Brain (2002), **125,** 276–289

Attention to action in Parkinson's disease
Impaired effective connectivity among frontal cortical regions

James Rowe,[1] Klaas Enno Stephan,[1,5,6] Karl Friston,[1] Richard Frackowiak,[1] Andrew Lees[2,3] and Richard Passingham[1,4]

[1]*Wellcome Department of Cognitive Neurology,* [2]*Department of Clinical Neurology, Institute of Neurology,* [3]*Reta Lila Weston Institute of Neurological Studies, University College London,* [4]*Department of Experimental Psychology, University of Oxford,* [5]*Department of Psychology, University of Newcastle-upon-Tyne, Newcastle, UK and* [6]*C. and O. Vogt Brain Research Institute Heinrich-Heine-University, Düsseldorf, Germany*

Correspondence to: J. Rowe, Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, UK
E-mail: j.rowe@fil.ion.ucl.ac.uk

Summary
The neural basis of attention to action was studied in 12 patients with Parkinson's disease (Hoehn and Yahr grades II and III) and 12 healthy age-matched controls. The subjects were studied by functional MRI (fMRI) during performance of a simple paced overlearned motor sequence task, with and without an additional attentional task. For the attentional task, subjects were instructed to attend either to their actions or to a visual distractor task. Statistical parametric mapping was used to implement a random effects analysis of the regional task-related activations in patient and control populations. Structural equation modelling of fMRI time series was used to measure effective connectivity among prefrontal and premotor areas. In both groups, the motor task was associated with activation of a distributed network including the premotor, motor and parietal cortex, striatum and cerebellum. In control subjects, but not patients, attention to action (relative to execution of an overlearned sequence) was associated with further activation of prefrontal, parietal and paracingulate cortex, and the supplementary motor area (SMA). Patients with Parkinson's disease showed greater than normal activation of the SMA during execution of the simple overlearned motor sequence, but less augmentation when attending to their actions. In control subjects, attention to action, but not attention to the visual distractor task, increased the effective connectivity between prefrontal cortex and both the lateral premotor cortex and the SMA. This represents a specific increase in effective connectivity. Attentional modulation of effective connectivity between the prefrontal, premotor cortex and SMA was not observed in patients. This deficit indicates a context-specific functional disconnection between the prefrontal cortex and the supplementary and premotor cortex in Parkinson's disease.

Keywords: attention to action; fMRI; SMA; Parkinson's disease; connectivity

Abbreviations: ANOVA = analysis of variance; ERP = event-related potential; fMRI = functional MRI; FWHM = full-width half-maximum; SEM = structural equation modelling; SMA = supplementary motor area; SPM = statistical parametric mapping; UPDRS = Unified Parkinson's Disease Rating Scale.

Introduction
It has long been observed that movements in patients with Parkinson's disease are more impaired when distracted from their primary motor task, whether by performance of a secondary motor task (Fleminger, 1992; Serrien *et al*., 2000) or a simultaneous cognitive task (Oliveira *et al*., 1998). Conversely, movements may be improved transiently by specific attention towards the goal of the primary motor task (Oliveira *et al*., 1997).

The phenomenon of attention to action has been studied in healthy young adults using PET (Jueptner *et al*., 1997*a, b*). When subjects were asked to 'think about the next move', there was greater activation of the dorsal prefrontal and

premotor cortex compared with simple execution of the same sequence. Similar activations are found when subjects are required to choose freely which fingers to move or when to move them, both requiring attention to action (Jahanshahi *et al*., 1995; Catalan *et al*., 1999; Jenkins *et al*., 2000).

The present study investigates whether the mechanism of attentional modulation of motor performance is normal in patients with Parkinson's disease. Neuropsychometric testing of patients has suggested impairments on tests sensitive to frontal lobe damage (Lange *et al*., 1993; Stam *et al*., 1993; Owen *et al*., 1997), proportional to the reduction in frontal and striatal dopamine metabolism (Rinne *et al*., 2000). However, the abnormalities in prefrontal function in patients with Parkinson's disease may result from abnormal interactions between areas, rather than abnormalities within areas. It is this possibility that is studied in the present paper using functional brain imaging. The motor programming deficits of Parkinson's disease have been proposed to result from a functional disconnection of the supplementary motor area (SMA) (Dick *et al*., 1986). In addition, effective treatment of Parkinson's disease by pallidotomy has been associated with changes in cortical and subcortical connectivity of the SMA (Grafton *et al*., 1995).

Functional imaging of patients during simple movements has yielded a complex pattern of results. A recurrent finding has been reduced activity of the SMA, as measured by PET (Jenkins *et al*., 1992; Playford *et al*., 1992; Rascol *et al*., 1992; Samuel *et al*., 1997*a*; Thobois *et al*., 2000), functional MRI (fMRI) (Sabatini *et al*., 2000; Haslinger *et al*., 2001) and event-related potential (ERP) (Jahanshahi *et al*., 1995), especially when the movement or its timing is chosen by the subjects themselves (Cunnington *et al*., 1995; Jahanshahi *et al*., 1995; Praamstra *et al*., 1996; Catalan *et al*., 1999). Furthermore, this underactivity has been reversed by treatments including L-dopa (Haslinger *et al*., 2001), apomorphine (Jenkins *et al*., 1992; Rascol *et al*., 1992), pallidotomy (Grafton *et al*., 1995; Samuel *et al*., 1997*b*) and stimulation of the subthalamic nucleus (Ceballos-Baumann *et al*., 1999).

However, impaired activation of the SMA is not a consistent finding. Catalan *et al*. (1999) showed that increasing complexity of a learned motor sequence task led to greater increases in activation of the SMA in patients than in controls. Sabatini *et al*. (2000) reported increased activity of the caudal SMA in patients during sequential finger movements, and Samuel *et al*. (2001) observed no difference in SMA activation in a task that required subjects to select freely between movements and hold the selected moves in memory. Many of the studies that have shown SMA impairment with parkinsonism used motor tasks requiring a degree of attention to action, including free selection of movement or freely selected timing of movement. In contrast, movements that were specified by an external cue, or by their place in a fixed overlearned sequence, were associated with lesser or no deficits in SMA activity (Cunnington *et al*., 1995; Jahanshahi *et al*., 1995; Praamstra *et al*., 1996; Catalan *et al*., 1999; Nakamura *et al*., 2001). It is therefore necessary to distinguish impairments related to movement *per se*, and deficits related to the selection of, or attention to, action.

Compensatory increases in premotor and parietal cortical activation have also been reported in some studies (Samuel *et al*., 1997*a*; Sabatini *et al*., 2000; Haslinger *et al*., 2001). It is possible that these represent neuronal plasticity for movement in the presence of a dysfunctional SMA in Parkinson's disease. However, they may represent different cognitive strategies for the initiation of movement, for example by greater attention to action than is given by normal subjects.

The first aim of this study was therefore to determine regional cortical activations in patients and control subjects during a motor sequence task and the additional activation attributable to attention to action. In addition, we aimed to distinguish the specific effects of attention to action from attentiveness *per se*, and therefore we also used a non-motor visual attention task.

The second aim of the present investigation was to study the interactions between brain frontal regions, not just activations within discrete brain regions. The influence one brain region has over another has been termed effective connectivity (Friston *et al*., 1997). It may be measured by structural equation modelling (SEM) of fMRI data over time (McIntosh and Gonzalez-Lima, 1994; Buchel and Friston, 1997, 2000), within specified constraints based largely on consideration of anatomical connectivity of the brain. Our hypothesis was that patients with Parkinson's disease are able to activate the SMA in association with some motor tasks, but that they are impaired at modulating this activity under different conditions, particularly those that include attention to action.

The third aim of this study was to take into account the variability between individuals. To permit a valid comparison between patient and control groups, it is necessary to estimate the variability of cortical activation during a task from subject to subject within each population (Friston *et al*., 1999*a*, *b*).

