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Summary

The relationship between atrophy of the hippocampus including the parahippocampal gyrus (the hippocampal area) and cerebral metabolic rate for glucose was investigated in dementia patients. The hippocampal area was evaluated using T1-weighted magnetic resonance images, and the cerebral metabolic rate for glucose was measured by positron emission tomography and the FDG (^{18}F -fluoro-deoxy-glucose) technique. We found that there were irreversible correlations between the hippocampal area and the cortical glucose metabolic rate, especially in the temporal and temporo-parietal regions in vascular dementia, and in the temporal, temporo-parietal region, and frontal lobe in senile dementia of Alzheimer's type. Neural networks between the hippocampus and such cortical regions were considered to be important in dementia.

Introduction

Neuroimaging studies on dementia have been mainly of two types, morphological studies employing CT or MRI (magnetic resonance imaging) and studies based on cerebral circulation and metabolism utilizing SPECT (single photon emission CT) or PET (positron emission tomography). Morphologically, previous studies have mainly yielded the following findings: 1) VD (vascular dementia), AD (Alzheimer's disease) and SDAT (senile dementia of Alzheimer's type) patients showed greater brain atrophy as compared with aged normal people¹⁻³): including cortical atrophy and ventricular enlargement. 2) The temporal lobe, especially the hippocampus, showed atrophy in VD as well as in SDAT (AD)⁴⁻⁹). 3) White matter changes, PVL (periventricular lucency) on CT or PVH (periventricular-hyperintensity) on T2-weighted MRI, were more prone to be severe in VD than in SDAT and normal patients¹⁰⁻¹²). 4) VD patients had cerebral infarctions etiologically in various regions.

Concerning neuroimaging studies based on cerebral circulation and metabolism (function), the following findings have been noted: 1) CBF (cerebral blood flow) and CMRO₂ (cerebral metabolic rate for oxygen) were more decreased in AD than in normal controls, especially in the temporal lobe and the temporo-parieto occipital region¹³⁻¹⁵. 2) CMRGlc (cerebral metabolic rate for glucose) of SDAT (AD) was also decreased in those areas, and decreased CMRGlc in the right and left temporo-parietal regions was associated with deteriorated visuospatial and verbal functions as shown by WAIS (Wechsler Adult Intelligence Scale), respectively¹⁶⁻¹⁹. 3) Cortical CMRGlc of VD was also lower than that of normal subjects²⁰, was associated with mental deterioration, and was characterized by more individuality in metabolic pattern²¹

In view of the relationship between morphological changes and metabolism, CMRGlc of AD with or without white matter lesions was investigated in a previous study in which it was found that the AD with white matter lesions showed elevated cerebellar CMRGlc compared with that of AD without such changes²²

Jobst et al. studied the relationship between an atrophy of the hippocamps shown by CT and cerebral blood flow shown by SPECT in SDAT patients²³. But there has been no study of the relationship between atrophy of the hippocamps and cerebral glucose metabolism, although both were found to be important in dementia. In this study, we examined VD as well as SDAT patients using MRI and PET with the FDG (¹⁸F-fluoro-deoxy-glucose) technique and investigated such correlation.

Subject and Methods

SUBJECTS

10 normal elderly people, 10 VD patients, and 10 SDAT patients were studied. The normal group consisted of 5 males and 5 females (age ranged from 68 to 78 years, mean age 73 years) the VD group consisted of 5 males and 5 females (age ranged from 70 to 79 years, mean age 75 years) and the SDAT group consisted of 5 males and 5 females (age ranged from 70 to 76 years, mean age 72 years). There was no statistical difference in the mean age among the groups.

The ten normal subjects underwent a medical interview, physical and neurological examinations, laboratory tests, ECG, and brain CT scanning. They displayed no mental deterioration or cognitive impairment based on clinical observation, no risk factors for cerebrovascular disease such as hypertension except for past smoking histories and no history of head injury or any other serious non-central nervous system disorders that could affect brain function. The brain CT findings were normal or age-related minimal changes.

