MRI-Guided SPECT Measurements of Medial Temporal Lobe Blood Flow in Alzheimer's Disease

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In this study, we assessed the accuracy and reliability of MRI-guided SPECT measurements of medial temporal lobe blood flow in Alzheimer's disease (AD). **Methods:** Interactively aligned three-dimensional MP-RAGE MRI and ^{99m}Tc-HMPAO SPECT images were used for MRI-guided measurement of medial temporal lobe CBF in eight control subjects and eight patients with probable AD. Intraoperator reliability was assessed by repeated alignment and measurement by one experienced operator. Accuracy was assessed by examining two subjects with fiducial markers. **Results:** The alignment error was less than 1 SPECT pixel size (3.5 mm) and the coefficient of variation in repeated measures of medial temporal-to-cerebellar CBF ratios was 3.2%. The difference in mean medial temporal-to-cerebellar CBF ratios between eight control subjects and eight AD patients was 12%. Also by using three-dimensional seed-grow defined healthy brain reference regions, there were significant differences between control subjects and AD patients in medial temporal blood flow. Furthermore, the volumes of the MRI-defined medial temporal ROIs were smaller in the AD patients. The best separation between AD patients and control subjects was achieved by combining MRI measurements of atrophy and SPECT measurements of CBF. **Conclusion:** These data show that the accuracy and reliability of MRI-guided SPECT measurements of medial temporal CBF clearly allow the detection of changes in AD. Also, a direct comparison of structural and functional changes is possible by this methodology, which might improve the early diagnosis of AD.

Key Words: magnetic resonance imaging; SPECT; temporal lobe; cerebral blood flow; brain atrophy; Alzheimer's disease

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Recent pathological and neuropsychological studies suggest that structures within the medial temporal lobes are the first to be affected by pathology in Alzheimer's disease (AD) (*1, 2*). These findings have also been confirmed by several MRI studies that have found medial temporal lobe atrophy in patients with AD, and this has been suggested as a potential diagnostic marker for the disease (*3–8*). As functional changes might precede structural changes in AD, there is a great interest in applying functional neuroimaging to visualize these structures. In SPECT cerebral blood flow (CBF) imaging, however, these regions are difficult to identify with certainty even if the images are projected onto the coronal plane because of the limits in anatomical resolution. By superimposing MRI and SPECT and then using the anatomical information from MRI scans to guide the placement of ROIs in SPECT, this problem might be solved. This methodology would also permit a more direct comparison of regional structural and functional brain changes. The critical methodological issues are the accuracy of the image alignment and the reliability of the MRI-guided ROI placement.

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In this study, we coregistered MR and SPECT image sets from control subjects and AD patients using manual alignment assisted by multimodal imaging software. After alignment the medial temporal ROIs were manually defined in the MR images and then automatically transferred to the corresponding region in the SPECT image by the software. Medial temporal CBF ratios were calculated with five different reference regions. One reference region was the cerebellar cortex, defined from MRI. Four other reference regions were defined using a seed-growing method with four different lower limit levels.

The aims of this study were to assess the accuracy of the image registration and the reliability of medial temporal CBF ratios as measured by MR-guided ROI placement and calculated with different reference regions.

MATERIALS AND METHODS

Subjects

Eighteen subjects were included in the study. Eight healthy control subjects and eight subjects with AD were examined with both MRI and SPECT with less than 1 wk interval. The AD patients (mean age 62 yr; range 52–67 yr; 4 men, 4 women) were arbitrarily selected among patients consecutively investigated for suspected dementia at the geriatric clinic. The MRI and SPECT examinations were routine exams included in the dementia investigation. All AD patients fulfilled the NINCDS-ADRDA criteria for probable AD. They had mild-to-moderate dementia (mean MMSE = 19, range = 13–24). The healthy control subjects (mean age 58 yr; range 38–74 yr; 4 men, 4 women) were selected from groups of control subjects used in other studies at the geriatric clinic. They were selected to match the eight AD patients in sex and age as close as possible and, although the AD patients had slightly higher mean age and a more narrow age range, there were no statistically significant differences in age (Student's t-test = 0.94, $p = 0.36$) between the groups. In addition, two other patients, investigated for suspected dementia at the geriatric clinic, were examined with three fixed external fiducials during the routine MRI and SPECT examinations.