Methods

Subjects

Twelve right-handed patients with idiopathic Parkinson's disease and 12 age-matched controls participated in this study, with written informed consent in accordance with the Declaration of Helsinki. The patients were recruited from outpatient clinics at the University College London Hospitals Trust. The study was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Inclusion criteria included a clinical diagnosis of idiopathic Parkinson's disease; without dementia; without symptomatic autonomic dysfunction; with normal ocular movements; bilateral disease of mild to moderate severity, Hoehn and Yahr grades II to III (Hoehn and Yahr, 1967); with no current depressive illness; and no history of other neurological or psychiatric disease. The patients' symptoms were either symmetric or greater on the

Table 1 *Demographic details of the patients, the severity of their parkinsonism and usual medication*

Age (years)	Gender	UPDRS motor score	Hoehn and Yahr grade	Years since diagnosis	L-dopa daily (mg)	Dopamine agonists (daily dose, mg)	Other medication (daily dose, mg)
61	F	13	2	2	300	–	–
61	F	36	3	5	400	Pergolide (3)	–
56	F	34	2	2	0	–	Amantadine (200)
61	M	32	2	12	900	Ropinirole (3)	–
63	M	35	2.5	8	800	Bromocriptine (20)	–
68	F	30	2	8	300	Pergolide (3)	–
72	F	32	2	2	0	–	–
50	F	39	2.5	5	0	Cabergoline (6)	–
63	F	42	3	2	200	–	–
57	M	42	2.5	6	400	–	–
69	M	25	3	2	600	–	–
62	M	44	3	10	300	Pergolide (3.5)	Amantadine (200) Benzhexol (2)
Mean 62 SD 6		Mean 33.7 SD 8.54	Median 2.5	Mean 5.4 SD 3.6	Mean 350 SD 295		

F = female; M = male.

right side. A unified Parkinson's Disease Rating Scale (UPDRS) interview and examination were conducted on all subjects, immediately prior to scanning. Anti-parkinsonian medication was stopped at least 12 (standard L-dopa preparations) or 24 (controlled release L-dopa and dopamine receptor agonist) h prior to scanning. Residual medication effects may still have been present, but all subjects were in a 'practical off' state. Demographic details, medication and UPDRS (Fahn *et al*., 1987) motor function scores are outlined in Table 1. Twelve right-handed, age-matched controls (mean age 62 ± 6 years, seven males) were recruited from patients' spouses and a departmental register of volunteers, and had no history of neurological or psychiatric disease.

Behavioural paradigm

Motor and cognitive tasks were based on those studied by Jueptner *et al*. (1997*b*) and Coull *et al*. (1998). Five principal tasks were performed, each lasting 30 s, with eyes open and auditory (beep) and visual (small central 'x') pacing cues given throughout. Brief written cues on the screen told the subject which task they were about to perform. The five tasks were as follows. (i) MOVE task: paced sequential right finger movements (1, 2, 3, 4, 1, 2, 3, 4 . . . .) at 0.33 Hz. Four lightly sprung buttons were mounted under the subjects' fingertips, on a moulded splint that supported a comfortable neutral hand–wrist position. (ii) SEARCH task: in this visual conjunction search task, a sequence of different coloured different letters was presented centrally at 0.33 Hz, and the subjects were required to detect red letter 'r's as targets. No immediate response was made to the target presentation. (iii) DUAL task: the subjects performed the visual conjunction search whilst performing the simple finger sequence. (iv) ATTEND task: subjects performed the motor sequence task (as in MOVE), but they were instructed to attend to the forthcoming action ('think about the next move'). (v) REST: subjects rested with eyes open, following each other task. For statistical parametric mapping (SPM), the MOVE, SEARCH, DUAL and REST tasks constituted a 2 × 2 factorial design, with movement and visual conjunction search as independent factors. For SEM, each motor condition (MOVE, ATTEND, DUAL) was coupled with a subsequent non-motor condition (REST or SEARCH). In addition to the principal tasks, there was a short response period lasting ~5 s, immediately following the SEARCH and DUAL tasks, in which subjects indicated by button press whether the target had appeared in the previous epoch.

Pre-training occurred on the same day as scanning. Subjects practised the MOVE condition continuously for 10 min in a quiet room. Forward digit span was then measured during performance of the MOVE task. Next, they were instructed in the other four conditions, and given practice for a further 10 min. All subjects clearly understood and reported a subjective difference between the ordinary MOVE task and the ATTEND task. A further 5 min practice of the MOVE task was given in the scanner prior to imaging.

Analysis of behavioural data

The time of each button press was recorded, from which we calculated the mean and variance of the time between consecutive button presses within each condition, and the latency between pacing cues and button presses. Subsequent behavioural data analysis used SPSS 8.0 for Windows NT. For each motor task (MOVE, ATTEND, DUAL), the response latency and standard deviation of response intervals were entered separately into repeated-measures analyses of variance (ANOVAs; using the Greenhouse–Geisser correction for non-sphericity), with factors of disease (patient versus control) and task (MOVE versus ATTEND versus DUAL). In addition, the response latency and interval standard deviation were fitted to the UPDRS motor severity

score, across all subjects, using linear and quadratic polynomial regression models in SPSS 8.0.

Functional imaging

Subjects lay supine with head fixation by firm foam pads. Instructions were projected onto a screen mounted on the head coil, and auditory pacing cues were delivered through padded headphones, controlled by an Apple Macintosh 7600 computer operating Cognitive Interface software (Wellcome Department of Cognitive Neurology, London, UK).

Functional imaging used T_2*-weighted echo-planar MRI at 2 tesla, repeat time 3650 ms, echo time 40 ms, throughout 28 min of continuous whole brain imaging ($64 \times 64 \times 40$ voxels, 3 mm isotropic resolution). The first five images were discarded to allow steady-state magnetization. SPM software was used for image processing and analysis (SPM99, http://www.fil.ion.ucl.ac.uk/spm), on Sun Ultra 60 workstations (SUN Microsystems, Calif., USA) using Matlab5.3 (Mathworks, Calif., USA). The images were realigned to the first image by rigid body transformation, sinc interpolated in time to correct for phase shift during volume acquisition and transformed by non-linear transformations to normal anatomic space (Talairach and Tournoux, 1988; Friston *et al*., 1995*b*), using the Montreal Neurological Institute template. For individual subject analyses, the data were smoothed spatially with a Gaussian kernel of full-width half-maximum (FWHM) 6 mm to allow valid statistical inference according to Gaussian random field theory (Friston *et al*., 1995*a*). High-resolution T_1-weighted images were acquired to permit anatomical localization of activation foci on each subject.

Individual subject analysis (level 1)

A general linear model was applied voxel-wise to the functional data (Friston *et al*., 1995*a*, 1996), using covariates for the epochs MOVE, SEARCH, DUAL, ATTEND, REST and the response period, and transient covariates for the instruction cues and responses. Each covariate was convolved by a canonical haemodynamic response function. The first temporal derivatives of movement parameters estimated during the realignment pre-processing were also included in the model, in case there were movement-related artefacts that could not be corrected by rigid body realignment. Subject-specific grand mean scaling was used, without proportional scaling of each image. The two groups did not differ in their mean brain T_2* MRI signal ($t = 0.1$, d.f. = 22, n.s.). Low frequency drifts in BOLD (blood oxygen level-dependent) signal were removed by a high pass filter with a cut-off of 400 s.

Parameter estimates and variance were derived for each covariate in a subject-specific fixed effects model. Contrast images of interest were calculated for each subject, including the main effects of movement (+ MOVE + DUAL – REST – SEARCH) and conjunction search (+ SEARCH + DUAL – REST – MOVE), interactions between movement and conjunction search [(+ MOVE – DUAL – REST + SEARCH) and (– MOVE + DUAL + REST – SEARCH)] and the subtraction contrast between MOVE and ATTEND conditions (+ ATTEND – MOVE). A statistical parametric map of the *F*-statistic for all conditions in the model was generated, SPM{*F*}, from which voxels later were selected for SEM.

