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Neural correlates of bimanual anti-phase and in-phase movements in Parkinson's disease

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Patients with Parkinson's disease have great difficulty in performing bimanual movements; this problem is more obvious when they perform bimanual anti-phase movements. The underlying mechanism of this problem remains unclear. In the current study, we used functional magnetic resonance imaging to study the bimanual coordination associated changes of brain activity and inter-regional interactions in Parkinson's disease. Subjects were asked to perform right-handed, bimanual in-phase and bimanual anti-phase movements. After practice, normal subjects performed all tasks correctly. Patients with Parkinson's disease performed in-phase movements correctly. However, some patients still made infrequent errors during anti-phase movements; they tended to revert to in-phase movement. Functional magnetic resonance imaging results showed that the supplementary motor area was more activated during anti-phase movement than in-phase movement in controls, but not in patients. In performing anti-phase movements, patients with Parkinson's disease showed less activity in the basal ganglia and supplementary motor area, and had more activation in the primary motor cortex, premotor cortex, inferior frontal gyrus, precuneus and cerebellum compared with normal subjects. The basal ganglia and dorsolateral prefrontal cortex were less connected with the supplementary motor area, whereas the primary motor cortex, parietal cortex, precuneus and cerebellum were more strongly connected with the supplementary motor area in patients with Parkinson's disease than in controls. Our findings suggest that dysfunction of the supplementary motor area and basal ganglia, abnormal interactions of brain networks and disrupted attentional networks are probably important reasons contributing to the difficulty of the patients in performing bimanual anti-phase movements. The patients require more brain activity and stronger connectivity in some brain regions to compensate for dysfunction of the supplementary motor area and basal ganglia in order to perform bimanual movements correctly.

Keywords: Parkinson's disease; bimanual movements; fMRI; brain activity; effective connectivity

Abbreviations: fMRI = functional magnetic resonance imaging; FWE = family-wise error; PPI = psychophysiological interaction; SM1 = primary sensorimotor cortex; SMA = supplementary motor area; UPDRS = Unified Parkinson's Disease Rating Scale

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Introduction

Bimanual movements are important to daily life and require temporal and spatial coordination. Patients with Parkinson's disease commonly show impaired bimanual coordination. This problem is more obvious when they perform bimanual anti-phase movements than in-phase movements (Johnson *et al.*, 1998; Serrien *et al.*, 2000; van den Berg *et al.*, 2000; Geuze, 2001; Almeida *et al.*, 2002; Ponsen *et al.*, 2006). Anti-phase bimanual movements, for example at the wrist, occur when both hands perform the same movement, but with a phase shift of 180° between the two hands (i.e. one hand flexes while the other extends). For in-phase bimanual wrist movements, the two hands move in and out together, requiring simultaneous flexion and extension at both wrists, without phase shift. Both in-phase and anti-phase movements require synchronization between the two hands, but the anti-phase movements additionally need contralateral movement suppression (of a mirrored movement) and the independence of the two movements. Transcranial magnetic stimulation during a bimanual in-phase task could simultaneously reset the rhythmic movements of both hands. In contrast, the transcranial magnetic stimulation has little effect on the bimanual anti-phase task, indicating that control of rhythm differs in the anti- and in-phase tasks (Chen *et al.*, 2005). In-phase rhythms are more stable than anti-phase rhythms (Tuller and Kelso, 1989) and are easier to perform than anti-phase movements.

It has been shown that patients with Parkinson's disease can perform bimanual in-phase movements correctly, but perform anti-phase movements with more error and variability (Johnson *et al.*, 1998; Almeida *et al.*, 2002). Patients have a tendency to revert anti- to in-phase movements (Johnson *et al.*, 1998). Additionally, the performance of anti-phase movements is not improved with the presence of external pacing cues (Johnson *et al.*, 1998; Almeida *et al.*, 2002). The difficulty in performing bimanual movements, especially in performing anti-phase movements, can be detected even in early Parkinson's disease (Ponsen *et al.*, 2006). Therefore, understanding the neural mechanism of this problem is not only useful for our understanding about the pathophysiology of movement in Parkinson's disease, but also may help to develop a sensitive clinical procedure to assess and quantify the illness (Johnson *et al.*, 1998; Ponsen *et al.*, 2006).

The aim of the current study was to use functional magnetic resonance imaging (fMRI) to explore brain activations, as well as interactions within brain networks during performance of bimanual movements in patients with Parkinson's disease. Previous studies have shown that the control of bimanual coordination cannot be assigned to a single area; rather, it seems to involve a distributed network in which interactive processes take place between many neural assemblies to ensure efferent organization and sensory integration (Debaere *et al.*, 2001; Swinnen, 2002). Thus, investigations about interactions among brain regions may play a more important role than simply exploring activity in understanding bimanual movement-related brain functional changes. The methods used to explore inter-regional interactions in a given task are analysis of functional connectivity (Friston *et al.*, 1993*a*) or effective connectivity (Friston *et al.*, 1993*b*). These methods are increasingly being used to investigate Parkinson's disease induced modifications of brain networks (Rowe *et al.*, 2002; Ma and Wang, 2008; Helmich *et al.*, 2009; Palmer *et al.*, 2009; van Eimeren *et al.*, 2009; Wu *et al.*, 2010). In healthy subjects, the supplementary motor area (SMA) has been suggested to be critical for bimanual coordination (Sadato *et al.*, 1997*b*; Stephan *et al.*, 1999; Toyokura *et al.*, 1999; Immisch *et al.*, 2001). In addition, impaired activity in the SMA is a common finding in Parkinson's disease (Playford *et al.*, 1992; Jahanshahi *et al.*, 1995; Rascol *et al.*, 1997; Haslinger *et al.*, 2001; Buhmann *et al.*, 2003). Thus, we investigated the effective connectivity in the SMA to explore Parkinson's disease-related changes in interactions of neural networks in bimanual movements.

Methods

Subjects

We studied 15 patients with Parkinson's disease, aged 44–71 years (mean 59.73 years) and included 10 males and 5 females. The diagnosis of Parkinson's disease was based on medical history, physical and neurological examinations, response to L-dopa and laboratory tests and MRI scans to exclude other diseases. Patients were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang and Fahn, 1989), the Hoehn and Yahr disability scale (Hoehn and Yahr, 1967) and Mini-Mental State Exam while off their medications. The Mini-Mental State Exam was ≥27 in all subjects and there was no difference between the patients and controls. The clinical data are shown in Table 1. We also investigated 15 age- and sex-matched normal subjects (aged 44–73 years, mean 60.30) as controls. All subjects were right handed as measured by the Edinburgh Inventory (Oldfield, 1971). The experiments were performed according to the Declaration of Helsinki and were approved by the Institutional Review Board. All subjects gave their written informed consent for the study.

Experimental design

Subjects were asked to perform three types of finger movements: (i) extension and flexion of the right index finger (unimanual right-hand movement); (ii) extension and flexion of both index fingers simultaneously (bimanual in-phase movement); and (iii) simultaneous extension of one index finger and flexion of the other index finger, and vice versa, to produce movement in the same spatial direction (bimanual anti-phase movement). All movements were self-paced and were executed at an interval of 2 s. No external cue was given to help the subjects move at the specified rate. Movement amplitude was determined as the maximal possible for both extension and

Table 1 Clinical details of patients with Parkinson's disease (mean ± SD)

Age (years)	59.73 ± 8.27
Sex	5 female, 10 male
Disease duration (years)	3.47 ± 1.60
UPDRS motor score (off medication)	20.67 ± 3.48
Hoehn and Yahr staging (off medication)	1.70 ± 0.37
L-dopa dose (mg/day)	333.33 ± 48.80

flexion. In the flexion direction, it was limited by a response device fixed to their hand. Before the fMRI, all subjects practiced until they could perform all the tasks properly and move at the required rate.

