(^{99m}Tc) -HM-PAO SPECT and cognitive impairment in Parkinson's disease: a comparison with dementia of the Alzheimer type

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Abstract

Regional cerebral perfusion was evaluated by single photon emission tomography (SPECT) using (^{99m}Tc) -HM-PAO as a tracer, in thirty Parkinsonian patients with (n = 15) or without (n = 15) dementia, nineteen patients with dementia of the Alzheimer type (DAT) and thirteen control subjects. HM-PAO uptake was measured in the frontal, parietal, temporal and occipital cortex and tracer perfusion was expressed as cortical/cerebellar activity ratios. Regional HM-PAO ratios in non-demented Parkinsonian patients did not differ from controls, whereas in demented patients with Parkinson's disease (DPD) a significant reduction was found in the parietal, temporal and occipital cortex. Tracer uptake ratios were significantly reduced in all regions in the DAT group. Thus DPD and DAT shared a common pattern of marked posterior hypoperfusion, although the perfusion defect was greater and more extensive in the DAT patients.

Intellectual deterioration occurs in 10–40% of patients with Parkinson's disease (PD),¹ especially in the delayed onset and akinetic-rigid forms of the disease.² However, the nature of this dementing process and particularly its relationship with dementia of the Alzheimer type (DAT) remain controversial.^{3,4}

Measurement of regional cerebral blood flow (rCBF) using positron emission tomography (PET) or single photon emission computed tomography (SPECT) techniques provide a useful approach to the study of human degenerative dementias.⁵ Whereas there is general agreement that a global reduction in rCBF and metabolism, predominantly affecting the parieto-temporal regions is encountered in DAT,^{6–9} the available data in PD are conflicting, and do not allow distinctions in specific patterns of rCBF or metabolism between Parkinsonian patients with or without dementia.^{10–13}

These results led us to further investigate regional cerebral perfusion modifications in PD with or without dementia, and to compare the observed modifications to those found in patients suffering from DAT. In this study, regional cerebral perfusion was measured by SPECT using technetium-99m d,l-hexamethyl-propyleneamine oxime ((^{99m}Tc) -HM-PAO) as tracer.¹⁴

Patients and methods

PATIENTS AND CONTROLS

Forty nine right handed patients, thirty with idiopathic PD and nineteen with probable DAT, according to the criteria of McKhann *et al*,¹⁵ participated in the study (table 1). General exclusion criteria were the following: hypertension, cardiovascular disease, diabetes, Hachinski ischaemic score¹⁶ equal to or above four, history of alcohol abuse, head trauma, serious physical illness that could affect the CNS function or a history of other psychiatric illness, and focal abnormalities on EEG or CT-scan. Patients with Parkinsonism that was post-encephalitic, drug-induced or a feature of multisystem disease, as well as with thalamotomies, were excluded. None of the patients was taking medication known to affect overall brain metabolism or cerebral circulation, except for levodopa¹¹ or dopamine (DA) agonists.¹⁷ Thirteen right handed volunteers were chosen as controls: none had a history of any CNS, metabolic, psychiatric and cardiovascular disorders, and were not taking any CNS-acting medication. Patients and controls were submitted to a neurological examination, the Mini Mental State (MMS)¹⁸ assessment (scores were above 27/30 for controls and non-demented subjects), blood tests, including thyroid function, serological tests for syphilis, estimation of B₁₂, CSF analysis (for DAT group only), brain CT scan, EEG and neck vessel Doppler sonography. To further evaluate cognitive functions, patients had a detailed neuropsychological assessment, including the Benton Visual Retention test, the Raven Progressive Matrices test (PM 47), the Binoit-Pichot Vocabulary test and the Wechsler Memory scale.¹⁹

On the basis of this clinical and neuropsychological assessment, patients with PD were divided into two subgroups: fifteen non-demented (NDPD) and fifteen demented (DPD) patients. The diagnosis of dementia was based on the neuropsychological test results with a history of progressive intellectual decline and impaired mental status with normal level of consciousness, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R).²⁰ The severity of intellectual deterioration was estimated from the MMS test score.¹⁸ Among the NDPD patients, fourteen were under levodopa treatment in combination with a peripheral decarboxylase inhibitor (carbidopa or benserazide), associated with DA agonists, bromocriptine (average 18 mg/day, range 5–30, n = 7) and/or piribedil (average 89 mg/

