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Parkinson's disease and dopaminergic therapy—differential effects on movement, reward and cognition

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Cognitive deficits are very common in Parkinson's disease particularly for 'executive functions' associated with frontal cortico-striatal networks. Previous work has identified deficits in tasks that require attentional control like task-switching, and reward-based tasks like gambling or reversal learning. However, there is a complex relationship between the specific cognitive problems faced by an individual patient, their stage of disease and dopaminergic treatment. We used a bimodality continuous performance task during fMRI to examine how patients with Parkinson's disease represent the prospect of reward and switch between competing task rules accordingly. The task-switch was not separately cued but was based on the implicit reward relevance of spatial and verbal dimensions of successive compound stimuli. Nineteen patients were studied in relative 'on' and 'off' states, induced by dopaminergic medication withdrawal (Hoehn and Yahr stages 1–4). Patients were able to successfully complete the task and establish a bias to one or other dimension in order to gain reward. However the lateral prefrontal cortex and caudate nucleus showed a non-linear U-shape relationship between motor disease severity and regional brain activation. Dopaminergic treatment led to a shift in this U-shape function, supporting the hypothesis of differential neurodegeneration in separate motor and cognitive cortico–striato–thalamo–cortical circuits. In addition, anterior cingulate activation associated with reward expectation declined with more severe disease, whereas activation following actual rewards increased with more severe disease. This may facilitate a change in goal-directed behaviours from deferred predicted rewards to immediate actual rewards, particularly when on dopaminergic treatment. We discuss the implications for investigation and optimal treatment of this common condition at different stages of disease.

Keywords: Parkinson's disease; reward; task-shift; fMRI; dopamine

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Parkinson's disease is usually regarded as a disorder of movement, but a third of patients have significant cognitive problems at presentation, doubling after 4 years (Foltynie *et al.*, 2004*a*; Williams-Gray *et al.*, 2007*a*) and dementia may be as common as 10% in early stages rising to 80% in late stages of disease (Galvin *et al.*, 2006; Williams-Gray *et al.*, 2007*a*). Such cognitive impairments are a major determinant of reduced quality of life in Parkinson's disease (Schrag *et al.*, 2000) and are a major challenge for treatment of patients. However, the cognitive deficits can appear complex or contradictory, and we will show how a more complex model of interactions between disease, cognition and treatment is needed.

Although many cognitive processes can be affected, the cognitive syndrome of Parkinson's disease is often described as a disorder of frontal executive function (Owen *et al.*, 1992; Robbins *et al.*, 1994). Two broad categories of executive functions are usually studied in patients with Parkinson's disease. One category includes functions of attentional control such as working memory, planning and task- or set-switching. The other category includes reward-based control of behaviours and the management of risk.

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There are clear abnormalities in Parkinson's disease within both categories but the nature of the deficit is not straightforward. It depends on a complex interaction between the specific cognitive task components, the severity of disease, genotype and treatment. For example, patients with mild to moderate disease are impaired at planning or at switching from one task to another when medication is withdrawn ('off' state), but they are not impaired on risk-taking paradigms or probabilistic reversal learning (Morris *et al.*, 1988; Owen *et al.*, 1990; Swainson *et al.*, 2000; Cools *et al.*, 2001, 2002*b*, 2003; Lewis *et al.*, 2003*a*; Foltynie *et al.*, 2004*a*, *b*). When treated with dopaminergic agents ('on' state) the planning and task-switching deficits are improved, but patients become impaired at risk-taking paradigms, gambling and reversal learning (Molina *et al.*, 2000; Swainson *et al.*, 2000; Cools *et al.*, 2001, 2003; Brand *et al.*, 2004; Mimura *et al.*, 2006; Pagonabarraga *et al.*, 2007; Voon and Fox, 2007).

It is proposed that these two categories of executive functions, like their motor and oculomotor counterparts, are mediated by distinct cortico–striato–thalamo–cortical circuits (Alexander *et al.*, 1990). Such anatomical dissociations are supported by functional neuroimaging data from healthy subjects (Rogers *et al.*, 2000; Nagahama *et al.*, 2001; Cools *et al.*, 2002*a*; Hampshire and Owen, 2006). In each circuit there is an optimal level of dopaminergic innervation, leading to a Yerkes–Dodson type U-shape relationship between dopaminergic state and neural function (Cools, 2006; Williams-Gray *et al.*, 2008) (Fig. 1). This hypothesis predicts the impaired performance following cortical dopaminergic treatment or antagonism away from this optimum (Brozoski *et al.*, 1979; Arnsten *et al.*, 1994; Roberts *et al.*, 1994). It has also been shown that in humans, the separate cortico–subcortical circuits are differentially affected by the cortical and subcortical pathology during the course of Parkinson's disease(Rinne *et al.*, 2001; Braak *et al.*, 2006; Wolters and Braak, 2006). On this basis, we predicted differential and non-linear effects of Parkinson's disease on motor and executive functions, at different stages of the disease (Gotham *et al.*, 1988).

This model also predicts that as the disease progresses, the optimal states of dopaminergic modulation for different cortico–cortical circuit functions progressively *diverge* (Fig. 1). When sampling across the patient population, in any given dopaminergic state, the result would be a different U-shape function relating disease motor-severity (e.g. UPDRS) to executive function. The optimal dopaminergic state to perform the function (indicated by the centre of the U-shape curve) would be shifted laterally along the abscissa (*x*-axis). A similar change would also be seen when comparing between 'on' and 'off' states (Fig. 1). The lateral shift means that dopaminergic treatment that moves a patient towards their motor optimum may move the same patient away from their cognitive optimum (Gotham *et al.*, 1988; Cools *et al.*, 2001, 2003).