Functional MRI procedure

Patients were scanned only after their medication had been withdrawn for at least 12 h. Imaging was performed on a 1.5 T Siemens Sonata scanner. High-resolution axial T_1- and T_2-weighted images were obtained in every subject to exclude other neurological disorders. We used an echo planar imaging gradient sequence sensitive enough to acquire functional images (repetition time = 2000 ms, echo time = 60 ms, flip angle = 90°, field of view = 24 × 24 cm, matrix = 64 × 64). Twenty axial slices were collected with 5 mm thickness and a 2 mm gap. We had three fMRI sessions and the three movement tasks were performed randomly once during each scan. Two conditions were contained in each scanning session and were defined as the 'rest' and 'active' conditions, respectively. Each condition lasted 20 s and was repeated six times in a session. During the rest condition, subjects were instructed to keep their eyes closed and to remain motionless. The active condition in each session contained one motor task. Each subject's performance during fMRI for each task was monitored by an investigator and recorded by video. If there were any errors of finger movement, we asked the subject to repeat that session until he/she could perform it correctly. Additionally, two response devices were fixed to each of their hands to record the rate of movements during fMRI scanning.

Data analysis

Behavioural data analysis

Each subject's performance for each task was recorded and compared between the patients and normal subjects (two-sample *t*-test, $P < 0.05$). Additionally, the frequencies of the movements were compared between the groups.

Brain activity analysis

Functional MRI data were analysed with Statistical Parametric Mapping 2 software (Wellcome Institute of Cognitive Neurology, London, UK). They were slice-time corrected and aligned to the first image of each session for motion correction. After spatial normalization, all images were resampled into voxels that were 2 × 2 × 2 mm in size and smoothed with a Gaussian filter of 6 mm full-width at half maximum. In the first-level, data were analysed for each subject separately on a voxel-by-voxel basis using the general linear model approach for the time series. We defined a model using a fixed effect boxcar design convolved with a haemodynamic response function to analysis of task-dependent activation. A contrast representing the effect of the active condition compared with the rest condition was defined and contrast images were calculated individually for each condition. These contrast images were used in the second-level for random effects analyses. For the within group analysis, a one-sample *t*-test model was used to identify the brain activity for each task [$P < 0.05$, family-wise error (FWE) corrected]. Then, a paired *t*-test was used to compare the results between anti-phase and right-hand movement, in-phase and right-hand movement, as well as between anti-phase and in-phase movement ($P < 0.05$, FWE corrected). For the between-group comparisons, a two-sample *t*-test ($P < 0.05$, FWE corrected) was used to explore the difference between patients and normal subjects in performing bimanual movements.

Finally, in order to explore whether the changes of brain activity relate to disease severity, a correlation analysis of activations during bimanual movements versus the UPDRS motor score was performed in patients.

Effective connectivity analysis

Effective connectivity was assessed using the method of psychophysiological interaction (PPI) (Friston *et al.*, 1997). PPI is defined as the change in contribution of one brain area to another due to a change in experimental condition or psychological context (Friston *et al.*, 1997). It aims to explain regionally specific responses in terms of the interaction between the psychological variable and the activity in a specific index area. The analysis was constructed to test for differences in the regression slope of the activity in all remaining brain areas on the activity in the index area depending on the movement type.

Given the critical role of the SMA in bimanual coordination and defective function of this region in Parkinson's disease, we chose this region as the index area for PPI analysis. The SMA contains two separate areas: the SMA-proper in the caudal portion and the pre-SMA in the rostral portion (Tanji and Hoshi, 2001). From previous reports, the region showing stronger activation during bimanual anti-phase than bimanual in-phase movements is the SMA-proper (Sadato *et al.*, 1997*b*; Toyokura *et al.*, 1999; 2002; Immisch *et al.*, 2001). A study compared the activation of pre-SMA and SMA-proper during unimanual and bimanual movements and found that the SMA-proper was more activated during bimanual movements than unimanual movements, whereas the pre-SMA was inconsistently activated (Toyokura *et al.*, 2002). Thus, the index volume in the current study was defined as centred on the voxel that showed the maximum magnitude of activation within the SMA-proper with a radius of 5 mm individually for each bimanual movement. The PPI term (referred to as 'PPI regressor') was computed as the element-by-element product of the deconvolved extracted time series of the SMA-proper and a vector coding for the main effect of task (Gitelman *et al.*, 2003; Stephan *et al.*, 2003; Garraux *et al.*, 2005; Wu *et al.*, 2010). For each subject, the PPI regressor, the task regressor (representing mode of bimanual movements) and the extracted time series were entered in a first-level model of effective connectivity in which the PPI regressor was orthogonalized with regard to the main effect of the task and the regional time series. Brain areas receiving context-dependent influences from the SMA-proper were determined by testing for positive slopes of the PPI regressor. Contrast images from the first-level PPI analysis for each bimanual task in each subject were entered into a second-level, random-effect model. A one-sample *t*-test was used to identify the connectivity for each bimanual task for each group ($P < 0.05$, FWE corrected). A paired *t*-test was used to compare the results between anti- and in-phase movement in each group ($P < 0.05$, FWE corrected). Then, a two-sample *t*-test model was used to explore the difference between patients and controls in performing each bimanual task ($P < 0.05$, FWE corrected).

Results

Task performance

All subjects had no obvious difficulty in performing unimanual and in-phase movements and only needed brief practice to perform the tasks without error. Both groups had more difficulty during the practice of anti-phase movements. Although the patients spent

significantly more time than normal subjects in practice (mean 21.3 ± 5.2 min versus 10.6 ± 3.8 min), in the end all of them could perform the anti-phase task correctly. During fMRI scanning, the normal subjects performed all tasks without any error. All patients performed unimanual and in-phase movements correctly. In contrast, while performing anti-phase movement, although there was no formal significant difference of performance between the groups, four patients inverted a few moves to in-phase movements (1.7 ± 3.3% errors, all in anti-phase movements), but recognized and corrected the errors by themselves. We asked these four patients to perform the anti-phase movement again and all of them performed the task without any error during the second session. We used the repeat performance for fMRI data analysis.

There was no between- or within-group difference for the rate of performance of motor tasks [repeated measures analysis of variance (ANOVA), $P > 0.05$]. In patients, the rates of movements were 0.56 ± 0.09 Hz for right-hand movement, 0.52 ± 0.11 Hz for in-phase movement and 0.52 ± 0.08 Hz for anti-phase movement. In normal subjects, the rates were 0.55 ± 0.06 Hz, 0.54 ± 0.03 Hz and 0.52 ± 0.06 Hz, respectively.

Brain activity

Within-group analysis

During performance of right-hand movements, normal subjects activated the left primary sensorimotor cortex (SM1), right premotor cortex, SMA-proper, right dorsolateral prefrontal cortex, right inferior frontal gyrus, bilateral insula, bilateral basal ganglia and bilateral cerebellum (Fig. 1A, left column; one-sample *t*-test, $P < 0.05$, FWE corrected). With a more liberal threshold ($P < 0.05$, false discovery rate corrected), the left premotor cortex was also activated. While performing both bimanual in- and anti-phase movements, the bilateral SM1, bilateral premotor cortex, right dorsolateral prefrontal cortex, left inferior frontal gyrus, SMA-proper, cingulate motor area, bilateral inferior and superior parietal lobule, precuneus, bilateral superior temporal gyrus, bilateral thalamus, bilateral basal ganglia and bilateral cerebellum were activated (Fig. 1B and C, left column; one-sample *t*-test, $P < 0.05$, FWE corrected).

