Glucose metabolism in primary auditory cortex of postlingually deaf patients: FDG-PET study

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Short title: FDG-PET study of postlingually deaf patients

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Abstract

[Background/Purpose] Previous FDG-PET studies have indicated neuroplasticity in the adult auditory cortex in cases of postlingual deafness. In the mature brain, auditory deprivation decreased neuronal activity in primary auditory and auditory-related cortices. In order to reevaluate these issues, we used statistical analytic software, three-dimensional stereotaxic region of interest (ROI) template (3DSRT), in addition to statistical parametric mapping (SPM).

[Materials and Methods] 18F-FDG brain PET scans were performed on 7 postlingually deaf patients and 10 healthy volunteers. Significant increases and decreases of regional cerebral glucose metabolism in the patient group were estimated by comparing their PET images with those of the healthy volunteers using SPM analysis and 3DSRT.

[Results] The glucose metabolism of deaf patients was found to be lower than that of the control subjects in the right superior temporal gyrus, both middle temporal gyri, left inferior temporal gyrus, right lobule parietalis inferior, and left insular cortex by SPM. 3DSRT data also revealed significantly decreased glucose metabolism in both primary auditory cortices in postlingually deaf patients.

[Conclusion] SPM and 3DSRT analyses indicated that glucose metabolism decreases in the primary auditory cortex of postlingually deaf patients. The previous results of PET studies were confirmed. Our method involving 3DSRT is useful.

Keywords: FDG-PET, neuroplasticity, auditory cortex, deafness

Introduction

Previous FDG-PET studies have indicated neuroplasticity in the adult auditory cortex in cases of postlingual deafness. In the early 1990s, this phenomenon was discussed on the basis of visual findings. In PET images, different colors indicate different rates of glucose metabolism. That is, red indicates a high rate, yellow moderate, and blue low [1]. Patient and normal control groups were compared in this way. Then, in the 2000s, such comparison was performed using voxel-based analysis software, such as statistical parametric mapping (SPM) [2]. SPM has been widely used for the objective analysis of brain images. This software package compares the differences between two anatomically standardized groups with the linear model at each voxel. However, it is sometimes not possible to detect slight differences because of technical issues. In the mature brain, auditory deprivation decreases neuronal activity transiently in the primary auditory and auditory-related cortices. In order to reevaluate these issues, we used other statistical analytic software, that is, three-dimensional stereotaxic region of interest (ROI) template (3DSRT) [3], in addition to SPM. 3DSRT is fully automated ROI-based analysis software for the brain. It was established to perform ROI analysis

of the brain with improved objectivity and excellent reproducibility [4]-[7].

Materials and Methods

In a resting state (eyes closed, ears unoccluded, in a dark and quiet environment), 185 MBq 18F-FDG (the dose was adjusted according to the body weight of each subject) brain PET scans were performed on 7 postlingually deaf patients and 10 healthy volunteers using the Biograph 16 PET scanner (Siemens). Seven patients (2 men, 5 women; mean age, 55.7 ± 8.7 y) underwent FDG-PET scans at Miyazaki University Hospital. The duration of deafness in patients ranged from 1 to 30 y (mean duration, 13.4 ± 10.8 y). The clinical features of the patients are listed in Table 1. They had neither cerebral disease nor visual disturbance. Ten age-matched healthy volunteers (2 men, 8 women; mean age, 57.9 ± 16.2 y) served as control subjects. Exclusion criteria for the control subjects included a history of any neurological, psychiatric, or significant medical illness or past history of drug abuse. All patients and control subjects were right-handed. Detailed explanations of the procedure, risk, and purpose of the FDG-PET study were provided to them. This study was approved by the Ethics Committee of Miyazaki University School of Medicine and written consent was obtained from each participant.

Significant increases and decreases of regional cerebral glucose metabolism in the patient group were estimated by comparing their FDG-PET images with those of the healthy volunteers using SPM (Institute of Neurology, University College of London, UK) analysis.

