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A functional MRI study of automatic movements in patients with Parkinson's disease

Tao Wu[1,2] and Mark Hallett[1]

[1]Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA and [2]Beijing Institute of Geriatrics, Department of Neurology, Xuanwu Hospital, Capital University of Medical Sciences, Beijing, China

Correspondence to: Mark Hallett, MD, Bldg 10, Rm 5N226, 10 Center Drive MSC 1428, Bethesda, MD 20892-1428, USA
E-mail: hallettm@ninds.nih.gov

Patients with Parkinson's disease have great difficulty performing learned movements automatically. The neural contribution to the problem has not been identified. In the current study, we used functional magnetic resonance imaging (fMRI) to investigate the underlying neural mechanisms of movement automaticity in Parkinson's disease patients. Fifteen patients with Parkinson's disease were recruited. Three patients were finally excluded because they could not achieve automaticity. The remaining 12 patients were aged from 52 to 67 years, with a mean age of 61.2 years. Controls included 14 age-matched normal subjects. The subjects were asked to practise four tasks, including two self-initiated, self-paced sequences of finger movements with different complexity until they could perform the tasks automatically. Two dual tasks were used to evaluate automaticity. For dual tasks, subjects performed a visual letter-counting task simultaneously with the sequential movements. Twelve normal subjects performed all sequences automatically. All patients performed sequences correctly; 12 patients could perform the simpler sequence automatically; and only 3 patients could perform the more complex sequence automatically. fMRI results showed that for both groups, sequential movements activated similar brain regions before and after automaticity was achieved. No additional activity was observed in the automatic condition. In normal subjects, many areas had reduced activity at the automatic stage, whereas in patients, only the bilateral superior parietal lobes and left insular cortex were less activated. Patients had greater activity in the cerebellum, premotor area, parietal cortex, precuneus and prefrontal cortex compared with normal subjects while performing automatic movements. We conclude that Parkinson's disease patients can achieve automaticity after proper training, but with more difficulty. Our study is the first to demonstrate that patients with Parkinson's disease require more brain activity to compensate for basal ganglia dysfunction in order to perform automatic movements.

Keywords: automatic movement; brain activity; dual task; fMRI; Parkinson's disease

Abbreviations: fMRI = functional magnetic resonance imaging; MMSE = Mini-Mental State Examination; SMA = supplementary motor area; SPM = statistical parametric mapping; UPDRS = Unified Parkinson's Disease Rating Scale

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Introduction

A general characteristic of the motor system is that people can perform some learned movements automatically. Automatic movements are executed without attention being clearly directed towards the details of the movement, and automaticity is common, particularly for movements that require low levels of precision or for movements that are frequently made (Bernstein, 1967). After a period of training, however, even some complex tasks can be executed automatically (Wu *et al.*, 2004). For example, musicians can perform music accurately while holding a conversation. According to Fitts's theory of motor learning, after passing through the stages of cognition and fixation, in the third stage, called the automatic phase, the motor skill is well established and can be performed in a range of contexts with limited demands on attentional resources (Fitts, 1964).

It has been suggested that multiple brain areas may contribute to movement automaticity. Most of the motor network participates in executing automatic movements

and becomes more efficient as movements become more automatic (Wu *et al.*, 2004; Wu and Hallett, 2005). The basal ganglia are also less activated at the automatic stage and may have a role in shifting a learned performance to the automatic stage (Wu *et al.*, 2004). The basal ganglia may support a basic attentional mechanism to bind input to output in the executive forebrain, which provides the automatic link between the voluntary effort and operation of a sequence of motor programmes or thoughts. Other motor cortical areas, such as the cerebellum, supplementary motor area (SMA), cingulate cortex, premotor areas, dorsolateral prefrontal cortex and parietal cortex, are also involved in performing automatic movements (Jenkins *et al.*, 1994; Jueptner and Weiller, 1998; Wu *et al.*, 2004). It is possible that the connectivity between the basal ganglia and other motor areas allows stringing together of submovements, thereby assisting in the execution of automatic skilled movements. Thus, automaticity may be difficult to achieve in some pathological conditions, such as in Parkinson's disease, because of the defective function of the basal ganglia.

Patients with Parkinson's disease commonly have difficulties in performing movements. For example, a clinical feature of Parkinson's disease is decreased stride length during walking, which progressively worsens as the disease advances. Patients must direct their attention to the walking and think about each step if they are to make adequately long steps; otherwise, their steps become small. Patients can achieve normal stride amplitude and perform normal walking if appropriately trained (Sheridan *et al.*, 1987; Morris *et al.*, 1994*a*, *b*). Furthermore, external cues or attentional strategies can help them improve movement (Sheppard *et al.*, 1996; Cunnington *et al.*, 1999). It has been suggested that the effect of external demand or attentional strategies is to allow movement to be mediated less by automatic processes and more by attentional motor control processes, which should help patients focus on the task (Morris *et al.*, 1996; Cunnington *et al.*, 1999). These observations suggest that the normal movement pattern may not be lost in the patients. Rather, the reason for these phenomena is that their ability to perform automatic movements is defective, or they have difficulty in switching a learned task to the automatic phase.

