

## PAPERS

## Differential diagnosis of Parkinson's disease, multiple system atrophy, and Steele-Richardson-Olszewski syndrome: discriminant analysis of striatal $^{18}\text{F}$ -dopa PET data

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### Abstract

Clinicopathological series indicate that the clinical diagnosis of Parkinson's disease is correct in only 80% of cases. Multiple system atrophy (MSA) and Steele-Richardson-Olszewski syndrome (SRO) comprise most of the misdiagnoses. By means of  $^{18}\text{F}$ -dopa PET the pattern of nigrostriatal dopaminergic dysfunction in 28 patients with clinically probable Parkinson's disease, 25 with MSA, and 10 patients with SRO, was assessed and compared with the pattern in 27 normal subjects. Discriminant function analysis was used to assess the ability of  $^{18}\text{F}$ -dopa PET to categorise individual parkinsonian patients on the basis of their caudate and putamen tracer uptake. Discriminant function analysis assigned all control subjects a normal category. One Parkinsonian patient out of 63 was classified as "normal" on the basis of PET findings, although this patient had significantly reduced putamen  $^{18}\text{F}$ -dopa uptake. Discriminant function analysis was less effective at distinguishing different categories of akinetic-rigid syndrome on the basis of their striatal  $^{18}\text{F}$ -dopa uptake, as judged against clinical criteria. Patients clinically labelled as having typical or atypical Parkinsonian syndromes were assigned the same category on PET criteria 64% and 69% of the time, respectively. When all three categories of Parkinson's disease, MSA, and SRO were considered together, clinical and  $^{18}\text{F}$ -dopa PET findings correlated in 64% of patients assigned a diagnosis of Parkinson's disease and 70% of those given a diagnosis of SRO; MSA was less readily discriminated, patients with MSA being assigned to MSA, Parkinson's disease, and SRO groups with equal frequency. The correlation between clinical and discriminant function analysis assignment improved when separate comparisons were made between Parkinson's disease and MSA, or Parkinson's disease and SRO groups. In these analyses, clinical and PET cate-

gorisation of MSA and Parkinson's disease agreed in 60% of cases, and of SRO and Parkinson's disease in 90% of cases. In summary,  $^{18}\text{F}$ -dopa PET successfully discriminates normal subjects from parkinsonian patients, and patients with Parkinson's disease from patients with SRO, but is less reliable in distinguishing Parkinson's disease from MSA. The concomitant assessment of striatal neuronal function with additional PET tracers may be necessary to reliably differentiate typical and atypical parkinsonian syndromes.

(*J Neurol Neurosurg Psychiatry* 1994;57:278-284)

Parkinson's disease, multiple system atrophy (MSA) and Steele-Richardson-Olszewski syndrome (SRO) are pathologically distinctive. Lewy body degeneration of the pigmented brainstem nuclei typifies Parkinson's disease,<sup>1,2</sup> whereas in MSA there are variable degrees of neuronal loss and gliosis affecting the striatum, especially the putamen, substantia nigra, ventral pons, inferior olives, cerebellar Purkinje cells, and intermediolateral columns of the spinal cord.<sup>3</sup> Argyrophilic cellular inclusions in both oligodendrocytes and neurons have recently been reported in cases of MSA.<sup>4,5</sup> SRO (also known as progressive supranuclear palsy) is characterised by neuronal loss, gliosis, and neurofibrillary tangle formation affecting particularly the pallidum-subthalamic complex, the zona compacta of the substantia nigra, the superior colliculus, periaqueductal grey matter, and pretectal areas.<sup>6</sup>

Clinically "typical" cases of MSA and SRO are sufficiently distinctive to allow differentiation from Parkinson's disease: MSA, a term suggested by Graham and Oppenheimer,<sup>7</sup> encompasses a group of patients with varying combinations of Parkinsonism poorly responsive to levodopa, cerebellar ataxia, and autonomic failure. SRO is characterised by a supranuclear down gaze palsy, combined with an akinetic-rigid syndrome poorly responsive to levodopa, increased axial tone, pseudobulbar palsy, and neck hyperextension.<sup>8</sup> Patients

