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Mapping Pathological ^{99m}Tc-*d,l*-Hexamethylpropylene Amine Oxime Uptake in Alzheimer's Disease and Frontal Lobe Dementia with SPECT

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Key Words

Alzheimer's disease · Brain atlas · Frontal lobe dementia · Regional cerebral blood flow · Single photon emission computed tomography

Abstract

Seventeen patients with probable Alzheimer's disease (AD), 7 patients with frontal lobe dementia (FLD) and 19 control subjects (NOR) were examined by ^{99m}Tc-*d,l*-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) SPECT. Images were standardised in the same 3D space and averaged within each group. After normalisation, the three sets of images were analysed in all cerebral lobes, hippocampus, thalamus and basal ganglia. In AD, the ^{99m}Tc-HMPAO uptake values were significantly reduced, as compared to NOR, in the parietal, temporal and insular lobes. In patients with FLD, the uptake was altered in all lobes with the exception of the parietal lobe. The uptake in the nucleus caudatus decreased significantly in both AD and FLD as compared to NOR. The uptake in the anterior cingulate cortex was significantly reduced in FLD. Subtraction images highlighted all significantly decreased areas. In conclusion, standardising SPECT in a common space and subtracting data from a control group improves the visual interpretation of images. In this study, the typical temporo-parietal and fronto-parietal ^{99m}Tc-HMPAO uptake reductions were found in AD and FLD, respectively. The uptake in the nucleus caudatus was found to decrease significantly in AD and FLD and the one in the anterior cingulate cortex was reduced in FLD.

Introduction

Probable Alzheimer's disease (AD) and frontal lobe dementia (FLD) are well-characterised primary dementia disorders [1]. In typical cases, they show a characteristic reduction of regional cerebral blood flow (rCBF) and metabolism as depicted by single photon emission computed tomography (SPECT) and positron emission tomography, respectively. The characteristic finding in AD

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Table 1. Demographic data, MMSE score and duration of the disease of the three groups of individuals studied

Variable	F	AD (n = 17)	FLD (n = 7)	NOR (n = 19)
Age, years	F(2,40) = 9.72, p = 0.001	75.5 ± 7.0	79.9 ± 6.7	69.6 ± 4.0
MMSE score	F(2,38) = 67.00, p = 0.001	13.3 ± 5.4	16.7 ± 6.3	29.4 ± 0.6
Duration	F(1,21) = NS	4.1 ± 4.5	3.4 ± 1.3	

Results are shown as means ± SD. The F value is related to the ANCOVA analysis. The differences between AD and FLD groups are not significant.

is a bilateral flow reduction in the temporo-parietal cortex [2, 3]. In patients suffering from FLD, the typical pattern is a reduced rCBF in the fronto-temporal lobes [4, 5]. In addition to these changes, a reduced frontal lobe perfusion has frequently been reported in AD [6–11], while patients with FLD may express parietal lobe rCBF deficits [6]. However, these deficits may vary, and the reported incidence of the typical rCBF pattern in AD varies from 30 to 100%, for more advanced stages [12, 13]. In general, such studies have preferably been focused on the tracer distribution in cortical brain tissues. The changes caused by AD and FLD on central structures [14–16] and the anterior [17, 18] and posterior [19] cingulate cortex have seldom been studied.

Most brain SPECT studies have been evaluated and analysed by visual rating of rCBF or outlining the regions of interest in a manual or semi-automatic mode, and building up ratios between reference and target regions. More recently, observer-independent methods for semi-quantitative assessment of perfusion changes in AD have been reported [20–23]. For evaluation and analysis of images obtained in this work, we adapted all ^{99m}Tc-*d,l*-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) SPECT studies to a computerised brain atlas (CBA), originally developed by Greitz et al. [24] and improved by Thurfjell et al. [25]. This diagnostic tool, which in principle can be used for any brain imaging modality, automatically defines and analyses up to 400 brain regions and volumes in a standardised space.

The aim of this retrospective study was to investigate the additional diagnostic information that is obtained by comparing the ^{99m}Tc-HMPAO uptake of AD and FLD with that of a group of normal individuals using the brain atlas at SPECT examination. Special attention has been paid to uptake changes in those structures not frequently being assessed or reported in previous studies, i.e. the anterior cingulate cortex and basal ganglia.