Another deficiency of Parkinson's disease patients is that they have difficulty performing two separate motor tasks at the same time (Benecke *et al.*, 1986, 1987; Castiello and Bennett, 1997). For example, a patient may be unable to draw a triangle with his/her dominant hand while squeezing with the other hand, or he/she may be very slow in performing simultaneous tasks, such as flexing the elbow and squeezing the thumb and index finger at the same time. The problem of performing two tasks simultaneously is not confined to motor tasks. It can also be observed in cognitive tasks or combined cognitive and motor tasks (Brown and Marsden 1991; Oliveira *et al.*, 1998), which suggests that the difficulty in performing two tasks at the same time in the patients is not purely a motor problem. Although a possible reason for the problem is that the patients have a limited global processing resource that interferes with their ability to execute more than one task at the same time (Brown and Marsden 1991), it is also plausible to assume that the global resource is relatively intact, but the patients perform the tasks less automatically than normal subjects.

It has been observed that Parkinson's disease patients have a greater abnormality of automatic associated movement than intended voluntary movement, which may be one of the bases of clinical symptoms in the early stage of the disease (Hoshiyama *et al.*, 1994). An adequate understanding of this problem may help in the development of optimal therapy strategies. However, compared with other deficits, the problem of automatic movement in patients is much less studied and poorly understood. It is unclear to what degree the ability of automatic performance in patients is defective, totally lost or relatively intact. Most importantly, the neural contribution to the problem has not been identified.

The aim of the present study is to study automatic movements in patients with Parkinson's disease. We speculate that the patients might be able to achieve automatic movement to some extent after proper training. Previous studies have demonstrated that patients can execute simple or sequential finger movements well after practice. Their performance was not significantly different from that of normal subjects (Samuel *et al.*, 1997; Catalan *et al.*, 1999). However, it is unclear in these studies whether the patients achieved automaticity or not. To avoid this problem, we used a dual task paradigm to evaluate the automatic movements in the current study, as we had done in previous studies with normal subjects (Wu *et al.*, 2004; Wu and Hallett, 2005). With this paradigm, automaticity can be evaluated by having subjects perform either a distraction or an interference secondary task simultaneously with the automatic task. The evidence that a task has become automatic can be proven by the fact that the secondary task can be performed with minimal interference (Passingham, 1996). We used functional magnetic resonance imaging (fMRI) technique to study automaticity related brain activity in the patients. We speculated that the patients would require more brain activity to compensate for striatal dysfunction to perform automatic movements.

Methods

Subjects

We studied 15 patients with Parkinson's disease. Three patients were excluded because they did not achieve automaticity in performing any motor sequence after extensive training. The remaining 12 subjects ranged in age from 52 to 77 years (mean 61.2 years), and included 8 males and 4 females. The diagnosis of Parkinson's disease was based on medical history, physical and neurological examinations, response to levodopa or dopaminergic drugs, and laboratory tests and MRI scans to exclude other diseases. Patients were studied only after their medication had been withdrawn for at least 12 h. Patients were assessed with the UPDRS (Unified Parkinson's Disease Rating Scale) (Lang and Fahn, 1989), the Hoehn and Yahr disability scale (Hoehn and Yahr, 1967) and Mini-Mental State Examination (MMSE) while off their medications. The clinical data are shown in Table 1.

Table 1 Clinical details of patients with Parkinson's disease

Patient	Age (years)	Gender	Duration (years)	UPDRS off medication	H&Y off medication	MMSE	Dose of L-dopa (mg/day)	Side most affected	Tremor
1	56	M	10	32.5	II.5	30	600 (r)	R	Yes
2	53	M	8	28	II.5	30	500 (p, m, c)	L	Yes
3	56	F	9	34	II.5	30	600 (r, a)	R	Yes
4	68	F	7	24.5	II	30	300 (m, a)	L	Yes
5	68	M	8	32	II.5	30	600 (c, r)	L	Yes
6	57	M	5	28	II.5	30	500 (m, c)	R	Yes
7	62	M	8	31.5	II.5	30	600 (m, a)	R	Yes
8	65	M	2	25	I.5	30	300	R	No
9	66	M	2	17	I.5	30	300	R	Yes
10	55	F	9	27.5	II.5	30	300	R	No
11	52	M	5	13	I	30	(p)*	R	Yes
12	77	F	3	13	I	30	450	L	Yes
Mean (SD)	61.2 (7.64)		6.33 (2.84)	25.50 (7.40)	2.04 (0.62)	30	459.09 (135.68)		

UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr Staging; MMSE, Mini-Mental-State Examination; F, female; M, male; R, right; L, left; (a), plus amantadine; (c), plus Comtan; (m), plus Mirapex; (p), plus pergolide; (r), plus Requip; *Not taking L-dopa at time of study.