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Received 10 December 1992  
and in revised form  
20 April 1993.  
Accepted 8 June 1993

with SRO typically develop a frontolimbic dementia, with impaired ability to formulate plans of action, apathy, irritability, and slowing of thought processes.<sup>9</sup>

Despite the apparently well defined clinicopathological status of MSA and SRO, problems may arise in differentiating these conditions from Parkinson's disease. Two large series of cases diagnosed as Parkinson's disease in life indicate that this antemortem diagnosis is only correct in about 80% of cases<sup>10,11</sup>; MSA and SRO constitute around 11% and 4% of misdiagnosed cases, respectively.<sup>12</sup> There are several factors leading to misdiagnosis: tremor may be a feature of all three of these parkinsonian conditions, and asymmetrical onset does not reliably differentiate Parkinson's disease from MSA and SRO.<sup>13</sup> Both MSA and SRO may show sustained levodopa responsiveness,<sup>13,14</sup> and, conversely, there are reports of pathologically verified Parkinson's disease where levodopa treatment in life was of little or no benefit.<sup>15</sup> The down gaze palsy of SRO may be a late development in the course of the illness,<sup>16</sup> and this eye movement disorder has also been reported in diffuse Lewy body disease,<sup>17,18</sup> as well as other neurological diseases.<sup>16</sup> Accurate diagnosis of these conditions is important from a prognostic point of view, and for assessing the findings of epidemiological and therapeutic studies. <sup>18</sup>F-6-L-fluoro-dopa PET (<sup>18</sup>F-dopa PET) provides a means of assessing the functional integrity of the presynaptic nigrostriatal dopaminergic projections.<sup>19,20</sup> After intravenous injection, this positron emitting tracer is taken up by the nigrostriatal nerve terminals in the caudate and putamen, where it is then converted by aromatic amino acid decarboxylase into <sup>18</sup>F-dopamine and its metabolites. In a previous study, Brooks *et al.*<sup>21</sup> reported differing patterns of striatal <sup>18</sup>F-dopa uptake in Parkinson's disease, MSA, and SRO; atypical Parkinsonian patients had similar putamen but lower caudate Ki values than patients with typical Parkinson's disease. There was, however, overlap in the ranges of individual caudate values within these groups. The aim of our <sup>18</sup>F-dopa PET study was to determine with discriminant function analysis how effectively patients diagnosed as clinically probable Parkinson's disease, SRO, and MSA could be distinguished on the basis of the pattern of their caudate and putamen <sup>18</sup>F-dopa uptake.

## Methods

### PATIENTS

Twenty-eight patients with clinically probable Parkinson's disease, as defined by the United Kingdom Parkinson's Disease Brain Bank criteria,<sup>1</sup> were studied (16 of these patients have been previously reported<sup>21</sup>). All had a levodopa-responsive akinetic-rigid syndrome, with no identifiable cause of Parkinsonism, such as neuroleptic exposure. None had a gaze palsy, cerebellar deficit, autonomic failure, or pyramidal signs. Mean age was 61 (range 38–77) years. Duration of clinical

disease was 7.2 (range 0.5–20) years and locomotor disability, assessed with the Hoehn and Yahr scale<sup>22</sup> after 12 hours without medication, ranged from I to IV.

Twenty five patients with clinically probable MSA had <sup>18</sup>F-dopa PET (18 have been previously reported).<sup>21</sup> All had a parkinsonian syndrome poorly or non-responsive to levodopa. Nineteen of these patients had documented autonomic failure, and 11 had cerebellar ataxia. Twenty of the 25 patients had had CT of the brain, or MRI, or both. In five patients the brain scans were normal, whereas in 15 there was evidence of cerebellar and brainstem atrophy. Mean age of the MSA group was 58 (range 40–73) years, and duration of clinical disease varied from one to 10 (mean 4.4) years. Locomotor disability ranged from Hoehn and Yahr grade II–V when assessed after 12 hours without medication.

