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The investigation of Alzheimer's disease with single photon emission tomography

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SUMMARY Twenty patients satisfying standard clinical criteria for Alzheimer's disease (AD) and six age-matched normal controls were studied using ^{99m}Tc hexamethyl-propyleneamine oxime and single photon emission tomography. The AD patients had lower regional cerebral blood flow (rCBF) in the temporal and posterior parietal lobes compared to controls. AD patients with apraxia and aphasia had lower rCBF in the lateral temporal and posterior parietal lobes than AD patients without these features. Within the AD group, correlations were found between neuropsychological tests and rCBF: praxis correlated with posterior parietal activity, memory with left temporal lobe activity and language with activity throughout the left hemisphere.

Neuroimaging has developed rapidly in the past few years with the introduction of *x*-ray computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission tomography (SPET). CT and MRI offer unique anatomical information while PET and SPET reveal physiological functions such as cerebral blood flow and cerebral metabolism. ^{99m}Tc hexamethyl-propyleneamine oxime (HMPAO) is a new radiopharmaceutical which crosses an intact blood brain barrier and is trapped inside functioning cells in proportion to cerebral blood flow (CBF).[1 2]

Alzheimer's disease (AD) affects between 6 to 7% of the population over the age of 65[3] and represents a major health issue. The cause is not known and no effective treatment exists. CT studies of subjects with AD have demonstrated abnormalities including cerebral atrophy and ventricular enlargement.[4] MRI has demonstrated white matter lesions and abnormal spin lattice relaxation times.[5] PET scanning has shown defects in metabolism in temporal and parietal lobes[6] and similar results have been found using SPET.[7 8] Although in some ways PET is the ideal way of studying functional imaging the technique is extremely expensive and requires a large highly trained technical staff.

The majority of SPET studies in dementia have attempted to describe the scan appearances in different types of dementia and to assess the ability of the technique to differentiate those with dementia from age matched controls. The aim of the present study was to quantify the regional distribution of ^{99m}Tc-HMPAO in the brain and is the first to determine how it relates to a number of clinical and neuropsychological characteristics of a group of AD patients.

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Subjects and methods

Subjects were selected from a series of consecutive referrals to the Memory Clinic at the Maudsley Hospital. All underwent a standard assessment including history, physical and mental state examination, blood tests and CT.[9] All satisfied current rigorous criteria for AD.[10] No patient had clinical signs of cerebellar dysfunction. Controls, who had no signs or symptoms of dementia, were selected from the relatives of patients chosen for the study. On the basis of clinical examination the AD patients were allocated to one of two groups: those in whom amnesia was the prominent feature, and those in whom significant aphasia and/or apraxia were also evident.

Psychological assessment

The following psychological tests were performed on each patient:

(1) Mini-Mental State Examination (MMSE),[11] a widely accepted 30 item scale assessing cognitive state with questions mainly testing memory and praxis.
(2) Abbreviated Mental Test Score (AMTS),[12] a 10 item scale based on the original Blessed Dementia Scale testing mainly memory.
(3) CAMCOG Battery,[13] a recently developed extensive cognitive battery which is part of a larger assessment schedule, the CAMDEX. It is divided into sections testing memory, language, praxis, attention, calculation and abstraction and has a maximum score of 107.

Table 1 *Imaging protocol and data analysis*

Imaging protocol:	
Positioning	— Supine, centred in the field of view, minimum circle of rotation
Collimation	— High resolution
Imaging time	— Rotation started 10–15 min p.i.
Resolution (projection)	— 128 × 128
Timer per projection	— 30 seconds
Projections	— 64
Uniformity correction	— 100 × 10^6 counts (^{99m}Tc scatter flood source)
Data analysis:	
Pre-processing	— Hanning 2D filtering (cut-off frequency = 0·8 cycles/cm)
Slice width	— 1 pixel (128 × 128 resolution)
Back-projection filter	— Ramp
Attentuation correction	— Yes (μ = 0·12 cm^{-1})
Post-processing	— Oblique reconstruction to standardise orientation (parallel to OM line) (slice width = 2 pixel (128 × 128 resolution))

Scanning

Written consent was obtained from each subject prior to the scan, which was approved by the local Ethical Committee. The imaging protocol and data analysis are summarised in table 1. ^{99m}Tc-HMPAO was prepared according to the manufacturer's instructions (Amersham International, plc). The tracer was injected intravenously into an ante-cubital vein with the patient sitting quietly in a well lit room.