During performance of right-hand movements, patients with Parkinson's disease activated the left SM1, left premotor cortex,

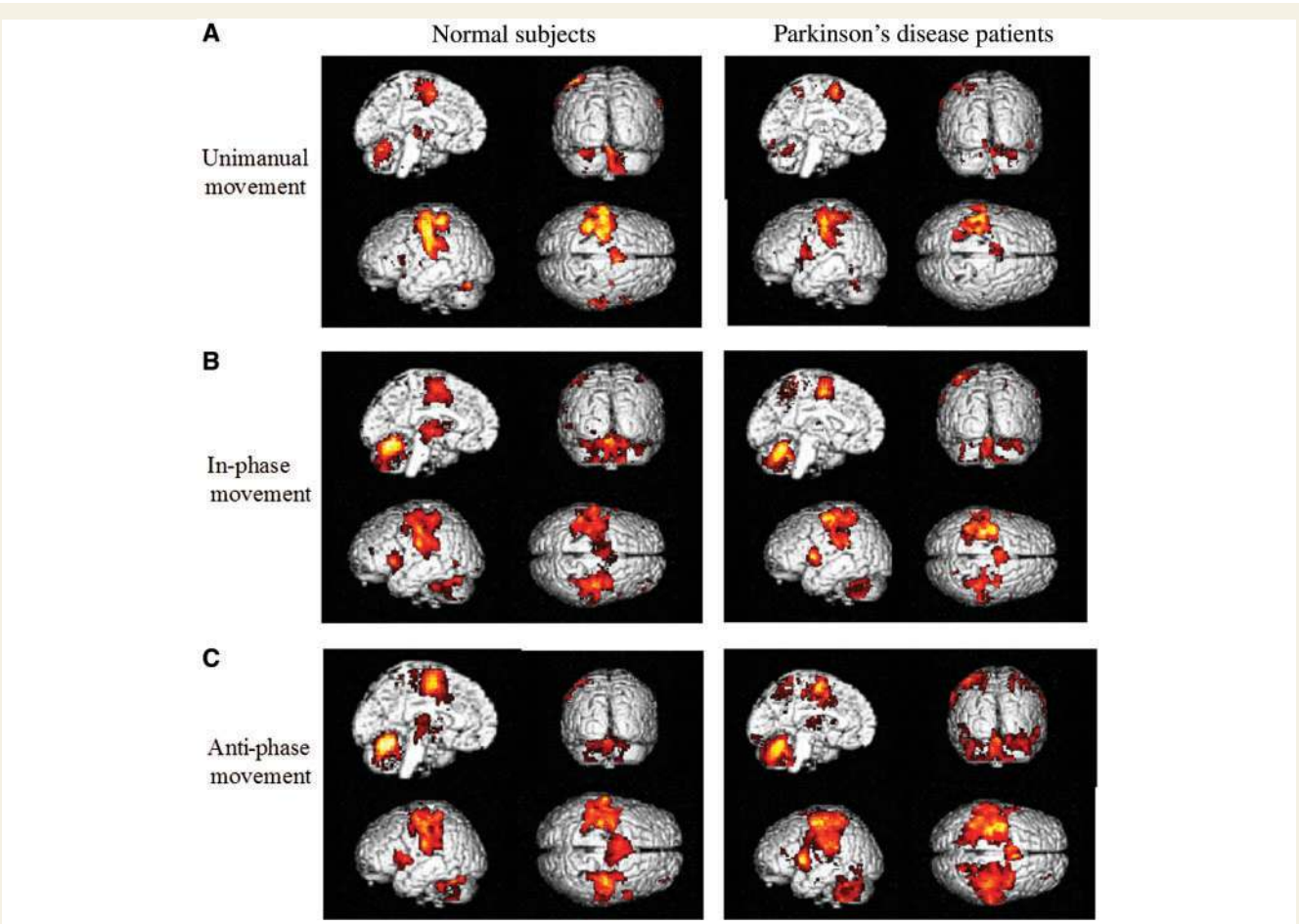

Figure 1 Brain regions activated during performing motor tasks in normal control group (left column), and in patients with Parkinson's disease group (right column). Results were thresholded at $P < 0.05$ (FWE corrected). (**A**) Brain areas activated during performing right-hand movements. (**B**) Brain areas activated during performing bimanual in-phase movements. (**C**) Brain areas activated during performing bimanual anti-phase movements.

SMA-proper, left inferior frontal gyrus, bilateral insula, left putamen and bilateral cerebellum (Fig. 1A, right column; one-sample *t*-test, $P<0.05$, corrected). While performing both bimanual in- and anti-phase movements, the bilateral SM1, bilateral premotor cortex, right dorsolateral prefrontal cortex, SMA-proper, cingulate motor area, bilateral inferior and superior parietal lobule, precuneus, bilateral superior temporal gyrus, left thalamus, bilateral basal ganglia and bilateral cerebellum were activated (Fig. 1B and C, left column; one-sample *t*-test, $P<0.05$, FWE corrected).

In patients with Parkinson's disease performing bimanual anti- or in-phase movements, there was more activation in the right SM1, left inferior frontal gyrus, right premotor cortex, bilateral superior parietal lobule, SMA-proper, cingulate motor area, precuneus and left cerebellum compared to right-hand movement alone. In normal subjects, in addition to these regions, the right dorsolateral prefrontal cortex, bilateral thalamus, right putamen and right globus pallidus were more activated in performing bimanual anti- or in-phase movements compared to right-hand movements (Fig. 2A; paired *t*-test, $P<0.05$, FWE corrected). In controls, the SMA-proper, bilateral premotor cortex, left inferior frontal gyrus, right post-central gyrus, left inferior parietal lobule and bilateral cerebellum were more activated for anti-phase movements than for in-phase movements. In patients, performing anti-phase movements utilized more activation in the bilateral inferior frontal gyrus, left middle frontal gyrus, bilateral premotor cortex, right precentral gyrus, bilateral post-central gyrus, left inferior temporal gyrus and bilateral cerebellum than in performing in-phase movements (Table 2 and Fig. 2B; paired *t*-test, $P<0.05$, FWE corrected).

Between-group comparisons

During the performance of in-phase movements, patients with Parkinson's diseasehad greater activity in the right SM1, left premotor cortex, bilateral post-central gyrus, left superior parietal lobule, right precuneus and bilateral cerebellum, and had less activity in the SMA-proper, bilateral thalamus, left putamen and right globus pallidus compared with normal subjects (Table 3; two sample *t*-test, $P<0.05$, FWE corrected).

During the performance of anti-phase movements, patients had more activation in the left SM1, left premotor cortex, right inferior frontal gyrus, bilateral precentral gyrus, bilateral postcentral gyrus, left superior parietal lobule, left inferior parietal lobule, bilateral paracentral lobule, bilateral precuneus and bilateral cerebellum, and less activity in the SMA-proper, bilateral thalamus and right globus pallidus compared with normal subjects (Fig. 3 and Table 4; two sample *t*-test, $P<0.05$, FWE corrected). With a more liberal threshold ($P<0.001$, uncorrected), we also found that the left SM1 was more activated during in-phase movements, whereas the right SM1 was more activated during anti-phase movements in patients compared with normal controls.

Correlation analysis

A correlation analysis found that during in-phase movement, brain activations in the left putamen and SMA-proper were negatively correlated with the UPDRS motor score, whereas the activations in the right inferior frontal gyrus, right inferior parietal lobule, bilateral precuneus and bilateral cerebellum were positively correlated with the UPDRS motor score ($P<0.05$, FWE corrected).

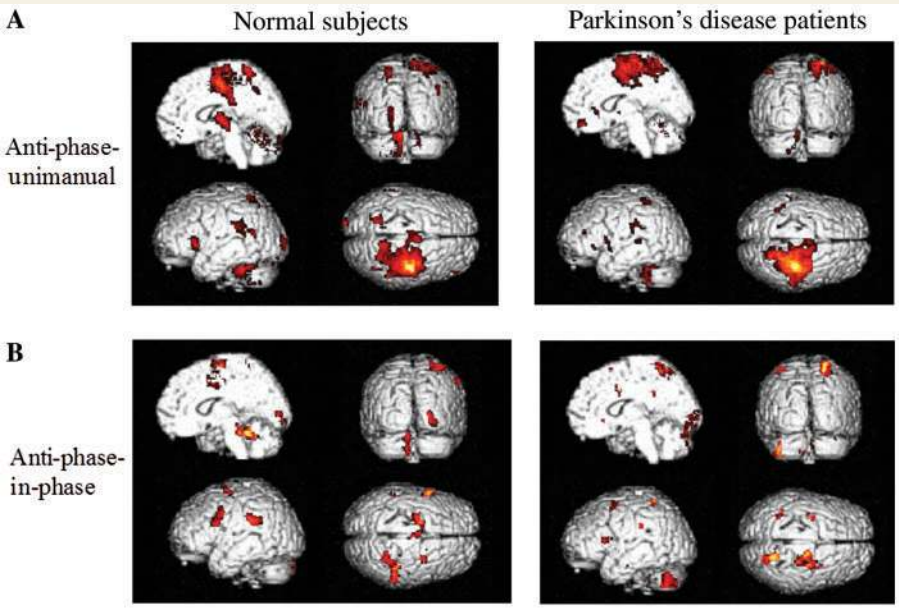

Figure 2 (**A**) Brain areas more activated for bimanual anti-phase movements than for right-hand movements in normal control group (left column) and in patients with Parkinson's disease group (right column). (**B**) Brain areas more activated for bimanual anti-phase movements than for bimanual in-phase movements in normal control group (left column) and in patients with Parkinson's disease (right column). Results were thresholded at $P<0.05$ (FWE corrected).

