^{18}F-FDG PET Imaging of the Inferior Colliculus in Asymmetric Hearing Loss

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Our purpose was to use PET to evaluate the glucose metabolism of the inferior colliculus (IC) and primary auditory cortex (PAC) in patients with asymmetric hearing loss (AHL). **Methods:** Normalized regional ^{18}F-FDG uptake of the IC and PAC (reference: cerebellum) was assessed in 13 subjects with AHL using a fully digital clinical PET/CT system. **Results:** Regional metabolism of both the IC and the PAC was significantly reduced contralateral to the most hearing-impaired ear compared with the ipsilateral side. Duration of deafness correlated positively with metabolism of the contralateral PAC but not with metabolism of the ipsilateral PAC or either of the ICs. **Conclusion:** Fully digital, high-resolution clinical PET scanners allow for investigating small brain stem nuclei. AHL has a significant impact on the regional glucose metabolism of the auditory pathway. Mitigation of this effect by a longer duration of deafness might indicate reorganization at the cortical level.

Key Words: ^{18}F-FDG PET; brain stem nuclei; asymmetric hearing loss; cochlear implant; unilateral hearing loss

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Novel fully digital high-resolution PET scanners permit investigation of glucose metabolism (as a measure of neuronal activity) of small brain stem nuclei in a clinical setting. Asymmetric hearing loss (AHL) was chosen as a model to demonstrate the ability to measure the glucose metabolism of the inferior colliculus (IC). This was also prompted by the need for additional outcome predictors in patients undergoing treatment with cochlear implants, especially in those with AHL and single-sided deafness (SSD). There is ample evidence that the primary auditory cortex (PAC) undergoes metabolic changes due to alterations in the afferent input from the cochlea (*1,2*). Hypometabolism of the PAC was described in subjects with short-term, postlingual hearing loss contralateral to the hearing-impaired ear (*3*). Thus, it was expected that the ICs also exhibit asymmetric hypometabolism in AHL. However, to our knowledge there are no investigations of possible metabolic changes of the IC resulting from AHL to date. Furthermore, earlier studies suggested cross-model reorganization processes that may interfere with the aforementioned observations over the long term (*4*).

Hence, the purpose of the present study was to evaluate the metabolism of the IC and PAC using ^{18}F-FDG PET in AHL subjects. We hypothesized that there is an association between AHL and asymmetric glucose metabolism of the IC and the PAC and that this association might be influenced by the duration of AHL.

MATERIALS AND METHODS

Subjects

The present study was approved by the local ethics committee of Freiburg University (vote 330/18, DRKS00015477), and all subjects gave written informed consent. All presented at our clinic for presurgical evaluation for a cochlear implant. They were included in the study if they had AHL or SSD, had received presurgical ^{18}F-FDG PET using a clinical high-resolution scanner (Vereos PET/CT; Philips) for a clinical indication (mostly for exclusion of other neurologic conditions), and were right-handed (*5*). Subjects' vision was essentially unimpaired. In total, 13 AHL subjects were included.

Presurgical Evaluation

Routinely performed presurgical audiometric measurements, as well as speech understanding of noise and the ability to localize sound sources, were performed during the presurgical evaluation. In addition, objective hearing evaluations, brain stem evoked response audiometry, and electrocochleography were performed. Table 1 displays subjects' demographic and audiometric characteristics.

^{18}F-FDG PET

All ^{18}F-FDG PET scans were performed using a fully digital Vereos PET/CT device (Philips Healthcare). Subjects fasted for at least 6 h before intravenous injection of 205 ± 20 MBq of ^{18}F-FDG under normoglycemic, resting conditions (i.e., eyes open, ears unplugged, and hearing aids turned on [if applicable], at reduced ambient light and noise). At 50 min after injection, a static 10-min PET scan was acquired, during which the position of the patient's head was gently restrained by elastic tape and carefully monitored under guidance of the laser system of the scanner and reference skin marks. Using low-dose CT for attenuation correction, a fully corrected emission dataset was reconstructed with the vendor-specific, line-of-response time-of-flight ordered-subsets 3-dimensional iterative reconstruction algorithm using spherically symmetric basis functions (so-called blob ordered-subset time-of-flight reconstruction; number of iterations, 5; number of subsets, 11; 2-mm gaussian postfiltering; resulting voxel size, 1.0 × 1.0 × 1.0 mm), yielding a reconstructed, isotropic image resolution of approximately 4.5–5 mm in full width at half maximum. We did not use resolution recovery to avoid Gibbs artifacts.

