Decreased cortical glucose metabolism correlates with hippocampal atrophy in Alzheimer's disease as shown by MRI and PET

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Abstract

Objective—To investigate the relation between atrophy of the hippocampus and parahippocampal gyrus (the % hippocampal area) and cerebral metabolic rate for glucose (CMRGlc) in Alzheimer's disease.

Methods—13 patients with probable Alzheimer's disease by NINCDS-ADRDA criteria (six men; seven women, mean age 71 years, mini mental state 13.8 (SD 4.6)) and age matched controls were studied. T1 weighted MRI (0.5T) images were used for evaluation of the hippocampal area. With a digitiser system, a percentage of the hippocampal area to the brain (the % hippocampal area) was calculated. Eight patients received another T1 weighted MRI (1.5T) for further evaluation of the minimum thickness of the hippocampus. Regional CMRGlc (rCMRGlc) was measured using PET and the FDG technique. **Results**—The hippocampal area in patients with Alzheimer's disease was significantly lower than that of controls ($P < 0.01$). All the cortical rCMRGlc values in patients with Alzheimer's disease were lower than those of controls ($P < 0.01$). A significant correlation ($P < 0.05$) was found between the % hippocampal area and rCMRGlc in the temporal lobe, temporoparieto-occipital (TPO) region, and frontal lobe in Alzheimer's disease. There was a significant correlation between minimal hippocampal thickness and ipsilateral TPO metabolism on both sides.

Conclusion—The ipsilateral correlation between hippocampal atrophy and decreased TPO metabolism in Alzheimer's disease suggests a functional relation and the asymmetries show that Alzheimer's disease is an asymmetric disease in its early stages.

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Keywords: Alzheimer's disease; hippocampus; cerebral metabolic rate for glucose

Neuroimaging studies on Alzheimer's disease have been performed using CT or MRI for morphology and single photon emission CT (SPECT) or PET for function. Previous morphological studies have shown that: (1) patients with Alzheimer's disease have greater brain atrophy than aged normal subjects,¹⁻³

including cortical atrophy and ventricular enlargement; (2) the temporal lobe, especially the hippocampus, shows atrophy in Alzheimer's disease.⁴⁻⁹ Functional studies (circulation and metabolism) have shown that: (1) cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO₂) are lower in Alzheimer's disease than controls, especially in the temporoparieto-occipital (TPO) region¹⁰⁻¹²; (2) CMRGlc in Alzheimer's disease is also decreased in the temporal lobe and TPO region, and decreased CMRGlc in the right and left TPO regions is associated with impaired visuospatial and verbal functions as shown by the Wechsler adult intelligence scale (WAIS).¹³⁻¹⁷

In view of the relation between morphology and function, Jobst *et al*¹⁸ studied the relation between atrophy of the hippocampus shown by CT and CBF by SPECT in Alzheimer's disease. They found an association between hippocampal atrophy and ipsilateral temporoparietal hypoperfusion. However, there has been no study of the relation between atrophy of the hippocampus and CMRGlc, although both were found to be important in Alzheimer's disease. In the present study, we tried to confirm the findings of Jobst *et al* by using PET measurements of glucose consumption in Alzheimer's disease.

Subjects and methods

SUBJECTS

Ten normal elderly subjects (five men and five women, ages 68-78 years, mean age 73 years) and 13 patients with Alzheimer's disease (six men and seven women, ages 56-88 years, mean age 71 years) were studied. There was no statistical difference in mean age between the groups. The normal subjects underwent medical interview, physical and neurological examinations, laboratory tests, ECG, and CT. They displayed no cognitive impairment based on clinical observation, no risk factors for cerebrovascular disease such as hypertension (except for smoking histories), and no history of head injury or any other disorders that could affect brain function. The brain CT findings were normal.