We also investigated 14 normal subjects. After training, two of them could perform only a part of the motor sequences automatically; therefore, their data were excluded. The remaining 12 normal subjects, aged 57–73 years (mean 61.8 years) as control, were gender matched with patients. The results from these normal subjects were previously reported (Wu and Hallett, 2005). All patients and normal 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

All procedures were identical to those of our previous reports (Wu *et al.*, 2004, Wu and Hallett, 2005) and are only briefly described here. Subjects were asked to perform two sequences of right-hand finger tapping referred to as sequence-4 and sequence-12, based on the number of movements in each unit of the sequence. 'Sequence-4' was 1-3-4-2, and 'Sequence-12' was 1-4-3-2-2-4-1-3-4-1-2-3, in which 1, 2, 3 and 4 refer to the index, middle, ring and little fingers, respectively. All sequential movements were self-initiated and self-paced and were executed at 0.5 Hz. No external cue was given to help the subjects move at the specified rate. Automaticity was evaluated by having subjects perform a visual letter-counting task simultaneously with these sequential movements. For the letter-counting task, letter sequences consisting of a random series of the letters A, G, L and O were presented on a screen and subjects were asked to identify the number of times they saw a specified target letter. Before the first scan, all subjects practised until they could move at the required rate. They briefly practised each sequential movement. In addition, subjects were given enough practise trials to ensure that they could perform the visual letter-counting tasks correctly with no difficulty. After the first scan, subjects practised these tasks until they could perform sequential movements from memory 10 times in a row without error, as well as the dual tasks accurately. During practice, the errors were recorded and feedback was provided to inform subjects whether their finger movements were correct or incorrect.

Functional MRI procedure

T2*-sensitive functional images were obtained using a whole-body 1.5 T MRI scanner (Signa, General Electric, Milwaukee, WI) and a standard head coil. Subjects lay supine in the MR scanner with a response device fixed to their right hand. The response device had four buttons, corresponding to the index, middle, ring and little fingers of the right hand and was used to record finger movements. The subjects viewed visual signals on a screen through a mirror built into the head coil. We used an EPI gradient echo sequence (21 slices, slice thickness = 5 mm, slice gap = 1 mm, TE = 30 ms, TR = 2500 ms, flip angle = 90°, FOV = 22 cm × 22 cm, matrix = 64 × 64, in-plane resolution = 3.44 mm × 3.44 mm) to obtain functional images. A time-course series of 100 images/slice were acquired for each trial, in an off/on cycle paradigm of rest and activation. Each scanning session lasted 4 min.

fMRIs were acquired both before and after the subjects achieved automaticity. Two conditions were contained in each scanning session and were defined as the 'rest' and 'active' condition. Each condition lasted 25 s and was repeated five times in a session. In the rest condition, subjects were asked to relax and focus on the screen in front of them. The active condition in each session contained either sequence-4 or sequence-12. No feedback was provided during scanning to tell subjects whether their finger movements were correct or incorrect.

Behavioural data analysis

Each subject's performance for each task was recorded. Errors were used to evaluate if these tasks were performed automatically. Only the performances achieving high accuracy in both single and dual tasks were considered automatic. Within each group, the difference in performance before and after training was calculated (repeated-measures ANOVA, $P < 0.05$). The performance between sequence-12 and sequence-4 was also compared (two-sample t-test, $P < 0.05$). The performance of each task of the patients was compared with the normal subjects (two-sample t-test, $P < 0.05$).

Imaging data analysis

Image analysis was performed with SPM 99 software (Wellcome Institute of Cognitive Neurology, London, UK). Functional images were aligned to the first image of each session for motion correction. After spatial normalization, all images were resampled into voxels that were 2 mm × 2 mm × 2 mm in size. Images were also smoothed