^{18}F-FDG PET scans were visually rated by 2 experienced readers in consensus (masked to clinical information) in a standardized fashion. Based on 5-by-6 axial displays, expert readers rated on a 7-point scale

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TABLE 1
Subjects' Demographic and Audiometric Characteristics

Subject	Age at scanning (y)	Sex	Impaired side	Visually read asymmetry of metabolism on PET		Etiology of AHL	Duration of deafness (y)	Bone conduction PTA4 (dB HL)		Air conduction PTA4 (dB HL)		Monosyllabic word recognition at 65 dB SPL (%)		Brain stem evoked response audiometry (worse ear)		Electrocochleography (worse ear)	
				IC	PAC			Better ear	Worse ear	Better ear	Worse ear	Better ear	Worse ear	Threshold (dB)	Interpeak latency (ms)	Sum action potential (ms)	Cochlear microphonic (dB HL)
1	35.9	M	R	Rightward, moderate	Rightward, moderate	Sudden hearing loss	1.5	2.50	95	6.25	>130	100	0	90	4.3	/	/
2	47.8	M	R	Rightward, moderate	Rightward, mild	Mumps	45	7.50	>130	16.25	>130	100	0	/	/	n/d	70
3	40.9	M	R	Rightward, strong	Rightward, strong	Fracture of right petrous bone	2.1	3.75	>130	7.5	>130	100	0	/	/	n/d	100
4	52.4	M	L	Leftward, strong	Leftward, mild	Intracochlear schwannoma	12	15	>130	15	>130	100	0	/	/	n/d	100
5	75.8	M	R	Rightward, strong	Rightward, mild	Sudden hearing loss	0.7	20	>130	38.75	>130	80	0	/	/	n/d	90
6	55.8	F	L	Leftward, moderate	Leftward, moderate	Sudden hearing loss	0.8	6.25	>130	11.25	>130	100	0	n/d	n/d	0.1	90
7	42.4	M	R	Rightward, moderate	Leftward, mild	Mumps	34	0	53.75	2.5	113.75	100	0	/	/	n/d	110
8	40.0	F	L	No asymmetry	Leftward, mild	Unknown	31	32.5	>130	36.25	>130	90	0	/	/	n/d	100
9	60.1	M	R	Leftward, mild	Rightward, mild	Sudden hearing loss	21	41.25	113.75	43.75	113.75	70	0	/	/	n/d	100
10	58.0	M	L	Leftward, mild	Rightward, mild	Mumps	53	25	>130	42.5	>130	45	0	/	/	n/d	100
11	84.2	M	L	Leftward, strong	Leftward, mild	Sudden hearing loss	0.5	35	>130	40	>130	70	0	/	/	n/d	90
12	55.5	F	R	No asymmetry	No asymmetry	Pertussis	48	35	>130	40	>130	45	0	/	/	/	/
13	17.9	F	L	Leftward, strong	Leftward, mild	Large aquaeductus vestibuli syndrome	15	12.5	>130	17.5	>130	100	0	/	/	n/d	100

HL = hearing loss; SPL = sound pressure level; PTA4 = pure tone average at frequencies 0.5, 1, 2, and 4 kHz; n/d = not derivable.
Slash indicates that test was not administered.

whether glucose metabolism showed no asymmetry (0) or showed mild, moderate, or strong asymmetry to the left (−1, −2, or −3) or to the right (1, 2, or 3) for PAC and IC separately.

^{18}F-FDG PET scans were furthermore evaluated using a volume-of-interest (VOI) analysis. ^{18}F-FDG uptake of the left and right IC, as well as the left and right PAC, and a reference region (cerebellar cortex) were read out as follows: scans were normalized to Montreal Neurologic Institute space using SPM12 (www.fil.ion.ucl.ac.uk/) and an in-house ^{18}F-FDG PET template. IC VOIs were created in Montreal Neurologic Institute space for fully automated, observer-independent readout of regional ^{18}F-FDG uptake. In the first 3 subjects, separate VOIs for the left and right IC (6-mm-radius spheres) were manually positioned on the individual spatially normalized ^{18}F-FDG datasets by an experienced ^{18}F-FDG PET reader using PMOD (version 3.7). The union of all 3 manual VOIs (bilateral) was used as the IC VOI in Montreal Neurologic Institute space in the following steps. The PAC VOI was taken from Morosan et al. (*6*) and comprised the subregions Te1.0, Te1.1, and Te1.2. The cerebellar cortex VOI was taken from the SUIT atlas (*7*). To reduce partial-volume effects and contributions from cerebrospinal fluid spaces, the average ^{18}F-FDG uptake of the 25% of all voxels with highest uptake was contemplated for the IC and PAC. Normalized regional ^{18}F-FDG uptake was calculated by division by the individual mean ^{18}F-FDG uptake of the cerebellar cortex.