We also compared the glucose metabolism of auditory cortices with that of visual cortices using 3DSRT. Because all patients and control subjects had neither cerebral disease nor visual disturbance, we adopted the primary visual cortex as a reference. 3DSRT applies constant ROIs on anatomically standardized images. 3DSRT enables the analysis of images of miscellaneous radioactive tracers (^{99m}Tc-ECD, ^{123}I-IMP, ^{15}O-H_2O, ^{18}F-FDG) with excellent reproducibility and objectivity. The analytical process of this method is as follows: 1) Anatomical standardization using the SPM algorithm. 2) Analysis using 318 constant ROIs divided into 12 groups (segments) on each hemisphere. 3) Calculation of the area-weighted average for each of the respective 24 segments on the basis of the value in each ROI. 4) Display of the results followed by saving of the respective values of the 636 ROIs (both hemispheres) in the CSV file format. For the 3DSRT analysis, 318 constant ROIs on each brain hemisphere were prepared. The constant ROIs were determined on the T1-weighted magnetic resonance (MR) images anatomically standardized by SPM and classified into 12 segments according to their arterial supply. 3DSRT enables quantitative analysis, in contrast to SPM, which involves statistical analysis.

Results

When we compared 18F-FDG brain PET images of postlingually deaf patients by the SPM method with those of healthy control subjects, the glucose metabolism of deaf patients was found to be lower than that of the control subjects (Figure 1) in the right superior temporal gyrus, both middle temporal gyri, the left inferior temporal gyrus, the right lobule parietalis inferior, and the left insular cortex (Table 2). 3DSRT data also revealed significantly decreased glucose metabolism in both primary auditory cortices in postlingually deaf patients. We found a 13% decrease in the right hemisphere and a 16% decrease in the left hemisphere (Figure 2).

Discussion

Generally, cortical glucose metabolism in the sensory system characteristically decreases with sensory deficits, owing to the absence of central sensory input. The same pattern has been observed in the auditory system [9].

In the early 1990s, glucose metabolism in the auditory cortices was compared by PET on a visual basis. In PET images, different colors indicate different rates of glucose metabolism. That is, red indicates a high rate, yellow moderate, and blue low [1]. Since the early 2000s, SPM has been used for these studies [2]. Voxel-based analysis software such as SPM has been widely used for the objective analysis of brain images with various imaging drugs. There are several reports about changes in the glucose uptake in the auditory cortex observed by FDG-PET.

In prelingually deaf children, the hypometabolic area of the auditory cortex was widest initially, but decreased as the duration of deafness increased. After 20 years of deafness, cortical glucose metabolism did not differ from that of normal controls [10]. This finding was supported by animal studies. In neonatal deafened rats, the same pattern was observed [12]. In addition, Lee et al. found a positive correlation between the hearing performance of prelingually deafened children after cochlear implantation and the extent of the preoperative hypometabolic area in the auditory cortex. Glucose metabolism in the temporal lobe of deaf children increases with age, and the hearing outcomes deteriorate accordingly [10]. We consider that this phenomenon involves the cross-modal plasticity of the brain. Because of long-term absence of auditory input in congenitally deaf children, the auditory cortex was gradually displaced for another sensory center. Therefore, as the child grew older and the duration of deafness increased, the hearing-capability score with cochlear implant grew worse. If so, FDG-PET study before cochlear implantation can be an examination to predict the prognosis for prelingually deaf children.

Indeed, there are some reports of visual language activation study by FDG-PET describing that the auditory association area of a deaf child develops to process visual aspects of language if it does not receive sufficient auditory signals in the developmental period. In addition, this cross-modal plasticity is suppressed and replaced by normal development if the child uses a hearing prosthesis such as a hearing aid or a cochlear implant sufficiently to increase his or her spoken language

skills [13][14].

This fact was confirmed by other methods, such as magnetoencephalography (MEG) or functional MRI. Levänen and colleagues reported that vibrotactile stimuli, applied on the palm and fingers of a congenitally deaf adult, activated his auditory cortices. The recorded MEG signals also indicated that the auditory cortices could discriminate between the applied 180 Hz and 250 Hz vibration frequencies [15]. The same as the visual language activation study by FDG-PET, these findings suggest that human cortical areas, normally subserving hearing, may process vibrotactile infomation in the congenitally deaf because of the lack of auditory signals. Sadato and colleagues used functional MRI to study prelingually deaf signers, hearing non-signers, and hearing signers. The visually presented tasks included mouth-movement matching, random-dot motion matching, and sign-related motion matching. During the mouth-movement matching tasks, the deaf subjects showed more prominent activation of the left planum temporale (PT) than the hearing subjects. During dot-motion matching, the deaf showed greater activation in the right PT [16]. These findings suggest that cross-modal plasticity is induced by auditory deprivation independent of the lexical processes or visual phonetics, and this plasticity is mediated in part by the neural substrates of audio-visual cross-modal integration.

