High-Resolution SPECT to Assess Hippocampal Perfusion in Neuropsychiatric Diseases

Takashi Ohnishi, Hiroaki Hoshi, Shigeki Nagamachi, Seishi Jinnouchi, Leo G. Flores II, Shigemi Futami and Katsushi Watanabe

Department of Radiology, Miyazaki Medical College, Miyazaki, Japan

The purpose of this study is to clarify the changes of hippocampal perfusion in neuropsychiatric diseases, including dementia, compared with control subjects, and to correlate hippocampal perfusion with the dementia rating scale and the severity of memory disturbance in patients with these diseases. **Methods:** A total of 45 right-handed patients were investigated (13 with dementia of Alzheimer type, 6 with multi-infarct dementia, 4 with progressive dementia with motor neuron disease (MND), 3 with transient global amnesia, 5 with other diseases and 14 control subjects). Regional cerebral blood flow (rCBF) in the parietal cortex and hippocampus was evaluated by high-resolution SPECT technique with HMPAO in all subjects. **Results:** The rCBF measurements in the bilateral parietal cortices and hippocampus were lower in dementia of Alzheimer type and multi-infarct dementia patients than in controls. Hypoperfusion in the hippocampus was a more sensitive marker than hypoperfusion in the parietal cortex in diagnosing dementia of Alzheimer type. Hippocampal hypoperfusion was observed in demented patients regardless of etiology and in patients having memory disturbance without dementia, such as transient global amnesia. Finally, hippocampal hypoperfusion reflected the severity of dementia and memory disturbance regardless of etiology. **Conclusion:** The rCBF image with high-resolution SPECT system may be useful in assessing the extent of dementia and memory disturbance in patients with neuropsychiatric diseases.

Key Words: single-photon emission computed tomography; regional cerebral blood flow; dementia; memory disorder; hippocampus

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PET and SPECT are useful methods for diagnosing and evaluating demented patients (*1–4*). The most frequently reported findings in SPECT and PET studies in patients with dementia of Alzheimer type are bilateral hypoperfusion and hypometabolism of the parietal and temporal lobes (*1–4*). Holman et al. observed that parietal lobes were the most severely affected in dementia of Alzheimer type and that parietal lobe hypoperfusion correlated well with the dementia rating scale (*1*). In our previous reports demonstrating this phenomenon, we suggested that the physiologic reduction in regional cerebral blood flow (rCBF) SPECT images in dementia patients should be correlated with clinical manifestations, such as personality disorder (frontal cortex hypoperfusion), visuospatial disorientation (parietal cortex hypoperfusion), aphasia and dysgraphia (dominant frontal and temporal hypoperfusion) (*3*).

It is well known that visuospatial disorientation, a characteristic disturbance of higher cortical function, is a personality disorder rarely noted in early stages of typical dementia of Alzheimer type. Parietal hypoperfusion and hypometabolism without hypofrontality, on the other hand, are commonly noted on SPECT and PET studies in early-stage dementia of Alzheimer type. Since hippocampal formation and associated limbic structures play an important role in memory processing and memory disturbances, the most characteristic and earliest clinical manifestation in dementia of Alzheimer type patients is disturbance of memory (*5*). Studies on hippocampal pathology have indicated that the hippocampus and its intimately connected parahippocampal gyrus are potential sites for the earliest neurodegenerative changes associated with dementia of Alzheimer type (*6,7*). A recent study with monkeys using ^{18}[F]-fluorodeoxyglucose (FDG) and PET showed that the hippocampus consumed more glucose during memory processing (*8*). We therefore expect that the earliest and most sensitive region to be assessed by rCBF-SPECT in demented patients may be the hippocampus, which is so highly associated with memory disturbances.

The old SPECT system does not allow evaluation of the hippocampus because of its poor spatial resolution. Recent advancements in SPECT imaging, however, including new three-detector technology, provide high spatial resolution

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For correspondence or reprints contact: Takashi Ohnishi, Department of Radiology, Miyazaki Medical College, 5200 Kihara Kiyotake, Miyazaki, Japan 889-16.

