Brain SPET abnormalities in Alzheimer's disease before and after atrophy correction

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Abstract. The aim of this study was to determine which brain structures show the greatest influence of partial volume effects (PVE) in single-photon emission tomography (SPET) studies on Alzheimer's disease (AD). Brain perfusion SPET was performed in 30 patients with probable AD and 62 age-matched healthy volunteers. SPET images were corrected for PVE using grey matter volume segmented from magnetic resonance images. The most prominent changes after PVE correction were observed in the medial temporal structures. The PVE correction revealed a selective decrease in regional cerebral blood flow (rCBF) in the parahippocampal gyrus of AD without rCBF decreases in the hippocampus, which had been observed before correction. This correction seems to be essential in order to achieve accurate measurements of rCBF in SPET, which has limited spatial resolution.

Keywords: Alzheimer's disease – Single-photon emission tomography – ^{99m}Tc-ethyl cysteinate dimer – Regional cerebral blood flow – Partial volume effects

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Introduction

The more limited spatial resolution of single-photon emission tomography (SPET) scanners as compared with positron emission tomography (PET) scanners precludes exact measurement of the local radiotracer concentration in brain tissue since partial volume effects (PVE) cause underestimation of activity in small structures of the brain. As brain atrophy accentuates the PVE on SPET measurements, actual regional cerebral blood flow (rCBF) could be underestimated in Alzheimer's disease (AD). It has therefore been unclear whether the reduction in rCBF observed in AD patients reflects an actual reduction in rCBF or PVE. Although a few PET studies on AD have included atrophy correction of metabolic values using estimates of brain tissue volume measured by magnetic resonance imaging (MRI) [1], there have been no SPET studies on atrophy correction of rCBF values. This SPET study was undertaken to determine accurately the reduction in rCBF after PVE correction in AD.

Materials and methods

Subjects. Thirty patients (10 men and 20 women) were identified from among consecutive new referrals to the memory clinic of the National Center Hospital for Mental, Nervous, and Muscular Disorders. They ranged in age from 56 to 78 years (mean±SD: 70.6±6.2). The clinical diagnosis of probable AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. Each patient underwent both SPET and MRI at the time of the evaluation. The score of the mini-mental state examination (MMSE) ranged from 18 to 23 (mean±SD: 20.8±1.8).

Sixty-two control subjects (26 men and 36 women) were healthy volunteers with no memory impairment or cognitive disorders. They ranged in age from 55 to 78 years (mean±SD: 68.3±6.1).

Their performance was within normal limits on both the Wechsler Memory Scale-Revised and the Wechsler Adult Intelligence Scale-Revised. Their MMSE score was 28.9±1.2. They did not differ significantly from the AD patients in terms of age or education. The Ethics Committee of the National Center of Neurology and Psychiatry approved this study in healthy volunteers, all of whom gave their informed consent to participation.

All of the subjects were right handed and were screened by questionnaire and medical history to exclude those with medical problems potentially affecting the central nervous system. In addition, none of them had asymptomatic cerebral infarction detected by T2-weighted MRI.

Brain MR procedure. All MR studies were performed on a 1.0-Tesla system (Magnetom Impact Expert, Siemens, Erlangen, Germany). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections using a magnetisation preparation rapid acquisition gradient-echo sequence (TE/TR, 4.4/11.4 ms; flip angle, 15°; acquisition matrix, 256×256; slice thickness, 1.23 mm). The acquired MR images were reformatted to gapless 2-mm-thick transaxial images.

Regional CBF measurements. All subjects were injected while lying in the supine position with the eyes closed in a dimly lit, quiet room. Each received a 600 MBq intravenous injection of technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD). The global CBF was non-invasively measured using graphical analysis as described in previous reports without any blood sampling [2]. Ten minutes after the injection of the tracer, brain SPET was performed using a triple-head gamma camera system equipped with high-resolution fanbeam collimators (MULTISPET3, Siemens, Hoffman Estates, Ill.). For each camera, projection data were obtained in a 128×128 format for 24 angles of 120° at 50 s per angle. A Shepp and Logan Hanning filter was used for reconstruction at 0.7 cycles/cm. Attenuation correction was performed using Chang's method. To calculate rCBF, the linearisation algorithm of a curve-linear relationship between the brain activity and blood flow was applied as described in previous reports [2].