The dementia patients were diagnosed as suffering from VD or SDAT based on the following criteria (Ministry of Education, Culture and Science of Japan, Meeting on Dementia, 1986): they were all diagnosed by a psychiatrist as suffering from dementia by

DSM-III R (American Psychiatric Association, 1987); the clinical course of VD patients showed a stepwise progression and/or focal neurological signs, while that of SDAT patients showed slowly progressive course to cognitive impairment and no focal neurological signs; Hachinski ischemic scores²⁴⁾ of VD patients were 7 points or more, and those of SDAT patients were 3 points or less; the brain CT findings of VD patients showed lacunar infarction and/or periventricular lucency (PVL), and those of SDAT patients revealed brain atrophy with no cerebrovascular disease nor PVL. All the patients were studied within 3 years of onset of symptoms and showed moderate severity of dementia. All the patients could walk by themselves and could communicate linguistically and tolerate PET examinations.

The clinical characteristics of the study population are shown in Table 1.

This study was approved by the Medical Ethics Committee of Tohoku University School of Medicine, and informed consent was received from all the subjects and their families.

METHODS

The MRI used was MRWectra (Yokogawa, Japan), which has a resistive magnet operating at 0.5 Tesla. T1-weighted images (TR/TE 160/15) were used for evaluation of atrophy of the hippocampus and parahippocampal gyrus. (We defined these areas as the hippocampal area). The actual images used in this study were obtained as follows: firstly, a sagittal slice through the midpoint of the eye was obtained; secondly, a slice parallel to the hippocampus was scanned; then planes perpendicular to the plane parallel to the hippocampus were obtained (the coronal slices).

The T1-weighted images of this coronal slice were input into the computer system which enlarged them about two times, and using a digitizer system, the hippocampal area was traced manually. This process is demonstrated in Fig.1. Similarly, the temporal area was measured using the same coronal plane. Using the horizontal planes OM (orbitomeatal)+50 mm and OM+70 mm, the brain area and the area of the skull cavity were also evaluated. The percentages 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 volume %) were calculated. The measurements were performed by a neuroradiologist independent of the study who did not know the PET findings, and the average values of two measurements were used.

The FDG technique was used to measure cerebral glucose metabolism. Transmission scan was not performed since patients in this study could not tolerate lengthy examination. CMRGlc was calculated according to the method of Phelps et al.²⁵⁾. The lumped constant used was 0.42. Two emission scans were performed 40-60 min. after injection of 5-12 mCi FDG. One scan consisted of seven slices, each slice being 7 mm in thickness with 1-mm gaps between the slices. One scan was done at OM+30 mm and the

other at OM+77 mm. The PET machine used was a PT 931-04 (CTI inc., USA), which has a resolution of 7 and 8 mm (FWHM) in the transaxial and axial planes, respectively .

The subjects were placed supine on the scanner bed with their eyes covered with patches. Head movements were monitored using a video sensor with an alarm system and corrected manually as necessary. Serial blood samples were obtained through a radial artery cannula, enabling reliable measurement of arterial isotope activity.

Regional values of CMRGlc (rCMRGlc) were obtained for regions of interest (ROI) from the tomographic images on the computer screen. The actual images used for ROI selection were OM+21 mm, OM+30 mm, OM+39 mm, OM+50 mm, OM+59 mm, OM+68 mm, OM+95 mm, and OM+104 mm. The rCMRGlc in the following bilateral regions were measured: upper frontal, anterior frontal, inferior frontal parietal, temporo-parieto-occipital, occipital, visual, primary auditory (Heschel), inferior temporal, basal ganglia, cerebellum, and the white matter (foramen centrum semiovale). The average value of the entire grey matter CMRGlc was calculated.

Statistical analysis was performed using one-way analysis of variance (oneway ANOVA) and Pearson's correlation coefficients.

Results

The hippocampal area % of the normal, the VD, and the SDAT groups were 5.5 %, 3.7 %, and 3.4 % and those of the VD and the SDAT groups were significantly lower than that of the normal group ($p < 0.01$). The brain volume % and the temporal area % of each group were also evaluated and those of the VD and the SDAT groups were found to be significantly lower than that of the normal group (data not shown).

The relationship between the brain volume % and the average value of the cortical CMRGlc of the VD and the SDAT groups are shown in Fig. 2: there were no significant correlations.

