doi:10.1093/brain/awq012 Brain 2010: 133; 727–745 | 727

BRAIN
A JOURNAL OF NEUROLOGY

Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease

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Patients with Parkinson's disease experience motor and perceptual timing difficulties, which are ameliorated by dopaminergic medication. We investigated the neural correlates of motor timing in Parkinson's disease, including the effects of dopaminergic medication on patterns of brain activation. Eight patients with Parkinson's disease and eight healthy controls were scanned with $H_2^{15}O$ positron emission tomography while engaged in three tasks: synchronization (right index finger tapping in synchrony with a tone presented at 1 Hz), continuation (tapping at 1 Hz in the absence of a tone), and a control simple reaction time task. During the first 6 scans, the patients were assessed after overnight withdrawal of medication. Scans 7–12 were completed with the patients in the 'ON' state, after injections of apomorphine, a dopamine receptor agonist. For the healthy controls, relative to the control reaction time task, motor timing (synchronization + continuation) was associated with significantly greater activation in left medial prefrontal cortex (Brodmann area 10, 32), right hippocampus, bilateral angular gyrus (Brodmann area 39), left posterior cingulate (Brodmann area 31) and left nucleus accumbens/caudate. This pattern of brain activation during motor timing was not observed for patients, who showed significantly greater activation in bilateral cerebellum, right thalamus and left midbrain/substantia nigra compared to the control participants. Relative to the externally-paced synchronization task, the internally controlled continuation task was associated with greater activation in the dorsolateral prefrontal cortex (Brodmann area 46/9) in both the control and Parkinson's disease groups. Analysis of medication-related effects indicated that cortical activation was significantly more predominant during motor timing when the patients were 'ON' medication, whereas pallidal

Received March 27, 2009. Revised November 24, 2009. Accepted November 11, 2010

and cerebellar activations were evident 'OFF' medication. Effective connectivity analysis established that activity in the left caudate nucleus was associated with increased activity in the right lentiform nucleus and cerebellum 'OFF' medication, and with increased activity in the prefrontal cortex 'ON' medication. These results suggest that in Parkinson's disease, in the 'OFF' medication state, excessive inhibitory pallidal outflow is associated with a lack of adequate frontal activation and reliance on the cerebellum for motor timing. In contrast, our results establish for the first time that administration of dopaminergic medication increases striatal-frontal connectivity between the caudate nucleus and prefrontal cortex during motor timing.

Keywords: motor timing; temporal processing; Parkinson's disease; apomorphine; positron emission tomography; synchronization

Abbreviations: BA = Brodmann area; rCBF = regional cerebral blood flow; PET = positron emission tomography; PPI = psychophysiological interaction; SPM = statistical parametric mapping; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Akinesia (absence or poverty of spontaneous movement) and bradykinesia (slowness of movement initiation and execution) are among the cardinal symptoms of Parkinson's disease. It is possible that impairments in motor timing contribute to bradykinesia in Parkinson's disease, and there is evidence that patients with Parkinson's disease have marked deficits in motor and perceptual timing within the milliseconds and seconds range (e.g. Pastor *et al.*, 1992*a, b*; O'Boyle *et al.*, 1996; Harrington *et al.*, 1998; Jones *et al.*, 2008). These findings have led to the suggestion that the basal ganglia and their associated subcortical dopaminergic system play a crucial role in temporal processing, acting as a hypothetical 'internal clock' (e.g. Pastor *et al.*, 1992*a, b*; Meck, 1996). The role of dopamine in temporal processing and motor timing has been supported by evidence that dopaminergic medication ameliorates timing problems in patients with Parkinson's disease (e.g. Pastor *et al.*, 1992*a, b*; O'Boyle *et al.*, 1996).

Lesion studies in rats have established that ablations of the caudate-putamen and substantia nigra result in deficits in temporal processing, and for lesions to the substantia nigra these deficits are improved with administration of levodopa (Meck, 2006). Furthermore, drugs that increase effective levels of dopamine (e.g. methamphetamine, cocaine) shorten the reproduction of a learned time interval in rats, whereas drugs that decrease dopaminergic transmission (e.g. haloperidol) increase the duration of reproduced intervals (e.g. Drew *et al.*, 2003; Matell *et al.*, 2004, 2006). Complementing these findings, dopaminergic drugs also affect temporal processing in healthy adults (Rammsayer, 1993; Rakitin *et al.*, 2006).

Despite the wealth of research investigating the neural correlates of hand/finger movements in Parkinson's disease (e.g. Jenkins *et al.*, 1992; Playford *et al.*,1992; Jahanshahi *et al.*, 1995; Sabatini *et al.*, 2000; Haslinger *et al.*, 2001), we are aware of only three studies that have used functional imaging to investigate motor timing in Parkinson's disease (Elsinger *et al.*, 2003; Cerasa *et al.*, 2006; Yu *et al.*, 2007) and none have compared the neural activity 'ON' dopaminergic medication to a fully 'OFF' medication state. As dopamine influences performance on timing tasks in patients with Parkinson's disease (Pastor *et al.*, 1992*a, b*; O'Boyle *et al.*, 1996), we were interested in using positron emission tomography (PET) to investigate the effect of dopamine on the neural correlates of motor timing in Parkinson's disease by assessing patients 'ON' versus 'OFF' medication. We used the most well-known test of motor timing: the synchronization-continuation repetitive tapping paradigm (Wing and Kristofferson, 1973*a, b*), which involves tapping in synchrony to a regularly paced tone (synchronization) as well as continuing to maintain the rhythmic tapping when tone presentation stops (continuation). Unlike the previous investigations of motor timing in Parkinson's disease, which used rest as a control condition, we used a control simple reaction time task that tightly controls for the non-temporal aspects of motor timing. This design allowed investigation of: (i) the neural correlates of motor timing in Parkinson's disease and controls; (ii) direct exploration of brain regions unique to synchronization versus continuation, which index externally guided and internally generated timing of movements, respectively; and (iii) the influence of dopaminergic stimulation on motor timing in Parkinson's disease by comparing the neural correlates of motor timing after overnight withdrawal of medication ('OFF' state) compared to following injection of apomorphine ('ON' state). Furthermore, effective connectivity analysis enabled exploration of the modulating effects of dopamine on striato-frontal coupling. Our primary predictions were that (i) motor timing would be associated with significant activity in the basal ganglia and frontal cortices in healthy controls but not in Parkinson's disease; and (ii) administration of apomorphine would largely 'normalize' patterns of brain activity and connectivity during motor timing in Parkinson's disease.

Methods

Participants

Eight patients with idiopathic Parkinson's disease (seven males) and eight healthy controls (four males) participated. The clinical diagnosis of idiopathic Parkinson's disease was established according to the criteria of the UK Parkinson's Disease Society Brain Bank (Hughes *et al.*, 1992). All participants were right handed, with a mean handedness score of 86 (SD = 7.7) in the Parkinson's disease group and 84 (SD = 5.2) in the control group on the Handedness Inventory (Oldfield, 1971). The two groups did not differ significantly ($P > 0.05$) in age [Parkinson's disease: mean = 57.9 years (SD 6.8); controls: mean = 61 years (SD 10.4)]. There was no history of neurological disease in the control group, or any other neurological disease in the Parkinson's disease group. None of the participants had a

history of head injury, psychiatric illness or drug/alcohol abuse. The Mini-Mental State Examination (Folstein *et al.*, 1975) was used for cognitive screening, with all participants scoring above the cut-off of 27, indicating absence of cognitive impairment [Parkinson's disease: mean = 28.6 (SD 1.1); controls: mean = 29.1 (SD 1.0)]. The Beck Depression Inventory (Beck *et al.*, 1961) was used to screen for depression. The Parkinson's disease patients had a significantly higher mean score (mean = 13; SD = 4.6) than the control group (mean = 6.5; SD = 4.1) [$t = 2.98(14)$; $P = 0.01$], mainly due to two patients having Beck Depression Inventory scores of 17 indicating moderate self-reported depression. Most importantly, none of the patients were clinically depressed or taking anti-depressant medication.

All eight patients with Parkinson's disease were receiving apomorphine drug therapy. Apomorphine is a rapidly acting dopamine receptor agonist that is administered by subcutaneous injection ('rescue therapy', offering short-lasting effect) or subcutaneous infusion (for symptom relief during waking hours) (Frankel *et al.*, 1990). All patients were also taking levodopa. A full summary of the clinical details of the patients can be found in Table 1.

The study was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Written, informed consent was obtained from all participants.

Design

During the PET scanning, three tasks: synchronization, continuation and control reaction time, were repeated four times, culminating in 12 scans per participant. The order of task presentation was pseudo-randomized using a Latin Square. To assess the influence of dopaminergic-stimulation on motor timing, the Parkinson's disease group were tested 'OFF' medication (following overnight withdrawal of their anti-parkinsonian medication) for the first six scans and 'ON' medication for the last six. The average duration of medication withdrawal was 12 h and 42 min (SD: 2 h 42 min). Thus the patient group completed each of the three tasks twice, once in each drug state. Participants were familiarized with the three tasks prior to scanning.

Synchronization task

Participants were instructed to tap in synchrony with a tone (1000 Hz, duration 50 ms), with an inter-stimulus interval of 1000 ms. The participants were told to listen, without responding, to the first few tones to establish the rhythm. A block ended when the participant had made 150 responses. Temporal accuracy (mean inter-tap interval) and variability (SD of inter-tap intervals) were recorded for each trial.

Continuation task

As in the synchronization task, participants were instructed to tap in time with a tone (1000 Hz, duration 50 ms, inter-stimulus interval 1000 ms), listening to the first few tones to establish the rhythm. After 30 button-presses the pacing tone ceased. Participants were instructed that when the pacing tone stopped, they should continue tapping and try and maintain the rhythm as accurately as possible (i.e. the 'continuation' phase). To control for the auditory component in the synchronization phase, button presses produced by the participants were followed by a tone of a lower frequency (950 Hz, duration 50 ms). A block consisted of 150 responses, 30 with the pacing tone and 120 without. PET data were acquired during the continuation phase of the task only.

Temporal accuracy (mean inter-tap interval) and variability (SD of inter-tap intervals) were recorded for each trial of the continuation phase.