TABLE 1
Breakdown of Patients by Diagnostic Category

Diagnostic category	No. of patients	Mean age (yr)
Nondemented control	14	63
Demented patients	23	66
Dementia of Alzheimer type	13	68
Multi-infarct dementia	6	75
Progressive dementia with motor neuron disease	4	55
Transient global amnesia	3	46
Others	5	61
Parkinson's disease	2	64
Schizophrenia	1	63
Affective disorder	2	63
Total	45	64

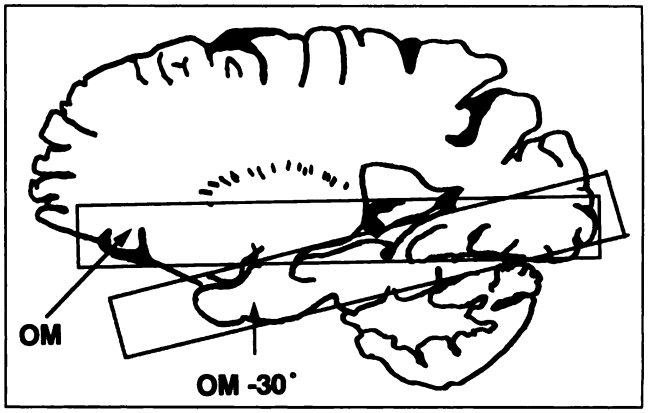

FIGURE 1. Schema for hippocampal scan. OM = orbitmeatal line.

and allow hippocampal evaluation. In the present study, we sought to clarify hippocampal perfusion changes in neuropsychiatric diseases, including dementia, as compared with control subjects, and to assess the relationship between hippocampal perfusion, the dementia rating scale and the severity of memory disturbance in these patients.

METHODS

Patients

A total of 45 right-handed patients were investigated (Table 1). Thirteen dementia of Alzheimer type patients met the criteria of the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* for primary degenerative dementia (*9*) and of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association for probable Alzheimer's disease (*10*). Clinical evaluation included complete history, physical and neurologic examinations and laboratory studies. All dementia of Alzheimer-type patients had Hachikinski ischemic scores of less than 4 and only generalized mild-to-moderate cerebral atrophy without focal abnormalities on CT or MRI of the brain. Multi-infarct dementia patients were selected on the basis of the Hachikinski ischemic scores (7 or more) and clinical presentation of dementia. MRI and CT scans in multi-infarct dementia patients showed infarctions in the basal ganglia or deep white matter and mild-to-moderate cerebral atrophy without cortical involvement. Progressive dementia with motor neuron disease (MND) was diagnosed using the criteria of Mitsuyama et al. (*11*). Other diseases were diagnosed using the criteria of the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*.

The control group was comprised of 14 subjects with no dementia (age 36–77 yr, mean 62 yr). Neuropsychological tests were performed in all demented patients and Parkinson's disease patients using Hasegawa's dementia score as a measure of disease severity. All patients with Parkinson's disease were judged to have no dementia by HDS. Severity of memory disturbance was measured with the Wecher memory scale-revised index scores.

SPECT Imaging Protocol

SPECT imaging was done after injection of 1110 MBq ^{99m}Tc-HMPAO using triple-headed rotating gamma cameras (PRISM 3000, Picker and GCA 9300, Toshiba) with ultra high-resolution fan-beam collimators that permit a spatial resolution of 9 mm (PRISM 3000) and 8 mm (GCA 9300) FWHM. Data were acquired from 5 min after intravenous injection of ^{99m}Tc-HMPAO to 20 min after injection. Transaxial, sagittal, coronal and hippocampal plane (HP) images were reconstructed by filtered backprojection using Butterworth and ramp filters (cut-off frequency 0.199 cycle/cm) with attenuation correction (Chan, 0.09 cm^{-1}) and Lassen's linearization (alpha value = 1.5, reference region; cerebellum, 50 ml/min/100 g). Matrix size and slice thickness of SPECT samples were 128 × 128 mm and 6.8 mm, respectively. The hippocampal plane images were reconstructed at 30° extensions to the orbitmeatal line (Fig. 1) because this angle provides a plane parallel to the hippocampus, as observed in MRI studies with 10 volunteers. A semiquantitative method of assessing regional variation was used; regional tracer uptake was measured in rectangular (10 mm × 20 mm) regions of interest (ROIs) over right and left hippocampus and parietal and cerebellar cortical regions. Tracer uptake was expressed as the lesion-to-cerebellum ratio. The ROIs for hippocampus were set on the HP scan and those for parietal cortices and cerebellum were set on transaxial scan (Fig. 2).