Subjects and Methods

Patients and Normal Controls

From all patients referred to the Department of Nuclear Medicine at the Karolinska Hospital for symptoms of dementia during 1994–1998, two groups of patients were retrospectively considered for the study. Demographic data are shown in table 1.

The first group (AD) included 17 patients (11 males and 6 females) with a diagnosis of probable AD. All these patients fulfilled the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) work group [26]. The diagnoses were supported by compatible changes on Mini-Mental State Examination (MMSE) [27], EEG and a CT examination of the brain without focal lesions.

The second group (FLD) included 7 patients (1 male and 6 females) with clinical diagnosis of FLD according to the Consensus Criteria on FLD [28]. The clinical diagnoses were made by an experienced geriatric neurologist (C.R.).

The ^{99m}Tc-HMPAO uptake values of these two groups of patients were compared to those of a control group consisting of 19 normal volunteers (NOR; 11 males and 8 females). These subjects were free of any cardiovascular and pulmonary disease and with scores on the MMSE within the range of normality (table 1). The selected 19 individuals were part of a larger group of healthy subjects recruited to build up the control brain SPECT reference material.

The study was approved by both the local ethical and radiation protection committees.

Radiopharmaceutical and SPECT Examination

After 30 min rest at a tranquil place with dimmed light, 1,000 MBq (27.0 mCi) of ^{99m}Tc-HMPAO (Ceretec®; Amersham International plc, Little Chalfont, UK) was injected intravenously within 15 min of reconstitution. The radiopharmaceutical was prepared strictly according to the manufacturer's instructions. SPECT brain imaging was performed using a three-headed gamma camera (TRIAD XLT 20; Trionix Research Laboratory Inc., Twinsburg, Ohio, USA) equipped with low-energy high-resolution collimators. The system spatial resolution, as measured with a line source on the central axis, was 11.0 mm, expressed as the full width at half maximum. Axial spatial resolution was 10.6 mm full width at half maximum. The projection data were acquired for 15 s per projection at 90 equal angles of a complete revolution (0–360°).

Before reconstruction, the projection data were pre-processed using a 2D Hamming filter with a cut-off frequency of 2.25 cycles/cm. Sectional images were reconstructed by filtered back projection using a Ramp filter with a cut-off frequency of 0.6 cycles/cm. During pre-processing, correction was made for attenuation using the uniform Chang method [29]. No scatter correction was performed. Both acquisition and reconstruction were performed in 128 × 128 matrices with a pixel size of 2.22 × 2.22 mm^2.

Computerised Brain Atlas

CBA is a software tool for analysis of neuroimaging data. It uses a detailed 3D atlas derived from a cryosectioned brain. In this study, the fully automatic method was systematically implemented [30]. All image sets were spatially normalised by reformatting them into the stereotactic space of the atlas using a series of image transformations. The atlas voxel (volume element) size was 2.22 × 2.22 × 2.81 mm^3.

For evaluation and statistical analysis of the reformatted data sets, 9 volumes of interest (VOIs) corresponding to the frontal lobes, parietal lobes, temporal lobes, insular lobes, occipital lobes as well as basal ganglia (putamen and nucleus caudatus), thalamus and hippocampus were chosen. In order to normalise the uptake data of each individual, a correction factor may be computed by averaging all brain voxels and setting the global brain average to a predefined value. However, in order to prevent an overestimation of uptake in cases where large regions with pathological low flow are present, histogram analysis was used to exclude those voxels with low uptake values from the normalisation process. A counts/voxel threshold was used to reject 87% of all voxels in each 3D image set, so that only the remaining 13% of all voxels were used for normalisation (i.e. those 13% of the voxels with the highest flow). The choice of the upper 13% of all voxels was made from an analysis of the volume involved in normal rCBF scans. It allows the inclusion in the normalisation process of almost all the voxels containing grey matter (including the cerebellar ones) and most of those containing white matter.

In our case, we set the normalisation value (the average counts rate in the 13% of all voxels) to 50 'uptake units'. All uptake values in this work are related to this normalisation value.