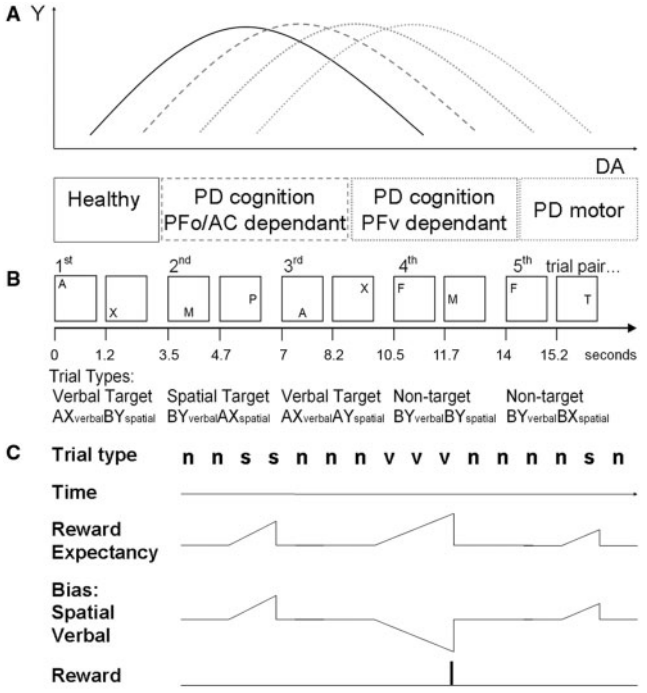

Fig. 1 (**A**) A schematic representation of the relationship between efficiency of neural functions (y-axis) and the state of dopaminergic modulation (x-axis). In healthy control subjects there is a Yerkes-Dodson type U-relationship between cognitive/motor functions and dopaminergic modulation. In Parkinson's Disease, there is a rightward shift in the U-shape function along the abscissa, more so for motor functions, and less so for different cognitive processes according to the specific underlying cortico-striatal loop (PFo/AC = orbital and medial prefrontal cortex, PFV = lateral prefrontal cortex). When sampling across many individuals in a population in a given dopaminergic state a U-shape function is therefore also observed (not shown).. These U-shaped relationships also depend on the stage of disease, and COMT genotype amongst other factors. (**B**). The task used a bi-modality continuous performance task, in which letters were shown at one of eight radial locations. Sequential letter pairs formed a spatial target if an 'A' was followed by a 'X', called a AX-verbal target trial. Similarly, a sequential letter pairs formed a verbal target if an 'A' was followed by a 'X', called a AX-verbal target trial. Some trials were non-targets, although either the first or second stimulus in the pair may include target relevant information eg a letter at 6 o'clock albeit not followed by a letter at 3 o'clock. (**C**) The order of spatial (s), neutral (n) or verbal (v) trial types was permuted (see methods) and included one, two or three successive target trials of the same type. If subjects correctly identified three successive target trials of the same type, they received a reward. The trial order orthogonalized the time-course of reward expectation (expected proximity to reward over successive trials) from the resulting bias towards spatial or verbal task set. The correlation between reward expectation and actual reward was greatly reduced by rewarding only trials with three consecutive targets of the same type, not target pairs or singles.

Although we have so far stressed the differences between the executive processes of attentional control and reward-based behaviour, it is clear that these two processes must operate together when the appropriate cognitive set depends on reward or reward expectation. We have previously

studied this interaction between cognitive set shifting and reward expectation in young healthy adults (Rowe *et al.*, 2008) using a bimodality version of the continuous performance task (AX-CPT) (Beck *et al.*, 1956). We used this paradigm to study patients with Parkinson's disease, in both 'on' and 'off' states, together with control participants matched for age, sex and COMT genotype. The experimental design allowed us to characterize the complex non-linear relationships between Parkinson's disease, disease progression, dopaminergic treatment and the integrated neural mechanisms underlying reward representation and cognitive set transitions. In particular, we tested whether patients with Parkinson's disease are able to appropriately modulate cognitive set according to reward expectations—a key feature of goal-directed behaviour.

Our overarching hypothesis is that different cognitive components are differentially affected as a function of the stage of disease, with dissociable non-linear (U-shape) relationships between neural activity (BOLD-fMRI signal) and disease severity (UPDRS). Furthermore, the effects of dopaminergic treatment will depend on the task element and its associated cortico–subcortical circuit. Specifically, we predicted that (i) patients could perform the task but that performance would depend on the stage of disease and dopaminergic treatment in a non-linear manner, (ii) that cortical and subcortical activations associated with task performance would depend on the stage of disease and dopaminergic treatment, with displacement of the dose response curve within prefrontal cortico–subcortical regions but no change for motor regions, (iii) that the rostral anterior cingulate would be associated with reward expectation and (iv) that reward expectation would lead to specific patterns of modality-specific cortical activation reflecting the induced cognitive bias.

Methods

Subjects

Nineteen patients with idiopathic Parkinson's disease were recruited from the Cambridge Centre for Brain Repair's Parkinson's disease research clinic. Inclusion criteria were: IPD according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria; age 50–80 years; heterozygote for the COMT val158met polymorphism; on dopaminergic medication; no current depressive illness; no known dementia based on prior cognitive assessment; Hoehn and Yahr stages 2 or 3 at last clinic visit. Exclusion criteria included incompatibility with MRI and adverse reactions to withdrawal or delay of dopaminergic medication. The patients' details are given in Table 1.

Patients were scanned on two occasions, at a similar time of day. On one day they took their normal medication and were in a relative 'on' state. On the other occasion they stopped medication prior to the examination to induce a relative and clearly defined 'off' state. Just as 'on' patients may not be maximally 'on', so the 'off' state is not as great as could have been achieved by prolonged withdrawal. However, the withdrawal period was sufficient to induce a clinically significant relative 'off' state (Table 1). Nonetheless, the range of UPDRS values across subjects overlapped considerably between 'on' and 'off' states. The order of 'on' and 'off' sessions was counterbalanced and randomly permuted within each sequential group of six recruits. Participants were asked to stop short acting dopaminergic medications (standard preparations of l-dopa and short acting dopamine agonists) at least 12 h before scanning (mean 18 h, SD 3.5), and long acting preparations (cabergoline, control release preparations of l-dopa) at least 24 h before scanning (mean 24 h, SD 9.8). Several patients were taking dopamine agonists alone or in combination with L-dopa.

Nineteen healthy subjects were recruited from the same database of COMT heterozygotes, aged 50–80 years, with no current neurological or psychiatric history and no contraindications to MRI. One subject had extensive idiopathic calcification of the basal ganglia and was removed from the analysis of fMRI data and another had hydrocephalus and was removed from subsequent analysis. Control subjects were scanned twice, and randomly assigned to a nominal 'on' or 'off' session, to balance for session effects including practice. The nominal 'on' and 'off' days were analysed separately, as for patients, in a pseudo-factorial design. However, control subjects were not treated with L-dopa.