Statistical Analysis

Statistical analyses were carried out by one-way analysis of variance and simple regression model. Results were expressed as mean (1 s.d.). Multiple comparisons between control group and groups with neuropsychiatric disease were tested with Bonferroni/Dunn test. These analyses were carried out using the Stat View 4.02 Macintosh program (Abacus Concepts, Inc.).

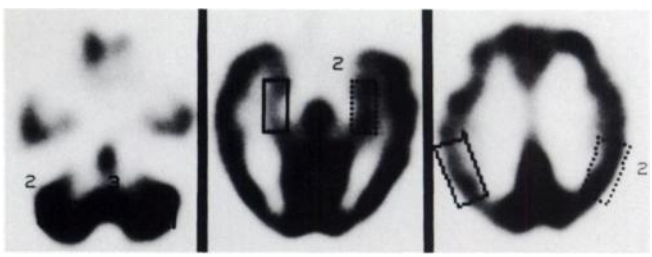

FIGURE 2. ROI setting for cerebellum, hippocampus and parietal cortices on SPECT images.

TABLE 2
Lesion-to-Cerebellum Ratio of Controls and Neuropsychiatric Patients

Lesion	Diagnostic category					
	Control (n = 14)	DAT (n = 13)	MID (n = 6)	PD with MND (n = 4)	TGA (n = 3)	Nondemented (n = 5)
Hippocampus						
Right	0.76/0.04†,‡,§	0.54/0.12*,**	0.52/0.11*,**	0.56/0.09*,**	0.70/0.04	0.79/0.11†,‡,§
Left	0.77/0.04†,‡,§,¶	0.57/0.16*,**	0.51/0.09*,**	0.60/0.07*,**	0.57/0.07*,**	0.80/0.12
Parietal cortex						
Right	0.96/0.08†,‡	0.69/0.12*,§,¶,**	0.74/0.05*,**	0.92/0.10†	0.93/0.08†	0.88/0.13†,‡
Left	0.95/0.09†,‡	0.72/0.10*,§,**	0.75/0.11*	0.92/0.07†	0.87/0.11	0.93/0.19†

DAT = dementia of Alzheimer type; MID = multi-infarct dementia; PD with MND = progressive dementia with motor neuron disease; TGA = transient global amnesia.

* Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with controls.

† Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with DAT.

‡ Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with MID.

§ Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with PD with MND.

¶ Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with TGA.

** Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with non-demented disease.

RESULTS

Lesion-to-Cerebellum Ratios for Nondemented Controls

Table 2 summarizes the results of lesion-to-cerebellum ratio in control subjects and those with neuropsychiatric disease. In nondemented control subjects, the mean lesion-to-cerebellum ratios were 0.76/0.04 on the right hippocampus, 0.77/0.04 on the left hippocampus, 0.96/0.08 on the right parietal cortex and 0.95/0.09 on the left parietal cortex. The lesion-to-cerebellum ratios on the hippocampus were lower than those on the parietal cortex. Figure 3 shows the correlation between hippocampal lesion-to-cerebellum ratios and age. The correlation coefficients were $r = -0.47$ (n.s.) in the right hippocampus and -0.45 (n.s.) in the left hippocampus.

