DOI: 10.1093/brain/awg035 *Brain* (2003), **126,** 312–325

Dopamine release during sequential finger movements in health and Parkinson's disease: a PET study

Ines K. Goerendt,[1] Cristina Messa,[1,3,4,5] Andrew D. Lawrence,[1,2] Paul M. Grasby,[1] Paola Piccini[1] and David J. Brooks[1]

[1]*MRC Clinical Sciences Centre and Division of Neuroscience, Faculty of Medicine, Imperial College, Hammersmith Hospital, London,* [2]*MRC Cognition and Brain Sciences Unit, Cambridge, UK,* [3]*INB-CNR,* [4]*University of Milano Bicocca and* [5]*S. Raffaele Institute Milano, Italy.*

Corresponding author: Andrew Lawrence, MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK
E-mail: andrew.lawrence@mrc-cbu.cam.ac.uk

Summary

Parkinson's disease is associated with slowness, especially of sequential movements, and is characterized pathologically by degeneration of dopaminergic neurons, particularly targeting nigrostriatal projections. In turn, nigrostriatal dopamine has been suggested to be critical for the execution of sequential movements. The objective of this study was to investigate *in vivo*, with [^{11}C]raclopride, PET changes in regional brain levels of dopamine in healthy volunteers and Parkinson's disease patients during the execution of paced, stereotyped sequential finger movements. Striatal [^{11}C]raclopride binding reflects dopamine D_2 receptor availability and is influenced by synaptic levels of endogenous dopamine. During execution of a pre-learned sequence of finger movements, a significant reduction in binding potential (BP) of [^{11}C]raclopride was seen in both caudate and putamen in healthy volunteers compared with a resting baseline, consistent with release of endogenous dopamine. Parkinson's disease patients also showed attenuated [^{11}C]raclopride BP reductions during the same motor paradigm in striatal areas less affected by the disease process. These findings confirm that striatal dopamine release is a component of movement sequencing and show that dopamine release can be detected in early Parkinson's disease during a behavioural manipulation.

Keywords: Parkinson's disease; dopamine; [^{11}C]raclopride PET; sequential movement; fMRI

Abbreviations: BP = binding potential; DA = dopamine; RAC = [^{11}C]raclopride; ROI = region of interest; SED = standard error of the difference of the means; SMA = supplementary motor area

Introduction

The sequencing of actions is fundamental to the survival of all animals and represents a major task for the motor system of the brain. Production of sequential movements involves multiple cortical and subcortical structures, and the basal ganglia, which include the striatum, are thought to play an important role (Marsden, 1980; Graybiel, 1998; Hikosaka *et al*., 2000; Middleton and Strick, 2000; Tanji, 2001). In particular, it has been suggested that the dorsal striatum, with the aid of the dopaminergic system, codes and implements sequential motor 'programmes' (Kimura, 1990; Kermadi and Joseph, 1995; Aldridge *et al*., 1997; Aldridge and Berridge, 1998; Graybiel, 1998; Matsumoto *et al*., 1999; Berridge and Aldridge, 2000).

This viewpoint is supported by single unit recording studies in awake, behaving monkeys and rats where striatal neurons have been found to fire selectively during different movement sequences (Kimura, 1990; Kermadi and Joseph, 1995; Aldridge and Berridge, 1998), by excitotoxic or pharmacological inactivation of dorsal striatum and by dopamine (DA)-specific lesions that are associated with impairment of the execution of sequential movements (Van den Bercken and Cools, 1982; Beninger, 1983; Berridge and

Table 1 *Demographic details of healthy and Parkinson's disease participants*

Healthy	Age*	PD	Age*	H&Y	UPDRS III	Phenotype	Laterality	Handedness	Disease duration (months)
1 (M)	38	1 (F)	50	1	12	Tremor	Right	Right	55
2 (M)	35	2 (M)	53	2	29	Akinetic	Right	Right	60
3 (M)	45	3 (F)	53	1	12	Tremor	Left	Left	24
4 (M)	35	4 (M)	51	1.5	15	Akinetic	Right	Left	18
5 (M)	42	5 (M)	45	2.5	21	Akinetic	Left	Right	42
6 (M)	43	6 (M)	50	1	18	Tremor	Right	Left	33
7 (M)	56								
8 (M)	55								
Mean	43.6		50.3	1.7	17.8				33.7
(SD)	(8.2)		(2.9)	(.6)	(6.5)				(13.2)

H&Y = Hoehn & Yahr; UPDRS III = Unified Parkinson's Disease Rating Scale, part III (motor score); phenotype = akinetic-rigid, or tremor-dominant; laterality = side of body that is worst affected by Parkinson's disease; M = male; F = female. *Non-significant ($Z = -1.5$, $P > 0.05$).

Fentress, 1987; Berridge, 1989; Cromwell and Berridge, 1996; Aldridge *et al*., 1997; Miyachi *et al*., 1997; Matsumoto *et al*., 1999).

The above experimental animal data indicating involvement of the basal ganglia in processing sequential movements is paralleled by functional brain imaging data in humans. Regional cerebral blood flow (rCBF) and functional MRI (fMRI) studies have demonstrated activations, not only in cortical motor and premotor areas, but also in the dorsal striatum during performance of sequential movements, the levels of which correlate with sequence complexity. This again is compatible with the suggestion that the striatum codes sequential patterns (Seitz and Roland, 1992; Jenkins *et al*., 1994; Jueptner *et al*., 1997; Samuel *et al*., 1997; Boecker *et al*., 1998; Catalan *et al*., 1998; Gordon *et al*., 1998; Menon *et al*., 1998).

Neurodegenerative diseases that affect DA neurotransmission in the striatum are associated characteristically with slow and inefficient production of sequential actions and, on occasion, motor arrest. In particular, patients who suffer from Parkinson's disease have difficulty executing sequential movements compared with single movements (Stern *et al*., 1983; Benecke *et al*., 1987; Roy *et al*., 1993; Martin *et al*., 1994; Weiss *et al*., 1997). They can, however, utilize external sensory stimuli partially to overcome this difficulty, suggesting that compensatory mechanisms are available (Martin, 1967; Dunne *et al*., 1987; Dietz *et al*., 1990; Georgiou *et al*., 1994).

In humans, it is possible to assess indirectly levels of striatal DA release *in vivo* with PET. Brain uptake of the DA D_2 receptor PET ligand, [^{11}C]raclopride (RAC), is sensitive to pharmacologically and behaviourally induced alterations in synaptic levels of endogenous DA in humans (Laruelle, 2000). Competition between endogenous DA and radioligand for binding to D_2 receptors is the principle underlying this approach, although receptor trafficking may also be involved. Administration of an intravenous 0.3 mg/kg bolus of methamphetamine to healthy humans leads to a mean 24% decrease in striatal RAC binding secondary to the increased synaptic levels of DA (Piccini *et al*., 1999). DA release can be detected not only in healthy volunteers but also in patients suffering from neurodegenerative diseases affecting nigrostriatal dopaminergic projections. Parkinson's disease patients show a significant though attenuated reduction in RAC binding after a 0.3 mg/kg methamphetamine challenge (Piccini *et al*., 1999). They also show striatal DA release in response to a placebo (de la Fuente-Fernandez *et al*., 2001). However, nobody has attempted, to date, to demonstrate reductions in RAC binding as a result of a behavioural challenge in Parkinson's disease.

In this study we wished to examine specifically the role of DA in mediating sequential stereotyped finger movements, employing a task that previously had been shown to activate striatal areas using $H_2{}^{15}O$ PET (Jenkins *et al*., 1994; Jueptner *et al*., 1997). The aims of the current study were 2-fold: (i) to establish whether DA plays a role in facilitating sequential motor behaviour; and (ii) to examine whether it is possible to detect DA release in Parkinson's disease during performance levels equivalent to those of healthy volunteers. Our hypothesis was that during the execution of repetitive sequential movements, there would be increased release of striatal endogenous DA, leading to decreased availability of DA receptors for RAC binding in healthy volunteers. Furthermore, this reduction in binding would be attenuated due to the dopaminergic striatal denervation, but nevertheless still be detectable, in Parkinson's disease.