Table 2 Brain areas more activated in performing anti-phase movements than in performing in-phase movements in normal subjects and patients with Parkinson's disease

Brain region	Coordinates			*t*-value	Cluster size
	x	*y*	*z*		
Normal subjects					
Right cerebellum, anterior lobe, culmen	10	−46	−16	10.28	698
Left inferior parietal lobule	−50	−30	31	9.62	231
Left inferior frontal gyrus	−58	13	23	9.35	194
Left premotor cortex	−16	−5	54	9.33	119
SMA-proper	0	−2	64	9.32	317
Left cerebellum, posterior lobe, uvula	−6	−81	−33	9.05	202
Right post-central gyrus	36	−36	64	8.71	347
Right premotor cortex	24	−6	42	8.69	303
Parkinson's disease patients					
Right inferior frontal gyrus	20	27	−3	10.09	161
Left middle frontal gyrus	−34	36	17	9.40	203
Left inferior frontal gyrus	−36	13	−14	9.11	103
Left cerebellum, posterior lobe, tuber	−36	−66	−30	9.06	200
Right post-central gyrus	26	−49	67	8.99	361
Left post-central gyrus	−24	−37	68	8.59	102
Left premotor cortex	−12	−2	65	8.26	206
Right cerebellum, posterior lobe, declive	48	−51	−18	8.17	196
Right premotor cortex	24	−2	58	8.15	216
Right precentral gyrus	51	12	5	8.10	164

List of the brain regions showing significantly more activity in performing anti-phase movements than in performing in-phase movements in each group (paired *t*-test, $P<0.05$, corrected). The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux (1988).

Table 3 Differences of brain activity between patients with Parkinson's disease and normal subjects in performing in-phase movements

Brain region	Coordinates			*t*-value	Cluster size
	x	*y*	*z*		
Normal–Parkinson's disease					
Left thalamus	−2	−8	−3	9.17	182
SMA-proper	2	−8	62	9.09	84
Left putamen	−20	−2	17	8.71	59
Right thalamus	18	−16	−2	8.37	87
Right globus pallidus	16	−8	−4	8.09	57
Parkinson's disease–normal					
Left post-central gyrus	−42	−22	32	10.29	511
Left superior parietal lobule	−28	−50	56	9.07	221
Right cerebellum, posterior lobe, tonsil	30	−42	−32	8.69	40
Right precuneus	24	−48	48	8.64	65
Right post-central gyrus	53	−21	53	8.41	24
Right SM1	14	−26	66	8.25	54
Right cerebellum, posterior lobe, tonsil	16	−54	−34	8.21	31
Left premotor cortex	−18	−9	54	8.21	34
Right cerebellum, anterior lobe, culmen	2	−36	−23	8.10	22
Left cerebellum, posterior lobe, tonsil	−36	−50	−38	8.06	33

List of the brain regions showing significantly more activity in normal subjects than in patients with Parkinson's disease (Normal–Parkinson's disease), or more activity in patients with Parkinson's disease than in normal subjects (Parkinson's disease–Normal), in performing in-phase movements (two sample *t*-test, $P<0.05$, corrected). The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux (1988).

A correlation analysis on anti-phase movement found that brain activations in the bilateral putamen and SMA-proper were negatively correlated with the UPDRS motor score, whereas the activity in the right inferior frontal gyrus, bilateral premotor cortex, bilateral inferior parietal lobule, bilateral precuneus and bilateral cerebellum was positively correlated the UPDRS motor score ($P<0.05$, FWE corrected). In this study, negative correlation means that as the UPDRS motor score increased, the brain

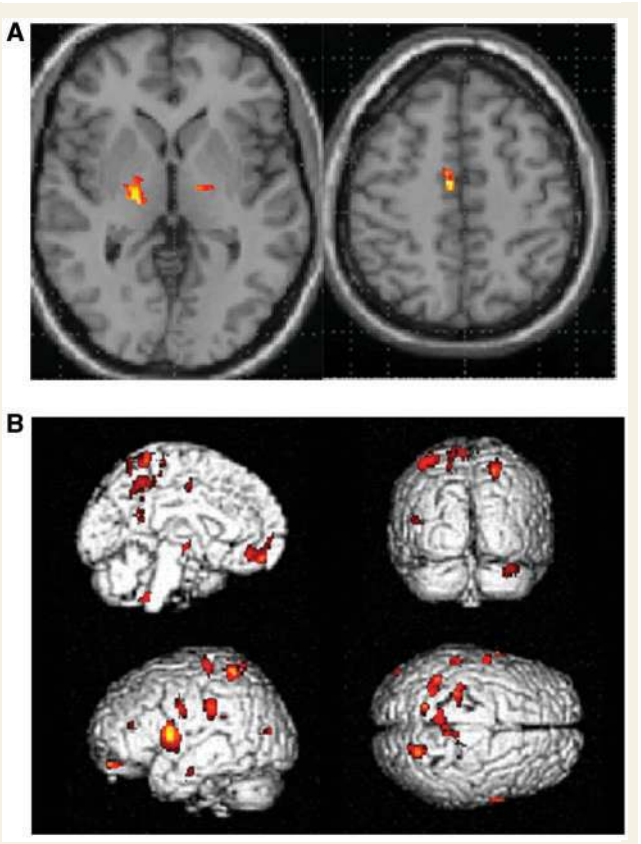

Figure 3 Brain areas more activated in normal subjects than in patients with Parkinson's disease (**A**) and more activated in patients with Parkinson's disease than in normal subjects during performing anti-phase movements (**B**). Results were thresholded at $P<0.05$ (FWE corrected).

activations are weaker, and positive correlation means that as the UPDRS motor score increased, the brain activations are stronger.

Effective connectivity analysis

Within-group analysis

PPI analysis found that in normal subjects during in-phase movement, the SMA-proper had significant connections with the bilateral SM1, right premotor cortex, right insula, right middle frontal gyrus, right globus pallidus, right putamen, right subthalamic nucleus, right substania nigra, left parahippocampal gyrus and bilateral cerebellum (Fig. 4A, left column; one-sample *t*-test, $P<0.05$, FWE corrected). In performing anti-phase movements, normal subjects had the bilateral SM1, SMA-proper, pre-SMA, bilateral premotor cortex, left dorsolateral prefrontal cortex, left cingulate motor area, left temporal lobe, left precuneus, left insula, right thalamus, left putamen, right globus pallidus and bilateral cerebellum effectively connected with the SMA-proper (Fig. 4A, right column; one-sample *t*-test, $P<0.05$, FWE corrected).

In patients with Parkinson's disease, the SMA-proper was connected with the bilateral SM1, right post-central gyrus, left inferior parietal lobule, right angular gyrus, left precuneus, right globus pallidus, right thalamus and bilateral cerebellum during performance of in-phase movements (Fig. 4B, left column; one-sample *t*-test, $P<0.05$, FWE corrected). In performing anti-phase movements, patients had the bilateral SM1, right postcentral gyrus, SMA-proper, right premotor cortex, right insula, bilateral superior parietal lobule, bilateral inferior parietal lobule, left inferior temporal gyrus, right globus pallidus, right putamen, right thalamus and bilateral cerebellum connected with the SMA-proper (Fig. 4B, right column; one-sample *t*-test, $P<0.05$, FWE corrected).

In normal subjects, the SMA-proper was more connected with the left SM1, right premotor cortex, left dorsolateral prefrontal cortex, left cingulate motor area, left precuneus, right limbic lobe, left putamen and bilateral cerebellum during anti-phase movement than in-phase movement (Table 5 and Fig. 5A; paired *t*-test, $P<0.05$, FWE corrected). The SMA-proper was more connected with the right SM1 ($x=30$, $y=-20$, $z=64$, cluster size 56) in performing in-phase movements than in performing anti-phase movements (paired *t*-test, $P<0.05$, FWE corrected).