with a Gaussian filter of 6 mm full-width at half maximum (FWHM). Both first- and second-level analyses were performed. In the first-level, data were analysed for each subject separately on a voxel-by-voxel basis using the principles of the general linear model extended to allow the analysis of fMRI data as a time series (Friston *et al.*, 1995*a*, *b*, *c*). The data were modelled using a fixed effect boxcar design, convolved with a haemodynamic response function chosen to represent the relationship between neuronal activation and blood flow changes. The model had the same on/off frequency as the alternation frequency of the active and rest conditions, and was constructed for analysis of task-dependent activation, identical for all subjects and for all conditions. 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 before and after training for each condition ($P < 0.001$, without correction for multiple comparisons). We chose this threshold because it is often more informative and may show a trend towards increased activation although not reaching the more conservative corrected statistical threshold. A paired *t*-test model was used to compare the before-training results with the after-training results for each condition ($P < 0.001$, uncorrected). For between-group comparisons, a two-sample *t*-test model ($P < 0.001$, uncorrected) was used to explore the difference between patients and normal subjects after training. Locations of activated areas for different conditions were displayed by superimposing them on the Montreal Neurological Institute (MNI) template.

Results

Task performance

The accuracies of sequential movements and dual tasks across all patients and normal subjects are shown in Table 2. Three patients could not perform any dual tasks correctly after extensive training, which suggests that they could not achieve automaticity in performing any sequential movements. Two normal subjects could only perform sequence-4 but not sequence-12 automatically (Wu and Hallett, 2005). Therefore, all data of these three patients and two normal subjects were excluded. Before training, both groups committed errors in performing all sequential movements and dual tasks. In both groups, there were more finger movement errors in performing sequence-12 than in performing sequence-4 (two-sample *t*-test, $P < 0.05$), and in performing dual tasks than in performing single tasks (ANOVA, $P < 0.05$). In addition, more errors were found when performing the dual task of sequence-12/letter counting than performing the dual task of sequence-4/letter counting (ANOVA, $P < 0.05$). The patients made significantly more errors than normal subjects while performing dual tasks (ANOVA, $P < 0.05$). They also had more errors than normal subjects in performing either sequence-4 or sequence-12, although the difference was not statistically significant (two-sample *t*-test, $P > 0.05$).

Training improved performance in both groups; all of them could execute sequence-4 and sequence-12 with high accuracy. After training (4.7 ± 1.0 h), 12 normal subjects could perform dual tasks of sequence-4/letter counting and sequence-12/letter counting correctly. In contrast, although they had spent significantly more time (6.0 ± 0.8 h), only 12 patients could perform the dual task of sequence-4/letter counting with high accuracy. Among them, only three patients performed the dual task of sequence-12/letter counting correctly. Patients had significantly more errors in performing sequence-12/letter counting compared with normal subjects (ANOVA, $P < 0.05$). For those subjects who performed sequential movements automatically, all reported that they could execute the tasks without paying attention to the sequential finger movements and had no more difficulty.

There was no between- or within-group difference for the rate of performance of sequential movements. Before and after training, the rates of movements in patients were 0.52 ± 0.12 Hz and 0.52 ± 0.08 Hz, whereas normal subjects were 0.54 ± 0.07 Hz and 0.52 ± 0.06 Hz, respectively. However, during practice, patients had more difficulty than normal subjects in acquiring the required rate (27.5 ± 7.2 min versus 21.1 ± 5.4 min).

fMRI results

Within-group analysis

Before training, for patients the performances of sequence-4 and sequence-12 were associated with activations in the left primary sensorimotor cortex, bilateral premotor areas,

Table 2 Performance (percentage of errors) of sequential finger movements and dual tasks before and after training in aged patients and normal subjects

Task	Patients		Normal subjects	
	Errors (%) (before training)	Errors (%) (after training)	Errors (%) (before training)	Errors (%) (after training)
Sequence-4	5.1 ± 8.8	0	4.8 ± 6.4	0
Sequence-12	22.4 ± 14.5	1.5 ± 2.0	18.5 ± 13.2	1.1 ± 1.8
Sequence-4/letter counting	15.4 ± 16.4	0.2 ± 1.0/1.2 ± 1.8	11.9 ± 12.8/9.9 ± 10.1	0.3 ± 0.8/1.2 ± 2.3
Sequence-12/letter counting	37.6 ± 25.2/22.4 ± 13.2	24.8 ± 20.6/15.2 ± 10.6	30.5 ± 19.6/18.7 ± 11.9	1.2 ± 1.9/2.0 ± 2.6

Values are given as mean ± SD for percentage of errors. The results of the dual task of sequential movements and visual letter counting are given as errors of finger movements/errors of letter counting.