Methods

Participants

These comprised eight right-handed healthy volunteers with a mean age of 44 years, and six Parkinson's disease patients with a mean age of 50 years, three of whom were right handed. Use of the dominant hand for our task meant that three Parkinson's disease patients were moving the hand contralateral and three the hand ipsilateral to the side clinically more affected by the disorder. We selected mild to moderately affected Parkinson's disease patients for this

study, as patients had to be able to perform the sequential motor task for a duration of 60 min. All patients showed clinical asymmetry, allowing us to observe laterality effects. Demographic details are listed in Table 1. PET was performed 24 h after withdrawal of anti-parkinsonian medication.

Participants with current or past psychiatric or neurological disease, head trauma, diabetes or medical conditions that may alter cerebral functioning, and past or present history of alcohol or substance abuse were excluded. The Beck Depression Inventory (Beck *et al*., 1961) was administered prior to scanning to exclude participants with significant abnormalities of mood. All parkinsonian patients were referred from specialist Movement Disorder clinics and assessed by a neurologist prior to scanning. All patients satisfied standard UK Brain Bank criteria for clinically probable idiopathic Parkinson's disease (Gibb and Lees, 1988). Three Parkinson's disease patients had an akinetic-rigid phenotype, and three patients had a tremor-predominant phenotype. The Parkinson's disease patients scored >24 on the Mini-Mental Parkinson (Mahieux *et al*., 1995), excluding the co-existence of significant dementia. Severity of disability in Parkinson's disease was rated using the Hoehn & Yahr (Hoehn and Yahr, 1967) and the Unified Parkinson's Disease Rating Scales (UPDRS; Fahn and Elton, 1987). Written informed consent was obtained from the participants. Approval for the study was given by the Ethics Committee of Hammersmith Hospitals Trust. Permission to administer radioactive RAC was given by the Administration of Radioactive Substances Advisory Committee of the Department of Health (UK).

Experimental design

Participants had two RAC PET scans on two separate days—one at rest and one while performing a paced pre-learned stereotyped sequential finger movement task. These scans were assigned in a counterbalanced order. The paced sequential movement condition involved pressing a sequence of keys on a keypad using the four fingers of the dominant hand. The sequence was eight moves long and involved touching the keys in ascending numerical order. The finger movements were paced by an auditory pacing tone at a frequency of 2.5 s with the tone signalling the initiation of the next movement in the sequence. We kept the pacing frequency deliberately slow in order to avoid any fatigue and to ensure equivalent numbers of finger movements by parkinsonian and healthy participants. A correct movement within a sequence was rewarded by a high-pitched tone, and an incorrect movement was punished by a low-pitched tone. The successful completion of one sequence was signified by a burst of short high-pitched tones. The participants then returned to the beginning of the sequence. Between eight-move sequences, participants had a rest period of 10 s. Reaction times were recorded for analysis off-line.

The task was started 5 min prior to tracer injection to ensure maximal sensitivity for detecting changes in endogenous striatal DA levels (Morris *et al*., 1995; Endres *et al*., 1997), and continued throughout the 55 min scan duration. Participants were fitted with headphones in order to hear the pacing tones. The two RAC scans were acquired an average of 6 days apart (range 1–20 days) for the Parkinson's disease group, and an average of 37 days apart (range 7–68 days) for the healthy volunteer group. Injection of RAC took place between 11 a.m. and 3 p.m. for all participants.

Data acquisition

Participants were studied using an ECAT EXACT HR++ PET camera (model 966, CTI, Knoxville, TN, USA) in 3D acquisition mode, with a total axial field of view of 23.4 cm (Spinks *et al*., 2000) covering the whole brain volume. Data were acquired in list mode (event-by-event), with post acquisition frame re-binning in order to obtain the following dynamic sequence: 1 × 15 s, 1 × 5 s, 1 × 10 s, 1 × 30 s, 4 × 60 s, 10 × 300 s time frames, for a total of 55 min. Participants lay supine in a darkened room with minimal noise, and the back of their heads rested in a foam-rubber support. Adjustable leather straps were used to minimize movement while ensuring the participant's comfort. Line markings were drawn parallel to the orbitomeatal line and centrally across the forehead. We used a laser beam aligned with the markings to check continuously throughout the scan that head position was maintained. RAC was injected i.v. as a bolus over 20 s. There were no significant differences between the amount of injected cold RAC in task and rest scans in Parkinson's disease patients (mean = 3.02 μg; range 1.66–5.29 μg; $t = -1.58$, $P = 0.189$) and in healthy volunteers (mean = 2.5 μg; range 1.22–5.22 μg; $t = 1.596$, $P = 0.171$). Between-group differences in amount of injected cold RAC were not significant ($Z = -1.259$, $P = 0.222$). The radiochemical purity of injected RAC was >96%. Images were corrected using in-house algorithms for scatter and attenuation of 511 KeV γ-radiation of the brain and skull by means of a 10 min transmission scan with a rotating point source of 137-caesium performed prior to radioligand injection (Watson *et al*., 1996; Spinks *et al*., 2000). Trans-axial images were reconstructed using a ramp filter (0.9 of Nyquist) yielding a spatial resolution of 5.1 mm (x) × 5.1 mm (y) × 5.9 mm (z) full-width half maximum (FWHM).

Tracer kinetic modelling

Quantitative tracer kinetic modelling was performed with a simplified reference tissue compartmental model (Lammertsma and Hume, 1996) using the implementation of Gunn *et al*. (1997). The cerebellum was used to generate a reference input function. The model allows the estimation of the parameters R_I (relative rate of radioligand delivery normalized to the cerebellum) and binding potential (BP).

$$BP = f_2\, B_{MAX}/\{K_D[1 + \Sigma_i\, F_i/K_{Di}\,]\}$$

where f_2 is the 'free fraction' of not specifically bound radioligand, B_{MAX} is the total concentration of specific binding sites, K_D is the dissociation constant of the radioligand, and F_i and K_{Di} are the free concentration and the dissociation constant, respectively, of competing endogenous ligand. Changes in BP are attributed to changes in F_i for endogenous DA. f_2 , F_i and B_{MAX} may differ between parkinsonian and healthy volunteers. Subsequent data analyses, therefore, have focused on the within-group analysis, although between-group comparisons were also performed. The reference tissue model was applied at a voxel level, using a basis function implementation, and parametric images of BP and R_I for the 55 min scan period were calculated as described previously (Gunn *et al*., 1997). The cerebellar reference region was generated within the Analyze™ software environment (Mayo Biomedical Engineering; Rochester, MN, USA) (Robb and Hanson, 1991) on a SUN Ultra 10 Workstation. Regular circular (15× 15) regions of interest (ROIs) were defined for each cerebellar hemisphere in five contiguous planes on an integrated emission PET (add) image of brain tracer activity from 1 to 30 min following i.v. administration for each individual scan.

Increased occupancy of the D_2 receptor sites by synaptic DA during task performance was inferred if a reduction of BP was observed, under the assumption that f_2 and K_D remain constant for the rest and active scans. We estimated the within-group induced effects on the synaptic levels of DA as the percentage change from baseline of the RAC BP values at rest and during sequential paced movement.

$$\%\ \text{change} = (\{BP_{task} - BP_{rest}\}/BP_{rest}) \times 100$$

Analysis of imaging data

In order to estimate D_2 site availability reflecting synaptic DA release in striatal subregions, two different analysis methods were undertaken: The first localized significant changes in RAC binding at a voxel level using statistical parametric mapping (Friston *et al*., 1995), while the second was an ROI approach.

Statistical parametric mapping

RAC parametric BP images were interrogated using SPM99 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Natick, MA, USA). Findings with SPM99 were displayed as statistical parametric maps of significant regional brain differences. For the purpose of the statistical analysis, the RAC parametric images of those Parkinson's disease patients whose left limbs were clinically more affected were reversed so that the main striatal DA degeneration of all Parkinson's disease patients appeared on the left hemisphere in all patients. Added images of radioactivity were transformed into the stereotactic space of an MNI-raclopride template previously described (Meyer *et al*., 1999), and the transformation matrix subsequently was applied to parametric images of BP and R_I. Images were smoothed spatially using a 5 × 5 × 5 mm (FWHM) Gaussian kernel. Significant differences were localized at a voxel level according to the general linear model. Regionally specific effects were compared using linear contrasts. Analyses were done with the *t* statistic with the threshold for significance set at $P < 0.001$, with a correction for multiple non-independent comparisons in small volumes ($P < 0.05$).