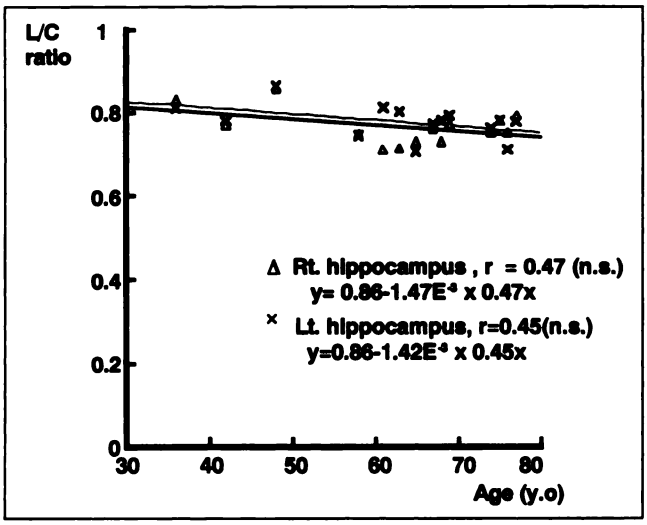

FIGURE 3. Correlation between age and lesion-to-cerebellum ratios in the hippocampus of control subjects.

Lesion-to-Cerebellum Ratios for Dementia and Neuropsychiatric Diseases

Table 2 presents the lesion-to-cerebellum ratios in patients with neuropsychiatric diseases. The lesion-to-cerebellum ratios of dementia of Alzheimer type patients were significantly lower than those of nondemented controls and patients with other diseases in the bilateral hippocampus and parietal cortices ($p < 0.005$). The lesion-to-cerebellum ratios of multi-infarct dementia patients were significantly lower than those of controls and patients with other diseases in the bilateral hippocampus ($p < 0.005$) and signif-

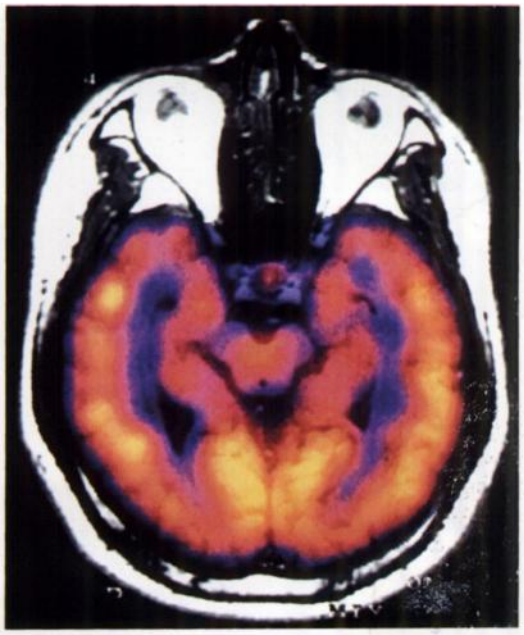

FIGURE 4. Superimposed SPECT image of normal control (37-yr-old man). The hippocampus is demonstrated as a large structure surrounding the midbrain on HP image.