Quantitative analysis

Square regions of interest of 4 × 4 pixels were used to obtain activity ratios in coronal slices (2 pixel width), taking the cerebellum as reference. Frontal, lateral and medial temporal, anterior and posterior parietal cortical samples were obtained. At least four measures were performed for each of the cortical areas on each hemisphere. Figure 1 shows the areas in which the regions of interest were measured. These were averaged to calculate the mean counts per voxel corresponding to each cortical region studied. This method was also applied to at least three contiguous slices of the cerebellum.

Table 2 *Regional cerebral activity in Alzheimer and control groups*

	Alzheimer N = 20	*Control N = 6*	*Significance of difference*
Age (yr, Mean, SD)	69·5, 9·2	67·5, 8·7	NS
Cerebral activity* (Mean, SD)			
R. Frontal	0·77, 0·04	0·78, 0·03	NS
R. Lateral temporal	0·72, 0·05	0·79, 0·04	$p < 0·01$
R. Medial temporal	0·69, 0·04	0·77, 0·05	$p < 0·01$
R. Anterior parietal	0·77, 0·04	0·78, 0·04	NS
R. Posterior parietal	0·72, 0·08	0·80, 0·04	$p < 0·01$
L. Frontal	0·76, 0·05	0·79, 0·03	NS
L. Lateral temporal	0·70, 0·08	0·79, 0·04	$p < 0·01$
L. Medial temporal	0·65, 0·08	0·76, 0·05	$p < 0·02$
L. Anterior parietal	0·76, 0·05	0·79, 0·05	NS
L. Posterior parietal	0·70, 0·08	0·80, 0·04	$p < 0·01$

Key: * expressed as ratio of cerebellar activity. L = left. R = right. SD = standard deviation. NS = not significant at $p < 0·05$. All statistics—Mann Whitney "U" test, two tailed (except age, Students *t* Test).

The counts per voxel of each cortical area were divided by the counts per voxel found in the cerebellar hemisphere with the highest average count, to determine the activity ratio (cerebrum/cerebellum).

These analyses were performed by one of us (DCC) blind to the clinical diagnosis or subgroup.

The ratios for AD patients were compared with those obtained from the subjects of the control group. Results were analysed using non-parametric statistics with an SPSS package.[14]

Results

Twenty patients (13 females, seven males) and six controls (three females, three males) were scanned. All subjects were right handed. No adverse reactions to the procedure occurred. Table 2 outlines the ages and metabolic activity of the regions of interest (ROIs) in

