Statistical parametric mapping with ^{18}F -dopa PET shows bilaterally reduced striatal and nigral dopaminergic function in early Parkinson's disease

K Ito, P K Morrish, J S Rakshi, T Uema, J Ashburner, D L Bailey, K J Friston, D J Brooks

MRC Cyclotron Unit,
Hammersmith
Hospital, London, UK
K Ito
P K Morrish
J S Rakshi
T Uema
D L Bailey
D J Brooks

Institute of Neurology,
Queen Square,
London, UK
J Ashburner
K J Friston
D J Brooks

Department of
Radiology, Nagoya
University School of
Medicine, Nagoya,
Japan
K Ito

Department of
Biofunctional
Research, National
Institute for Longevity
Sciences, Obu, Japan
K Ito

Correspondence to:
Dr Kengo Ito, Department
of Biofunctional Research,
National Institute for
Longevity Sciences, 36-3
Gengo Morioka-cho, Obu,
Aichi Prefecture, 474-8522
Japan. Telephone 0081 562
46 2311, ext 843 or 836; fax
0081 562 44 6596; email
kito@nils.go.jp

Received 16 March 1998 and
in revised form
1 October 1998
Accepted 3 November 1998

Abstract

Objective—To apply statistical parametric mapping to ^{18}F -dopa PET data sets, to examine the regional distribution of changes in dopaminergic metabolism in early asymmetric Parkinson's disease.

Methods—Thirteen normal volunteers (age 57.7 (SD 16.5) years; four women, nine men) and six patients (age 50.3 (SD 13.5) years; three women, three men) with asymmetric (right sided) Parkinson's disease were studied. Images from each dynamic dopa PET dataset were aligned and parametric images of ^{18}F -dopa influx (Ki) were created for each subject. The Ki images were transformed into standard stereotactic space. The Ki values of the caudate and putamen on spatially normalised images were compared with the Ki values before normalisation. The application of statistical parametric mapping (SPM) allowed statistical comparison of regional Ki values on a voxel by voxel basis between healthy volunteers and patients with Parkinson's disease.

Results—There was a strong correlation between the Ki values before and after spatial normalisation ($r=0.898$, $p=0.0001$). Significant decreases in the Ki values were found for the Parkinson's disease group throughout the entire left putamen ($p<0.001$) and focally in the dorsal right putamen ($p<0.001$). Decreased Ki values were also shown bilaterally in the substantia nigra ($p<0.01$).

Conclusion—Using (SPM) and ^{18}F -dopa PET, reductions in both striatal and nigral brain dopaminergic function could be demonstrated in early Parkinson's disease.

(J Neurol Neurosurg Psychiatry 1999;66:754-758)

Keywords: ^{18}F -dopa; positron emission tomography; Parkinson's disease; statistical parametric mapping

^{18}F -Dopa positron emission tomography (PET) permits presynaptic dopaminergic ter-

minal function to be studied in vivo in both healthy volunteers and in patients with Parkinson's disease. In Parkinson's disease this technique has been used to provide a measure of severity of disease and to identify those with early, and even preclinical, disease.¹⁻⁴ The technique has also provided a method of monitoring the survival of fetal mesencephalic cells after implantation.^{5,6}

Numerous analytical methods have been proposed to quantify biochemical function from ^{18}F -dopa PET images. The most often used method, the multiple time graphical approach (MTGA), provides rate constants (Ki) for the storage of ^{18}F -dopa within regions of interest (ROI) placed over the striatum.^{7,8} In most studies such ROIs have been placed manually by visual inspection of an aggregate image with reference to a stereotactic atlas of the brain. This approach has proved useful for the clinical evaluation of Parkinson's disease, but has significant drawbacks.^{9,10} The positioning of ROIs is observer dependent and may be prone to bias. It may also be difficult to place ROIs accurately in severe Parkinson's disease where the decreased striatal ^{18}F -dopa uptake means that the aggregate image provides an inaccurate representation of striatal anatomy.¹⁰ Additionally, there may be involvement of extrastriatal dopamine terminals to varying extents in different subgroups of idiopathic Parkinson's disease (tremulous, akinetic-rigid) and other parkinsonian syndromes. Accurate detection of changes in extrastriatal areas, where uptake constants are lower than those in the striatum, is unreliable using conventional ROI analysis and a judgement must be made about the sites of loss of dopaminergic function before analysis. As a consequence the ROI approach is not really suited for use as an exploratory technique with ^{18}F -dopa PET.