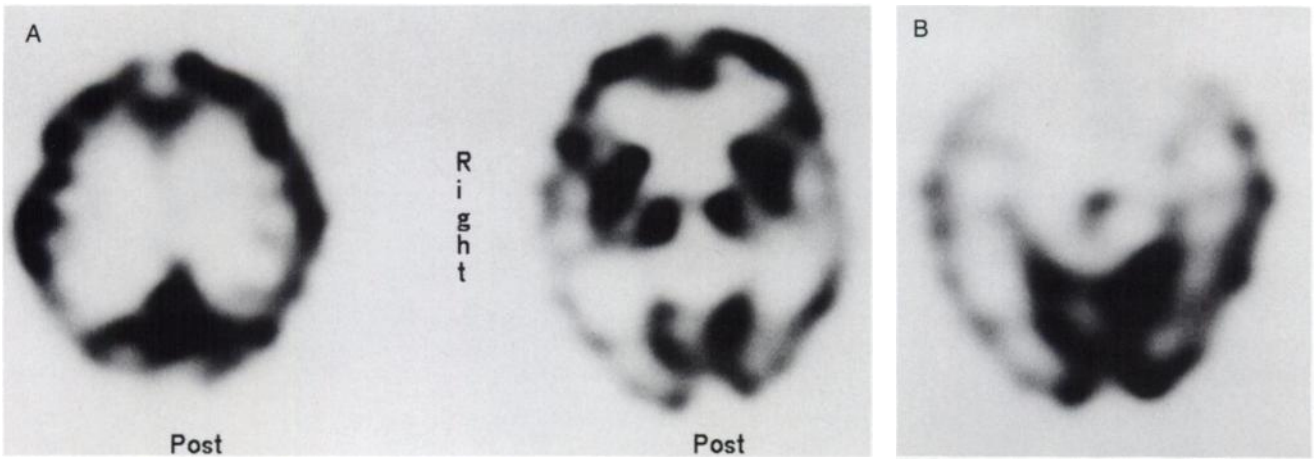

FIGURE 5. (A) Transaxial SPECT image demonstrates typical rCBF pattern of bilateral temporal and parietal hypoperfusion in a woman with dementia of Alzheimer type who had memory disturbance and visuospatial disorientation. (B) Hippocampal SPECT image demonstrates bilateral hippocampal hypoperfusion in the same patient.

icantly lower than those of control subjects in the bilateral parietal cortices ($p < 0.005$). In patients with progressive dementia with MND, lesion-to-cerebellum ratios in the parietal cortex did not differ from those of control subjects, and lesion-to-cerebellum ratios in the hippocampus were significantly lower than those of control subjects. No significant differences were observed between each group of demented patients in the bilateral hippocampus. The lesion-to-cerebellum ratios of nondemented neuropsychiatric patients did not differ from those of nondemented controls. The lesion-to-cerebellum ratios of patients with transient global amnesia (TGA), however, were significantly lower than those of control subjects in the left hippocampus. The SPECT images in nondemented control subjects did not demonstrate hypoperfusion in the hippocampus (Fig. 4) but those in patients with dementia of Alzheimer type, multi-infarct dementia and transient global amnesia did demonstrate hypoperfusion in the hippocampus (Fig. 5–7).

Lesion-to-Cerebellum Ratios of Hippocampus versus Those of Parietal Cortex in Dementia of Alzheimer Type

The relationship between lesion-to-cerebellum ratios of hippocampus and those of parietal cortices is shown in Figure 8. The lower limits of control were defined as mean lesion-to-cerebellum ratio of control minus 2 s.d. (right hippocampus 0.68, left hippocampus 0.69, right parietal 0.80, left parietal 0.77). In 13 dementia of Alzheimer type patients, 3 right lesion-to-cerebellum ratios and 4 left lesion-to-cerebellum ratios of parietal cortices were higher than the lower limit of control. In contrast, 2 lesion-to-cerebellum ratios of hippocampus were higher than the lower limit of control.

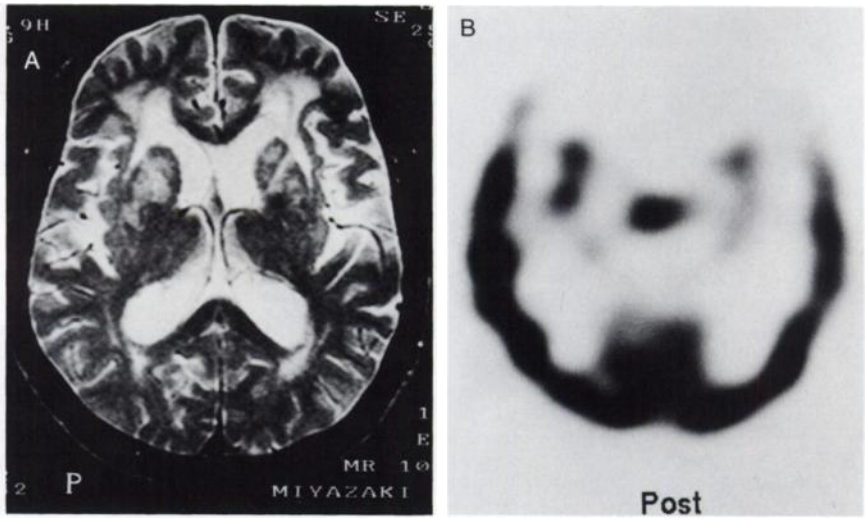

FIGURE 6. (A) T2-weighted MR image shows multiple lacunar infarctions in the basal ganglia and white matter of a 67-yr-old man with multi-infarct dementia. (B) Hippocampal SPECT image demonstrating bilateral hippocampal hypoperfusion in the same patient.