Data analysis. Calculations were performed on a Sun SPARC computer using ANALYZE version 2.5 (Biological Imaging Resource, Mayo Foundation, Rochester, Minn.), Automated Image Registration (AIR) version 3.08, and Statistical Parametric Mapping 99 (SPM99) [3].

MR images were converted to the same isometric matrix size as that for SPET images using ANALYZE. Then SPM99 segmented these isometric MR images into grey matter, white matter, cerebrospinal fluid and other compartments. The segmentation procedure involved calculating for each voxel a Bayesian probability of belonging to each tissue class based on a priori MRI information with inhomogeneity correction for magnetic field. The AIR software was used to align the SPET to the MRI scan of each subject using a six-parameter rigid-body transformation. To correct rCBF for the PVE of the SPET scanner, we used an algorithm based on the methods described by Mueller-Gaertner et al. and Ibanetz et al. [1, 4]. A three-dimensional convolution with the point spread function of the SPET device [assumed to be a simple three-dimensional Gaussian with a full-width at half-maximum (FWHM) of 9.0×9.0×9.0 mm], was performed to obtain coefficients of dispersion for each voxel.

These convoluted grey matter and white matter images were normalised to have a maximum count of 1.0 as 32 bit real values. Regions of interest (ROIs) were automatically extracted from the white matter MR image as areas over 95% of maximum count density and then overlaid on co-registered SPET images. Multiplication of the normalised white matter MR images by the maximum SPET count for these white matter ROIs yielded white matter SPET images. The grey matter SPET images were obtained by subtraction of these white matter SPET images from the original SPET images. Lastly, the grey matter SPET image was divided by the normalised grey matter MR image on a voxel-by-voxel basis. A global grey matter CBF value after PVE correction was set to the same value as that before PVE correction. The grey matter SPET images before and after PVE correction were spatially normalised using SPM99 to an original template for ^{99m}Tc-ECD [5] with 12-parameter linear affine normalisation and a further 12 non-linear iteration algorithms. Then, images were smoothed with a 12-mm FWHM isotropic Gaussian kernel.

Statistical analysis. The processed images were analysed using SPM99. We studied differences in the absolute values of the grey matter rCBF in AD patients and healthy volunteers using the *t* statistics. The resulting sets of *t* values constituted statistical parametric maps {SPM(*t*)}. The SPM(*t*) were transformed to the unit normal distribution {SPM(*Z*)} and thresholded at $P<0.001$. The significance of each region was estimated with a threshold of $P=0.05$ using distributional approximations from the theory of Gaussian fields [3] to correct for multiple non-independent comparisons.

Results

Tables 1 and 2 list the peaks of the most significant declines in absolute rCBF obtained in this analysis with Talairach coordinates *x,y,z* in millimetres as well as the corresponding *Z* values before and after PVE correction.

Table 1. Location and peaks of significant decreases in absolute rCBF before correction for PVE

Structure	Coordinates			Z score
	x	*y*	*z*	
Right posterior cingulate gyrus	2	–45	39	6.85
Left inferior parietal lobules	–46	–64	40	6.43
Right hippocampus	24	–16	–11	6.37
Right precuneus	4	–60	35	6.31
Right amygdala	20	–6	–11	6.0
Left amygdala	–22	–8	–11	5.9
Right inferior parietal lobules	44	–66	40	5.82
Left hippocampus	–28	–24	–11	5.29
Right parahippocampal gyrus	24	3	–15	5.26
Right middle frontal gyrus	26	22	45	4.7
Left anterior cingulate gyrus	–4	39	13	4.69
Right lingual gyrus	18	–88	–9	4.67
Right superior temporal gyrus	53	0	–8	4.46
Right insula	36	–11	15	4.3
Right superior frontal gyrus	10	50	31	4.29
Right medial frontal gyrus	14	5	57	4.23
Right inferior frontal gyrus	50	36	13	4.14