Table 1 Clinical details of the patients with Parkinson's disease

Patient number	Gender	Age (years)	Hoehn & Yahr (OFF)	Duration of illness (years)	Dose of apomorphine	Dose of additional medication/day[a]
1	M	49	4	11	7.5 mg/h[b]	Madopar 500 mg (400 mg)
2	M	70	3	18	2.5 mg (N/A)[c]	Sinemet Plus 1000 mg (800 mg) Amantadine 200 mg Cabergoline 2 mg
3	M	56	4	13	6.3 mg/h[b]	Madopar 625 mg (500 mg)
4	M	61	3	18	4 mg (0–2/day)[c]	Sinemet CR 1000 mg (800 mg) Entacapone 800 mg Pergolide 4 mg
5	M	54	3	13	4 mg (2/week)[c]	Madopar 1000 mg (800 mg) Madopar dispersible 250 mg (200 mg) Madopar CR 125 mg (100 mg) Entecapone 1200 mg Cabergoline 6 mg
6	M	51	4	11	3 mg (3/day)[c]	Madopar 1125 mg (900 mg) Madopar CR 1125 mg (900 mg) Selegeline 10 mg Cabergoline 5 mg
7	M	60	4	18	6 mg (2–3/day)[c]	Sinemet Plus 1000 mg (800 mg) Sinemet CR 250 mg (200 mg) Entacapone 400 mgPergolide 0.75 mg
8	F	62	3	20	4 mg (2/week)[c]	Madopar 870 mg (700 mg) Cabergoline 2 mg
Mean		57.88	3.50	15.25		
SD		6.79	0.53	3.62		

[a]Relative amount of levodopa given in brackets.
[b]Subcutaneous infusion: in mg/h given each day during waking hours.
[c]'Rescue injection': frequency of administration given in brackets.

Control simple reaction time task (control reaction time)

A tone (1000 Hz, duration 50 ms) was presented at a mean inter-stimulus interval of 1000 ms (varying randomly between 850 and 1150 ms to prevent anticipation of the tone). Participants were instructed to press the response button as quickly as possible in response to each tone. A block consisted of 150 responses. Mean reaction time and variability (SD of reaction time) were recorded for each trial.

A response box with a response button (2.5-cm diameter) was used in all conditions and responses were made with the right index finger. The distance the button travelled when fully pressed was 2.5 mm and the force needed to fully press the button was 0.8 N. Response times were recorded to the nearest millisecond. During the practice trials, the tones were presented through a loudspeaker. When the participants were in the scanner the tones were presented through earphones, with sound level adjusted for comfort.

Apomorphine administration

Prior to the scanning sessions, consultation with each patient established his or her optimal dose to be administered during scanning (see online supplementary material). Participants who used 'rescue' injections were given their normal dose; those who used a pump were given a dose established after a discussion with the patient and the result of their initial apomorphine 'challenge' test. The dose was given at the half way point (after scan 6). When the patients subjectively felt they were 'ON', and this agreed with the neurologist's motor assessment, the scanning continued. Before the patients entered the scanner, the severity of motor symptoms was assessed using a modified version (items 20, 22, 23, 24 and 25 of Part III: Motor Examination) of the Unified Parkinson's Disease Rating Scale (UPDRS, Fahn *et al.*, 1987). A modified version was used so that all selected items could also be administered when the patient was in the scanner. The second UPDRS assessment occurred after the apomorphine injection, when the patient was in the 'ON' state and before the latter half of the scanning. A final UPDRS rating was completed at the end of the scanning session. UPDRS ratings and apomorphine injections were completed by a neurologist (JZ or RK).

Additional tests

Medication can have non-specific effects on arousal, which could account for a change in the performance of patients with Parkinson's disease. Therefore, a measure of self-reported arousal (Mackay *et al.*, 1978) was completed three times: immediately prior to scanning, before the start of scan 7 (after the patients had been assessed as being 'ON' medication) and at the end of the scanning session. The Paced Auditory Serial Addition Test (Gronwall and Wrightson, 1981) was completed as a measure of attention.

Data acquisition

Measurements of regional cerebral blood flow (rCBF) were obtained using a Siemens/CPS ECAT EXACT HR+ PET scanner (Siemans/CTI Inc., Knoxville, TN) in 3D mode with inter-detector collimating septa retracted. An axial field of view of 155 mm provided coverage of the whole brain, including the cerebellum. Prior to data collection, a transmission scan was conducted to correct for attenuation effects. rCBF measurement was enabled by intravenous injection of approximately 9 mCi of $H_2^{15}O$ through a forearm cannula over 20 s, followed by a 20 s saline flush. rCBF data were collected over a 90 s activation period that began 5 s before the rising phase of radioactivity in the head. 12 such scans were collected, with an 8 minute rest period between scans to allow for the radioactivity to decay. The images were reconstructed using 3D filtered back projection into 63 transverse planes and into a 128×128 pixel image matrix (pixel size 2.4 mm $\times$ 2.1 mm $\times$ 2.1 mm), with a resolution of 6 mm at full-width half maximum. Additionally, T_1-weighted structural magnetic resonance imaging (MRI) scans were obtained for each subject using a Siemens Magnetom VISION MRI scanner operating at 2 Tesla (Siemans, Erlangen, Germany).

Data analysis

PET images were analysed using statistical parametric mapping software (SPM99, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.a.cuk/spm) executed in MATLAB (Mathworks Inc., Sherbon, MA). For each participant, the 12 scans were realigned to the first to adjust for the effects of any head movements. All images were then spatially normalized (Friston *et al.*, 1995*a*) into a template based upon the Montreal Neurological Institute reference brain that conforms to a standard anatomical space (Talairach and Tournoux, 1988). The scans were then smoothed using an isotropic Gaussian kernel of 12 mm full-width at half maximum. This accommodated for intersubject differences in anatomy, increased the signal to noise ratio and aligned the data more closely to a Gaussian field model.

Subsequent analysis used the general linear model to estimate effects at each voxel in the brain (Friston *et al.*, 1995*b*). Scan to scan differences in global blood flow were modelled as a confounding covariate. Hypotheses about regionally specific condition effects were tested using linear contrasts to compare task differences in the mean rCBF at each voxel. For each contrast, a t statistic was computed for every voxel to form an SPM $\{t\}$. The SPM $\{t\}$ values were then transformed to the unit normal distribution to give an SPM $\{z\}$. Unless otherwise stated, the level of significance was $P<0.001$, uncorrected for multiple comparisons.

We used the psychophysiological interaction method (PPI: Friston *et al.*, 1997) to investigate how apomorphine modulated effective connectivity between the basal ganglia and the rest of the brain in the Parkinson's disease group. PPIs aim to explain regionally specific responses in terms of an interaction between activity in a particular brain region (seed area) and the influence of an experimental parameter. The physiological variable was defined as the first eigenvariate of the rCBF signal from a sphere (radius 8 mm) centred on the voxel in the left head of the caudate nucleus that showed significantly greater activation during motor timing than the control reaction time for the controls compared to the Parkinson's disease group. The experimental variable was whether the patients were in the 'ON' or 'OFF' medication state. Thus, the PPI reveals the modulatory effect of apomorphine on a region of the basal ganglia that is not activated normally during motor timing in Parkinson's disease. Modelled within SPM, these two regressors were multiplied together to create a third regressor (covariate of interest), which represented the interaction between the two variables. The resulting SPM $\{t\}$ reflected the significance of the PPI, where a significant value reflects a difference in the regression slopes linking the activity in the seed to activity in other brain areas, depending on whether the patients were 'ON' or 'OFF' medication. A positive PPI denotes significant increase in task-related coupling between the seed area and another brain area (target area) when ON medication, as compared to the OFF medication state. It is equivalent to describing it as a significant decrease in task-related coupling from target to seed

area OFF medication when compared to the ON medication state, as the PPI analysis does not contain directional information. A negative PPI reflects areas where there is a significant decrease in task-related coupling between the seed and target areas ON medication compared with OFF medication, or a significant increase in coupling from target to seed area OFF medication when compared to the ON medication state.

Anatomical localization of the significant voxel coordinates was determined using the participants' structural MRIs, group average MRIs, and with reference to the atlas of Durvenoy (1999). The standard stereotactic atlas of Talairach and Tournoux (1988) was used for determining Brodmann areas (BA). An atlas of the cerebellum was also used (Schmahmann *et al.*, 2000) as well as probabilistic cytoarchitectonic atlases of the primary motor cortex and somatosensory area (Geyer *et al.*, 1996; 1999; 2000).

Results

Behavioural data

The two groups scored similarly on the Paced Auditory Serial Addition Test ($P > 0.05$), suggesting they did not significantly differ in their ability to maintain focused attention.

Self-reported arousal

The patients' rated level of arousal remained almost static (assessment point 1: mean = 8.4, SD = 3.9; assessment point 2: mean = 8.2, SD = 2.4; assessment point 3: mean = 8.6, SD = 4.3); whereas the controls showed a decrease at assessment point 2 (mean = 4.9, SD = 4.5), relative to assessment points 1 (mean = 12.6, SD = 0.99) and 3 (mean = 9.5, SD = 4.9). A mixed-factorial ANOVA showed a significant main effect of assessment point [$F(2,28) = 7.58$; $P = 0.002$] and Group × Assessment point interaction [$F(2,28) = 6.72$; $P = 0.004$]. The main effect of Group was not significant.

Temporal accuracy (mean inter-tap interval)

The data from the timing tasks were analysed using a mixed-factorial ANOVA: 2 Group (Parkinson's disease versus Control) × 2 Task (Synchronization versus Continuation) × 2 Scan (1st six versus 2nd six). The main effect of Task was significant [$F(1,14) = 29.88$, $P < 0.001$], indicating faster performance in the continuation task. The mean difference in tapping rate between the continuation and synchronization tasks was less than 100 ms, so is unlikely to have affected brain activation. No other effects were significant ($P > 0.05$). For the control reaction time task, the data were analysed using a mixed factorial ANOVA, with the within group factor of Scan (1st six or 2nd six) and the between group factor of Group (Parkinson's disease versus control). There was a main effect of Group [$F(1,14) = 16.87$, $P < 0.001$], reflecting significantly slower reaction times in the patient group. There were no other significant effects ($P > 0.05$). See Table 2.

Variability

A mixed-factorial ANOVA [(2 Group × 2 Task) × 2 Scan] showed a significant main effect of Task [$F(1,14) = 21.43$, $P < 0.0001$], reflecting greater variability on the Continuation task. No other effects were significant ($P > 0.05$). For the control reaction time task, data were analysed with an ANOVA with Scan and Group as the factors. There was a significant main effect of Group [$F(1,14) = 11.55$, $P < 0.004$], reflecting lower variability in the control group. No other effects were significant ($P > 0.05$). See Table 2.