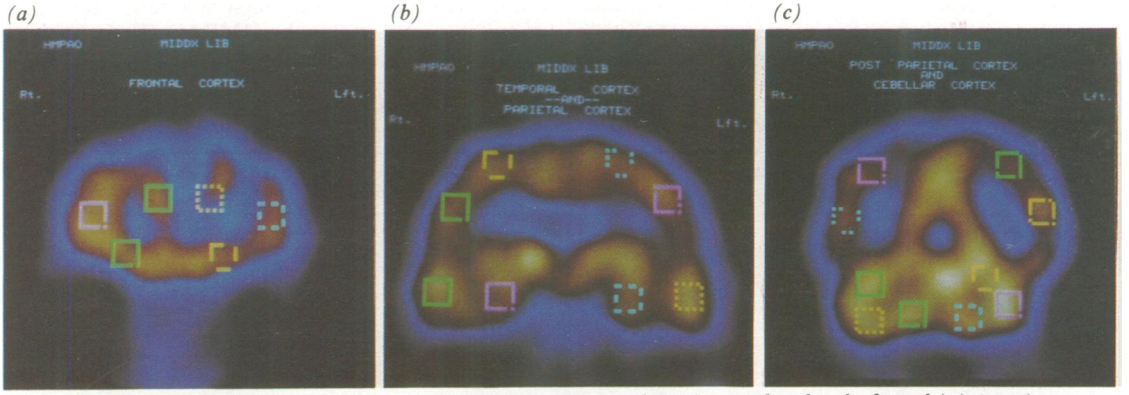

Fig 1 *Squared regions of interest, 4 × 4 pixel (128 × 128 matrix resolution) were placed in the frontal (a), anterior parietal, lateral and medial temporal (b), posterior parietal and cerebellar (c) areas of the brain. This figure shows the distribution of the regions of interest used for data analysis. At least three contiguous slices were used for each area of the brain. R–right: m–medial temporal cortex; l–lateral temporal cortex.*

Table 3 *Comparisons within the Alzheimer group*

	Aphasia/ Apraxia absent N = 8	*Aphasia/ Apraxia present N = 12*	*Significance of difference*
Age (yr, Mean, SD)	72·6, 10·3	67·4, 8·1	NS
CAMCOG-language (Mean, SD)	26·8, 1·8	11·8, 9·4	$p < 0.001$
CAMCOG-praxis (Mean, SD)	10·8, 1·8	5·7, 4·1	$p < 0.003$
Regional cerebral activity* (Mean, ± SD)			
R. Frontal	0·79, 0·02	0·76, 0·05	NS
R. Lateral temporal	0·75, 0·05	0·70, 0·05	$p < 0.05$
R. Medial temporal	0·69, 0·04	0·69, 0·04	NS
R. Anterior parietal	0·78, 0·03	0·77, 0·05	NS
R. Posterior parietal	0·76, 0·05	0·69, 0·09	$p < 0.05$
L. Frontal	0·75, 0·05	0·75, 0·05	NS
L. Lateral temporal	0·75, 0·05	0·66, 0·07	$p < 0.01$
L. Medial temporal	0·68, 0·08	0·64, 0·07	NS
L. Anterior parietal	0·77, 0·04	0·75, 0·05	NS
L. Posterior parietal	0·77, 0·04	0·66, 0·07	$p < 0.01$

Key: * expressed as ratio of cerebellar activity. L = left. R = right. SD = standard deviation. NS = not significant at $p < 0.05$. All statistics—Mann Whitney "U" test, two tailed (except age, Students *t* Test).

the two groups. The AD group had significantly lower activity bilaterally in the temporal and posterior parietal lobes.

Table 3 shows that the clinical differentiation of the AD patients into groups with and without aphasia and/or apraxia is validated by their scores on the relevant subtests of the CAMCOG. AD patients with apraxia and aphasia had significantly lower activity bilaterally in the lateral temporal lobes and posterior parietal lobes.

Correlations were examined between activity in the various ROIs and age of onset of disease, disease duration and the psychological test results (table 4). Age of onset of disease correlated positively with left posterior parietal activity and negatively with right medial temporal activity while disease duration correlated positively with left lateral temporal activity. Among the psychological tests, significant correlations existed between posterior parietal lobe activity and apraxia (measured by the MMS and CAMCOG-praxis); between temporal lobe activity (mainly left) and memory loss (as measured by the AMTS and CAMCOG-memory) and between language dysfunction and left frontal, left lateral temporal and left posterior parietal activity. Additionally, there were weaker correlations between MMS performance and left frontal and lateral temporal rCBF, CAMCOG-memory and left frontal and posterior parietal rCBF: between CAMCOG-praxis and right and left lateral temporal and CCAMCOG-language and right lateral temporal and posterior parietal rCBF.

There was no correlation between age and rCBF in the control group. A negative Spearman correlation of 0·53 ($p < 0.01$) was found between age and right medial temporal blood flow in the Alzheimer group.

Figures 2, 3 and 4 show representative scans from patients with and without aphasia and apraxia and from a normal control.

Discussion

Measurement of cerebral activity using SPET scanning has wide implications for the investigation of brain diseases. The technique is more widely available, easier to administer and cheaper than PET. Most importantly, it is less arduous for the patient and therefore is more applicable to subjects with dementia whose ability to cooperate with procedures may be impaired.