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Table 1 Clinical features of controls and patients

Features	Controls (n = 13)	NDPD (n = 15)	DPD (n = 15)	DAT (n = 19)
Sex (M:F)	5:8	11:4	9:6	6:13
Age (years)	71 (6)* 58–81	69 (8) 59–80	74 (5) 63–83	70 (8) 58–87
Hohen and Yahr stage	—	3.5 (0.8) 2–5	4.1 (0.7) 3–5	—
Disease duration (years)	—	12 (8) 2–26	11 (8) 3–28	—
Levodopa therapy: dosage (mg/day)	—	675 (371) 300–1400	456 (268) 150–1250	—
duration (years)	—	9 (6) 2–19	7 (5) 2–18	—
Dementia duration (years)	—	—	3 (1.3) 2–7	3 (1.2) 2–7
MMS score	30 (0.6) 28–30	29 (1.1) 27–30	14 (6)** 2–23	9 (6)** 2–19

NDPD = non-demented patients with Parkinson's disease, DPD = demented patients with Parkinson's disease, DAT = dementia of the Alzheimer type.

*Mean (SD)/range. M = Male, F = Female, MMS = Mini Mental State.

Data were analysed by ANOVA followed, in the case of significance ($p < 0.05$), by Scheffé's test. Unpaired Student's *t* test was used when appropriate.

** $p < 0.001$ compared with controls, Scheffé's test.

day, range 60–140, $n = 9$). One patient had been treated only with piribedil (160 mg/day). All DPD patients were being treated with levodopa; three were also receiving bromocriptine (range 7.5–15 mg/day). None of the NDPD or DPD patients was taking anticholinergic drugs. Neuropsychological tests could not be administered to five of the demented patients. Tremor was more frequently observed in the NDPD group (10 out of 15 patients), whereas the akinetic-rigid syndrome was predominant in the DPD group (14 out of 15). CT scan revealed a mild diffuse cortical atrophy in four NDPD and 13 DPD patients. The EEGs were slightly altered in all the DPD, but only in four of the NDPD patients.

All patients with DAT met clinical criteria for probable Alzheimer's disease.¹⁵ Thirteen DAT patients were unmedicated, six were taking benzodiazepines, and three were receiving low doses of antipsychotic drugs. For the DAT patients, medication was discontinued 48 hours before the SPECT scan. Neuropsychological tests could not be administered to six of the DAT patients. For all DAT patients, CSF was normal, CT scan showed a mild to moderate diffuse cortical atrophy and EEGs were slightly altered, with slowing of posterior alpha rhythm and sometimes increasing diffuse alpha activity.

REGIONAL HM-PAO UPTAKE

Cerebral perfusion was assessed by SPECT with (^{99m}Tc)-HM-PAO as tracer. HM-PAO has been shown to cross the blood-brain barrier and to distribute in the brain in proportion to blood flow.¹⁴ Thus selective modifications of cerebral tracer uptake reflect changes in rCBF. Assuming that blood flow and cerebral metabolism are linked in the normal and chronically diseased brain,⁶ rCBF may represent an index of cerebral functional activity.²¹

Experiments were carried out under resting conditions in a quiet room with reduced lighting and background noise to eliminate external acoustic and visual stimulation which are known to affect rCBF and brain metabolism.²²

Patients lay supine, but awake with their eyes covered, for at least 20 minutes before injection of the radiotracer. The HM-PAO freeze-dried kit (Ceretek, Amersham International, London, UK) was reconstituted with (^{99m}Tc)-pertechnetate solution, and a dose of 925 MBq (25 mCi) was injected within 20 minutes of tracer preparation through an indwelling cannula into an antecubital vein. Computed imaging was carried out between 15–45 minutes after the injection using a single-head rotating gamma camera (Gamma-Tome Sopha Medical) coupled to a brain SPECT designed collimator (THR-BE) and a dedicated computer system (Sopha Medical S 4000). Data acquisition was performed in a sagittal plane (from 0 to 180°) from nose to occiput. For each subject, 32 angular views, each collected over 50 seconds, were recorded into a 64 × 64 matrix. Slices were then reconstructed from the prefiltered raw data (pseudo-Wiener), by the filtered backprojection algorithm using a ramp filter. No correction for attenuation was made. Reconstructed brain slices were then reorientated on the orbitomeatal line and a set of 12 axial, sagittal and coronal sections at 6 mm increments was finally obtained for each subject.