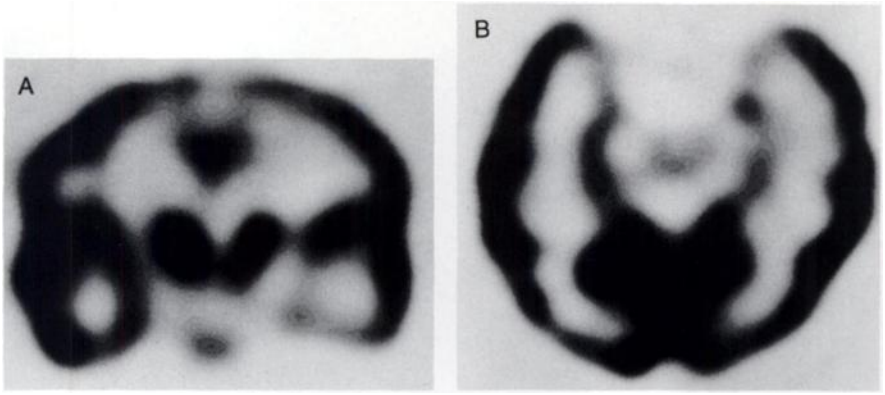

FIGURE 7. (A) Coronal SPECT image demonstrates left medial temporal hypoperfusion in a 35-yr-old man with transient global amnesia. (B) Hippocampal SPECT image shows left hippocampal hypoperfusion in the same patient.

Relationship between HDS and Lesion-to-Cerebellum Ratio

Significant correlations ($p < 0.01$) were observed between decreasing Hasegawa's dementia score and decreasing lesion-to-cerebellum ratios in bilateral hippocampus for neuropsychiatric patients (right hippocampus, $r = 0.85$; left hippocampus, $r = 0.81$) (Fig. 9A). In contrast, no significant correlations were found between decreasing Hasegawa's dementia score and decreasing lesion-to-cerebellum ratios in bilateral parietal cortices for these patients (right parietal, $r = 0.59$; left parietal, $r = 0.61$) (Fig. 9B).

Relationship between Severity of Memory Disturbance and Lesion-to-Cerebellum Ratio

Lesion-to-cerebellum ratios in patients with mild memory disturbance were significantly lower than those in patients without memory disturbance in the right hippocampus ($p < 0.005$) (Table 3). The lesion-to-cerebellum ratios in patients with moderate or severe memory disturbance were significantly lower than those in patients without memory disturbance in the bilateral hippocampus ($p < 0.005$). In addition, the lesion-to-cerebellum ratios in patients with severe memory disturbance were significantly lower than those in patients with mild or moderate memory disturbance in the bilateral hippocampus ($p < 0.005$). In parietal cortices, the lesion-to-cerebellum ratios in patients having moderate or severe memory disturbance were significantly lower than those in patients without memory disturbance ($p < 0.005$). Thus, the lesion-to-cerebellum ratios of the hippocampus were more reflective of the severity of memory disturbance than those of the parietal cortex.

DISCUSSION

The hypoperfusion and hypometabolism of parietal cortex that were observed in PET and SPECT studies have been said to be the most sensitive and characteristic markers in diagnosing dementia of Alzheimer type (*1–4*). The earliest and most characteristic clinical manifestation in dementia of Alzheimer type patients is memory disturbance since hippocampal formation and the associated limbic system play an important role in memory processing (*5*). We theorize that the easily detectable rCBF change may be observed earliest in the hippocampus.