Ten patients with SRO were studied (all of these patients have been previously reported<sup>21</sup>). All had an akinetic-rigid syndrome poorly responsive to levodopa; eight had a frank supranuclear down gaze palsy, and two had absent vertical optokinetic nystagmus. All had axial rigidity and nine had a pseudobulbar palsy. Eight of the 10 patients had dementia of frontal type. In six cases, CT scans were normal, three showed generalised atrophy, and one showed cerebellar and brainstem atrophy. Mean age of the SRO group was 68 (range 62–75) years and duration of disease varied from six months to eight years (mean 3.5 years). Locomotor disability ranged from Hoehn and Yahr grades III–V when assessed after 12 hours without medication.

Striatal <sup>18</sup>F-dopa influx constants obtained for these three patient groups were compared with those obtained for 27 healthy normal subjects with no evidence of neurological disease.

The mean age of the normal subjects was 63 (range 30–77) years. The ethics committee of the Royal Postgraduate Medical School, Hammersmith Hospital, approved this study. Permission to administer <sup>18</sup>F-dopa was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom.

### SCANNING PROCEDURE

Scans were performed on a Siemens CTI 931/12/8 scanner (CTI, Knoxville, TN) at the MRC Cyclotron Unit. Reconstructed spatial resolution for 15 simultaneously acquired slices is 7.0 × 8.5 × 8.5 mm (full width half maximum). Other performance characteristics for this scanner have previously been described.<sup>23</sup>

The head was immobilised in the scanner by means of an individual polyurethane mould. Scanning was performed with the orbitomeatal line parallel to the detector rings. A 10-minute transmission scan, with a retractable <sup>68</sup>Ga/<sup>68</sup>Ge ring source, was performed to correct for tissue attenuation. All dopaminergic agents were stopped for 12

hours before PET and subjects ate only a light breakfast that day. Subjects were given 100 mg carbidopa orally one hour before, and a further 50 mg immediately before the study to block peripheral aromatic amino acid decarboxylase. A dose of between 3 and 5 mCi of  $^{18}\text{F}$ -dopa was given to each subject over two minutes by infusion pump. Serial dynamic emission scans were collected from the start of infusion, initially at one minute, and extending to five-minute intervals. Twenty-five time frames were collected over 94 minutes.

#### DATA ANALYSIS

Data were analysed with image-analysis software (Analyze version 3.0, BRU, Mayo Foundation, Rochester, MN) after transfer to SUN 3/60 workstations (Sun Microsystems, Inc, Mountain View, CA). The position of striatal structures was determined by the inspection of summed time frames, creating an integrated image representing activity collected 30–94 minutes after giving  $^{18}\text{F}$ -dopa. Region of interest placement was defined in a standard template arrangement: one square of length 8.2 mm was placed over the head of the caudate, and three squares 8.2 mm in length were aligned contiguously along the axis of the putamen for each hemisphere. A circular region, of diameter 32.8 mm, was placed over the occipital lobe of each hemisphere.

Striatal and occipital region placement was performed on the two optimal contiguous planes, and then applied to individual time frames to derive regional time-activity plots. Side-to-side averaged values for each of these regions over two planes were then calculated from data from the individual hemispheric region of interest.

Influx constants ( $K_i \text{ min}^{-1}$  values) were calculated for caudate and putamen regions with a multiple time graphical analysis approach with an occipital tissue input function.<sup>24,25</sup> The  $K_i$  value is a rate constant that reflects uptake and decarboxylation of  $^{18}\text{F}$ -dopa into  $^{18}\text{F}$ -dopamine and its metabolites by the nigrostriatal nerve terminals.

#### STATISTICAL METHODS

Data were analysed with the Systat (SYSTAT Inc, Evanston, IL) statistics package installed on a Macintosh SE30 personal computer. Caudate and putamen  $K_i$  values for each of the four groups (normal, Parkinson's disease, MSA, and SRO) were analysed by one way

analysis of variance (ANOVA), with Tukey's honestly significant difference procedure as a post hoc test.