In patients, the SMA-proper was more connected with the left SM1, right precentral gyrus, right premotor cortex, right post-central gyrus, bilateral inferior parietal lobule, left paracentral lobule and right precuneus during anti-phase movement than in-phase movement (Table 5 and Fig. 5B; paired *t*-test, $P<0.05$, FWE corrected). The SMA-proper was more connected with the right SM1 ($x=32$, $y=-20$, $z=70$, cluster size 87) in performing in-phase movements than in performing anti-phase movements (paired *t*-test, $P<0.05$, FWE corrected).

Between-group comparisons

During the performance of in-phase movements, patients with Parkinson's disease had more connectivity to the left SM1, left post-central gyrus, left precuneus and bilateral cerebellum with the SMA-proper compared with normal controls (Table 6 and Fig. 6A, upper row; paired *t*-test, $P<0.05$, FWE corrected). Normal subjects showed more connectivity in the right premotor cortex and right putamen compared to patients (Table 6, Fig. 6A, lower row; paired *t*-test, $P<0.05$, FWE corrected).

During the performance of anti-phase movements, patients had more connectivity to the bilateral SM1, bilateral superior parietal lobule, right precuneus and bilateral cerebellum with the SMA-proper compared with controls (Table 7 and Fig. 6B, upper row; paired *t*-test, $P<0.05$, FWE corrected). Normal subjects showed more connectivity to the left dorsolateral prefrontal cortex and left putamen compared to patients (Table 7 and Fig. 6B, lower row; paired *t*-test, $P<0.05$, FWE corrected).

Discussion

The present study, for the first time, explored the neural mechanisms underlying the difficulty in performing bimanual tasks in Parkinson's disease. The novel findings are that the patterns of brain activity, as well as interactions of brain networks, are changed in patients with Parkinson's disease, revealing how dysfunction of the basal ganglia influences the rest of the brain.

Table 4 Differences of brain activity between patients with Parkinson's disease and normal subjects in performing anti-phase movements

Brain region	Coordinates			*t*-value	Cluster size
	x	*y*	*z*		
Normal–Parkinson's disease					
SMA-proper	4	−6	54	8.86	136
Right thalamus	14	−10	2	8.59	106
Right globus pallidus	20	−14	−1	8.48	42
Left thalamus	−14	−12	0	8.16	31
Parkinson's disease–Normal					
Left precentral gyrus	−54	−3	9	9.46	323
Left cerebellum, posterior lobe, tonsil	−8	−45	−40	8.77	55
Left inferior parietal lobule	−51	−30	29	8.55	182
Left post-central gyrus	−36	−44	61	8.33	170
Left superior parietal lobule	−34	−46	50	8.14	114
Left precuneus	−16	−44	46	8.11	212
Right cerebellum, posterior lobe, declive	38	−67	−20	7.91	63
Right precentral gyrus	63	5	18	7.74	90
Right inferior frontal gyrus	46	−3	18	7.67	133
Right cerebellum, posterior lobe, tonsil	14	−56	−36	7.49	79
Left post-central gyrus	−14	−53	65	7.46	59
Left SM1	−28	−22	67	7.40	160
Left premotor cortex	−18	−14	62	7.35	84
Left paracentral lobule	−8	−39	68	7.34	120
Right paracentral lobule	6	−34	68	7.06	62
Right precuneus	2	−36	46	7.04	53

List of the brain regions showing significantly more activity in normal subjects than in patients with Parkinson's disease (Normal–Parkinson's disease), or more activity in patients with Parkinson's disease than in normal subjects (Parkinson's disease–Normal), in performing anti-phase movements (two sample *t*-test, $P<0.05$, corrected). The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux (1988).

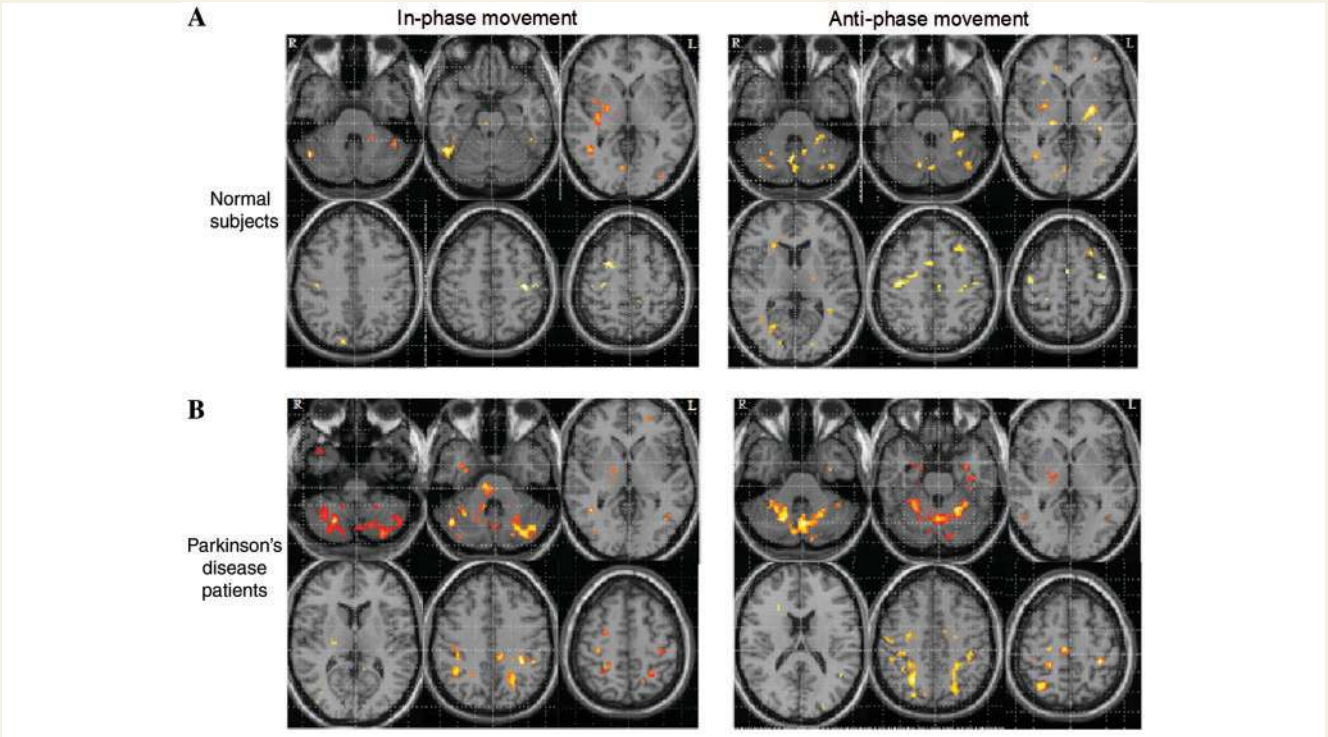

Figure 4 Brain regions effectively connected with the SMA-proper during performing in-phase (left column) and anti-phase movements (right column), in (**A**) normal subjects and (**B**) patients with Parkinson's disease. Results were thresholded at $P<0.05$ (FWE corrected) and rendered over a standard anatomical brain.

Table 5 Brain areas stronger connected with the SMA in the anti-phase state compared to the in-phase state in normal subjects and patients with Parkinson's disease

Brain region	Coordinates			*t*-value	Cluster size
	x	*y*	*z*		
Normal subjects					
Left cerebellum, anterior lobe	−2	−35	−32	10.44	86
Right cerebellum, posterior lobe, tonsil	38	−64	−32	10.12	411
Left precuneus	−14	−50	41	9.85	156
Right cerebellum, anterior lobe, culmen	14	−54	−2	9.82	63
Left cerebellum, posterior lobe, pyramis	−40	−77	−33	9.71	217
Left putamen	−24	−6	6	9.60	142
Left cingulate motor area	−16	13	32	9.41	52
Left SM1	−38	−23	42	9.36	89
Right cerebellum, posterior lobe, pyramis	18	−62	−27	9.36	42
Left dorsolateral prefrontal cortex	−26	31	35	9.10	69
Left cerebellum, anterior lobe, culmen	−40	−56	−28	9.04	36
Right limbic lobe	20	−66	11	8.91	45
Right premotor cortex	20	−9	58	8.84	21
Patients with Parkinson's disease					
Right precentral gyrus	55	−10	32	9.98	76
Left SM1	−18	−30	68	9.44	168
Left inferior parietal lobule	−42	−32	33	9.07	64
Right inferior parietal lobule	36	−42	40	8.76	51
Left paracentral lobule	−20	−42	54	8.57	38
Right precuneus	30	−44	50	8.47	26
Right premotor cortex	22	−11	46	8.42	22
Right post-central gyrus	26	−34	50	8.41	38

List of the brain regions showing a significant connectivity with the SMA ($P < 0.05$, corrected). The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux (1988).

