SHORT REPORT

Longitudinal change in $^{99m}\text{TcHMPAO}$ cerebral perfusion SPECT in Parkinson's disease over one year

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Background: Brain perfusion deficits have been reported previously in subjects with Parkinson's disease in comparison with healthy controls.

Objective: To carry out a longitudinal study of perfusion in patients with Parkinson's disease and controls to find areas showing a reduction in perfusion over one year.

Methods: Two HMPAO cerebral perfusion scans were acquired one year apart in 30 subjects with Parkinson's disease (mean (SD) age, 76 (5) years) and 34 healthy comparison subjects (76 (7) years). Scans were normalised to the mean intensity in the cerebellum.

Results: Using SPM99 within groups to investigate regions that showed a decrease in perfusion between scans, it was found that in Parkinson's disease subjects but not controls there was a significant cluster in the frontal lobe (Brodmann area 10) where perfusion decreased over the year.

Conclusions: The progressive frontal perfusion deficits in Parkinson's disease are consistent with results from previous structural and neuropsychological studies suggesting frontal lobe involvement and executive dysfunction even in early Parkinson's disease.

Studies of cerebral perfusion in cognitively intact subjects with Parkinson's disease have found either no difference from controls^{1,2} or hypoperfusion in parietal,^{3,4} frontal,^{3,5} and temporal areas.⁶ Those with more advanced disease have more severe hypoperfusion, particularly in the frontal area.^{7,8} A previous longitudinal study found a reduction in parietal perfusion over a year in Parkinson's disease,⁴ which correlated with cognitive decline.

Studies in Parkinson's disease using statistical parametric mapping (SPM) have reported occipito-parietal⁹ and parietal¹⁰ hypoperfusion, which correlated respectively with visual and cognitive functioning. Cognitive decline is frequent in Parkinson's disease,¹¹ and studies on parkinsonian patients with dementia have shown marked temporoparietal and occipital hypoperfusion.^{1,5,12}

Executive dysfunction is common in Parkinson's disease,¹³ and has been shown to worsen longitudinally,¹⁴ to correlate with decrease frontostriatal activity,¹⁵ and to be an independent predictor of incident dementia.¹⁶

Our aim in this study was to measure longitudinal changes in perfusion in a group of older people with Parkinson's disease in comparison with healthy controls. We hypothesised that decreases in perfusion would be seen in the parietal and frontal lobes, and that the parietal changes would relate to changes in cognition, especially to any global cognitive impairments (that is, dementia) developing in the course of the disease.

METHODS

Subjects

We recruited 38 subjects with Parkinson's disease from a community dwelling population of patients referred to geographically based neurology services. Diagnosis was made by consensus between experienced clinicians who were blind to the single photon computed emission tomography (SPECT) results, using the UK Parkinson's Disease Society brain bank criteria for Parkinson's disease.¹⁷ Thirty nine normal subjects were recruited from among friends and spouses of patients. Subjects with evidence of stroke, significant cognitive decline, or dementia (either from the history or from the presence of focal neurology or cognitive impairment on examination) were excluded from the study. All subjects underwent SPECT cerebral perfusion scans at recruitment, and again after one year. Eight of the parkinsonian subjects and five of the normal subjects refused a repeat SPECT scan, and all the data presented here are from the 30 parkinsonian and 34 normal subjects who were rescanned.

At baseline 21 of the 30 parkinsonian subjects were taking levodopa (mean (SD) dose, 462 (338) mg). This increased to 27/30 after one year (mean dose 449 (288) mg). No other antiparkinsonian drugs were being used. Treatment was not stopped for scanning. Two control and five parkinsonian subjects were taking antidepressant drugs.

The study was approved by the local research ethics committee and UK Department of Health's Administration of Radioactive Substances Advisory Committee (ARSAC). All participants gave their informed written consent.