Region of interest approach

For this approach, a volumetric MRI of the brain was obtained for each Parkinson's disease patient and five of the eight healthy volunteers. We used a 1.0 T Marconi Medical Systems HPQ scanner with a 3D RF spoiled sequence [repetition time (TR) = 24 ms, echo time (TE) = 6 ms, field of view = 25 cm, slice thickness = 1.6 mm, image matrix = 152 × 256, NEX = 2]. To facilitate co-registration, the brain was segmented from extra-brain tissues in the MRI using Analyze™ software. Each MRI was then co-registered separately to rest and task corresponding RAC PET add images using co-registration software (MPR; Guy's Hospital, London, UK) (Studholme *et al*., 1997).

The paired co-registered MRIs and corresponding PET parametric images of RAC BP were visualized and regions were then traced around caudate and putamen of the left and right hemispheres on the MRI for all planes where these structures were clearly defined. The total number of voxels in each ROI was recorded.

ROIs were traced directly on PET add images of integrated tracer uptake from 15 to 55 min for the three healthy volunteers who did not have MRI scans. Regular elliptical ROIs were drawn on the head of caudate [5w, 7h, angle –10r, +10l] and putamen [6w, 16h, angle +14r, –14l] of the left and right hemispheres. The five (caudate) or four (putamen) planes displaying maximum activity in the striatum were chosen for this analysis. To obtain regional BP and R_I values, the ROIs described above were applied to the parametric images.

Statistical analysis

Due to the differences in sample size, the between-group ROI data were analysed using the non-parametric Wilcoxon–Mann–Whitney test. The BP data were distributed non-normally and the BP values from the paired scans were, therefore, analysed with the one-tailed Wilcoxon signed ranks test as we had a directional *a priori* hypothesis. Other data were analysed with the two-tailed paired samples *t* test.

To ensure uniformity, we present the means rather than medians to describe the data. As index of variation, the 'standard error of the difference of the means' (SED) is used. This index is used when one is interested in the relationship between two variables rather than the variables themselves,

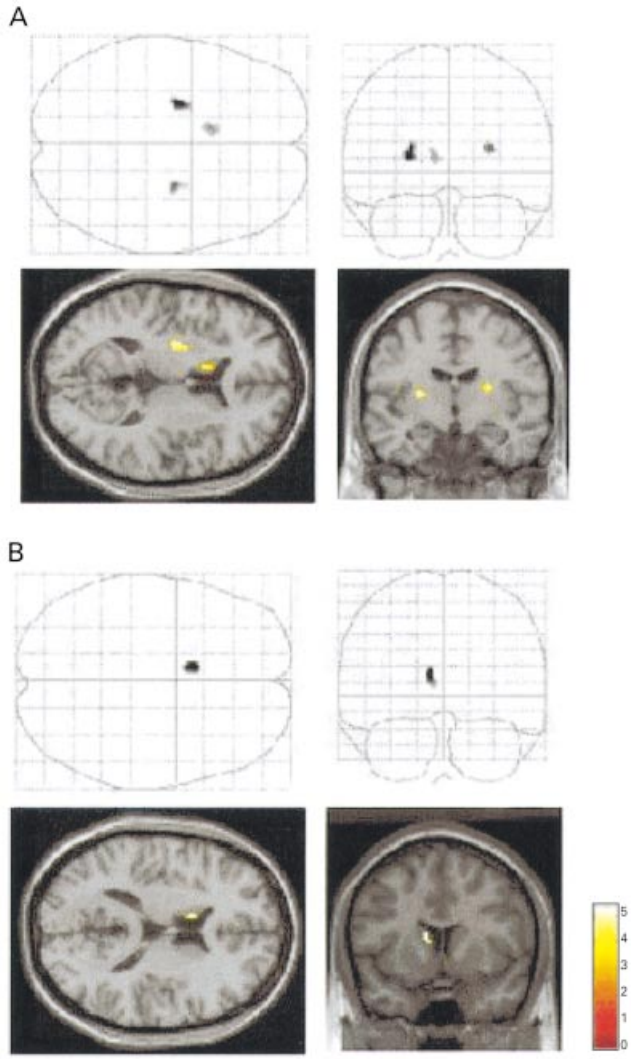

Fig. 1 Location of significant BP reductions in the voxel-by-voxel analysis during sequential paced movement as compared with rest in healthy controls (**A**) and Parkinson's disease patients (**B**). Images are transverse and coronal projections of statistical parametric maps. Areas of significant difference are shown as black areas projected onto the standard stereotactic grid or in yellow on a standard MRI (right hemisphere on right).

and is, therefore, the most suitable index of between-subject variability for this design. The SED can be calculated using the formula provided in Cochran and Cox (1957, p. 131):

$$\text{SED} = \sqrt{\{(2 \times \text{MSe})/n\}}$$

Where MSe = mean square for the error, or residual, term and n = number of observations made.

Results

Performance data

There was no significant difference between the healthy (mean = 0.33 s, SD = 0.12) and Parkinson's disease (mean = 0.33 s, SD = 0.08) groups in reaction time (Z = –0.225, $P > 0.05$) defined as time taken to press a key after hearing the pacing tone.

Statistical parametric mapping

Paced, pre-learned sequential finger movements compared with rest in the healthy volunteer group were associated with significant reductions in RAC binding bilaterally in putamen and in left caudate. In contrast, this comparison only localized significant BP reductions in the caudate contralateral (to the more affected limbs) in the Parkinson's disease cohort. Exclusive masking, which identifies regions more 'reduced' in the healthy volunteers than in the Parkinson's disease patients, identified the putamen bilaterally. Conversely, a conjunction analysis, which indicates the regions that commonly are reduced in both groups, identified the left caudate, contralateral to the more affected limbs in Parkinson's disease. The statistical parametric maps are displayed in Figs 1 and 2, and the corresponding coordinates are listed in Table 2.

ROI approach—healthy volunteers

All striatal ROIs showed significant reductions in RAC BP during task performance compared with rest in the healthy volunteers. The mean percentage reduction in BP during paced sequential movement was –8.3% (minimum 12.8%, maximum –26.9%) for the right caudate and –6.4% (minimum 13.5%, maximum –22.8%) for the left caudate (both, Z = –1.68, $P < 0.05$). Averaging for both hemispheres, this reduction was –7.4% for head of caudate.

The mean percentage reduction in BP was –8.8% (minimum 1.4%, maximum –23.5%) for the right dorsal putamen (Z = –2.24, $P < 0.05$) and –5.1% (minimum 0.02%, maximum –24.0%) for the left dorsal putamen (Z = –2.1, $P < 0.05$). Averaging for both hemispheres, the reduction was –6.4% for dorsal putamen.

There was little evidence of a linear relationship between age and RAC binding reductions in healthy volunteers (all $r < 0.26$, all $P > 0.54$) and of a non-linear (quadratic) relationship [all $r^2 < 0.29$, all F (1,5) < 1, all $P > 0.43$], suggesting that in our paradigm and in our group of healthy volunteers, DA response does not change with age over this particular age range, i.e. the third to the fifth decade.

The magnitude of change of BP associated with sequential finger movements was greater for all striatal ROIs than the previously reported within-subject test/re-test variation in striatal RAC BP (mean –5%) (Volkow *et al.*, 1993; Hietala *et al.*, 1999).

R_I, the tracer delivery parameter, showed trends for differences between conditions in the left putamen and left caudate regions (t = 2.319, P = 0.053; t = 2.209, P = 0.063) but not in the right structures (all $t < 0.8$, $P > 0.05$).

Our findings in healthy volunteers are, therefore, compatible with a task-related increase in levels of extracellular DA reducing the number of D_2 receptor sites available for binding

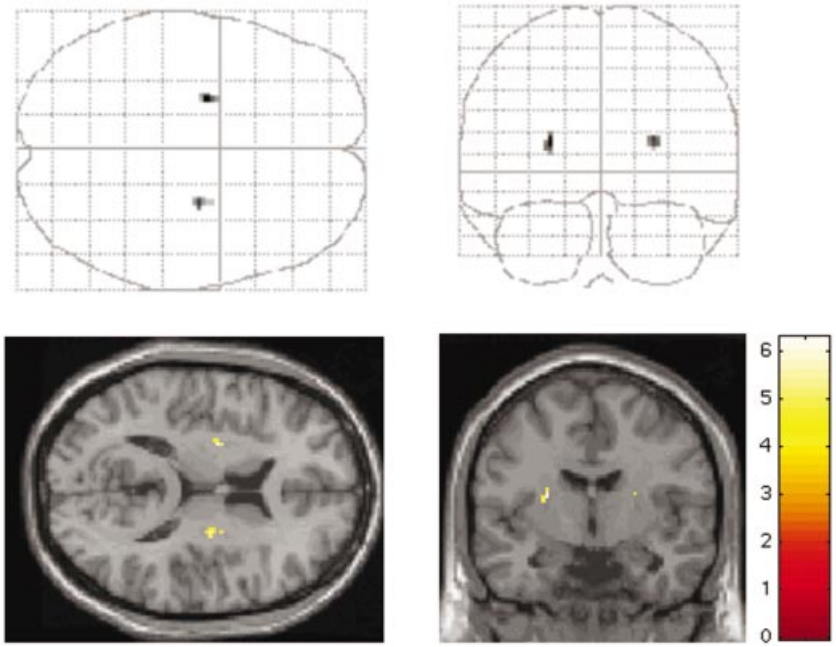

Fig. 2 Location of significant BP reductions in the voxel-by-voxel analysis during sequential paced movement as compared with rest that are greater in healthy controls than in Parkinson's disease patients. Images are transverse and coronal projections of statistical parametric maps.