All ^{18}F-FDG PET images were clinically read as normal with the exception of 1 patient (subject 3 in Table 1), who had a fracture of the right petrous bone (resulting in right-sided hearing loss) and traumatic brain injury of the frontal lobes bilaterally (right more than left). This patient's ^{18}F-FDG PET scan was clinically read as showing bilateral orbitofrontal hypometabolism (besides asymmetry of IC and PAC).

Statistics

Visual reads were evaluated descriptively, with cross-tables relating the side of more severe hearing impairment to visually rated asymmetry of glucose metabolism, for IC and PAC separately. VOI analyses were done as follows. First, normalized regional glucose metabolism was compared between ipsilateral and contralateral (referring to the side of the more severely hearing-impaired ear) IC, as well as ipsilateral and contralateral PAC, with paired *t* tests. Second, the effect of the duration of deafness on glucose metabolism of the IC and the PAC was tested using linear regression analyses. Third, separately for ipsilateral and contralateral sides, the association between normalized regional glucose metabolism of the IC and that of the PAC was tested with linear regression analyses. To test for effects of duration of deafness on the relationship between IC and PAC metabolism, these analyses were repeated with additional inclusion of the duration of deafness as a covariate. Fourth, a Spearman correlation analysis between the duration of deafness and the VOI of each IC and each PAC (ipsi- or contralateral) was performed.

RESULTS

On visual inspection, asymmetry (mild to strong; Table 1) of the IC and PAC was detected in 11 of 13 and 12 of 13 patients, respectively. The side of lower uptake corresponded to the side contralateral to the side of more severe hearing impairment in 10 of 11 and 10 of 12 patients (Fig. 1). In fact, patients without visually appreciable asymmetry had bilateral hearing impairment with little asymmetry. The results of the VOI analyses are as follows.

First, the regional glucose metabolism of the contralateral IC was reduced compared with the ipsilateral side ($P = 0.003$, Cohen d = 1.02). Normalized glucose metabolism was also reduced in the contralateral PAC compared with the ipsilateral side ($P = 0.01$, Cohen d = 0.85) (Fig. 2).

Second, the duration of deafness predicted normalized regional glucose metabolism of the contralateral PAC ($r^2 = 0.33$; $P = 0.042$), with a longer duration being associated with higher metabolism. Spearman correlation analysis confirmed this association ($\rho = 0.60$, $P = 0.034$). By contrast, duration of deafness did not predict regional glucose metabolism of the ipsilateral PAC or either IC (all $P > 0.1$) (Fig. 3).

Third, the glucose metabolism of the contralateral PAC was not significantly predicted by that of the contralateral IC ($r^2 = 0.19$, $P = 0.14$). The regression model improved when the duration of deafness was included as a covariate ($r^2 = 0.42$, $P = 0.068$): higher contralateral glucose metabolism of the PAC was associated with higher metabolism of the contralateral IC (though not significantly: predictor "glucose metabolism of IC", $P = 0.24$), whereas the predictor "duration of deafness" showed a tendency toward significance ($P = 0.075$). The glucose metabolism of the ipsilateral PAC was not predicted by that of the ipsilateral IC, and this did not change after inclusion of duration of deafness as a covariate (both $P > 0.1$).

Exploratory correlation analyses failed to demonstrate any significant correlation between scaled ^{18}F-FDG uptake and auditory performance measures (i.e., monosyllabic word recognition, BCTPA4, or ACTPA4; all $P > 0.1$).

DISCUSSION

The use of newest-generation, fully digital clinical PET scanners permits imaging and quantitative assessment of small brain stem nuclei such as the IC. To the best of our knowledge, ours is the first demonstration that the glucose metabolism of the IC contralateral to the side of the more severe hearing impairment in AHL is significantly reduced compared with the ipsilateral IC, as is already appreciable by visual inspection. Similarly, the metabolism of the contralateral PAC was reduced, and a longer duration of deafness attenuated this effect.