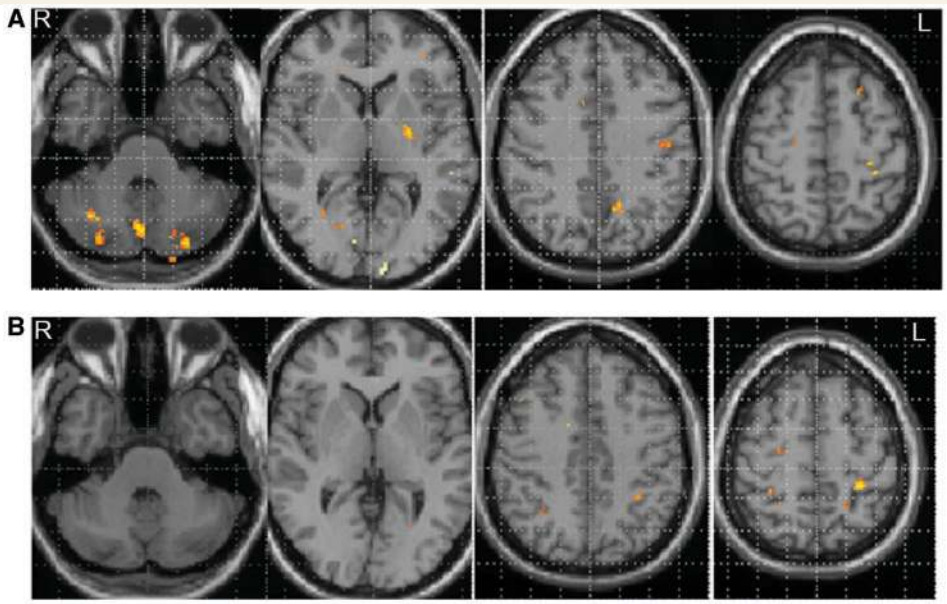

Figure 5 Brain areas more connected with the SMA-proper for bimanual anti-phase movements than for in-phase movements in normal subjects (**A**) and in patients with Parkinson's disease (**B**). Results were thresholded at $P < 0.05$ (FWE corrected).

The abnormal neural activity appears to explain the difficulty of bimanual coordination in Parkinson's disease.

After practice, although a few patients still made infrequent errors while performing anti-phase movements, all patients could perform the bimanual anti- and in-phase movements correctly. The significantly more time needed for practice, and more errors made, demonstrated that patients with Parkinson's disease had more difficulty in performing bimanual movements, especially

Table 6 Differences of effective connectivity in the SMA between patients with Parkinson's disease and normal subjects during performing in-phase movements

Brain region	Coordinates			*t*-value	Cluster size
	x	*y*	*z*		
Normal–Parkinson's disease					
Right putamen	26	−6	4	9.46	79
Right premotor cortex	20	−6	54	8.48	25
Parkinson's disease–Normal					
Right cerebellum, posterior lobe, tonsil	24	−62	−32	9.97	81
Left cerebellum, posterior lobe, vermis	−2	−74	−36	9.83	32
Left cerebellum, posterior lobe, pyramis	−18	−68	−30	9.43	54
Left post-central gyrus	−32	−29	38	9.27	106
Left cerebellum, posterior lobe, tuber	−30	−79	−30	9.07	97
Right cerebellum, posterior lobe, declive	−30	−57	54	8.88	24
Left precuneus	−14	−50	41	8.76	82
Left SM1	−46	−17	36	8.72	31

List of the brain regions showing a significant connectivity with the SMA ($P < 0.05$, corrected). The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux (1988).

Table 7 Differences of effective connectivity in the SMA between patients with Parkinson's disease and normal subjects during performing anti-phase movements

Brain region	Coordinates			*t*-value	Cluster size
	x	*y*	*z*		
Normal–Parkinson's disease					
Left dorsolateral prefrontal cortex	−30	26	34	9.56	323
Left Putamen	−26	−8	0	8.69	118
Parkinson's disease–Normal					
Left SM1	−32	−30	55	9.04	83
Right superior parietal lobule	30	−55	56	8.93	130
Left cerebellum, posterior lobe, pyramis	−20	−62	−29	8.57	104
Left superior parietal lobule	−30	−57	54	8.29	28
Right cerebellum, posterior lobe, pyramis	30	−69	−31	8.19	36
Left cerebellum, posterior lobe, pyramis	−8	−73	−28	8.02	26
Right precuneus	18	−62	−27	7.96	74
Right SM1	22	−25	66	7.88	26

List of the brain regions showing a significant connectivity with the SMA ($P < 0.05$, corrected). The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux (1988).

anti-phase movements, than normal controls (Johnson *et al.*, 1998; Almeida *et al.*, 2002; Ponsen *et al.*, 2006). We used a slow movement rate (0.5 Hz) because it was easier for our patients to perform. It has been observed that both in- and anti-phase tasks are easily maintained in a stable rhythm at low frequencies, but anti-phase tasks often spontaneously convert to in-phase at higher frequencies (Kelso, 1984; Johnson *et al.*, 1998). An external timing cue could help patients with Parkinson's disease to perform in-phase movement with more accuracy and stability, and with better coordination. However, for anti-phase movements, the external cue accentuated the tendency for patients to revert to in-phase movements (Johnson *et al.*, 1998). The external cue may increase the complexity of bimanual tasks; patients have to perform the complex movement correctly and in time with the external cue. From our experience, patients with Parkinson's disease can perform movements at the required slow rate without external cues (Wu and Hallett, 2005). Therefore, we did not use an external timing cue in the current study. Since the rate of movement has a significant effect on brain activity (van Meter *et al.*, 1995; Sadato *et al.*, 1997*a*; Deiber *et al.*, 1999), we gave all subjects sufficient time to practice the rate until they could perform it correctly. Actually, all patients could execute tasks properly at the required rate. There was no difference in the frequency of movements between groups. Since each subject's performance during fMRI was monitored by an investigator and recorded by video, we can assure that all subjects performed all tasks correctly and there was no phase error. Movement amplitude was controlled by asking the subjects to move the maximum amount possible for extension; whereas the amplitude of flexion was limited by the response device fixed to their hand. Therefore, it is unlikely that behavioural performance had obvious effects on the observed different brain activity or effective connectivity between groups.