The diagnosis of Alzheimer's disease was based on the NINCDS-ADRDA criteria for probable Alzheimer's disease.¹⁹ Brain MRI (described below) in Alzheimer's disease disclosed brain atrophy without any infarctions. All the patients with Alzheimer's disease were studied within five years of onset of symptoms and showed mild to moderate decline of intelli-

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Table 1 Clinical characteristics of the patients with Alzheimer's disease

Patient No	Age (y)	Sex	Duration (y)	MMS	TK-IQ	WAIS-R subscore		
						VIQ	PIQ	TIQ
1	88	F	3	10	20	12	0	12
2	74	F	2	17	52	27	30	57
3	58	M	3	9	19	15	0	15
4	77	M	5	9	18	0	8	8
5	60	F	2	16	62	33	13	46
6	77	F	3	22	55	57	35	92
7	82	M	3	15	36	27	3	30
8	80	F	2	16	43	45	8	53
9	74	F	5	10	34	18	10	28
10	79	M	5	21	45	54	20	74
11	59	F	2	14	40	63	0	63
12	64	M	5	12	40	39	13	52
13	56	M	2	8	54	18	8	6

MMS = mini mental state; WAIS-R = Wechsler adult intelligence scale-revised; VIQ = verbal IQ; PIQ = performance IQ; TIQ = total IQ; TK = Tanaka-Binet test.

gence (mini mental state (MMS)²⁰ range, 8–22, mean (SD) 13.8 (4.6)). They did not receive any medication which might affect CBF and metabolism. All received WAIS-R (revised)²¹ and Tanaka-Binet tests.²² Table 1 gives the clinical characteristics of the patients with Alzheimer's disease.

This study was approved by the medical ethics committee of the Cyclotron Radioisotope Center at Tohoku University, and informed consent was received from all the subjects and their families.

MAGNETIC RESONANCE IMAGING

The MRI was carried out with a 0.5 T MRVectra (GE-YMS, Japan). T1 weighted images (TR/TE 300/15) were used for evaluation of atrophy of the hippocampus and parahippocampal gyrus, which we defined as the % hippocampal area. The hippocampus was identified by the sagittal slices, then a semi-axial slice parallel to the hippocampus was

Figure 1 MRI measurement of the hippocampal area and the temporal lobe. A sagittal slice through the midpoint of the eye is obtained, and a slice parallel to the hippocampus is scanned; then planes perpendicular to the plane parallel to the hippocampus are obtained (the semicoronal planes). The T1 weighted images of this slice are input into the computer system which enlarged them about twofold, and using a digitiser system, the hippocampus and the parahippocampal gyrus (the hippocampal area) is traced manually. Similarly, the temporal area is measured using the same plane. The percentage of the hippocampal area to the brain area (the % hippocampal area) and the temporal area to the brain area (the % temporal lobe) are calculated.

Temporal lobe (%) = $\frac{TL\ (blt)}{Brain} \times 100$
Hippocampal area (%) = $\frac{HA\ (blt)}{Brain} \times 100$

scanned. Finally, planes perpendicular to the semiaxial planes were obtained (the semicoronal planes).

The T1 weighted image of the semicoronal plane which had the largest area of the hippocampus was transferred to a computer system which enlarged the image about twofold, and the hippocampal area was traced manually using a digitiser system. Figure 1 shows this process. Similarly, the temporal area was measured from the same semicoronal plane. Using routine orbitomeatal axial planes +30, +50, and +70 mm, the brain area and the area of the skull cavity were also evaluated.

The percentage of the hippocampal area to the brain area (the hippocampal area), the temporal area to the brain area (the temporal area), and the brain area to the skull cavity (the brain area) were calculated. The measurements were performed by two neuroradiologists who did not know the PET findings: each neuroradiologist made two measurements and the average values of the four measurements were used. The average values of the bilateral hippocampal area and the % temporal area were calculated and used for analysis as it was difficult to show a left-right difference with this system. The within and between reader reproducibility of all the MRI variables were calculated as follows:

1 – (value 1 – value 2) / (value 1 + value 2) / 2

For the within reader reproducibility, values 1 and 2 were assessed by two radiologists. For the between reader reproducibility, values 1 and 2 were assessed by the same radiologist. Both reproducibilities were better than 0.95.

An axial T1 weighted MRI parallel to the orbitomeatal line was examined at the same head position as in the PET study to obtain accurate overlaps (described below), and an axial T2 weighted (TR/TE 2000/100) MRI was performed to exclude infarctions.

Additional MRI

To show left-right differences, eight patients in the Alzheimer's disease group received another T1 weighted MRI (1.5T, Magnetom, Siemens, FRG) for further evaluation of the hippocampus as the digitiser system of 0.5T MRI could not detect small differences. Using a new semi-axial plane, the minimum thickness of the hippocampus was measured and divided by the brain width of the same plane ⁷.

