Published in final edited form as:
Neuroimage. 2010 February 1; 49(3): 2581. doi:10.1016/j.neuroimage.2009.10.051.

Automatic Movements in PD patients Effective Connectivity of Neural Networks in Automatic Movements in Parkinson's Disease

Tao Wu[1,2], **Piu Chan**[1], and **Mark Hallett**[2]

[1]Department of Neurobiology, Key Laboratory on Neurodegenerative Disorders of Ministry of Education, Beijing Institute of Geriatrics, Xuanwu Hospital, Capital Medical University, Beijing, China

[2]Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Patients with Parkinson's disease (PD) have difficulty in performing learned movements automatically. The neural mechanism of this deficiency remains unclear. In the current study, we used functional MRI (fMRI) and psychophysiological interaction (PPI) methods to investigate the changes in effective connectivity of the brain networks when movements become automatic in PD patients and age-matched normal controls. We found that during automaticity, the rostral supplementary motor area, cerebellum, and cingulate motor area had increased effective connectivity with brain networks in PD patients. In controls, in addition to these regions, the putamen also had automaticity-related strengthened interactions with brain networks. The dorsal lateral prefrontal cortex had more connectivity at the novel stage than in the automatic stage in normal subjects, but not in PD patients. The comparison of the PPI results between the groups showed that the rostral supplementary motor area, cerebellum, and cingulate motor area had significantly more increased effective connectivity with several regions in normal subjects than in PD. The changes of effective connectivity in some areas negatively correlated with the Unified Parkinson's Disease Rating Scale (UPDRS). Our findings show that some of the factors related to PD patients having difficulty achieving automaticity are less efficient neural coding of movement and failure to shift execution of automatic movements more subcortically. The changes of effective connectivty become more abnormal as the disorder progresses. In addition, in PD, the connections of the attentional networks are altered.

Keywords

Parkinson's disease; Automatic movement; fMRI; Effective connectivity; Brain networks

A general characteristic of the motor system is that people can perform some learned movements automatically. Automatic movements are performed without attention being clearly directed toward the details of the movement; automaticity is common particularly for movements requiring low levels of precision or for frequently executed movements (Bernstein 1967). After a period of training, even some complex tasks can be executed automatically in healthy people (Wu et al., 2004). In contrast, patients with Parkinson's disease (PD) commonly

Correspondence to: Mark Hallett, MD, Bldg 10, Rm 7D37, 10 Center Drive MSC 1428, Bethesda, Maryland 20892-1428, USA, Telephone: (301) 496 9526, Fax: (301) 480 2286, hallettm@ninds.nih.gov..

have difficulties in performing movements automatically. For example, PD patients must direct their attention to walking and think about each step if they are to make adequately long steps; otherwise, their steps become small. It has been observed that PD 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).

Previously, we found that PD patients can achieve automaticity in some relatively simple movements after proper training, but with more difficulty than normals. The automatic process was accompanied by reduced activity in many brain regions in normal subjects; in contrast, only a few areas were less activated in PD patients. PD patients require more brain activity in several regions, such as the cerebellum, premotor area (PMA), and parietal cortex compared with controls to perform automatic movements (Wu and Hallett 2005). While this study provided some important insights, we still do not completely understand the mechanisms of this deficiency in PD. So far, we have only explored the changes in magnitude of brain activity; however, we did not investigate whether the interactions within brain networks during the process of automaticity are changed in PD. Investigations about interactions among human brain regions may play a more important role in understanding automaticity-related brain functional changes because multiple areas are likely to be involved in the control of a given task. The method used to explore interregional interactions in a given task is analysis of functional connectivity (Friston et al., 1993a) or effective connectivity (Friston et al., 1993b). In a recent study of a young group of healthy subjects, we found that automaticity is accompanied by a strengthened effective connectivity of motor networks even though the magnitude of the activation is decreased in healthy subjects (Wu et al., 2008). We speculate that the difficulty PD patients have in obtaining automaticity may be due to abnormalities in achieving enhanced connectivity. To test this assumption, we investigated the effective connectivity of neural networks during the process of automaticity in PD compared with age-matched healthy controls.