The relationship between the temporal area % and the average value of the cortical CMRGlc of the VD and the SDAT groups are presented in Fig. 3: there were no significant relationships.

The correlation between the hippocampal area % and the average value of the cortical CMRGlc of the VD and the SDAT groups are shown in Fig. 4. A significant correlation ($p < 0.05$) was found in each group.

Fig. 5 shows the relationship between the hippocampal area % and the regional CMRGlc in each group. As for the VD, the rCMRGlc of the temporal lobe and that of the temporo-parieto-occipital region were irreversibly correlated with the hippocampal area % ($p < 0.05$). As for the SDAT, the rCMRGlc values of the temporal lobe, the temporo-parieto-occipital region, and the frontal lobe were irreversibly correlated ($p < 0.05$).

Discussion

In this study, we examined dementia patients using MRI and PET and found that the hippocampal area was irreversibly correlated with the average value of CMRGlc of the cortex. As for regional metabolism, that of the temporal lobe and that of the temporo-parieto-occipital region were correlated in the VD patients, and those of the frontal lobe, temporal lobe, and temporo-parieto-occipital region were correlated in the SDAT patients.

Regarding methodology, we performed tracing technique of the hippocampus and parahippocampal gyrus on the computer screen which enlarged the MRI images. Jack Jr CR. et al.²⁶⁾ compared three different techniques for MRI based volume measurements of the hippocampus, i.e., tracing, thresholding, and random marking. Their findings were as follows: accuracy and reproducibility were best for the thresholding technique; however, the tracing technique was more accurate, especially for the smaller cylinders than the random marking technique. They concluded that the tracing-thresholding method for MRI based volume measurement was the best technique. Because the MRI used in this study did not allow use of the thresholding technique, we used the tracing method. Although the results of the method may possibly have been affected by observer perception of object boundary, experience, knowledge of relevant anatomy, skill and experience with measurement software, and complexity of object boundary, as pointed out by Jack Jr CR. et al.²⁶⁾, measurement in this study was performed by neuroradiologist independent of this study who was not familiar with the PET findings, and the average values of two measurements were used.

As for the measurement of CMRGlc, we employed the calculation method of Phelps et al.²⁵⁾ without transmission scan, since dementia patients cannot tolerate lengthy examination. Bone thickness of the scalp, greater in males than in females, affects CMRGlc in this method. However, such effect could be neglected because there was no gender difference in the sample number in this study.

The importance of the hippocampus for memory has been pointed out in previous neuropsychological studies²⁷⁻²⁹⁾ as well as in animal experiments³⁰⁻³²⁾. According to these studies, the hippocampal, perirhinal, and parahippocampal gyri were important for short-term memory and consolidation of short-term memory to long-term memory^{33,34)}. Dementia is a clinical syndrome based on a memory impairment, and the hippocampus including the parahippocampal gyrus measured in this study is important. Jack Jr CR. et al.⁸⁾ reported MR-based hippocampal volumetry using the tracing-threshold technique, and demonstrated that AD had a smaller volume than normal.

Neuropathologically, neuronal cell loss, neurofibrillary tangles, senile plaques, and granulovacuolar degeneration were especially found in the hippocampus and the parahippocampal gyrus in aging and AD; such changes of AD were more severe than those of normal aged people³⁵⁻³⁷⁾.

While the reason for atrophy of the hippocampal area in our SDAT subjects was degeneration as the case in AD, the reason for atrophy of the hippocampal area of the VD is unclear. The VD patients studied in this study were all lacunar-type without large infarctions in the cortices. Previous studies^{38,39)} showed that the hippocampal area is easily vulnerable to ischemic changes in the brain. Therefore, it is probable that ischemic changes which occur in VD brains with lacunar infarctions are considerable and affect the hippocampal areas, resulting in atrophy.

As for the result that the hippocampal area % of the VD as well as that of the SDAT were irreversibly correlated with the cortical CMRGlc, especially the rCMRGlc in the temporal, temporo-parieto-occipital, and the frontal (only SDAT significant) lobe, it suggested that the neural networks between the hippocampal area and these regions were important in dementia.