^{99m}Tc hexamethyl-propyleneamine oxime (HMPAO) crosses the intact blood brain barrier to be trapped in brain tissue according to the distribution of regional blood flow. The brain uptake of HMPAO correlates well with the regional distribution of radioactive labelled microspheres in samples of grey and white matter and mixed brain substance in dog brain.[15] However, for very high flow rates there is an underestimation of flow by HMPAO. These findings have recently been confirmed in man.[16] Based on a

Table 4 *Correlations within the Alzheimer group (n= 20)*

	Age of onset	*Disease duration*	*MMSE*	*AMTS*	*CAMCOG (MEM)*	*CAMCOG (PRAX)*	*CAMCOG (LANG)*	*CAMCOG TOTAL*
Cerebral activity								
R. Frontal	− 0·07	− 0·05	0·20	0·15	0·29	0·08	0·21	0·21
R. Lateral temporal	0·22	− 0·26	0·40*	0·03	0·33	0·47*	0·42*	0·47*
R. Medial temporal	− 0·44*	− 0·31	− 0·05	0·25	0·39*	− 0·15	0·02	0·05
R. Anterior parietal	0·08	− 0·31	0·07	− 0·08	0·08	− 0·03	− 0·01	0·05
R. Posterior parietal	0·25	− 0·17	0·64‡	0·24	0·29	0·54†	0·41*	0·51*
L. Frontal	− 0·01	0·18	0·43*	0·32	0·39*	0·34	0·55†	0·46*
L. Lateral temporal	0·28	0·48*	0·41*	0·51*	0·44*	0·42*	0·70‡	0·59†
L. Medial temporal	0·04	0·31	0·08	0·61†	0·40*	− 0·02	0·34	0·27
L. Anterior parietal	0·17	− 0·01	0·26	0·25	0·27	0·13	0·26	0·23
L. Posterior parietal	0·52†	0·17	0·53†	0·50*	0·41*	0·51*	0·68‡	0·61†

Key: L = left. R = right. All statistics are Spearman correlations.
* = $p < 0.05$; † = $p < 0.01$; ‡ = $p < 0.001$.

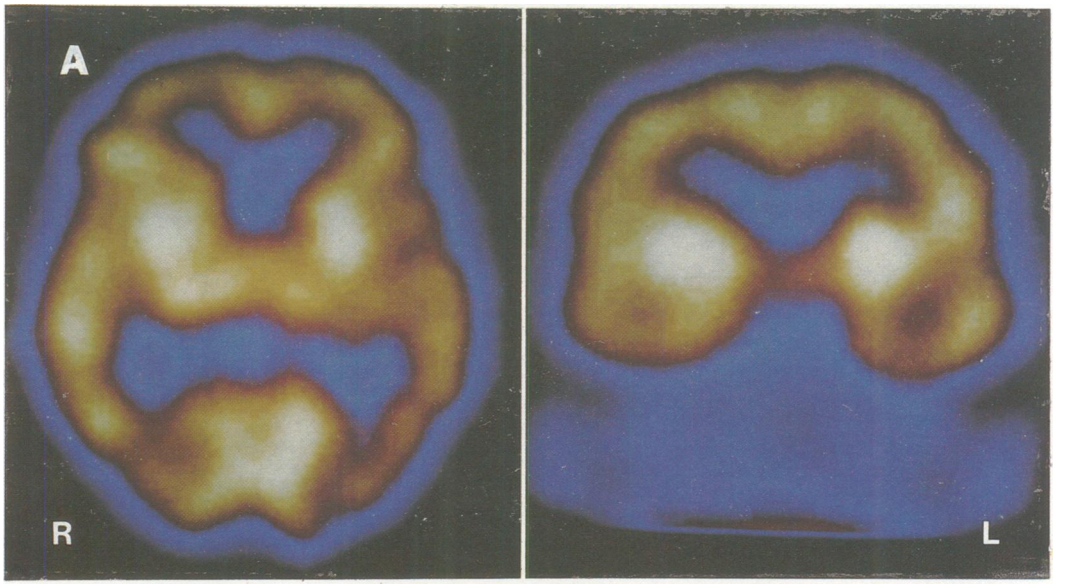

Fig 2 *Normal control—69 year old male. (No areas of hypoperfusion seen).*
Key: A = Anterior, R = Right, L = Left, Left hand image = transverse section, Right hand image = coronal section, Arrows indicate areas of hypoperfusion.