POSITRON EMISSION TOMOGRAPHY

A PET study was performed with a model PT-931 scanner (CTI Inc, USA: axial/transaxial resolutions; 8 mm), according to the FDG method.^{23,24} A short cannula was placed in a radial artery for blood sampling. Each subject was positioned in the scanner, with the orbitomeatal line parallel to the detector rings according to the brain slices by MRI. A cross of light was projected on to marks on the subject's head from three dimensions, and the heads were set at the standard points of 30 and 77 mm above and parallel to the orbitomeatal line. All studies were conducted in a quiet, semidarkened room. The subjects' eyes were open and their ears were not plugged.

Table 2 Cerebral metabolic rate for glucose for (rCMRGlc) the two groups

Brain regions	rCMRGlc	
	Normal (n = 10)	AD (n = 13)
Mean	6.81 (1.25)	4.50 (0.52)
Upper frontal	8.35 (1.86)	5.18 (1.11)
Anterior frontal	7.42 (1.80)	4.28 (0.63)
Inferior frontal	6.42 (1.48)	4.62 (0.90)
Parietal	8.03 (1.95)	4.71 (1.06)
TPO	6.87 (1.44)	3.74 (0.45)
Primary auditory	8.57 (1.81)	4.76 (0.68)
Temporal	6.42 (1.48)	4.31 (0.93)
Hippocampus	5.41 (1.95)	3.22 (1.85)
Primary visual	8.88 (1.75)	5.04 (0.80)
Occipital	7.43 (1.48)	4.06 (0.57)
Basal ganglia	6.53 (1.24)	5.17 (0.79)
Cerebellum	7.31 (1.55)	5.04 (0.14)
White matter	5.72 (1.33)	5.07 (0.74)

Values are mean (SD) in mg/100 ml/min.

A 20 minute transmission scan using a $^{68}\text{Ge}/^{68}\text{Ga}$ external ring source was performed. A total of 5 mCi to 12 mCi FDG were injected as an intravenous bolus. Thirty to 45 minutes after the injection, a series of two emission scans was performed. Each emission datum was simultaneously collected from seven contiguous axial sections. Fourteen slices parallel to the orbitomeatal line with a slice thickness of 6 mm, encompassing virtually the whole brain, were analysed. Twenty blood samples were collected as follows: from the FDG injection to two minutes, every 20 seconds, then at 2.5, 3, 4, 5, 7.5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes. The samples were immediately centrifuged, and the plasma radioactivities were measured with a cross calibrated well counter. The plasma glucose concentrations were measured every 10 minutes.

DATA ANALYSIS

Two different pairs of axial MRI and PET images were roughly registered and matched with each other at the same brain slices.²⁵ To ascertain the anatomical position of each brain structure, the position of regions of interest (round ROIs, 2.7 cm²) were manually defined using the overlapped images. A total of 13 ROIs in each hemisphere were placed on these images. Each ROI was positioned in the relevant region with reference to the anatomical atlases^{26,27} with no overlapping. The rCMRGlc was measured in the following bilateral regions: upper frontal, anterior frontal, inferior frontal, primary auditory, temporal, parietal, TPO, hippocampus, primary visual, occipital, basal ganglia, cerebellum, and white matter. The mean value of left and right cortical CMRGlc in each ROI was calculated and used for analysis.

Statistical analysis was performed using Student's *t* test, and Pearson's and Spearman's correlation coefficients.

Additional analysis

For the eight patients with Alzheimer's disease who received a 1.5T MRI, a χ^2 test was used to detect a relation between the hippocampal asymmetry and the CMRGlc asymmetry in all ROIs measured.

Results

The mean hippocampal areas of the normal group and the Alzheimer's disease group were 5.5 (SD 0.8)% and 3.4 (SD 1.4)% respectively (*t* test, *P* < 0.01). The brain area and the temporal area of the patients with Alzheimer's disease were also significantly lower than those of the normal (data not shown).

Table 2 shows the rCMRGlc values of the two groups. All the rCMRGlc values except for that of the white matter of the Alzheimer's disease group were lower than those of the normal group (*t* test, *P* < 0.01).