Neuropathologically, neural connections between the hippocampus and the cortices (primary, primary association, secondary association) via the perirhinal and parahippocampal gyri have been reported⁴⁰⁻⁴¹⁾. Although further study is needed, we consider these neural networks to be important for memory and in the pathogenesis of dementia.

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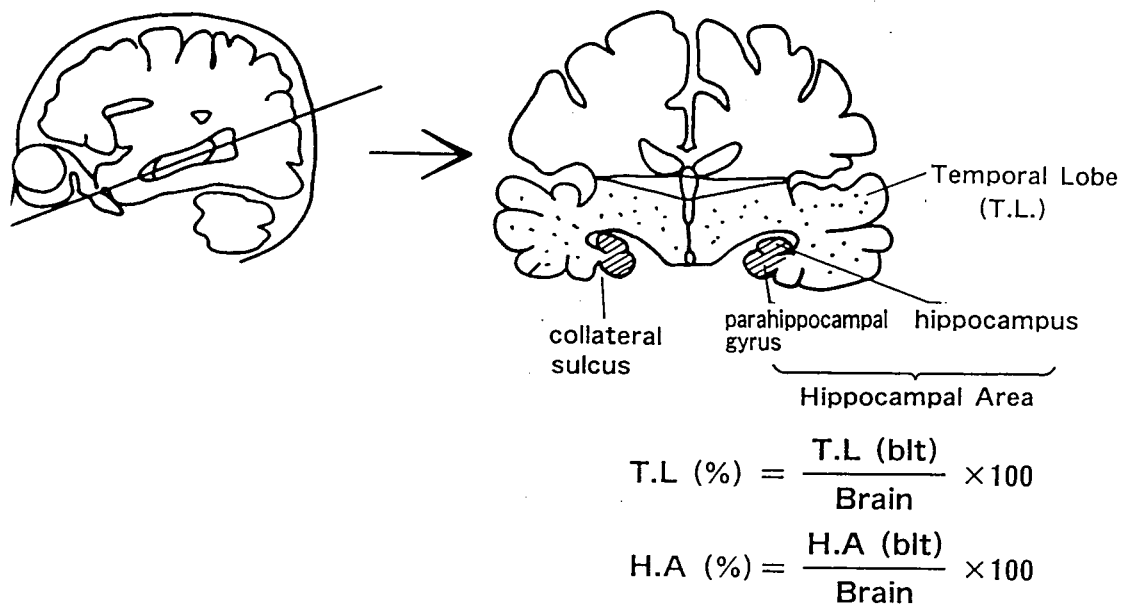


Fig. 1. Hippocampal Area (%) and Temporal Lobe (%).