All participants gave written informed consent according to the 1991 Declaration of Helsinki. The study was given a favourable opinion by the local research ethics committee. Prior to scanning, all patients were examined according to the UPDRS motor rating scale (Fahn *et al.*, 1987) and classified with the Hoehn and Yahr (1967) and Schwab and England (1969) scales. After scanning on the 'on' day, all subjects completed the MMSE (Folstein *et al.*, 1975), verbal fluency tests for letter (p) and category (animals) and the NART (Nelson, 1982). Patients also completed the Beck Depression Inventory II (Psychological Corporation, Boston, MA) and 16/18 completed the South Oaks Gambling Screen (Lesieur and Blume, 1987). None endorsed any indices of pathological gambling, nor were any subjects currently depressed.

Behavioural tasks

The task details have been published previously with young healthy adults (Rowe *et al.*, 2008). It was based on the AX-continuous performance task (Beck *et al.*, 1956; Braver *et al.*, 1999), but included letter stimuli that were defined both by their spatial location (eight positions, in a circle) and verbal letter identity (one of eight capital letters). Stimuli were presented sequentially as pairs forming a single trial. In each pair the first letter was the pre-cue and the second letter was the response cue. Each letter was presented for 500 ms, with an interval between letters in each trial of 900 ms. Trial onset asynchrony was 3500 ms.

Target trials were trials in which both the pre-cue and the response-cue were associated with targets and reward. Spatial targets were trials in which the first letter of the pair appeared at 6 o'clock and the second letter appeared at 3 o'clock. Verbal targets were trials in which the first letter was an 'A' and the second was an 'X'. A double target trial (i.e. an A at 6 o'clock followed by an X at 3 o'clock) was never presented, although trials could include ambiguous cues (e.g. an A at 6 o'clock or an X at 3 o'clock). The spatial and verbal trial types are formally similar. For ease of reference, all target pre-cues (spatial and verbal) are denoted as 'A', and all target response cues are denoted as 'X'. All other pre-cues that are not targets, and thus are neutral cues, are collectively known as 'B'. Similarly all other response-cues that are

Table 1 Demographic and drug details of PD Patients and controls

No	Sex	Age	Sw-En	HY Off	HY On	UPDRS Off	UPDRS On	Years (diagnosis)	L-dopa mg/d	L-dopa equivalent[1]	Nart error	Predicted FullScale IQ	MMSE	Fluency		Medications (mg)				
														P	Animals	A	C	R	E	Other
1	F	53	80	2	2	24	14	8.7	900	2200	6	123	30	20	28	100		21		
2	M	61	70	4	2	53	17	15.4	2200	2585	5	124	30	24	24	300				T 300
3	M	78	80	4	3	50	30	13.5	700	512	29	104	25	13	20					O 120
4	F	65	100	2	2	12	7	5.0	250	1090	30	103	30	17	24			21		O 50, D 30
5	M	65	70	2.5	2.5	36	19	13.5	700	1196	36	98	27	22	25				800	S 10
6	F	50	90	2.5	2	34	15	9.5	300	1200	27	105	27	11	19	200		15		
7	F	78	90	2	1	14	1	5.7	600	600	28	105	29	12	17					
8	M	64	90	2	2	20	17	3.0	400	1290	5	124	30	19	28	100				P 2.1
9	M	69	80	2	2	29	18	4.8	400	1120	45	91	29	10	19		4			S 1.25
10	F	65	90	3	2.5	38	30	4.6	600	1560	32	101	27	6	20			24		
11	M	59	80	2.5	2	36	29	5.7	500	1140	13	117	30	23	24	200	4			
12	F	59	70	2.5	2	34	31	5.5	300	1260	12	118	30	31	35		6			
13	M	68	80	2.5	2	32	20	9.0	250	915	33	100	28	9	11		4			S 5
14	M	66	80	2.5	2	33	25	6.9	800	1009	37	97	26	11	16	200	1		600	
15	F	75	80	2.5	2	34	26	10.7	1200	1745	2	127	27	23	17	200		18	800	
16	F	62	90	3	1	26	10	5.4	500	1020	42	93	29	21	12			18	600	
17	M	62	100	2.5	2	30	19	5.2	800	1640	42	93	28	8	24	100				P 1
18*	M	75	70	3	2	32	22	5.6	1300	1475	15	115	26	18	16			9		
19**	M	63	70	2.5	2	39	14	10.1	600	1680	12	118	29	12	24	200		24	800	
Patients																				
11m	**Mean**	**65.1**	**82.1**	**2.6**	**2.0**	**31.9**	**19.2**	**7.8**	**700.0**	**1328.3**	**23.7**	**108.2**	**28.3**	**16.3**	**21.2**					
8 f	SD	7.7	9.8	0.4	0.5	10.2	8.2	3.5	467.6	502.7	14.2	11.9	1.6	6.7	5.9					
Controls																				
8 m	**Mean**	**67.4**									**14**	**116**	**29.1**	**16.1**	**21.8**					
9 f	SD	6.1									7.2	6	0.8	4.6	5					

[1]Equivalent levodopa dose = [levodopa (× 1.2 if COMT inhibitor)(× 1.2 if 10 mg of S or × 1.1 if 5 mg of S)] + [P × 400] + [R × 40] + [C × 160] + [pergolide × 200] + [bromocriptine × 10] + [lisuride × 160]; all doses are in milligrams. [Williams Gray C. J Neurosci 2007 27 4832–38]. *arachnoid cyst, excluded from imaging analysis, SwEn = Schwab and England; H Y = Hoehn and Yahr; UDPRS = Unified Parkinson's Disease Rating Scale motor subscale III; MMSE = Folstein Mini-Mental State Examination; NART = national adult reading test estimate of premorbid IQ. **dyskinetic 'on', excluded from imaging analysis. Other drugs as mg/day are: A = amantadine; C = Cabergoline; R = Ropinirole; E = entacapone; T = tolcapone; S = selegiline; P = pramipexole; O = orphenadrine, D = domperidone.

not targets, are collectively known as 'Y'. Therefore, the pair of stimuli that make up a trial give rise to four formal trial types: AX, AY, BX, BY, suffixed with the appropriate dimension (spatial, verbal or neutral) (see Fig. 1 for details). Overall, 33% were spatial targets ($AX_{spatial}$), 33% were verbal targets (AX_{verbal}) and 33% of trials were not targets (non-$AX_{spatial}$ non-AX_{verbal}).

Target trials for one dimension can also be defined independently in the other dimension, according to the type of pre- or response-cues in other non-target dimension. For example in a spatial target trial the pre-cue at 6 o'clock could be an A, which is also a target-relevant cue for the verbal dimension. Formally, the context of the other dimension is denoted by three forms: AY, BX, BY, where A and B refer to the pre-cue and X and Y refer to response cue. For example a spatial target trial containing an A at 6 o'clock, followed by a T at 3 o'clock would be defined as an $AX_{spatial}$ AY_{verbal} trial. Other examples are given in Fig. 1.

