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

M J Firbank, S Molloy, I G McKeith, D J Burn, J T O’Brien

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 and temporal 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 controls1, 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,9 which correlated with cognitive decline.

Studies in Parkinson’s disease using statistical parametric mapping (SPM) have reported occipito-parietal10 and parietal11 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.12, 13 Executive dysfunction is common in Parkinson’s disease,14 and has been shown to worsen longitudinally,15 to correlate with decrease frontostriatal activity,16 and to be an independent predictor of incident dementia.17

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.

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
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 7×8×7 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 4×4×4 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. 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.

Table 1  Demographic factors for the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Parkinson’s disease</th>
<th>p Value (two sided)</th>
<th>t Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>75.7 (6.9)</td>
<td>75.5 (5.2)</td>
<td>0.6</td>
<td>−0.5</td>
</tr>
<tr>
<td>Sex, F:M</td>
<td>14:20</td>
<td>8:22</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>CAMCOG baseline</td>
<td>94.2 (3.8)</td>
<td>90.0 (6.1)</td>
<td>0.001</td>
<td>3.3</td>
</tr>
<tr>
<td>CAMCOG increase</td>
<td>0.2 (4.7)</td>
<td>−1.2 (5.5)</td>
<td>0.29</td>
<td>1.1</td>
</tr>
<tr>
<td>CAMCOG executive function baseline</td>
<td>19.9 (4.3)</td>
<td>16.6 (3.6)</td>
<td>0.002</td>
<td>3.3</td>
</tr>
<tr>
<td>CAMCOG executive function increase</td>
<td>0.31 (4.0)</td>
<td>0.23 (3.6)</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>MMSE baseline</td>
<td>28.2 (1.4)</td>
<td>26.8 (1.7)</td>
<td>0.001</td>
<td>3.6</td>
</tr>
<tr>
<td>MMSE increase</td>
<td>−0.48 (2.2)</td>
<td>0.43 (2.2)</td>
<td>0.11</td>
<td>−1.6</td>
</tr>
<tr>
<td>UPDRS baseline</td>
<td>1.1 (1.9)</td>
<td>24.1 (8.3)</td>
<td>&lt;0.001</td>
<td>−15.7</td>
</tr>
<tr>
<td>UPDRS increase</td>
<td>1.1 (2.0)</td>
<td>3.7 (9.0)</td>
<td>0.11</td>
<td>−1.6</td>
</tr>
<tr>
<td>GDS</td>
<td>1.3 (1.1)</td>
<td>3.9 (3.1)</td>
<td>&lt;0.001</td>
<td>−5.0</td>
</tr>
<tr>
<td>Increase in GDS</td>
<td>0.3 (2.4)</td>
<td>0.0 (3.2)</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>−</td>
<td>45 (34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days between HMPAO scans</td>
<td>376 (27)</td>
<td>387 (45)</td>
<td>0.2</td>
<td>−1.3</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n; χ² 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.

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).
The most significant clusters from the statistical parametric mapping analysis

<table>
<thead>
<tr>
<th>p Value (cluster), corrected*</th>
<th>Cluster size</th>
<th>p Value (cluster), uncorrected†</th>
<th>Talairach coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant perfusion decrease over one year in the Parkinson’s disease group</td>
<td>0.006</td>
<td>111</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>0.098</td>
<td>46</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>0.161</td>
<td>36</td>
<td>0.051</td>
</tr>
<tr>
<td>Significantly lower perfusion in Parkinson’s disease v control at one year</td>
<td>&lt;0.001</td>
<td>1570</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>353</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.024</td>
<td>126</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*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.

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-frontal regions. These findings are in keeping with previous perfusion studies comparing early with late stage disease, 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 frontal-striatal circuitry. We have also shown loss of grey matter in the right dorsolateral cortex in this parkinsonian group, and it is possible that the frontal hypoperfusion may reflect ongoing atrophy, which could be secondary to dysfunction of dopaminergic fronto-striatal 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., 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 test 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. Thanks are due to the patient volunteers for their time, and to Elise Rowan for help with the database. This work was supported by a programme grant from the UK Medical Research Council.

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