Statistical parametric mapping is an approach developed to localise statistically significant changes in spatially normalised images on a voxel by voxel basis, without previous assumption of the distribution of differences between the images. In theory it should be applicable to ^{18}F -dopa PET data sets allowing assessment of dopaminergic function throughout the whole brain. Using a labour intensive MRI to PET coregistration approach we have previously showed that there are topographical patterns of striatal dopaminergic loss that may be more predictive of impending Parkinson's disease than whole striatal or putamen Ki values alone.¹¹ In particular, we were able to identify dorsal to ventral and caudal to rostral

Table 1 Patients with Parkinson's disease

Patients	Age	Sex	Disease duration	UPDRS	Hoehn and Yahr
1	34	M	1 y	12	1
2	47	F	1.5 y	29	1
3	38	M	4 y	40	2
4	62	F	9 months	9	1
5	69	M	5 y	16	2
6	48	F	2 y	14	1

Table 2 Peak coordinates in SPM analysis

Area	Coordinate			Z score	p Value(uncorrected)
	x	y	z		
R putamen	26	-4	4	4.53	<0.001
L putamen	-26	-10	0	3.88	<0.001
R substantia nigra	6	-20	-8	2.59	0.005
L substantia nigra	-10	-22	-8	2.84	0.002

gradients in putamen Ki similar to those shown for postmortem dopamine concentrations in early disease.¹² We were interested in studying whether the statistical parametric mapping (SPM) approach would detect a similar striatal gradient of abnormality in Parkinson's disease and also localise extrastriatal regions of impaired dopaminergic function.

Subjects and methods

SUBJECTS

Six patients (age 50.3 (SD 13.5) years; three women, three men) with early Parkinson's disease were recruited from the Hammersmith Hospital Movement Disorder clinic. The United Kingdom brain bank criteria for prospective diagnosis of Parkinson's disease¹³ were fulfilled by all patients. Each patient was assessed clinically by a single observer (PKM) before PET at least 12 hours after stopping medication. Their illness was clinically staged with the unified Parkinson's disease rating scale (UPDRS),¹⁴ and the Hoehn and Yahr¹⁵ rating scale. Four patients had pure right hemiparkin-

sonism and two had asymmetric right predominant parkinsonism. The details of patients are shown in table 1. A separate group of 13 normal volunteers (age 57.7 (SD 16.5) years; four women, nine men) were recruited and scanned over the same time period. All subjects gave written informed consent before PET. Permission to perform these studies was obtained from the ethics committee of the Hammersmith Hospital, London, United Kingdom, and from the Administration of Radioactive Substances Advisory Committee (ARSAC), United Kingdom.

PET

All subjects were given 100 mg oral carbidopa 1 hour before and 50 mg 5 minutes before scanning. PET was performed using a CTI 931/08/12 tomograph (CTI, Knoxville, TN, USA) yielding 15 simultaneous planes with an axial full width half maximum resolution of 7 mm and an in plane resolution of 8.5 mm×8.5 mm. Correction for tissue attenuation of 511 KeV γ radiation was measured using an external Ge-68 ring.¹⁸ ^{18}F -Dopa (80–180 MBq) in normal saline solution was infused intravenously over 30 seconds. Scanning began at the start of the tracer infusion with a protocol of 25 time frames (4×1 min, 3×2 min, 3×3 min, 15×5 min) over 94 minutes.

IMAGE ANALYSIS AND STATISTICAL PARAMETRIC MAPPING

Analysis of data was performed on SUN workstations (Sun Microsystems, Silicon Valley, CA, USA). To correct for head movements between scans, all images from each subject were aligned using Automated Image Registration (AIR) software.¹⁶ After realignment of images conventional region of interest (ROI) analysis was performed for each subject using in house software written in IDL image analysis software (Research Systems, Inc, Boulder, CO, USA) based on the MTGA approach of Patlak and Blasberg. We used the time frames from 25 to 94 minutes postinjection with occipital counts as the input function.¹⁷ Occipital ROIs were located on the occipital cortex of each of two planes, avoiding the midline and the ventricles. The ROIs were placed on two contiguous planes containing caudate and putamen, by image inspection with reference to the stereotactic atlas of Talairach and Tournoux.¹⁸ One circular ROI of 84.0 mm² (diameter=10.3 mm) was positioned by inspection on each caudate nucleus. One elliptical ROI of 156.0 mm² was placed on each putamen. ^{18}F -dopa influx (Ki) was calculated for each of right and left caudate and putamen. The Ki values of the caudate and putamen were compared with the Ki values without realignment to test the effect of alignment in six normal subjects and six patients with Parkinson's disease.