Motor disability in the ON and OFF scanning states

In addition to the pre-arranged apomorphine dose, two patients needed an extra dose to switch them 'ON'. Three patients needed an extra 'top-up' dose prior to the final 'ON' scan because they were beginning to show signs that the medication effects were wearing off. UPDRS ratings were significantly lower following apomorphine administration, indicating that the patients were in an 'ON' state when the second half of scanning began [UPDRS at assessment point 1 compared to 2: $t(7) = 7.49$; $P < 0.001$]. Patients remained in this 'ON' state to the end of the scanning session [assessment point 1 compared to 3: $t(7) = 7.06$; $P < 0.001$], and there was no significant change in UPDRS ratings during the 'ON' stage [assessment point 2 compared to 3: $t(7) = -1.39$; $P = 0.208$] (see online Supplementary material).

Table 2 Mean accuracy/reaction time and mean standard deviation in the three tasks (SD in brackets)

	Parkinson's disease-OFF	Parkinson's disease-ON	Control group
Mean accuracy/reaction time (seconds)			
Synchronization	992.42 (12.59)	998.25 (1.80)	1000.14 (0.38)
Continuation	910.73 (41.97)	933.14 (43.88)	937.25 (63.95)
Control reaction time	365.52 (91.81)	338.45 (121.30)	205.48 (58.07)
Variability (SD)			
Synchronization	51.65 (16.59)	62.72 (17.30)	53.01 (18.63)
Continuation	72.33 (6.36)	73.45 (15.38)	64.78 (15.73)
Control reaction time	232.92 (125.40)	208.80 (143.52)	70.01 (42.82)

For the control group, the data are collapsed across all scans as there was no significant difference in scanning procedures or performance between the first and second six scans for this group.

Table 3 Within group effects of task (motor timing versus control reaction time) for the control and Parkinson's disease groups

	BA	MNI coordinates of peak activation			Z-score	P-value*
		x	y	z		
(i) Control group						
Timing tasks > control reaction time task						
Left angular gyrus	39	−42	−64	36	4.59	<0.001
Right hippocampus		32	−38	−8	4.05	<0.001
Left medial prefrontal cortex	10	−2	54	18	3.93	<0.001
Left anterior cingulate	10/32	−10	50	12	3.39	<0.001
Left medial prefrontal cortex	10	−4	52	−8	3.74	<0.001
Right angular gyrus	39	42	−84	32	3.52	<0.001
Left posterior cingulate	31	−8	−44	48	3.13	0.001
Left nucleus accumbens/caudate		−8	14	−8	3.10	0.001
(ii) Parkinson's disease group						
Timing tasks > control reaction time task						
Left parieto-occipital fissure		−12	−66	20	4.23	<0.001
Left parieto-occipital fissure		−8	−64	12	3.73	<0.001
Right thalamus		26	−26	6	3.96	<0.001
Left midbrain/substantia nigra pars reticulata		−10	−28	−16	3.45	<0.001
Right cerebellar hemisphere (VI)		32	−26	−42	3.36	<0.001
Left cerebellar hemisphere (V)		−18	−50	−20	3.30	<0.001
Left occipital lobe	17/18	−24	−88	−10	3.29	<0.001
Left parieto-occipital fissure		24	−70	28	3.27	<0.001
Right precuneus	7	4	−62	40	3.20	0.001
Left middle occipital gyrus	17/18	36	−88	18	3.18	0.001
Left inferior temporal gyrus	20	−22	0	−48	3.18	0.001
Left superior temporal gyrus	38	−48	4	−18	3.14	0.001
Left insula	13	−44	−12	0	3.11	0.001
Right calcarine sulcus	17	20	−96	4	3.10	0.001

*All significant at $P < 0.001$, uncorrected.

Functional imaging data

The analysis was centred on three topics of interest: (i) the functional anatomy of motor timing (synchronization and continuation tasks combined) versus control reaction time task, both within and between groups; (ii) the differential neural activation in the synchronization versus continuation tasks; and (iii) the effect of apomorphine on patterns of brain activation during synchronization and continuation motor timing in the Parkinson's disease group, including changes in neural coupling relative to the dopamine-depleted state.

The neural correlates of motor timing

Within group effects: healthy controls

Significantly greater activation in the timing tasks (synchronization task + continuation task) than the control reaction time task (Table 3) was found in the bilateral angular gyrus (BA 39), right hippocampus, a region extending from the left medial prefrontal cortex (BA 10) to left anterior cingulate (BA 10/32) alongside an additional medial prefrontal region (BA 10), left posterior cingulate (BA 31) and left nucleus accumbens. At a less stringent threshold of $P < 0.01$, the nucleus accumbens activation extended to include additional striatum, particularly the caudate nucleus. Areas significantly more activated for the control reaction time task than the timing tasks can be found in the online Supplementary material, section 1.

Within group effects: patients with Parkinson's disease

Significantly greater activation for the timing tasks than the control reaction time task (Table 3) was found in the left parieto-occipital fissure, right precuneus (BA 7), left inferior (BA 20) and left superior (BA 38) temporal gyri, left insula (BA 13), right thalamus, regions of the occipital cortex, bilateral cerebellar hemispheres and in a midbrain region that was considered to be in the lateral and caudal region of the substantia nigra (pars reticulata). Areas significantly more activated for the control reaction time task than the timing tasks can be found in the Supplementary material, section 1.

Between group effects: Group × Task interaction

A 2 Group (Parkinson's disease versus Controls) × 2 Task (timing tasks versus control reaction time task) ANOVA was used to analyse between group effects (Table 4). Greater activation for the control than the Parkinson's disease group in the timing tasks than the control reaction time task was found in the right middle frontal gyrus (BA 8), medial orbitofrontal cortex (BA 11), regions of the right inferior and left middle temporal gyri (BA 20/21/37) and left head of caudate nucleus. Greater activation for the Parkinson's disease than the control group in the timing tasks than the control

Table 4 Interaction of Group (Control versus Parkinson's disease) and Task (motor timing versus control reaction time)

	BA	MNI coordinates of peak activation			Z-score	P-value*
		x	y	z		
(i) [Control group > Parkinson's disease group] × [motor timing > control reaction time] interaction						
Right middle frontal gyrus	8	56	16	44	4.31	<0.001
Medial orbitofrontal cortex	11	0	54	−12	3.52	<0.001
Left middle temporal gyrus	20	−68	−28	−14	3.41	<0.001
Left middle temporal gyrus	21	−58	−44	−4	3.27	0.001
Right inferior temporal gyrus	20	70	−34	−22	3.20	0.001
Left middle temporal gyrus	20/37	−62	−52	−14	3.20	0.001
Left head of caudate nucleus		−8	12	−4	3.10	0.001
(ii) [Parkinson's disease group > control group] × [motor timing > control reaction time] interaction						
Midline vermis (IV)		6	−48	−4	3.82	<0.001
Left cerebellar hemisphere (V)		−18	−50	−20	3.71	<0.001
Right thalamus/internal capsule		26	−24	6	3.57	<0.001
Left midbrain/substantia nigra pars reticulata		−10	−28	−16	3.55	<0.001
Left cerebellum bordering on fusiform gyrus		−36	−52	−22	3.20	0.001
Right cerebellum bordering on fusiform gyrus		36	−58	−18	3.17	0.001
Midline vermis		2	−72	−22	3.13	0.001

*All significant at $P < 0.001$, uncorrected.

reaction time task was found in the cerebellum, including left cerebellar hemisphere (V), midline vermis and areas of bilateral cerebellar hemisphere bordering the fusiform gyrus. Increased activation was also found in the right thalamus/internal capsule and in a similar midbrain/substantia nigra pars reticulata region that was found in the motor timing > control reaction time contrast for Parkinson's disease reported above. To illustrate the relative rCBF values across the different tasks and groups and to confirm the direction of the interaction, parameter estimates are provided for activations in areas for which we had an *a priori* hypothesis (Fig. 1).

The neural correlates of externally (synchronization) versus internally (continuation) timed movement

Within group effects: healthy controls

Significantly greater activation in the synchronization task than the continuation task was found primarily in posterior regions including areas of temporal and parietal cortices. Conversely, significantly greater activation in the continuation task than the synchronization task was primarily observed in the prefrontal cortex, including the right dorsolateral prefrontal cortex (BA 9/46) (Table 5).

Within group effects: patients with Parkinson's disease

Similar to the control group, significantly greater activation in the synchronization task than the continuation task was most prominent in posterior cortical regions. Significantly greater activation in the continuation task than the synchronization task was present in the dorsolateral prefrontal cortex (BA 9/46), as observed in the controls, as well as in the cerebellum (Table 5).

Between group effects: Group × Task interaction

A 2 Group (Parkinson's disease versus Controls) × 2 Task (Synchronization versus Continuation) ANOVA was used to analyse between group effects, specifically the differential neural modulation in the two groups as a function of whether the task included internally- or externally-generated motor timing. Driven by our greater interest in group differences in the neural correlates of internally controlled motor timing, when reporting the results of this interaction we focused on the brain areas that showed greater activation in the control than Parkinson's disease group and also areas that showed greater activation for the Parkinson's disease than the control group during the continuation relative to the synchronization task. For regions we were particularly interested in, the parameter estimates in Fig. 2 plot the relative rCBF across the two tasks and groups and illustrate the direction of the interaction. Greater activation for the controls than the Parkinson's disease group in the continuation task than the synchronization task was found in the superior parietal gyrus ($x = -20$, $y = -82$, $z = 46$; $Z = 3.74$; $P < 0.001$), right premotor cortex (BA 6, $x = 64$, $y = 8$, $z = 36$; $Z = 3.33$, $P < 0.001$), right orbitofrontal cortex (BA 11, $x = -8$, $y = 52$, $z = -30$; $Z = 3.15$; $P = 0.001$), left insula (BA 13, $x = -36$, $y = 16$, $z = -6$; $Z = 3.11$; $P = 0.001$) and the left cerebellar hemisphere/midline (V) ($x = -12$, $y = -56$, $z = -10$; $Z = 3.44$, $P < 0.001$). Greater activation for the Parkinson's disease group than the controls in the continuation task than the synchronization task was found in the right anterior cingulate (BA 10/32, $x = 18$, $y = 44$, $z = -6$, $Z = 3.23$; $P = 0.001$) and bilateral cerebellar hemispheres (right: $x = 28$, $y = -92$, $z = -24$; $Z = 3.35$; $P < 0.001$, left: $x = -12$, $y = -90$, $z = -32$; $Z = 3.20$; $P = 0.001$).