Average images, containing the information about regional brain perfusion of all subjects belonging to same group, were then created. On this basis, average images of AD and FLD were subtracted from the average image of NOR. After having performed this procedure, a high-intensity region corresponding to the anterior cingulate cortex was visualised in both NOR minus FLD and AD minus FLD subtractions. Following this finding, the anterior cingulate cortex (Brodmann 32) was outlined by CBA and added to the 9 VOIs for statistical analysis.

Data Analysis

After VOI analysis using the CBA software, VOI data for all subjects were exported to a statistical package (SYSTAT 6) for subsequent statistical analysis of ^{99m}Tc-HMPAO uptake in all the ten predefined brain regions. Because AD, FLD and NOR differed significantly for age [$F(2,40) = 9.72$, $p = 0.001$; table 1], we covariated this variable. Analysis of covariance (ANCOVA) was performed on the normalised values.

Table 2. Means ± SD of the AD, FLD and NOR groups related to the VOIs under study

VOIs	AD (n = 17)	FLD (n = 7)	NOR (n = 19)
Frontal lobe	44.0 ± 1.2	41.0 ± 2.0	44.6 ± 1.1
Anterior cingulate	48.5 ± 2.3	42.5 ± 2.6	48.9 ± 1.5
Insular lobe	43.7 ± 2.6	41.2 ± 2.1	46.5 ± 1.7
Occipital lobe	40.6 ± 2.0	44.4 ± 1.3	41.4 ± 1.0
Parietal lobe	40.1 ± 1.7	43.3 ± 1.4	43.6 ± 1.1
Temporal lobe	35.0 ± 1.8	36.0 ± 1.3	39.2 ± 1.1
Hippocampus	38.8 ± 2.6	38.9 ± 1.2	42.2 ± 1.6
Nucleus caudatus	38.1 ± 4.5	32.0 ± 5.6	41.7 ± 1.8
Putamen	50.5 ± 2.1	48.3 ± 2.5	50.3 ± 1.6
Thalamus	49.0 ± 3.3	47.0 ± 2.9	49.9 ± 1.7

The results are normalised to the arbitrary unit of 50, representing the average uptake of ^{99m}Tc-HMPAO in the 13% of voxels with the highest counts.

Results

Putamen and thalamus were the VOIs with the highest radiopharmaceutical uptake in all 3 groups (table 2). In patients with FLD, the VOI with the lowest uptake was the nucleus caudatus (31.96). In AD, as well as in NOR, the lowest uptake was seen in the temporal lobe (35.03 and 39.17, respectively). The most striking decrease between patients and NOR was found in the nucleus caudatus, where patients with FLD had a 23.3% uptake reduction. When entire lobes were considered, the ^{99m}Tc-HMPAO uptake in the temporal lobe was lowest in all three groups.

As shown in table 3, ANCOVA demonstrated a significant difference between groups [$F(2,39) = 24.42$; $p = 0.001$] and a significant group × VOI interaction [$F(18,351) = 12.51$; $p = 0.001$]. Since hemispheres did not interact with both groups and VOIs, values were averaged across the left and right hemisphere. Separate ANCOVAs were then performed for each VOI. All ANCOVAs, except for the putamen and thalamus (table 3), revealed significant differences among group means. The Tukey-Kramer HSD test was implemented for pairwise comparisons of these VOIs.

When comparing AD to NOR, a significant reduction was found in the parietal and temporal lobes and in the hippocampus (table 3). No differences were found in the frontal lobe and anterior cingulate cortex. In the comparison between FLD and NOR, a significant fronto-temporal

Table 3. F and p-values for ANCOVA and post hoc test (Tukey-Kramer HSD test)

VOIs	Groups		Pairwise comparison probabilities (p value)		
	F(2,39)	p	AD–NOR	AD–FLD	FLD–NOR
Frontal lobe	17.46	0.001		0.001	0.001
Anterior cingulate	28.10	0.001	0.001		0.001
Insular lobe	8.74	0.001	0.01		0.001
Temporal lobe	27.65	0.001	0.001		0.001
Hippocampus	10.58	0.001	0.001		0.01
Parietal lobe	31.24	0.001	0.001	0.001	
Occipital lobe	13.64	0.001		0.001	0.001
Nucleus caudatus	5.82	0.01	0.025	0.025	0.001
Putamen					
Thalamus					
All: F(2,39) = 24.42, p = 0.001			Groups × VOIs: F(18,351) = 12.51, p = 0.001		

Following a significant groups × VOIs interaction separate ANCOVAs were performed for each VOI (left part of the table). The post hoc probabilities for VOIs in which the group effect was significant are shown on the right side of the table.

decrease was found. In FLD, there was also a significantly reduced uptake of ^{99m}Tc-HMPAO in the anterior cingulate cortex. In this group, the parietal lobe was the only region that did not change significantly from NOR (43.6 and 43.3, respectively). The flow in all considered VOIs was significantly changed when comparing the AD and the FLD groups, with the exception of the insular and temporal lobes and the hippocampus.