Parametric images of ^{18}F -dopa influx constants (Ki) were created for each subject using the same software. The Ki images were transformed into a standard stereotactic space.¹⁹ The integrated images from 0 to 20 minutes postinjection was used to identify the

Figure 1 Correlation between the caudate and putamen Ki values before and after realignment for six normal subjects and six patients with Parkinson's disease.

Figure 2 Correlation between individual Ki values before and after spatial normalisation for six normal subjects and six patients with Parkinson's disease.

transformation parameters. Stereotactic normalisation of PET images allows the comparison of scan data in identical voxels across different subjects. After normalisation, a gaussian filter of $10 \times 10 \times 8$ mm (full width half maximum in the x, y, z planes, respectively) was applied to remove high frequency noise in the images and to accommodate differences in gyral and functional anatomy between subjects.

The Ki values of the caudate and putamen on spatially normalised images were compared with the Ki values before normalisation in six normal subjects and six patients with Parkinson's disease. The same set of ROIs, defined from the stereotactic atlas of Talairach and Tournoux, was applied to the normalised images from all subjects. Statistical differences in mean regional Ki values between all normal

Figure 3 (A) SPMs showing the spatial distribution of significant regions ($p < 0.01$ uncorrected—that is, $Z > 2.33$) where Ki decreased in Parkinson's disease. Images are shown as integrated projections along sagittal, coronal, and transverse views of the Talairach and Tournoux brain atlas. (B) Significant regions ($p < 0.01$) of subnormal dopamine metabolism (Ki) in hemiparkinsonism, superimposed on a normalised MRI of the brain. Statistical parametric mapping of ^{18}F -dopa PET images shows regional change in the striatum and substantia nigra in Parkinson's disease.

subjects and patients with Parkinson's disease were characterised with SPM on a voxel by voxel basis. Appropriate contrasts were used to derive the between group (unpaired) t statistic using the general linear model. The resulting set of voxel t values constitutes an SPM $\{t\}$ that is used to make inferences about regionally specific changes in Ki.²⁰ The SPM $\{t\}$ s were transformed to the unit normal distribution (SPM $\{Z\}$). When regional effects were predicted in advance, a threshold of $p < 0.01$ uncorrected—that is, $Z > 2.33$ was accepted as significant (anatomically specified hypotheses). For these regions comprising the caudate, putamen, and substantia nigra, the p values associated with other regional effects were corrected for multiple dependent comparisons using the theory of gaussian fields (anatomically exploratory hypotheses).

Results

Caudate and putamen Ki values derived from ROI analysis before and after image realignment with AIR software showed a close correlation ($r = 0.974$, $p = 0.0001$, fig 1). We confirmed by visual inspection that normalisation into Talairach space worked successfully for all subjects and the ROI analysis showed a high correlation between the Ki values before and after spatial transformation ($r = 0.898$, $p = 0.0001$, fig 2). The SPM showed a significant decrease in mean Ki for the Parkinson's disease group in voxels throughout the entire left putamen ($p < 0.001$ uncorrected). In the right putamen voxels showing a significant difference between the Parkinson's disease group and the normal group were confined to the dorsal posterior putamen ($p < 0.001$ uncorrected). Voxels demonstrating a significantly reduced Ki value from the normal mean were also seen showing in the substantia nigra ($p < 0.01$ uncorrected). In the caudate no significant decreases in Ki were seen. The corresponding SPMs and peak coordinates are shown in fig 3 and table 2, respectively. No significant increases in Ki were seen anywhere at a corrected level of 0.05.

Discussion

We have shown that SPM can be successfully applied to ^{18}F -dopa PET images.