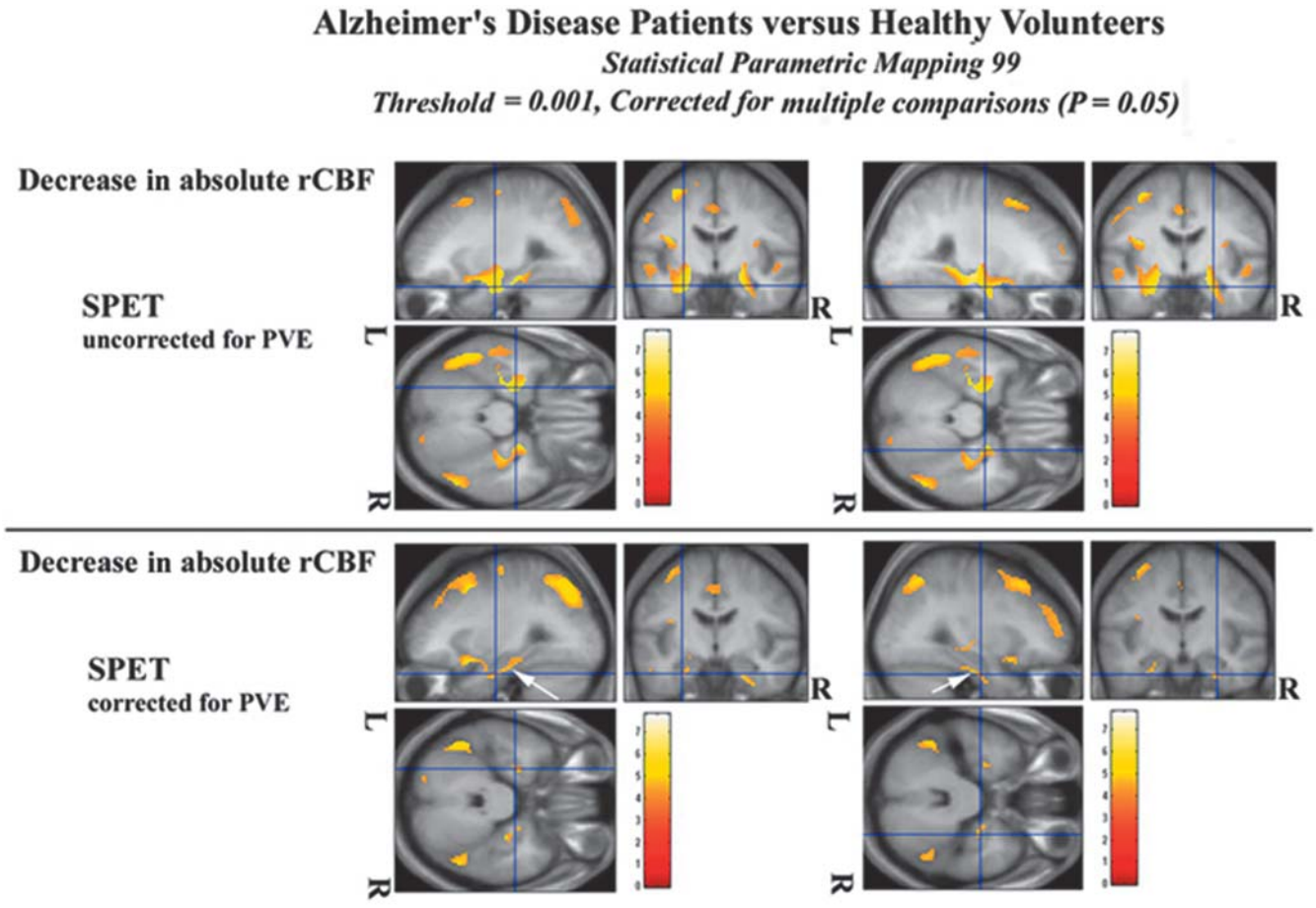

Table 2. Location and peaks of significant decreases in absolute rCBF after correction for PVE