The uptake in the nucleus caudatus was 41.68 in NOR, 38.05 in AD and 31.96 in FLD (table 2). All differences between these average values were statistically significant.

No correlation was found in the pathological groups between the MMSE and/or the duration of the disease and the rCBF in any of the analysed VOIs.

The subtraction of the average AD data from the NOR average data shed light bilaterally on the parietal and temporal cortex, nucleus caudatus and the white substance underlying the parietal and temporal cortex (fig. 1). When the average data of FLD patients were subtracted from the NOR average data (fig. 1), the frontal, insular, temporal and anterior cingulate cortex, as well as the nucleus caudatus were bilaterally highlighted. Subtracting FLD data from AD data (fig. 1) accentuated the intensity signal in the frontal and anterior cingulate cortex and in the nucleus caudatus.

Discussion

Many investigations of patients with AD have reported reduced rCBF also in regions outside the temporo-parietal lobes [6–11], particularly in the frontal lobe. Recent studies have also pointed out the presence of a decreased basal ganglia rCBF in AD patients [14–16]. Other investigations have stressed the involvement of the anterior as well as the posterior cingulate cortex in both AD and FLD [17–19].

In this study, there was a significantly reduced ^{99m}Tc-HMPAO uptake in the frontal lobe between FLD and both NOR and AD, but not between NOR and AD (table 3, fig. 1). This means that the reduced frontal lobe uptake was specific of FLD, and that the controls had a frontal lobe uptake similar to that of AD patients. This finding is in accordance with a study by Bartenstein et al. [21]. Using a similar 3D standardisation technique, in a group of 81 AD patients, they did not find a significantly reduced frontal lobe rCBF as compared to an age-matched control group. The implementation of standardisation techniques may have caused the difference when comparing these investigations to those previously reported.

The second main finding of the study was the significantly reduced uptake in the nucleus caudatus of AD and FLD patients as compared to NOR and the reduced anterior cingulate cortex uptake in FLD patients.