Regional tracer uptake was measured by a semi-quantitative method⁹ with minor modifications. For each subject, three adjacent axial slices (4 pixel thick = 24 mm) were considered: one corresponding to the cerebellum and two supratentorial (superior and inferior). On each slice, regions of interest (ROIs: 3 × 3 pixels, 18 × 18 mm), were drawn as symmetrically as possible on the cerebellar hemispheres (two pairs) and on the cortical ribbon at the following levels (fig 1): superior frontal (three pairs) and parietal (four pairs) for the superior supratentorial slice, inferior frontal (three pairs), temporal (four pairs) and occipital (one pair) for the inferior supratentorial one. Cerebral regions were defined according to a standard CT scan brain atlas.²³ However, the limited anatomical precision inherent in this method should be borne in mind. ROIs were analysed by one investigator who was unaware of the clinical findings, and had no contact with the patients. For each right-left cortical region, as well as for the whole cerebellum, the radioactivity count densities of corresponding ROIs were averaged. Relative cortical regional perfusion was expressed as the ratio of cortical/cerebellar activities. In this study, a semi-quantitative assessment of regional cerebral perfusion comparing cortical to cerebellar ROIs was used. At present, quantitative data cannot be retrieved from SPECT. This method has been used to analyse changes in rCBF in DAT^{9,24} and PD,¹⁰ and relies on the assumption that cerebellar rCBF is unaffected in these conditions, which is borne out by pathological^{25,26} and metabolic^{11,24} findings.

STATISTICAL ANALYSIS

Mean (SD) values of cortical/cerebellar ratios were calculated for all the cortical regions studied in each group. Comparisons among groups for clinical parameters (age, disease and

Figure 1 SPECT images showing supratentorial (1 = upper; 2 = lower) and cerebellar (3) slices of a control subject. Regions of interest (ROIs) were symmetrically outlined on the cortical ribbon and cerebellar hemispheres. Pictures were normalised to the maximum pixel value of all frames. SF = Superior Frontal, IF = Inferior Frontal, P = Parietal, T = Temporal, O = Occipital. R = Right hemisphere, L = Left hemisphere.

duration of dementia, levodopa dosage and treatment duration, MMS score) and for cortical/cerebellar ratios of HM-PAO uptake were made by one-way analysis of variance. When significant ($p < 0.05$), these were followed by Scheffé's test for multiple comparisons, or by unpaired Student's t tests as appropriate. For categorical data, the Chi square test was used. Right-left regional ratio asymmetries, calculated as a right minus left/right plus left activity ratio, were evaluated in each group by a one sample Student's t test. Relationships between clinical parameters and changes in regional ratios were assessed by calculating the Spearman linear coefficient of correlation r (significance was accepted for $p < 0.05$).

Table 2 Cortical/cerebellar activity ratios for the different cerebral regions

Region		Controls (n = 13)	NDPD (n = 15)	DPD (n = 15)	DAT (n = 19)
SF	R	1.01 (0.08)*	1.02 (0.07)	0.96 (0.09)	0.85 (0.11) ^{bb}
	L	1.01 (0.06)	1.01 (0.08)	0.97 (0.07)	0.86 (0.10) ^{bb}
IF	R	1.09 (0.08)	1.08 (0.06)	1.05 (0.11)	0.95 (0.12) ^b
	L	1.08 (0.10)	1.09 (0.08)	1.05 (0.07)	0.94 (0.15) ^b
P	R	1.07 (0.06)	1.05 (0.07)	0.92 (0.10) ^{***}	0.81 (0.12) ^{bb}
	L	1.06 (0.05)	1.03 (0.09)	0.93 (0.09) ^{***}	0.80 (0.10) ^{bbb}
T	R	1.02 (0.04)	1.00 (0.06)	0.84 (0.08) ^{***}	0.78 (0.08) ^b
	L	1.03 (0.05)	0.99 (0.07)	0.84 (0.06) ^{***}	0.78 (0.09) ^b
O	R	1.13 (0.08)	1.14 (0.07)	1.03 (0.12) ^a	1.04 (0.07)
	L	1.14 (0.10)	1.12 (0.07)	1.01 (0.09) ^{aa}	1.02 (0.12)

NDPD = non-demented patients with Parkinson's disease, DPD = demented patients with Parkinson's disease, DAT = dementia of the Alzheimer type.