Random effects analysis (level 2)

To accommodate inter-subject variability in group analyses, a secondary spatial smoothing kernel of FWHM 10 mm was applied to the contrast images from level 1, equivalent to an overall smoothing of the functional images by a kernel of FWHM 12 mm (the square root of the sum of squares of the FWHM for each component smoothing kernel). For each contrast, the contrast images from level one were entered into a second level *t*-test, to create an SPM{*t*}. For within-group analysis, a one-sample *t*-test was used (11 degrees of freedom) and, for group by contrast interactions, a two-sample *t*-test was used (22 degrees of freedom). This two-stage analysis is equivalent to a mixed effects ANOVA and enables the inference based on specific contrasts to be extended to the general population from which the subjects were drawn (Friston *et al*., 1999*b*), thereby permitting direct comparison of patients with control subjects.

For whole brain analysis, voxels were identified at which $P < 0.05$ (corrected for multiple comparisons). Given our hypotheses regarding the effect of attention within the motor system, anatomically constrained inferences were also made, with small volume correction for multiple comparisons (again $P < 0.05$). The regions of interest were defined as spheres of 2 cm diameter, centred on voxels of peak activation that had been identified on a separate group of young subjects using the identical behavioural paradigm (J. B. Rowe, K. J. Friston, R. S. J. Fruckowiak and R. E. Passingham, unpublished). These included the primary motor cortex, premotor cortex, SMA, prefrontal cortex, intraparietal cortex, cerebellum and putamen.

Individual structural equation modelling (level 1)

Analyses of effective connectivity were performed using the method described for fMRI time series by Buchel and Friston (1997, 2000). SEM of fMRI time series does not itself result in the model of regional interactions in the brain; rather it estimates the effects of experimental manipulation on connectivity among variables within a specified model. We adopted a hypothesis-led theoretical perspective to constrain the model to principal anatomic and cognitive elements. Our model is illustrated in Fig. 1, and included the prefrontal, premotor and primary motor cortex of the dominant hemisphere, and the SMA. It was based on known anatomical

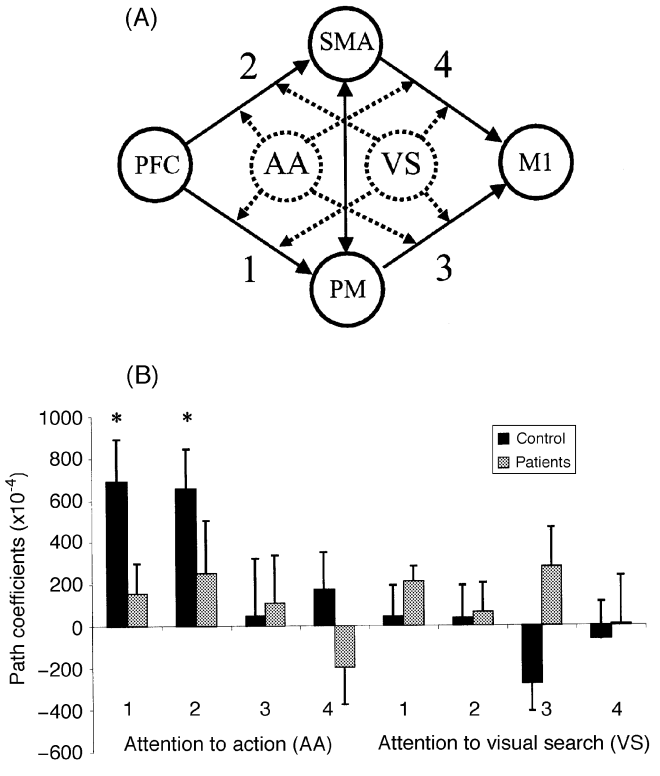

Fig. 1 (**A**) The model used for structural equation modelling. The prefrontal cortex (PFC), premotor cortex (PM), supplementary motor area (SMA) and primary motor cortex (M1) are interconnected in an anatomical model (solid lines). The strengths of these connections may be modulated by attention to action (AA) or, during the time when not attending to action, the connections may be modulated by attention to the visual search task (VS; dashed lines). The mean (±SE) path coefficients for each of the four modulatory connections illustrated in **A**, are plotted in **B**, separately for control subjects and patients with Parkinson's disease. The asterisks highlight the difference between groups: normal subjects show a specific modulatory influence of attention to action on inter-regional motor-related connectivity. This is not caused by attention to the visual search task, and is also not seen in patients (details of ANOVA in the Results section).

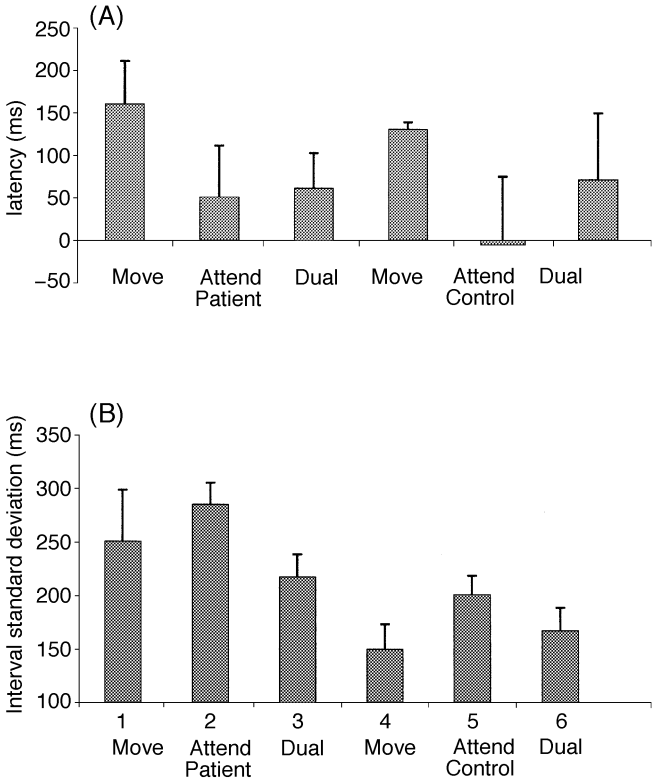

Fig. 2 (**A**) The mean (±SE) latency between pacing cue and button press and (**B**) the mean (±SE) of the subjects' response interval variability, expressed as the standard deviation of response intervals, shown for each group (left patients, right controls) for each of the motor tasks (MOVE, ATTEND, DUAL). Both patients and controls show increased variability of response intervals when attending to action (ATTEND) but not when attending to the visual conjunction search (DUAL).

interconnections between primary and non-primary cortical motor areas in primates, indicated by solid arrows (Muakkassa and Strick, 1979; Barbas and Pandya, 1987; Johnson *et al*., 1996; Rizzolatti *et al*., 1998).

The specific coordinates for these four regions, for each subject, were taken from the nearest maxima in the first-level SPM{F}. Two subjects showed no task-related activation of left prefrontal cortex ($y > 15$), and were excluded from the SEM. Regions were defined as 5 mm radius spheres, including all voxels that exceeded $P < 0.001$ (uncorrected) in the SPM{F} for all effects. The first principal component of the adjusted BOLD signal was entered into the model as used by Buchel and Friston (Buchel and Friston, 1997, 2000).

Our application of SEM included data from all conditions. To allow for task-related changes in coupling, we included moderator variables that modelled how changing conditions altered the connectivity between two areas. These can be thought of as interactions between the psychological causes (e.g. attention) of a regional response in a target area (e.g. premotor cortex) and the physiological causes (i.e. activity in source area such as prefrontal cortex). For the analysis of fMRI data, this is preferable to comparing separate models for each condition, because the sequential scans are not independent: the gradual BOLD response to neuronal events means that the early scans of one condition may include residual effects of the previous task. The moderator variables incorporate these gradual changes and comprise the product of regional activity in the source area and the relevant psychological factor (following convolution by a canonical haemodynamic response function) (Buchel and Friston 1997). In our model, these variables were principally motor-related responses, moderated by attention. Figure 1A illustrates how attention to action and attention to visual search task may have influenced the coupling between the anatomic regions (dashed lines).