Subjects indicated whether a trial was a target or non-target by pressing their right index or middle finger, respectively. An audible click acknowledged their correct button press. Subjects were instructed that successful detection of three sequential targets within a given dimension would lead to a monetary bonus (10 pence bonus, paid after scanning) and a salient cash-register sound ('ka-ching'). This induces an incremental shift or bias to one or other dimension, as a subject successfully identifies a series of targets. The shift is orthogonal to the expectation of reward that rises over successive targets (Fig. 1C).

The presentation of data was controlled using Cogent 2000 software (www.vislab.ucl.ac.uk/Cogent2000) using Matlab 7.1 (www.mathworks.com) in Windows XP (www.microsoft.com). Reaction time to presentation of the second stimulus and the accuracy of target detection were recorded. RT and arcsin-transformed accuracies were analysed in SPSS 11.0 (SPSS Inc., Chicago). Repeated measures ANOVAs were performed both on the arcsin-transformed accuracy values and RT data. For the ANOVAs, treatment assignment ('on' versus 'off'), sequential target repetitions (non-target, first AX, second AX, third AX) and trial type (AX–BY, AX–BX, AX–AY) for each dimension (spatial and verbal) were within-subject variables. Patient versus control group was a between-subjects variable. Since control subjects were assigned to a nominal treatment category, but not given dopaminergic medication, an effect of medication in Parkinson's

disease may be seen as an interaction between medication and subject variables, or as a simple main effect of medication within the patient group. We retain the division of control subjects into their assigned nominal treatment, to retain a pseudo-factorial design with *a priori* identity between the control subject cells. Any difference between control subjects' cells would indicate either noise or biased distribution of other effects, such as fatigue.

MRI data acquisition and analysis

fMRI data acquisition, pre-processing and analysis of subject-specific effects at the first level were the same as previously published, and outlined in supplementary material (Rowe *et al.*, 2008). Second level models (random effects) for each contrast of interest were made using an ANOVA of the contrast images from each subject's analysis at the first level, correcting for non-sphericity assuming inequality of variance between groups and sessions, and non-independence of error terms. The non-sphericity correction estimates hyperparameters for the different error variance and covariance terms using a maximum likelihood procedure, pooling across voxels that exceed an omnibus *F*-test of the effects of all conditions at $P<0.001$ (in effect, weighting the estimation to grey matter voxels). Based on this estimate of non-sphericity, the statistics are adjusted when making statistical inferences.

The second level ANOVAs had a similar design for each contrast of interest. They included four separate regressors (0/1) specifying each group for each session (patient 'off', patient 'on', control 'off', control 'on'). In addition, there were two regressors specifying the mean corrected UPDRS within each session for patients (UPDRS-off, UPDRS-on) and two regressors specifying the square of the mean-corrected UPDRS (UPDRS-sq-off, UPDRS-sq-on). This enables an assessment of linear, quadratic or compound effects of UPDRS on regional neuronal activation for any given contrast. SPM{t} maps were generated using *t*-contrasts for example to assess the averaged effects across all subjects for a contrast (e.g. [1 1 1 1 0 0 0 0]) or the difference between patient and control groups (e.g. [1 1 –1 –1 0 0 0 0]). *F*-contrasts were used to assess whether for example activations differed between groups and/or between 'on' and 'off' l-dopa (e.g. [1 –1 0 0 0 0 0 0; 0 1 –0.5 –0.5 0 0 0 0]); or whether there was a linear and/or quadratic effect of UPDRS on regional brain activation (e.g. [0 0 0 0 1 0 –1 0; 0 0 0 0 0 1 0 –1]).

SPMs were thresholded such that the familywise error rate was $P<0.05$ corrected for whole brain comparisons using Gaussian Random Field Theory. In view of the hypotheses regarding specific effects, we also corrected for multiple comparisons within specified regions of interest (20 mm radius spherical ROIs). The centre of ROIs are drawn for the peak foci from equivalent contrasts in a separate group of younger subjects without Parkinson's disease (Rowe *et al.*, 2008) or an independent contrast in the current dataset. They are centred on fronto-polar cortex (–42, 52, –4), caudate nuclei (0, 15, 4) substantia nigra (–4, –24, –12), anterior cingulate (6, 26, 14) and Broca's area (–54, 34, 0). The use of ROIs is indicated in parenthesis in the 'Results' section. Where ROIs are used, we report statistical inferences with correction for multiple comparisons within the ROI, but also inferences corrected for whole brain comparisons and without correction.

Results

Behavioural results

Patients could perform the task despite its apparent complexity, even those in a severe 'off' state. There was evidence for graded cognitive set shift towards reward-relevant dimensions (Figs 2 and S1). The additional effects of disease severity on behavioural indices are detailed in supplementary online material.

For spatial and verbal targets, RT reduced with successive targets [spatial: $F(3,99)=39$, $P<0.001$, verbal: $F(3,99)=56$, $P<0.001$] and was overall faster for patients [spatial: $F(1,33)=5$, $P<0.05$, verbal: $F(1,33)=5$, $P<0.05$, Fig. 2]. RT for spatial or verbal targets depended also on the context, defined by the non-target verbal or spatial dimension, respectively. Responses were slower when a misleading pre-cue was give i.e. AY trials (an A at 6 o'clock) versus BX trials (an X at 3 o'clock) or BY trials (neither A nor X) trials [spatial: $F(2,66)=83$, $P<0.001$, verbal: $F(2,66)=97$, $P<0.001$, Supplementary Figure S1]. There was a significant interaction between the number of target repetitions (first AX, second AX, third AX) and the context defined by the non-target trial type (AY, BY, BX) indicating an increase in the specificity of attention to the spatial