*Mean (SD). SF = Superior Frontal, IF = Inferior Frontal, P = Parietal, T = Temporal, O = Occipital. R = Right hemisphere, L = Left hemisphere.

Data were analysed by ANOVA followed, in the case of significance ($p < 0.05$), by Scheffé's test for multiple comparisons among controls, NDPD and DPD. DPD and DAT were compared using the unpaired Student's t test.

^a $p < 0.05$, ^{aa} $p < 0.01$, ^{***} $p < 0.001$ compared with NDPD, Scheffé's test.

^b $p < 0.05$, ^{bb} $p < 0.01$, ^{bbb} $p < 0.001$ compared with DPD, Students t test.

Significant differences between DAT and controls are mentioned in the text.

Results

PATIENT DETAILS

Clinical features of controls and patients are shown in table 1. No significant differences in age among the four groups was found (ANOVA, $F = 1.8957$, $df = 3$, $p = 0.15$). NDPD and DPD did not differ in duration of illness or dosage and duration of levodopa therapy (Student's t test, $p > 0.05$). NDPD displayed a milder form of the disease than DPD as evaluated on the Hoehn and Yahr scale,²⁷ but the difference was not significant (Chi square test, $p > 0.05$). Moreover, in our population, dementia was mainly associated with the akinetic-rigid forms of PD,² whereas tremor was the major motor symptom when cognition was better preserved.

All DAT patients presented a progressive decline in memory function, impaired judgement and abstract thinking, together with difficulties in language, perception and praxis. In the DPD group, memory disorders, impaired judgement and abstract thinking were associated with aphasia in six cases; apraxia was present in only three cases. The duration of dementia was similar in the DPD and DAT groups (Student's t test, $p > 0.05$). As shown in table 1, the demented patients (DPD and DAT) scored significantly lower on the MMS examination than controls and NDPD group (Scheffé's test, $p < 0.001$). The MMS score was not significantly different between the DPD and DAT groups, nor between controls and the NDPD group (Scheffé's test, $p > 0.05$). The duration of dementia was significantly correlated with the MMS score in the DAT patients ($r = -0.47$, $p < 0.05$), but not in the DPD group ($r = -0.23$, $p > 0.05$).

REGIONAL CORTICAL HM-PAO UPTAKE

Table 2 shows the mean (SD) values of the cortical/cerebellar activity ratios obtained from the different brain regions of control subjects and patients. Although right to left asymmetries in cortical regions were occasionally observed in individual cases, overall regional mean cortical values were not significantly different on the two sides in all the groups studied (Student's t test, $p > 0.05$). Controls showed a homogeneous distribution of the radiotracer over all cortical regions, similar to that reported in normal subjects.⁹ The highest activity ratios were found in the occipital cortex, and the lowest in the superior frontal cortex. No significant differences in HM-PAO uptake ratios were found between NDPD and controls for any of the cortical regions (Scheffé's test, $p > 0.05$). In contrast, mean tracer uptake was significantly reduced in the parietal, temporal and occipital cortex, but not in the superior and inferior frontal regions of DPD, compared with the NDPD group and controls (Scheffé's test, $p < 0.05$). In the NDPD and DPD groups, regional perfusion bore no relation to the severity of the disease evaluated on the Hoehn and Yahr scale²⁷ (ANOVA, $p > 0.05$).

In the DAT group, HM-PAO uptake ratios were significantly lower than those of controls

Figure 2 Percentage reduction from control values of HM-PAO ratios in demented Parkinsonian and Alzheimer's disease groups. Right and left values for each cortical region were averaged. DPD = demented patients with Parkinson's disease, DAT = dementia of the Alzheimer type. SF = Superior Frontal, IF = Inferior Frontal, P = Parietal, T = Temporal, O = Occipital.

in all the regions considered (Student's *t* test, $p < 0.001$ for superior frontal, parietal, temporal; $p < 0.01$ for inferior frontal and occipital cortex). The hypoperfusion predominantly affected the parieto-temporal regions as well as the superior frontal cortex. Compared with DPD patients, perfusion values in the patients with DAT were significantly reduced in all cortical regions, except the occipital cortex (Student's *t* test, $p < 0.05$ for significances, table 2).