Subjects and Methods

Subjects

This study represents the further analysis of data already reported (Wu and Hallett 2005). Clinical data of these patients were previously shown (Wu and Hallett 2005), and are briefly described here. We have data from 12 patients aged 53 to 77 years old (mean 61.2), and included eight males and four females. Patients were studied after their medication had been withdrawn for at least 12 h. Off medication, their UPDRS scores were from 13 – 37 (mean 26.7); MMSE was 30 in all subjects. We also had data on 12 age- and sex-matched healthy subjects. The experiments were approved by the Institutional Review Board and all subjects gave their written informed consent.

Tasks

All experimental procedures 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. Automaticity was evaluated by having subjects perform a visual letter-counting task simultaneously with these sequential movements (dual tasks). The dual tasks were performed only before fMRI scanning to assess whether the subjects achieved automaticity. Before the first scan, all subjects practiced until they could move at the required rate. They briefly practiced each sequential movement. After the first scan, subjects

practiced these tasks until they could perform both of the sequential movements from memory 10 times in a row without error as well as the dual tasks accurately.

Functional MRI acquisition

All subjects were scanned on a 1.5 T MRI system (Signa, General Electric, Milwaukee, WI). A response button was used to record finger movements inside the scanner. We used an EPI gradient echo sequence (21 slices, TE=30 ms, TR=2500 ms, flip angle=90°, FOV=22×22 cm, matrix=64×64) to obtain functional images. Data 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, respectively. During 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. Each condition lasted 25 s and was repeated five times within a session.

Data Analysis

Image analysis was performed with SPM2 software (Wellcome Institute of Cognitive Neurology, London, UK). The magnitudes of brain activations during automatic movements in PD have been previously reported (Wu and Hallett 2005). Therefore, we only describe the effective connectivity in this study. Automaticity-dependent changes in effective connectivity were 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. PPI computes whole-brain connectivity between the time series of the index area and the time series of all other voxels. The analysis is constructed to test for the differences in the regression slope of activity in all areas, on the activity in the index area, under the two conditions (automatic vs. novel condition in the present study). We used first session data as the novel condition, and used second session data as the automatic condition. The bi-linear term in PPI represents the interaction between physiological activity and a psychological context input which modulates the connectivity between the index area and the other brain regions, and has a directional character (Stephan et al., 2003). In the current study, PPI identifies areas in which the degree of coupling with the index region is significantly modulated by the process of automaticity.

Similar to our previous study (Wu et al., 2008), we chose the left primary motor cortex (M1), bilateral dorsal premotor area (PMA), bilateral dorsal lateral prefrontal cortex (DLPFC), bilateral cerebellum, left putamen, rostral supplementary motor area (pre-SMA), cingulate motor area (CMA), and precuneus as index areas because these regions are thought to be involved in the process of automaticity or are important in motor learning. Separate PPI analyses were conducted for each index area. The mean corrected and high-passed-filtered time series in each index area were obtained on a subject-by-subject basis by extracting the first principal component from all voxel time series in a 5-mm radius sphere centered at the coordinates of the subject specific activations. The psychophysiological interaction term (referred to as "PPI regressor") was computed as the element-by-element product of the deconvolved extracted time series of the selected index area and a vector coding for the main effect of task (1 for automatic stage, −1 for before automatic stage, 0 elsewhere) (Stephan et al., 2003; Gitelman et al., 2003; Garraux et al., 2005). The PPI regressor was mean corrected to remove subject-specific effects and convolved by the canonical hemodynamic response function to account for possible hemodynamic lag. For each subject, the PPI regressor, the task regressor (representing the automatic minus novel contrast for the main effect of automaticity), 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 index areas that were greater during the automatic stage than the novel stage were determined by testing for positive slopes of the PPI regressor, i.e., by applying a t-contrast that was 1 for the PPI regressor and 0 elsewhere. Conversely, brain areas receiving context-dependent influences from the index areas that were greater during the novel stage than the automatic stage were determined by testing for negative slopes of the PPI regressor, i.e., by applying a t-contrast that was −1 for the PPI regressor and 0 elsewhere. Contrast images from the first-level PPI analysis in each subject were entered into a second-level random-effect model. At the second-level, to detect the regions that receive greater influences from each index area during the automatic stage, the contrast images from each subject showing greater influences during the automatic stage than the novel stage were calculated by a one-sample t-test in either patients and controls ($p < 0.05$, FWE corrected). Then, contrast images from each subject showing greater influence during the novel stage than the automatic stage were calculated by another one-sample t-test to detect the regions that receive greater influences from each index area during the novel stage in each group ($p < 0.05$, FWE corrected). In addition, we entered the contrast images from each PD patients and controls showing greater influence during the novel stage than the automatic stage into a two-sample t-test model to compare the PPI results between the groups ($p < 0.05$, FWE corrected).

