SHORT REPORT

Tc-99m HMPAO SPECT in the evaluation of Alzheimer's disease: correlation between neuropsychiatric evaluation and CBF images

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Abstract

The purpose of this study was to evaluate the effects of various covariants on the distribution pattern of Tc-99m HMPAO in patients with Alzheimer's disease by correlation analysis. Twenty patients with Alzheimer's disease and 15 age matched normal subjects participated. Tc-99m HMPAO brain SPECT and *x* ray computed tomography (CT) were acquired for each subject. SPECT images were transformed to a standard size and shape by automated image registration (AIR) and were used for group comparison by means of SPM96. Voxel based covariance analysis was performed on standardised images taking the age of patients, severity of disease (clinical dementia rating scale, mini mental state examination, physical self maintenance scale), and atrophy indices as variables. There was significantly decreased regional cerebral blood flow (rCBF) in the frontal, parietal, and temporal regions in the patient group ($p<0.001$), more marked in those patients having severe dementia. Covariance analysis disclosed that aging and severity of disease have a pronounced effect on rCBF, especially that of the left parietal region.

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Single photon emission computerised tomography (SPECT) is being widely used for cerebral blood flow (CBF) studies. These studies provide unique information for the identification of functional abnormalities relevant to Alzheimer's disease.[1–3] The appearance of SPECT CBF images in patients with Alzheimer's disease is dependent on complex interactions of influencing factors that include age of the patient, severity and duration of disease, and brain atrophy in addition to variation due to methodology and instrumentation. Effects of these variables have not been objectively evaluated. We have considered this issue by using the concept of group statistics with the help of an image registration technique.

There are various techniques available for image registration and standardisation. Automated image registration (AIR, version 3.0) is a program, recently developed by Woods *et al*,[4 5] which standardises any brain image with respect to another specified reference image using linear and non-linear models. It has been validated for various types of registrations, including intersubject transformation of brain SPECT images.[6]

In the present study we used AIR to standardise the size and shape of individual brain SPECT images of patients with Alzheimer's disease and age matched normal subjects. Arithmetic and statistical calculations were performed on voxel based values of individual images, and these were used to generate three dimensional group mean images for further analyses. Effects of atrophy, age of individual patients, and severity of disease were evaluated by variance analysis.

Patients' group profiles

Patients	*Age*	*MMS*	*CDR*	*PSMS*	*Brain atrophy index*
All (n=20)	71.1 (7.4)	17.8 (5.3)	1-3	0-6	0.904 (0.042)
Group A (n=7)	73.3 (7.9)	12.3 (5.6)	2-3	0-4	0.891 (0.048)
Group B (n=13)	69.8 (7.2)	20.7 (1.3)	1	4-6	0.911 (0.038)

MMSE=Mini mental state examination, CDR=clinical dementia rating scale. PSMS=physical self maintenance scale. Values are mean (SD).

Materials and methods

SUBJECTS

All the procedures were approved by the ethics committee for clinical research of Tohoku University. A total of 20 patients with Alzheimer's disease (age 71.1 (SD 7.4) detailed profiles listed in the table) and 15 normal subjects (age 70.2 (SD 8.4) participated in the study. All the subjects were right handed as assessed by the Hatla Nakata handedness inventory. Written informed consent was obtained in all cases according to the declaration of human rights of Helsinki 1975.

None of the control subjects had a lifetime history of any psychiatric disorders, including drug misuse. Their medical histories and physical examinations did not disclose any signs or symptoms that could effect CBF stud-