Figure 2 shows the ratios of regional HM-PAO uptake reduction in the DPD and DAT groups expressed as percentages of control values. Perfusion values for right and left hemispheres were averaged. DPD and DAT groups shared a pattern of prominent posterior hypoperfusion, but in the DPD group, superior and inferior frontal cortices were

spared (3–4% versus 15–17% reduction in DAT) and parieto-temporal hypoperfusion was less severe (13–19% versus 24% reduction in DAT group).

Figure 3 shows a typical pattern of the HM-PAO uptake defect observed in DPD and DAT.

CORRELATIONS BETWEEN REGIONAL CORTICAL/CEREBELLAR HM-PAO RATIOS AND CLINICAL FEATURES

No significant correlations between HM-PAO ratios and age, duration of disease, duration and severity of dementia evaluated from the MMS score, were found in either the NDPD or the DPD groups. In the DAT group, a positive correlation between age and cerebral perfusion was found in the left (L) and right (R) parietal (P), left temporal (LT) and left occipital (LO) regions (RP: $r = 0.55$; LP: $r = 0.67$; LT: $r = 0.58$; LO: $r = 0.54$; $p < 0.05$). Moreover, in this group the duration of dementia, but not the MMS score, was significantly correlated with the extent of the reduction in tracer uptake ratios in the left parietal and temporal cortical regions (LP: $r = -0.54$; LT: $r = -0.47$; $p < 0.05$).

Discussion

In this study, regional cortical HM-PAO uptake was measured in non-demented and demented Parkinsonian patients, in patients with DAT and in age-matched control subjects. The results demonstrate that dementia in PD is associated with marked changes in posterior cortical perfusion. A significant bilateral decrease in HM-PAO ratios was found in the parietal, temporal and occipital cortex of the DPD patients (table 2). Moreover, this pattern of hypoperfusion was similar to that found in patients with DAT (fig 2). In contrast to DPD, HM-PAO ratios in NDPD were not significantly different from controls. This agrees with other PET and SPECT studies showing a lack of reduction in rCBF in NDPD patients under levodopa treatment.¹⁰ However, a mild reduction in rCBF or metabolism has been described in NDPD patients who were not receiving levodopa at the time of investigation.¹¹ The presence of levodopa at the time of the investigation may account for this discrepancy. However, it should be noted that although levodopa increases rCBF following acute administration,¹¹ flow values return almost to their baseline after some weeks of regular therapy.¹¹

A reduction in cerebral perfusion¹⁰ or in metabolism¹³ predominantly affecting posterior cortical regions in Parkinsonian patients with dementia has also been described by other workers. However, Globus *et al*¹² did not find any relationship between the extent of the reduction in rCBF and the presence or the severity of intellectual deterioration in Parkinsonian patients. Although a frontal lobe dysfunction has been described clinically in PD,²⁸ no significant frontal hypoperfusion under basal conditions was observed either in our population of DPD or in other studies.^{10,13}

Figure 3 SPECT images showing cortical HM-PAO uptake distribution in one patient with dementia of the Alzheimer type (DAT; 1A = upper, 1B = lower slices) and in one demented Parkinsonian patient (DPD; 2A = upper, 2B = lower supratentorial slices). For each subject, pictures were normalised to the maximum pixel value of all frames. R = Right hemisphere, L = Left hemisphere.

In our study, the NDPD and DPD groups were well matched for age, disease duration, as well as for the amount and the duration of levodopa medication (table 1). Most of the NDPD patients and only three of DPD were receiving DA agonist medication at the time of investigation. It is unlikely that DA agonists were responsible for the observed effects on cortical perfusion since it has been shown that they have similar effects to levodopa on rCBF.¹⁷

A major difference between the NDPD and DPD groups was the presence of cortical atrophy (CA) in the DPD group: 13 out of 15 DPDs and only four out of 15 NDPDs had some evidence of mild and diffuse CA on CT scans. CA may bias regional measurement of rCBF and metabolism in ageing and dementia,²⁹ and may lead to spuriously low values of regional radioactivity uptake because of volume averaging between brain and non-brain (CSF) spaces. CA has, however, been shown to have a relatively small effect on regional brain metabolism or rCBF measured by PET,²⁹ and focal metabolic abnormalities are only partially associated with regional CA changes.³⁰ It should be noted that in our patients (NDPD and DPD), CA affected all cortical areas equally, and was not restricted to the posterior regions where alterations in perfusion were observed. It is therefore unlikely that atrophy alone can account for the observed differences in regional cerebral perfusion between the DPD and NDPD groups.