Discriminant function analysis is a multivariate linear technique that examines a series of dependent variables for two or more groups, and produces the optimal way of classifying individual subjects within groups, in the form of discriminant scores. The discriminant scores determine the probability of each patient belonging to a particular group. This technique was used to calculate discriminant scores for each subject in this study, on the basis of their caudate and putamen  $K_i$  values, to see whether the classification from the statistical analysis matched the clinical classification. Because MSA and SRO generally run a more malignant course, with a shorter time from diagnosis to death than Parkinson's disease,<sup>8,12</sup> duration of disease was considered as a dependent variable, as well as caudate and putamen  $K_i$  values, and its effect on the discriminant scores was examined. Also, because typical and atypical parkinsonian syndromes may be particularly difficult to distinguish from one another clinically in the early stages, discriminant function analysis was also performed for those patients with durations of disease of three years or less, with caudate and putamen  $K_i$  values as dependent values.

## Results

#### ANALYSIS OF VARIANCE FOR CAUDATE AND PUTAMEN $K_i$ VALUES

Table 1 shows the mean caudate and putamen  $K_i$  values, together with the standard deviations (SDs), for normal, Parkinson's disease, and "atypical" parkinsonian groups, with the last comprising patients with MSA and those with SRO. As expected, both Parkinson's disease and atypical parkinsonian group caudate and putamen  $K_i$  means differed significantly from those of the normal group ( $p < 0.001$ ). Also, there was a significant difference ( $p < 0.001$ ) between Parkinson's disease ( $0.0081 \text{ min}^{-1}$ ) and atypical parkinsonian ( $0.0062 \text{ min}^{-1}$ ) group caudate  $K_i$ , but not putamen  $K_i$  ( $0.0042 \text{ min}^{-1}$  v  $0.0039 \text{ min}^{-1}$ ) means.

Table 1 also shows the mean caudate and putamen  $K_i$  values for the four groups considered individually. For the caudate values analysis of variance gave an F value of 26.03 ( $p < 0.0001$ ). There were significant differences ( $p < 0.001$ ) between the mean caudate  $K_i$  values for the normal volunteers and the Parkinson's disease, MSA, and SRO groups. Mean caudate tracer uptake was significantly less in the SRO group ( $0.0051 \text{ min}^{-1}$ ) than in the Parkinson's disease group ( $0.0081 \text{ min}^{-1}$ ;  $p < 0.001$ ), but Parkinson's disease and MSA ( $0.0067 \text{ min}^{-1}$ ), and MSA and SRO mean values were not significantly different from one another.

For the mean putamen  $K_i$  values (table 1) ANOVA gave an F value of 124.0 ( $p < 0.0001$ ), with the Parkinson's disease ( $0.0042 \text{ min}^{-1}$ ), MSA ( $0.0039 \text{ min}^{-1}$ ), and SRO

Table 1 Mean caudate and putamen  $^{18}\text{F}$ -dopa uptake constants ( $K_i \text{ min}^{-1}$  values) in normal subjects and patients with Parkinson's disease, atypical parkinsonian, MSA, and SRO

Group (n)	Caudate (mean (SD))	Putamen (mean (SD))
Normal subjects (27)	0.0109 (0.0016)	0.0099 (0.0011)
Parkinson's disease (28)	0.0081 (0.0026)*	0.0042 (0.0013)*
Atypical parkinsonian (35)	0.0062 (0.0021)*†	0.0039 (0.0015)*
MSA (25)	0.0067 (0.0021)*	0.0039 (0.0016)*
SRO (10)	0.0051 (0.0018)*†	0.0040 (0.0014)*

\* $p < 0.001$  v normal; † $p < 0.001$ , v Parkinson's disease.

Table 2 Discriminant function analysis of normal, subjects and patients with Parkinson's disease, or atypical parkinsonism, with caudate and putamen  $^{18}\text{F}$ -dopa uptake as dependent variables

Clinical group (n)	Predicted numbers (%)		
	Normal	Parkinson's disease	Atypical parkinsonian
Normal (27)	27 (100)	0 (0)	0 (0)
Parkinson's disease (28)	0 (0)	18 (64)	10 (36)
Atypical parkinsonian (35)	1 (3)	10 (28)	24 (69)

Overall "correct" classification = 77%.