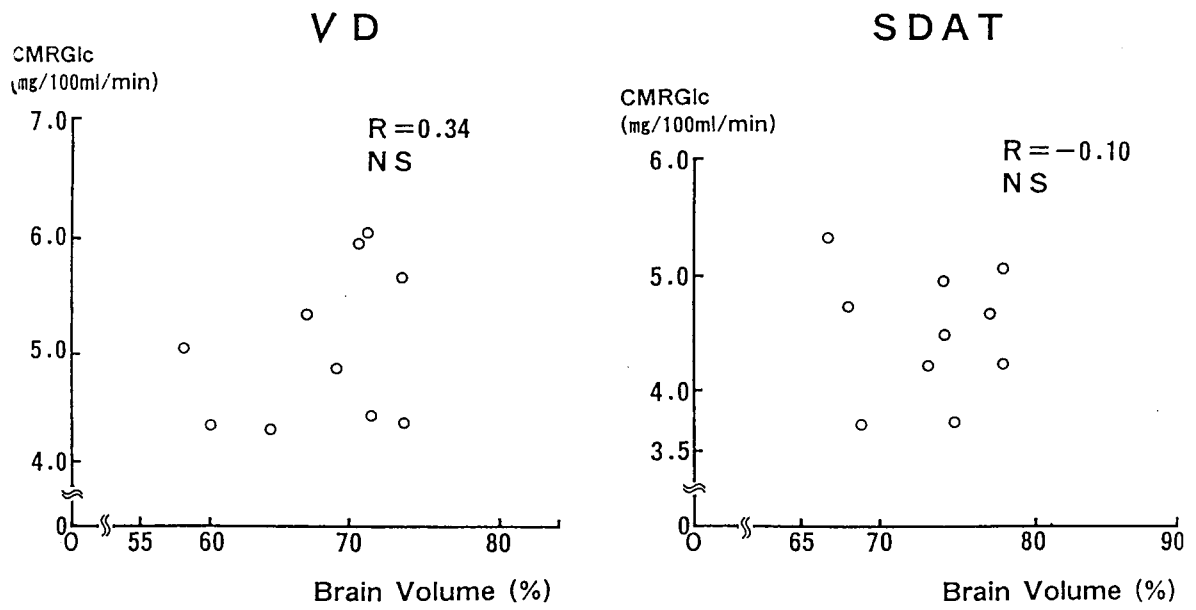


Fig. 2. Correlation between Brain Volume and Cortical CMRGlc.

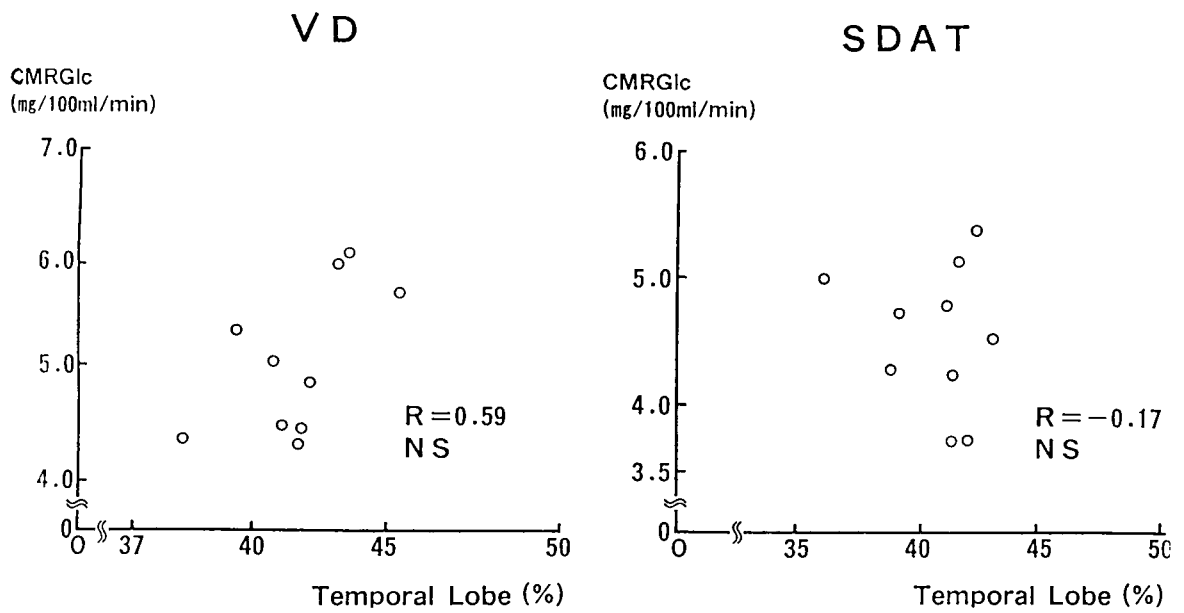


Fig. 3. Correlation between Temporal atrophy and Cortical CMRGlc.