Magnetic Resonance Imaging

All MRI examinations were performed with a 1.5 Tesla MR Imager (Siemens Magnetom, Erlangen, Germany) using a magnetization-prepared rapid gradient echo (MP-RAGE) pulse sequence with TR = 10 ms, TE = 4 ms, flip angle 10°, matrix 256 × 256 and field of view 255 mm producing 64 continuous coronal slices (partitions) of the whole brain with 3-mm slice thickness. The coronal plane was chosen to be perpendicular to the bicommisural line as defined in a midsagittal scout image. No other alignment or fixation procedure was used.

Single-Photon Emission Tomography

Each subject was injected with 1000 Mbq ^{99m}Tc-HMPAO in a quiet surrounding with eyes closed. Acquisition started within 30

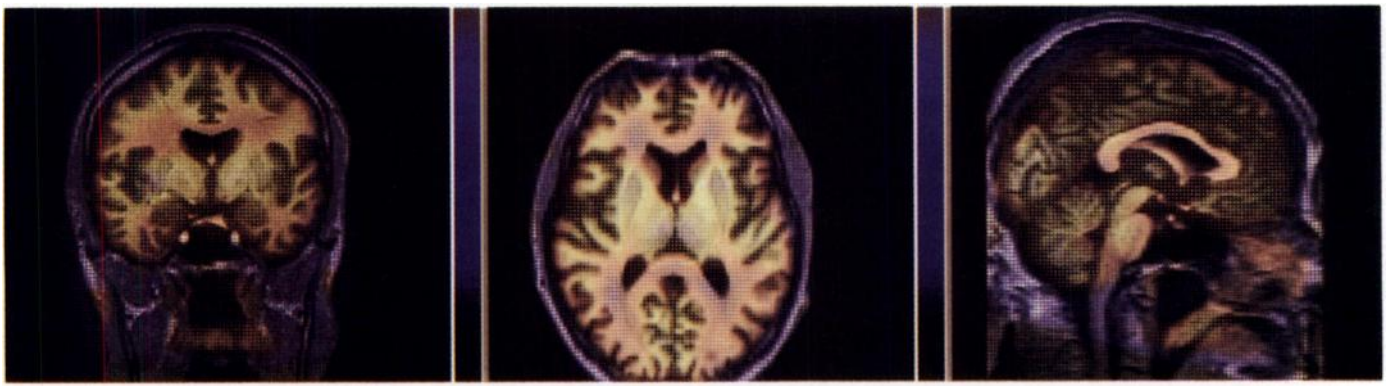

FIGURE 1. MR and SPECT images overlaid in coronal, transaxial and sagittal planes. Interactive alignment of MR and SPECT images was performed by manual step-by-step rotation and translation of the SPECT image sets. The interactive stepwise alignment was guided by visual inspection of images in different orientations to get the optimal overall agreement of neuroanatomy.

