. Error bars show minimum and maximum values.

NH, normal hearing ; UHL, unilateral hearing loss ; R group, right unilateral hearing loss group ; L group, left unilateral hearing loss group

chl's and superior temporal gyri, shift to the right was seen in 6 subjects, no change in 2 subjects, and shift to the left in no subjects in the R group. In the L group, shift to the right was seen in 2 subjects, no change in 5 subjects, and shift to the left in 1 subject.

In terms of laterality shift of the combined BA41 and BA42, shift to the right was seen in 1 subject, no

Table 2 Laterality shift after wearing earplugs
LI, laterality index

A. Combined Heschl's gyrus and superior temporal gyrus

R group						L group					
Subject number	normal hearing condition		unilateral hearing loss condition		laterality shift	Subject number	normal hearing condition		unilateral hearing loss condition		laterality shift
	LI	laterality	LI	laterality			LI	laterality	LI	laterality	
01	0.15	bilateral	-0.97	right	right	02	0.10	bilateral	0.06	bilateral	no change
03	0.04	bilateral	-0.64	right	right	04	0.30	left	-0.18	bilateral	right
05	0.53	left	0.04	bilateral	right	06	0.03	bilateral	-0.02	bilateral	no change
08	0.00	bilateral	0.00	bilateral	no change	07	0.90	left	1.00	left	no change
09	0.16	bilateral	-1.00	right	right	10	0.21	left	0.41	left	no change
11	0.02	bilateral	-0.25	right	right	12	0.21	left	-0.05	bilateral	right
13	0.00	bilateral	-0.21	right	right	14	-0.07	bilateral	1.00	left	left
16	-0.08	bilateral	-0.15	bilateral	no change	15	0.01	bilateral	0.02	bilateral	no change

B. Combined BA41 and BA42

R group						L group					
Subject number	normal hearing condition		unilateral hearing loss condition		laterality shift	Subject number	normal hearing condition		unilateral hearing loss condition		laterality shift
	LI	laterality	LI	laterality			LI	laterality	LI	laterality	
01	0.22	left	-1.00	right	right	02	0.01	bilateral	-0.09	bilateral	no change
03	-0.10	bilateral	-0.05	bilateral	no change	04	-0.04	bilateral	-0.04	bilateral	no change
05	-0.06	bilateral	-0.03	bilateral	no change	06	-0.06	bilateral	-0.05	bilateral	no change
08	-0.11	bilateral	-0.08	bilateral	no change	07	-0.06	bilateral	-0.06	bilateral	no change
09	-0.05	bilateral	0.00	bilateral	no change	10	-0.08	bilateral	-0.01	bilateral	no change
11	-0.10	bilateral	-0.04	bilateral	no change	12	-0.04	bilateral	-0.08	bilateral	no change
13	-0.03	bilateral	-0.01	bilateral	no change	14	-0.03	bilateral	-0.05	bilateral	no change
16	-0.07	bilateral	-0.05	bilateral	no change	15	-0.03	bilateral	-0.04	bilateral	no change

change in 7 subjects, and shift to the left in no subjects in the R group. In the L group, shift to the right was seen in no subjects, no change in 8 subjects, and shift to the left in no subjects.

IV Discussion

In this study, activations in the combined Heschl's and superior temporal gyri, including the auditory cortex (BA41 and BA42), were evaluated. Under NH conditions, brain activations were observed on both sides. The cluster size on the left side was larger than that on the right side, and may be explained by the anatomically larger Heschl's gyrus on the left²⁵⁾²⁶⁾. Under UHL conditions, the main significant activation was observed in the auditory cortex ipsilateral to the ear with hearing loss. In healthy subjects, auditory cortex activation contralateral to the stimulated ear becomes domi-

nant⁸⁾⁹⁾. Assuming that our study simulated unilateral ear stimulation by wearing earplugs, this result was consistent with that of previous reports. Bilecen et al. reported a case of UHL after excision of a right auditory nerve tumor¹⁰⁾. In the report, although strong activation was observed to be right-dominant on fMRI in the first postoperative week, it was almost bilateral after more than one year. If the artificial UHL condition in our study was assumed to simulate clinical acute UHL, our results were consistent with this report.

After wearing earplugs, the cluster size of the activated area was reduced at the hemisphere ipsilateral to the ear with hearing loss. Because UHL sessions were performed after NH sessions, it was considered that brain activation was reduced by habituation and repetition²⁷⁾.

In the analysis of the % signal change of the

combined Heschl's and superior temporal gyri, the right hemisphere became significantly dominant under UHL conditions in the R group. In the L group, the left hemisphere was significantly dominant under NH conditions, but there was no laterality under UHL conditions. We expected that ipsilateral (left) hemisphere dominance would be clearer under UHL conditions in the L group, but our result was different. In the analysis of LI of each individual after wearing earplugs, shift to the right side was the most commonly observed trend in the R group and the second most common trend in the L group. Among five subjects with no change in the L group, two subjects demonstrated left hemispheric dominance under NH conditions. It is possible that displacement to the left side was masked. However, compared with the R group, the L group had a weaker tendency for shift in laterality ipsilateral to the side of hearing loss.