This differs from the alternative approach, which uses separate analyses of inter-regional covariance under different

Table 2 *Regions of significant activation for the main effect of motor sequence execution (MOVE and DUAL versus REST and SEARCH)*

Region	L/R	*x*	*y*	*z*	*t*	Pu	Pc-SVC	Size
Controls								
Premotor	L	–32	–8	60	7.54	0.0001	0.001	0.63
	R	40	–4	64	5.41	0.001	0.01	0.31
SMA	–	0	2	68	7.86	0.0001	0.001	0.89
Paracingulate	L	0	4	52	6.21	0.0001	0.001	0.92
Primary motor	L	–50	–28	48	7.88	0.0001	0.001	1.10
Parietal	L	–38	–46	52	5.41	0.001	0.01	0.53
Putamen	L	–28	2	2	5.44	0.001	0.01	0.26
Thalamus	L	–16	–18	–2	4.85	0.001	0.05	0.21
Cerebellum	L	–22	–56	–26	5.55	0.001	0.01	0.62
	R	26	–52	–24	10.6	0.001	0.001	1.36
Patients								
Premotor	L	–32	–4	66	6.95	0.0001	0.01	1.36
	R	–32	–4	60	3.94	0.01	0.05	0.58
SMA	L	–6	–12	74	7.16	0.0001	0.01	0.96
Paracingulate	L	–6	–2	52	5.28	0.001	0.01	1.02
Primary motor	L	–42	–28	64	7.46	0.0001	0.01	1.26
Parietal	L	–36	–46	32	5.54	0.0001	0.01	0.47
Thalamus	L	–4	–14	8	4.62	0.001	0.05	0.53
Cerebellum	L	–26	–64	–22	5	0.001	0.05	0.71
	R	36	–60	–26	5.47	0.0001	0.01	0.92
Controls greater than patients								
Putamen	R	28	0	–8	3.89	0.001	0.05	0.31
Patients greater than controls								
SMA	R	2	–12	72	3.57	0.001	0.05	0.78

The voxel-wise threshold of uncorrected *P* value (Pu) and corrected value within regions of interest (Pc-SVC) are shown, together with the mean effect size (Size), expressed as BOLD signal change as a percentage of whole brain mean signal. The peak voxel coordinates and *t* values are also shown. L = left; R = right.

conditions (McIntosh and Gonzalez-Lima, 1994; Nyberg *et al*., 1996; Coull *et al*., 1999; Horwitz *et al*., 1999). In this form, the covariance between two regions within a condition arises from scan-to-scan variability, which is not under direct experimental control and for which the causes are not specified by the paradigm. Furthermore, dispersion of the responses by the haemodynamic response function in fMRI cannot be accommodated easily if the fMRI data are divided between different epochs.

In constructing the moderator variables, the time course for the conjunction search (SEARCH) was orthogonalized with respect to attention to action (ATTEND), such that the search task was treated as 'not attending to action'. The task covariates were convolved by a canonical haemodynamic response function and multiplied by the activity in the prefrontal and parietal cortex to form the interaction or moderator variables.

The structural model was implemented by the SEM Toolbox of SPM99 using an iterative maximum likelihood algorithm (Higham, 1993) to estimate covariances that best predict the observed variance–covariance structure of the empirical data. Statistical inferences about the path coefficients were based on the comparison of a free model with a model constrained to zero for a given connection. The difference in goodness of fit between free and constrained models was expressed as χ^2 (with degrees of freedom determined by the number of constraints). Under the null hypothesis, that one area has no influence over another, the free and constrained models do not differ in goodness of fit.

Group effects structural equation modelling (level 2)

A path coefficient from the subject-specific structural equation model indicates the influence of one region, or one moderator variable, over another. Although the significance of a path coefficient can be determined for each subject separately, our primary interest was to compare the patient and control groups in terms of the attentional effects on their inter-regional coupling. Therefore, for each interaction term representing attentional modulation of cortico-cortical connectivity, the path coefficient was entered into a second-level three-way repeated measures ANOVA (SPSS 8.0). The three factors were disease (two levels: patient versus control), attentional moderator (two levels: attention to action and attention to search) and the connection (four levels: prefrontal to premotor, prefrontal to SMA, SMA to primary motor and premotor to primary motor cortex).

Table 3 *Regions of significant activation for the main effect of visual conjunction search (SEARCH and DUAL versus REST and MOVE)*

Region	L/R	*x*	*y*	*z*	*t*	Pu	Pc-SVC	Size
Controls								
DLPFC	L	–46	32	26	4.48	0.0001	0.01	0.62
	R	42	40	26	5.3	0.001	0.01	0.81
ITc	L	–44	–54	–8	12.3	0.00001	0.001	0.92
	R	48	–66	–18	22.4	0.00001	0.001	1.51
Parietal	L	–32	–62	58	7.59	0.0001	0.001	1.38
	R	38	–56	44	10.04	0.00001	0.001	1.10
Patients								
ITc	L	–48	–64	–18	6.38	0.0001	0.01	1.36
	R	44	–58	–20	6.12	0.0001	0.01	1.36
Parietal	L	–38	–58	56	6.78	0.0001	0.01	1.02
	R	38	–56	56	5.51	0.0001	0.01	1.11
Controls greater than patients								
Parietal	L	–26	–56	44	3.73	0.001	0.05	0.71
VLPFC	L	50	20	14	4	0.001	–	–
DLPFC	L	42	28	30	4	0.001	–	–

The voxel-wise threshold of uncorrected *P* value (Pu) and corrected value within regions of interest (Pc-SVC) are shown, together with the mean effect size (Size), expressed as BOLD signal change as a percentage of whole brain mean signal. The peak voxel coordinates and *t* values are also shown. L = left; R = right; DLPFC = dorsal lateral prefrontal cortex; VLPFC = ventral lateral prefrontal cortex; ITc = inferotemporal cortex.

Results

Behavioural data

The variability of the response interval (the standard deviation of response intervals) for each subject was averaged for each group for each task, and is shown in Fig. 2. The response interval variability differed significantly between tasks [$F(1.6,35.2) = 3.8$, $P < 0.05$], but also between groups [$F(1,22) = 5.9$, $P < 0.05$]. The task by group interaction was not significant [$F(1.6, 35.2) = 0.8$, n.s.].

The response latencies for the two groups on the three movement tasks are shown in Fig. 2. ANOVA indicated a significant main effect of task [$F(1.8,36.7) = 3.7$, $P < 0.05$], but no main effect of disease [$F(1,21) = 0.2$, n.s.] and no disease by task interaction [$F(1.8,36.7) = 0.3$, n.s.].

Forward digit span during the MOVE condition (before scanning) was 5.4 [SE (standard error) 0.2] in control subjects and 5.0 (SE 0.2) in patients. This difference was not significant, by a two-sample *t*-test [$t(22) = 1.7$, n.s.]. In DUAL and SEARCH conditions, half of scanned epochs included the target red letter 'r'. Three of 60 targets were missed by patients, and two of 60 targets were missed by control subjects.

There was no significant linear or non-linear relationship between the UPDRS severity score and the mean response latency across subjects for the MOVE condition [$F(1,21) = 1$, n.s., and $F(2,20) = 1.9$, n.s., respectively]. The variability of response intervals (as indicated by the standard deviation of response intervals for each subject) did increase linearly with severity of motor symptoms [$F(22) = 4.3$, $P < 0.05$], at ~3 ms per point on the motor scale of the UPDRS.

SPM

Table 2 lists those areas for which there was a significant main effect of movement (MOVE + DUAL – REST – SEARCH) in normal subjects, patients, and the difference in this effect between groups. The pattern of activations is similar in patients and control subjects, including medial and lateral premotor regions, primary motor cortex, parietal cortex and cerebellum. Significant disease by contrast interactions are present, including relative underactivity of the putamen in patients, and overactivity of the caudal SMA.