(0.0040  $\text{min}^{-1}$ ) group means all significantly less than the normal mean putamen Ki value (0.0099  $\text{min}^{-1}$ ;  $p < 0.001$ ). There were no significant differences in the mean putamen tracer uptake between the groups studied.

#### DISCRIMINANT FUNCTION ANALYSIS

Table 2 shows the results of discriminant function analysis, with caudate and putamen Ki values as the dependent variables. When discriminant function analysis was performed with groups clinically labelled as normal, Parkinson's disease, and atypical parkinsonian, all 27 normal subjects were assigned a normal category on the basis of their striatal tracer uptake, whereas one of 63 parkinsonian patients was classified as normal. Eighteen of the 28 patients (64%) clinically labelled as typical Parkinson's disease were assigned by discriminant function analysis to the Parkinson's disease category. The 10 other patients with Parkinson's disease were placed in the atypical group. Twenty four of the 35 (69%) clinically atypical parkinsonian patients were assigned by discriminant function analysis to the atypical category. Ten of the atypical parkinsonian patients were labelled as Parkinson's disease, whereas a single atypical case was labelled as normal. There were no clinical features of any of the Parkinson's disease or atypical parkinsonian cases assigned alternative categories by discriminant function analysis, which, on review of the case records, led to any suspicion that the initial clinical diagnosis was wrong. The single atypical parkinsonian patient clinically diagnosed as having MSA but labelled normal by discriminant function analysis, had a putamen  $^{18}\text{F}$ -dopa uptake 2.5 SDs below the normal mean (Ki = 0.0072), but a caudate tracer uptake that fell within the low "normal range" (Ki = 0.0087). She was grossly dis-

abled on follow up five years after her PET scan with autonomic failure, cerebellar eye signs, severe akinesia, increased limb tone, and rest tremor.

When discriminant function analysis was performed on four groups: normal, Parkinson's disease, MSA, and SRO, with caudate and putamen Ki values as the dependent variables, 27 out of 27 clinically normal subjects (100%), 18 out of 28 patients with Parkinson's disease (64%), eight out of 25 with MSA (32%), and seven out of 10 with SRO (70%) were assigned their clinical category by discriminant function analysis on the basis of their striatal  $^{18}\text{F}$ -dopa uptake data (table 3). Cases of MSA fell with almost equal frequency into Parkinson's disease and SRO groups. Three out of 10 cases of SRO were placed in the MSA group, but none were assigned a Parkinson's disease classification.

When caudate and putamen  $^{18}\text{F}$ -dopa Ki values for the two groups clinically labelled as either Parkinson's disease or MSA were analysed separately by discriminant function analysis, 60% (15 out of 25) of the cases labelled clinically as MSA were assigned to this category, whereas 64% (18 out of 28) of the clinically labelled cases of Parkinson's disease were placed into the Parkinson's disease group. Performing a similar, separate, discriminant function analysis on the Parkinson's disease and SRO groups alone led to  $^{18}\text{F}$ -dopa PET assigning 90% (nine out of 10) and 79% (22 out of 28) of the clinically labelled patients with SRO and Parkinson's disease to their respective categories.

Taking disease duration into account did not affect findings on discriminant function analysis in patients clinically labelled as Parkinson's disease and SRO. Ten, rather than eight, out of 25 patients clinically labelled as MSA were assigned to this category with this discriminant function analysis; a small but non-significant improvement compared with the use of putamen and caudate Ki values alone.