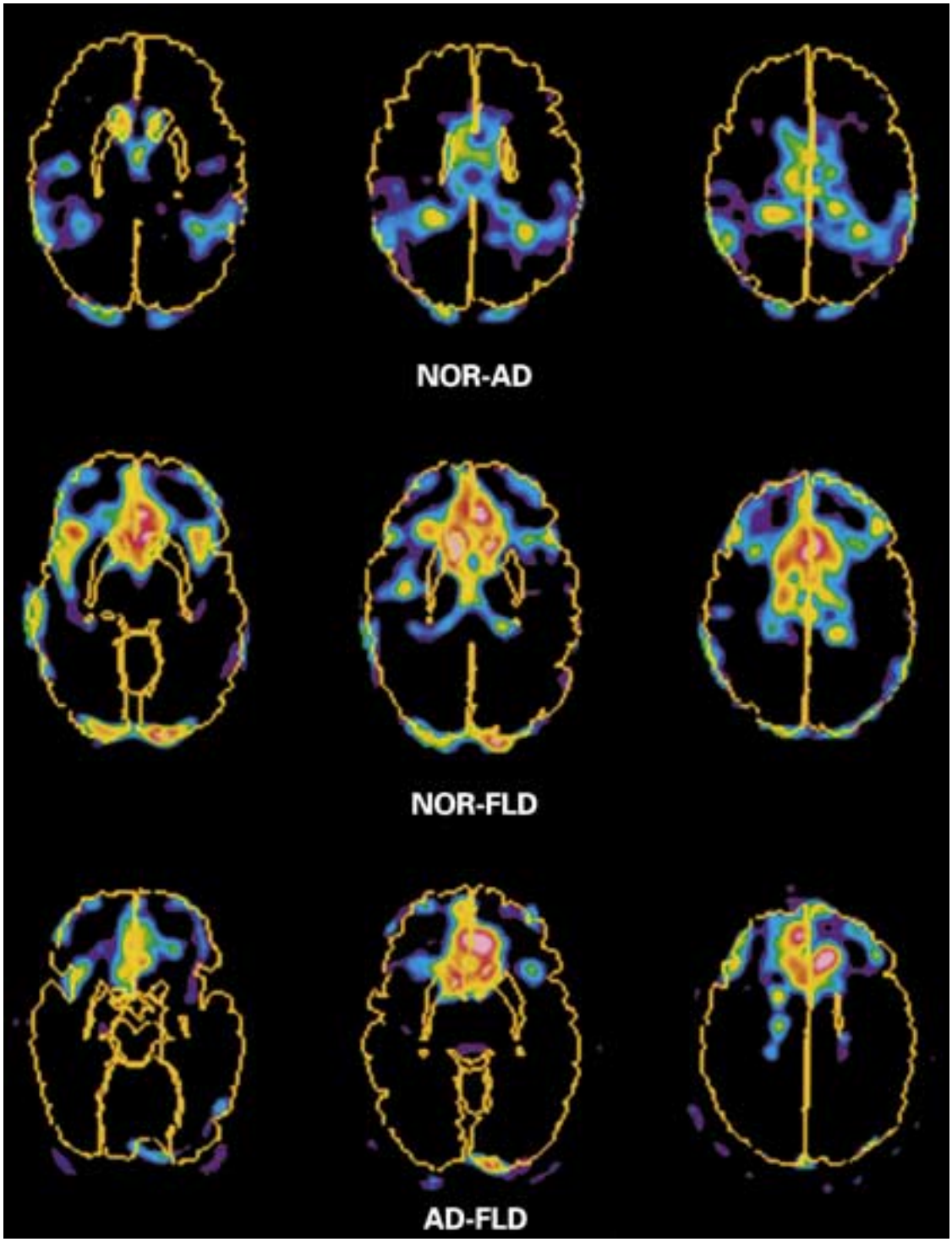

Fig. 1. Images obtained subtracting the average data pool of the three groups under study: NOR minus AD (top), NOR minus FLD (centre) and AD minus FLD (bottom). The colour scale is in arbitrary units.

It has been reported [31, 32] that prefrontal and parietal associative cortices project to the striatum in a segregate manner and mainly to the nucleus caudatus. Similarly, the anterior cingulate cortex has reciprocal connections with anterior para-hippocampal areas, the prefrontal and orbito-frontal cortex, inferior temporal lobe and rostral insula [33]. The decreased uptake in the nucleus caudatus could so be related to the strong anatomical and functional connections of this structure with the frontal and parietal lobes. Hence, one may speculate that the reduced radiopharmaceutical uptake in the nucleus caudatus could be the effect of a diaschisis phenomenon rather than of a direct regional involvement due to the disease. The diaschisis may involve the reciprocal connections of the nucleus caudatus with the cerebral areas involved in the pathological process underlying AD and FLD. The same phenomenon might apply to the anterior cingulate cortex, even if the vicinity of the pathological process in FLD may favour a direct involvement of this region.

The selection of the AD patients included in this work was very strict. Only those patients clearly fulfilling the NINCDS-ADRDA criteria and with AD diagnosis supported by CT findings and/or non-specific EEG changes were included in the study.

Nevertheless, no correlation was found in the pathological groups between MMSE and/or the duration of the disease and the rCBF in any of the investigated VOIs. This observation is in agreement with the studies of McKelvey et al. [34] and Pickut et al. [35], but is in contrast with the results from other investigators that reported a significant correlation between the MMSE and the posterior temporo-parietal cortex [36–38], mainly on the left hemisphere. In the design of this study, we have chosen to analyse the entire lobes and, since we found no interactions with the hemispheres, we have averaged between them. This might have hidden some correlation between particular cortical regions and the only two clinical variables that we could collect in this retrospective study.