Finally, in order to explore whether the changes of effective connectivity of brain networks correlate with the disease severity, a correlation analysis of effective connectivity in each index area versus the UPDRS score was performed in PD patients.

RESULTS

The behavioral data have been shown before (Wu and Hallett 2005), and only briefly described here. Before training, both groups committed errors in performing all sequential movements. After extensively training, 12 patients could only perform sequence 4, but not sequence 12 automatically. The finger movement errors in performing sequence 4 at the novel stage were 5.1 ± 8.8 %, and 4.8 ± 6.4 % in patients and controls, respectively. At the automatic stage, both groups made no errors. There was no between-group difference in performing sequence 4 at the both before and after training stage (two sample t-test, $p > 0.05$). In addition, 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 healthy subjects were 0.54 ± 0.07 Hz and 0.52 ± 0.06 Hz, respectively. Therefore, we only performed automatic-related effective connectivity analysis during performance of sequence 4.

The mean coordinates of the index areas across all subjects are: left M1, x = −28, y = −21, z = 54; left dorsal PMA, x = −36, y = 9, z = 52; right dorsal PMA, x = 41, y = −2, z = 49; left DLPFC, x = −42, y = 32, z = 44; right DLPFC, x = 44, y = 34, z = 24; left cerebellum, x = −16, y = −41, z = −11; right cerebellum, x = 12, y = −62, z = −8; left putamen, x = −24, y = −11, z = 4; pre-SMA, x = 4, y = 4, z = 56; CMA, x = 4, y = 30, z = 26; precuneus, x = −6, y = −64, z = 46. PPI analysis showed that in PD, only the pre-SMA, CMA and left cerebellum had significantly stronger psychophysiological interactions ($p < 0.05$, FWE corrected) with a number of brain regions at the automatic stage compared to the novel stage (Table 1). In healthy controls, the pre-SMA, CMA, bilateral cerebellum and left putamen had increased interactions ($p < 0.05$, FWE corrected) with brain networks at the automatic stage compared to the novel stage (Table 2). In addition, more brain regions showed strengthened connectivity with the pre-SMA, CMA, or cerebellum in controls than that in PD patients during the process of automaticity (Tables 1 and 2). Figure 1 shows the areas that receive a significant automaticity-process dependent influence from the pre-SMA in PD (A) and healthy controls (B).

In healthy subjects, we found that the left DLPFC had a stronger connection with the left PMA and bilateral middle frontal gyrus at the novel stage than at the automatic stage (Figure 2; $p < 0.05$, FWE corrected). In contrast, PD patients did not show any greater interactions at the novel stage compared to the automatic stage in any index area.

Because both groups had significantly stronger psychophysiological interactions in the pre-SMA, CMA and left cerebellum with a number of brain regions at the automatic stage compared to the novel stage (Table 1 and 2), we performed between-group comparisons of PPI results in these index areas. We found that all three index areas had significantly more increased effective connectivity with several regions in healthy subjects than in PD patients (Table 3).

