

## SPECT findings in Alzheimer's disease and Parkinson's disease with dementia

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We examined, with single photon emission tomography (SPECT) and (<sup>99m</sup>Tc)-HMPAO, 18 patients with idiopathic Parkinson's disease and no dementia (PD), 12 patients with PD and dementia, 24 patients with probable Alzheimer's disease (AD), and 14 controls. While the three patient groups showed significantly lower perfusion in frontal inferior and temporal inferior areas as compared to controls, both demented groups showed significantly more severe bilateral hypoperfusion in superior frontal, superior temporal and parietal areas as compared to non-demented PD patients and controls. On the other hand, no significant differences in cerebral perfusion were found between patients with AD and patients with PD and dementia. In conclusion, our findings demonstrated specific but similar cerebral perfusion deficits in demented patients with either AD or PD.

**Keywords:** Alzheimer's disease – Parkinson's disease – SPECT

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### INTRODUCTION

Cerebral perfusion studies have consistently demonstrated significant bilateral perfusion deficits involving association areas of temporal, parietal and frontal lobes in patients with probable Alzheimer's disease (AD) (Spampinato *et al.*, 1991). On the other hand, few studies examined specific cerebral perfusion changes in patients with Parkinson's disease (PD) and dementia.

Spampinato *et al.* (1991) evaluated 15 patients with PD and no dementia, 15 patients with both PD and dementia, 19 patients with AD and 13 normal controls using single photon emission tomography (SPECT) and (<sup>99m</sup>Tc)-HMPAO as a tracer. While both AD and PD-dementia groups showed significantly lower parietal, temporal and occipital perfusion as compared to non-demented PD patients and normal controls, there were no significant differences in any brain region between the AD and the PD-dementia groups. While these findings suggest that AD and PD with dementia share a common pattern of temporo-parietal hypoperfusion, one important limitation of the study was that both the AD and the PD groups were moderately to

severely demented [mean Mini-Mental State Exam (Folstein *et al.*, 1975) scores for AD and PD-dementia groups were 9 and 14, respectively]. Thus, whether AD and PD-dementia groups have different brain metabolic correlates in the early stages of dementia but similarly widespread hypoperfusion in late stages of the disease (when brain pathology is more extensive) could not be determined.

In a recent study, we found that 79% of patients with AD showed extrapyramidal signs [23% with parkinsonism (i.e. bradykinesia and rigidity, and/or tremor) and 56% with isolated extrapyramidal signs (e.g. shuffling gait, hypophonia, masked faces, etc.)] (Merello *et al.*, 1994). Spampinato *et al.* did not state whether they ruled out parkinsonism in their AD patients and the inclusion of such patients may explain the similar profile of cerebral perfusion deficits in AD and PD-dementia groups.

Thus, to examine cerebral perfusion differences between AD and PD with dementia we assessed, with <sup>99m</sup>Tc-HMPAO and SPECT, a series of patients with probable AD and no parkinsonism, patients with PD

and dementia, patients with PD without dementia and a group of age-comparable controls.

## PATIENTS AND METHODS

### Patients

We examined a consecutive series of patients with either probable AD or PD attending the neurology outpatient clinic of our institute. The inclusion criteria were as follows:

*AD group.* This group consisted of 24 patients who met the NINCDS-ADRDA (Mc Khann *et al.*, 1984) criteria for probable AD. Additional inclusion criteria were the absence of focal lesions on the MRI scan, a Hachinski ischemic score  $\leq 4$  (Hachinski *et al.*, 1975) and a score of zero on the items of tremor, rigidity and bradykinesia on the motor section of the Unified Parkinson's Disease Rating Scale (Fahn and Elton, 1987).

*PD group without dementia.* This group consisted of 18 patients meeting the United Kingdom PD Society brain bank clinical criteria for PD (Hughes *et al.*, 1992) but not the DSM-IV (APA, 1994) criteria of dementia due to PD. All patients had typical clinical features of PD and responded to levodopa.

*PD group with dementia.* This group consisted of 12 patients meeting both the United Kingdom PD Society brain bank clinical criteria for PD and the DSM-IV criteria of dementia due to PD. All patients had typical PD and responded to levodopa. Patients with a history of cognitive decline before or less than 1 year after the onset of PD were excluded.