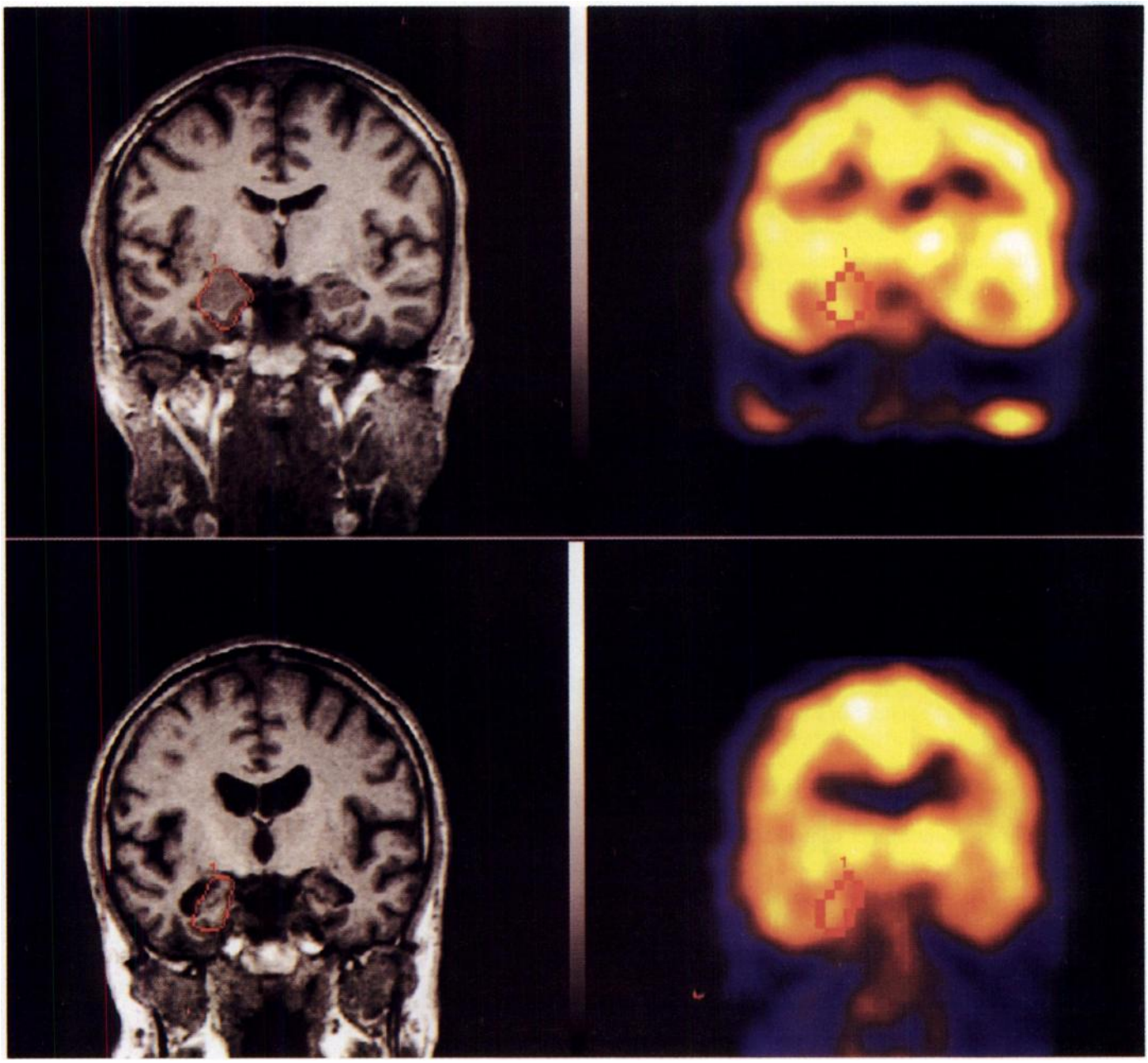

FIGURE 2. Medial temporal ROIs in coronal MR and SPECT images from a healthy control subject (top row) and an AD patient (bottom row), MRI (left) with manually outlined MTL-ROIs and SPECT (right) with the MTL-ROIs transferred from MRI. Both the mean volume and the mean CBF ratio of the MTL-ROIs were lower in AD patients as compared to the control subjects.

min after injection. Data were collected in 64 projections evenly spread through 360° with a single-head rotating gamma camera with a total acquisition time of 32 min. A Metz prefilter was applied to the projections before transversal sections were calculated using filtered backprojection and attenuation correction. The dataset was reformatted in a coronal plane as 64 × 64 matrices with a pixel size of 3.5 mm. The resolution of the system was 10.2 mm FWHM at a 10-cm depth. The postprocessing was performed at the nuclear medicine department with HERMES software developed by Nuclear Diagnostics Ltd. (Stockholm, Sweden and London, UK) running on SUN Sparcstations (Sun Microsystems Inc., Mountain View, CA).