Table 2 *Coordinates for [^{11}C]raclopride displacement identified with SPM99*

Area	Coordinates* Talairach space			*Z* Score+
	x	*y*	*z*	
Reductions in healthy controls				
L Putamen	–26	–9	10	4.24
R Putamen	26	–10	15	3.81
L Caudate	–10	12	9	3.53
Reductions in Parkinson's disease				
Contralateral caudate	–8	10	14	3.76
Reductions common to Parkinson's disease and healthy controls (conjunction)				
Contralateral/L Caudate	–10	10	12	5.3
Areas more reduced in healthy controls than in Parkinson's disease (exclusive masking)				
L Putamen	–24	–5	13	4.11
R Putamen	26	–9	15	3.81

*Converted from MNI to Talairach space (see www.mrc-cbu.cam.ac.uk/Imaging) (Talairach and Tournoux, 1988). +Small volume corrected $P < 0.05$. R = right, L = left.

to RAC across dorsal striatal areas. These results are detailed in Table 3 and Fig. 3.

ROI approach— Parkinson's disease patients

In the Parkinson's disease group, only one striatal region showed a significant reduction in RAC BP during task performance. There was a significant fall in BP in the less affected putamen ipsilateral (to the clinically more affected limbs) ($Z = –2.2$, $P < 0.05$). The mean percentage reduction in BP during paced sequential finger movement, compared with rest, was –4.15% (minimum –1.5%, maximum –8.5%). In the caudate contralateral (to the clinically more affected limbs), the reduction in BP approached significance (Z = –1.57,

Table 3 *[^{11}C]Raclopride binding potential, relative tracer delivery and average change (Δ) expressed in means and SEDs (see text for details) for healthy participants*

	Putamen						Caudate					
	Right			Left			Right			Left		
	Rest	Task	Δ (%)	Rest	Task	Δ (%)	Rest	Task	Δ (%)	Rest	Task	Δ (%)
BP	3.44	3.16	–8.79	3.44	3.25	–5.09	3.19	2.9	–8.34	3.21	3	–6.38
(SED)	(0.09)			(0.08)			(0.1)			(0.09)		
R_I	0.88	0.86	–2.99	0.95	0.89	–5.82	0.8	0.79	–1.55	0.85	0.79	–6.97
(SED)	(0.03)			(0.02)			(0.02)			(0.02)		

BP = binding potential; R_I = relative tracer delivery; SED = standard error of the difference of the means (see text for details); rest = baseline condition; task = sequential movement condition; Δ = % changes in BP, R_I (see text for calculation details).

Table 4 *[^{11}C]Raclopride binding potential, relative tracer delivery and average change (Δ) expressed in means and SEDs (see text for details) for Parkinson's disease participants*

	Putamen						Caudate					
	Contralateral			Ipsilateral			Contralateral			Ipsilateral		
	Rest	Task	Δ (%)	Rest	Task	Δ (%)	Rest	Task	Δ (%)	Rest	Task	Δ (%)
BP	3.46	3.43	–0.18	3.49	3.35	–4.15	2.6	2.46	–5.41	2.58	2.51	–2.53
(SED)	(0.03)			(0.02)			(0.07)			(0.08)		
R_I	0.93	0.91	–1.65	0.81	0.9	–6.79	0.86	0.74	–13.72	0.86	0.78	–9.62
(SED)	(0.13)			(0.03)			(0.04)			(0.04)		

BP = binding potential; R_I = relative tracer delivery; SED = standard error of the difference of the means (see text for details); contralateral = hemisphere opposite to the side affected by Parkinson's disease; ipsilateral = hemisphere concurrent to the side affected by Parkinson's disease; rest = baseline condition; task = sequential movement condition; Δ = % changes in BP, R_I (see text for calculation details).

$P = 0.058$). The mean percentage reduction in BP during paced sequential finger movement, compared with rest, was –5.4% (minimum 14.3%, maximum –11.7%). Contralateral putamen and ipsilateral caudate showed no significant reductions in BP during paced sequential movement (all $Z < -1$, all $P > 0.05$).

It has been established that Parkinson's disease patients display an adaptation in the D_2 receptor system. Early on in the disease process, putamen RAC binding is enhanced and caudate RAC binding is normal (Rinne *et al*., 1990; Antonini *et al*., 1997). However, 3–5 years after disease onset and after chronic exposure to dopaminergic medication, putamen RAC binding decreases to the levels of healthy controls while caudate RAC binding is reduced (Antonini *et al*., 1997). The Parkinson's disease patients in our study had normal levels of baseline putamen RAC binding accompanied by a D_2 downregulation in the caudate. This is, therefore, analogous to previous imaging studies, as our group of Parkinson's disease patients had a mean disease duration of 3 years.

Although no formal test/re-test studies of variation in striatal RAC BP have been reported in Parkinson's disease, Rinne *et al*. (1993) have serially examined resting striatal RAC uptake in Parkinson's disease and found no significant change in binding over a 6 month interval (mean change = 0.03%).

With regard to the R_I delivery parameter, there were no significant differences between conditions for the striatal ROIs in Parkinson's disease (all $t < 2.3$, all $P > 0.05$).

Our results, therefore, are compatible with a task-related significant increase in levels of extracellular DA reducing the number of D_2 receptor sites available for binding to RAC in the ipsilateral less affected putamen, and with an increase approaching significance in the contralateral caudate of Parkinson's disease patients. These results are detailed in Table 4, and Fig. 3.

ROI approach—between-group comparison

A between-group analysis was performed comparing the percentage changes in BP between rest and task of the combined caudal and putaminal regions in the healthy volunteers and of the ipsilateral and contralateral striatal regions in the Parkinson's disease patients. No significant between-group differences were observed in any striatal region (all $Z < 0.7$, all $P > 0.05$). The lack of statistical significance possibly was due to the large variances observed

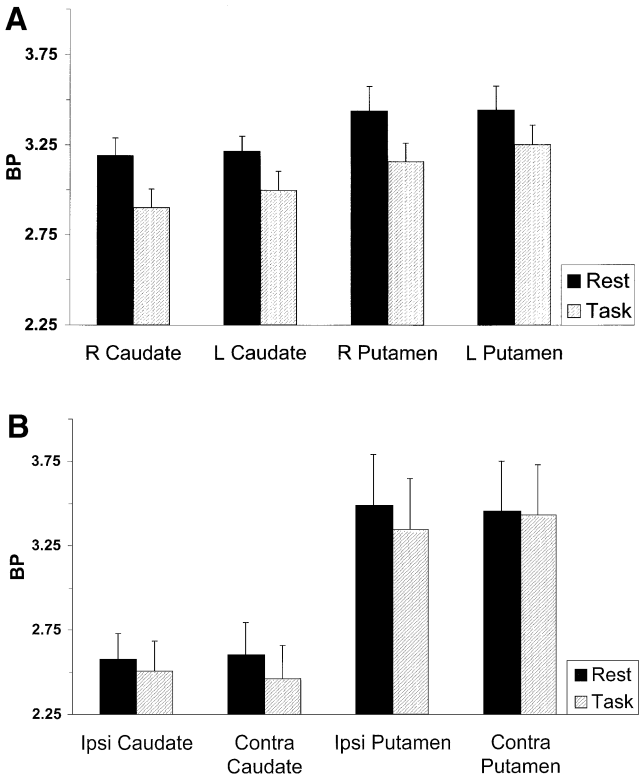

Fig. 3 Mean and SEM values of the binding potential (BP) for striatal regions during the paced sequential movement and rest conditions in healthy controls (**A**) and Parkinson's disease (**B**).

in each of the groups combined with a small number of participants.