The effect of apomorphine on patterns of brain activation in Parkinson's disease

The main effect of medication and the effect of medication on timing (synchronization + continuation) versus control reaction time task are presented in the Supplementary material, sections 2 and 3, respectively. We were specifically interested in examining the effect of medication on timing in the synchronization and

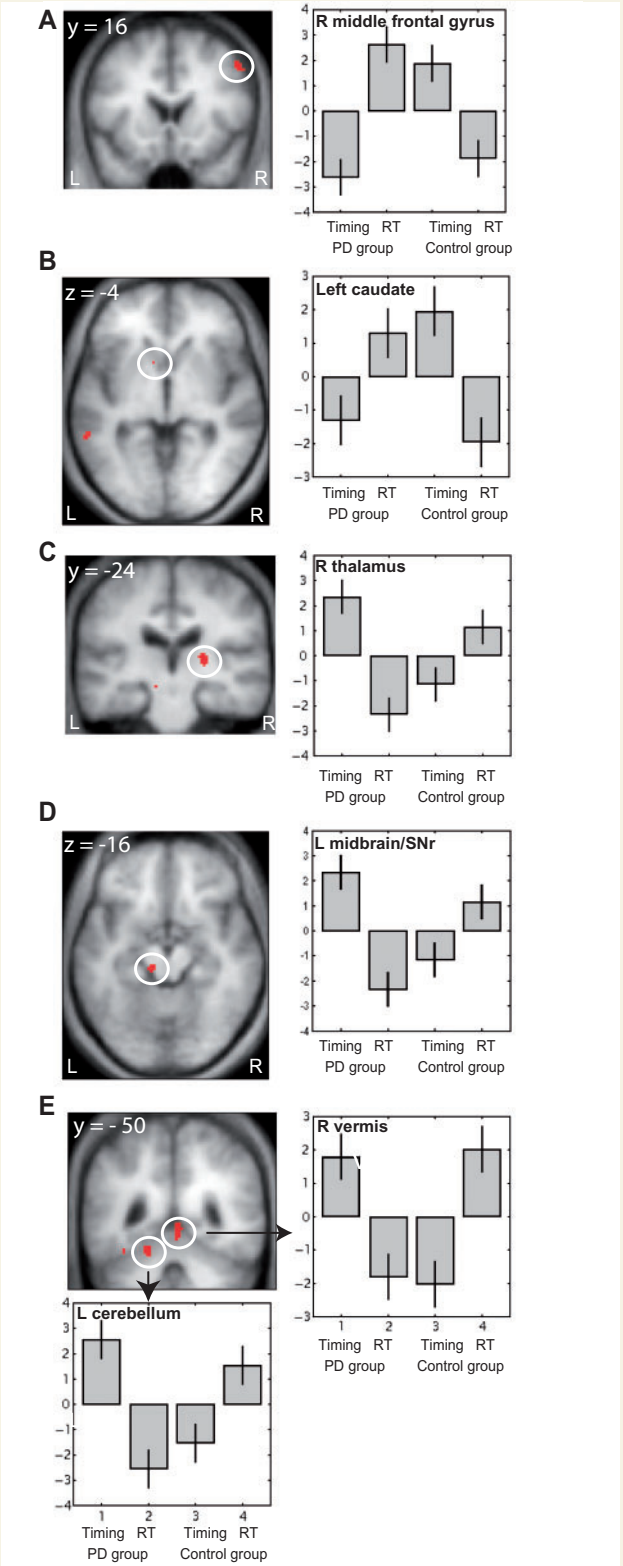

Figure 1 Group × Task interaction showing: (**A**, **B**) areas of significantly greater activation for the control group than the Parkinson's disease group when comparing the timing tasks (synchronization + continuation) with the control reaction time task; (**C**, **D**, **E**) areas of significantly greater activation for the Parkinson's disease group than the control group when comparing the timing tasks with the control reaction time task. (**A**) Increased right (R) middle frontal gyrus (BA 8) ($x = 56$, $y = 16$, $z = 44$) and (**B**) increased left (L) caudate nucleus ($x = –8$, $y = 12$, $z = –4$) activation for control group, compared to Parkinson's disease group, during the timing tasks [versus control reaction time (RT) task]; (**C**) increased right thalamus ($x = 26$, $y = –24$, $z = 6$), (**D**) increased midbrain/substantia nigra pars reticulate (SNr) ($x = –10$, $y = –28$, $z = –16$) and (**E**) increased left cerebellar hemisphere (V) ($x = –18$, $y = –50$, $z = –20$) and right cerebellar vermis (IV) ($x = 6$, $y = –48$, $z = –4$) activation for Parkinson's disease subjects, compared to control subjects, during the timing tasks (versus control reaction time task). Results are displayed as statistical parametric maps in coronal and transverse projections in stereotactic space. Parameter estimates showing mean activation during the timing tasks and control reaction time task, for each group, are also displayed. Significant at $P < 0.001$, uncorrected.

continuation tasks separately and whether this was manifest as an increase or decrease in timing-related activity. Therefore, we investigated the interactions from two separate two-way ANOVAs: 2 Task (synchronization or continuation versus control reaction time task) × 2 Medication state (ON versus OFF medication).

Synchronization task

For the synchronization versus control reaction time task comparison, areas that showed significantly greater activation 'ON' than 'OFF' medication included the bilateral superior frontal gyrus (BA 8 and 9) and right anterior cingulate (BA 24), left somatosensory cortex (BA 2), bilateral temporal cortex, bilateral parietal regions, and bilateral calcarine suclus. For the synchronization versus control reaction time task comparison, the areas that showed significantly greater activation 'OFF' than 'ON' medication included the left orbitofrontal cortex (BA 11), right insula (BA 13), right temporal cortex, right red nucleus, left globus pallidus and left cerebellar hemisphere. To illustrate the relative rCBF values across the different tasks and medication state and to confirm the direction of the interaction, parameter estimates are provided for activations of particular interest (Table 6 and Fig. 3). Particularly, we focus on similar regions activated in both sets of Task × Medication interactions.

Continuation task

For the continuation versus control reaction time task comparison, the areas that showed significantly greater activation 'ON' versus 'OFF' medication were areas of the frontal cortex including left inferior (BA 47), middle (BA 10) and superior (BA 9) frontal gyrus and the orbitofrontal cortex (BA 11), alongside the left insula (BA 13), bilateral temporal and parietal cortices and two foci in the right cerebellar hemispheres. Conversely, areas showing significantly greater activation 'OFF' than 'ON' medication during the continuation relative to the control reaction time task were a region encompassing the right anterior cingulate (BA 24) and right middle frontal gyrus (BA 6), left subcentral gyrus, left superior parietal gyrus (BA 7), left globus pallidus and left cerebellar hemisphere. To illustrate the relative rCBF values across the different tasks and medication states and to confirm the direction of

Table 5 Within group comparisons of externally guided (synchronization) and internally generated motor timing (continuation) for the control and Parkinson's disease groups

	BA	MNI coordinates of peak activation			Z-score	*P*-value*
		x	*y*	*z*		
(i) Control group						
Synchronization > Continuation						
Right superior temporal sulcus	39	48	−70	18	4.20	<0.001
Right middle occipital gyrus	19	54	−78	0	3.43	<0.001
Right precuneus	7	4	−56	42	3.85	<0.001
Right lingual gyrus	17	18	−86	−14	3.89	<0.001
Left cuneus	18	−12	−84	16	3.64	<0.001
Right cuneus	17/18	4	−80	4	3.55	<0.001
Left medial prefrontal cortex	10/11	−4	52	−10	3.43	<0.001
Right parieto-occipital fissure		16	−62	14	3.42	<0.001
Right hippocampus		30	−20	−20	3.41	<0.001
Right hippocampus		26	−16	−26	3.12	0.001
Right parieto-occipital fissure		6	−66	24	3.32	<0.001
Right somatosensory area	1/2	32	−50	62	3.21	0.001
Left calcarine sulcus	18	−20	−66	0	3.18	0.001
Left insula	13	−34	−24	−6	3.12	0.001
Continuation > Synchronization						
Right inferior frontal gyrus	44	60	8	14	3.54	<0.001
Right middle temporal gyrus	21	68	−40	−10	3.49	<0.001
Left insula	13	−32	16	−4	3.47	<0.001
Right dorsolateral prefrontal cortex	9/46	42	40	30	3.32	<0.001
Right inferior frontal gyrus	45/46	58	38	6	3.14	0.001
(ii) Parkinson's disease group						
Synchronization > Continuation						
Left occipital lobe	18	−4	−74	20	4.59	<0.001
Left occipital lobe	19	−14	−80	32	3.57	<0.001
Left orbitofrontal cortex	11	−8	54	−30	3.58	<0.001
Right motor cortex	4	42	−10	40	3.42	<0.001
Left hippocampus		−20	−16	−24	3.37	<0.001
Right calcarine sulcus	18	18	−88	4	3.31	<0.001
Right superior temporal gyrus	22	60	−10	4	3.29	0.001
Right middle temporal gyrus	21	58	0	−24	3.28	0.001
Left supramarginal gyrus	40	−48	−52	30	3.28	0.001
Right calcarine sulcus		28	−64	2	3.28	0.001
Right parieto-occipital fissure		24	−72	26	3.72	0.001
Right precuneus	7	6	−72	32	3.21	0.001
Left middle frontal gyrus	6	−32	−2	44	3.14	0.001
Right calcarine sulcus	19	26	−56	−6	3.13	0.001
Right superior frontal gyrus	6	30	−4	66	3.12	0.001
Left superior parietal gyrus	7	−18	−80	48	3.10	0.001
Continuation > Synchronization						
Right supramarginal gyrus	40	70	−42	40	4.29	<0.001
Right dorsolateral prefrontal cortex	46	52	46	8	4.04	<0.001
Right dorsolateral prefrontal cortex	9/46	44	40	28	3.52	<0.001
Right insula	13	56	6	2	3.93	<0.001
Left cerebellar hemisphere (Crus I)		−34	−78	−24	3.73	<0.001
Left cerebellar hemisphere (Crus I)		−34	−88	−22	3.30	<0.001
Right anterior cingulate	10/32	18	42	−8	3.56	<0.001
Right orbital gyrus	11	20	16	−26	3.54	<0.001
Left cerebellar hemisphere (Crus II)		−12	−90	−32	3.47	<0.001
Right orbitofrontal cortex	11	36	46	−12	3.27	0.001
Right superior temporal gyrus	22/42	50	−28	6	3.24	0.001
Left superior temporal gyrus	22	−66	−40	20	3.15	0.001
Right superior parietal gyrus	7	48	−52	60	3.11	0.001
Left cerebellar hemisphere (Crus I)		−44	−60	−30	3.09	0.001

*All significant at $P < 0.001$, uncorrected.