Relative to normal subjects, overall cortical perfusion was depressed in patients with DAT, with the largest reduction in the parieto-temporal and superior frontal cortices, whereas occipital regions were relatively spared. These results agree with previous PET and SPECT studies reporting similar changes either in flow⁶⁻⁹ or in brain metabolism.⁶ In contrast to previous reports,⁶ but in common with others,^{7,9} we did not find any significant positive correlation between the defects in regional perfusion and the severity of the cognitive impairment as evaluated by the MMS score. Our lack of significance, however, may have been due to the limited number of cases examined. Furthermore, the relative insensitivity of the MMS test should not be overlooked.³¹

Interestingly, the pattern of HM-PAO uptake reduction observed in DPD was similar to that found in DAT (fig 2). In both groups, lesions were predominantly in the parieto-temporal regions, although hypoperfusion was more severe in the DAT group. CT scans showed that the DPD and DAT patients had comparable diffuse CA. Single observations have indicated that DPD may be accompanied by a parieto-temporal hypometabolism that has been considered to be characteristic of DAT.¹³

The nature of the dementia observed in PD is still controversial. The problem is to decide whether the dementia is due to coincidental DAT or to pathology specific to PD itself. The cognitive deficit in PD has generally been referred to as subcortical dementia,⁴ in contrast to cortical dementia such as that found in DAT, but the clinical and anatomical bases of this

distinction are open to criticism. First, the neuropsychological features in the two conditions are not always clear-cut.⁴ Second, several studies have provided evidence for an overlap of histological^{26,32} and neurochemical^{33,34} cortical and subcortical lesions underlying the dementia in both diseases. Taken together, these findings indicate that dementia in PD may be due to the coexistence of PD with DAT.^{3,4} Cognitive impairment may be present in Parkinsonian patients with no evidence of DAT brain pathology.³⁵ In addition, DAT-like dementia may be associated with Parkinsonism in patients with widespread cortical Lewy bodies, but without the histological lesions that are characteristic of DAT.³⁶

In conclusion, our results demonstrate that dementia in PD, as defined by DSM-III-R criteria,²⁰ is accompanied by marked defects in the perfusion of posterior cortical structures, which resemble the pattern of defects observed in DAT. Further neuropsychological and clinicopathological studies will be needed to clarify the relationship between these two disorders.

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- 1 Mayeux R, Stern Y, Rosenstein R, *et al.* An estimate of the prevalence of dementia in idiopathic Parkinson's disease. *Arch Neurol* 1988;45:260-2.
- 2 Garron DC, Klawans HL, Narin F. Intellectual functioning of persons with idiopathic parkinsonism. *J Nervous Mental Dis* 1972;154:445-52.
- 3 Rossor MN. Parkinson's disease and Alzheimer's disease as disorders of the isodentritic core. *BMJ* 1981;283:1588-90.
- 4 Whitehouse PJ. The concept of subcortical and cortical dementia: another look. *Ann Neurol* 1986;19:1-6.
- 5 Fazio F, Messa G. Perfusion and metabolism in the dementias. A comparison between PET and SPECT. In: Agnoli A, Cahn J, Lassen N, Mayeux R, eds. *Senile dementia*. II International Symposium. Paris: John Libbey Eurotext 1988:393-7.
- 6 Frackowiak RSJ, Pozzilli C, Legg NJ, *et al.* Regional cerebral oxygen supply and utilization in dementia. A clinical and physiological study with oxygen-15 and positron tomography. *Brain* 1981;104:753-78.
- 7 Deutsch G, Tweedy JR. Cerebral blood flow in severity-matched Alzheimer and multi-infarct patients. *Neurology* 1987;37:431-8.
- 8 Neary D, Snowden JS, Shields RA, *et al.* Single photon emission tomography using ^{99m}Tc-HM-PAO in the investigation of dementia. *J Neurol Neurosurg Psychiatry* 1987;50:1101-9.
- 9 Perani D, Di Piero V, Vallar G, *et al.* Technetium-99mHM-PAO-SPECT study of regional cerebral perfusion in early Alzheimer's disease. *J Nucl Med* 1988;29:1507-14.
- 10 Pizzolato G, Dam M, Borsato N, *et al.* (^{99m}Tc)-HM-PAO SPECT in Parkinson's disease. *J Cereb Blood Flow Metab* 1988;8(suppl 1):S101-8.
- 11 Leenders KL, Wolfson L, Gibbs JM, *et al.* The effects of L-Dopa on regional cerebral blood flow and oxygen metabolism in patients with Parkinson's disease. *Brain* 1985;108:171-91.
- 12 Globus M, Mildworf B, Melamed E. Cerebral blood flow and cognitive impairment in Parkinson's disease. *Neurology* 1985;35:1135-9.
- 13 Kuhl DE, Metter EJ, Riege WH. Patterns of local cerebral glucose utilization determined in Parkinson's disease by the (18F)-fluorodeoxyglucose method. *Ann Neurol* 1984;15:419-24.
- 14 Neirinckx RD, Canning LR, Piper IM, *et al.* Technetium-99m d,l-HM-PAO: a new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion. *J Nucl Med* 1987;28:191-202.
- 15 McKhann G, Drachman D, Folstein M, *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;34:939-44.
- 16 Hachinski VC, Ilif LD, Zihka E, *et al.* Cerebral blood flow in dementia. *Arch Neurol* 1975;32:632-7.
- 17 Bes A, Guell A, Fabre N, Arne-Bes MC, Gerand G. Effects of dopaminergic agonists (Piribedil and bromocriptine) on cerebral blood flow in Parkinsonism. *J Cereb Blood Flow Metab* 1983;3(suppl 1):S490-1.
- 18 Folstein MF, Folstein SE, McHugh PR. Mini-mental state of practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.