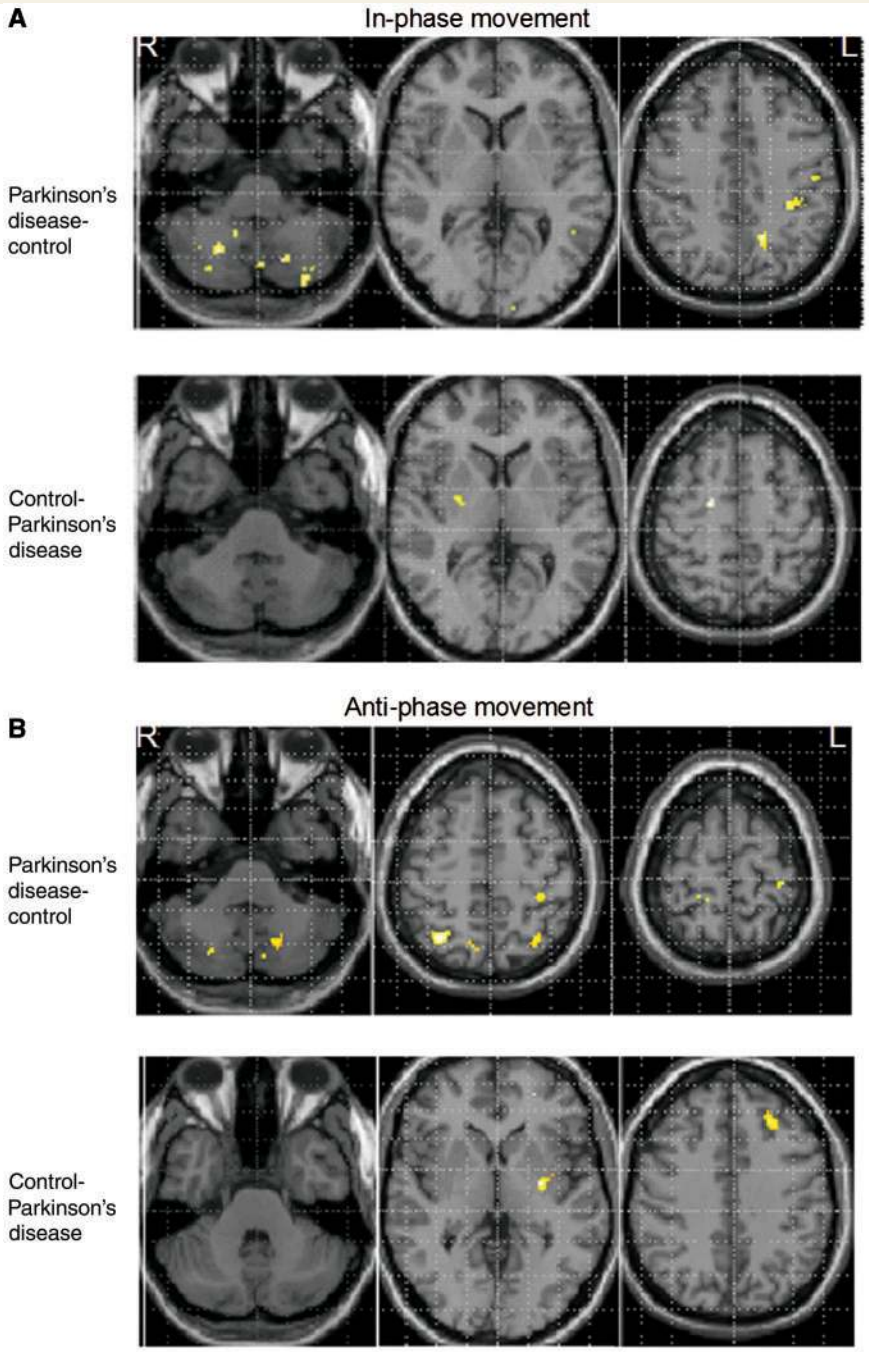

Figure 6 (**A**) Brain areas more connected with the SMA-proper in patients with Parkinson's disease than in controls (upper row) and more connected in normal subjects than in patients with Parkinson's disease (lower row), during performance of in-phase movements; (**B**) Brain areas more connected with the SMA-proper in patients with Parkinson's disease than in controls (upper row) and more connected in normal subjects than in patients with Parkinson's disease (lower row), during performance of anti-phase movements. Results were thresholded at $P < 0.05$ (FWE corrected).

Changes in brain activity

Both patients and normal subjects had more activation in the SMA-proper, right SM1, cingulate motor area, premotor cortex and left cerebellum in performing bimanual movements compared with unimanual movement. An important finding is that the putamen and globus pallidus showed more activity in bimanual movements compared with unimanual movement in controls, but not in patients with Parkinson's disease (Fig. 2A). This finding demonstrated that the basal ganglia could be more activated to perform bimanual tasks in healthy controls. In contrast, the dysfunction of basal ganglia appears not to allow further recruitment for the more complex bimanual movements in Parkinson's disease. We also found that the activation in the basal ganglia was

decreased in patients with Parkinson's disease compared with controls during the performance of bimanual movements (Fig. 3). It has been suggested that the basal ganglia may be crucial in the neural control of bimanual coordination and may be specifically involved in the initiation phase of bimanual movements (Cardoso de Oliveira, 2002; Kraft *et al.*, 2007). Thus, it can certainly be possible that the damaged function of the basal ganglia may impair the ability of patients with Parkinson's disease to perform bimanual tasks.

Agreeing with previous findings (Johnson *et al.*, 1998; Serrien *et al.*, 2000; van den Berg *et al.*, 2000; Geuze, 2001; Almeida *et al.*, 2002; Ponsen *et al.*, 2006), our patients had more errors in performing anti-phase movements than in performing in-phase movements. To perform in-phase movements, homologous muscles are active simultaneously and symmetrically. For anti-phase movements, the homologous muscles are activated 180° out of phase; whereas contralateral antagonist muscles must move simultaneously. Performing anti-phase movement requires specific, sequential timing of muscle activation to maintain the required difference between the two hands, and is mirror-asymmetrical. In addition, attention needs to be maintained in order to keep the required phase relationship between the two hands. Thus, anti-phase movement is more complex than in-phase movement (Spencer and Ivry, 2007).

In both groups, several brain areas were more activated for anti-phase movements than for in-phase movements, including the premotor cortex, inferior frontal gyrus, postcentral gyrus and cerebellum. In contrast, the SMA-proper was more activated in anti-phase movements than in in-phase movements in controls (Sadato *et al*. 1997*b*; Toyokura *et al.*, 1999, 2002; Immisch *et al.*, 2001), but not in patients with Parkinson's disease. There was decreased activation in the SMA-proper in patients compared with controls in the performance of bimanual movements (Fig. 3). The hypoactivation of SMA secondary to dopamine deficiency in Parkinson's disease has been extensively reported in neuroimaging studies (Jenkins *et al.*, 1992; Playford *et al.*, 1992; Rascol *et al.*, 1994; Jahanshani *et al.*, 1995; Samuel *et al.*, 1997; Haslinger *et al.*, 2001; Buhmann *et al.*, 2003). Our observation that the SMA-proper had more activation in bimanual movements than in unimanual movements suggests that the SMA could be more activated to perform bimanual movements in Parkinson's disease, at least at the early stage of the disorder. However, the activation in the SMA-proper could not be further increased in anti-phase movements than in in-phase movements, which indicates that there are no further resources in the SMA to be utilized during the more complex anti-phase movements in patients with Parkinson's disease. Some of our patients reverted anti-phase movement occasionally to in-phase movement. Studies on monkeys and humans with SMA damage have also revealed such a tendency to revert from mirror-asymmetrical to mirror-symmetrical movement (Luria, 1966; Brinkman, 1981; Chan and Ross, 1988). Given the crucial role of the SMA in bimanual coordination, we speculate that dysfunction of the SMA is likely to be an important contributor to the deficiency of patients with Parkinson's disease in performing bimanual movements, especially for anti-phase movements.

Besides the hypoactivation of the SMA and basal ganglia, we also observed hyperactivity in the SM1, premotor cortex, inferior frontal gyrus, superior parietal lobule, inferior parietal lobule, precuneus and cerebellum in patients with Parkinson's disease compared with controls in performing anti-phase movements (Fig. 3). All these regions have been suggested to have specific roles in bimanual coordination (Sadato *et al.*, 1997*b*; Donchin *et al.*, 1998, 2002; Toyokura *et al.*, 1999; Kermadi *et al.*, 2000; Tracy *et al.*, 2001; de Jong *et al.*, 2002; Iwamura *et al.*, 2002; Meyer-Lindenberg *et al.*, 2002; Ullen *et al.*, 2003; Debaere *et al.*, 2004; Wenderoth *et al.*, 2004, 2005). The premotor cortex may have an important role in the higher control of bimanual coordination (Debaere *et al.*, 2004), especially for anti-phase than for in-phase tasks (Sadato *et al.*, 1997*b*; de Jong *et al.*, 2002; Meyer-Lindenberg *et al.*, 2002; Ullen *et al.*, 2003). Wenderoth *et al.* (2005) found that the precuneus is more activated while performing bimanual movements than unimanual tasks, and attributed this to the more attention required for bimanual movements. The posterior lobe of the cerebellum is more specific to timing of more complex bilateral limb movements (Ullen *et al.*, 2003). Blood flow increases in the anterior cerebellar vermis and hemisphere with increasing frequency for anti-phase coordination but not for the in-phase pattern (Meyer-Lindenberg *et al.*, 2002). Furthermore, the cerebellum may specifically relate to the monitoring and correction of the spatiotemporal relationship between the limbs and its implementation into the required rhythm (Debaere *et al.*, 2004).