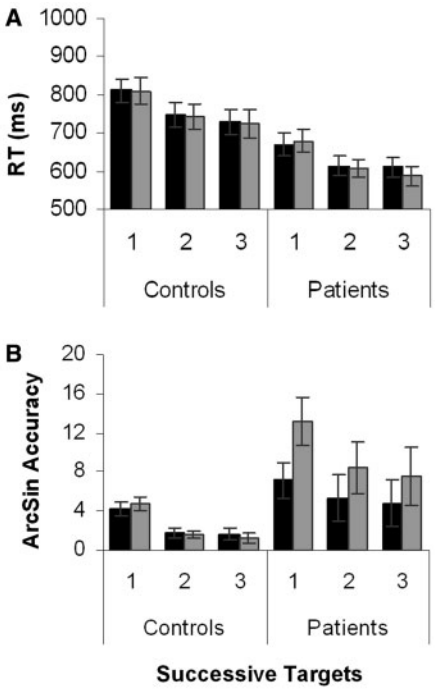

Fig. 2 (**A**) Reaction time (RT) to trials for spatial (grey) and verbal (black) target trials, for first, second and third successive target trials. Although patients were overall faster than controls, both groups showed faster reaction times across successive target trials. (**B**) Arc-sin accuracy (cf. error rates) to target trials, separately for spatial (grey) and verbal (black) target trials, for first, second and third target trials. Although patients were overall less accurate than controls, both groups showed enhanced accuracy across successive target trials. 'On' versus 'off' effects are shown in Supplementary Fig. SIe and f.

dimension with successive targets [spatial: $F(6,198) = 6.8$, $P < 0.001$, verbal: $F(6,198) = 15$, $P < 0.001$]. Thus, when a spatial target trial had not been preceded by previous spatial trials, RT was slower when the pre-cue cued both the spatial and verbal dimensions compared to when the pre-cue was neutral. However, with successive spatial targets the effect of the pre-cue in the verbal dimension diminished. There were no other significant interactions among groups, target, context or medication or high-order interactions among these factors for spatial or verbal trials.

Control subjects were more accurate than patients in both dimensions [spatial: $F(1,34) = 5.7$, $P < 0.05$, verbal: $F(1,34) = 6.1$, $P < 0.05$, Figs 2 and S1]. Accuracy improved with successive targets for both dimensions [spatial: $F(1,102) = 6$, $P < 0.001$; verbal: $F(1,102) = 4.5$, $P < 0.05$, Fig. 2]. Accuracy varied with the non-target context for the verbal dimension only [verbal: $F(2,68) = 5$, $P < 0.05$; spatial: $F(2,68) = 1$, ns, Supplementary Figure S1]. For verbal targets, being 'off' in the patient group exaggerated the effect of successive targets on accuracy in patients [significant three-way interaction between medication, group and targets, $F(3,102) = 5.3$, $P < 0.01$, with higher errors made on neutral trials and fewer errors on the first verbal targets, see Supplementary Figure S1]. There were no other significant interactions among groups, target, context or medication or high-order interactions among these factors.

Neuroimaging results

The performance of the AX-CPT task (versus baseline, FEW $P < 0.05$) was associated with activation of an extensive network of cortical regions bilaterally, including dorsal prefrontal cortex, SMA, pre-SMA, superior frontal sulci, parietal and intraparietal cortex, prestriate and fusiform cortex. There was unilateral activation of left motor and premotor cortex, left inferior frontal gyrus and right cerebellum (Supplementary Table ST1).

The motor severity of disease, as assessed by the UPDRS, was associated with significant positive non-linear differences in activation related to task performance in three regions: left fronto-polar cortex [–30, 48, –2, $F(4,58) = 8.96$: FWE $P < 0.05$ within ROI, FWE $P = 0.07$ whole brain corrected, $P < 0.001$ unc], the caudate nucleus [8, 10, 4, $F(4,58) = 6.49$: FWE = 0.05 within ROI, FWE $P > 0.1$ whole brain corrected, $P < 0.001$ unc] and left substantia nigra [–8, –18, –20, $F(4,58) = 5.67$: FWE $P = 0.05$ within ROI, FWE $P > 0.1$ whole brain corrected, $P < 0.001$ unc]. In these regions (Fig 3A and B), there are non-linear functions relating BOLD response to UPDRS. This function is shifted leftwards along the abscissa with dopaminergic treatment.

The motor severity of disease was also associated with significant negative non-linear differences in activation in two regions that were not on average activated with task performance (all subjects contrast of task versus baseline). These were the left frontal operculum [–42, 26, –12, $F(4,58) = 10.68$, FWE $P < 0.05$] where all groups deactivated during task performance; and ventral striatum [–4, 20, –6, $F(4,58) = 9.77$, FWE $P < 0.05$] in which 'on' patients showed deactivation with increased UPDRS, but 'off' patients showed deactivation early in disease, crossing over at a point of deactivation at UPDRS ~25. Control subjects had non-significant trend towards deactivation at this location.

The magnitude of the lateral shift (along the abscissa) of the U-shaped BOLD-UPDRS function between 'on' and 'off' states was calculated for all voxels. In Fig. 4, it is plotted for all voxels (top panel), and sampled from cortex at 10 mm rostro-caudal intervals in the parasaggital planes of $y = -30$ and $y = -40$ (lower panel). It can clearly be seen that there is minimal shift in primary sensorimotor cortex and medial prefrontal cortex. In contrast, the lateral prefrontal cortex and parietal association cortex have a lateral shift reaching ~40 UPDRS points. This shift pertains to a combination of the sensory, motor, attentional and executive components associated with the principal task covariate. The contributory cognitive processes may vary between locations.

The expectation of reward was associated with activation of the anterior cingulate (6, 26, 14 $t = 3.8$, FWE $P < 0.05$ within ROI, FWE $P > 0.1$ whole brain corrected, $P < 0.001$ unc]. Increasing bias toward the spatial dimension, orthogonal to the expectation of reward, was associated with activation of occipital prestriate cortex (18, –72, –6, $t = 5.28$, FWE $P < 0.05$). Bias towards the verbal dimension did not elicit significantly different responses, at FWE $P < 0.05$ (whole brain or within the ROI centred on Broca's area).

The severity of disease also influenced BOLD responses to reward expectation in the anterior cingulate [Fig. 3C, peak 2, 18, 22, $F(4,58) = 6.48$, FWE $P < 0.05$ within ROI, FWE $P > 0.1$ whole brain corrected, $P < 0.001$ unc] (*F*-contrast of effects of linear and quadratic UPDRS covariates on reward expectation contrast images, with inclusive masking of activation associated with reward expectation, $P < 0.05$ unc). Interestingly, as can be seen from the data plots in Fig. 3E(iii), the anterior cingulate regions showed a decline in activation with higher disease severity.

An opposite effect of motor severity of disease (UPDRS) was observed on the BOLD response to actual reward, in the anterior cingulate [4, 16, 22, $F(4,58) = 10.3$, FWE $P < 0.05$ within ROI, FWE $P = 0.05$ whole brain corrected, $P < 0.001$ unc] as shown in Fig. 3D and E(iv). Subjects with more severe disease, in both 'on' and 'off' states, show increasing BOLD response on trials which were actually rewarded (as opposed to those on which rewards were expected).