Table 3 lists those areas in which there was a significant main effect of conjunction search (DUAL + SEARCH – MOVE – REST) in normal subjects, patients, and the difference in this effect between groups. Parietal and inferotemporal regions are activated in both groups, but the patients failed to show the normal pattern of prefrontal activation during the visual search task. There were no significant interactions between the motor task and visual search task, in terms of activation within the specified regions of interest.

Table 4 lists those areas in which there was activity attributable to attention to action (ATTEND – MOVE), in both groups and the difference in this effect between groups. There was increased activation of prefrontal cortex, SMA, paracingulate cortex and cerebellum in control subjects, but not patients. The patients showed significantly less activation in the SMA and parietal cortex.

Figure 3 shows the SPM results for normal controls, patients, and the group differences, superimposed on a T_1 image of a representative brain. The results are shown for the main effects of each task, and the additional activation

Table 4 *Regions of significant activation for attention to action (ATTEND) compared with simple execution of the same moves (MOVE)*

Region	L/R	*x*	*y*	*z*	*t*	Pu	Pc-ROI	Size
Controls								
DLPFC	L	–38	52	18	5.51	0.0001	0.01	0.22
SMA	L	–6	–16	74	4.17	0.001	0.05	0.27
Paracingulate	L	–6	8	54	5.85	0.001	0.01	0.20
Cerebellum	R	28	–60	–32	5.66	0.001	0.01	0.09
Controls more than patients								
SMA	L	–6	–14	74	3.76	0.001	0.05	0.18
Parietal	R	32	–50	52	4.16	0.001	0.05	0.15

The voxel-wise threshold of uncorrected *P* value (Pu) and corrected value within regions of interest (Pc-ROI) are shown, together with the mean effect size (Size), expressed as BOLD signal change as a percentage of whole brain mean signal. The peak voxel coordinates and *t* values are also shown. L = left; R = right; DLPFC = dorsal lateral prefrontal cortex.

associated with attention to action. The formal statistical comparisons of controls versus patients, shown in Fig. 3C and D, show fewer areas of significant difference than do anecdotal visual comparisons of the thresholded images shown in Fig. 3A and B. This difference highlights the importance of random effects analyses in comparing two populations.

Structural equation modelling

Path coefficients for the moderator variables were calculated for each subject. The modulation of each connection by each attentional level for each group is summarized by the group mean ($\pm$SE) path coefficient. These are displayed in Fig. 1B. In normal subjects, attention to action was associated with greater coupling between prefrontal and premotor cortex, and between prefrontal cortex and SMA. In patients, this attentional modulation of coupling did not occur, either to premotor or to SMA. Attention to the visual conjunction search was not associated with changes in inter-regional connectivity in either controls or patients.

ANOVA of these values indicated a significant difference between the two attention tasks [$F(1,19) = 10.1$, $P < 0.01$] and an interaction between the effects of task and the patient group [$F(1,19) = 16.8$, $P < 0.001$], confirming the greater modulatory effect of attention to action in the control group. There was a trend to an overall effect of connection [$F(3,57) = 2,2$, $P < 0.1$], but no overall effect of patient group [$F(1,19) = 0.6$, n.s.],

Discussion

Task-related activations: within and between groups

SPM was used to identify activations associated with motor and attentional tasks, and the interaction between disease and task-related regional activation. Our attention tasks were designed to be as similar as possible to those used by Jueptner *et al*. (1997*b*) to study attention to action and Coull *et al*. (1998) to study visuospatial attention with no motor component. In normal subjects, performance of the motor sequence (MOVE and DUAL) was associated with a typical network of cortical (primary motor cortex, premotor, paracingulate, parietal cortex and SMA) and subcortical (putamen, thalamus, cerebellum) regions. The absence of significant prefrontal activation is consistent with the motor task having become automatic (Toni *et al*., 1998). The behavioural data also suggest that after pre-training, the motor task was automatic or 'directly' processed (Cohen *et al*., 1990), in that the addition of a visual distractor task did not significantly increase the response time variance (DUAL versus MOVE) (see Fig. 2).

The patients showed a broadly similar pattern of motor-related activations (see Fig. 3B), with two notable exceptions. First, there was increased activation of the caudal SMA (see Fig. 3D and Table 2). Secondly, there was diminished putamen activation associated with movement (Table 2), consistent with functional imaging and metabolic studies that have shown reduced putamen metabolism in Parkinson's disease (Brooks, 1997).

The dysfunction of the SMA in Parkinson's disease has been emphasized in previous neuroimaging studies. We have shown that on a simple overlearned motor sequence task, patients with Parkinson's disease do show activation of the SMA relative to rest, as part of a typical distributed network of non-primary motor areas. In fact, the caudal SMA activation was significantly greater than that in normal subjects. This has been reported previously (Sabatini *et al*., 2000). These authors speculated that it may have been due to the early stage of disease in their subjects; the complexity of their motor sequence (cf. Catalan *et al*., 1999); or to a greater functional similarity between caudal SMA and parietal-premotor cortex than rostral SMA. Against the first two of these explanations, our result was obtained from more severely affected patients, on a simple sequence.

However, when asked to attend to their actions, patients failed to show the normal increase in SMA activation (see Fig. 3C). Reduced activation of the SMA in motor tasks that are attentionally demanding has been reported in PET and