The choice of 3D VOIs instead of 2D regions of interest renders the analysis more sensitive to changes in perfusion and less dependent on errors in outlining positioning [39, 40]. Another feature of analysing the data in 3D regions instead of 2D sections is that the variance due to counting statistics is reduced since the number of voxels in a functional region is larger than the number of pixels in a region of interest, and hence also the number of recorded events. Moreover, the 3D analysis investigates the uptake in a whole functional region, including both grey and white matter, rather than in a selected grey matter sector of a brain section. This uptake may therefore be more representative of global neurodegenerative changes in defined functional regions of the brain. Nevertheless, the inclusion of the white matter in the analysis is a conservative choice, reducing the differences in those VOIs, i.e. the frontal and the parietal lobes, containing a large amount of it.

A drawback of this study was the lack of age matching between normal subjects and patients. This was mainly due to a very high age of the patients and due to the concomitant difficulty to recruit controls over 80 years. This discrepancy has been taken in account by covariating the continuous variable by age.

The numerical evaluation of ^{99m}Tc-HMPAO uptake within each VOI was made after normalisation of the brain uptake data. The choice of setting the normalisation threshold at 87%, including only voxels with the highest uptake, prevents overestimation when large low-uptake regions are present. However, since SPECT data are not quantitative, but represent a percentage of the voxel with the highest uptake, diffuse uptake deficits could affect the data normalisation and hence the semi-quantitation, especially when normal and pathological groups are compared. This could partially explain the high relative values obtained in the occipital lobe of FLD patients and in the frontal lobe of AD patients.

The normalisation procedure we used is some kind of a 'global normalization', that is a widely accepted normalisation method, but with a built-in security procedure. Normalising to the upper 13% of all voxels means to include all voxels with 'normal' grey matter flow and some of the voxels with white matter flow. In fact, the total volume defined by the SPECT grid as a whole (the whole field of view) exceeds very much the volume of the brain. Ordinary global normalisation in stroke or in very severe circulatory disease suffers from adding pathological low values to the normalisation procedure. In our procedure, this is counterbalanced by selecting only the more relevant voxel data, including all the cerebellar ones. Furthermore, normalising all values to the average of the whole brain radioactivity would enhance the risk of overestimating low-uptake regions in advanced stages of AD and FLD.

On the other hand, both the cerebellum and thalamus, frequently used for normalisation as reference regions, might be affected in the last stages of AD [41, 42].

The changes depicted in the figures are qualitative, and the colour scale is in arbitrary units. Nevertheless, even if the pictures obtained by subtracting the average data pools do not have a statistical meaning, they paralleled the

significant statistical changes by ANCOVA. The decreased perfusion in the anterior cingulate cortex was first highlighted by subtracting FLD from NOR data sets and then shown to be a significant index of pathological brain.

In conclusion, the standardisation of brain data and the comparison between patient studies and a control data pool may represent an improvement in the diagnosis of neurodegenerative disorders. The visual interpretation of data can benefit from subtracted images and the creation of reliable pathological data banks may extend the knowledge of perfusion changes in neurodegenerative disorders. In this study, the classical pattern of reduced radiopharmaceutical uptake reduction in AD and FLD was confirmed by 3D data pool analysis. The uptake in the nucleus caudatus decreased significantly in both AD and FLD as compared to NOR. The uptake in the anterior cingulate cortex was significantly reduced in FLD.