In the analysis of the % signal change and the LI of the combined BA41 and BA42, the right hemisphere was significantly dominant under UHL conditions in the R group, but the LI remained constant. In the L group, the right hemisphere was significantly dominant under NH and UHL conditions, but the LI remained constant. In terms of individual LI, change in laterality was poor after wearing earplugs.

Therefore, in the combined Heschl's and superior temporal gyri, excluding the auditory cortex, there may be regions in which the % signal change becomes right-dominant after wearing earplugs. In general, attention effects on the auditory cortex increase along with task difficulty²⁸. In the combined Heschl's and superior temporal gyri, the regions associated with characteristic sound stimuli may be activated predominantly in the right hemisphere with increasing task difficulty. Based on our results, the right temporal lobe was suggested to be the dominant brain region associated with sound localization. However, the stimulus sound that we used in this study was non-verbal. There are reports that non-verbal sound stimulation is predominantly associated with the right hemisphere²⁹⁾³⁰. It is also

possible that these factors affected our results.

Our study had some limitations. Firstly, our study was limited by the small sample size. In the analysis of the % signal change, under NH conditions, a significant difference was not observed in the R group, but was observed in the L group (**Fig. 3, Fig. 5**). It was considered that these results had been affected by the bias between the R group and the L group. Secondly, subtraction of NH data, as control, from UHL data would have been ideal to identify and evaluate changes in the activation area after wearing earplugs. The protocol of performing the UHL experiments after the NH experiments may have attenuated some brain activations under the UHL conditions due to habituation and repetition²⁷. Moreover, UHL in this study was simulated by using earplugs on one side, instead of unilateral ear stimulation without using earplugs, which would have simulated a different condition (deafness). Because it was necessary to attach the earplugs, it was not feasible to set up two conditions in one session. Therefore, we could not successfully perform the subtractions. Third, experiments under the three conditions (NH, right UHL, and left UHL) for each subject were ideal. However, extended experiment time and decreased concentration of subjects were avoided. Fourth, in our study duration of data acquisitions was 2.5 sec in TR (10 sec) for silent auditory fMRI studies. The images were not able to be captured in the remaining 7.5 sec. In the usual fMRI, activation areas have been identified under presumed or typical hemodynamic response during a task³¹. In the auditory cortex, there are regions exhibiting a different pattern of blood flow change³²⁾³³. Therefore, detailed evaluation of blood flow pattern may be difficult with the settings that we used in this study. To capture blood flow changes in detail, it would be necessary to attenuate acoustic noise at the time of image acquisition.

V Conclusion

In an artificial acute-phase UHL, the ipsilateral combined Heschl's and superior temporal gyri showed significant activation in a sound localization

task. Asymmetrical shift of laterality was observed after wearing an earplug. The right temporal lobe was suggested to be the dominant brain region associated with sound localization.

VII Acknowledgment

The authors would like to thank Enago (www.enago.jp) for the English language review.

VI Conflict of Interest

There are no conflicts of interest to declare.