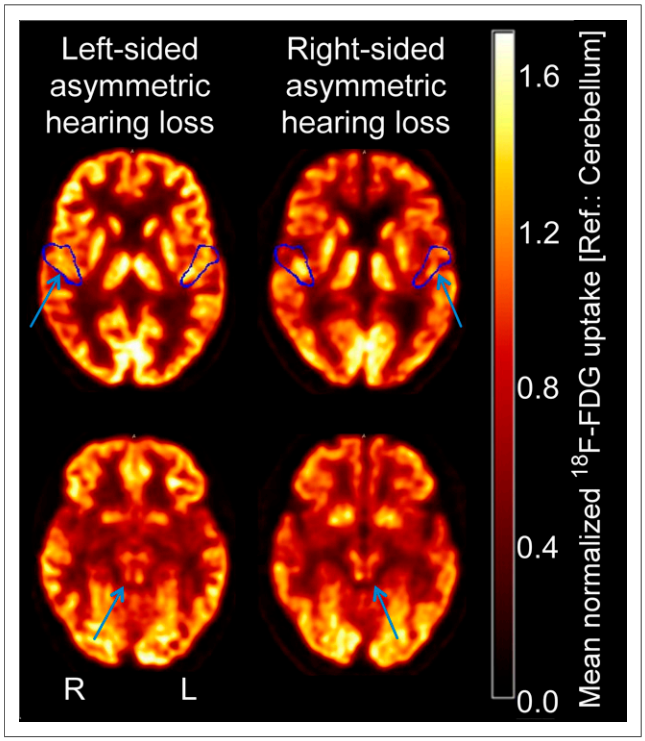

FIGURE 1. Axial ^{18}F-FDG PET scans at level of PAC (top, VOI outline in blue) and IC (bottom) in 2 representative patients with left-sided (left image) and right-sided (right image) AHL. Arrows indicate side of decreased metabolism.

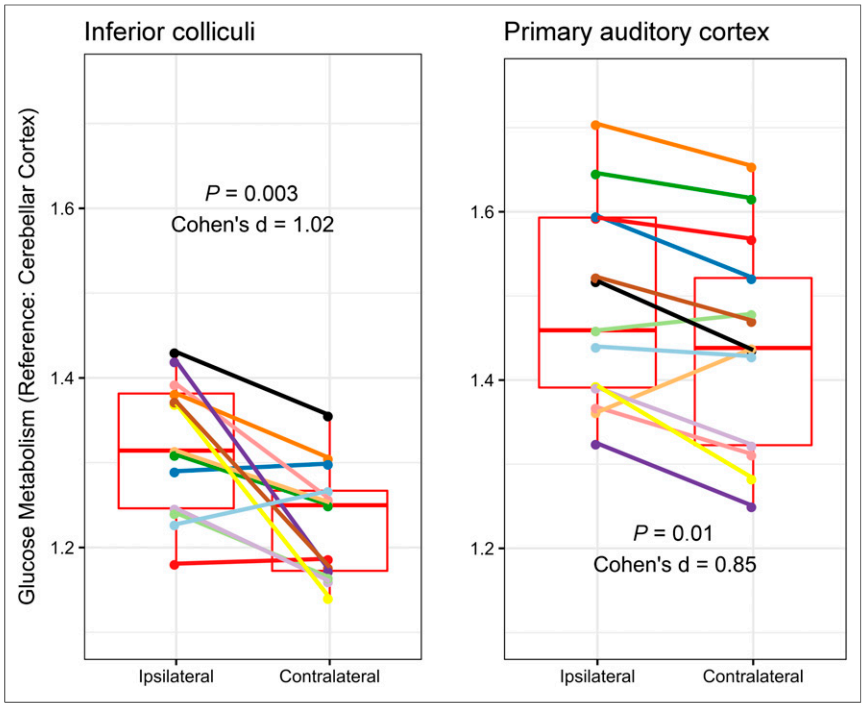

FIGURE 2. Contralateral glucose metabolism was reduced in IC and in PAC, compared with ipsilateral side ($P = 0.003$ and $P = 0.01$, paired t tests). Shown are box plots (red) and individual values (other colors) of glucose metabolism of IC and PAC.

We showed that impaired hearing attenuates glucose metabolism as a measure of neuronal activity of the contralateral IC and PAC, as is in line with the primarily decussated, contralateral neuronal processing of auditory input within the human brain. Reduced metabolism of the auditory system in bilateral deafness has been reported recently (*8*): glucose metabolism was reduced (compared with control subjects) bilaterally in the PAC and near (and presumably including parts of) the IC. However, ^{18}F-FDG PET imaging in that study was performed at substantially lower spatial resolution than in the present study, making it much more difficult to assign a hypometabolic area (derived from a whole-brain, voxelwise group comparison) to a small anatomic structure such as the IC (*8*).