In this study we found that a group of early hemiparkinsonian patients showed significantly reduced F-dopa uptake in voxels distributed over the entire putamen contralateral to the most symptomatic limb, and confined to the dorsal caudal putamen in the putamen contralateral to the asymptomatic or least symptomatic limb. These findings compare favourably with our previous study using MRI to PET coregistration,¹² in which the greatest loss of dopaminergic function was found in the dorsal caudal putamen. In that study we suggested that in early Parkinson's disease the ventral and rostral putamen may have Ki values indistinguishable from normal, suggesting that the dopaminergic loss in Parkinson's disease is initially a focal process targeting specific areas within the striatum. These PET findings are also in line with postmortem studies which

have shown greatest dopamine losses from the dorsal posterior putamen in Parkinson's disease.²¹ The present study confirms this finding and reinforces our view that the clinical presentation and progression of Parkinson's disease may be explained largely by progression of the dopaminergic deficit throughout the striatum. By contrast with our work with MRI coregistration,¹² we did not identify significant abnormality in the caudate in this study. This may be a reflection of the different technique, or a different patient group. Application of SPM also allowed us to examine loss of dopaminergic function in regions outside the striatum. The substantia nigra of our patients with Parkinson's disease also showed a reduction in dopaminergic metabolism, confirming our previous report with conventional ROI analysis.²² We think that the application of SPM to Parkinson's disease may in the future enable us to objectively investigate the progression of Parkinson's disease in the whole brain in detail. By applying a statistical analysis to compare people suspected to have preclinical Parkinson's disease with a large group of normal individuals identification of such people should also become more sensitive and specific. In the future it should also be possible to use SPM to compare regional striata and extrastriatal differences in dopaminergic metabolism between idiopathic Parkinson's disease and atypical parkinsonian syndromes, between tremulous and akinetic rigid Parkinson's disease, and between mild and severe Parkinson's disease.

In this provisional study we had relatively few subjects. The ensuing low degrees of freedom reduce the overall power or sensitivity of our analysis. This means that, although we can be confident that the differences shown to be significant do in fact exist, we cannot infer that there are no other differences just because we fail to show them. It should be noted that it is generally the case that the null hypothesis cannot be accepted just because of failure to reject it. However, with greater degrees of freedom (greater numbers of subjects) the power of our analyses would increase and the probability of missing true differences would decrease. Having said this our results suggest that the present study was sufficiently sensitive to identify differences in regional tracer distribution and we can assert that, for example, the contralateral putamen was more significantly affected than the ipsilateral putamen.

There are other advantages in the application of SPM. Sources of error in conventional ROI analyses of ^{18}F -dopa PET include variance in head positioning and ROI placement. Realignment of images and stereotactic normalisation counter errors arising from head positioning. ROI analysis using anatomically normalised images reduces error arising from ROI positioning, particularly in those in which the ^{18}F -dopa metabolism is severely impaired. To determine that there was a close correlation between Ki values obtained with ROI analysis before and after image realignment and then spatial normalisation we combined the data for normal subjects and patients into one plot to disclose the overall tendency. It could be

argued that correlation coefficients obtained from combined patient and control data are invalid and we would accept this point. It is still clear, however, that the transformation process led to little change in Ki values derived by ROI placement. The image alignment program was originally developed for $^{15}\text{O}\text{-H}_2\text{O}$ activation studies and so the reliability of this alignment program for other tracers, especially for a data set of dynamic images, remains unproved. In this study there was a good correlation between the caudate and putamen Ki values before and after realignment suggesting there were no serious problems in the process of realignment, but further evaluation is necessary to confirm the reliability of applying alignment programs to ^{18}F -dopa PET data sets. During anatomical normalisation cerebral blood flow images are conventionally used as a normalised brain template. Images of ^{18}F -dopa PET are very different from rCBF template images but an add image of the early time frames (0–20 minutes) reflects rCBF and can be used as an anatomical template. Then normalised ^{18}F -dopa Ki images can be generated using the parametric information of transformation obtained from the normalisation of the early add image. The Ki values obtained from the images anatomically normalised in this way closely correlated with those derived before normalisation. In a previous study we used PET to MRI coregistration to evaluate regional changes in striatal ^{18}F -dopa metabolism in Parkinson's disease. A great advantage of the method that we have shown here is that each patient need only undergo PET to derive essentially similar information. In this study we have simplified the analysis further by using occipital counts as an input function in the generation of parametric images. This approach avoids the need for arterial plasma sampling and is likely to be as reliable as using metabolite corrected plasma counts as an input function.²³