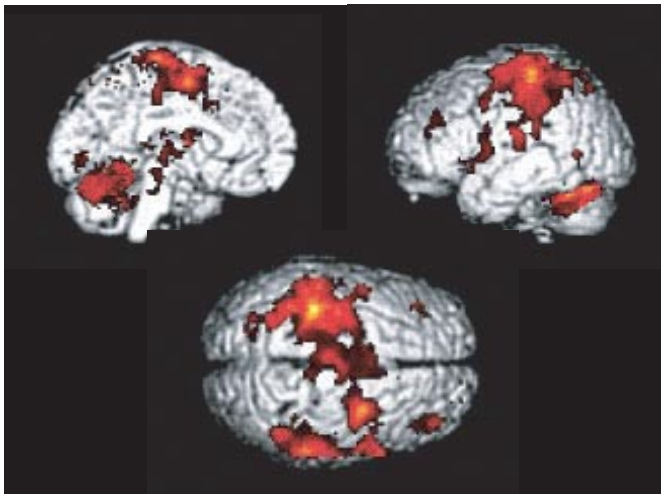

Fig. 1 Brain regions activated during performing sequence-4 at the automatic stage in Parkinson's disease patients. Results were thresholded at $P < 0.001$ (uncorrected) and rendered over a standard anatomical brain.

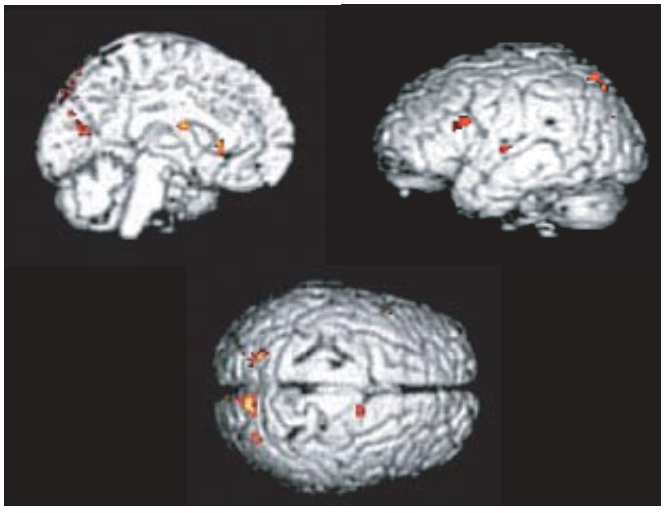

Fig. 2 Brain areas more activated at the pretraining stage than at the automatic stage while performing sequence-4 in Parkinson's disease patients. Results were thresholded at $P < 0.001$ (uncorrected) and rendered over a standard anatomical brain.

bilateral parietal cortex, bilateral dorsal lateral prefrontal cortex, bilateral SMA, bilateral anterior cingulate motor cortex, bilateral basal ganglia, bilateral insular cortex and bilateral cerebellum. After training, the pattern of brain activity was similar to that before training and no additional activation was observed for both sequence-4 and sequence-12 (Fig. 1). There was less activation in the bilateral superior parietal lobes and left insular cortex compared with the before-training stage (Fig. 2).

In normal subjects, the brain activations before training were similar to those for patients. After training there was less activation in the bilateral premotor area, bilateral superior and inferior parietal lobes and pre-SMA compared with the before-training stage (Wu and Hallett, 2005).

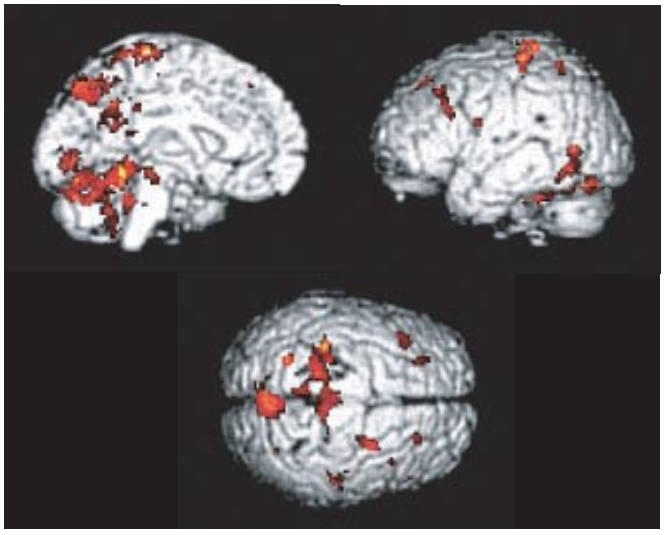

Fig. 3 Brain areas more activated in Parkinson's disease patients than in normal subjects during automatic execution of sequence-4 ($P < 0.001$, uncorrected) and rendered over a standard anatomical brain.

Between-group analysis

Since only three patients could achieve automaticity in performing sequence-12, we only performed between-group comparison of brain activity during performance of sequence-4. Compared with normal subjects, at the before-training stage, patients had greater activation in the bilateral cerebellum, bilateral premotor area, bilateral parietal cortex, bilateral precuneus and bilateral dorsal lateral prefrontal cortex while performing sequence-4. Normal subjects had greater activity in the pre-SMA than in patients.