MRI-SPECT Alignment

The MR and SPECT images were loaded into a mulimodality image software (Multimodality, Nuclear Diagnostics Ltd.). This software was originally developed for the automatic registration and analysis of cardiac (*9, 11*) SPECT images. It has been adapted for the registration of MRI and SPECT images of the brain. In this study, alignment was achieved by interactive rotation and translation of the SPECT image set. The effects of stepwise rotation and translation were visually evaluated in coronal, sagittal and transaxial planes (Fig. 1). After each stepwise adjustment the software interpolated the SPECT images from original data. The whole cerebral volume as visualized by the two different modalities were thus stepwise adjusted by interactive rotation and translation to find the optimal overall agreement of neuroanatomy. With an experienced operator, this procedure usually took less than 20 min. Because the voxel-sizes from MRI and SPECT were well known, the scaling of the image sets was not changed. In this study, one experienced operator performed all alignments and measurements.

MRI-Guided Regions of Interest

After alignment, ROIs were manually outlined on the MR images. ROIs were automatically transferred by the software to the corresponding regions in the SPECT images and the statistics of the ROIs were automatically calculated and displayed. In this study, we recorded the size and the mean count of each ROI. The ROIs outlining the medial temporal lobes/hippocampal complex were defined bilaterally in the four MR images just posterior to the anterior commisure, including parts of amygdala, hippocampus and the parahippocampal gyrus (Fig. 2). The cerebellar reference regions were outlined in four MR-images including cerebellar cortex in midcerebellum. Medial temporal/cerebellar CBF ratios were calculated by dividing the mean counts of respective ROIs. These ratios were then corrected for backdiffusion with the formula developed by Lassen et al. (*12*). As the interoperator reliability of interactive methods always is dependent on the skill and experience of the operators, many studies are made with one experienced operator performing all measurements. In this study, the procedure of alignment and ROI definition was performed by one trained operator in all 16 subjects. To assess the intraoperator reliability of the medial temporal CBF measurements, this procedure was repeated by the same operator after an interval of about 3 mo.

Whole-Brain Reference Regions

Four different seed- (or region-) growing defined reference regions were calculated once from the SPECT images of the eight control subjects and eight AD patients. The three-dimensional region growing was performed using the multimodality software (*9–11*), and the algorithm used thresholding criteria without an edge weight. A seed voxel was manually selected in the cerebellar cortex in a transaxial slice approximately at a similar level in all subjects. The lower limit of the region growing was selected interactively, and upper limit was defined as the maximum count of the study. The lower limits of the four different reference regions used in this study were 75%, 65%, 55% and 40% of maximum of study, respectively. With a region growing with a 75% lower limit, the resulting regions were usually confined to cerebellum and visual cortex but increased in size with decreasing the lower limit to include the whole brain at a 40% lower limit (Fig. 3). The mean count of the regions was used as reference. The variation in region mean count when repeating region growing in the same subject with the same lower limit and a seed voxel in approximately the same region was less than 1%. Hippocampal/region-growing ratios were also corrected for backdiffusion as described above.

Accuracy Assessment

To assess the accuracy of the interactive alignment procedure, two subjects were investigated with MRI immediately after the SPECT examinations. Both subjects had three external fiducials strictly fixed to the skin by adhesive plastic tape. One set of fiducials was used for both MRI and SPECT without removal between the examinations. The fiducials were plastic cylinders with cavities 8 mm deep and 5 mm inner diameter. The cavities were filled with both diluted ^{99m}Tc (≈100 kBq, for SPECT) and MgCl and water (for MRI). One marker was fixed with plastic adhesive tape to the subject's forehead and two to the chin just in front of the external auditory meatus bilaterally. Before alignment these markers were digitally removed and masked from each image set. After the alignment of image sets without markers, image sets with markers were positioned according to the translation and rotation of the alignment. The center of each marker was visually determined in the SPECT and MR image sets. The distance in x, y and z directions between the center of each marker in MR and SPECT images was then measured. To reduce the effect of measurement error, the measurements were repeated with the images sets interpolated in coronal, axial and sagittal planes. The displacement in each direction for each marker was then calculated as the mean of the three measurements. This procedure was also repeated on two different occasions by one operator.