Discussion

We have shown for the first time that the execution of paced, stereotyped sequential finger movements results in a reduction of dorsal striatal RAC binding in healthy volunteers, reflecting enhanced striatal synaptic DA release, and suggesting that DA plays a role in facilitating stereotyped sequential movements. In contrast, in Parkinson's disease, paced, stereotyped sequential finger movements only resulted in a reduction of RAC binding in those dorsal striatal regions (caudate and ipsilateral putamen) known to be less affected by the disease process.

The role of the dorsal striatum in sequence execution

In healthy subjects, we detected DA release in both the head of caudate nucleus and the dorsal putamen during stereotyped sequential finger movements, suggesting that their execution depend on the whole dorsal striatum, supporting an effector-independent representation of movement sequences (Bapi *et al*., 2000). Several factors could have contributed to this: first, the caudate has been shown to encode temporally and spatially the serial order of events in electrophysiological and neural network studies, and could, therefore, contribute to the 'working memory' representations of previous stimuli in the sequences that have to be encoded, and consequently to the progression of the sequence (Kermadi and Joseph, 1995; Aldridge and Berridge, 1998; Beiser and Houk, 1998; Berns and Sejkowski, 1998; Fukai, 1999; Nakahara *et al*., 2001). Dominey (1995) has proposed a frontostriatal model of sensory–motor sequencing in which the prefrontal cortex encodes the sequence and the caudate behaves as an associative memory structure that binds a sensory event, incorporating memory signals, to the corresponding motor output, and, therefore, decodes and generates sequences (see also Hikosaka *et al*., 2000). Secondly, the execution of sequences is influenced by attention, in this case to the auditory pacing tone, which has been shown to be associated with caudal DA release as well as caudate bloodflow activation during sequence execution (Jueptner *et al*., 1997; Jueptner and Weiller, 1998; Shinba *et al*., 1998; Hikosaka *et al*., 2000). Thirdly, the putamen has been shown to be particularly involved in executing sequential movements (Jueptner *et al*., 1997; Miyachi *et al*., 1997; Aldridge and Berridge, 1998; Matsumoto *et al*., 1999; Nakahara *et al*., 2001). This may reflect, in part, its linkage to the supplementary motor area (SMA) (Alexander and Crutcher, 1990; Parent, 1990) which has been suggested to be a storage site for 'motor memories' (Jenkins *et al*., 1994; Petersen *et al*., 1998).

The role of dopamine in sequence execution

DA can modify activity in corticostriatal circuits (Graybiel, 1998; Schultz, 1998). Nigral dopaminergic neurons terminate on the necks of the dendrites of dorsal striatal neurons in close proximity to inputs from the cortex synapsing at the apices of these dendrites (Smith and Bolam, 1990). Previously, microdialysis and voltammetry studies have reported the involvement of DA in complex locomotor behaviour (Trulson, 1985; Heyes *et al*., 1988; Hattori *et al*., 1994). Specifically, activation of nigral DA neurons has been shown during sequential repetitive movement (Magarinos-Ascone *et al*., 1992). During execution of movement sequences, DA has been suggested to facilitate temporal and spatial coding of the sequence (Cools, 1980). As such, DA release may be taken as a signal prioritizing response to sensory events, such as the auditory signal in our paradigm, or to motor events such as the previous movement made in a sequence. This viewpoint is supported by the oberservation that DA release in the dorsal striatum facilitates response selection (Robbins and Everitt, 1992; Schultz *et al*., 1997; Matsumoto *et al*., 1999).

DA appears to have two principal neurophysiological effects that potentially could play an important role in the execution of sequences. (i) Neural 'focusing': DA acts as a modulator altering the efficiency of neuronal responses to

other inputs, particularly to glutamate. DA may, therefore, enhance strong cortical inputs while suppressing weaker inputs (Berretta *et al*., 1999; Joel and Weiner, 2000; Nicola *et al*., 2000). (ii) Long-term plasticity depends on DA receptor activation (Nicola *et al*., 2000; Reynolds *et al*., 2001). DA affects the capacity of cortical stimulation to induce gene expression in striatal neurons via an NMDA (*N*-methyl-D-aspartate)-dependent mechanism and modulates the flow of information through the striatum (Berretta *et al*., 1999). DA can thus affect the plasticity and efficacy of corticostriatal transmission and so affect striatum-based memory (Aosaki *et al*., 1994; Houk *et al*., 1995; Calabresi *et al*., 1996; Wickens *et al*., 1996; Schultz *et al*., 1997; Schultz, 1998; Hikosaka *et al*., 2000; Reynolds and Wickens, 2000).

Considering these two main effects of DA in relation to our paradigm, it is likely that we observed striatal DA release specifically because the sequence in our study was highly stereotyped and predictable. It has been shown that caudate activation correlates with an increasing degree of event predictability (Bischoff-Grethe *et al*., 2001; Knutson *et al*., 2001) and is sensitive to sequence order (Bischoff-Grethe *et al*., 2001). It has been suggested that striatal DA signals keep track of progress through a sequence (Kermadi and Joseph, 1995; Beiser and Houk, 1998; Berns and Sejkowski, 1998; Shidara *et al*., 1998; Nakahara *et al*., 2001). Dopaminergic activity may, therefore, be involved in facilitating prediction, ordering and progression through its focusing and efficacy effects in the striatum, which consequently optimizes selection of the correct response in a highly stereotyped sequence.

The role of phasic and tonic dopamine

Our RAC PET approach provides an integrated measurement of both phasic and tonic DA release. Therefore, we cannot distinguish whether the pattern of dopaminergic firing observed in this study reflects activity of one pattern of dopaminergic firing over the other. Tonic DA release has been suggested to allow plasticity at corticostriatal synapses (Moore *et al*., 1999) and therefore to be necessary to retain and to provide a response such as in the initiation and sequencing of movements (DeLong *et al*., 1983; Schultz *et al*., 1983; Salamone *et al*., 1997; Robbins *et al*., 1998; Moore *et al*., 1999); while phasic release is generally believed to play a role in reward mechanisms and is therefore less likely to be relevant to our paradigm (Berridge and Robinson, 1998; Schultz, 1998).

Execution of sequences in Parkinson's disease

The execution of sequential finger movements by Parkinson's disease patients evoked striatal DA release in a regionally distinct pattern. Whereas healthy volunteers released DA uniformly in all striatal subregions, Parkinson's disease patients only released DA in the putamen ipsilateral to the more affected limbs and the contralateral head of caudate, both regions that are relatively spared from DA terminal loss. The symptoms of Parkinson's disease are estimated to occur when 80% of DA content is lost in the dorsal putamen (Bezard *et al*., 2001). In the initial hemiparkinsonian stage of the disease, the degenerative process targets the dopaminergic fibres innervating the dorsal putamen contralateral to the clinically affected limbs (Bernheimer *et al*., 1973; Kish *et al*., 1988; Tissingh *et al*., 1998), with milder reductions in DA in the ipsilateral putamen and the heads of caudate. As the disease progresses, DA loss becomes significant in the ipsilateral striatum, the rostral caudate and finally the ventral putamen (Kish *et al*., 1988; Morrish *et al*., 1996).

Previous RAC binding studies in Parkinson's disease have reported only pharmacological effects (Tedroff *et al*., 1996; Piccini *et al*., 1999; de la Fuente-Fernandez *et al*., 2001). When Parkinson's disease patients were challenged with amphetamine, the reductions in RAC uptake were greatest in the striatal regions least affected by DA terminal degeneration (Piccini *et al*., 1999). [^{11}C]CFT PET is also a marker of synaptic DA release as evidenced by changes in DA transporter availability. When Parkinson's disease patients underwent [^{11}C]CFT PET during walking, they showed DA release only in the caudate and not in the putamen (Ouchi *et al*., 2001). These studies combined with our present results confirm that DA release is best preserved in Parkinson's disease in the more intact striatal regions when patients are pharmacologically or behaviourally challenged.

During our sequential motor task, the performance of the Parkinson's disease patients was not significantly different from that of healthy volunteers, though the finger movements were deliberately paced at a slow frequency. The fact that performance was not impaired therefore suggests that the amount of DA released in the Parkinson's disease group was still sufficient to perform appropriately at this level of difficulty. Presumably, in our Parkinson's disease group, the preserved striatal or other cortical areas were able to compensate enough in order to be able to facilitate a well-learned sequence.