When discriminant function analysis was performed on the patients with a disease duration of three years or less, with caudate and putamen Ki values as the dependent variables, seven of 12 patients with typical Parkinson's disease (58%) and 13 of 18 (72%) atypical Parkinsonian patients were assigned their clinical category from analysis of  $^{18}\text{F}$ -dopa Ki values. When the three patients groups were considered separately, seven out of 12 patients with Parkinson's disease (58%), seven out of 12 with MSA (58%), and three out of six with SRO (50%) were assigned their clinical category by statistical analysis on the basis of their striatal tracer uptake data. Three of the 12 cases with Parkinson's disease were placed in the SRO group, whereas two were placed in the MSA group. Four of the clinically labelled MSA cases fell into the SRO group, with one given a Parkinson's disease classification. The correlation between clinical and discriminant

Table 3 Discriminant function analysis of normal subjects and patients with Parkinson's disease, MSA, or SRO with caudate and putamen  $^{18}\text{F}$ -dopa uptake as dependent variables

Clinical group (n)	Predicted numbers (%)			
	Normal	Parkinson's disease	MSA	SRO
Normal (27)	27 (100)	0 (0)	0 (0)	0 (0)
Parkinson's disease (28)	0 (0)	18 (64)	4 (14)	6 (22)
MSA (25)	1 (4)	9 (36)	8 (32)	7 (28)
SRO (10)	0 (0)	0 (0)	3 (30)	7 (70)

Overall "correct" classification = 67%.

function analysis assignment remained similar to that for the whole patient database when separate comparisons were made between early cases of Parkinson's disease and MSA, or Parkinson's disease and SRO. Clinical and  $^{18}\text{F}$ -dopa PET categorisation of Parkinson's disease and MSA agreed in 67% of patients from each group, whereas in a separate discriminant function analysis PET assigned 83% (five out of six) and 75% (nine out of 12) of the clinically labelled patients with SRO and with Parkinson's disease to their respective categories.

### Discussion

In this study we have extended the results of Brooks *et al.*<sup>21</sup> and confirmed that in Parkinson's disease, MSA, and SRO, both mean putamen and caudate  $^{18}\text{F}$ -dopa uptake are significantly reduced when compared with normal and that mean caudate tracer uptake in SRO is significantly lower than in Parkinson's disease. Mean caudate  $^{18}\text{F}$ -dopa uptake in MSA lies between that of Parkinson's disease and SRO. Mean  $^{18}\text{F}$ -dopa uptake by the putamen was reduced by about 60% in the Parkinson's disease, MSA, and SRO groups.

Discriminant function analysis has been previously applied to PET studies: in 1989, De Volder *et al.*<sup>26</sup> reported the results of  $^{18}\text{F}$ -fluoro-deoxyglucose uptake in seven patients with a clinical diagnosis of striatonigral degeneration, and 16 normal controls. No explanation of which variables were included in the discriminant analysis was given, although the authors reported that this approach was able to separate striatonigral degeneration cases from control subjects. Clark *et al.*<sup>27</sup> performed  $^{18}\text{F}$ -fluoro-deoxyglucose PET scans on groups of normal subjects and patients with Huntington's disease, and used a discriminant function analysis of relative caudate metabolic rates to predict group membership. An overall correct classification of 98.3% was achieved, with one patient being incorrectly classified as normal. These workers then went on to generate discriminant scores and related probabilities for a group of persons at risk.

Sawle *et al.*<sup>28</sup> measured  $^{18}\text{F}$ -dopa uptake into left and right caudate and putamen in 27 normal subjects and 18 clinically defined patients with Parkinson's disease. Discriminant function analysis was used to show that the persons within these groups were separated by a function of the most severely affected putamen and the best preserved caudate Ki values. One normal subject, however, was misclassified, raising the possibility that he represented a case of preclinical Parkinson's disease.

Discriminant function analysis is a descriptive statistical approach, rather than a predictive one. In other words, in the data presented, the programme analysed the variables given to it and determined the best means of separating the individual patients into assigned clinical categories. If more

patients are studied, their striatal  $^{18}\text{F}$ -dopa uptake constants can be included in a new discriminant analysis and the optimal statistical way of separating the patients may then change.