At the after-training stage, patients still had greater activation in the bilateral cerebellum, bilateral premotor area, bilateral parietal cortex, bilateral precuneus and bilateral dorsal lateral prefrontal cortex while performing sequence-4 (Fig. 3 and Table 3). We found no area in normal subjects with greater activation than in patients at this stage.

Discussion

After training, although it took more time, all patients with Parkinson's disease could perform both sequence-4 and sequence-12 with high accuracy, at the same level as normal subjects (Table 2). This finding is consistent with previous studies and demonstrates that although the ability of selection and sequencing movements is damaged in the patients, they still can learn and perform a complex sequence of movements normally (Frith *et al.*, 1986; Roy *et al.*, 1993; Catalan *et al.*, 1999). Most of our patients could perform the sequence-4 automatically, although they were unable to perform the sequence-12 automatically, as proved by their poor performance on the dual task. Our results demonstrate that patients have great difficulty in switching learned motor sequences into the automatic stage, but their ability in achieving

Table 3 Brain areas more activated in Parkinson's disease patients than in normal subjects while performing sequence-4 at the automatic stage

Cluster size	Activated areas	*x*	*y*	*z*	*Z*-value
2113	R cerebellum	12	−64	−7	6.83
235	R temporal lobe	32	−29	11	6.78
441	L premotor area	−38	9	44	6.70
486	R precuneus	2	−66	44	6.61
873	L cerebellum	−14	−41	−14	6.59
303	R premotor area	48	−18	34	6.21
154	L temporal lobe	−46	−60	7	6.21
106	L parietal cortex	−24	−52	50	6.16
300	R prefrontal cortex	44	9	24	6.12
156	R parietal cortex	30	−53	54	6.08
92	L precuneus	−8	−72	40	6.06
89	L prefrontal cortex	−24	37	44	5.62

The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux. Cluster size is the number of voxels. All areas were significant at $P < 0.001$ (uncorrected). Abbreviations: L, left; R, right.

automaticity is not totally lost. They can perform some relatively complex motor tasks automatically after proper training.

Automaticity-related brain activity in patients with Parkinson's disease

Parkinson's disease patients had similar brain activation patterns before and after achieving automaticity. No brain area was additionally activated in the automatic stage. These observations are similar to the results of normal subjects and supported our previous observation that no additional areas are activated specifically for automaticity in a self-initiated, memorized sequential movement (Wu *et al.*, 2004, Wu and Hallett, 2005). In patients, after training only the bilateral superior parietal lobes and left insular cortex were less activated (Fig. 2). In contrast, in normal subjects at the automatic stage, there was less activation in the bilateral premotor area, bilateral superior and inferior parietal lobes and pre-SMA compared with the before-training stage (Wu and Hallett, 2005). That the motor network is less activated at the automatic stage suggests that it becomes more efficient as movements become more automatic. Our results demonstrated that unlike normal subjects, brain activity in patients was not becoming obviously efficient during the process of automaticity. Patients had greater activation in the bilateral cerebellum, bilateral premotor area, bilateral parietal cortex, bilateral precuneus and bilateral dorsal lateral prefrontal cortex than normal subjects while performing automatic movements. No area displayed greater activation in normal subjects than in patients.

In recent years, it has been realized that the basal ganglia are not only involved in motor execution, but also in motor learning (Jueptner and Weiller, 1998). They project to motor cortical areas including primary motor cortex, premotor area, SMA-proper, pre-SMA and cingulate motor areas through the thalamus. These connections are thought to be involved in acquiring and coordinating motor sequences (Nakano, 2000). They receive projections from the dorsal lateral prefrontal cortex, pre-SMA and other frontal association areas (Selemon and Goldman-Rakic, 1985), and it is known that the prefrontal cortex is important in learning a new motor sequence (Jenkins *et al.*, 1994; Jueptner *et al.*, 1997*a*). Extensive studies on monkey (Brotchie *et al.*, 1991*a*, *b*), normal subjects (Seitz *et al.*, 1990; Grafton *et al.*, 1994; Jenkins *et al.*, 1994; Doyon *et al.*, 1997), and patients (Georgiou *et al.*, 1994, 1995; Doyon *et al.*, 1998) suggested that the striatum is critically involved in the late phases of learning where automatization is about to happen. Our results that Parkinson's disease patients had great difficulty executing the learned motor sequences automatically gave further evidence that the basal ganglia are important in shifting a learned motor task to the automatic stage.