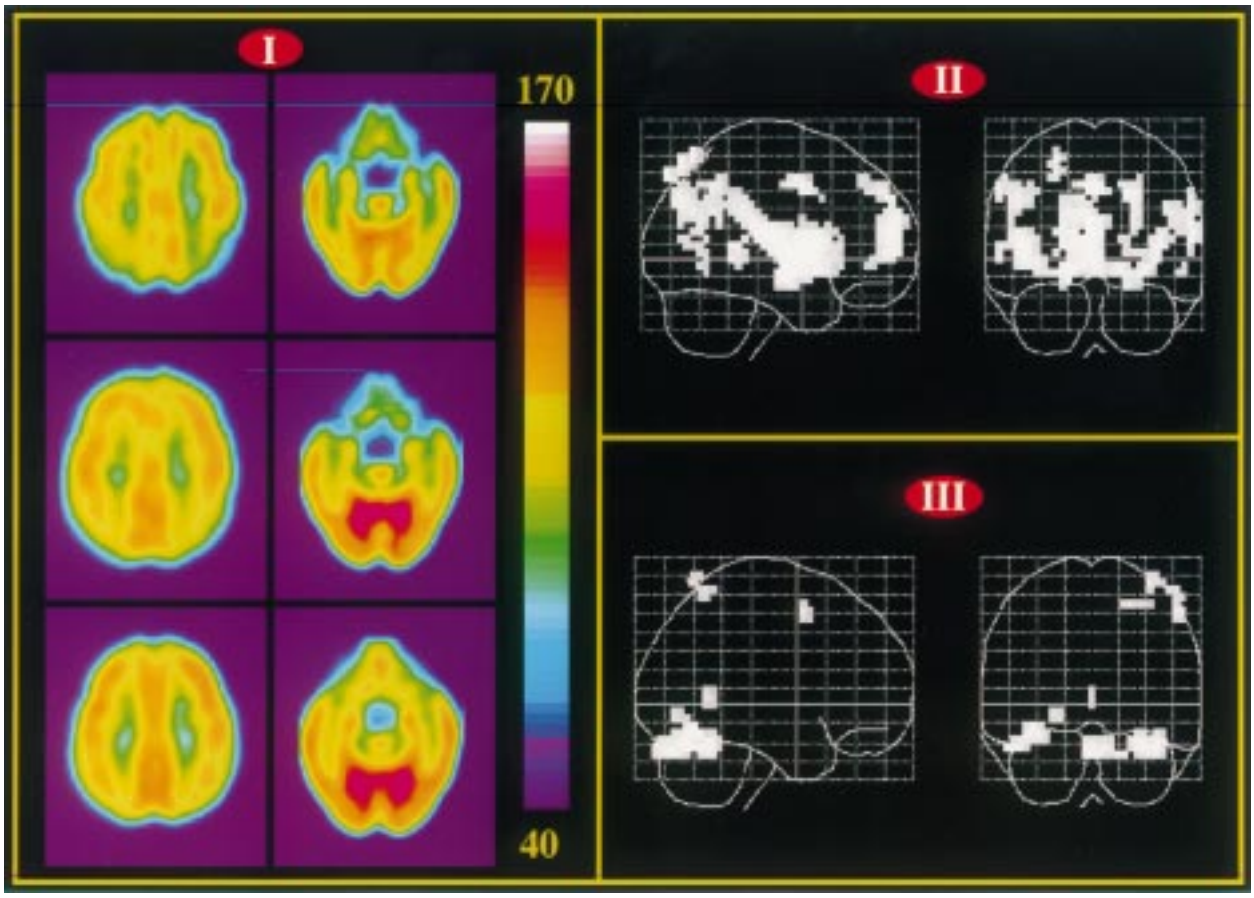

Figure 1 (I) Group mean Tc-99m HMPAO SPECT images of Alzheimer's patients and normal subjects. The mean global value is 100 counts/pixel. Transverse slices are with reference to the Telairach grid and parallel to intercommissural line. The anterior represents the top of the image and the subject's right is on the left. Top row shows mean images of group A patients with severe dementia, middle row shows mean images of group B patients with early and mild dementia, and the bottom row shows mean images of normal controls. (II) z map (mean image of normal subjects−mean image of patients with Alzheimer's disease) displayed on a glass brain. Significant differences in frontal, parietal, and temporal regions are shown. That for periventricular regions is due to the effect of global normalisation. (III) z Map (mean image of Alzheimer's disease group B−mean image of Alzheimer's disease group A) displayed on a glass brain. A significant difference in the left parietal region is shown.

ies. Brain CT taken immediately after SPECT was rated normal by radiologists.

Patients were diagnosed as having probable Alzheimer's disease according to the diagnostic and statistical manual of mental disorders (DSM-IV) and National Institute for Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) by experienced psychiatrists. Severity of disease was assessed on mini mental state examination (MMSE) and clinical dementia rating (CDR) scales. Activity of daily living was assessed by physical self maintenance scale (PSMS). Patients with CDR ≥ 2 were placed in group A (severe dementia) and those having CDR ≤ 1 were placed in group B (mild dementia). SPECT of patients with Alzheimer's disease was done immediately after the initial diagnosis. However, scans were only included in the present study of those subjects for whom after 1 year of follow up the diagnosis remained the same. This strict screening was adopted to avoid inclusion of falsely diagnosed Alzheimer's disease.

IMAGE ACQUISITION AND PROCESSING

A SPECT scanner (SPECT-2000H, Hitachi Medico Corp, Japan)[7] was used to acquire data after a bolus injection of 1036 MBq Tc-99m HMPAO. Image reconstruction was performed by filtered back projection using a Butterworth filter (dimension 12, cut off 0.25 cycles/pixel). Attenuation correction was made numerically with a uniform coefficient factor (0.1/cm). Correction for scatter photons was not performed. After SPECT measurements, CT was obtained. All reconstructed images were transferred to a UNIX work station for further analysis.