In our previous study, we did not evaluate the medial temporal lobe because of its poor spatial resolution. The coronal scan was used because it is better for evaluating the medial temporal region than the usual transaxial scan. A structure of interest can be reconstructed adequately

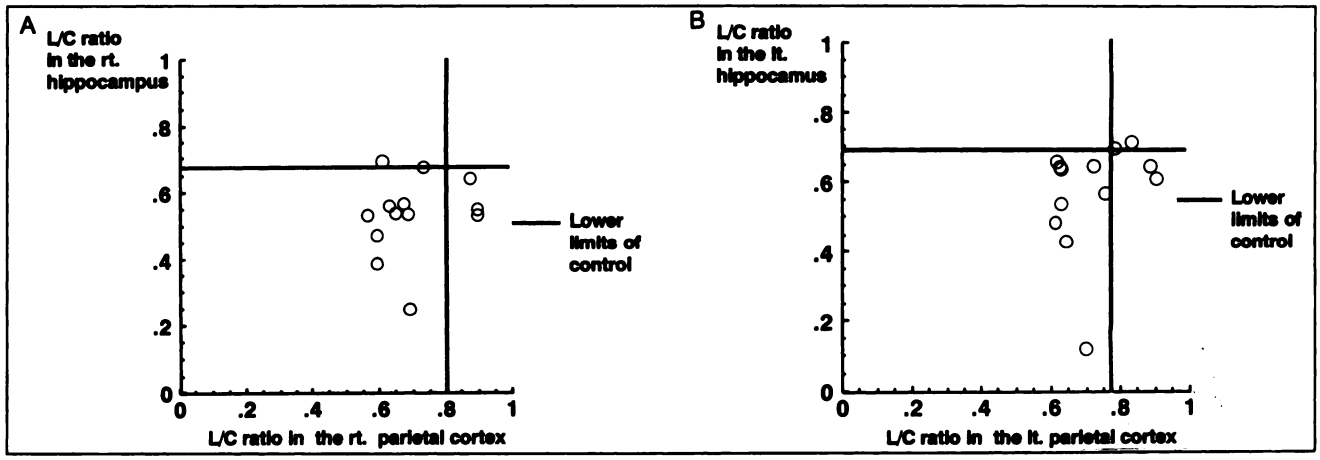

FIGURE 8. Relationship between the lesion-to-cerebellum ratios of (A) right hippocampus and right parietal cortex and (B) left hippocampus and left parietal cortex.

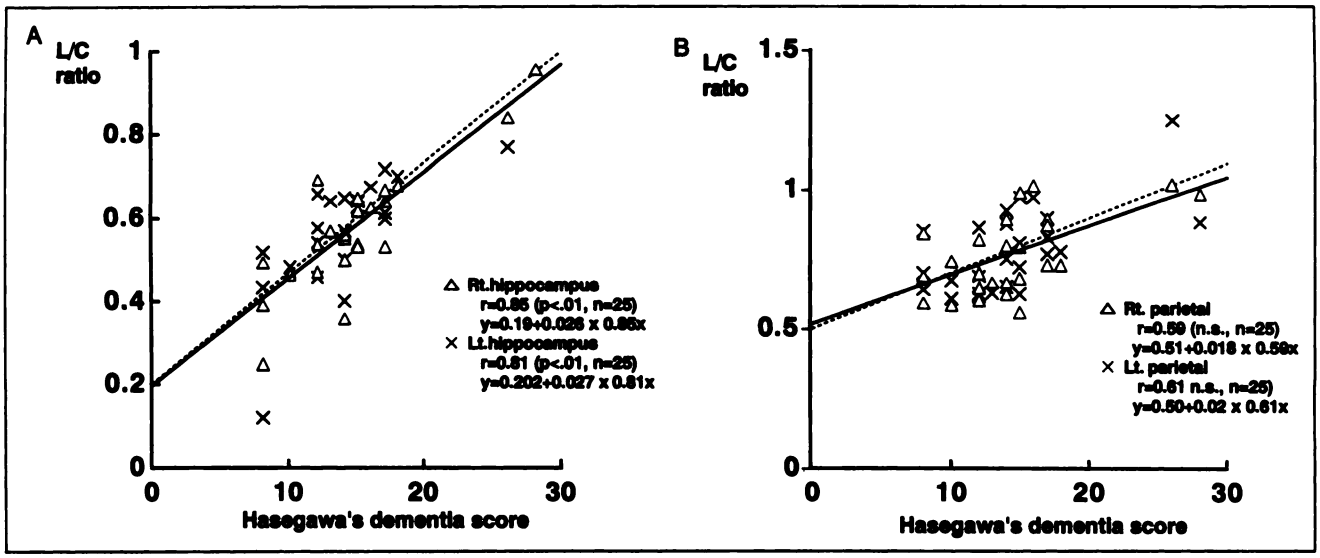

FIGURE 9. Correlation between Hasegawa's dementia score and lesion-to-cerebellum ratios of (A) hippocampus and (B) parietal cortices.