The most significant area with greater activation in Parkinson's disease patients than in normal subjects is the bilateral cerebellum (Fig. 3, Table 3). Similar to the basal ganglia, the cerebellum is also critical in motor learning. Neuroimaging studies have shown that the cerebellar activity was greater during the early learning stage and decreased once the task became more automatic (Jenkins *et al.*, 1994; Doyon *et al.*, 1996; Jueptner *et al.*, 1997*b*; Toni *et al.*, 1998; Wu *et al.*, 2004). Observations on cerebellar damaged patients further proved the role of the cerebellum in motor learning (Martin *et al.*, 1996; Doyon *et al.*, 1997; Molinari *et al.*, 1997), as well as in switching learned motor tasks into a more automatic stage (Lang and Bastian, 2002). Although still debatable, considerable evidence supports that the cerebellum is critical in both acquisition and execution of automatic movements (Thach *et al.*, 1992; Jenkins *et al.*, 1994; Doyon *et al.*, 1996; Jueptner *et al.*, 1997*a*, *b*; Shadmehr and Holcomb, 1997; Jueptner and Weiller, 1998; Thach, 1998; Toni *et al.*, 1998; van Mier *et al.*, 1998; Lang and Bastian, 2002; Wu *et al.*, 2004). However, the cerebellum and the basal ganglia apparently have distinct roles in the learning process (Pascual-Leone *et al.*, 1993; Grafton *et al.*, 1994; Laforce and Doyon 2001), as well as in movement control (Jueptner and Weiller, 1998). For example, the striatum is involved in building a repertoire of motor actions that can be triggered in response to appropriate environmental stimuli, whereas the cerebellum plays a more important role in combining learned movements together to produce a well-executed motor skilled behaviour (Laforce and Doyon 2001). The corticobasal ganglia-thalamocortical and the cortico-cerebello-thalamo-cortical loops constitute two separate neural systems (Asunama *et al.*, 1983; Yamamoto *et al.*, 1992; Middleton and Strick, 1994; Sakai *et al.*, 1996). The basal ganglia and the cerebellum project through the thalamus to diverse target cortical areas including the motor, premotor, prefrontal, temporal and parietal cortices, and constitute multiple 'parallel' channels (Hoover and Strick, 1999; Middleton and Strick, 2000). Our results suggest that although they have different physiological roles, under some pathological conditions, or as a

result of the reorganization of the central neural system following brain damage, the cortico-cerebello-thalamo-cortical loops can compensate for the dysfunction of corticobasal ganglia-thalamocortical loops.

Consistent with previous reports, we also found greater activity in the premotor and parietal (including precuneus) cortices in patients than in normal subjects (Samuel *et al.*, 1997; Catalan *et al.*, 1999). Each premotor area is a nodal point for a discrete set of afferent inputs from subcortical nuclei and cortical areas comprising different systems of movement control (Dum and Strick, 1991; He *et al.*, 1993). The premotor cortex is important in the temporal organization of sequential movements (Halsband *et al.*, 1990, 1993), selection of movements (Deiber *et al.*, 1991) and in the generation of motor sequences from memory that fit into a precise plan (Grafton *et al.*, 1992; Shibasaki *et al.*, 1993). The parietal cortex is related to motor selection with external information, such as auditory and visual cues, based on integration of spatial information (Deiber *et al.*, 1991; Grafton *et al.*, 1992). Parietal areas also play a role in the temporal aspects of the sequence to ensure that each movement occurs after successfully completing the preceding move. Patients with parietal cortex damage have difficulty in predicting the time required to perform differentiated finger movements (Sirigu *et al.*, 1996). Posterior parietal areas could be recruited to store information about the motor sequence (Sadato *et al.*, 1996) and may have a role in selecting and monitoring a sequence. Deiber *et al.* (1996) reported activation in this region when subjects prepare to make finger movements. The precuneus may be related to preparation (Astafiev *et al.*, 2003) and monitoring (Gusnard and Raichle, 2001) of movements. Both the premotor and parietal cortices participate in motor learning and execution (Jenkins *et al.*, 1994; Jueptner *et al.*, 1997*a*, *b*; Toni *et al.*, 1998; Wu *et al.*, 2004). In normal subjects, the premotor and the superior and inferior parietal lobes were significantly less activated in the automatic condition than in the before-training stage (Wu and Hallett, 2005). In patients, only the superior parietal lobes were less active after training (Fig. 2). These results suggest that patients need more premotor–parietal circuit activity to compensate for their inefficient brain activity in executing automatic movements.