References

- 1) Yost WA, Gourevitch G : Directional Hearing, Springer Verlag, New York, 1987
- 2) Abel SM, Alberti PW, Haythornthwaite C, Riko K : Speech intelligibility in noise : effects of fluency and hearing protector type. *J Acoust Soc Am* 71 : 708-715, 1982
- 3) Humes LE, Allen SK, Bess FH : Horizontal sound localization skills of unilaterally hearing-impaired children. *Audiology* 19 : 508-518, 1980
- 4) Griffiths TD, Green GG, Rees A, Rees G : Human brain areas involved in the analysis of auditory movement. *Hum Brain Mapp* 9 : 72-80, 2000
- 5) Baumgart F, Gaschler-Markefski B, Woldorff MG, Heinze HJ, Scheich H : A movement-sensitive area in auditory cortex. *Nature* 400 : 724-726, 1999
- 6) Belin P, McAdams S, Smith B, Savel S, Thivard L, Samson S, Samson Y : The functional anatomy of sound intensity discrimination. *J Neurosci* 18 : 6388-6394, 1998
- 7) Zatorre RJ, Penhune VB : Spatial localization after excision of human auditory cortex. *J Neurosci* 21 : 6321-6328, 2001
- 8) Jancke L, Wustenberg T, Schulze K, Heinze HJ : Asymmetric hemodynamic responses of the human auditory cortex to monaural and binaural stimulation. *Hear Res* 170 : 166-178, 2002
- 9) Ponton CW, Vasama JP, Tremblay K, Khosla D, Kwong B, Don M : Plasticity in the adult human central auditory system : evidence from late-onset profound unilateral deafness. *Hear Res* 154 : 32-44, 2001
- 10) Bilecen D, Seifritz E, Radu EW, Schmid N, Wetzel S, Probst R, Scheffler K : Cortical reorganization after acute unilateral hearing loss traced by fMRI. *Neurology* 54 : 765-767, 2000
- 11) Maslin MR, Munro KJ, El-Deredy W : Source analysis reveals plasticity in the auditory cortex : evidence for reduced hemispheric asymmetries following unilateral deafness. *Clin Neurophysiol* 124 : 391-399, 2013
- 12) Scheffler K, Bilecen D, Schmid N, Tschopp K, Seelig J : Auditory cortical responses in hearing subjects and unilateral deaf patients as detected by functional magnetic resonance imaging. *Cereb Cortex* 8 : 156-163, 1998
- 13) Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, Kennedy DN, Finklestein SP, Rosen BR : A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke* 28 : 2518-2527, 1997
- 14) Cao Y, D'Olhaberriague L, Vikingstad EM, Levine SR, Welch KM : Pilot study of functional MRI to assess cerebral activation of motor function after poststroke hemiparesis. *Stroke* 29 : 112-122, 1998
- 15) Jaillard A, Martin CD, Garambois K, Lebas JF, Hommel M : Vicarious function within the human primary motor cortex ? A longitudinal fMRI stroke study. *Brain* 128 : 1122-1138, 2005
- 16) Nudo RJ, Wise BM, SiFuentes F, Milliken GW : Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 272 : 1791-1794, 1996
- 17) Okamoto H, Fukushima M, Teismann H, Lagemann L, Kitahara T, Inohara H, Kakigi R, Pantev C : Constraint-induced sound therapy for sudden sensorineural hearing loss-behavioral and neurophysiological outcomes. *Scientific Reports* 4 : 3927, 2014
- 18) Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K : Intrinsic signal changes accompany-

- ing sensory stimulation : functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci U S A* 89 : 5951-5955, 1992
- 19) Yost WA, Wightman FL, Green DM : Lateralization of filtered clicks. *J Acoust Soc Am* 50 : 1526-1531, 1971
 - 20) Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M : Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15 : 273-289, 2002
 - 21) Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K : A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* 25 : 1325-1335, 2005
 - 22) Zilles K, Amunts K : Centenary of Brodmann's map--conception and fate. *Nat Rev Neurosci* 11 : 139-145, 2010
 - 23) Brett M, Anton J-L, Valabregue R, Poline J-B : Region of interest analysis using an SPM toolbox [abstract]. *Neuroimage* 16 (Suppl.), 2002
 - 24) Seghier ML : Laterality index in functional MRI : methodological issues. *Magn Reson Imaging* 26 : 594-601, 2008
 - 25) Rademacher J, Caviness VS Jr., Steinmetz H, Galaburda AM : Topographical variation of the human primary cortices : implications for neuroimaging, brain mapping, and neurobiology. *Cereb Cortex* 3 : 313-329, 1993
 - 26) Penhune VB, Zatorre RJ, MacDonald JD, Evans AC : Interhemispheric anatomical differences in human primary auditory cortex : probabilistic mapping and volume measurement from magnetic resonance scans. *Cereb Cortex* 6 : 661-672, 1996
 - 27) Grill-Spector K, Henson R, Martin A : Repetition and the brain : neural models of stimulus-specific effects. *Trends Cogn Sci* 10 : 14-23, 2006
 - 28) Jancke L, Mirzazade S, Shah NJ : Attention modulates activity in the primary and the secondary auditory cortex : a functional magnetic resonance imaging study in human subjects. *Neurosci Lett* 266 : 125-128, 1999
 - 29) Knox C, Kimura D : Cerebral processing of nonverbal sounds in boys and girls. *Neuropsychologia* 8 : 227-237, 1970
 - 30) Kimura D : The asymmetry of the human brain. *Sci Am* 228 : 70-78, 1973
 - 31) Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R : Event-related fMRI : characterizing differential responses. *Neuroimage* 7 : 30-40, 1998
 - 32) Seifritz E, Esposito F, Hennel F, Mustovic H, Neuhoff JG, Bilecen D, Tedeschi G, Scheffler K, Di Salle F : Spatiotemporal pattern of neural processing in the human auditory cortex. *Science* 297 : 1706-1708, 2002
 - 33) Bellgowan PS, Saad ZS, Bandettini PA : Understanding neural system dynamics through task modulation and measurement of functional MRI amplitude, latency, and width. *Proc Natl Acad Sci U S A* 100 : 1415-1419, 2003
(2015. 12. 7 received ; 2016. 1. 13 accepted)
-