Applying discriminant function analysis to the striatal Ki values calculated in this study showed the ability of  $^{18}\text{F}$ -dopa PET to separate normal from parkinsonian subjects on an individual basis. None of the 27 controls was classified as abnormal, whereas only one parkinsonian subject out of 63 was classified as "normal", although this subject had a putamen Ki value 2.5 SDs below the normal mean. Discriminant function analysis was less effective, however, at distinguishing the different akinetic-rigid syndromes on the basis of their striatal  $^{18}\text{F}$ -dopa uptake when judged against clinical criteria. Those clinically labelled as having probable Parkinson's disease or atypical parkinsonism were assigned the same PET category 64% and 69% of the time, respectively. When three parkinsonian categories (Parkinson's disease, MSA, and SRO) were considered together, patients with Parkinson's disease and SRO were assigned to their clinical grouping in 64% and 70% of cases, respectively; patients with MSA were assigned to MSA, Parkinson's disease, and SRO groups with roughly equal frequency.

The correlation between clinical and discriminant function analysis assignment improved when separate comparisons were made between Parkinson's disease and MSA, or Parkinson's disease and SRO groups. In these analyses, MSA could be discriminated from Parkinson's disease in 60% of cases, whereas patients with SRO were discriminated from Parkinson's disease in 90% of cases.

Because it is particularly in the early stages that typical and atypical parkinsonian syndromes may be difficult to distinguish clinically, further discriminant function analyses were performed on those patients with a duration of disease of three years or less. The numbers of patients involved in these analyses were modest, but the results indicated that the correlations between clinical labelling and statistical assignment were at least as good as those obtained from the analysis of the complete patient cohorts.

When assessing the correlation between the discriminant function analysis and clinical classification, it must be remembered that the initial clinical diagnosis may be incorrect. At present there are no *in vivo* markers that reliably discriminate the akinetic-rigid syndromes. Pathological studies have suggested that most cases with the full syndrome of MSA and SRO are diagnosed correctly in life. For instance, in the clinicopathological study of Rajput *et al.*<sup>11</sup> 27% of 59 patients with akinetic-rigid syndrome had pathologically verified MSA or SRO, and in all cases the final clinical diagnosis was correct. Of note, however, is that the initial clinical diagnosis was wrong in all three cases with SRO. Stringent clinical diagnostic criteria were used

for cases with MSA and SRO in our current PET study, so it is likely that most of these patients were assigned the appropriate clinical diagnosis.

Unfortunately, the same cannot be said of Parkinson's disease, where, despite the use of various diagnostic criteria, misdiagnoses still occur in 20% of cases.<sup>10</sup> Striatonigral degeneration, a component of MSA, is the most common pathological cause of misdiagnosis in these cases.<sup>10,11,13</sup> Discriminant function analysis may thus have correctly assigned a clinically diagnosed Parkinson's disease case to an atypical parkinsonian group. Correlation of <sup>18</sup>F-dopa PET findings with clinicopathological studies will be needed to truly determine the specificity of the PET approach.

The ability of discriminant function analysis to distinguish the pattern of caudate and putamen <sup>18</sup>F-dopa uptake in patients with clinically probable Parkinson's disease and SRO reflects the differing underlying nigral pathological processes of these two conditions. Both akinetic-rigid syndromes are characterised by neuronal loss in the substantia nigra. The pathological process in Parkinson's disease (Lewy body degeneration) targets the ventrolateral area of the substantia nigra, the pars compacta.<sup>29</sup> Neurons from this area project preferentially to the posterior putamen.<sup>30</sup> In SRO, uniform involvement of the pars compacta by neurofibrillary tangle disease has been reported, with similar reductions in dopamine concentrations in the caudate and putamen.<sup>31,32</sup> The selectivity of nigral cell loss in Parkinson's disease and SRO is, in turn, reflected in their caudate <sup>18</sup>F-dopa uptake: This was relatively preserved in patients with Parkinson's disease (caudate: putamen ratio 2:1) but reduced to a pronounced degree (caudate:putamen ratio 1:1) in cases with SRO. Hence, in a direct comparison, discriminant function analysis separated patients with SRO from those with Parkinson's disease 90% of the time.