The dorsal prefrontal cortex has been suggested as being critical in the learning process (Jenkins *et al.*, 1994; Deiber *et al.*, 1997; Jueptner *et al.*, 1997*a*, *b*; Jansma *et al.*, 2001). It is important in generating a new movement (Deiber *et al.*, 1991; Jueptner *et al.*, 1997*a*, *b*), in the early performance of a novel movement (Grafton *et al.*, 1995; Jueptner *et al.*, 1997*a*, *b*; Honda *et al.*, 1998), in task rehearsal (Petrides *et al.*, 1993), and in performance monitoring (Owen *et al.*, 1996). In normal young subjects, the activity in this region is significantly decreased at the more automatic stage (Jenkins *et al.*, 1994; Jueptner *et al.*, 1997*a*, *b*; Toni *et al.*, 1998; Wu *et al.*, 2004). However, in healthy aged subjects, the change within this area was not significant after training and suggested that aged subjects need more brain activity to compensate for their inefficient strategy (Wu and Hallett, 2005). In patients, the activity in the dorsal prefrontal cortex also did not diminish during the process of automaticity and had greater activation than age-matched normal subjects while performing automatic movements (Fig. 3, Table 3). These observations suggest that for patients, even if there is no subjective behavioural difference compared with normal subjects, their brain must work harder to perform automatic movements.

Similar to our previous studies (Wu *et al.*, 2004, Wu and Hallett, 2005), we did not use external cues to help subjects maintain the rates because the need for attention to follow the pace would weaken the claim for automaticity. Since the rate of movement has a significant effect on brain activity (Sadato *et al.*, 1997; Deiber *et al.*, 1999), we gave all subjects sufficient time to practise the rate until they could perform it correctly, before the first fMRI scan. We chose a slow movement rate because it was easier for the patients to perform. Actually, all our patients could execute sequences properly at this rate. There was no difference in the frequency of finger movements between patients and normal subjects. Therefore, movement rate had no effect on the observed different brain activity between groups. However, patients had more difficulty than normal subjects in achieving the required rate. Some brain areas, i.e. the cerebellum, dorsal lateral prefrontal cortex and basal ganglia, are involved in generating accurate movement timing (Kawashima *et al.*, 2000; Dreher and Grafman, 2002). The dorsal lateral prefrontal cortex is especially important for self-paced movements (Wessel *et al.*, 1995; Kawashima *et al.*, 2000). Therefore, the dysfunction of the basal ganglia may impair the ability of patients in timing control. The increased activity in some brain areas may be partly because of the additional brain effort patients used for timing control.

Several previous studies found a relatively underactivated rostral pre-SMA in Parkinson's disease patients than in normal subjects when performing self-initiated motor tasks (Playford *et al.*, 1992; Rascol *et al.*, 1994; Jahanshani *et al.*, 1995; Catalan *et al.*, 1999; Haslinger *et al.*, 2001). We also observed that normal subjects had greater activity in the pre-SMA than patients before training. In contrast, we did not find such difference in the pre-SMA between groups at the automatic stage. The reason for the phenomenon should be owing to the different learning stage achieved. In these previous reports, although patients performed tasks correctly, there was no evidence that automaticity had been achieved. Actually, the pre-SMA was still extensively activated in normal subjects in order to perform self-initiated motor tasks, which suggested that these patients were at a less automatic stage. Studies on monkey and normal human subjects have shown that the pre-SMA is critical in acquiring new motor sequences (Nakamura *et al.*, 1998, 1999; Hikosaka *et al.*, 1999). It particularly plays a primary role in the early preparation of self-initiated movements (Deiber *et al.*, 1991; Jenkins *et al.*, 2000; Cunnington *et al.*, 2002). Neuroimaging studies have found that the pre-SMA activity significantly decreased or disappeared when subjects performed a sequential movement

more automatically (Sakai *et al.*, 1998; Wu *et al.*, 2004). Therefore, at the less automatic stage, the impaired striato-mesial frontal loops in Parkinson's disease patients induced an underactivated pre-SMA compared with normal subjects. In contrast, at the more automatic stage, pre-SMA was no longer strongly activated in normal subjects. Thus, the comparison between groups found no difference in this area.

Dual task performance in patients with Parkinson's disease

In our study, at the before-training stage, performance of dual tasks for Parkinson's disease patients was significantly worse than normal subjects. Even after training, their performance of dual task of sequence-12/letter counting was still not correct (Table 2). This result supports the previous finding that patients have great difficulty in performing two tasks simultaneously (Benecke *et al.*, 1986, 1987; Brown and Marsden 1991; Castiello and Bennett 1997; Oliveira *et al.*, 1998). However, after training most of the patients could perform the dual task of sequence-4/letter counting at the same level as normal subjects. Our results demonstrated that the ability to perform the dual task is not totally lost in patients with Parkinson's disease. With proper training, they can execute some dual tasks correctly. The dual task performance-related central neural processes in patients with Parkinson's disease will be explored in a subsequent paper.

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