The correlation between the brain area and the mean cortical CMRGlc of the Alzheimer's disease group was not significant; nor were the temporal area and the mean cortical CMRGlc. Figure 2 shows the correlation between the hippocampal area and the mean cortical CMRGlc of the Alzheimer's disease group; a significant correlation was found (*P* < 0.05, Pearson).

Figure 3 shows the relation between the hippocampal area and the rCMRGlc in the Alzheimer's disease group. The rCMRGlc values of the temporal lobe, the TPO region, and the frontal lobe were significantly correlated (*p* < 0.05, Pearson). For the rCMRGlc ratio to that of the mean cortical CMRGlc (rCMRGlc/CMRGlc), that of the TPO region was significantly correlated with the hippocampal area (Spearman rank correlation). There was no correlation with the other ROIs, such as the frontal lobe.

Figure 2 Correlation between the % hippocampal area and mean cortical cerebral metabolic rate for glucose (CMRGlc) for the Alzheimer's disease group.

Figure 3 Correlation coefficients between the hippocampal area and cortical cerebral metabolic rate for glucose (CMRGlc). The relations between the hippocampal area and the regional CMRGlc (except for those of the basal ganglia, hippocampus, and white matter) in the Alzheimer's disease group are shown. The numbers in the boxes are Pearson's correlation coefficients in each area of the brain. Underlining indicates significant data: the CMRGlc values of the temporal lobe, the temporo-parieto-occipital region, and the frontal lobe are correlated (*P* < 0.05).

ADDITIONAL ANALYSIS

In five of the eight patients with Alzheimer's disease, the minimum thickness of the left hippocampus was smaller than the right, and in the remaining three, the reverse pattern was present. For metabolic asymmetry, all three with smaller right hippocampi had right TPO metabolism lower than the left; and all five with smaller left hippocampi had left TPO metabolism lower than the right. A $2 \times 2 \chi^2$ test disclosed that left-right hippocampal asymmetry and metabolic asymmetry (right < left or right > left) were significantly correlated ($\chi^2 > \chi_{1,2}^2$ ($P < 0.005$)). There was no such relation for the other ROIs, such as the frontal lobe.

Discussion

In this study, we examined patients with Alzheimer's disease, using MRI and PET, and found that the hippocampal area was significantly correlated with the average value of cortical CMRGlc. For regional metabolism, those of the frontal lobe, the temporal lobe, and the TPO region were correlated. For rCMRGlc of the hippocampus, there were no significant correlations, probably because of a partial volume due to atrophy giving larger SDs to rCMRGlc values.

Regarding the MRI assessment, we performed tracing of the hippocampal area enlarged on a computer screen. Jack *et al.*²⁸ studied MRI based area measurements of the hippocampus and found that the tracing technique was more accurate, especially for the smaller cylinders, than the random marking technique, although the results of the method may have been affected by the observer's perception of object boundary, experience, knowledge of relevant anatomy, and complexity of the object boundary.²⁸ The measurements in this study were taken by two radiologists (each made two observations), and the average values of four measurements was used. As the between and within reader reproducibilities were found to be better than 0.95, we assume that the MRI data were reliable.

The pathological features of Alzheimer's disease, such as neuronal cell loss, neurofibrillary tangles, and senile plaques, are found in the hippocampal area and in the association neocortices.²⁹⁻³² Hippocampal atrophy as shown by CT or MRI as well as decreased rCMRGlc in the temporal lobe, parietal lobe, or TPO region as shown by PET are well known neuroimaging findings. The fact that both were correlated indicates a possibility that the hippocampal area and the TPO region are "related". This speculation is supported by the result that the rCMRGlc/CMRGlc ratio of the TPO region was significantly correlated with the hippocampal area in Alzheimer's disease.

However, according to Haxby and Grady *et al.*,^{17,33,34} Alzheimer's disease is an inherently asymmetric disease: metabolic reductions in the parietal association cortex and increased left-right metabolic asymmetry were found in mild to moderate Alzheimer's disease, and this

metabolic asymmetry is evident before the neuropsychological consequences of that dysfunction are demonstrable. Jobst *et al.*¹⁸ noted that hippocampal atrophy was accompanied by ipsilateral temporoparietal perfusion. Our additional data that morphological asymmetry of the hippocampus and a metabolic asymmetry of the TPO region was correlated, support the findings of others.^{17,33,34} Further analysis with larger sample size is needed to determine the possible role of other regions such as the frontal lobe.

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