The dysfunction of the basal ganglia and SMA should induce deterioration in performing bimanual tasks. However, after practice, our patients could execute the bimanual tasks at the same level as the normal subjects. Therefore, we speculate that the greater activity in the SM1, premotor cortex, parietal cortex, precuneus and cerebellum in our patients compared with controls is likely to provide the compensation for the dysfunction of the SMA and basal ganglia required in order to perform bimanual movements correctly (Rascol *et al.*, 1997; Catalan *et al.*, 1999; Sabatini *et al.*, 2000; Wu and Hallett, 2005). In addition, we found that activations in the basal ganglia and SMA-proper were negatively correlated with UPDRS, whereas activations in the cerebellum, premotor cortex, parietal cortex and precuneus were positively correlated with UPDRS. These findings indicate that as the disorder progresses, dysfunction of the basal ganglia and SMA becomes more severe and contributions of these regions to the performance of bimanual movements may decrease. At the same time, the apparent compensatory effect in the cerebellum, premotor cortex, parietal cortex and precuneus is more significant.

The SM1, cerebellum, parietal cortex, precuneus and premotor cortex have been demonstrated to show increased activity as movements become more complex (Shibasaki *et al.*, 1993; Chen *et al.*, 1997; Catalan *et al.*, 1998; Ziemann and Hallett, 2001; Wu *et al.*, 2004; Verstynen *et al.*, 2005). Additionally, the cerebellum and premotor cortex were identified as the principal regions responding to the manipulation of complexity in bimanual coordination (Tracy *et al.*, 2001; Dabaere *et al.*, 2004). Thus, the greater activity in these regions may also partially be due to more difficulty in patients with Parkinson's disease than controls in performing bimanual tasks.

Changes in effective connectivity

In both groups, the SMA-proper connected with extensive areas during the performance of either in-phase or anti-phase tasks, such as the bilateral SM1, premotor cortex, basal ganglia and cerebellum (Fig. 4). These results indicate that brain motor networks, especially the regions related to bimanual coordination, are tightly connected in order to perform bimanual movements.

A significant difference between anti-phase and in-phase movements is that the connectivity between the left (dominant) SM1 and SMA-proper was increased, while the connectivity between the right (non-dominant) SM1 and SMA-proper was decreased in the anti-phase compared with in-phase conditions. An EEG study found that interhemispheric transmission of information is selectively driven between the bilateral SM1 as a function of task requirements, and bimanual movements are mainly controlled by the dominant hemisphere (Serrien *et al.*, 2003). Using the Structural Equation Modelling method, Walsh *et al.* (2008) showed that the dominant hemisphere appears to initiate activity responsible for bimanual movement. Serrien *et al.* (2002) observed that repetitive transcranial magnetic stimulation of the SMA could impair temporal accuracy of bimanual movement performance, especially for anti-phase tasks, and suggested that the SMA has an important integrative role in the organization of bimanual configurations as a function of task complexity, and operates bilaterally with interhemispheric interactions adjusting the activity of both SM1. It is likely that the interregional interactions between the SMA and SM1 need to be shifted to the dominant side in order to perform the more complex anti-phase movement, which induces the observed different pattern of connectivity of the bilateral SM1 and SMA between anti-phase and in-phase movements.

Both groups also showed more connectivity with SMA-proper in some other regions, like the premotor cortex and precuneus during performing anti-phase movement than in performing in-phase movement (Table 5 and Fig. 5). These results suggest that to perform the more complex anti-phase movements, bimanual coordination-related brain areas should be more tightly connected.

During performing anti-phase movement, patients with Parkinson's disease had less connectivity in the left putamen and left dorsolateral prefrontal cortex compared with controls (Table 7 and Fig. 5). Using diffusion tensor imaging method, it has been shown that the SMA-proper connects to the putamen bilaterally (Lehéricy *et al.*, 2004). In Parkinson's disease, the dopamine uptake is mostly reduced in the putamen (Brooks *et al.*, 1990). Thus, the decreased connectivity between the putamen and SMA in Parkinson's disease is probably a consequence of the dysfunction of the basal ganglia. This, in turn, may disrupt the function of SMA and contribute to the difficulty in performing bimanual movements in Parkinson's disease.

The dorsolateral prefrontal cortex is specialized for 'attentional-cognitive' functions (Jueptner *et al.*, 1997; Yamasaki *et al.*, 2002). This region has been reported to be more activated for bimanual anti-phase tasks than for an in-phase task (Haslinger *et al.*, 2004). The connectivity between the dorsolateral prefrontal cortex and SMA was increased in anti-phase movements compared with the in-phase tasks in normal subjects, which suggests that a higher level of attention is required to carry out the demanding bimanual anti-phase movements (Haslinger *et al.*, 2004). In contrast, the connectivity between the dorsolateral prefrontal cortex and SMA was not increased in the anti-phase condition in Parkinson's disease and was decreased compared with controls. A previous study reported that when performing movements that require attention to action, the connectivity between the prefrontal cortex and the premotor cortex was increased in healthy subjects but not in patients with Parkinson's disease (Rowe *et al.*, 2002). Our previous study suggested that limited attentional resources might be a reason related to the difficulty in performing two tasks simultaneously in Parkinson's disease (Wu and Hallett, 2008). Thus, the abnormal connectivity between the dorsolateral prefrontal cortex and SMA may also be an indication of the disrupted attentional networks in Parkinson's disease, which is possibly a reason contributing to deteriorated bimanual coordination in performing anti-phase movements.

Patients with Parkinson's disease showed increased connectivity in the bilateral SM1, bilateral superior parietal lobule, right precuneus and bilateral cerebellum with SMA-proper in performance of anti-phase movements compared with controls (Table 7 and Fig. 5B). As these regions are involved in bimanual coordination, these increased connections are also likely to compensate for the defective basal ganglia to perform bimanual tasks correctly (Helmich *et al.*, 2009; Palmer *et al.*, 2009). However, the increased interregional interactions may also reflect a facet of the primary pathophysiology of Parkinson's disease, such as an inability to inhibit contextually inappropriate circuits secondary to abnormal basal ganglia outflow (Mink, 1996; Turner *et al.*, 2003; Grafton *et al.*, 2006).

The cerebellum and basal ganglia have distinct loops connecting with largely overlapping cortical areas (Middleton and Strick, 2000), and some motor control functions might be shared by basal ganglia and cerebellar motor systems (Desmurget *et al.*, 2004). Both the basal ganglia and cerebellum regulate cortical excitability, but may have somewhat opposing influences (Liepert *et al.*, 2004; Tamburin *et al.*, 2004; Hallett, 2006). Thus, changed connectivity may also reflect a compensatory reaction of the cerebellum secondary to the damage of the basal ganglia. However, because the SMA receives significantly more basal ganglia input than cerebellar input (Akkal *et al.*, 2007), even though the cerebellar compensation exists, it may not be strong enough to normalize the dysfunction in the SMA due to the damage of basal ganglia. We observed a significant increase of connectivity between the cerebellum and SMA in anti-phase than in in-phase movements in normal subjects but not in patients with Parkinson's disease. Possibly, the interaction between the cerebellum and SMA already achieves the limit in performing bimanual in-phase movements and could not be further increased to give more compensation for the more complex bimanual anti-phase movements. An alternative view is that the changes of the connectivity between the SMA and cerebellum may not always produce an adaptive response to restore normal motor function; it may be a part of the problem of motor deficits, rather than a solution (Grafton, 2004).

In conclusion, our findings suggest that several reasons may contribute to the difficulty of performing bimanual anti-phase movements in patients with Parkinson's disease. The SMA and basal ganglia are hypoactivated. The pattern of interactions of neural networks is abnormal; the connectivity between the SMA and putamen is decreased. In addition, the attentional network is disrupted. The patients need to recruit more brain activity and increase connectivity in some brain regions, like the primary motor cortex and cerebellum to compensate for dysfunction of the basal ganglia and SMA in order to perform bimanual movements correctly.

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