Discussion

The key findings of this study in relation to our hypotheses are that (i) patients can modulate cognitive set according to

reward relevance of anticipated stimuli, in both 'on' and 'off' states, despite previous reports of impaired task switching; (ii) cortical and subcortical activations associated with task performance depend in a non-linear manner on the severity of disease and dopaminergic treatment (iii) the anterior cingulate cortex is associated with reward expectation, less so in patients with more severe disease and (iv) reward expectation leads to specific patterns of modality-specific cortical activation, reflecting induced cognitive bias.

Behavioural effects of Parkinson's disease

Patients were overall quicker than control subjects. Given the bradykinesia of Parkinson's disease, this may seem paradoxical. However, faster reaction times by Parkinson's disease patients 'off' versus 'on' or in comparison with control subjects has been described previously in several cognitive paradigms (Cools *et al.*, 2002*b*; Mattay *et al.*, 2002; Frank *et al.*, 2007). The shorter reaction times may result from the loss of conflict or response monitoring even in the presence of bradykinesia.

Patients with Parkinson's disease have previously been reported to be impaired at task switching in 'off' states (Fimm *et al.*, 1994; Cools *et al.*, 2001, 2003). We did not find this deficit, either 'on' or 'off' medication. There are several possibilities for why our patients did not show a deficit for set-shifting. First, that the critical process that is impaired in Parkinson's disease is only required for a subset of task-shift paradigms e.g. when the shift-cost depends on the events of the previous trial (Astle *et al.*, 2006) or the predictability of future events (Swainson *et al.*, 2006). Second, the set transitions in our study did not depend on negative feedback. Patients with mild disease may be poor at set shifting because of disordered cortical and subcortical responses to negative feedback (Monchi *et al.*, 2004, 2006, 2007) and are largely unaffected on cued set-shift tasks without negative feedback (Rogers *et al.*, 1998; Ravizza and Ciranni, 2002). Third, it may be that the preserved set-transitions in our task are due to the incremental bias towards one dimension or the other rather than large or dichotomous transitions in set. Finally, it is possible that the previous set-shifting deficits reflect a goal-neglect for externally cued tasks changes. Such goal-neglect is a feature of impaired frontal lobe function following lesions (Duncan *et al.*, 1996) and might in principle be part of the 'dysexecutive' cognitive syndrome of Parkinson's disease.

The contribution of functional neuroimaging

The fMRI data confirm that trial performance was associated with a wide network of cortical and subcortical areas. The breadth of this network reflects the complexity of each trial, requiring motor responses based on judgements of compound visual stimuli according to spatial and lexical information. In contrast to many previous studies, we did not find a simple group difference in terms of task-related regional BOLD activation, however, there were significant non-linear differences according to the UPDRS, in both 'on' and 'off' states (Fig. 3).

The BOLD–UDPRS relationship may reflect changes in neural efficiency (the degree of activation associated with similar performance). It has been reported to be reduced in Parkinson's disease in motor and working memory tasks (Haslinger *et al.*, 2001; Mattay *et al.*, 2002) and increased in other working memory and planning tasks (Lewis *et al.*, 2003*b*; Williams-Gray *et al.*, 2007*b*). Critically, the changes in neuronal efficiency may depend on the extent to which the task is modulated by cortical dopamine. Fluorodopa PET scanning suggests that medial and lateral prefrontal cortical dopaminergic system are up-regulated in early Parkinson's disease (Rakshi *et al.*, 1999; Kaasinen *et al.*, 2001; Nagano-Saito *et al.*, 2004) but not late disease (Rakshi *et al.*, 1999; Rinne *et al.*, 2000). This implies early frontal compensation for striatal dopaminergic deficiency, by enhancing neuronal efficiency for the task. Direct evidence comes from a combined fluorodopa-PET and FDG-PET study in Parkinson's disease patients tested during performance of Raven's Matrices task: the enhanced fluoro-DOPA uptake was associated with a fall in anterior cingulate glucose metabolism for similar performance (Nagano-Saito *et al.*, 2004).

Why should the effects of dopamine depletion or treatment lead to non-linear, U-shaped relationships with performance or neural activation? Cools' comprehensive synthesis of animal and human data suggests that the optimum dopaminergic state depends on a cognitive task's competing requirements for cognitive plasticity—to update, adapt or switch neural representations of rules, events or actions—and the need for cognitive stability of representations over time, especially in the face of interference between trials or distraction within trials (Cools, 2006). A plausible cellular mechanism is provided by the differential distribution of D1 and D2 receptors in prefrontal cortex and striatum (Camps *et al.*, 1990) and the time- and concentration-dependent opposing effects D1 and D2 stimulation (Durstewitz and Seamans, 2002; Lapish *et al.*, 2007). The result is that both dopamine deficiency and over-dose affect performance, but that the mechanism of impairment differs.

The AX-CPT task requires cognitive control to update and maintain trial-specific information (Braver *et al.*, 1999). Our paradigm also required set-bias to one or other stimulus dimension. These processes of cognitive control contribute to the activation of prefrontal cortical during the task (Rowe *et al.*, 2008). A critical role of dopamine in modulating control by prefrontal cortex during the AX-CPT was demonstrated in earlier computational and clinical models (Braver *et al.*, 1999; Cohen *et al.*, 2002). Our analysis confirms dopamine dependence of the prefrontal cortex in these control processes, rather than the specific induced biases to spatial or verbal dimensions. Moreover, the caudate nucleus to which our lateral prefrontal