These facts constitute evidence that the operation of a cochlear implant for prelingually deaf children should be started as early as possible.

On the other hand, in postlingually deaf patients, is there a positive correlation between the degree of hypometabolism and a good cochlear implant outcome? If such a correlation is confirmed, FDG-PET study before cochlear implantation can be an examination to predict the prognosis for not only prelingually deaf children but also for postlingually deaf patients.

As such, initially, we estimated the auditory cortical glucose metabolism of postlingually deaf patients in our hospital, using SPM analysis. The result was the same as reported for previous studies. Namely, low glucose metabolism in the auditory-related cortices was observed in postlingually deaf patients.

Incidentally, in postlingual human deafness, metabolism in the auditory cortex was significantly decreased after long-term deafness [2]. Ito et al. described that the glucose metabolic rate in the auditory cortex in patients who have been deaf for a short period of time is nearly normal or slightly decreased [1]. On the other hand, patients who have been deaf for a long time show decreased activity in the auditory cortex. If the period of deafness is long, for example, over 10 years, the primary auditory cortex, as well as the secondary associated cortex, will exhibit a low glucose metabolic rate [1]. Similarly, in postlingual human deafness, glucose metabolism in the auditory cortex was found to be significantly decreased after 8 years of deafness [2]. We assume that the ability for cross-modal plasticity declines with age.

However, in adult deaf animals, there is a report that metabolism in the auditory cortex returns. In adult deafened cats, four months after the induction of deafness,

glucose metabolism was significantly reduced bilaterally in the primary auditory cortex and the temporal auditory fields. Eventually, after 33 months, these changes disappeared [8]. Cross-modal plasticity of adult animals may differ from that of humans. Alternatively, this difference may result from the use of statistical tools such as SPM.

SPM is a program developed for the analysis of functional images of the human brain. We should be careful in the use and selection of controls when utilizing it [17]. We should also be careful when considering the results of reports because there are some previous FDG-PET studies that compared the brains of prelingually deafened children with those of a control group of normal-hearing adults by a t test in the basic model of SPM [10][13]. Needless to say, we should perform analysis under age-matched conditions, and we also need a sufficient number of control subjects to ensure the validity of the obtained results. In addition, when we select controls, we should only include subjects judged to be healthy after careful neurological examination. In SPM analysis, there are occasionally some regions that appear to show a decrease of regional cerebral glucose metabolism that is not statistically significant, and other regions that we consider to show a minor difference become significant.

Our method involving 3DSRT aimed to overcome these faults of SPM. SPM was effective for the statistical analysis of regional cerebral blood flow (rCBF) changes, but a lack of suitability for the quantification of rCBF values was noted owing to the positioning or selection of the region of interest (ROI), an essential step for the quantification of brain images. So long as the ROIs were manually selected, the obtained results fluctuated considerably with subtle changes in their positioning, and it was possible to overlook important information in an area in which ROI had not been set. Caution should also be taken with regard to SPM in that it is impossible to evaluate the rCBF when the blood flow of the whole brain is decreased. In such cases, when there is a high-blood-flow area, the normal-blood-flow area will be considered as exhibiting low blood flow, which will lead to erroneous results.