*Control group.* This group consisted of eight normal volunteers from our institute and six individuals who complained of dizziness that were referred for a SPECT study. All had a normal brain CT or MRI, a normal neurological and neuropsychological evaluation, and no history of psychiatric disorders or cognitive decline.

### Neurological examination

After informed consent, patients were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS). This scale has 3 sections: (1) activities of daily living; (2) motor examination; and (3) complications of antiparkinsonian therapy. Patients were also examined with the Hamilton Depression Scale (Hamilton, 1960) and the Mini Mental State Exam (Folstein *et al.*, 1975). All the neurological eval-

uations were carried out by a neurologist blind to the remaining clinical and SPECT data.

### Neuropsychological examination

Each patient was assessed by a neuropsychologist blind to neurologic findings using the following test battery:

*Buschke Selective Reminding Test (Buschke & Fuld, 1974).* This test measures verbal learning and memory during a multiple-trial list learning task. The patient listens to a list of words and recalls as many words as possible. Each subsequent learning trial involves the presentation of only those words that were not recalled on the immediately preceding trial. The outcome measure is the number of words in long term storage.

*Benton Visual Retention Test (Benton, 1974).* This test assesses visual perception and nonverbal memory. Patients are exposed to geometric designs for 10 s and are immediately presented with a card containing the correct design among three foils. The patient is asked to select the previously presented design. There are 10 trials.

*Digit Span (Wechsler, 1955).* This sub-test of the Wechsler Memory Scale examines auditory attention and includes two parts. Both consist of seven pairs of number sequences that the examiner presents at the rate of one per second. In the first part (digits forward), the patient is asked to simply repeat a string of numbers (from two to eight numbers in length) exactly as it is given. In the second part (digits backwards) the patient is asked to repeat the string of numbers (from two to eight numbers in length) in reversed order.

*Wisconsin Card Sorting Test (Nelson, 1976).* This test measures the ability to develop and apply new concepts, and, subsequently shift sets, which requires the subjects to suppress a learned response that was previously correct, and learn a new one. Assessment of the overall proficiency of the test was judged by the number of categories achieved (maximum 6).

*Controlled Oral Word Association Test (Benton, 1968).* This test examines access to semantic information with a time constraint. Patients were instructed to name as many words beginning with the letter F as they could in one minute. People's names and proper nouns were not permitted. The letters A and S were then presented successively, one minute being allowed for each letter. The score was the combined number of appropriate words produced in 3 min.

*Raven's Progressive Matrices* (Raven et al., 1986). This test measures visuospatial reasoning. Patients are presented with a spatial pattern problem with one part removed and four pictured inserts, one of which contains the correct pattern. The patient has to select the correct piece to match the original spatial patterns. The patterns become increasingly complex over trials. The performance score is the number correctly identified.

### SPECT examination

After obtaining informed written consent, a brain SPECT study using  $^{99m}\text{Tc}$ -HMPAO (25 mCi) (Ceretek, Exametazime, Amersham International) was performed using previously published methods (Starkstein et al., 1994). The scan was acquired within 1 month of the clinical and MRI evaluations. Patients sat with eyes closed and ears unplugged in a quiet room with dim lights. Fifteen minutes after the injection, patients were positioned within the scanner, parallel to the orbitomeatal line. The alignment was carried out using vertical and horizontal laser beams and the head was held still by an ad-hoc head-holder. SPECT scans were acquired with a General Electric 400 AC/T rotating gamma camera using a high resolution collimator and a  $64 \times 64$  matrix. Sixty-four images were obtained over  $360^\circ$ , with a 30 s acquisition time and a zoom of 1.6. Image reconstruction used a Butterworth filtering, a critical frequency of 0.44, and a slice-width of 1 pixel. Reconstructed brain slices were then reoriented in the orbitomeatal line using the sagittal and axial views and a set of 30 axial, sagittal and coronal sections at 6.4 mm increments were obtained. Final image resolution was 12 mm full-width at half-maximum in the plane of reconstructed transverse sections.