Conclusion

The technique of spatial normalisation allows regions of interest (ROIs) to be applied to identical anatomical regions of ^{18}F -dopa PET in different people. The approach of SPM to localise significant changes in mean Ki values between groups of normal subjects and patients with early Parkinson's disease has enabled us to objectively demonstrate reductions in regional dopa metabolism in the patients, without a priori knowledge. In this study we showed significant reduction in dopaminergic function throughout the entire putamen contralateral to the most symptomatic limb whereas the reduction was confined to the dorsal caudal putamen contralateral to the less affected or asymptomatic limb. Although further studies will be necessary to confirm this finding, it is in agreement with the

concept that clinical progression of Parkinson's disease is associated with a loss of dopaminergic metabolism beginning in the dorsocaudal putamen and spreading ventrally. Additionally, this study was able to show a significant reduction in nigral ^{18}F -dopa uptake in early Parkinson's disease.

We thank Andrew Blyth, Andreana Williams, and Graham Lewington for their help with scanning.

- Brooks DJ. Detection of preclinical Parkinson's disease with PET. *Neurology* 1991;41(suppl 2):24–7.
- Burn DJ, Mark MH, Playford ED, et al. Parkinson's disease in twins: studies with ^{18}F -dopa and positron emission tomography. *Neurology* 1992;42:1894–900.
- Sawle GV, Wroe SJ, Lees AJ, et al. The identification of presymptomatic parkinsonism: clinical and ^{18}F -dopa positron emission tomography studies in an Irish kindred. *Ann Neurol* 1992;32:609–17.
- Bhatt M, Snow BJ, Martin WRW, et al. Positron emission tomography suggests that the rate of progression of idiopathic parkinsonism is slow. *Ann Neurol* 1991;29:673–7.
- Guttmann M, Burns RS, Martin WRW, et al. PET studies of parkinsonian patients treated with autologous adrenal transplants. *Can J Neurol Sci* 1989;16:305–9.
- Sawle GV, Bloomfield P, Bjorklund A, et al. Transplantation of fetal dopamine neurons in Parkinson's disease: PET [^{18}F]-6-L-fluorodopa studies in two patients with putaminal implants. *Ann Neurol* 1992;31:166–73.
- Patlak CS, Blaberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 1983;3:1–7.
- Patlak CS, Blaberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data generalization. *J Cereb Blood Flow Metab* 1985;5:584–90.
- Pate BD, Snow BJ, Hewitt KA, et al. The reproducibility of striatal uptake data obtained with positron emission tomography and fluorine-18 L-6 fluorodopa tracer in non-human primates. *J Nucl Med* 1991;32:1246–51.
- Vingerhoets FJG, Snow BJ, Schulzer M, et al. Reproducibility of fluorine-18-6 fluorodopa positron emission tomography in normal human subjects. *J Nucl Med* 1993;35:18–24.
- Morrish PK, Sawle GV, Brooks DJ. A clinical and F-18-dopa PET study of early Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1995;59:597–600.
- Morrish PK, Sawle GV, Brooks DJ. Regional changes in F-18-dopa metabolism in the striatum in Parkinson's disease. *Brain* 1996;119:2097–103.
- Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745–52.
- Fahn S, Elton RL. Members of the UPDRS Development Committee. United Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, et al, eds. *Recent developments in Parkinson's disease*. Florham Park, NJ: MacMillan Healthcare Information 1987;153–63.
- Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967;17:427–42.
- Woods RP, Cherry SR, Mazziotta JC. Rapid automated algorithm for aligning and reslicing PET images. *J Comput Assist Tomogr* 1992;16:620–33.
- Brooks DJ, Salmon EP, Mathias CJ, et al. The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure and Parkinson's disease, studied with PET. *Brain* 1990;113:1539–52.
- Talairach J, Tournoux P. *Coplanar stereotaxic atlas of the human brain*. New York: Georg Thieme Verlag, 1988.
- Friston KJ, Frith CD, Liddle PF, et al. Plastic transformation of PET images. *J Comput Assist Tomogr* 1991;15:634–9.
- Friston KJ, Frith CD, Liddle PF, et al. Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab*. 1991;11:690–9.
- Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med*. 1988;318:876–80.
- Morrish PK, Sawle GV, Brooks DJ. Imaging the midbrain in Parkinson's disease using F-18-dopa PET. *Neurology* 1995;45(suppl 4):A204.
- Vingerhoets FJG, Schulzer M, Ruth TJ, et al. Reproducibility and discriminating ability of fluorine-18-6-fluoro-L-dopa PET in Parkinson's disease. *J Nucl Med* 1996;37:421–6.