To perform ROI analysis of the brain with improved objectivity and excellent reproducibility, 3DSRT, which is fully automated ROI-based analysis software for the brain, was established [3]. In quantifying rCBF or cerebral glucose metabolism, we cannot adapt the radiological activity count from 3DSRT directly. This limitation is due to differences in blood volume among individuals or differences in radioisotope (RI) doses, among others. However, in quantifying rCBF using SPECT, there are simple procedures available, such as the Patlak plot method [11]. We can compare rCBF directly among individuals. In contrast, in measuring brain glucose metabolism using FDG-PET, the procedure is complicated and invasive. Therefore, we used RI count ratio to that of a reference region as a semi-quantitative method. Namely, we set the primary visual cortex as the reference region and compared the RI count ratios of the primary auditory cortex and the primary visual cortex among cases. All patients and control subjects had no cerebral disease or visual disturbance. Using the newly developed method, we could compare the cerebral glucose metabolism among the patients statistically. In addition, the previous results of FDG-PET study were

confirmed.

Our method, namely, to set the primary visual cortex as the reference region and to compare the RI count ratios of the primary auditory cortex and the primary visual cortex from 3DSRT among patient group and control group cases, is useful. This method enables us to perform quantitative analysis, in contrast to SPM, which involves statistical analysis, and it can indicate the ratio of difference. Our data indicated that glucose metabolism decreases in the primary auditory cortex of postlingually deaf patients, with a duration of deafness in patients ranging from 1 to 30 years.

It is not only us to be going to overcome the weak point of SPM. SPM requires an initial step of spatial normalization to align all images to a standard anatomic model (the template), but this may lead to image distortion and artifacts, especially in cases of marked brain abnormalities. Person et al. aimed to assess a block-matching (BM) normalization algorithm, where most transformations are not directly computed on the overall brain volume but through small blocks, a principle that is likely to minimize artifacts [18].

Conclusions

The two statistical tools indicated that glucose metabolism decreases in the primary auditory cortex of postlingually deaf patients. Our results show the same pattern as described in previous reports. Our method involving 3DSRT is useful. This method enables us to perform quantitative analysis, in contrast to SPM, which involves statistical analysis, and it can indicate the ratio of difference.

Functional brain imaging is after all indirect assessment that evaluates the cortical activity by regional cerebral blood flow or metabolic changes. Moreover, the assessment requires reasonable control subjects. In terms of accepting the obtained results, we should keep this in mind at all times.

In terms of determining whether FDG-PET study before cochlear implantation will contribute to predict the prognosis, we are going to obtain more subjects, compare our subjects individually with controls, and continue to evaluate the correlation between the degree of auditory cortical hypometabolism and a good cochlear implant outcome in detail.

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Tables and figure legends

(Table 1) Clinical Features of Deaf Patients

(Figure 1) Brain areas with significantly decreased glucose metabolism in postlingually deaf patients ($P<0.01$, uncorrected). Metabolism was decreased in the right superior temporal, lobulus parietalis inferior, posterior cingulate gyri, and in both middle temporal and left inferior temporal and insular cortices.

a: 3D-volume rendering image

b: Axial image

c: MIP (maximum intensity projection)

(Table 2) Significantly decreased glucose metabolism. (Deafness vs. Control)

Brain areas with significantly decreased glucose metabolism in postlingually deaf patients ($P<0.01$, uncorrected).

(Figure 2) 3DSRT data also revealed significantly decreased glucose metabolism in both primary auditory cortices in postlingually deaf patients.

Table1

Clinical Features of Deaf Patients

Pt No.	Age (y)	Sex	Cause of Deafness	Duration of Deafness(y)
1	50	F	Unknown	1
2	52	F	Unknown	24
3	63	F	Unknown	1
4	49	F	Head injury	30
5	47	M	Otosclerosis	13
6	72	M	Unknown	5
7	57	F	Unknown	20