The fact that in our group of Parkinson's disease patients DA release was found in two striatal subregions suggests that adaptive processes may act to maintain function in mild Parkinson's disease. It has been postulated that a number of factors can compensate for the deficits arising from extensive loss of DA in the striatum, including formation of new axonal branches or sprouting and formation of new synapses (Finkelstein *et al*., 2000; Song and Haber, 2000); increased number of synapses (Anglade *et al*., 1996); increased DA release per pulse (Bezard *et al*., 2000); increased turnover of DA in the remaining dopaminergic neurons (Hornykiewicz, 1993; Zigmond *et al*., 1990); increased DA synthesis and release from the remaining terminals (Bernheimer *et al*., 1973; Zigmond *et al*., 1984; Altar and Marien, 1989); reduced DA clearance from extracellular fluid (van Horne *et al*., 1992); and diffusion of DA from the remaining terminals to more distant receptor sites (Zigmond *et al*., 1997). Indeed, animal models of

Parkinson's disease have already shown that despite severe loss of striatal DA terminals, extracellular DA is maintained at normal levels (Robinson and Whishaw, 1988; Zhang *et al*., 1988). Furthermore, electrical stimulation of neurons in the striata in animal models of Parkinson's disease evokes similar levels of extracellular DA in DA-depleted and control striata, confirming, again, that DA can be released and utilized even in affected striata (Onn *et al*., 1986; Zhang *et al*., 1988; Garris *et al*., 1997). We now provide evidence in human Parkinson's disease in line with the above-mentioned studies of animal models of Parkinson's disease that the remaining elements of the striatal dopaminergic neurotransmitter system are able to release DA, because in our group of mild to moderate Parkinson's disease, RAC BP was significantly reduced during task performance, similar to controls.

Our findings of reduced DA release in the putamen in Parkinson's disease may also help explain the observation that activation of the SMA is attenuated in these patients during performance of a variety of movement paradigms including sequential movement (Jenkins *et al*., 1992; Playford *et al*., 1992; Jahanshahi *et al*., 1995; Samuel *et al*., 1997; Sabatini *et al*., 2000; Haslinger *et al*., 2001). This defective SMA activation is thought to reflect the decrease in the efferent feedback arising from the basal ganglia–thalamocortical motor loop, and specifically the feedback arising from the putamen. We now provide evidence that the efferent dopaminergic signal arising from the putamen is indeed diminished in the putamen contralateral to the more affected limbs in Parkinson's disease, and signal arising from the more intact ipsilateral putamen may be insufficient to induce an SMA activation signal. Our results may also explain why motor control in Parkinson's disease is improved by sensory cues rather than prediction and forward planning (Flowers, 1978). The postulated role of DA in facilitating prediction, ordering and progression cannot be carried out with an insufficient DA input and/or supply magnitude in Parkinson's disease.

Conclusions

In conclusion, using RAC PET, we have demonstrated DA release in healthy subjects in both the head of caudate nucleus and dorsal putamen during stereotyped sequential finger movements. This suggests that execution of sequential actions depends on integrity of the DA system in the whole dorsal striatum. We have also shown for the first time attenuated striatal DA release in Parkinson's disease patients during sequence execution. These results support the existence of dopaminergic adaptive processes in Parkinson's disease and suggest that parkinsonian impairments are related to increasing demands on a dysfunctional dopaminergic system.

Acknowledgements

We wish to thank all the volunteers for their participation in this study, the chemistry, radiography, instrumentation and methodology staff of the Cyclotron Unit for their contributions, and Philip Nixon for computer programming. This work was supported by the Medical Research Council, UK, the British Brain and Spine Foundation, and the Royal Society. I.K.G. was supported by a Parkinson's Disease Society prize studentship. *O*-Desmethyl raclopride hydromobide, precursor for the preparation of [^{11}C]raclopride, was generously provided by the Astra Arcu Pharmaceutical Company (Sodertalje, Sweden).

References

Aldridge JW, Berridge KC. Coding of serial order by neostriatal neurons: a 'natural action' approach to movement sequence. J Neurosci 1998; 18: 2777–87.

Aldridge JW, Thompson JF, Gilman S. Unilateral striatal lesions in the cat disrupt well-learned motor plans in a GO/NO-GO reaching task. Exp Brain Res 1997; 113: 379–93.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. [Review]. Trends Neurosci 1990; 13: 266–71.

Altar A, Marien MR. Preservation of dopamine release in the denervated striatum. Neurosci Lett 1989; 96: 329–34.

Anglade P, Mouatt-Prigent A, Agid Y, Hirsch E. Synaptic plasticity in the caudate nucleus of patients with Parkinson's disease. Neurodegeneration 1996; 5: 121–8.

Antonini A, Schwarz J, Oertel WH, Pogarell O, Leenders KL. Long-term changes of striatal dopamine D2 receptors in patients with Parkinson's disease: a study with positron emission tomography and [^{11}C]raclopride. Mov Disord 1997; 12: 33–8.

Aosaki T, Tsubokawa H, Ishida A, Watanabe K, Graybiel AM, Kimura M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. J Neurosci 1994; 14: 3969–84.

Arbib MA, Dominey PF. Modelling the roles of basal ganglia in timing and sequencing saccadic eye movements. In: Houk JC, Davis JL, Beiser DG, editors. Models of information processing in the basal ganglia. Cambridge (MA): MIT Press; 1995. p. 149–62.

Bapi RS, Doya K, Harner AM. Evidence for effector independent and dependent representations and their differential time course of acquisition during motor sequence learning. Exp Brain Res 2000; 132: 149–62.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiat 1961; 4: 561–71.

Beiser DG, Houk JC. Model of cortical–basal ganglionic processing: encoding the serial order of sensory events. J Neurophysiol 1998: 79: 3168–88.

Benecke R, Rothwell JC, Dick JP, Day BL, Marsden CD. Disturbance of sequential movements in patients with Parkinson's disease. Brain 1987; 110: 361–79.

Beninger RJ. The role of dopamine in locomotor activity and learning. [Review]. Brain Res 1983; 287: 173–96.

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K,

Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci 1973; 20: 415–55.

Berns GS, Sejnowski TJ. A computational model of how the basal ganglia produce sequences. J Cogn Neurosci 1998; 10: 108–21.

Berretta S, Sachs Z, Graybiel AM. Cortically driven Fos induction in the striatum is amplified by local dopamine D2-class receptor blockade. Eur J Neurosci 1999; 11: 4309–19.

Berridge KC. Substantia nigra 6-OHDA lesions mimic striatopallidal disruption of syntactic grooming chains: a neural systems analysis of sequence control. Psychobiology 1989; 17: 377–85.

Berridge KC, Aldridge JW. Super-stereotypy I: enhancement of a complex movement sequence by systemic dopamine D1 agonists. Synapse 2000; 37: 194–204.

Berridge KC, Fentress JC. Disruption of natural grooming chains after striatopallidal lesions. Psychobiology 1987; 15: 336–42.

Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? [Review]. Brain Res Brain Res Rev 1998; 28: 309–69.

Bezard E, Jaber M, Gonon F, Boireau A, Bloch B, Gross CE. Adaptive changes in the nigrostriatal pathway in response to increased 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine-induced neurodegeneration in the mouse. Eur J Neurosci 2000; 12: 2892–900.

Bezard E, Dovero S, Prunier C, Ravenscroft P, Chalon S, Guilloteau D, *et al*. Relationship between the appearance of symptoms and the level of nigrostriatal degeneration in a progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque model of Parkinson's disease. J Neurosci 2001; 21: 6853–61.

Bischoff-Grethe A, Martin M, Mao H, Berns GS. The context of uncertainty modulates the subcortical response to predictability. J Cogn Neurosci 2001; 13: 986–93.

Boecker H, Dagher A, Ceballos-Baumann AO. Passingham RE, Samuel J, Friston KJ, *et al*. Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with H2150 PET. J Neurophysiol 1998; 79: 1070–80.

Calabresi P, Pisani A, Mercuri NB, Bernardi G. The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. Trends Neurosci 1996; 19: 19–24.

Catalan MJ, Honda M, Weeks RA, Cohen LG, Hallett LG. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. Brain 1998; 121: 253–64.

Cochran WG, Cox GM. Experimental designs. 2nd edn. New York: John Wiley; 1957.