We further performed a correlation analysis in the pre-SMA, CMA and left cerebellum in PD patients. In each index area, PPI results were negatively correlated with the UPDRS in some brain regions ($p < 0.05$, FWE corrected; Fig. 3 and Table 4), which means as the UPDRS increased, the psychophysiological interactions between the index area and these brain regions are weakened. We did not find any regions that showed positive correlation between PPI results and UPDRS.

DISCUSSION

Our previous study explored brain activity contributing to the deficiency of performing learned movements automatically in PD (Wu and Hallett 2005). The current investigation further revealed that the changes of interactions of brain networks accompanying the automatic process were different between PD patients and healthy controls. The addition of results from this study to those of the previous research (Wu and Hallett 2005) better defines the underlying mechanisms of difficulty in automatic movements in PD.

In healthy controls, the development of automaticity is accompanied by a modification of the effective connectivity of the brain networks; several areas have strengthened psychophysiological interactions with numerous brain areas at the automatic stage (Table 2). These observations are consistent with previous findings on young subjects and demonstrate that the process of automaticity is accompanied by a strengthened interaction within the motor networks even though the magnitude of the activation is decreased (Wu et al., 2008). In PD patients, we also found stronger automaticity process-dependent interactions of brain networks in the pre-SMA, CMA, and left cerebellum (Tables 1). However, from our previous study (Wu and Hallett 2005), these regions are not less activated as movements become automatic in PD. This finding indicates that the change of effective connectivity is independent from the change of activity; even without significant modification of activation, brain networks can become more tightly connected.

The pre-SMA has a role in storing learned motor sequences in monkeys as well as in human subjects (Grafton et al., 1994; Jenkins et al., 1994; Tanji and Shima 1994). It may be involved in preparing and executing highly practiced, remembered movement sequences, especially in programming and executing movement sequences (Grafton et al., 1994; Jenkins et al., 1994; Tanji and Shima 1994; Nakamura et al., 1999). The CMA has a role in preparing and executing highly practiced, remembered movement sequences (Picard and Strick 1996). The cerebellum is also important for learning skilled movements (Doyon et al., 1998; Thach 1998; Laforce et al., 2001; Lang and Bastian 2002), and is critical for both switching learned motor tasks into a more automatic stage and executing automatic movements (Doyon et al., 1996; Toni et al., 1998; Lang and Bastian 2002; Wu et al., 2004). Therefore, more efficient connectivity in these regions indicates an increased efficacy of connections, which presumably allows the brain to function more efficiently in a given task, and is likely an important reason that PD patients can perform some relatively simple learned movements automatically. However, more index areas

showed increased connectivity in the automatic stage in controls than in patients (right cerebellum and putamen). In addition, there were more brain regions that receive automaticity-dependent influence from the pre-SMA, CMA, or left cerebellum in controls than that in patients (Table 3). Thus, in PD patients, not only do they need more brain activity (Wu and Hallett 2005), but also their brain networks are not becoming as tightly connected as that in controls. It appears that the brain networks are less efficient in PD compared to those in healthy controls, which might explain why it is more difficult for PD patients to achieve automaticity in performing more complex movements.

We found stronger effective connectivity between the putamen and several cortical areas in the automatic stage in controls, which is consistent with a previous finding that motor learning is associated with increased effective connectivity in cortico-striatal circuits (Toni et al., 2002). The basal ganglia are involved in movement programming and executing (Alexander et al., 1990). The stronger automaticity-related effective connectivity of networks in the basal ganglia and cerebellum, but not in the DLPFC, PMA, or M1, suggests that executing automatic movements is shifted more subcortically in controls (Wu et al., 2008). In PD, dopamine uptake is reduced in the striatum and the most severely affected region is the putamen (Brooks et al., 1990). Possibly, due to the dysfunction of the basal ganglia, PD patients have difficulty shifting automatic movement performance subcortically; thus, we could not find automaticity-related increase of connectivity in the putamen in PD.

PPI results in the pre-SMA, CMA, and cerebellum all show significantly negative correlation with UPDRS in PD in some brain regions (Fig. 3 and Table 4). This finding suggests that as the disorder progresses, the changes of effective connectivity during automatic process in PD become more abnormal.