Structure	Coordinates			Z score
	x	*y*	*z*	
Left inferior parietal lobules	–48	–50	45	6.79
Right precuneus	2	–44	43	6.39
Right inferior parietal lobules	42	–66	46	6.17
Left middle frontal gyrus	–38	16	42	5.75
Left inferior frontal gyrus	–22	11	–16	5.25
Right subcallosal gyrus	16	7	–14	5.11
Right inferior frontal gyrus	22	11	–17	4.9
Bilateral cunei	0	–67	16	4.87
Right middle frontal gyrus	30	29	43	4.77
Right parahippocampal gyrus	26	–20	–7	4.76
Left anterior cingulate gyrus	–4	40	15	4.69
Left posterior cingulate gyrus	–4	0	41	4.67
Left parahippocampal gyrus	–26	–24	–9	4.65
Right superior frontal gyrus	26	58	4	4.5
Left precentral gyrus	–44	–15	52	4.27
Left middle temporal gyrus	–53	–1	–10	4.21
Left superior frontal gyrus	–10	50	29	4.19
Left medial frontal gyrus	–2	48	–11	4.14
Right insula	40	6	–4	4.12

Fig. 1. Statistical parametric maps. The figure shows the orthogonal projections of voxels with significant declines in absolute grey matter rCBF in medial temporal areas before (*upper*) and after (*lower*) PVE correction. After PVE correction, the significance of the rCBF decrease in the bilateral amygdala and hippocampi disappeared. In contrast, bilateral parahippocampal gyri (*arrows*) showed a selective decrease in rCBF after the correction. The global CBF of AD patients was 36.8±4.6 ml 100 g^{-1} min^{-1}, which was significantly lower ($P<0.001$) than that of control subjects (41.6±4.7 ml 100 g^{-1} min^{-1}) using Student's *t* test

Figure 1 shows the voxels with significant declines in absolute grey matter rCBF in medial temporal areas, where the biggest differences were found between SPM results before and after PVE correction. After the correction, the significance of the rCBF decrease in the bilateral amygdala and hippocampi disappeared, while the significant decrease in the bilateral parahippocampal gyri remained.

Discussion

Previous PET investigations in AD patients reported that no area with a significant reduction in glucose metabolism became normal after correction of the diluting effects of cerebrospinal fluid [1]. In the present study, the

significantly decreased rCBF in the amygdala and hippocampus became normal after the correction. These areas have been reported to show marked atrophy from the early stage of AD [6]. Therefore PVE will mostly affect these areas in SPET images. Several previous reports on brain perfusion SPET observed low rCBF in the hippocampus of probable AD patients [7]. However, recent investigations using PET scanners with better spatial resolution have not reported such a decrease in the hippocampus [8]. These observations suggest that the decreased rCBF in the hippocampus may be mainly attributable to the PVE in SPET images. The rCBF per unit volume may be maintained in the medial temporal areas in patients with mild to moderate AD. This maintenance may result from a neuroplastic response in Alzheimer's disease. The perforant path, arising from the entorhinal cortex, which has been reported to be the first to be affected in AD [9], is the major cortical input to the hippocampus. It appears that the neuronal loss in the entorhinal cortex of AD patients acts as a stimulus in a similar manner to lesions in the rat brain, where loss of one set of axons induces the sprouting of the remaining afferents and replacement of the lost connections to maintain synaptic activity [10]. This compensatory response of re-innervation would result in milder functional changes than morphological changes. After PVE correction, selective rCBF decreases were observed bilaterally in the parahippocampal gyrus containing the entorhinal cortex. Measures of PET glucose metabolism in the entorhinal cortex were most accurate in differentiating mild cognitive impairment from normality [11]. The selective rCBF decrease in the parahippocampal regions may be due not to incomplete correction for PVE but rather to disclosure of accurate pathophysiology hindered the limited spatial resolution of SPET.

In conclusion, PVE correction of brain SPET in AD revealed a preferential decrease in rCBF in the bilateral parahippocampal gyri and preserved rCBF in the hippocampus and amygdala. This correction may be essential for SPET investigation of the atrophied brain.

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