Cools AR. Role of the neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: facilitation of processes involved in selecting the best strategy in a stressful situation. Behav Brain Res 1980; 1: 361–78.

Cromwell HC, Berridge KC. Implementation of action sequences by a neostriatal site: a lesion mapping study of grooming syntax. J Neurosci 1996; 16: 3444–58.

de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 2001; 293: 1164–6.

DeLong MR, Crutcher MD, Georgopoulos AP. Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. J Neurosci 1983; 3: 1599–606.

Dietz MA, Goetz CG, Stebbins GT. Evaluation of a modified inverted walking stick as a treatment for parkinsonian freezing episodes. Mov Disord 1990; 5: 243–7.

Dominey PF. Complex sensory–motor sequence learning based on recurrent state representation and reinforcement learning. Biol Cybern 1995; 73: 265–74.

Dunne JW, Hankey GJ, Edis RH. Parkinsonism: upturned walking stick as an aid to locomotion. Arch Phys Med Rehabil 1987; 68: 380–1.

Endres CJ, Kolachana BS, Saunders RC, Su T, Weinberger D, Breier A, *et al*. Kinetic modelling of [^{11}C]raclopride: combined PET–microdialysis studies. J Cereb Blood Flow Metab 1997; 17: 932–42.

Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent developments in Parkinson's disease, Vol. II. Florham Park (NJ): MacMillan Healthcare Information; 1987. p. 153–163.

Finkelstein DI, Stanic D, Parish CL, Tomas D, Dickson K, Horne MK. Axonal sprouting following lesions of the rat substantia nigra. Neuroscience 2000; 97: 99–112.

Flowers K. Lack of prediction in the motor behaviour of parkinsonism. Brain 1978; 101: 35–52.

Friston KJ, Holmes AP, Worsley KJ, Poline J-B, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995; 2: 189–210.

Fukai T. Sequence generation in arbitrary temporal patterns from theta-nested gamma oscillations: a model of the basal ganglia-thalamo-cortical loops. Neural Netw 1999; 12: 975–87.

Garris PA, Walker QD, Wightman RM. Dopamine release and uptake rates both decrease in the partially denervated striatum in proportion to the loss of dopamine terminals. Brain Res 1997; 753: 225–34.

Georgiou N, Bradshaw JL, Iansek R, Phillips JG, Mattingley JF, Bradshaw JA. Reduction in external cues and movement sequencing in Parkinson's disease. J Neurol Neurosurg Psychiatry 1994; 57: 368–70.

Gibb WR, Lees AJ. The relevance of the lewy body to the pathogenesis of idiopathic Parkinson's disease. [Review]. J Neurol Neurosurg Psychiatry 1988; 51: 745–52.

Gordon AM, Lee JH, Flament D, Ugurbil K, Ebner TJ. Functional magnetic resonance imaging of motor, sensory, and posterior parietal cortical areas during performance of sequential typing movements. Exp Brain Res 1998; 121: 153–66.

Graybiel AM. The basal ganglia and chunking of action repertoires. [Review]. Neurobiol Learn Mem 1998; 70: 119–36.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 1997; 6: 279–87.

Haslinger B, Erhard P, Kämpfe N, Boecker H, Rummeny E, Schwaiger M, *et al*. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 2001; 124: 558–70.

Hattori S, Naoi M, Nishino H. Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. Brain Res Bull 1994; 35: 41–9.

Heyes MP, Garnett ES, Coates G. Nigrostriatal dopaminergic activity is increased during exhaustive exercise stress in rats. Life Sci 1988; 42: 1537–42.

Hietala J, Nagren K, Lehikoinen P, Ruotsalainen U, Syvalahti E. Measurement of striatal D_2 dopamine receptor density and affinity with [^{11}C]raclopride *in vivo*: a test–retest analysis. J Cereb Blood Flow Metab 1999; 19: 210–7.

Hikosaka O, Takikawa Y, Kawagoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. [Review]. Physiol Rev 2000; 80: 953–78.

Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967; 17: 427–42.

Hornykiewicz O. Parkinson's disease and the adaptive capacity of the nigrostriatal dopamine system: possible neurochemical mechanisms. [Review]. Adv Neurol 1993; 60: 140–7.

Houk JC, Adams JL, Barto A. A model of how the basal ganglia generate and use neural signals that predict reinforcement. In: Houk JC, David JL, Beiser DB, editors. Models of information processing in the basal ganglia. Cambridge (MA): MIT Press, 1995. p. 249–70.

Jahanshahi M, Jenkins HI, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 1995; 118: 913–33.

Jenkins IH, Fernandez W, Playford ED, Lees AJ, Frackowiak RS, Passingham RE, *et al*. Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. Ann Neurol 1992; 32: 749–57.

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RSJ, Passingham RE. Motor sequence learning: a study with positron emission tomography. J Neurosci 1994; 14: 3775–90.

Joel D, Weiner I. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. [Review]. Neuroscience 2000; 96: 451–74.

Jueptner M, Weiller C. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. [Review]. Brain 1998; 121: 1437–49.

Jueptner M, Stephan KM, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. I. Frontal cortex and attention to action. J Neurophysiol 1997; 77: 1313–24.

Kermadi I, Joseph JP. Activity in the caudate nucleus of monkey during spatial sequencing. J Neurophysiol 1995; 74: 911–33.

Kimura M. Behaviorally contingent property of movement-related activity of the primate putamen. J Neurophysiol 1990; 63: 1277–96.

Kish SJ, Shannak K, Hornykiewicz O. Uneven patterns of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N Engl J Med 1988; 318: 876–80.

Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 2001; 21: RC159.

Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. Neuroimage 1996; 4: 153–8.

Laruelle M. Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. [Review]. J Cereb Blood Flow Metab 2000; 20: 423–51.

Magarinos-Ascone C, Buno W, Garcia-Austt E. Activity in monkey substantia nigra neurons related to a simple learned movement. Exp Brain Res 1992; 88: 283–91.

Mahieux F, Michelet D, Manifacier MJ, Boller F, Fermanian J, Guillard A. Mini-Mental Parkinson: first validation study of a new bedside test constructed for Parkinson's disease. Behav Neurol 1995; 8: 15–22.

Marsden CD. The enigma of the basal ganglia and movement. Trends Neurosci 1980; 3: 284–7.

Martin JP. The basal ganglia and posture. London: Pitman; 1967.

Martin KE, Phillips JG, Iansek R, Bradshaw JL. Inaccuracy and instability of sequential movements in Parkinson's disease. Exp Brain Res 1994; 102: 131–40.

Matsumoto N, Hanakawa T, Maki S, Graybiel AM, Kimura M. Role of nigrostriatal dopamine system in learning to perform sequential motor tasks in a predictive manner. J Neurophysiol 1999; 82: 978–98.

Menon V, Glover GH, Pfefferbaum A. Differential activation of dorsal basal ganglia during externally and self paced sequences of arm movements. Neuroreport 1998; 9: 1567–73.

Meyer JH, Gunn RN, Myers R, Grasby PM. Assessment of spatial normalization of PET ligand images using ligand-specific templates. Neuroimage 1999; 9: 545–53.

Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. [Review]. Brain Res Brain Res Rev 2000; 31: 236–50.

Miyachi S, Hikosaka O, Miyashita K, Karadi Z, Rand MK. Differential roles of monkey striatum in learning of sequential hand movement. Exp Brain Res 1997; 115: 1–5.

Moore H, West AR, Grace AA. The regulation of forebrain dopamine transmission: relevance to the pathophysiology and psychopathology of schizophrenia. [Review]. Biol Psychiatry 1999; 46: 40–55.

Morris ED, Fisher RE, Alpert NM, Rauch SL, Fischman AJ. In vivo imaging of neuromodulation using positron emission tomography: optimal ligand characteristics and task length for detection of activation. Hum Brain Mapp 1995; 3: 35–55.

Morrish PK, Sawle GV, Brooks DJ. Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease. Brain 1996; 119: 2097–103.

Nakahara H, Doya K, Hikosaka O. Parallel cortico-basal ganglia mechanisms for acquisition and execution of visuomotor

sequences—a computational approach. J Cogn Neurosci 2001; 13: 626–47.

Nicola SM, Surmeier DJ, Malenka RC. Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. [Review]. Annu Rev Neurosci 2000; 23: 185–215.