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References

1 Wallin A, Brun A, Gustafson L, the Swedish Consensus Group: Swedish Consensus on dementia disease. Acta Neurol Scand 1994;90 (suppl):1–31.
2 Smith FW, Gemmell HG, Sharp PF: The use of ^{99}Tcm-HM-PAO for the diagnosis of dementia. Nucl Med Commun 1987;8:525–533.
3 Hunter R, McLuskie R, Wyper D, Patterson J, Christie JE, Brooks DN, McCulloch J, Fink G, Goodwin GM: The pattern of function-related regional cerebral blood flow investigated by single photon emission tomography with ^{99m}Tc-HMPAO in patients with presenile Alzheimer's disease and Korsakoff's psychosis. Psychol Med 1989;19:847–855.
4 Neary D, Snowden JS, Shields RA, Burjan AW, Northen B, MacDermott N, Prescott MC, Testa HJ: Single photon emission tomography using ^{99m}Tc-HM-PAO in the investigation of dementia. J Neurol Neurosurg Psychiatry 1987; 50:1101–1109.
5 Jagust WJ, Reed BR, Seab JP, Kramer JH, Budinger TF: Clinical-physiologic correlates of Alzheimer's disease and frontal lobe dementia. Am J Physiol Imaging 1989;4:89–96.
6 Julin P, Wahlund LO, Basun H, Persson A, Måre K, Rudberg U: Clinical diagnosis of frontal lobe dementia and Alzheimer's disease: Relation to cerebral perfusion, brain atrophy and electroencephalography. Dement Geriatr Cogn Disord 1995;6:142–147.
7 Risberg J, Gustafson L: Regional cerebral blood flow measurements in the clinical evaluation of demented patients. Dement Geriatr Cogn Disord 1997;8:92–97.
8 Holman BL, Johnson KA, Gerada B, Carvalho PA, Satlin A: The scintigraphic appearance of Alzheimer's disease: A prospective study using technetium-99m-HMPAO SPECT. J Nucl Med 1992;33:181–185.
9 Waldemar G, Bruhn P, Kristensen M, Johnsen A, Paulson OB, Lassen NA: Heterogeneity of neocortical cerebral blood flow deficits in dementia of the Alzheimer type: A [^{99m}Tc]-d,l-HMPAO SPECT study. J Neurol Neurosurg Psychiatry 1994;57:285–295.
10 Frisoni GB, Pizzolato G, Bianchetti A, Chierichetti F, Ferlin G, Battistin L, Trabucchi M: Single photon emission computed tomography with [^{99}Tc]-HM-PAO and [^{123}I]-IBZM in Alzheimer's disease and dementia of frontal type: Preliminary results. Acta Neurol Scand 1994; 89:199–203.
11 Jagust WJ, Eberling JL, Reed BR, Mathis CA, Budinger TF: Clinical studies of cerebral blood flow in Alzheimer's disease. Ann N Y Acad Sci 1997;826:254–262.
12 Ryding E: SPECT measurements of brain function in dementia; A review. Acta Neurol Scand Suppl 1996;168:54–58.
13 Syed GMS, Eagger S, O'Brien J, Barrett JJ, Levy R: Patterns of regional cerebral blood flow in Alzheimer's disease. Nucl Med Commun 1992;13:656–663.
14 Ebmeier KP, Prentice N, Ryman A, Halloran E, Rimmington JE, Best JK, Goodwin GM: Temporal lobe abnormalities in dementia and depression: A study using high resolution single photon emission tomography and magnetic resonance imaging. J Neurol Neurosurg Psychiatry 1997;63:597–604.
15 Starkstein SE, Migliorelli R, Teson A, Sabe L, Vazquez S, Turjanski M, Robinson RG, Leiguarda R: Specificity of changes in cerebral blood flow in patients with frontal lobe disease: A population-based study. Neurology 1994;44: 454–461.
16 Ishii K, Sakamoto S, Sasaki M, Kitagaki H, Yamaji S, Hashimoto M, Imamura T, Shimomura T, Hirono N, Mori E: Cerebral glucose metabolism in patients with frontotemporal dementia. J Nucl Med 1998;39:1875–1878.
17 Hirono N, Mori E, Ishii K, Ikejiri Y, Imamura T, Shimomura T, Hashimoto M, Yamashita H, Sasaki M: Frontal lobe hypometabolism and depression in Alzheimer's disease. Neurology 1998;50:380–383.
18 Kitagaki H, Mori E, Yamaji S, Ishii K, Hirono N, Kobashi S, Hata Y: Frontotemporal dementia and Alzheimer disease: Evaluation of cortical atrophy with automated hemispheric surface display generated with MR images. Radiology 1998;208:431–439.
19 Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE: Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol 1997;42:85–94.
20 Imran MB, Kawashima R, Awata S, Sato K, Kinomura S, Ono S, Yoshioka S, Sato M, Fukuda H: Parametric mapping of cerebral blood flow deficits in Alzheimer's disease: A SPECT study using HMPAO and image standardization technique. J Nucl Med 1999;40: 244–249.
21 Bartenstein P, Minoshima S, Hirsch C, Buch K, Willoch F, Mosch D, Schad D, Schwaiger M, Kurz A: Quantitative assessment of cerebral blood flow in patients with Alzheimer's disease by SPECT. J Nucl Med 1997;38:1095–1101.
22 Hirsch C, Bartenstein P, Minoshima S, Mosch D, Willoch F, Buch K, Schad D, Schwaiger M, Kurz A: Reduction of regional cerebral blood flow and cognitive impairment in patients with Alzheimer's disease: Evaluation of an observer-independent analytic approach. Dement Geriatr Cogn Disord 1997;8:98–104.
23 Houston AS, Kemp PM, Macleod MA, Francis JR, Colohan HA, Matthews HP: Use of significance image to determine patterns of cortical blood flow abnormality in pathological and at-risk groups. J Nucl Med 1998;39:425–430.