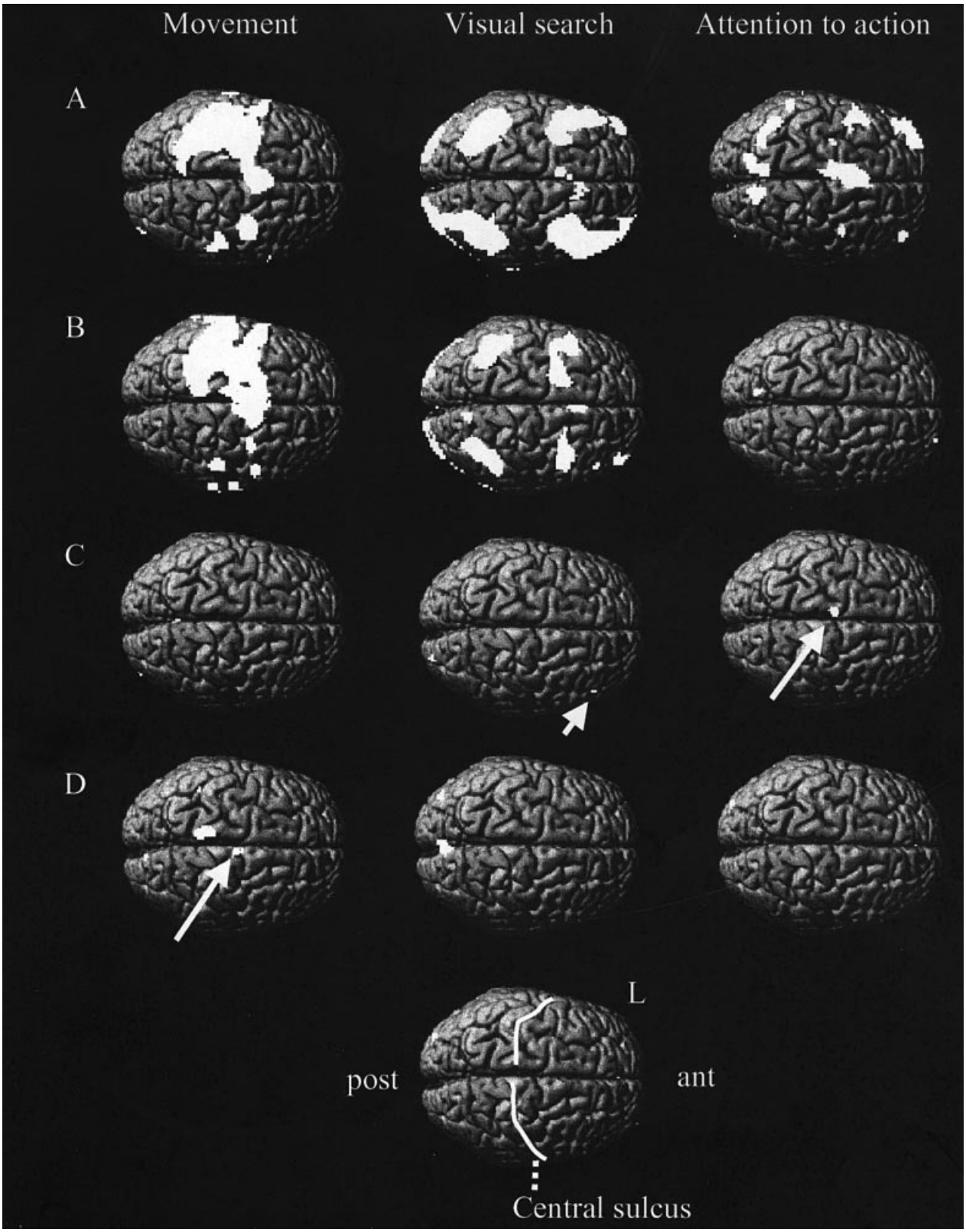

Fig. 3 Statistical parametric maps, SPM{t}, rendered to the surface of a representative brain in standard anatomic space for (**A**) normal controls, (**B**) patients, (**C**) the contrast of controls versus patients and (**D**) the contrast of patients versus controls. For each group or group contrast, the data are displayed for the main effect of movement (first column) (MOVE + DUAL versus SEARCH + REST), the main effect of visual search (second column) (SEARCH + DUAL versus MOVE + REST) and the contrast of attention to action (third column) (ATTEND versus MOVE). The arrows highlight that patients show greater than normal activation of the caudal SMA during simple movement (**D**), but are impaired at further activation of the SMA when attending to action (**C**). There is a trend towards reduced activation of the right prefrontal cortex during the visual search task. The annotated image at the bottom is to assist orientation to the surface images. The threshold corresponds to $P < 0.05$ corrected for multiple comparisons within the regions of interest.

ERP studies of Parkinson's disease (Cunnington *et al*., 1995; Jahanshahi *et al*., 1995; Praamstra *et al*., 1996; Catalan *et al*., 1999; Nakamura *et al*., 2001). We have shown that in normal subjects, attention to action is associated with greater coupling between prefrontal cortex and both the SMA and lateral premotor area; but that this is not true for patients with Parkinson's disease (see Fig. 1B). In other words, in this disease, the SMA is not differentially sensitive to input from prefrontal cortex under different task demands. This represents a context-sensitive functional disconnection or deafferentation of the SMA, rather than persistent underactivity.

One might have expected compensatory increases in activation of premotor and parietal cortex in patients (Samuel *et al*., 1997*a*; Sabatini *et al*., 2000; Haslinger *et al*., 2001). Although these areas were not significantly different on direct comparison of the two groups, the magnitude of premotor activation associated with movement was greater for patients than controls bilaterally (percentage signal change left 1.36 versus 0.55, right 0.58 versus 0.31). This was not significant on the formal group comparison, because of the high inter-subject variability within each group.

The performance of the visual search task (SEARCH and DUAL) by control subjects was associated with activation of prefrontal, parietal and inferotemporal cortex bilaterally, These areas had been identified in young healthy subjects by Coull *et al*. (1998), using the same task. The patients showed significant activation only in parietal and inferotemporal cortex. On direct comparison between groups, the only significant difference ($P < 0.05$ corrected) was in parietal cortex. However, at reduced threshold ($P < 0.001$ uncorrected), patients did show less activation than normal subjects in dorsal (42, 28, 30, $t = 4$) and ventral (50, 20, 14, $t = 4$) prefrontal cortex. There were no regions of greater activity in patients than controls. Although patients with Parkinson's disease often perform less well on cognitive tests typically associated with frontal lobe function (Lange *et al*., 1993; Stam *et al*., 1993; Owen *et al*., 1997), they do not necessarily show frontal hypometabolism during these tasks (Owen, 1997; Owen *et al*., 1998), and the cognitive impairments have been attributed to a dysfunction of connectivity within corticostriatal circuits.

Attention to action

In control subjects, attended action compared with simple execution was associated with greater activation within the prefrontal, paracingulate and supplementary motor cortex (see Fig. 3A). Jueptner *et al*. (1997*b*) also reported greater activation in prefrontal and cingulate cortex, with trends towards greater activation of SMA, premotor cortex and cerebellum, when subjects attended to their action. Patients failed to show this pattern of enhanced activation at all (see Fig. 3B), and direct comparison confirmed significant impairments in the attention-related activation of SMA and parietal cortex (see Fig. 3C).

In control subjects, the instruction to attend to action was also associated with increased coupling between prefrontal areas and both the medial and lateral premotor regions. It has been proposed that the prefrontal cortex exerts cognitive control by a general mechanism of attentional selection of neuronal representations (Miller, 1999). This may operate in the motor domain, as well as sensory (Rees *et al*., 1997; Brefczynski and DeYoe, 1999) and mnemonic (Rowe *et al*., 2000) domains. The consequence would be increased activity in neuronal populations representing actions (e.g. in premotor regions), in response to specific input from the prefrontal cortex, appropriate to a particular task.

In the patients, attended action compared with simple execution was associated with less additional activation of the SMA than in controls. A reduction of activation associated with attention to action could account for the deficits in SMA activity reported in many earlier motor studies in Parkinson's disease. In previous studies, SMA activation was reduced in tasks that required attention to action, rather than the automatic execution of pre-learned sequences or set responses to external cues (Cunnington *et al*., 1995; Jahanshahi *et al*., 1995; Praamstra *et al*., 1996; Catalan *et al*., 1999). Both new sequence learning and free selection tasks require the representation of a set of alternative actions and selection of one of these in preference to the others. Biased competition models of attention (Desimone and Duncan, 1995; Desimone, 1999) have proposed that alternate representations are mediated by mutually inhibitory neuronal populations. One representation may dominate temporarily if the balance of mutual inhibition is disturbed. This perturbation may result from 'bottom-up' or 'top-down' influences, including inputs from prefrontal cortex. In the prefrontal cortex, there are neurones whose activity may encode arbitrary task-specific rules or goals (Asaad *et al*., 1998, 2000), or the context of behaviour (Cohen *et al*., 1996). These neurones may control the selection of representations within remote regions, by top-down influence appropriate to the current task, in a process called 'attentional selection' (Miller, 1999).

We propose that both the free selection of movements and attention to action require such a process. For this experiment, the consequence is increased activation of premotor cortex under the influence of prefrontal cortex, specific to the attention to action condition, and not during attention to the visual conjunction search. In contrast to studies of visual attentional selection (Brefczynski and DeYoe, 1999), we have not attempted to show the selectivity for one motor representation over another within premotor cortex, since there is limited motor somatotopy in premotor cortex (Fink *et al*., 1997).

The ATTEND condition required subjects to 'think about the next move'. Although this may seem at first open to different interpretations, the consistency of the behavioural and neuroimaging results across all subjects suggests that the instruction induced a common set of cognitive processes. The short latencies for ATTEND in both patients and controls

shows that the subjects were thinking about the moves before the pacing cues. Tasks requiring imagination or preparation of movement may involve attention to action, and have been associated with increased activity in a similar distributed network including prefrontal, premotor, parietal cortex and SMA. An attentional formulation of imagination, preparation and free selection of action has several advantages. First, attentional selection of action by prefrontal modulation of premotor regions represents a parsimonious explanation of the effects of these multiple motor-related paradigms. Secondly, by drawing on the mechanisms of attentional selection of visual representations in occipital and infero-temporal cortex, it presents a testable hypothesis of the mechanism of underlying neuronal interactions. Thirdly, it acknowledges that individual neurones of the prefrontal cortex have different properties according to the specific current task (Asaad *et al*., 2000), and that attentional selection by these neurones may be supra-modal, occurring in the sensory, mnemonic and motor domains (Miller, 1999).