In MSA, like Parkinson's disease, the ventrolateral nigra is targeted by the pathology (neuronal loss with glial inclusions), although cell loss is generally more extensive.<sup>33</sup> Reductions in caudate <sup>18</sup>F-dopa uptake ranged from mild to severe in these patients, and so discriminant function analysis had greater difficulty in separating MSA reliably from Parkinson's disease and SRO. In a comparison of patients clinically labelled with Parkinson's disease, MSA, and SRO, only 32% of cases of MSA were correctly assigned. When the analysis was performed with only patients with Parkinson's disease and those with MSA, cases with MSA were separated from cases with Parkinson's disease 60% of the time.

In summary, whereas striatal <sup>18</sup>F-dopa uptake discriminates between normal subjects and parkinsonian patients reliably, patterns for patients with Parkinson's disease, MSA, and SRO are less readily distinguished. <sup>18</sup>F-dopa PET satisfactorily discriminates SRO from Parkinson's disease, but can only distinguish MSA from Parkinson's disease 60% of

the time. The concomitant examination of striatal as well as nigral function, with <sup>18</sup>F-fluoro-deoxyglucose or dopamine D<sub>1</sub> and D<sub>2</sub> radioligands, could be useful in reliably categorising the typical and atypical Parkinsonian syndromes with PET.

Dr DJ Burn is supported by a Wellcome Trust Project Grant. We are grateful to all the physicians who referred patients to us, in particular, Professor CD Marsden, Professor CJ Mathias, Dr NP Quinn, and Dr AJ Lees. We thank colleagues at the MRC Cyclotron Unit, and Chemistry and Physics sections for their expert assistance, and also Mrs A Williams, Mr GC Lewington, and Mr A Blythe for their considerable help with scanning.

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## Neurology in literature

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### Hemifacial spasm

Authors of neurological texts seldom match the felicity for expression demonstrated by writers of fiction. Though none of the extracts describing probable hemifacial spasm in this issue antedate the neurological literature on the subject, they impress (and, in one case, amuse) by the accuracy of their observation and their use of language.

*Nikolai Gogol, 1852, Dead souls*

The public prosecutor with his very black, thick eyebrows and with his left eye that kept winking slightly, ... winking with his left eye and flicking his beard with his handkerchief to brush the snuff from it.

*Fedor Dostoevsky, 1866, Crime and punishment*

It would have seemed good natured were it not for the expression of the eyes, which had a watery, glassy gleam under the lids with nearly white eyelashes, which twitched almost as though he were continually winking.

Again he suddenly seemed to wink at him with his left eye, and laugh noiselessly—exactly as before.

*Sherwood Anderson, 1919, Winesburg Ohio*

There was something strange about his eyes. The lid of the left eye twitched; it fell down and snapped up; it was exactly as though the lid of the eye were a window shade and someone stood inside the doctor's head playing with the cord.

*Evelyn Waugh, 1932, Black mischief*

There was once a man who got run in for winking at girls in the street. So he said it was a permanent affliction and he winked all through his trial and got off,

but the sad thing is that now he can't stop and he's been winking ever since.

*Thomas Mann, 1947, Dr Faustus*

One side of his cheek was drawn up in a sort of tic, the corner of the mouth as well, and the eye winked in sympathy.

*Graham Greene, 1948, The heart of the matter*

The French officer returned his salute—a drained-out figure with a twitch in the left eyelid.

*George Orwell, 1949, 1984*

They were a few metres apart when the left side of the man's face was suddenly contorted by a sort of spasm. It happened again just as they were passing one another. It was only a twitch, a quiver, rapid as the clicking of a camera shutter, but obviously habitual.

*Joseph Heller, 1979, Good as gold*

Since his dental practice had ceased growing, Irv had developed a tic in his right cheek that often gave him the appearance of smiling inexplicably.

*John Fowles, 1985, A Maggot*

Most unexpectedly his right eye flickers, in the ghost of a wink...and again his right eye flickers, almost as if it is a tic, outside his control...and once again she sees that tic in his right eye...and then again there comes that minute spasm of his eyelid...she receives one last tic of his right eyelid; and then he is gone.

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