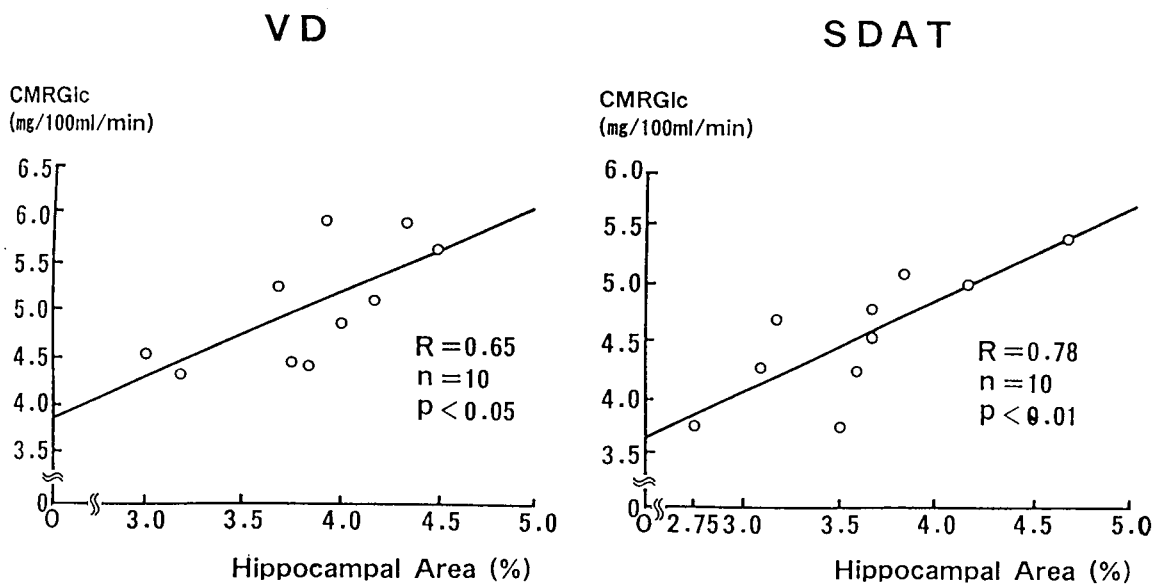


Fig. 4. Correlation between Hippocampal Atrophy and Cortical CMRGlc.

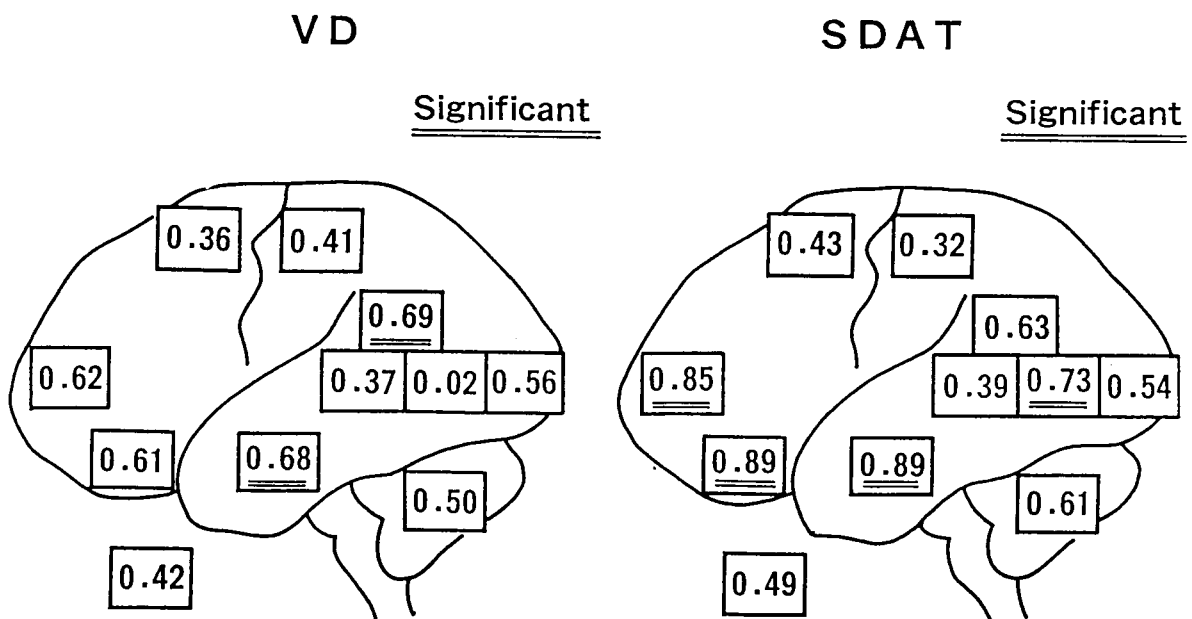


Fig. 5. Correlation Coefficients between Hippocampal Atrophy and rCMRGlc.