Interpretation of between-group comparisons

To make inferences about patient abnormalities in functional neuroimaging data, there are two essential criteria, First, that the patients and controls are actually performing the same tasks (Price and Friston, 1999). In the current study, the equality of tasks and performance between our groups is suggested by the behavioural data. Secondly, that the inferences may be extended to the general patient population, and are not restricted to the particular subjects studied on particular days. This second criterion is especially important for fMRI studies, in which there are significant differences in MRI BOLD signal and sensitivity in different subjects, and between different days even for the same subject under the same conditions (McGonigle *et al*., 2000).

It could be argued that patients attend to their actions more in the MOVE condition than controls, contributing to greater activation of SMA in the contrast MOVE versus REST. When instructed to attend to their moves, the 'additional' attention to action might then be less, associated with reduced activation of SMA in the contrast ATTEND versus MOVE. It is possible that patients did attend to their actions during the MOVE condition, but there are three reasons to believe that this is not a significant contributor to the group by task interactions. First, the simple motor task is very easy in its cognitive and motor demands. It is a simpler sequence than many finger tapping sequences used previously (cf. Catalan *et al*., 1999). At 0.33 Hz, it is also much slower than the 2–3 Hz finger tapping used as a common clinical test for bradykinesia. Secondly, the forward digit span during performance of the tapping task did not differ significantly between groups. If attention to action was necessary for the simple motor task, then digit span would be expected to be reduced. Thirdly, the behavioural data during scanning suggest that the patients were able to attend more to their actions in ATTEND compared with MOVE, like the controls. Although patients' response times were more variable overall, the differences between tasks were similar to those of control subjects. Relative to the MOVE condition, both groups increased response variance during the ATTEND condition (35 and 50 ms, respectively), and reduced response latencies (110 and 130 ms, respectively). There was no group by task interaction in response variance or response latencies.

Extension of statistical inference from the particular subjects to the general population of patients and controls requires a random effects model (Friston *et al*., 1999*b*). The two-stage 'random effects' model implemented by SPM in our study calculates the statistics based on variance estimates that include both within- and between-subject variance. Further, in fixed effects models, significant group differences may arise from large effects occurring in just one or two subjects. The consequence of this is that the inference from fixed effects analyses cannot be extended properly to the general population of either group (Friston *et al*., 1999*a*).

Other sources of bias must be considered. Our within-subjects analyses at the first level used grand mean scaling. This preserves the regional independence of task-related activations, in preference to proportional scaling. Systematic group differences in signal intensity could affect between-group comparison for a given task effect. However, in our study, there was no significant difference of global MRI signal between our groups.

Inferences based on regional interactions (effective connectivity)

SEM has many advantages in the analysis of the interactions between psychological conditions such as attention, and physiological variables such as BOLD fMRI time series (McIntosh and Gonzalez-Lima, 1994; Horwitz *et al*., 1999). An anatomical model is used to specify which regions are interconnected, and this is the basis of a mathematical model used to determine how strong the interconnections are. The model may also include terms for the interaction between cognitive and physiological variables. These interaction terms behave as moderator variables, indicating the extent to which the covariance between source and target region activity changes with cognitive context such as attention (Buchel and Friston, 1997, 2000).

The path coefficients of the moderator variables describe the extent to which the interaction between source area activity (prefrontal or parietal cortex) and cognitive processes (attention to action or to conjunction search) influence the target (premotor cortex). There are two interpretations of a significant positive value in the model. First, the activity of the source area influences target area activity more under one cognitive condition than another. An alternative interpretation is that the activity of the source area changes the extent to which the cognitive condition influences target area

activity. Both interpretations are valid and are identical to psychophysiological interactions as defined for neuroimaging (Friston *et al*., 1997). These effects of attention are specific, and not merely due to increased attentiveness *per se*: attention to a non-motor task does not change the coupling between prefrontal and premotor regions.

We used a simplified model of the brain to characterize the changes in effective connectivity in the frontal lobe. This model is clearly not a complete account of all possible regions engaged in the five tasks, or all possible direct and indirect connections between them. Such a comprehensive model may be useful in an exploratory sense, but it would be much less powerful in relation to our specific hypothesis. Elaborate models, permitting cyclical connections between regions for example, can become computationally unstable (McIntosh and Gonzalez-Lima, 1994). Therefore a theoretical perspective is necessary for SEM (McIntosh and Gonzalez-Lima, 1994). Our model of interactions among frontal cortical regions was based on known primate anatomy of direct cortico-cortical interactions. It is sufficient to address key questions regarding the influence of prefrontal cortex over medial and lateral premotor cortices under different conditions.

Although our model is based on primate cortico-cortical interconnections, inferences cannot be drawn about whether the connections are mono- or polysynaptic, or whether they are excitatory or inhibitory. The interpretation remains limited to the systems level (Horwitz *et al*., 2000). Indeed, indirect cortico-striatal-thalamo-cortical connections of the type proposed by Alexander and DeLong (1990) could contribute to the influence of prefrontal cortex on the medial and lateral premotor cortex. For example, Owen and colleagues have shown that in parkinsonian patients, performance of tasks sensitive to frontal lobe damage was associated with abnormal basal ganglia activation in PET, rather than intrinsic frontal cortical dysfunction (Owen *et al*., 1998). The patients' impaired performance may have resulted from impaired connectivity between frontal regions, without reduced activation *per se*. Analogous changes in connectivity between regions rather than activation within regions have been demonstrated in normal subjects after manipulation of mono-aminergic neurotransmission by clonidine (Coull *et al*., 1999).

Conclusion

Attention to action was associated with increased coupling between prefrontal cortex and the medial and lateral premotor regions in healthy adults. This is not the result of increased attentiveness *per se*, since another attentional task was not associated with increased coupling. Our results suggest that the motor abnormalities in Parkinson's disease are due, at least in part, to a functional disconnection of the SMA and premotor cortex from prefrontal influences, measured here as a reduction in effective connectivity. The consequence is task-specific abnormalities of function in the SMA. We suggest that in comparison with the execution of automatic movements, tasks that require attentional selection of motor representations (including attention to action and free selection of movement) are associated with lesser activation of the SMA in Parkinson's disease.

Acknowledgement

This work has been supported by the Wellcome Trust.

References

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. 1990; 85: 119–46.

Asaad WF, Rainer G, Miller EK. Neural activity in the primate prefrontal cortex during associative learning. Neuron 1998; 21: 1399–407.

Asaad WF, Rainer G, Miller EK. Task-specific neural activity in the primate prefrontal cortex. J Neurophysiol 2000; 84: 451–9.

Barbas H, Pandya DN. Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. J Comp Neurol 1987; 256: 211–28.

Brefczynski JA, DeYoe EA. A physiological correlate of the 'spotlight' of visual attention. Nat Neurosci 1999; 2: 370–4.

Brooks DJ. Advances in imaging Parkinson's disease. [Review]. Curr Opin Neurol 1997; 10: 327–31.

Buchel C, Friston KJ. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. Cereb Cortex 1997; 7: 768–78.

Buchel C, Friston K. Assessing interactions among neuronal systems using functional neuroimaging. Neural Netw 2000; 13: 871–82.

Catalan MJ, Ishii K, Honda M, Samii A, Hallett M. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. Brain 1999; 122: 483–95.

Ceballos-Baumann AO, Boecker H, Bartenstein P, von Falkenhayn I, Riescher H, Conrad B, et al. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. Arch Neurol 1999; 56: 997–1003.

Cohen JD, Dunbar K, McClelland JL. On the control of automatic processes: a parallel distributed processing account of the Stroop effect. [Review]. Psychol Rev 1990; 97: 332–61.