Subjects underwent detailed physical, neurological, and neuropsychiatric examinations, which included history, mental state, and physical examination. Standardised schedules administered included the mini-mental state examination (MMSE),¹⁸ the Cambridge cognitive examination (CAMCOG),¹⁹ the geriatric depression (15 item) scale (GDS)²⁰ and the unified Parkinson's disease rating scale motor subsection (UPDRS III).²¹ Data from the subjects studied here have been included in other reports.^{12,22}

SPECT data acquisition

Data acquisition was as previously described.¹² Briefly, subjects were imaged approximately 10 minutes after a bolus intravenous injection of 500 MBq of ^{99m}Tc -HMPAO (Ceretec, GE-Healthcare, UK). Images were reconstructed with a pixel size of $3.54 \times 3.54 \times 3.54$ mm.

Abbreviations: CAMCOG, Cambridge cognitive examination; GDS, geriatric depression (15 item) scale; HMPAO, hexamethylpropyleneamine oxime; MMSE, mini-mental state examination; SPECT, single photon computed emission tomography; SPM, statistical parametric mapping; UPDRS, unified Parkinson's disease rating scale

Table 1 Demographic factors for the study subjects

	Control	Parkinson's disease	p Value (two sided)	t Value
n	34	30		
Age (years)	75.7 (6.9)	75.5 (5.2)	0.6	-0.5
Sex, F:M	14:20	8:22	0.29	
CAMCOG baseline	94.2 (3.8)	90.0 (6.1)	0.001	3.3
CAMCOG increase	0.2 (4.7)	-1.2 (5.5)	0.29	1.1
CAMCOG executive function baseline	19.9 (4.3)	16.6 (3.6)	0.002	3.3
CAMCOG executive function increase	0.51 (4.0)	0.23 (3.6)	0.7	0.2
MMSE baseline	28.2 (1.4)	26.8 (1.7)	0.001	3.6
MMSE increase	-0.48 (2.2)	0.43 (2.2)	0.11	-1.6
UPDRS baseline	1.1 (1.9)	24.1 (8.3)	<0.001	-15.7
UPDRS increase	1.1 (2.0)	3.7 (9.0)	0.11	-1.6
GDS	1.1 (1.1)	3.9 (3.1)	<0.001	-5.0
Increase in GDS	0.3 (2.4)	0.0 (3.2)	0.7	0.3
Disease duration (months)	-	45 (34)		
Days between HMPAO scans	376 (27)	387 (45)	0.2	-1.3

Values are mean (SD) or n; χ^2 used for sex, all others unpaired *t* tests; 62 degrees of freedom (df). CAMCOG, Cambridge cognitive examination; GDS, geriatric depression scale; HMPAO, hexamethylpropyleneamine oxime; MMSE, mini-mental state examination; UPDRS, unified Parkinson's disease rating scale.

Data processing

Image data were transferred to a personal computer and converted to Analyze format using MRIcro (www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). Data were analysed using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm/spm99.html>).

A template image was generated by spatially normalising all the HMPAO scans to the generic SPECT template in SPM99. The average of the spatially normalised scans was calculated, and this was used as a template for further spatial normalisation. A region of interest (ROI) encompassing the whole cerebellum was defined from the template image.

For each subject, the repeat HMPAO scan was co-registered with the baseline scan for the same subject using rigid body registration. The baseline scan was then spatially normalised to our template using the standard 12 parameter affine transform, with $7 \times 8 \times 7$ basis functions to account for global non-linear shape differences. The same normalisation parameters were applied to the repeat scan. Images were resliced with a voxel size of $4 \times 4 \times 4$ mm. The scans were smoothed with a 10 mm Gaussian. The scan intensity was then

normalised by dividing each image by the mean intensity in the cerebellar region of interest (ROI). To determine the change in perfusion, a difference image was calculated by subtracting the spatially and intensity normalised smoothed repeat SPECT scan from the same subject's baseline scan. This produced for each subject an image in SPM standard space, with the image intensity representing changes over a year in perfusion. We also used an ROI template²³ to calculate, on the intensity and spatially normalised images, the mean perfusion in the temporal, frontal, parietal, and occipital lobes.