Statistical Analysis

Differences in repeated measures were tested using paired Student's t-test. Correlation was calculated as Pearson's correlation coefficient. The method error in repeated measurement of CBF ratios was calculated as the variability of the difference between two measurements, in other words, as the square root of the sum of squared differences between two measurements divided by the number N of paired measurements. The coefficient of variation was defined as the error divided by the mean CBF ratio for N measurements. The variability of a single measurement can be calculated from the data in the table by dividing this figure by $\sqrt{2}$. All calculations were performed using JMP software (SAS Institute Inc., Cary, NC) on Macintosh computers (Apple Computer Inc., Cupertino, CA).

RESULTS

Accuracy of Interactive Alignment

The distances between the centers of the three markers in two subjects aligned twice are shown in Table 1. There was no statistically significant systematic displacement in coronal, axial or sagittal directions (paired Student's t-test). The mean absolute distances (error) between markers was 2.5 mm in the coronal plane, 3.5 mm in the axial plane and 3.1 mm in the sagittal plane. The maximum displacement in any dimension for any marker was 8 mm.

CBF Ratio Reliability

In repeated alignment and measurements of medial temporal-to-cerebellar CBF ratios in eight control subjects and eight AD patients, the difference of the mean medial temporal ratios, of

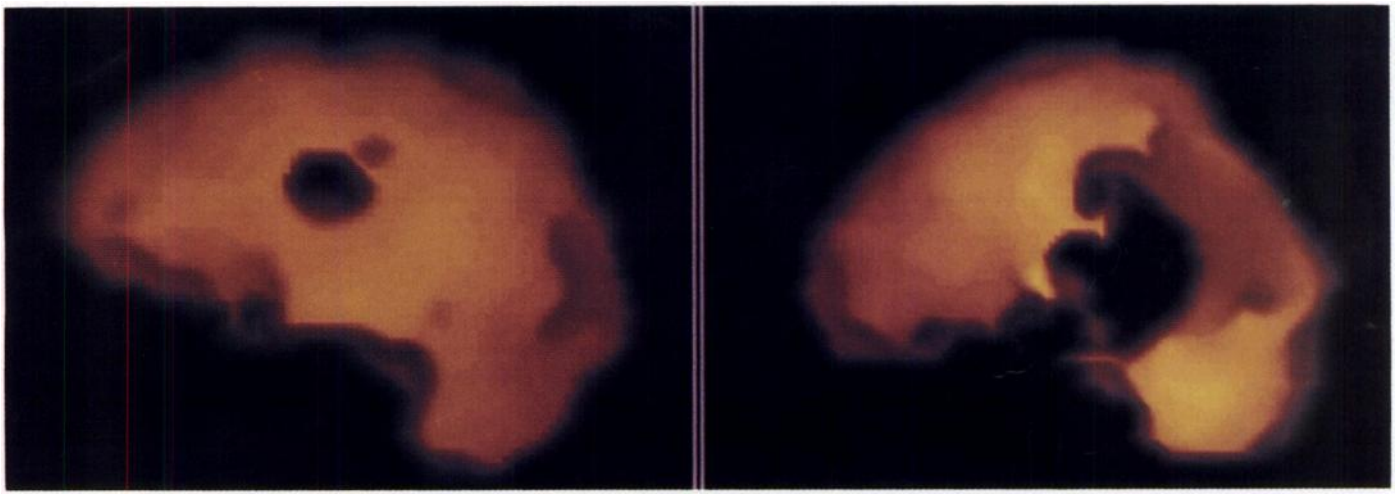

FIGURE 3. Whole-brain reference regions in three-dimensional display. Whole healthy brain reference region in a healthy control (left) and in an AD patient (right). Reference regions were created by three-dimensional region growing with a 65% lower limit. These images illustrate that these regions with relatively high activity, 65%–100%, are smaller in AD patients as low-activity regions are excluded. These regions might be used as healthy brain reference regions.

all subjects, between the two measurements was 0.01 (1.6%). This was not statistically significant (paired Student's t-test, $p = 0.25$). There was a high correlation between the two measurements ($r = 0.9$, $p < 0.001$), and the coefficient of variation was 3.2%. There was a significant difference between the mean ratios of the control subjects group and the AD patients of 0.08 (12%) in both measurements (Table 2).