only if its size is greater than 2 × FWHM. Since the hippocampus matrices demonstrated on coronal scan were too small for uptake measurement we used hippocampal plane images to evaluate hippocampal uptake. As the hippocampus in normal controls appears as a large structure on hippocampal plane images, we believe the hippocampal plane image may be useful in evaluating the hippocampus on SPECT imaging.

In this study we found that aging had no effect on hippocampal perfusion in normal control subjects and hippocampal perfusion in dementia of Alzheimer type patients was significantly lower than that of control and nondemented neuropsychiatric patients. Hippocampal hypoperfusion was a more sensitive marker than parietal hypoperfusion in diagnosing dementia of Alzheimer type. A recent study demonstrated that neurofibrillary tangles accumulate preferentially in ventromedial temporal lobe structures in the early stages of Alzheimer's disease and contribute to early memory impairment, and patients with longer duration of disease had neurofibrillary tangles in neocortical association areas as well as in the medial temporal lobe (*7*). These results support our theory.

Recent quantitative assessment of the hippocampal region using MR imaging reported by Ikeda et al. showed hippocampal atrophy in patients with early-stage Alzheimer's disease (*12*). Since we did not preform correction for atrophy in this study may prove be a potential pitfall because reduced uptake of tracer in the hippocampus can be caused by partial volume effect due to atrophy. We think that hippocampal atrophy and hippocampal hypoperfusion may contribute to reduced uptake in the hippocampus. In our study, hippocampal hypoperfusion reflected the severity of dementia and memory disturbance. Ikeda et al. reported that quantitative assessment of hippocampal atrophy can distinguish normal-aged people from possible Alzheimer's patients but it cannot classify dementia of Alzheimer type according to its severity (*12*), suggesting that hippocampal atrophy occurs in early-stage dementia of Alzheimer type but does not reflect disease severity. This is the main difference between the results of volumetric

TABLE 3
Relationship between Memory Disturbance and Lesion-to-Cerebellum Ratios

	Memory		Disturbance	
Legions	None (n = 19)	Mild (n = 4)	Moderate (n = 13)	Severe (n = 9)
Right hippocampus	0.77/0.06[†,‡,§]	0.66/0.02[*,‡,§]	0.60/0.07[*,†,‡]	0.44/0.09[*,†,‡]
Left hippocampus	0.78/0.07[‡,§]	0.67/0.05[‡,§]	0.61/0.06[*,§]	0.44/0.13[*,†,‡]
Right parietal cortex	0.94/0.09[‡,§]	0.84/0.14	0.78/0.15[*]	0.71/0.09[*]
Left parietal cortex	0.95/0.12[‡,§]	0.84/0.10	0.78/0.13[*]	0.71/0.10[*]

[*] Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with None.
[†] Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with Mild.
[‡] Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with Moderate.
[§] Bonferroni/Dunn test for multiple comparison, $p < 0.005$ compared with Severe.

studies using MRI and those from our SPECT study, which suggest that reduced tracer uptake in the hippocampus may reflect hypoperfusion in addition to atrophy. Hippocampal hypoperfusion was observed not only in dementia of Alzheimer type patients but also in other patients with memory disorder. We think it is not a specific finding in dementia of Alzheimer type but points to the presence of memory disturbance in general. Cognitive studies of amnesia patients provides useful information about the functional organization of normal memory since no anatomical tract or structure disturbance can be attributed to memory disturbance in clinical patients. The rCBF image using high-resolution SPECT permits visualization of the hippocampal formation, revealing hypoperfusion in patients with memory disturbance.

CONCLUSION

The rCBF high-resolution SPECT system can demonstrate hippocampal perfusion. In patients with memory disturbance, hypoperfusion was noted that correlates with the severity of dementia and memory disturbance. We believe this technique may be useful in assessing the extent of dementia and memory disturbance in patients suffering from these ailments.

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