In controls, the left DLPFC has more effective connectivity with the PMA and middle frontal gyrus in the novel stage than in the automatic stage (Fig. 2). In our previous study, we found that the precuneus, but not the DLPFC, had stronger effective connectivity at the novel stage (Wu et al., 2008). The reason for this difference is likely due to the effect of aging: healthy controls in this investigation were older (53 – 77 years old, (mean 61.2)), whereas in the former study the subjects were considerably younger (21 – 38, (mean 27.2); Wu et al., 2008). We have previously shown that there are differences with the effect of healthy aging on the magnitude of brain activity for automatic movements (Wu and Hallett 2005). Thus, it is likely that the current finding shows that aging also affects the interactions of brain networks during the process of automaticity, which should be further explored in the future. Because the DLPFC is important in motor attention (Grafton et al., 1995;Jueptner et al., 1997), less connectivity from this area to other motor regions may indicate that cortical attention networks are no longer critical as movement becomes automatic in healthy controls. Since the precuneus is also implicated in attention, this is a similar argument to what we made for the younger healthy subjects. In contrast to the older controls, no stronger connectivity at the novel stage was found in PD. This finding is consistent with a previous report that when performing movements that require attention to action, the effective connectivity between the prefrontal cortex and the PMA was increased in healthy subjects, but not in PD patients (Rowe et al., 2002). These findings demonstrate that the attentional networks are disrupted in PD. The connectivity of these networks is not decreased during automaticity in PD, either because the attentional networks are still important in the automatic stage or because those networks are not working properly at both the novel and automatic stages.

In PD patients, their brain networks are not as strongly connected as those in healthy controls during the process of automaticity. The tendency of shifting execution of automatic movements subcortically in PD is not as clear as that in controls, and the attentional networks are also

altered in PD. All these changes should be important reasons contributing to the difficulty PD patients have when performing learned movements automatically.

In animal studies, it has been demonstrated that dopamine depletion alters functional connectivity of brain networks (Loucif et al., 2005; Dejean et al., 2008), and dopamine replacement may be important for maintenance of stability in local neuronal networks (Bandyopadhyay and Hablitz 2007). In healthy human subjects, dopamine administration increases functional connectivity of cortico-striato-thalamic systems (Honey et al., 2003), or in motor pathways connecting the putamen with the cerebellum in normal human subjects (Kelly et al., 2009). In a recent study, we found that dopamine administration could relatively normalize the pattern of connectivity of motor networks in PD in the resting state (Wu et al., 2009). Presumably, dopamine replacement may relatively normalize the interactions of brain networks during process of automaticity in PD, and this aspect is worth further study.

Because the current study was focused on the automatic process related changes of effective connectivity, we did not investigate the pattern of effective connectivity within the novel or automatic stages themselves in PD patients. PPI analysis can only investigate changes of interactions of brain networks due to a change in experimental stage or psychological context (Friston et al., 1997); in the future, other connectivity methods, like correlation, structural equation modeling (SEM), or dynamic causal modeling (DCM) could be used to explore the connectivity of brain networks within the automatic stage in PD, which might provide further insights to our understanding about deficits of automaticity in PD.

Acknowledgments

T. Wu was supported by a National Institute of Neurological Disorders and Stroke Intramural Competitive Fellowship. This work was partially supported by the National Science Foundation of China, Grant No. 30570530 and 30870693. In addition, this work was supported in part by the Intramural Research Program of the NINDS, NIH.

REFERENCES

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990;13:266–271. [PubMed: 1695401]

Bandyopadhyay S, Hablitz JJ. Dopaminergic modulation of local network activity in rat prefrontal cortex. J Neurophysiol 2007;97:4120–8. [PubMed: 17392423]

Bernstein, N. The co-ordination and regulation of movements. Pergamon Press Ltd.; London: 1967.