In the present study, data from patients could not be compared with data from healthy control subjects. However, we conducted an exploratory comparison (not shown in detail) with datasets from 40 patients, for whom ^{18}F-FDG PET scans were acquired with the same PET/CT system and clinically read as showing normal findings (no known hearing impairment; predominantly scanned because of cognitive impairment, parkinsonism, or epilepsy). This analysis revealed that the metabolism of the contralateral IC was significantly lower in patients with AHL (−8%; $P = 0.0002$, t test). The contralateral PAC also showed a somewhat lower metabolism, which, however, failed to reach statistical significance (−1%; $P > 0.1$). Metabolism did not relevantly differ between the ipsilateral IC and PAC ($P > 0.1$). Thus, the reported asymmetry of metabolism toward the ipsilateral side is likely caused by a contralateral reduction rather than an ipsilateral increase in neuronal activity.

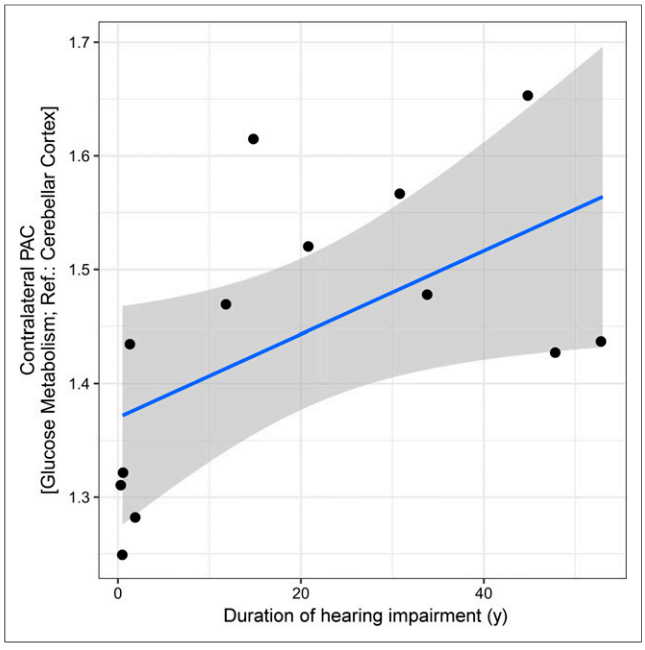

FIGURE 3. Longer duration of hearing impairment was associated with higher glucose metabolism of contralateral PAC ($r^2 = 0.33$; $P = 0.042$).

A longer duration of deafness was associated with greater metabolism of PAC, as is consistent with previous reports (*8–10*). It has been suggested that the association between longer duration and greater metabolism indicates cortical reorganization (*10,11*). An increase in neuronal activity with a longer duration of deafness might be due to cross-modal takeover of the auditory cortex by other sensory systems, such as the visual or vibrotactile system (*12,13*). In contrast, the duration of deafness was not associated with contralateral IC metabolism. Thus, reorganization presumably occurs at a downstream cortical level but not in upstream brain stem nuclei.

The results might be of clinical value regarding prediction of the therapeutic outcome after cochlear implants in AHL and SSD subjects. Previous studies indicated that the benefit from cochlear implants is least in bilateral deafness with extensive reorganization within the auditory system (*9,10*). Thus, prediction of a successful outcome might benefit from improved imaging with fully digital PET/CT systems, as large parts of the auditory system become accessible for preoperative patient characterization, including small brain stem nuclei such as the IC. To confirm these predictions based on presurgical ^{18}F-FDG PET, further research linking preoperative glucose metabolism with postoperative outcome in patients is under way.

CONCLUSION

Fully digital, high-resolution clinical PET scanners allow for investigating glucose metabolism of small brain stem nuclei. AHL has a significant impact on regional glucose metabolism of parts of the auditory pathway. Mitigation of this effect by a longer duration of deafness might indicate reorganization at the cortical level. This might be of clinical value concerning prediction of outcome after cochlear implantation.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: Does fully digital, high-resolution clinical PET permit investigation of the glucose metabolism of the inferior colliculi in patients with asymmetric hearing loss?

PERTINENT FINDINGS: Normalized regional ^{18}F-FDG uptake of the inferior colliculi and primary auditory cortex (reference: cerebellum) was assessed in 13 subjects with asymmetric hearing loss using a fully digital clinical PET/CT system. Regional metabolism of both the inferior colliculus and the primary auditory cortex was significantly reduced contralateral to the most hearing-impaired ear compared with the ipsilateral side.

IMPLICATIONS FOR PATIENT CARE: Results might be of clinical value regarding the prediction of the therapeutic outcome after cochlear implantation in asymmetric hearing-impaired and single-sided deaf subjects.

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