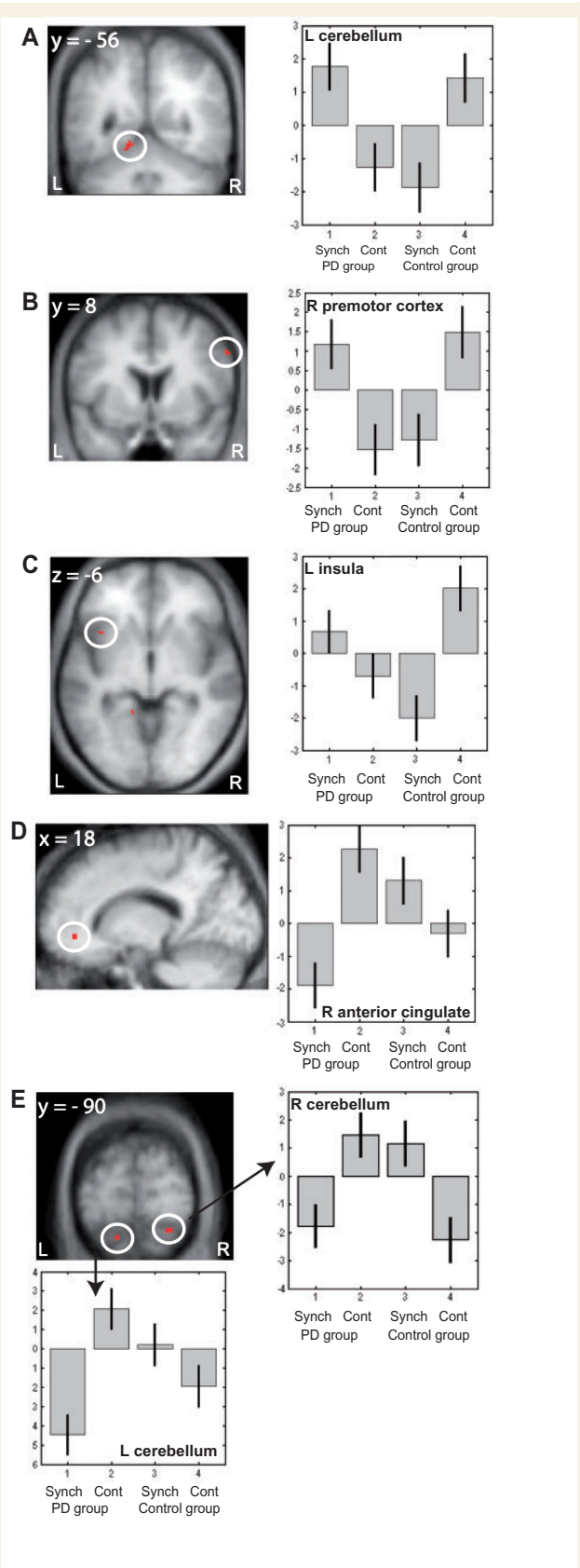

Figure 2 Group × Task interaction showing: (**A**, **B**) areas of significantly greater activation for the control group than Parkinson's disease group when comparing continuation > synchronization; (**C**, **D**, **E**) areas of significantly greater activation for the Parkinson's disease group than control group when comparing continuation > synchronization. (**A**) increased left (L) cerebellar hemisphere/midline (V) ($x = -12$, $y = -56$, $z = -10$), (**B**) increased right (R) premotor cortex (BA 6) ($x = 64$, $y = 8$, $z = 36$), (**C**) increased left insula ($x = -36$, $y = 16$, $z = -6$), for the controls than Parkinson's disease group when comparing continuation > synchronization. Additionally, (**D**) increased right anterior cingulate (BA 10/32) ($x = 18$, $y = 44$, $z = -6$), (**E**) right cerebellar hemisphere ($x = 28$, $y = -92$, $z = -24$) and left cerebellar hemisphere ($x = -12$, $y = -90$, $z = -32$) for the Parkinson's disease group than controls when comparing continuation > synchronization. Results are displayed as statistical parametric maps in sagittal, coronal and transverse projections in stereotactic space. Parameter estimates showing mean activation during the continuation task and synchronization task, for each group, are also displayed. Significant at $P < 0.001$, uncorrected.

the interaction, parameter estimates are provided for activations of particular interest (Table 6 and Fig. 3).

Changes in effective connectivity 'ON' and 'OFF' medication

The Group × Task interaction supported our hypothesis that the basal ganglia and frontal cortex are more activated during motor timing in the control group than in Parkinson's disease. We used an analysis of effective connectivity (PPI) to explore the effects of apomorphine on the patterns of connectivity of a focus of activation in the left head of the caudate nucleus ($x = -8$, $y = 12$, $z = -4$) that was significantly more engaged in motor timing in the control than Parkinson's disease group. This area formed the physiological variable for the PPI. Fig. 4A(i) illustrates regions with a significant positive PPI and Fig. 4B(i) illustrates regions with a significant negative PPI. In particular, significant increases in task-related coupling ON medication compared to OFF were found between the left caudate nucleus and prefrontal regions, including the left middle frontal gyrus (BA 8) ($x = -34$, $y = 24$, $z = 46$; $Z = 4.32$), left dorsolateral prefrontal cortex (BA 46) ($x = -44$, $y = 40$, $z = 14$; $Z = 3.87$) and right medial prefrontal cortex (BA 10/32) ($x = 6$, $y = 48$, $z = -4$; $Z = 3.41$) [Fig. 4A(ii and iii)]. Notably, the medial prefrontal activation is similar to a region in the main effect of timing for the control group ($x = -4$, $y = 52$, $z = -8$) and a region that was significantly more active for the control group than Parkinson's disease group during motor timing than the control reaction time task ($x = 0$, $y = 54$, $z = -12$). In contrast, significant increases in task-related coupling OFF medication compared to ON medication were found between the left caudate nucleus and the right lentiform nucleus ($x = 26$, $y = 12$, $z = 0$; $Z = 3.30$) [Fig. 4B(ii)]. Further notable activations were found in the supplementary motor area ($x = 2$, $y = -14$, $z = 72$; $Z = 4.16$) and several loci in the cerebellum {including $x = 12$, $y = -68$, $z = -12$; $Z = 3.28$; $x = 16$, $y = -56$, $z = -34$; $Z = 3.24$ [Fig. 4B(iii)] and $x = 52$, $y = -54$, $z = -40$; $Z = 3.11$}.

Discussion

In investigating the neural correlates of motor timing and the effect of dopaminergic medication on motor timing in Parkinson's disease we present four main findings. First, patients

Table 6 Interaction of Task (synchronization versus control reaction time and continuation versus control reaction time) and Medication ('ON' versus 'OFF') for the Parkinson's disease group

	BA	MNI coordinates of peak activation			Z-score	P-value*
		x	y	z		
(i) [ON > OFF] × [synchronization > control reaction time] interaction						
Right superior temporal sulcus		52	−14	−10	4.07	<0.001
Right superior frontal gyrus	9	12	60	34	3.84	<0.001
Right anterior cingulate	24	20	24	22	3.71	<0.001
Right calcarine sulcus	17	14	−84	2	3.54	<0.001
Right calcarine sulcus	18	18	−84	14	3.39	<0.001
Right supramarginal gyrus	40	56	−34	34	3.49	<0.001
Left intraparietal sulcus		−26	−54	42	3.44	<0.001
Right inferior temporal gyrus	20	36	6	−44	3.32	<0.001
Left inferior parietal gyrus	40	−64	−24	40	3.32	<0.001
Right superior parietal gyrus	7	22	−84	44	3.25	0.001
Left occipital lobe	19	−18	−58	0	3.19	0.001
Left somatosensory cortex	2	40	−28	42	3.17	0.001
Left superior parietal gyrus	19	−22	−82	38	3.14	0.001
Left calcarine sulcus	17	−14	−96	0	3.12	0.001
Left middle temporal gyrus	21	−46	8	−34	3.12	0.001
Left superior frontal gyrus	8	−2	24	58	3.11	0.001
(ii) [OFF > ON] × [synchronization > control reaction time] interaction						
Left globus pallidus		−16	0	−2	4.24	<0.001
Left cerebellar hemisphere		−12	−88	−38	3.47	<0.001
Left orbitofrontal cortex	11	−8	48	−20	3.43	<0.001
Right middle temporal gyrus	21	74	−34	−8	3.42	<0.001
Right posterior cingulate gyrus	31	8	−30	42	3.40	<0.001
Right insula	13	48	−8	18	3.35	<0.001
Right red nucleus		0	−20	−6	3.25	0.001
Right inferior temporal sulcus	20	64	−8	−36	3.24	0.001
Left somatosensory cortex	1/3	−52	−18	46	3.16	0.001
(iii) [ON > OFF] × [continuation > control reaction time] interaction						
Left middle/superior temporal gyrus	21	−38	4	−32	4.37	<0.001
Left insula	13	−48	12	−6	4.21	<0.001
Left inferior frontal gyrus	47	−38	32	−2	4.20	<0.001
Medial orbitofrontal cortex	11	0	58	−28	3.84	<0.001
Right cerebellar hemisphere		48	−80	−26	3.59	<0.001
Left orbitofrontal cortex	11	−24	60	−16	3.55	<0.001
Left intraparietal sulcus		−32	−52	40	3.45	<0.001
Left angular gyrus	39	−40	−52	30	3.12	0.001
Right inferior temporal gyrus	20	52	−34	−18	3.42	<0.001
Left middle frontal gyrus	10	−34	60	4	3.38	<0.001
Right superior frontal gyrus	9	16	60	30	3.30	<0.001
Right supramarginal gyrus	40	50	−48	54	3.17	0.001
Right cerebellar hemisphere		16	−48	−26	3.09	0.001
(iv) [OFF > ON] × [continuation > control reaction time] interaction						
Left cerebellar hemisphere		−16	−86	−42	3.79	<0.001
Left cerebellar hemisphere		−20	−88	−32	3.33	<0.001
Right anterior cingulate	24	22	−14	42	3.68	<0.001
Right middle frontal gyrus	6	24	−8	52	3.54	<0.001
left subcentral gyrus		−64	2	4	3.38	<0.001
Left globus pallidus		−20	−4	−4	3.21	0.001
Left superior parietal gyrus	7	−4	−74	54	3.21	0.001

*All significant at $P < 0.001$, uncorrected.