IMAGE STANDARDISATION AND DATA ANALYSIS

SPECT images were globally normalised with averaging the whole brain radioactivity to 100 counts/pixel. After this normalisation, all SPECT images were registered with respect to a reference image to make target images similar in size and shape using linear and non-linear parometers. The standardised images were used to calculate the mean images for patients and control subjects. Group comparison of patients and controls was performed on a voxel by voxel basis using statistical parameteric mapping (SPM96).

A brain atrophy index (BAI) was calculated for each subject using a computer program and the morphometric data from CT.[8]

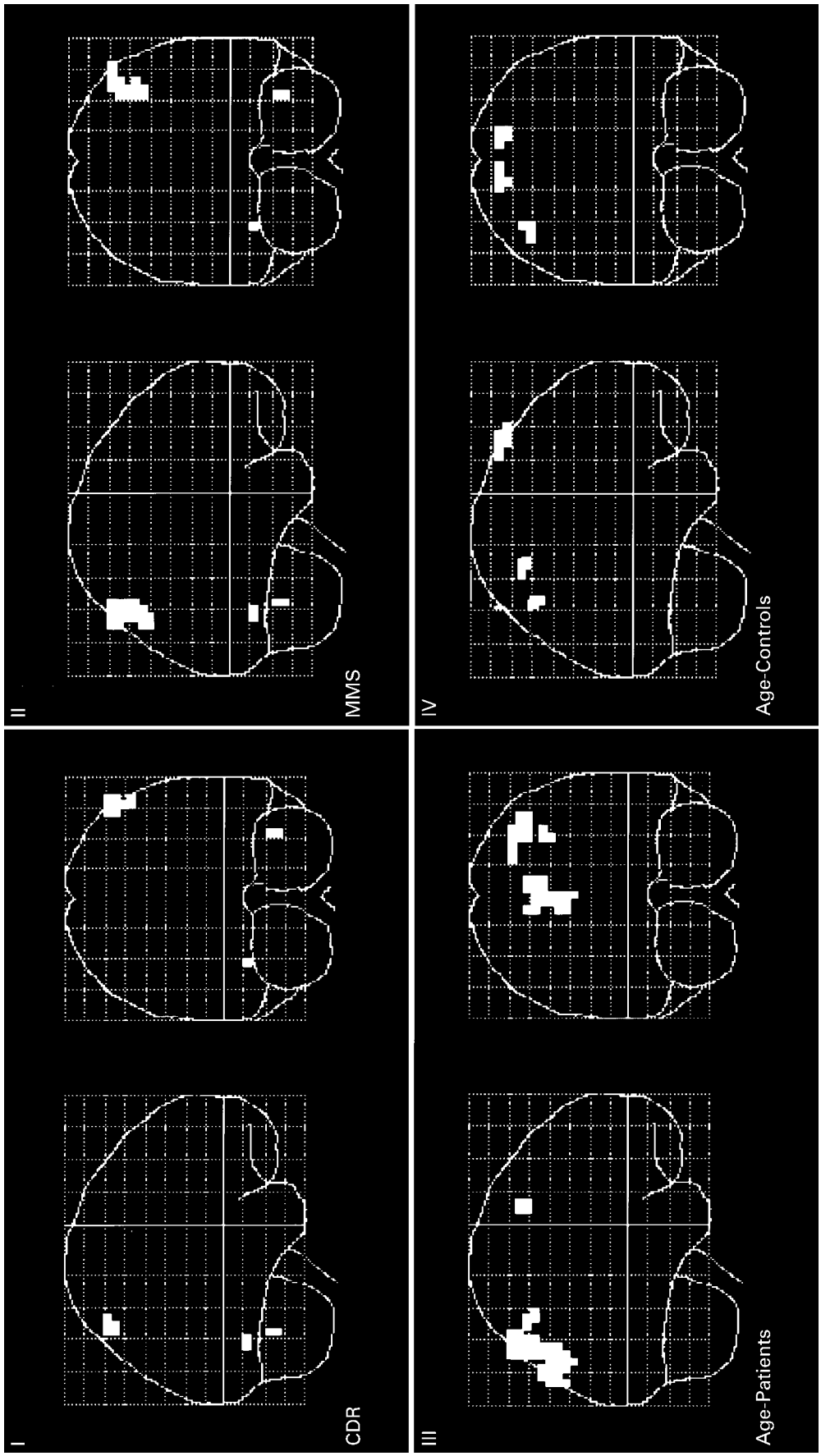

Figure 2 (I and II) Statistical maps showing correlation severity of disease scaled on CDR and MMS versus rCBF (Tc-99m HMPAO) images of Alzheimer's patients. (III and IV) Statistical maps showing correlation between age (in years at the time of SPECT) of patients and controls v rCBF (Tc-99m HMPAO) images.