three compartmental model with flow dependent back diffusion of HMPAO, a linearisation correction has been applied which improved further the correlation of HMPAO uptake in the brain with regional cerebral blood flow (rCBF) as measured with PET and the ^{15}O steady state method. Although not perfectly linear, there is a straight relationship between HMPAO brain uptake and rCBF in the range of flow rates generally

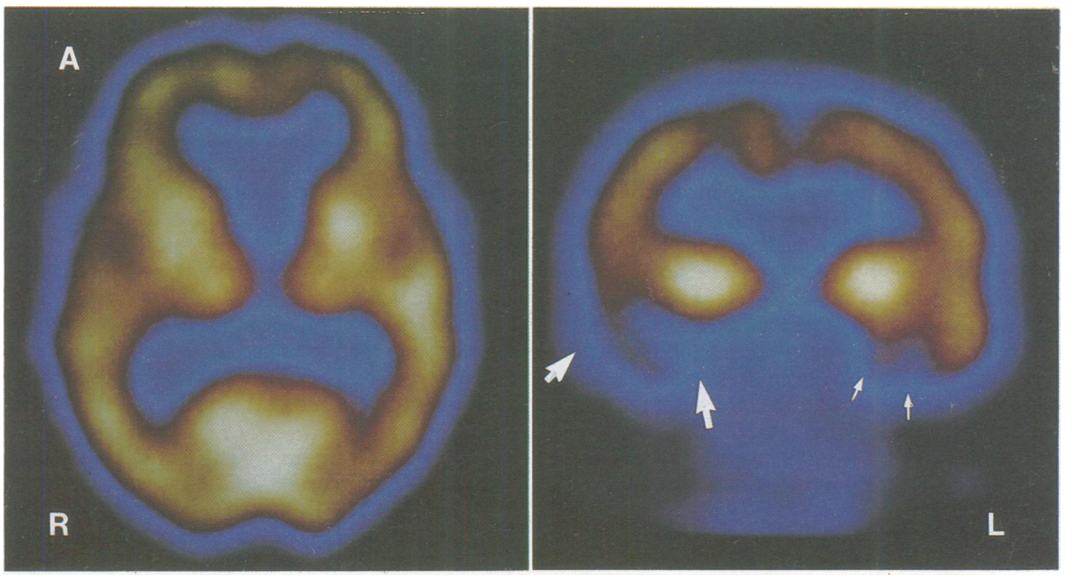

Fig 3 *Alzheimer's disease without apraxia/aphasia. Seventy two year old female with a 10 year history of deteriorating memory. Defects in the temporal lobe (mainly on the right) seen.*
Key: A = Anterior, R = Right, L = Left, Left hand image = transverse section, Right hand image = coronal section, Arrows indicate areas of hypoperfusion.