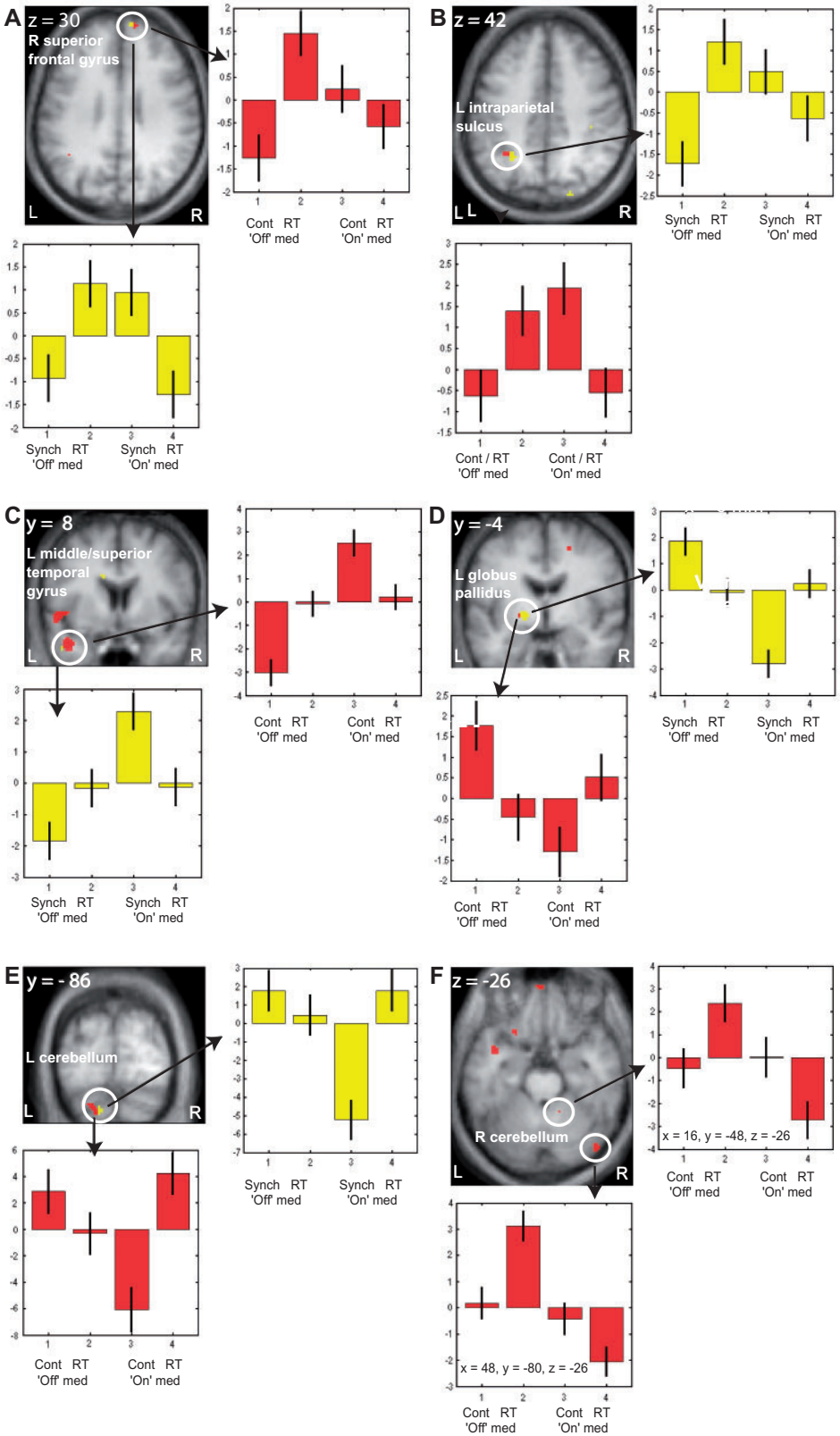

Figure 3 Medication (ON versus OFF) × Task (synchronization/continuation versus control reaction time) interactions for the patients with Parkinson's disease. (**A**) Right (R) superior frontal gyrus from (ON > OFF) × [synchronization (synch) > control reaction time (RT)] ($x = 12$, $y = 60$, $z = 34$; marked in yellow) and from (ON > OFF) × [continuation (cont) > control reaction time] ($x = 16$, $y = 60$, $z = 30$; marked in red); (**B**) left intraparietal sulcus from (ON > OFF) × (synchronization > control reaction time) ($x = –26$, $y = –54$, $z = 42$; marked in

Continued

with Parkinson's disease failed to show the typical pattern of basal ganglia and frontal activity during motor timing that was seen in controls. Instead, during motor timing relative to the control reaction time task, neural activity in Parkinson's disease was significantly greater in the cerebellum, thalamus and midbrain/substantia nigra pars reticulata compared to the controls. Second, compared to the externally guided motor timing of the synchronization task, internally controlled motor timing during the continuation task was associated with greater activation of the dorsolateral prefrontal cortex in both groups. Third, pallidal over-activation together with under-activation of cortical regions was observed in the Parkinson's disease group when 'OFF' medication compared to 'ON' medication, interpreted as an effect of excessive inhibitory outflow from the globus pallidus to the cortex. Fourth, and concurring with the latter proposal, there was increased effective connectivity between striatal and prefrontal regions 'ON' medication compared to the dopamine depleted state, specifically in an area of the basal ganglia that showed significantly less motor timing-related activity in Parkinson's disease patients than in healthy controls. This is the first demonstration of a significant dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease.

Neural correlates of motor timing

Motor timing in healthy controls

The two motor timing tasks, when contrasted with the control reaction time task, elicited activity in areas specifically associated with motor timing while controlling for activation involved in motor preparation and execution and tone anticipation. The greater activation of the left nucleus accumbens/caudate nucleus during the motor timing task is consistent with previous functional imaging research that suggested the basal ganglia play a key role in temporal processing (e.g. Rao *et al.*, 2001; Jahanshahi *et al.*, 2006; Beudel *et al.,* 2009). In a previous PET study with healthy participants, we found activation of a midbrain focus localized in the region of the substantia nigra pars compacta when time reproduction tasks were compared with a control reaction time task (Jahanshahi *et al.*, 2006). As the control reaction time task used in both the present and our previous study controlled for the basic motor components of the timing tasks this provides convincing evidence for the role of the basal ganglia in timing *per se*.

The increased hippocampal activation is likely to reflect the memory demands of the motor timing tasks; in the synchronization task the interval is being encoded to memory and in the continuation task the interval is being retrieved. Direct comparison of the synchronization and continuation tasks suggested that hippocampal activation was more prominent during externally paced motor timing for both groups. Previous imaging (Harrington *et al.*, 2004) and animal (McEchron and Disterhoft, 1997) research support a role of the hippocampus in encoding and learning of timed intervals. The motor timing tasks also require continuous monitoring of elapsed time, which may explain the presence of bilateral activation in the angular gyrus. Activation in this region has been observed during duration discrimination (Lewis and Miall, 2003) and time reproduction (Jahanshahi *et al.*, 2006) and is usually ascribed a role in attentional processes. Additionally, the angular gyrus is implicated in action awareness, specifically in detecting mismatch between intended and actual movement (Farrer *et al.*, 2008), which is pertinent to monitoring motor timing where the interval between consecutive movements must match a temporal template. The left lateralized medial prefrontal activation may reflect the maintenance and manipulation of the temporal intervals in working memory prior to their reproduction (e.g. Ragozzino and Kesner, 2001).

Motor timing in Parkinson's disease

Most previous studies have found impaired behavioural performance on the motor timing tasks in Parkinson's disease relative to controls and an improvement with dopaminergic medication (e.g. Pastor *et al.*, 1992*b*; O'Boyle *et al.*, 1996; Harrington *et al.*, 1998; although see Ivry and Keele, 1989 and Elsinger *et al.,* 2003 for exceptions). These behavioural effects were not significant for our sample. However, we used a longer inter-stimulus interval than most previous studies, which may have served to reduce the repetitive tapping deficits in Parkinson's disease. Further, due to the constraints of PET our participants were required to tap for a longer period than in other studies. Importantly, these behavioural findings mean that the task and medication-specific blood flow effects in this study were not confounded by a significant alteration in performance of the timing tasks. Additionally, there were no relevant differences in self-reported arousal. The specific striato-frontal activation associated with motor timing in the control group was absent for patients with Parkinson's disease. This was confirmed by the Group × Task interaction, where the control group significantly activated areas including the left head of the caudate nucleus, right middle frontal gyrus (BA 8) and medial orbitofrontal cortex (BA 11) during motor timing compared to the patients with Parkinson's disease. Studies with simple motor tasks used to investigate neural activity related to bradykinesia find a similar pattern

Figure 3 Continued
yellow) and from (ON > OFF) × (continuation > control reaction time) ($x = -32$, $y = -52$, $z = 40$; marked in red); (**C**) left middle/superior temporal gyrus from (ON > OFF) × (synchronization > control reaction time) ($x = -46$, $y = 8$, $z = -34$; marked in yellow) and from (ON > OFF) × (continuation > control reaction time) ($x = -38$, $y = 4$, $z = 32$; marked in red); (**D**) left globus pallidus from (OFF > ON) × (synchronization > control reaction time) ($x = -16$, $y = 0$, $z = -2$; marked in yellow) and from (OFF > ON) × (continuation > control reaction time) ($x = -20$, $y = -4$, $z = -4$; marked in red); (**E**) left cerebellar hemisphere from (OFF > ON) × (synchronization > control reaction time) ($x = -12$, $y = -88$, $z = -38$; marked in yellow) and from (OFF > ON) × (continuation > control reaction time) ($x = -16$, $y = -86$, $z = -42$; marked in red); (**F**) right cerebellar activation ($x = 48$, $y = -80$, $z = -26$ and $x = 16$, $y = -48$, $z = -26$) from (ON > OFF) × (continuation > control reaction time). Results are displayed as statistical parametric maps in coronal and transverse projections in stereotactic space. Parameter estimates showing mean activation during the timing tasks and control reaction time task, for each medication condition, are also displayed. Significant at $P < 0.001$, uncorrected.