Statistical analysis

A mask was generated by thresholding the HMPAO template image with a threshold of 0.5 of the cerebellar intensity. This was used to limit the statistical tests largely to grey matter.

The images were statistically analysed using the SPM99 general linear model. One sample *t* tests were calculated on the images of perfusion change in the Parkinson's disease and control groups separately to identify regions that showed a significant decrease in perfusion (relative to the

Figure 1 The SPM99 map of cerebral perfusion decrease over one year in the Parkinson's disease group (thresholded at $p < 0.001$ uncorrected).

Figure 2 The SPM99 map of lower cerebral perfusion at one year in the Parkinson's disease group compared with controls (thresholded at $p < 0.001$ uncorrected).

Table 2 The most significant clusters from the statistical parametric mapping analysis

p Value (cluster), corrected*	Cluster size	p Value (cluster), uncorrected†	Talairach coordinates			
			x	y	z	
Significant perfusion decrease over one year in the Parkinson's disease group						
0.006	111	0.002	−8	66	−10	L superior frontal gyrus BA10
			20	66	−7	R superior frontal gyrus BA10
			−32	62	−10	L superior frontal gyrus BA10
0.098	46	0.03	40	−84	26	R superior occipital gyrus BA19
			48	−81	15	R middle occipital gyrus BA19
0.161	36	0.051	−40	−32	53	L inferior parietal BA40
			−32	−32	64	L postcentral gyrus BA2
Significantly lower perfusion in Parkinson's disease v control at one year						
<0.001	1570	<0.001	−40	−76	37	L angular gyrus BA19
			−40	−32	61	L postcentral gyrus BA2
			−32	44	31	L superior frontal gyrus BA9
			−52	25	32	L middle frontal gyrus BA9
			−40	7	59	L middle frontal gyrus BA6
0.001	353	<0.001	44	−76	30	R angular gyrus BA39
0.024	139	0.015	−32	58	−13	L superior frontal gyrus BA11
0.032	126	0.019	44	14	51	R middle frontal gyrus BA6

*Corrected for multiple comparisons.
†Uncorrected for multiple comparisons.
For each cluster, local maxima (at least 8 mm apart), as indicated by SPM99 output, are listed.

cerebellum) over the year. We examined in each group the correlation between change in CAMCOG score and other clinical variables and the change in perfusion. A two sample *t* test was used to compare, at one year, the perfusion in the Parkinson's disease group *v* the controls.

The statistical parametric maps were thresholded at *p* < 0.001 uncorrected. All images are presented in neurological format, with the left side of the brain being on the left of the image. Regions were reported as significant if they had a probability (*p*) value of < 0.05 corrected for multiple comparisons at the cluster level. Coordinates presented here have been converted from MNI to Talairach space using the mni2tal routine (<http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml>). The Talairach daemon²⁴ was used to assign anatomical labels to voxel coordinates. We used SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA) for all statistical calculations on non-image data. From the ROI data we calculated percentage change in perfusion by dividing the difference in perfusion between scans by the baseline perfusion. One sample *t* tests were used in each region in each group to look for significant changes in perfusion.

RESULTS

Patient demographic data are presented in table 1. All Parkinson's disease subjects were non-demented and had CAMCOG scores in the normal range, though mean scores were lower than controls at baseline. CAMCOG score did not change significantly over the year in either group. The executive function subscore of the CAMCOG test was also lower in Parkinson's disease subjects, but again there was no decrease over the year.