After specifying the appropriate design matrix, the covariant effects (negative correlation) of aging and atrophy, severity of disease (CDR and MMS score), and activities of daily living (PSMS) on CBF were estimated according to the general linear model at each and every voxel by SPM96. Results of statistical calculations were displayed as z maps ($p<0.001$).

Results

Figure 1, panel I shows mean rCBF images of patients (top row severe dementia group A, middle row mild dementia group B, and bottom row age matched control subjects. Patient group images showed bilateral parietotemporal deficits, along with decreased CBF in the upper frontal region. These findings were more marked on the left side. In the temporal lobe, the medial area showed more marked deficits than the lateral region. All these described areas demonstrated a pronounced decrease in CBF in the severe dementia group A. Ventricular/periventricular regions, and the distance between the caudate nuclei and lateral sulci were larger in the patient group than in the normal group. These findings were consistent with the morphometric data from CT with calculated atrophy indices of 0.974 (SD 0.012) and 0.904 SD (0.042) for controls and patients respectively. Within the group of patients, atrophy was more marked in group A than in group B.

The comparison between patients and controls (fig 1 panel II) showed a significant difference in the parietotemporal and frontal regions as well as the periventricular area, in line with the findings of mean images. Figure 1, panel III shows a comparison between patients of group A and group B. A significant difference was found for the left parietal region. Figure 2 shows the results of voxel based covariance analysis. Among the cortical regions, the left parietal area showed a significant correlation with the severity of disease scaled on CDR as well as MMSE (fig 2, panels I and II). The effect of aging is shown in fig 2 panels III and IV (Alzheimer's disease group and normal controls respectively). A difference in the pattern of aging was found between the two groups. In the Alzheimer's disease group, CBF of the left parietal region showed a significantly strong correlation with age. Correlation maps for atrophy and the PSMS score did not show any particular pattern of correlation, indicating no specific relation of these two variables with blood flow in the intact cortical regions.

Discussion

There are two important findings of this study. Firstly, bilateral parietotemporal deficits of CBF along with a definite decrease in blood flow in the frontal region were established in patients with Alzheimer's disease compared with normal controls. This is at least partly consistent with previous studies, which showed parietotemporal deficits as characteristic findings of Alzheimer's disease.[9 10] However, a decrease in frontal region CBF at an early stage of Alzheimer's dementia might be an effect of signal averaging, as such procedures are well known to increase sensitivity by increasing the signal to noise ratio.[11] The second finding is the significant correlation of left parietal CBF values with patient age and severity of dementia. This suggests that metabolic images not only provide diagnostic and prognostic information but also help in determination of the stage of disease.

The regional distribution of Tc-99m HMPAO in the brain is influenced by a complex combination of factors.[12] Although important, the sources of variation in measurements due to technical factors (such as statistical noise and positioning errors) can be either avoided altogether or neglected safely without any risk of loss in sensitivity and specificity of the test in routine clinical studies. However, certain factors such as the effect of aging cannot be filtered out easily. Moreover, the pattern of influence of all such factors on cerebral flow and perfusion images is not well understood. Their behaviour alone or in combination with other factors might be linear, curvilinear, or may actually not follow any particular model. In our population, CBF values on the left side were generally lower, bilateral asymmetry was not significant in the normal population, however.[6] From the present research it is clear that age and severity of Alzheimer's disease have negative correlational effects on CBF in the left parietal region in patients with Alzheimer's disease.

Changes in functional coupling between various regions of the brain leading to a decrease in CBF values cannot be explained by any single factor. Interestingly, although atrophy caused expansion of CSF space, the effects on blood flow of shrunken but intact cortical areas were minimal. Functional abnormalities may be detected earlier than counterpart anatomical changes on morphometric data.

In the present study we coupled image analysis of consecutive cases with a clinical follow up of sufficient duration to reduce diagnostic uncertainty. To confirm the diagnosis of Alzheimer's disease, a follow up of at least 1 year and then re-examination by a psychiatrist were made mandatory for inclusion of SPECT CBF images in the analysis. Because medication may effect CBF images through metabolic alterations,[13–15] we performed our studies before medication was started.

To our knowledge this is the first study aimed at a voxel based covariance analysis of SPECT CBF images of patients with Alzheimer's disease after spatial normalisation of individual images with the use of AIR.

Conclusions

Cerebral blood flow in the left parietal region correlates strongly with stage of Alzheimer's dementia.

The age of patients as a variance factor has a more pronounced effect on CBF in the intact cortical areas than that of atrophy.

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