Onn SP, Berger TW, Stricker EM, Zigmond MJ. Effects of intraventricular 6-hydroxydopamine on the dopaminergic innervation of striatum: histochemical and neurochemical analysis. Brain Res 1986; 376: 8–19.

Ouchi Y, Kanno T, Okada H, Yoshikawa E, Futatsubashi M, Nobezawa S, *et al*. Changes in dopamine availability in the nigrostriatal and mesocortical dopaminergic systems by gait in Parkinson's disease. Brain 2001; 124: 784–92.

Parent A. Extrinsic connections of the basal ganglia. [Review]. Trends Neurosci 1990; 13: 254–8.

Petersen ES, van Mier H, Fiez AJ, Raichle EM. The effects of practice on the functional anatomy of task performance. [Review]. Proc Natl Acad Sci USA 1998; 95: 853–60.

Piccini P, Brooks DJ, Bjoerklund A, Gunn RN, Grasby PM, Rimoldi O, *et al*. Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient. Nat Neurosci 1999; 2: 1137–40.

Playford ED, Jenkins IH, Passingham RE, Nutt J, Frackowiak RS, Brooks DJ. Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. Ann Neurol 1992; 32: 151–161.

Reynolds JN, Wickens JR. Substantia nigra dopamine regulates synaptic plasticity and membrane potential fluctuations in the rat neostriatum in vivo. Neuroscience 2000; 99: 199–203.

Reynolds JN, Hyland BI, Wickens JR. A cellular mechanism of reward-related learning. Nature 2001; 413: 67–70.

Rinne JO, Laihinen A, Rinne UK, Nagren K, Bergman J, Ruotsalainen U. PET study on striatal dopamine D2 receptor changes during the progression of early Parkinson's disease. Mov Disord 1993; 8: 134–8.

Rinne UK, Laihinen A, Rinne JO, Nagren K, Bergman J, Ruotsalainen U. Positron emission tomography demonstrates dopamine D2 receptor supersensitivity in the striatum of patients with early Parkinson's disease. Mov Disord 1990; 5: 55–9.

Robb RA, Hanson DP. A software system for interactive and quantitative visualization of multidimensional biomedical images. Australas Phys Eng Sci Med 1991; 14: 9–30.

Robbins TW, Everitt BJ. Functions of dopamine in the dorsal and ventral striatum [Review]. Semin Neurosci 1992; 4: 119–27.

Robbins TW, Granon S, Muir JL, Durantou F, Harrison A, Everitt BJ. Neural systems underlying arousal and attention. Implications for drug abuse. [Review]. Ann NY Acad Sci 1998; 846: 222–37.

Robinson TE, Whishaw IQ. Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: a microdialysis study in freely moving rats. Brain Res 1988; 450: 209–24.

Roy EA, Saint-Cyr J, Taylor A, Lang A. Movement sequencing disorders in Parkinson's disease. Int J Neurosci 1993; 73: 183–94.

Sabatini U, Boulanouar K, Fabre N, Martin F, Carel C, Colonnese C, *et al*. Cortical motor reorganization in akinetic patients with Parkinson's disease. Brain 2000; 123: 394–403.

Salamone JD, Cousin MS, Snyder BJ. Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. [Review]. Neurosci Biobehav Rev 1997; 21: 341–59.

Samuel M, Ceballos-Baumann AO, Blin J, Uema T, Boecker H, Passingham RE, *et al*. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements: a PET study. Brain 1997; 120: 963–76.

Schultz W. Predictive reward signal of dopamine neurons. [Review]. J Neurophysiol 1998; 80: 1–27.

Schultz W, Ruffieux A, Aebischer P. The activity of pars compacta neurons of the monkey substantia nigra in relation to motor activation. Exp Brain Res 1983; 51: 377–87.

Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997; 275: 1593–1599.

Seitz RJ, Roland PE. Learning of sequential finger movements in man: a combined kinematic and positron emission tomography (PET) study. Eur J Neurosci 1992; 4: 154–65.

Shidara M, Aigner TG, Richmond BJ. Neuronal signals in the monkey ventral striatum related to progress through a predictable series of trials. J Neurosci 1998; 18: 2613–25.

Shinba T, Andow Y, Shinozaki T, Ozawa N, Yamamoto K. Phasic increase of monoamine-related electrochemical signal in the rat caudate nucleus following conditioned auditory stimulation during the reaction-time task. Brain Res 1998; 781: 284–90.

Smith AD, Bolam JP. The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. [Review]. Trends Neurosci 1990; 13: 259–65.

Song DD, Haber SN. Striatal response to partial dopaminergic lesion: evidence for compensatory sprouting. J Neurosci 2000; 20: 5102–14.

Spinks TJ, Jones T, Bloomfield PM, Bailey DJ, Miller M, Hogg D, *et al*. Physical characteristics of the ECAT EXACT3D positron tomograph. Phys Med Biol 2000; 45: 2601–18.

Stern Y, Mayeux R, Rosen J, Ilson J. Perceptual motor dysfunction in Parkinson's disease: a deficit in sequential and predictive voluntary movement. J Neurol Neurosurg Psychiatry 1983; 46: 145–51.

Studholme C, Hill DL, Hawkes DJ. Automated three-dimensional registration of magnetic resonance and positron emission tomography brain images by multiresolution optimization of voxel similarity measures. Med Phys 1997; 24: 25–35.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Tanji J. Sequential organization of multiple movements: involvement of cortical motor areas. [Review]. Annu Rev Neurosci 2001; 24: 631–51.

Tedroff J, Pedersen M, Aquilonius SM, Hartvig P, Jacobsson G, Langstrom B. Levodopa-induced changes in synaptic dopamine in

patients with Parkinson's disease as measured by [^{11}C]raclopride displacement and PET. Neurology 1996; 46: 1430–6.

Tissingh G, Bergmans P, Booij J, Winogrodzka A, van Royen EA, Stoof JC, *et al*. Drug-naïve patients with Parkinson's disease in Hoehn and Yahr stages I and II show a bilateral decrease in striatal dopamine transporters as revealed by [1-123]β-CIT SPECT. J Neurol 1998; 245: 14–20.

Trulson ME. Simultaneous recording of substantia nigra neurons and voltammetric release of dopamine in the caudate of behaving cats. Brain Res Bull 1985; 15: 221–3.

Van den Bercken JH, Cools AR. Evidence for a role of the caudate nucleus in the sequential organization of behavior. Behav Brain Res 1982; 4: 319–27.

van Horne C, Hoffer BJ, Stromberg I, Gerhardt GA. Clearance and diffusion of locally applied dopamine in normal and 6-hydroxydopamine-lesioned striatum. J Pharmacol Exp Ther 1992; 263: 1285–92.

Volkow ND, Fowler JS, Wang GJ, Dewey SL, Schlyer D, MacGregor R, *et al*. Reproducibility of repeated measures of carbon-11-raclopride binding in the human brain. J Nucl Med 1993; 34: 609–13.

Watson CC, Newport D, Casey M. A single scatter simulation technique for scatter correction in 3D PET. In: Grangeat P, Amans JL, editors. Three-dimensional image reconstruction in radiation and nuclear medicine. Dordrecht: Kluwer; 1996. p. 255–68

Weiss P, Stelmach GE, Hefter H. Programming of a movement sequence in Parkinson's disease. Brain 1997; 120: 91–102.

Wickens JF, Begg AJ, Arbuthnott GW. Dopamine reverses the depression of rat corticostriatal synapses which normally follows high-frequency stimulation of cortex in vitro. Neuroscience 1996; 70: 1–5.

Zhang WQ, Tilson HA, Nanry KP, Hudson PM, Hong JS, Stachowiak MK. Increased dopamine release from striata of rats after unilateral nigrostriatal bundle damage. Brain Res 1988; 461: 335–42.

Zigmond MJ. Do compensatory processes underlie the preclinical phase of neurodegenerative disease? Insights from an animal model of parkinsonism. [Review]. Neurobiol Dis 1997; 4: 247–53.

Zigmond MJ, Acheson Al, Stachowiak MK, Stricker EM. Neurochemical compensation after nigrostriatal bundle injury in an animal model of preclinical parkinsonism. Arch Neurol 1984; 41: 856–61.

Zigmond MJ, Abercrombie ED, Berger TW, Grace AA, Stricker EM. Compensations after lesions of central dopaminergic neurons: some clinical and basic implications. [Review]. Trends Neurosci 1990; 13: 290–6.

Received April 3, 2002. Revised July 1, 2002.
Accepted September 10, 2002