Whole-Brain Reference Regions

The results when using the seed-grown regions with different lower limits as reference regions to the medial temporal region are seen in Table 3. There were clear relationships between the lower limit of the region and the differences between control subjects and AD patients, both concerning ratios with these regions as references and the sizes of the reference regions themselves. The reference with 75% limit was quite small, with a large interindividual variation in size in both the control and AD group. This region was most often confined to the cerebellum and visual cortex. When used as reference, the medial temporal CBF ratio was significantly lower in the AD group. The 65% low-limit reference usually contained quite large parts of the brain including cerebellum, visual cortex, parts of parieto-temporal and frontal cortex and the basal ganglia (Fig. 3). When used as reference for the medial temporal region, the difference between the groups was preserved. The size of this region and the 55% region was also significantly smaller in the AD group as compared to the control subjects. When using regions with 55% and 40% lower limits to the seed grow as references, the differences between the groups are no longer significant. The size of the 40% region also is not significantly different between the groups.

TABLE 1
Accuracy of Manual MRI-SPECT Alignment as Measured by the Distance Between the Centers of Three Fiducial Markers

Subject marker	Coronal	Axial shift (mmm)	Sagittal Shift (mm)	Sagittal Shift (mm)
A1	1	+1.0	−1.0	+6.8
	2	+3.0	−5.0	−3.4
	3	±0.0	−4.0	±0.0
A2	1	+2.0	+1.0	+3.4
	2	−1.0	+3.0	−3.4
	3	+1.0	−3.0	+6.8
B1	1	−3.0	−6.0	±0.0
	2	−2.0	−4.0	−3.3
	3	−6.0	−8.0	+3.3
B2	1	−5.0	+5.0	−3.3
	2	−2.0	±0.0	±0.0
	3	−4.0	+2.0	+3.3
Mean shift (mm)		−1.3	−1.6	+0.85
Mean distance (mm)		±2.5	±3.5	±3.1

Mean shift = measure of systematic displacement; mean distance = mean absolute distance between marker centers (error).

Volume and Perfusion

We found a relationship between the medial temporal CBF ratio and the actual volume of the MRI-defined medial temporal ROI. (Table 4) As shown earlier, the CBF ratios were significantly different between the groups, but also the volume of the medial temporal ROIs is smaller in the AD group. To be able to compare deviations in volume and perfusion, we calculated the data as z-scores with the eight control subjects as reference group. Then a composite z-score was calculated as the arithmetic mean z-score of the volume and perfusion scores. This combination of volume and perfusion is more significantly different between the groups than either parameter alone.

DISCUSSION

Alignment Accuracy

The interactive image alignment showed no systematic bias, and the displacement error of fiducial markers was 3.1 mm. As the SPECT pixel size was 3.5 mm and the resolution of our

TABLE 2
Difference Between Control Subjects and AD Patients in Repeated Alignment and Measurement of Hippocampal-to-Cerebellar CBF Ratios

Measurement	Hippocampal/Cerebellar control subjects (n = 8)	CBF ratios AD (n = 8)	Difference	t-test
1	0.66 ± 0.05	0.58 ± 0.03	0.08 (12%)	p = 0.0008
2	0.67 ± 0.04	0.59 ± 0.03	0.08 (12%)	p = 0.0007

TABLE 3
Hippocampal CBF Ratios Calculated with Healthy Brain Reference Regions Created by the Region-Growing Method in Control Subjects and AD Patients