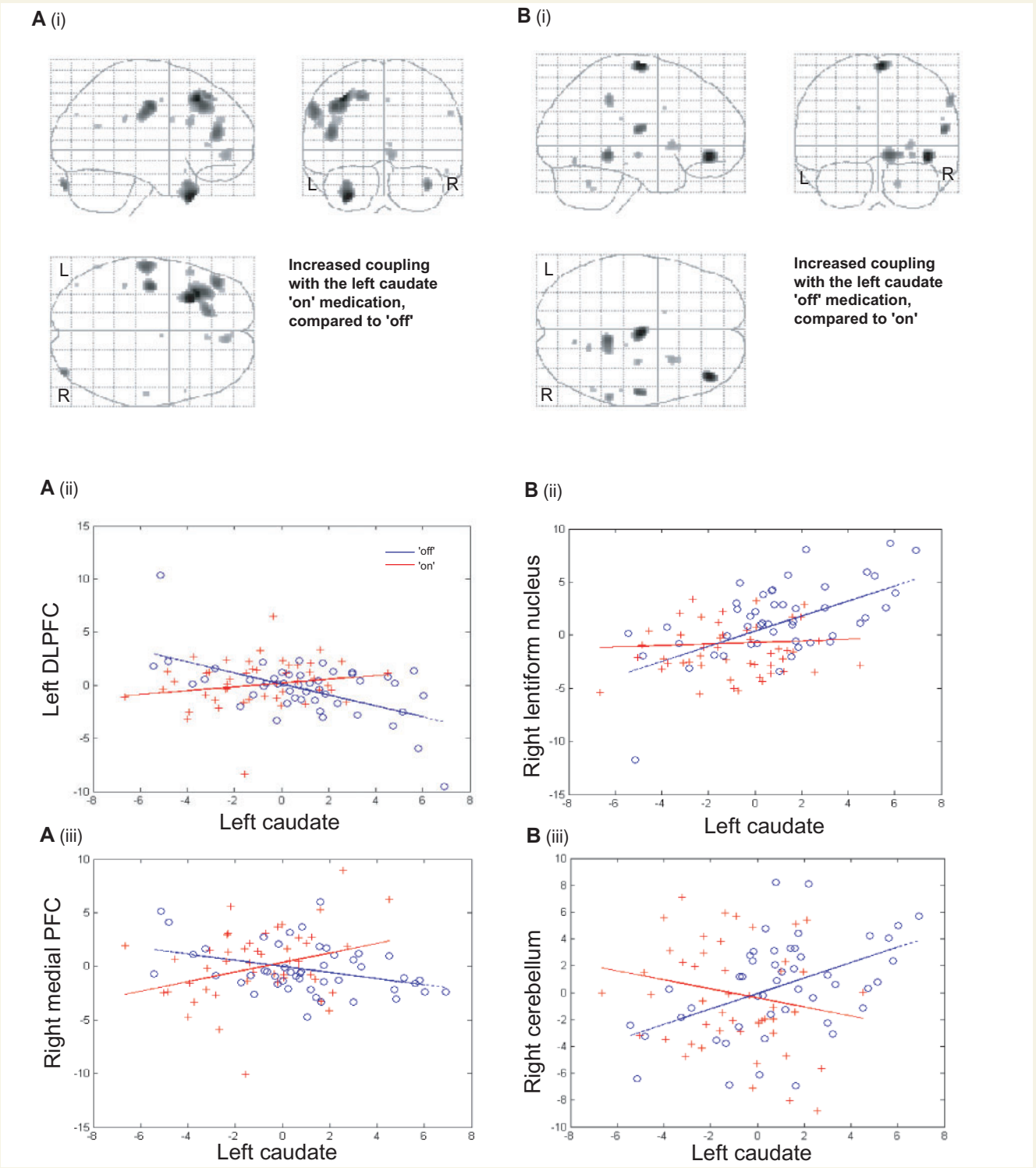

Figure 4 Changes in effective connectivity (psychophysiological interaction) for the left head of the caudate nucleus in patients with Parkinson's disease ON and OFF medication. (**Ai**) Areas showing increased coupling with the left caudate nucleus ($x = -8$, $y = 12$, $z = -4$) in the 'ON' medication condition relative to the 'OFF' medication condition. (**Aii**) Activity in the left caudate nucleus plotted against the right dorsolateral prefrontal cortex (DLPFC) (region of interest) ($x = -44$, $y = 40$, $z = 14$). (**Aiii**) Activity in the left caudate nucleus plotted against the right medial prefrontal cortex (PFC) (region of interest) ($x = 6$, $y = 48$, $z = -4$). (**Bi**) Areas showing increased coupling with the left caudate nucleus in the 'OFF' medication condition relative to the 'ON' medication condition. (**Bii**) Activity in the left caudate nucleus plotted against the right lentiform nucleus (region of interest) ($x = 26$, $y = 12$, $z = 0$). (**Biii**) Activity in the left caudate nucleus plotted against the right cerebellum (region of interest) ($x = 16$, $y = -56$, $z = -34$). Results in (**Ai**) and (**Bi**) are displayed as statistical parametric maps in sagittal, coronal and transverse projections in stereotactic space. Significant at $P < 0.001$, uncorrected. For the plotted correlations, the blue circles indicate the correlation between the two regions in the 'OFF' medication state and the red crosses indicate the correlation between the two regions in the 'ON' medication state. Regression lines have been fitted.

of striato-frontal underactivity in Parkinson's disease (e.g. Jenkins *et al.*, 1992; Playford *et al.*, 1992; Jahanshahi *et al.*, 1995; Sabatini *et al.*, 2000; Haslinger *et al.*, 2001). The Group × Task interaction showed that the bilateral cerebellar hemispheres and vermis, right thalamus/internal capsule and left midbrain were more active for patients with Parkinson's disease than controls during motor timing. While the limited spatial resolution of PET means that caution must be taken with localization of small subcortical structures, the midbrain area activated was in the region of the substantia nigra pars reticulata. The substantia nigra is rich in dopaminergic neurons. The pars compacta section of the substantia nigra is more medial and the primary site of neuronal degeneration in Parkinson's disease. The more lateral substantia nigra pars reticulata together with the globus pallidus form the main output pathways of the basal ganglia and are overactive in Parkinson's disease.

Over-activation of the cerebellum has previously been described in patients with Parkinson's disease during simple hand movements and has been interpreted as a switch to using alternative and intact motor pathways (Rascol *et al.,* 1997; Samuel *et al.,* 1997; Thobois *et al.,* 2000; Wu and Hallett, 2005; Yu *et al.,* 2007). Alternatively, it has also been proposed that neural over-activation in Parkinson's disease may be driven by diminished selectivity, i.e. an inability to suppress the activation of inappropriate circuits (e.g. Turner *et al.,* 2003). However, the cerebellum has previously been ascribed a role in temporal processing (e.g. Ivry *et al.,* 1988; Ivry and Keele, 1989; Penhune *et al.,* 1998; Penhune and Doyon, 2002) and there is little in the data to suggest relative over-activation of other brain areas such as the lateral premotor or parietal cortices in Parkinson's disease, as previously observed with performance of some motor tasks (e.g. Samuel *et al.,* 1997; Sabatini *et al.,* 2000; Thobois *et al.,* 2000). Therefore, the most parsimonious explanation for the greater cerebellar activation in the Parkinson's disease group during the performance of repetitive timed movements is a compensatory 'switch' to reliance on alternative pathways. Similar over-activation of the cerebellum during motor timing in patients with Parkinson's disease tested OFF medication has been previously observed by some (Cerasa *et al.,* 2006), whereas others noted reduced activity in the cerebellum and the sensorimotor cortex in Parkinson's disease relative to controls during motor timing (Elsinger *et al.,* 2003); although, patterns of brain activation across groups were not directly compared in the latter study.

The neural correlates of externally versus internally timed movement

Direct comparison of the synchronization and continuation tasks identified regions of activation that are specific to externally guided (synchronization) and internally generated (continuation) motor timing. For both groups, the synchronization task was associated with activation in the parieto-occipital fissure and additional parietal regions, as well as the calcarine sulcus. It has been argued that the parietal cortex maps sensory representations of a rhythm into motoric representations (Ramnani and Passingham, 2001), perhaps the principal demand of the synchronization task. Activation of the calcarine sulcus has been attributed to visual-mental imagery (e.g. Klein *et al.*, 2000) and therefore may reflect the application of learning strategies during the synchronization phase. This region was also identified for both healthy controls and patients with Parkinson's disease in the synchronization > continuation comparison of Cerasa *et al.* (2006), although this earlier study used a visual pacing stimulus. The continuation task was associated with greater activation of the right dorsolateral prefrontal cortex for both groups, this region has been implicated in 'willed' or internally generated movements (Jahanshahi *et al.*, 1995).

The Group × Task interaction explored regions differentially active for the two groups as a function of whether the task engaged internally or externally generated motor timing. The controls showed greater activation of regions of the left superior parietal gyrus, right premotor cortex, right orbitofrontal cortex, left insular and left cerebellum compared to the patients with Parkinson's disease for the continuation task compared to the synchronization task. The premotor cortex has previously been implicated in the preparation of timed movements (Ramnani and Passingham, 2001) and also in the reproduction of rhythms from memory (Halsband *et al.,* 1993). Greater activation of the insula has been observed in continuation > synchronization analysis in healthy participants (Lewis *et al.,* 2004) and is activated by passively listening to trains of clicks (Ackermann *et al.,* 2001). Thus, the insula may have a role in the perception and analysis of sequences of auditory stimuli, which were present to varying extents in both tasks. For the healthy controls, the direct comparison of the two motor timing tasks with each other and jointly with the control reaction time task did not reveal any timing-specific activation of the cerebellum. However, the Group × Task interactions indicate differential activation of the cerebellum for the two groups dependent upon type of motor timing task. This is consistent with the proposal that the cerebellum may be acting as an alternative route for motor timing in Parkinson's disease (Table 4). In addition, the cerebellum has previously been found to be activated during both synchronization and continuation motor timing in healthy controls compared to rest (Rao *et al.,* 1997), and was ascribed a role in integrating externally and internally generated stimulus events with motor output i.e. relating to the role of the cerebellum in multisensory integration. Such an interpretation is equally applicable to the cerebellar activations observed in the present study. For the patients with Parkinson's disease, performance of the continuation task was associated with greater activation of the anterior cingulate cortex than the synchronization task (Table 5), with a similar region activated in the Group × Task interaction. The anterior cingulate has been considered to play a role in error-monitoring (Falkenstein *et al.,* 1991; Gehring *et al.,* 1993), particularly in the rapid online detection of errors (Modirrousta and Fellows, 2008). The greater anterior cingulate activation in the continuation task for the Parkinson's disease group may therefore relate to the demands of performance monitoring. It has also been suggested that the anterior cingulate is relevant to the amount of effort demanded by a task (Mulert *et al.*, 2008). It is plausible that the greater anterior cingulate activation observed for the patients with Parkinson's disease during the continuation than the synchronization task may result

from these patients experiencing the internally generated timing as more effortful than the externally-paced synchronization. This fits in with the difficulty that internally generated movements pose for individuals with Parkinson's disease (e.g. Jahanshahi *et al.,* 1995).