For the eight Parkinson subjects who were not rescanned, the baseline mean (SD) CAMCOG score was 84.8 (9.5), compared with 90.0 (6.1) for the rescanned group (unpaired *t* test, *t* = -1.9, *p* = 0.063). In the healthy comparison group, those who were not rescanned had a mean baseline CAMCOG score of 91.8 (4.4) *v* 94.2 (3.7) for the rescanned group (unpaired *t* test, *t* = -1.3, *p* = 0.2).

Figure 1 shows areas of decreasing perfusion over the year in the Parkinson's disease group. The clusters of perfusion decrease in this group are shown in table 2. There were no significant clusters in the control group. We also repeated the analysis including only those whose dosage of levodopa did not change over the year (*n* = 15), and found essentially the

same results, with perfusion loss in frontal and parietal regions. Figure 2 shows areas where the perfusion in the parkinsonian group at one year was greater than in the control group.

For the ROI data, the mean (SD) percentage changes (and *p* values from one sample *t* test) for each group were as follows:

Control: frontal, 1.2 (8.4)% (*p* = 0.4); parietal, 0.7 (8.3)%, *p* = 0.6); temporal, 1.1 (6.8)% (*p* = 0.3); occipital, 0.1 (5.5)% (*p* = 0.9).

Parkinson's disease: frontal, -1.9 (3.9)% (*p* = 0.01); parietal, -1.5 (4.5)% (*p* = 0.08); temporal, -0.4 (4.8)% (*p* = 0.7); occipital, -0.2 (2.5)% (*p* = 0.6).

There were no significant correlations in either the control or the Parkinson's disease group between change in perfusion and changes in either total CAMCOG score or the executive function subscore, or change in GDS or UPDRS. There were no significant correlations in the Parkinson's disease group between change in perfusion and baseline age, levodopa dosage, UPDRS, GDS, or CAMCOG score.

DISCUSSION

We found evidence of a significant decrease in cerebral perfusion in non-demented subjects with Parkinson's disease over one year. This loss was most pronounced in the frontal region, though there were trends to reduced perfusion in the parieto-occipital regions. These findings are in keeping with previous perfusion studies comparing early with late stage disease,^{7 10} demonstrating that a progressive decrease in cerebral perfusion is a feature of non-demented older subjects with Parkinson's disease.

Hypoperfusion in the prefrontal area may reflect disruption or deafferentation of frontostriatal circuitry.²⁵ We have also shown loss of grey matter in the right dorsolateral cortex in this parkinsonian group,²² and it is possible that the frontal hypoperfusion may reflect ongoing atrophy, which could be secondary to dysfunction of dopaminergic frontostriatal circuitry. Hypoperfusion might also precede or precipitate atrophy.

We hypothesised that parietal perfusion would decrease in the Parkinson's disease group, and that this would correlate with cognitive decline. Although we did not see a significant decline in perfusion in the parietal lobe, neither did the CAMCOG score decrease, which is still consistent with our

hypothesis. This contrasts somewhat with the findings of Tachibana *et al.*,⁴ who did find such a correlation, though their subjects were 10 years younger and had a longer duration of disease than ours. It may be that in the present study the time period between the scans was too short for reliable detection of the relatively slow rate of cognitive change in Parkinson's disease. The CAMCOG test¹⁹ was designed primarily for use in diagnosing dementia and not as a measure of longitudinal change in cognition. Hence it may not have been sensitive enough to detect any cognitive changes present in these groups whose cognition was relatively intact. However, we cannot exclude a drop out effect—that the eight parkinsonian subjects who refused the repeat SPECT scan had a greater degree of cognitive decline than the re-scanned patients.

In conclusion, we have shown decreases in frontal perfusion in Parkinson's disease over one year. We did not see any cognitive change, but this may have reflected the relatively short time between examinations, or the relative insensitivity of the CAMCOG test. Further longitudinal studies are needed to investigate whether hypoperfusion, either at baseline or over follow up, predicts the development of dementia in Parkinson's disease. Studies are also needed to investigate the relation between hypoperfusion and dopaminergic receptor systems.

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