Low limit of seed grow		Control subjects	AD	Difference	t-test
75%	CBF ratios	**0.63 ± 0.06**	**0.54 ± 0.06**	14%	p = 0.016
	Volumes (cm^3)	162 ± 110	89 ± 31	45%	p = 0.094
65%	CBF ratios	**0.73 ± 0.06**	**0.63 ± 0.09**	14%	p = 0.016
	Volumes (cm^3)	**653 ± 114**	**398 ± 137**	39%	p = 0.001
55%	CBF ratios	0.80 ± 0.07	0.72 ± 0.10	10%	p = 0.095
	Volumes (cm^3)	**1095 ± 155**	**921 ± 159**	16%	p = 0.044
40%	CBF ratios	0.93 ± 0.08	0.86 ± 0.14	8%	p = 0.283
	Volumes (cm^3)	**1067 ± 209**	**1485 ± 276**	8%	p = 0.336

CBF ratios ± s.d. or volumes ± s.d. that are significantly different ($p < 0.05$) between the groups are in boldface.

SPECT images was 10.2 mm, this accuracy of alignment is clearly adequate. These findings are in accordance with a previous study where the authors found that a fully interactive three-dimensional technique for image registration had a reproducibility and accuracy comparable or superior to previously published automatic techniques (*13*).

Measurement Reliability

The accuracy of alignment also is confirmed by the high reliability of medial temporal-to-cerebellar CBF ratios with a coefficient of variation of 3.2%, which was less than half of the standard deviation in both control subjects and AD patients. We found a significant difference between control subjects and AD patients in medial temporal CBF that was highly reliable and three times larger than the method error. It has been previously shown for other larger ROIs that MRI-guided ROI placement in SPECT had a higher reliability than ROI placement directly on SPECT images (*14*). The medial temporal lobes are relatively small structures in a region with a rather high regional variability of blood flow (Fig. 2) and, thus, are practically impossible to define with any anatomic certainty using only SPECT images. We believe that our results show that by using MRI-guided SPECT measurements the blood-flow specific of these regions can be measured with acceptable reliability.

Reference Regions

The choice of reference region is a critical issue in quantitative SPECT. The cerebellum is usually preferred. At least in studies of AD patients, it has been shown to give better information than other reference regions as whole-slice mean etc. (*15*). However, no reference region is the perfect reference region because we have to assume that this region is unaffected by the disease we want to study. The use of different whole-brain reference regions clearly affected the difference in medial temporal CBF between control subjects and the AD patients. When calculating seed-grow reference regions, we found that a lower limit of 65% of maximum counts in the study seemed to be a good estimate of a whole healthy brain reference region. This region contained large parts of the brain but still preserved the difference between the groups. This region was also smaller in AD patients as compared to control subjects. The difference in reference region size between the groups diminished as the lower limit was decreased and larger parts of areas with lower activity was included in the reference. In the same way, the difference in CBF ratios between the groups diminished as the reference region grew to include these larger regions with more low activity. Thus, it seems that AD patients have a smaller proportion of high activity in the brain, but the overall brain size is not affected to the same degree. These findings are consistent with the previous findings that whole-brain reference regions might diminish the differences between AD patients and control subjects referred to above. However, by three-dimensional region growing it seems possible to define a whole healthy brain reference that might have advantages if cerebellar disorder is suspected. The medial temporal lobe CBF ratios, thus, were most significantly different between the groups when using the MRI-defined cerebellar reference, still significant when using whole healthy brain reference regions but failed to reach significant levels when using larger parts of the brain that included lower activity regions.