- 19 Lezak MD. *Neuropsychological assessment*, 2nd ed. New York: Oxford University Press, 1983.
- 20 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 3rd ed, Revised (DSM-III-R). Washington: American Psychiatric Association, 1987.
- 21 Lou HC, Edvinsson L, Mackenzie ET. The concept of coupling blood flow to brain function: revision required? *Ann Neurol* 1987;22:289-97.
- 22 Mazziotta JC, Phelps ME, Carson RE, Kuhl DE. Tomographic mapping of human cerebral metabolism: sensory deprivation. *Ann Neurol* 1982;12:435-44.
- 23 Matsui T, Hirani A. *An atlas of the human brain for computed tomography*. New York: Igaku-Shoin Medical, 1978.
- 24 Johnson KA, Mueller ST, Walsher TM, et al. Cerebral perfusion imaging in Alzheimer's disease: use of SPECT and I-123 IMP. *Arch Neurol* 1987;44:165-8.
- 25 Brun A, Englund E. Regional pattern of degenerative in Alzheimer's disease: neuronal loss and histopathological grading. *Histopathology* 1981;5:549-64.
- 26 Forno LS. Pathology of Parkinson's disease. In: Marsden CD, Fahn S, eds. *Movements disorders*. London: Butterworth Scientific, 1982:25-40.
- 27 Hoehn MM, Yahr MD. Parkinsonism: Onset, progression and mortality. *Neurology* 1967;17:952-60.
- 28 Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. *Brain* 1986;109:845-83.
- 29 Yoshii F, Barker WW, Chang JY, et al. Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy and cerebro-vascular risk factor. *J Cerebr Flow Metab* 1988;8:654-61.
- 30 Fazekas F, Alavi A, Chawluk JB, et al. Comparison of CT, MR and PET in Alzheimer's dementia and normal aging. *J Nucl Med* 1989;30:1607-15.
- 31 Huff FJ, Becker JT, Belle SH, et al. Cognitive deficits and clinical diagnosis of Alzheimer's disease. *Neurology* 1987;37:1119-24.
- 32 Ditter SM, Mirra SS. Neuropathologic and clinical features of Parkinson's disease in Alzheimer's disease patients. *Neurology* 1987;37:754-60.
- 33 Perry EK, Curtis M, Dick DJ, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1985;43:413-21.
- 34 Hardy J, Adolfsson R, Alafuzoff I, et al. Transmitter deficit in Alzheimer's disease. *Neurochem Int* 1985;7:545-63.
- 35 Hornykiewicz O, Kish SJ. Neurochemical basis of dementia in Parkinson's disease. *Can J Neurol Sci* 1984;11:185-90.
- 36 Hansen L, Salmon D, Galasko D, et al. The Lewy body variante of Alzheimer's disease: a clinical and pathologic entity. *Neurology* 1990;40:1-8.