Cohen JD, Braver TS, O'Reilly RC. A computational approach to prefrontal cortex, cognitive control and schizophrenia: recent developments and current challenges. [Review]. Philos Trans R Soc Lond B Biol Sci 1996; 351: 1515–27.

Coull JT, Frackowiak RS, Frith CD. Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. Neuropsychologia 1998; 36: 1325–34.

Coull JT, Buchel C, Friston KJ, Frith CD. Noradrenergically mediated plasticity in a human attentional neuronal network. Neuroimage 1999; 10: 705–15.

Cunnington R, Iansek R, Bradshaw JL, Phillips JG. Movement-related potentials in Parkinson's disease. Presence and predictability of temporal and spatial cues. Brain 1995; 118: 935–50.

Desimone R. Visual attention mediated by biased competition in extrastriate visual cortex. In: Humphreys G, Duncan J, Treisman A, editors. Attention, space and action, Vol. 1. Oxford: Oxford University Press; 1999. p. 13–30.

Desimone R, Duncan J. Neural mechanisms of selective visual attention. [Review]. Annu Rev Neurosci 1995; 18: 193–222.

Dick JP, Benecke R, Rothwell JC, Day BL, Marsden CD. Simple and complex movements in a patient with infarction of the right supplementary motor area. Mov Disord 1986; 1: 255–66.

Fahn S, Elton R, Committee atmotUPsDRSD C. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Calne D, editors. Recent developments in Parkinson's disease. New York: MacMillan, 1987. p. 153–63.

Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE. Multiple nonprimary motor areas in the human cortex. J Neurophysiol 1997; 77: 2164–74.

Fleminger S. Control of simultaneous movements distinguishes depressive motor retardation from Parkinson's disease and neuroleptic parkinsonism. Brain 1992; 115: 1459–80.

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

Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RS. Spatial registration and normalization of images. Hum Brain Mapp 1995b; 3: 165–89.

Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD. Detecting activations in PET and fMRI: levels of inference and power. Neuroimage 1996; 4: 223–35.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 1997; 6: 218–29.

Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ. Multisubject fMRI studies and conjunction analyses. Neuroimage 1999a; 10: 385–96.

Friston KJ, Holmes AP, Worsley KJ. How many subjects constitute a study? Neuroimage 1999b; 10: 1–5.

Grafton ST, Waters C, Sutton J, Lew MF, Couldwell W. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. Ann Neurol 1995; 37: 776–83.

Haslinger B, Erhard P, Kampfe 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.

Higham NJ. Optimization by direct search in matrix computations. SIAM J Matrix Anal Appl 1993; 14: 317–33.

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

Horwitz B, Tagamets MA, McIntosh AR. Neural modeling, functional brain imaging, and cognition. Trends Cogn Sci 1999; 3: 1–98.

Horwitz B, Friston KJ, Taylor JG. Neural modeling and functional brain imaging: an overview. [Review]. Neural Netw 2000; 13: 829–46.

Jahanshahi M, Jenkins IH, 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 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, Jahanshahi M, Jueptner M, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. Brain 2000; 123: 1216–28.

Johnson PB, Ferraina S, Bianchi L, Caminiti R. Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. Cereb Cortex 1996; 6: 102–19.

Jueptner M, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. J Neurophysiol 1997a; 77: 1325–37.

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 1997b; 77: 1313–24.

Krimer LS, Muly EC, Williams GV, Goldman-Rakic PS. Dopaminergic regulation of cerebral cortical microcirculation. Nat Neurosci 1998; 1: 286–9.

Lange KW, Paul GM, Robbins TW, Marsden CD. L-dopa and frontal cognitive function in Parkinson's disease. [Review]. Adv Neurol 1993; 60: 475–8.

McGonigle DJ, Howseman AM, Athwal BS, Friston KJ, Frackowiak RS, Holmes AP. Variability in fMRI: an examination of intersession differences. Neuroimage 2000; 11: 708–34.

McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 1994; 2: 2–22.

Miller EK. The prefrontal cortex: complex neural properties for complex behavior. [Review]. Neuron 1999; 22: 15–7.

Muakkassa KF, Strick PL. Frontal lobe inputs to primate motor cortex: evidence for four somatotopically organized 'premotor areas'. Brain Res 1979; 177: 176–82.

Nakamura T, Ghilardi MF, Mentis M, Dhawan V, Fukuda M, Hacking A, et al. Functional networks in motor sequence learning: abnormal topographies in Parkinson's disease. Hum Brain Mapp 2001; 12: 42–60.

Nyberg L, McIntosh AR, Cabeza R, Nilsson LG, Houle S, Habib R,

et al. Network analysis of positron emission tomography regional cerebral blood flow data: ensemble inhibition during episodic memory retrieval. J Neurosci 1996; 16: 3753–9.

Oliveira RM, Gurd JM, Nixon P, Marshall JC, Passingham RE. Micrographia in Parkinson's disease: the effect of providing external cues. J Neurol Neurosurg Psychiatry 1997; 63: 429–33.

Oliveira RM, Gurd JM, Nixon P, Marshall JC, Passingham RE. Hypometria in Parkinson's disease: automatic versus controlled processing. Mov Disord 1998; 13: 422–7.

Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW. Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 1997; 35: 519–32.

Owen AM, Doyon J, Dagher A, Sadikot A, Evans AC. Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. Brain 1998; 121: 949–65.

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: 151–61.

Praamstra P, Cools AR, Stegeman DF, Horstink MW. Movement-related potential measures of different modes of movement selection in Parkinson's disease. J Neurol Sci 1996; 140: 67–74.

Price CJ, Friston KJ. Scanning patients with tasks they can perform. [Review]. Hum Brain Mapp 1999; 8: 102–8.

Rascol O, Sabatini U, Chollet F, Celsis P, Montastruc JL, Marc-Vergnes JP, et al. Supplementary and primary sensory motor area activity in Parkinson's disease. Regional cerebral blood flow changes during finger movements and effects of apomorphine. Arch Neurol 1992; 49: 144–8.

Rees G, Frackowiak R, Frith C. Two modulatory effects of attention that mediate object categorization in human cortex. Science 1997; 275: 835–8.

Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, et al. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. Arch Neurol 2000; 57: 470–5.

Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: new concepts. [Review]. Electroencephalogr Clin Neurophysiol 1998; 106: 283–96.

Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE. The prefrontal cortex: response selection or maintenance within working memory? Science 2000; 288: 1656–60.

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

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 1997a; 120: 963–76.

Samuel M, Ceballos-Baumann AO, Turjanski N, Boecker H, Gorospe A, Linazasoro G, et al. Pallidotomy in Parkinson's disease increases supplementary motor area and prefrontal activation during performance of volitional movements: an H2(15)O PET study. Brain 1997b; 120: 1301–13.

Samuel M, Ceballos-Baumann AO, Boecker H, Brooks DJ. Motor imagery in normal subjects and Parkinson's disease patients: an H2O15 PET study. Neuroreport 2001; 12: 821–8.

Serrien DJ, Steyvers M, Debaere F, Stelmach GE, Swinnen SP. Bimanual coordination and limb-specific parameterization in patients with Parkinson's disease. Neuropsychologia 2000; 38: 1714–22.

Stam CJ, Visser SL, Op de Coul AA, De Sonneville LM, Schellens RL, Brunia CH, et al. Disturbed frontal regulation of attention in Parkinson's disease. Brain 1993; 116: 1139–58.

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

Thobois S, Dominey P, Decety J, Pollak P, Gregoire MC, Broussolle E. Overactivation of primary motor cortex is asymmetrical in hemiparkinsonian patients. Neuroreport 2000; 11: 785–9.

Toni I, Krams M, Turner R, Passingham RE. The time course of changes during motor sequence learning: a whole-brain fMRI study. Neuroimage 1998; 8: 50–61.

Received April 4, 2001. Revised July 30, 2001.
Accepted October 1, 2001