Volumes and Perfusion

We found that the actual size of the MRI-defined medial temporal ROIs were reduced in the AD patients. This is in accordance with previous MR studies finding an early atrophy

TABLE 4
Volumes and CBF Ratios (Cerebellar) of Medial temporal ROI in Control Subjects and AD Patients

		Control subjects (n = 8)	AD (n = 8)	T-value	
ROI volume	Mean ± s.d.(voxels)	81 ± 11	49 ± 21	—	—
	Mean ± s.d. (cm^3)	3.89 ± 0.5	2.35 ± 1.0	3.79	p = 0.002
CBF ratio	Mean ± s.d.	0.67 ± 0.04	0.59 ± 0.03	4.32	p = 0.0007
CBF + volume	Mean z-scores ± s.d.	0.00 ± 0.85	−1.76 ± 0.42	5.26	p = 0.0001

Both volume and CBF are significantly lower in AD patients compared to control subjects. The most significant difference between the groups is, however, achieved by combining both volumes and CBF by means of z-scores.

of these regions in AD (*3–8*). This also implies that with the MRI-guided method we have actually compensated the CBF measurements for atrophy. The partial volume effects of SPECT still make it impossible to clearly rule out atrophy as the cause of the CBF reduction. However, in the clinical context, it may be more interesting if we find that better separation is achieved between AD and control subjects by combining volume and CBF data than by either volume or CBF alone.

CONCLUSION

This study shows that reliable measurements of medial temporal lobe blood flow can be performed by MRI-guided SPECT measurements. The error of interactive alignment was less than one SPECT pixel size. The CV of the medial temporal-to-cerebellar CBF ratio found in this study was only 3.2%. In patients with AD, it was possible to detect clear reductions in blood flow in the medial temporal lobes with high reliability using MRI-defined cerebellar reference and also using healthy whole-brain reference regions created by three-dimensional region growing. Also, the volumes of the medial temporal lobes were smaller in the AD group. The best separation between the groups was found when combining medial temporal volume and blood flow data into a composite z-score. Larger clinical studies are needed to evaluate if the combination of MRI and SPECT measurements of medial temporal lobe changes can improve the early diagnosis of AD.

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Comparative Quantitation of Cerebral Blood Volume: SPECT Versus PET

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Quantification of cerebral blood volume (CBV) measured by SPECT has been used for evaluation of cerebral hemodynamics in patients with cerebrovascular diseases. The accuracy of such quantification, however, has not been validated with PET. **Methods:** CBV was assessed using SPECT and in vitro ^{99m}Tc-labeled red blood cells and PET with the ^{15}O steady-state inhalation method and C^{15}O. In 23 patients with carotid artery disease, we measured hemispheric (including cortical and subcortical areas) CBV, and in 11 patients, we measured regional CBV in small cortical regions. We further evaluated the interhemispheric and inter-regional asymmetry of CBV with both methods. **Results:** Quantitative values of both hemispheric and regional CBV measured by SPECT were significantly correlated with those measured by PET in the same patients. There was a significant correlation between the side-to-side asymmetry of CBV for both methods. **Conclusion:** This study demonstrates usefulness and the accuracy of SPECT for quantitative CBV assessment in comparison with the less widely available PET procedures.

Key Words: cerebral blood volume; PET; SPECT

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Occlusive carotid artery disease with insufficient collateral supply results in a dilatation of the peripheral vessels that compensates for the decrease in cerebral perfusion pressure (*1*). In regions where compensatory dilatation has already occurred, vasodilatory capacity is diminished and such regions are assumed to be more susceptible to an ischemic stroke of both a hemodynamic and embolic origin. Therefore, evaluation of the vasodilatory capacity could contribute to management of patients with internal carotid artery (ICA) disease.

Measurements of cerebral blood flow (CBF) with or without inhalation of carbon dioxide (*2,3*) or injection of acetazolamide (*4,5*) may be useful for an assessment of this vasodilatory capacity. Cerebral blood volume (CBV) is also a major factor in the regulation of cerebral hemodynamics (*6*). Augmentation of CBV is associated with the dilatation of pial vessels, as the consequence of decreased perfusion pressure, and may itself reflect a diminished vasodilatory capacity. Moreover, combined measurements of CBF and CBV allow one to evaluate the CBF/CBV ratio. This ratio has been reported previously as being a reliable index of the local cerebral perfusion pressure (*6–8*). Thus, the assessment of CBV has a particular significance in cerebrovascular diseases.

Several methods for measuring CBV have been proposed (*9*), with PET being the most reliable method. However, PET is