24 Greitz T, Bohm C, Holte S, Eriksson L: A computerized brain atlas: Construction, anatomical content, and some applications. J Comput Assist Tomogr 1991;15:26–38.
25 Thurfjell L, Bohm C, Bengtsson E: CBA – An atlas-based software tool used to facilitate the interpretation of neuroimaging data. Comput Methods Programs Biomed 1995;4:51–71.
26 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
27 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
28 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554.
29 Chang L-T: A method for attenuation correction in radionuclide computed tomography. IEEE Trans Nucl Sci 1978;25:638–643.
30 Andersson JLR, Thurfjell L: Implementation and validation of a fully automatic system for intra- and inter-individual registration of PET brain scans. J Comput Assist Tomogr 1997;21: 136–144.
31 Selemon LD, Goldman-Rakic PS: Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. J Neurosci 1985;5:776–794.
32 Parent A, Hazrati LN: Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 1995;20:91–127.
33 Mega MS, Cummings J, Salloway S, Malloy P: The limbic system: An anatomic, phylogenetic and clinical perspective; in Salloway S, Malloy P, Cummings JL (eds): The Neuropsychiatry of Limbic and Subcortical Disorders. Washington, American Psychiatric Press, 1997, pp 3–18.
34 McKelvey R, Bergman H, Stern J, Rush C, Zahirney G, Chertkow H: Lack of prognostic significance of SPECT abnormalities in non-demented elderly subjects with memory loss. Can J Neurol Sci 1999;26:23–28.
35 Pickut BA, Saerens J, Marien P, Borggreve F, Goeman J, Vandevivere J, Vervaet A, Dierckx R, de Deyn PP: Discriminative use of SPECT in frontal lobe-type dementia versus (senile) dementia of the Alzheimer's type. J Nucl Med 1997;38:929–934.
36 Benoit M, Dygai I, Migneco O, Robert PH, Bertogliati C, Darcourt J, Benoliel J, Aubin-Brunet V, Pringuey D: Behavioral and psychological symptoms in Alzheimer's disease. Relation between apathy and regional cerebral perfusion. Dement Geriatr Cogn Disord 1999;10: 511–517.
37 Blanco A, Alberca R, Marques, Lopez Dominguez JM, Gil Neciga E, Carrizosa E: Usefulness of SPECT in the study of Alzheimer's disease. Neurologia 1998;13:63–68.
38 Waldemar G, Walovitch RC, Andersen AR, Hasselbalch SG, Bigelow R, Joseph JL, Paulson OB, Lassen NA: ^{99m}Tc-bicisate (neurolite) SPECT brain imaging and cognitive impairment in dementia of the Alzheimer type: A blinded read of image sets from a multicenter SPECT trial. J Cereb Blood Flow Metab 1994; 14(suppl 1):S99–S105.
39 Pagani M, Jonsson C, Lundqvist R, Thurfjell L, Jacobsson H, Larsson SA: Comparison between regional 2D and volumetric 3D brain SPECT data evaluation in resting state human brain. J Nucl Med 1998;39:A106.
40 Tikofsky RS, Hellman RS: Brain single photon emission tomography: Newer activation and intervention studies. Sem Nucl Med 1991;1: 40–57.
41 Akiyama H, Harrop R, McGeer PL, Peppard R, McGeer EG: Crossed cerebellar and uncrossed basal ganglia and thalamic diaschisis in Alzheimer's disease. Neurology 1989;39:541–548.
42 Ishii K, Sasaki M, Kitagaki H, Yamaji S, Sakamoto S, Matsuda K, Mori E: Reduction of cerebellar glucose metabolism in advanced Alzheimer's disease. J Nucl Med 1997;38:925–928.