Figure1a

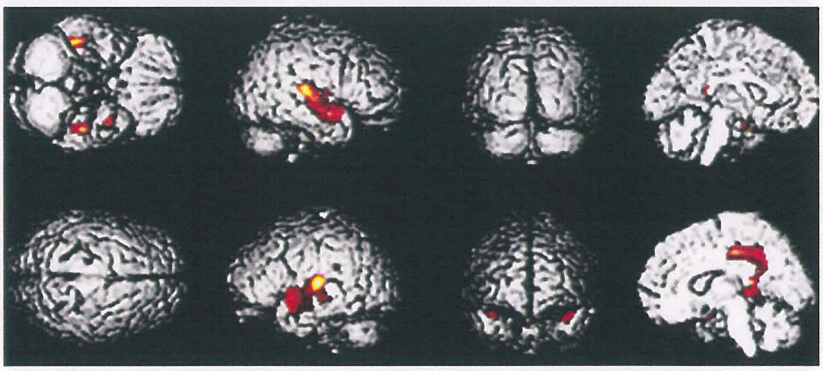


Figure1b

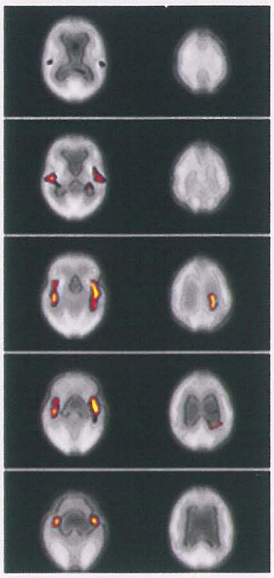


Figure1c

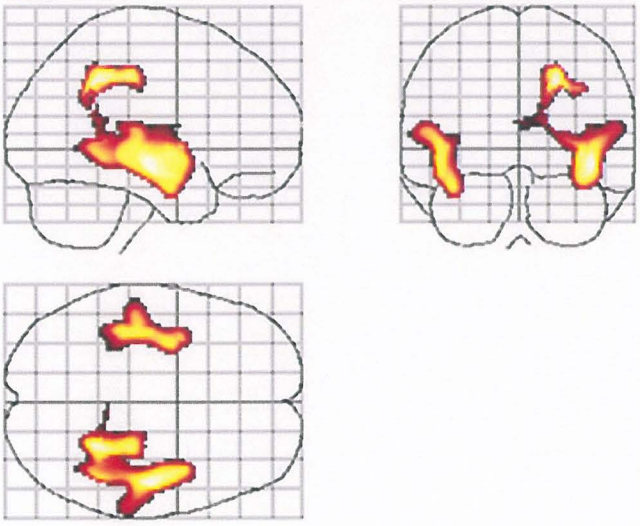


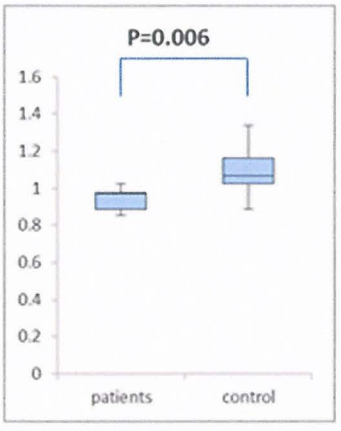
Table2

Significantly decreased glucose metabolism. (Deafness vs. Normal)

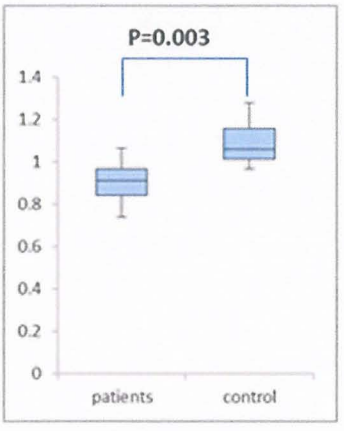
Region	Coordinates*			Analysis**	
	X	Y	Z	Z	p
Rt middle temporal	43.6	-12.1	-8.6	3.67	0.001
Rt Lobulus parietalis inferior	23.8	-38.9	40.0	3.61	0.002
Rt superior temporal	39.6	-2.2	-5.4	3.44	0.002
Rt posterior cigulate gyrus	23.8	-39.1	37.0	3.61	0.003
Rt posterior cigulate gyrus	23.8	-23.4	38.0	3.41	0.035
Lt middle temporal	-41.6	-25.5	-4.3	3.35	0.008
Lt inferior temporal	-35.6	-3.0	-20.1	3.29	0.009
Lt insula	-39.6	3.8	-2.03	3.09	0.011

*Coordinates : International Consortium on Brain Mapping coordinates for the location where the significant difference between conditions was centered.
** Z values refer to comparison of normalized glucose metabolism between deafness group and normal group.

Figure2



Rt auditory / visual



Lt auditory / visual