Square regions of interest (ROI) consisting of  $3 \times 3$  pixels [voxel ( $3 \times 3 \times 1$  pixels) =  $2.35 \text{ cm}^3$ ] were used to obtain regional activity ratios in axial slices,

using the cerebellum as reference. Specific ROIs were identified using the Matsui and Hirano Atlas (1978) and defined using each patient's MRI scan. Three measurements (anterior, medial and posterior) were carried out for each of the following areas: frontal inferior (orbital), frontal superior (dorsal), temporal inferior, temporal superior, parietal and cerebellum. These measurements were averaged for each cortical region on the right and left hemispheres separately. To determine the activity ratio (brain region/cerebellum), the counts in each ROI was divided by the average counts per ROI found in each cerebellar hemisphere. This ratio was used as a measure of relative perfusion. All SPECT measurements were performed by a neuroradiologist blind to the clinical data. This study was approved by the Ethical Review Committee of the Raúl Carrea Institute of Neurological Research.

### Statistical analysis

Statistical analysis was carried out using means and standard deviations, analysis of variance (ANOVA) with repeated measures and post-hoc comparisons. Frequency distributions were calculated with a  $\chi^2$  test and a Yates' correction for expected cell sizes  $< 5$ . All  $p$  values given are two-tailed.

## RESULTS

### Demographic and neurological findings (Table I)

While there were no significant between-group differences in gender distribution, PD patients without dementia and controls were younger than both demented groups. Patients with PD and dementia had significantly higher UPDRS motor scores than non-demented PD patients (Table I). No significant differences were found between demented and non-demented PD patients on levodopa dosage and no patient was on anticholinergic drugs.

TABLE I. Demographic and neurological findings

	PD group	PD-DEM group	AD group	Control group
Age (mean years) <sup>1</sup>	66.2 (4.8)	71.4 (8.3)	71.5 (5.7)	65.0 (2.6)
Gender (% females)	47	31	54	64
Hamilton Depression Scale	6.5 (4.6)	11.6 (10.9)	8.6 (7.1)	—
Mini-Mental State Exam <sup>2</sup>	27.1 (1.3)	23.0 (4.3)	23.3 (4.5)	29.2 (0.8)
UPDRS-motor section <sup>3</sup>	12.9 (8.7)	22.2 (9.8)	4.0 (5.5)	—
Levodopa (mean mg/day)	482 (384)	621 (388)	—	—

<sup>1</sup>  $F(3,64) = 6.04$ ,  $p < 0.01$  (PD versus PD-DEM and AD  $p < 0.05$ ; controls versus PD-DEM and AD  $p < 0.01$ ).

<sup>2</sup>  $F(3,64) = 6.62$ ,  $p < 0.001$  (PD-DEM versus control and AD  $p < 0.001$ ; AD versus control and PD  $p < 0.0001$ ).

<sup>3</sup>  $F(2,50) = 30.4$ ,  $p < 0.0001$  (PD versus AD  $p < 0.01$ , PD versus PD-DEM  $p < 0.01$ , PD-DEM versus AD  $p < 0.0001$ ). S.D.s are in parentheses.

TABLE II. Neuropsychological findings

	PD-DEM	AD group
Education (years)	8.7 (1.6)	10.7 (4.6)
Buschke Selective Reminding Test		
LTR	27.0 (14.2)	24.5 (18.9)
delayed	4.2 (2.3)	2.7 (2.3)
Benton Visual Retention Test	6.6 (1.6)	5.8 (1.8)
Wisconsin Card Sorting Test — categories	2.6 (2.3)	2.3 (2.1)
Controlled Oral Word Association Test	31.7 (8.0)	32.2 (10.5)
Raven's Progressive Matrices — percentile	30.2 (26.4)	38.8 (33.4)
Digits forward	4.8 (1.2)	5.1 (1.5)
Digits backward	3.5 (0.8)	3.2 (1.1)

S.D.s are in parentheses.

### SPECT findings

A three-way ANOVA with repeated measures (group  $\times$  region  $\times$  side) using age as a covariate showed a significant group effect [ $F(3,63) = 4.48, p < 0.01$ ] (patients with AD, PD with dementia and PD without dementia had a significantly lower perfusion across all

brain regions examined than the normal control group) and a significant group  $\times$  region interaction [ $F(18,384) = 1.98, p < 0.01$ ]. On individual comparisons, all three patient groups had significantly lower bilateral perfusion in the inferior frontal and temporal regions as compared to the control group (Fig. 1).