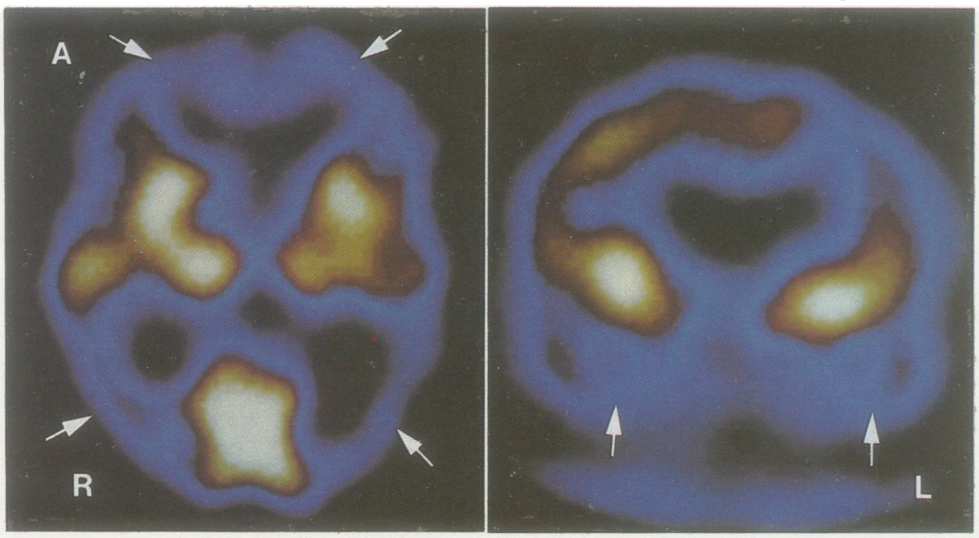

Fig 4 *Alzheimer's disease with apraxia/aphasia. Sixty seven year old man with a 6 yr history of memory impairment with apraxia and aphasia. Defects in perfusion seem bilaterally in the frontal, parietal, posterior parietal and extending into the temporal lobes.*
Key: A = Anterior, R = Right, L = Left, Left hand image = transverse section, Right hand image = coronal section, Arrows indicate areas of hypoperfusion.

observed in normal and diseased humans.

Defects in rCBF and metabolism have been demonstrated in subjects with AD. Using PET, decreased rCBF and metabolic rates have been demonstrated with ^{15}O.[17] ^{18}F deoxyglucose has been used to show decreased metabolism in frontal and temporo-parietal regions.[6 18] Protein synthesis, as measured by ^{11}C methionine, is also decreased in frontal and parietal regions.[19] SPET studies have shown broadly similar patterns. Decreased activity has been shown using I^{123}-n-isopropyl-iodoamphetamine in the posterior parietal lobe[20] and rCBF reduction in temporo-parietal and frontal regions has been demonstrated with ^{133}Xe.[17] Using ^{99m}Tc-HMPAO, posterior defects have been found commonly in dementia of Alzheimer type but not in other dementias.[8] The present study confirms these findings but helps further to localise the defects to the posterior parietal and temporal lobes.

The relationship between these metabolic deficits and clinical features has been less widely studied. Generally, it has been found that the more severe the dementia syndrome the lower the activity.[17] Specifically, decreased activity has been shown in the right parietal lobe in subjects with apraxia and in the left tempora parietal lobe in those with aphasia.[21] No specific lesion was associated with memory loss. In this study there is evidence that amnesia is associated with decreased rCBF in the temporal lobe, apraxia with reduced rCBF to the parietal lobe and aphasia with reduced rCBF throughout the left hemisphere.

Sub-classification of AD has much empirical support from a neurochemical,[22] neuropathological[23] and clinical[24] viewpoint. Younger cases tend to have a more severe illness with prominent visuo-spatial abnormalities. Studies using PET suggest that early cases show regional decrements in the parietal lobe.[25] Using HMPAO, posterior reductions were shown more commonly in AD subjects with aphasic and apraxic disorders compared to those without.[8] The present study confirms the differences in these two groups; those with visuo-spatial disorder had decreased rCBF in the lateral temporal and posterior parietal lobe. In addition, an early age of onset correlated with lower activity in the left posterior parietal lobe showing that younger age of onset results in more severe damage to this region.

Right/left asymmetries have been found in studies of AD patients using both PET[26] and SPET.[8] The cause of this is not known but it is more common in AD patients than in controls. It has been found that late onset AD is associated with deficits of the left side whereas early onset AD is associated with deficits on the right.[28]

Future research employing SPET should not be limited to replicating the now well-documented differences in rCBF between patients with AD and normal controls but should also include investigation of the effects of cerebral activation tasks. New radiopharmaceuticals may be developed to image receptor systems such as in the case of the muscarinic receptor[26] which has particular relevance to AD in view of the cholinergic hypothesis.

In conclusion, the present study validates the use of HMPAO in producing distinct patterns of cerebral blood flow in AD patients. It is the first study to correlate regional cerebral blood flow with discrete neuropsychological functions.

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