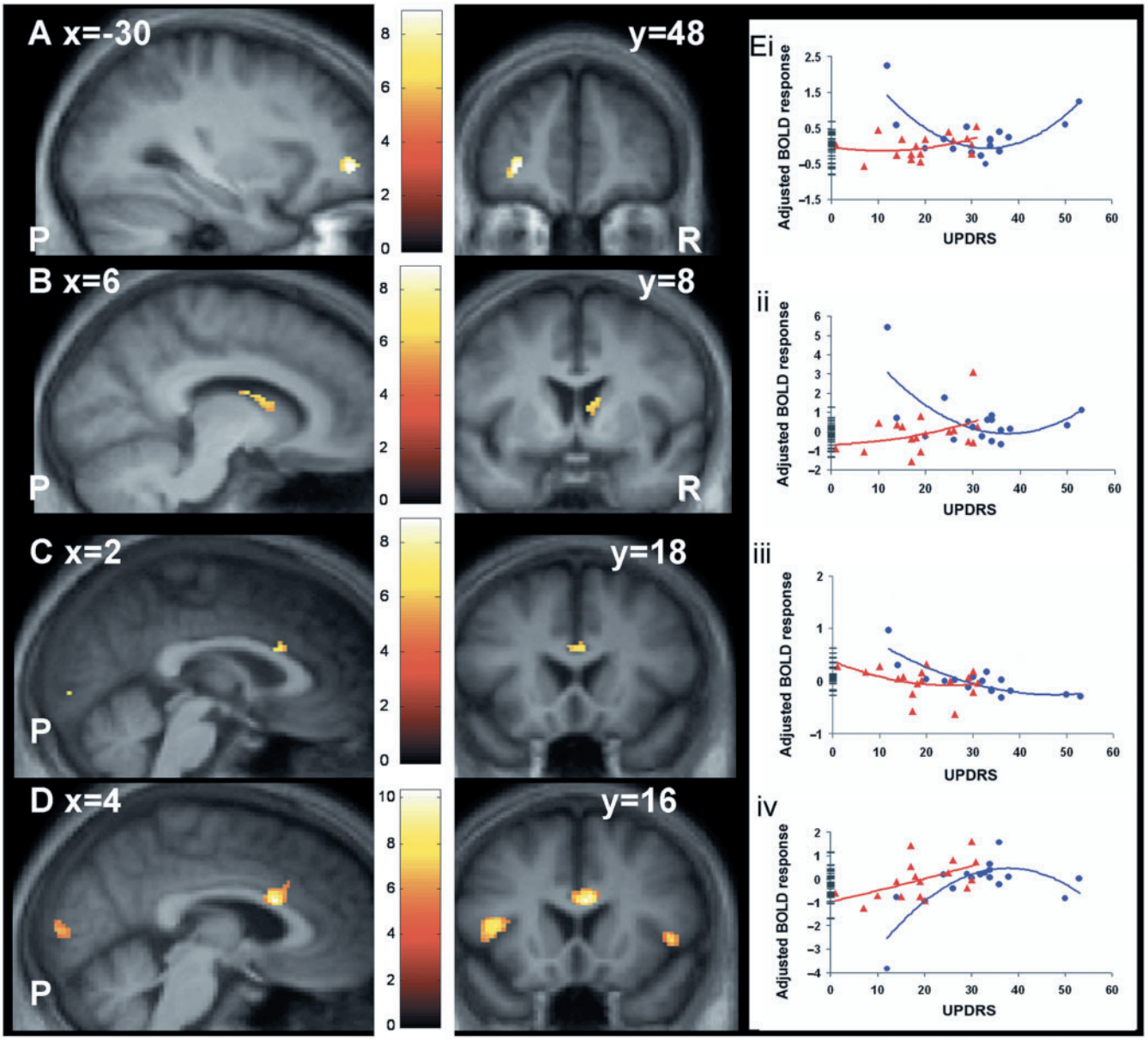

Fig. 3 SPM(F) maps indicating that the ventrolateral prefrontal cortex (**A**) and caudate nucleus (**B**) show differential activation with disease severity for activity associated with task performance. (**C**) SPM(F) map of the anterior cingulate cortex, with a significant effect of UPDRS on the activations associated with expectation of reward across successive trials. (**D**) SPM(F) map of regions with a significant effect of UPDRS on the activation in response to actual receipt of rewards including a peak in anterior cingulate cortex extending into medial frontal cortex. For the prefrontal, caudate and cingulate foci shown in A–D, the adjusted BOLD response (% BOLD signal change) to each trial type is plotted against the UPDRS in Ei to Eiv respectively. Control subjects responses are indicated by black ticks on the y-axis, 'on' patients shown in red and 'off' patients shown in blue. Note the difference between blue 'off' and red 'on' curves. Lines show best least squares quadratic fits. A contrast relying on a simple contrast of patient vs control would have missed the effects of Parkinson's disease at different stages of disease.

cortex ROI projects (Calzavara *et al.*, 2007; Leh *et al.*, 2007) showed a similar non-linear relationship between UPDRS and BOLD response, emphasizing the cortico–striatal circuits underlying task performance.

In terms of these fronto-striatal activations a UPDRS of 10 in the 'on' state is very different from a UPDRS of 10 in the 'off' state. The 'on' BOLD–UPDRS curve is shifted to the left of the 'off' curve (along the abscissa). This is expected if the dopaminergic treatment changes an index of disease severity that is relevant to the motor system, but not the cognitive systems (Fig. 1A and B). The greater the difference between the motor cortico–subcortical network and the cortico–subcortical network mediating another function (cognitive, affective, oculomotor, etc) the greater the expected shift. In Fig. 4 the shift is minimal around the central sulcus and inferior

mesocortex, but increases towards lateral frontal and parietal cortex, consistent with regional differences in neuropathological progression (Braak *et al.*, 2006).

Reward and reward expectation

We specifically distinguished reward and reward expectation from other cognitive and motor aspects of the task, because of their association with central dopaminergic systems. Increasing reward expectancy over successive trials was associated with activation of the anterior cingulate cortex, consonant with animal electrophysiology (Shidara and Richmond, 2002, 2004) and neuroimaging of healthy adults (O'Doherty *et al.*, 2001, 2003; Schott *et al.*, 2007; Rowe *et al.*, 2008). There was no significant main effect of patient group on activation related to reward-expectation in the anterior cingulate, but there was again an effect of disease severity (Fig. 3). In both 'on' and 'off' states, there is a fall in activation associated with reward expectancy with more severe disease. This means that patients with more advanced disease are failing to respond to the proximity of reward, in terms of ACC neural representation of reward. Behaviourally, this is seen in the negative correlation between UPDRS and the expectancy effect on RT (in 'on' state) and expectancy effect on accuracy (Fig. S2 cd).

However, the patients are not insensitive to reward *per se*. Patients with more advanced disease show increased activation in anterior cingulate regions (Fig. 3), in both 'on' and 'off' states. Increased activation in ACC in response to expected rewards has been noted in early unmedicated Parkinson's disease patients (Schott *et al.*, 2007) but our data show that this effect is seen in early and middle-stage disease, both 'on' and 'off' medication. Considering Fig. 3C and D together it seems that as disease progresses, reward-related activations in ACC change to the actual receipt of reward rather than anticipated reward. This might contribute to the apathy sometimes associated with Parkinson's disease (Czernecki *et al.*, 2002).