### rCBF findings in patients with Parkinson's disease (PD), PD with dementia (PD+DEM), Alzheimer's disease (AD), and controls

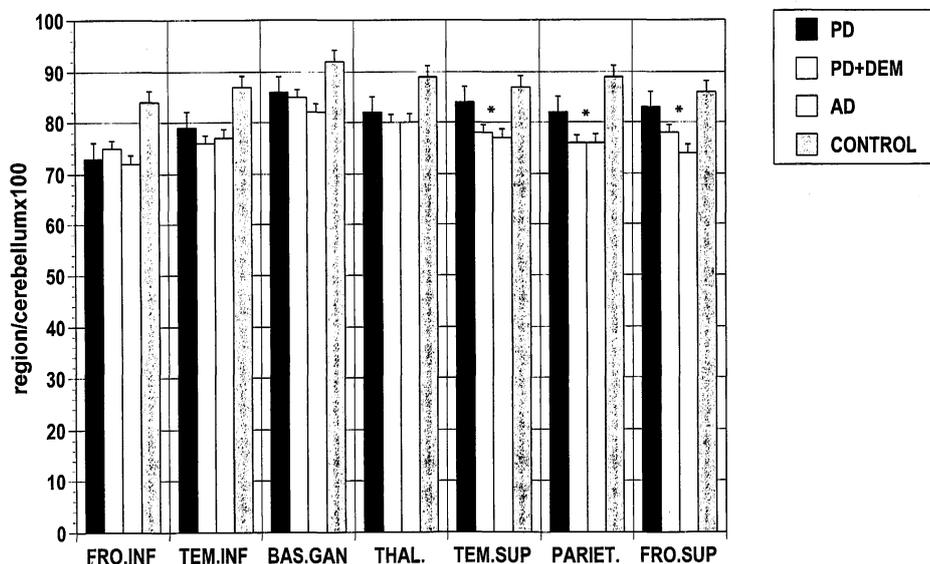


FIG.1. Patients with AD had significantly lower perfusion in temporal superior (TEM.SUP), parietal (PARIET.) and frontal superior areas (FRO.SUP) than non-demented patients with PD (\* $p < 0.01$ ,  $p < 0.05$ , and  $p < 0.0001$ , respectively) and controls (\* $p < 0.01$ ,  $p < 0.0001$ , and  $p < 0.0001$ , respectively). Patients with PD and dementia had significantly lower perfusion in temporal superior, parietal, and frontal superior than non-demented patients with PD (all  $p < 0.01$ ), and controls (\* $p < 0.01$ ,  $p < 0.001$  and  $p < 0.0001$ , respectively). All three patients groups had significantly lower bilateral perfusion in inferior frontal and temporal regions as compared to the control group ( $p < 0.05$ ).

Both the AD and the PD with dementia groups had significantly lower perfusion in superior frontal, superior temporal and parietal regions as compared to both the PD without dementia and the control groups (Fig. 1). On the other hand, there were no significant differences in regional perfusion between the AD and the PD with dementia groups. Finally, there were no significant effects for side [ $F(1,73) = 1.60, p = \text{N.S.}$ ], group  $\times$  side [ $F(3,73) = 0.76, p = \text{N.S.}$ ], or group  $\times$  region  $\times$  side interaction [ $F(18,438) = 1.12, p = \text{N.S.}$ ].

Since PD patients with dementia had significantly higher UPDRS motor scores than non-demented PD patients, a three-way ANOVA with repeated measures (group  $\times$  side  $\times$  region) using UPDRS motor scores as a covariate was carried out. A significant group  $\times$  region interaction [ $F(6,168) = 2.16, p < 0.05$ ] demonstrated that PD patients with dementia had significantly lower perfusion in superior frontal, superior temporal and parietal regions as compared to non-demented PD patients. There were no other significant main effects or interactions.

#### Neuropsychological findings (Table II)

A MANOVA for neuropsychological tests for patients with either AD or PD-dementia showed no significant between-group differences (Wilks' lambda = 0.64,  $df = 8,27, p = \text{N.S.}$ ).

## DISCUSSION

The present study examined cerebral perfusion differences between patients with AD, patients with PD and dementia, patients with PD without dementia and controls; there were two important findings. Firstly, patients with either AD or PD with dementia had significantly bilateral hypoperfusion in superior frontal, superior temporal and parietal regions as compared to both patients with PD but no dementia and controls. Secondly, there were no significant differences in perfusion in any brain region between patients with AD or PD with dementia.