The effect of apomorphine on patterns of brain activation during motor timing in Parkinson's disease

When given to patients with Parkinson's disease chronically treated with apomorphine or levodopa, administration of these medications does not cause global or focal changes in cerebral blood flow and apomorphine does not modify the pattern of brain activation by a pure vasodilatory action (Jenkins *et al.,* 1992). For the synchronization and continuation timing tasks, separate interaction effects revealed that apomorphine significantly increased cortical activation in regions including bilateral frontal, temporal and parietal cortices. In particular, very similar/adjacent regions of the right superior frontal gyrus (BA 9), left intraparietal sulcus and left middle/superior temporal gyrus were more activated 'ON' than 'OFF' medication for both the synchronization and continuation tasks. It can be extrapolated that these regions are involved in the shared elements of the two tasks, i.e. motor timing, when patients are in a medicated compared to non-medicated state (see Supplementary material 4 for confirmation). Despite this overall similarity, there were also some differences in the specific patterns of medication-related activation for the synchronization and continuation tasks, suggesting that the impact of medication on neural activity depends in part upon the unique demands of each motor timing task. Particularly notable is that relative to the dopamine-depleted state, the 'ON' medication condition was associated with greater activation of the calcarine sulcus only for the synchronization task, and that parietal activation was more dominant for this task. Conversely, greater activation of the left insula and right cerebellar hemisphere was present only for the continuation task, alongside a more dominant presence of prefrontal activation. The red nucleus, a region considered important in motor response initiation (e.g. Martin and Ghez, 1988), was more activated for the synchronization task when 'OFF' medication than 'ON'. Relative to the control reaction time task, for both motor timing tasks 'OFF' medication, activation was significantly greater in subcortical regions including the left cerebellar hemisphere and left globus pallidus, which is compatible with previous discussion of the role of the cerebellum as an alternative motor timing pathway. When the two timing tasks were collapsed across (Supplementary material 4), there was greater activation in the habenular nucleus (an area of the epithalamus) OFF than ON medication, which may be related to increased error monitoring during motor timing in the OFF state. A functional MRI study of error monitoring identified activation of the habenular complex in an almost identical focus to the present study ($x = -5$, $y = -25$, $z = 8$) and implicated this area in processing negative feedback (Ullsperger and von Cramon, 2003). Primate studies have shown that habenular neurons act in a fashion opposite to dopamine neurons, being excited by reward omission and inhibited by reward predicting stimuli (Matsumoto and Hikosoaka, 2007). In Parkinson's disease, it has been proposed that learning from negative feedback is impaired ON medication as the tonic increase of dopamine with levodopa overshadows phasic changes that are necessary for learning (Frank *et al.,* 2004, 2007). Little is known about the habenular complex in Parkinson's disease, and further investigation of the potential role of this structure in learning from negative feedback ON and OFF medication in Parkinson's disease would be of interest. The functional significance of the medication-related rCBF changes is reflected in the significant improvement of UPDRS scores 'ON' versus 'OFF' medication. In Parkinson's disease, dopaminergic medication partially 'normalizes' the dysfunctional pattern of neural activity during simple motor tasks (Jenkins *et al.,* 1992; Rascol *et al.*, 1997; Haslinger *et al.*, 2001). Our results are consistent with a relative 'normalization' of the pattern of timing-related activation during the 'ON' medication state for both motor timing tasks, as this was associated with increased frontal activation as well as a reduction of the excessive activation of the pallidum and cerebellum observed 'OFF' medication.

While levodopa medication improves motor function in Parkinson's disease, it can impair some aspects of cognitive functioning (e.g. Gotham *et al.,* 1988; Swainson *et al.,* 2000; Cools *et al.,* 2001). Comparing the effects of dopaminergic medication on patterns of brain activation in Parkinson's disease during motor timing (present study), motor (Jenkins *et al.,* 1992; Rascol *et al.,* 1997; Haslinger *et al.,* 2001; Peters *et al.,* 2003) and cognitive (Cools *et al.,* 2002; Mattay *et al.,* 2002) tasks suggests task-specific and/or circuit-specific effects of dopaminergic medication, a proposal that requires direct verification. Parallels can be drawn with the differential effects of deep brain stimulation of the subthalamic nucleus on motor and cognitive function. Deep brain stimulation of the subthalamic nucleus has beneficial motor effects in Parkinson's disease, both in terms of improving motor symptoms and increasing movement-related neural activation (e.g. Limousin *et al.,* 1997), whilst in contrast impairing performance on cognitive tasks requiring response selection under competition/conflict, which is coupled with decreased activation in cortical regions such as the prefrontal cortex and anterior cingulate and reduced pallidal-frontal coupling (Schroeder *et al.,* 2002; Thobois *et al.,* 2007). Deep brain stimulation of the subthalamic nucleus improves time reproduction in Parkinson's disease (Koch *et al.,* 2004). In future studies, comparing and contrasting the modulatory influence of dopaminergic medication and deep brain stimulation on patterns of brain activation and fronto-striatal connectivity during predominantly 'cognitive' versus 'motor' timing tasks in patients with Parkinson's disease would be of interest. This would also further attempts to fractionate temporal processing into components that may engage differing neural networks (Lewis and Miall, 2003; Jones *et al.,* 2008).

The striatum and the frontal cortex are intimately connected (Alexander *et al.*, 1986). On the basis of the pathophysiological model of bradykinesia proposed by De Long (1990) and Albin *et al.* (1989), the net result of dopamine depletion in the substantia nigra pars compacta and the imbalance of activity in the direct and indirect pathways is that there is excessive inhibitory outflow from the globus pallidus to the thalamus, which is in turn

associated with underactivation of key areas of the frontal cortex involved in movement preparation, initiation and execution. In the present study, the increased activation of the globus pallidus in the 'OFF' state during motor timing (Medication × synchronization/continuation interactions) most likely reflects the excessive inhibitory output from the basal ganglia in Parkinson's disease. Conversely, cortical activation including prefrontal areas was significantly increased in the 'ON' compared to the 'OFF' medication state during motor timing.

We examined effective connectivity in Parkinson's disease ON and OFF medication, to explore the influence that different neural systems have on one another as a function of dopaminergic efficacy. Using a region of the caudate that showed greater timing-related activation in the control than Parkinson's disease group, and thus seeking to demonstrate the modulating effect of dopamine on a region of the basal ganglia that did not function normally during motor timing (across both tasks) in Parkinson's disease, we found a decrease in task-related coupling between the caudate and the prefrontal cortex in the 'OFF' medication state alongside increased coupling with the lentiform nucleus and cerebellum. This supports the proposal that 'OFF' medication excessive inhibitory output from the basal ganglia in Parkinson's disease limits the activation of the prefrontal cortex (i.e. reduced striato-frontal connectivity), with compensatory activity seen in alternative pathways. When patients were in the 'ON' state, increased caudate-prefrontal coupling was established, including with a region of medial prefrontal cortex that was similar to that activated by motor timing in the control group. Although PPIs do not establish the direction of the influence between the seed area and other brain regions, the proposed changes in patterns of connectivity are based on well-documented anatomical and physiological connections of these striato-frontal circuits. Thus, the effective connectivity analysis demonstrates how dopaminergic deficiency in Parkinson's disease is associated with pathological coupling of an area of the caudate that is critical to motor timing in healthy individuals. The increase in striatal-supplementary motor area connectivity OFF medication compared to ON medication is harder to interpret, particularly given the lack of task-related activity in the supplementary motor area in patients with Parkinson's disease or controls in this study. Some previous studies have reported increased supplementary motor area activation for patients with Parkinson's disease tested OFF medication compared to healthy controls during simple motor tasks (e.g. paced serial finger movements: Rowe *et al.*, 2002; synchronized finger tapping: Catalan *et al.*, 1999). Indeed, Rowe *et al.* (2002) described increased supplementary motor area activation in Parkinson's disease OFF medication in an almost identical focus ($x = 2$, $y = -12$, $z = 72$). Functional MRI and computational modelling data by Forstmann *et al.* (2008) suggest that the striatum and the pre-supplementary motor area are involved in decision-making under time pressure and that the activation of these areas may be adjusted in relation to the person's level of response caution. It is possible that the increased connectivity of the caudate with the lentiform nucleus and the supplementary motor area OFF medication in our study represent such adjustments in response caution OFF compared to ON medication during the time pressurized temporal processing tasks. This increased striatal-supplementary motor area connectivity during motor timing OFF medication warrants further investigation.

Summary

For healthy participants, motor timing was associated with significant striato-frontal activation. This motor timing related striato-frontal activation was absent in Parkinson's disease; instead, the patients showed significant activation of the cerebellum, possibly reflecting reliance on compensatory neural circuits. When 'OFF' medication, patients with Parkinson's disease had significantly greater activation in the pallidum than 'ON' medication, whereas cortical activation was greater 'ON' medication. Analysis of effective connectivity established that caudate-prefrontal coupling increased 'ON' medication, consistent with dopamine replacement increasing striatal-frontal connectivity during motor timing in Parkinson's disease.

Acknowledgements

We would like to thank three anonymous reviewers for their helpful suggestions.

Funding

Brain Research Trust and the Centre for Consciousness Studies, University of Arizona; MRC Ph.D. studentship awarded to C.J.

Supplementary material

Supplementary material is available at *Brain* online.

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