The failure to represent and behave according to anticipated reward but to remain sensitive to actual reward resembles the dopamine-dependant processes of early learning. Dopaminergic neurons in the midbrain, projecting to the striatum and medial frontal cortex respond to received reward prior to learning, but less so as rewards are better predicted. Instead, they become responsive to events that reliably predict reward (Hollerman *et al.*, 2000; Schultz and Dickinson, 2000; Schultz, 2002). Our results suggest that patients with more severe Parkinson's disease are less able to adapt the function of the cingulate-striatal reward system from representation of actual reward to representation of expected reward. Similarly in healthy humans, dopaminergic antagonism by haloperidol impairs learning to predict reward, relative to L-dopa treatment (Pessiglione *et al.*, 2006).

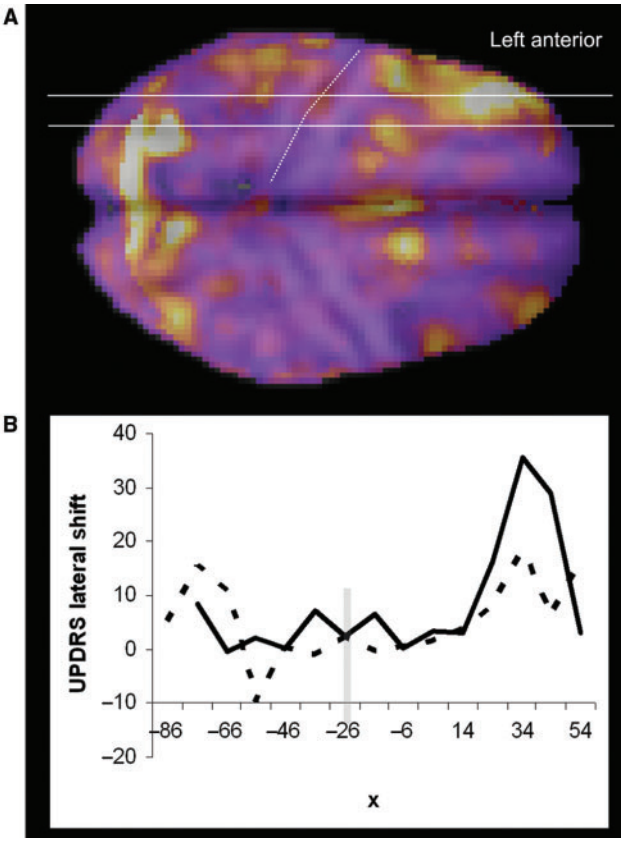

Fig. 4 (**A**) The peak or nadir of the U-shaped function between BOLD response and the UPDRS is different between 'on' and 'off' states. This is seen in figure 3E as a lateral shift along the x-axis. It is not a shift in anatomical location of the BOLD-UPDRS function. The magnitude of the difference between 'on' and 'off' conditions is shown for all voxels, illustrated from above. Note the minimal shift (purple) of BOLD-UPDRS around the central sulci (dashed line) and medial prefrontal cortex, but a significant shift in parietal and lateral prefrontal cortex (positive values indicate that the peak/nadir of the U-shape function is at a higher UPDRS value in the 'off' state). (**B**) The shift in the BOLD-UPDRS relationship (expressed in UPDRS points at each voxel) has been plotted for cortical voxels along the rostro-caudal x axis at 10 mm intervals in the planes of $x = -30$ (dotted lines, cf figure 3A) and $x = -40$ (solid line).

Limitations of the study

There are a number of limitations to the current study. Whilst there is no doubt that for some cognitive functions prefrontal cortical dopamine is essential (Brozoski *et al.*, 1979) or detrimental (Arnsten *et al.*, 1994) fMRI studies are not able to distinguish the relative contributions of cortical and subcortical dopamine depletion to abnormal behaviour. It is useful to exploit the functional polymorphisms of the COMT gene that alter the balance between cortical and subcortical dopamine and affect performance and activation on executive tasks (Egan *et al.*, 2001; Foltynie *et al.*, 2004*b*; Winterer *et al.*, 2006; Williams-Gray *et al.*, 2007*b*). However, for practical reasons we were not able to study

enough homozygote patients to add COMT genotype as an independent factor in this study.

Our main therapeutic manipulation was of dopaminergic transmission. However, dopamine is just one of many neurotransmitter systems that are severely impaired in Parkinson's disease e.g. noradrenaline, serotonin, acetylcholine. Moreover, different dopaminergic therapies have differential effects on receptor subtypes (Gerlach *et al.*, 2003; Glickstein *et al.*, 2005). Therefore our treatment and withdrawals would not have been equivalent across all patients. In addition, two of our patients used pramipexole, the dopamine agonist most associated with pathological gambling (Voon and Fox, 2007) perhaps related to its greater affinity for D3 receptors. Although none of our subjects exhibited pathological gambling, subtler effects may have been present due to dopamine agonists in terms of the response to reward expectation and reward.

Finally, one must consider whether the dopaminergic treatment has a direct effect on the prefrontal BOLD fMRI response because of vasoactive afferents from dopaminergic neurons (Williams and Goldman-Rakic, 1995; Krimer *et al.*, 1998). Fortunately, BOLD-fMRI designs of the type used here are relatively protected from tonic vasoactive effects of oral dopaminergic drugs for several reasons. First, the modelling uses a high-pass filter that removes the effects of slow drifts in the BOLD signal. Second, one identifies regionally specific foci of differential activation. These foci are much smaller than the region of dopaminergic vascular innervation, and therefore unlikely to arise from a global change in BOLD sensitivity caused by dopaminergic treatment. More specifically, only some task-functions are sensitive to the effects of treatment, which again argues against a non-selective effect on the BOLD response. Nonetheless, an interaction between dopaminergic vasoconstriction and the neuroimaging indices of activation must remain a caveat in fMRI studies with L-dopa.

Conclusion

In Parkinson's disease the prefrontal cortex and caudate have a non-linear relationship between disease severity and activation. This U-shape function changed with dopaminergic treatment, suggesting differential disease progression and/or compensation in the neural substrates of movement and cognition. Our results have implications for both clinical management and future studies of Parkinson's disease. Treatments aimed at optimization of motor function may push non-motor systems beyond their optimal dose-response curve, especially if non-selective dopaminergic therapies are used. However, studies of simple group differences, or of linear relationships with disease severity, are at risk of missing the effects of disease or treatment, unless they sample patients from one section of the U-shape curve.

Supplementary material

Supplementary material is available at *Brain* online.

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