Before further discussion, some limitations of our study should be pointed out. Firstly, PD patients without dementia and the control group were younger than the two demented groups. However, this difference may not account for the significant cerebral perfusion differences, since the age difference was low and the statistical analysis was carried out using age as a covariate. Another limitation is that we have no neuropathological confirmation of our clinical diagnoses. Thus, whether the PD-dementia group had the neuropathological changes of PD, a Lewy-body dementia, or the neuropathological changes of both AD and PD could

not be determined. However, all our patients with PD met the stringent criteria of the United Kingdom PD brain bank society for PD, and all showed a positive clinical response to levodopa. Finally, PD patients with dementia had significantly higher UPDRS scores than PD patients without dementia. While this discrepancy may explain between-group differences in cerebral perfusion, a significant correlation between cortical perfusion and severity of parkinsonism could not be consistently demonstrated (Montastruc *et al.*, 1987), and we used UPDRS motor scores as a covariate.

Several studies have examined clinical differences between patients with AD and PD with dementia. We have recently compared 33 patients with AD and 33 patients with PD and dementia matched for age, gender and MMSE scores using a comprehensive psychiatric assessment and a neuropsychological evaluation (Starkstein *et al.*, 1996). Whereas PD patients with dementia had a significantly higher prevalence of major depression than AD patients, the latter showed more severe anosognosia and disinhibition than PD patients. On the other hand, there were no significant between-group differences in the severity of delusions, apathy, irritability and emotional lability. Moreover, no significant between-group differences were found on tests of memory and language, although demented patients with PD had a significantly greater impairment on a test of visual reasoning. Taken together, neuropsychiatric and neuropsychological findings in AD and PD with dementia suggest that differences between the so-called cortical and subcortical dementias are not widespread but may be restricted to specific behavioral and cognitive domains.

Several studies examined differences in cerebral perfusion between AD and PD. Jagust *et al.* (1992) carried out SPECT studies using [ $^{123}\text{I}$ ]N-isopropyl-p-iodoamphetamine in 21 patients with AD, 20 non-demented patients with PD and 24 healthy controls. They found that whereas AD patients had significantly lower bilateral temporo-parietal perfusion as compared to the control group, PD patients had cerebral perfusion values intermediate between the AD group and the controls. However, when they selected those PD patients who scored in the lower 50th percentile on the overall neuropsychological assessment, no significant differences in cerebral perfusion were found between them and the group with AD. Our present study produced similar results, since non-demented PD patients showed cerebral perfusion values that were intermediate between those in PD patients with dementia and controls. On the other hand, neither Spampinato *et al.* (1991) nor Sawada *et al.* (1992) could demonstrate significant cerebral perfusion differences

between non-demented PD patients and controls. One explanation for this discrepancy is that in the study by Spampinato *et al.*, the PD non-demented group only included patients with MMSE scores > 27, whereas Jagust *et al.* and the present study used clinical criteria for the diagnosis of dementia and not a cut-off score on the MMSE. Moreover, mean MMSE scores in PD patients without dementia in both the present study and that of Jagust *et al.* were lower than in the study by Spampinato *et al.* (27.8, 27.1 and 29, respectively).

The main finding of the present study was that patients with PD and dementia had similar cerebral perfusion deficits than patients with AD. Both groups showed significant hypoperfusion involving temporal superior, frontal superior and parietal areas as compared to patients with PD and no dementia and the controls. In a study that compared 13 PD demented patients and 13 age-matched non-demented patients with PD, Sawada *et al.* (1992) reported fronto-parietal perfusion deficits in demented as compared to non-demented PD patients. They suggested that whereas the frontal hypoperfusion may be secondary to disturbances of biogenic amine nuclei projecting to the frontal cortex, the parietal perfusion deficits may be secondary to the cortical neuropathological changes of AD. However, Schapiro *et al.* (1993) recently reported a patient with PD and dementia who showed bilateral temporo-parietal metabolic deficits despite no neuropathological changes in those brain areas. They suggested that the cortical hypometabolism may have resulted from cortical cholinergic abnormalities due to loss of neurons in the nucleus basalis of Meynert.

In conclusion, the present study showed that AD and PD patients with mild-moderate dementia have similar perfusion deficits involving frontal superior, temporal superior, and parietal areas. Whether these metabolic deficits result from similar neuropathological changes or constitute a final common pathway after damage to different brain regions may need future neuropathological studies.

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