Brooks DJ, Ibanez V, Sawle GV, Quinn N, Lees AJ, Mathias CJ, Bannister R, Marsden CD, Frackowiak RS. Differing patterns of striatal 18F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Ann. Neurol 1990;28:547–555. [PubMed: 2132742]

Dejean C, Gross CE, Bioulac B, Boraud T. Dynamic changes in the cortex-basal ganglia network after dopamine depletion in the rat. J Neurophysiol 2008;100:385–396. [PubMed: 18497362]

Doyon J, Laforce R, Bouchard G, Gaudreau D, Roy J, Poirer M, Bedard PJ, Bedard F, Bouchard JP. Role of the striatum, cerebellum, and frontal lobes in the automatization of a repeated visuomotor sequence of movements. Neuropsychologica 1998;36:625–641.

Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur. J Neurosci 1996;8:637–648. [PubMed: 9081615]

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 1997;6:218–229. [PubMed: 9344826]

Friston KJ, Frith CD, Frackowiak RS. Time-dependent changes in effective connectivity measured with PET. Hum. Brain Mapp 1993b;1:69–80.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal component analysis of large (PET) data sets. J Cereb. Blood Flow. Metab 1993a;13:5–14. [PubMed: 8417010]

Garraux G, McKinney C, Wu T, Kansanku K, Nolte G, Hallett M. Shared brain areas but not functional connections controlling movement timing and order. J Neurosci 2005;25:5290–5297. [PubMed: 15930376]

Gitelman DR, Penny WD, Ashburner J, Friston KJ. Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. NeuroImage 2003;19:200–207. [PubMed: 12781739]

Grafton ST, Hazeltine E, Ivry R. Functional mapping of sequence learning in normal humans. J Cognit. Neurosci 1995;7:497–510.

Grafton ST, Woods RP, Tyszka M. Functional imaging of procedural motor learning: relating cerebral blood flow with individual subject performance. Hum. Brain Map 1994;1:221–234.

Hoshiyama M, Kaneoke Y, Koike Y, Takahashi A, Watanabe S. Hypokinesia of associated movement in Parkinson's disease: a symptom in early stages of the disease. J Neurol 1994;241:517–521. [PubMed: 7798998]

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RSJ, Passingham RE. Motor sequence learning: a study with positron emission tomography. J Neurosci 1994;14:3775–3790. [PubMed: 8207487]

Jueptner M, Stephan KM, Frith CD, Brooks DJ, Frackowiak RSJ. Anatomy of motor learning. I. Frontal Cortex and attention to action. J Neurophysiol 1997;77:1313–1324. [PubMed: 9084599]

Kelly C, de Zubicaray G, Di Martino A, Copland DA, Reiss PT, Klein DF, Castellanos FX, Milham MP, McMahon K. L-dopa modulates functional connectivity in striatal cognitive and motor networks: a double-blind placebo-controlled study. J Neurosci 2009;29:7364–78. [PubMed: 19494158]

Laforce RJ, Doyon J. Distinct contribution of the striatum and cerebellum to motor learning. Brain Cogn 2001;45:189–211. [PubMed: 11237366]

Lang CE, Bastian AJ. Cerebellar damage impairs automaticity of a recently practiced movement. J Neurophysiol 2002;87:1336–1347. [PubMed: 11877508]

Loucif KC, Wilson CL, Baig R, Lacey MG, Stanford IM. Functional interconnectivity between the globus pallidus and the subthalamic nucleus in the mouse brain slice. J Physiol 2005;567:977–87. [PubMed: 16037086]

Nakamura K, Sakai K, Hikosaka O. Effects of local inactivation of monkey medial frontal cortex in learning of sequential procedures. J Neurophysiol 1999;82:1063–1068. [PubMed: 10444698]

Picard N, Strick PL. Medial wall motor areas: a review of their location and functional activation. Cereb. Cortex 1996;6:342–353. [PubMed: 8670662]

Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. Brain 2002;125:276–289. [PubMed: 11844728]

Stephan KE, Marshall JC, Friston KJ, Rowe JB, Ritzl A, Zilles K, Fink GR. Lateralized cognitive processes and lateralized task control in the human brain. Science 2003;301:384–386. [PubMed: 12869765]

Tanji J, Shima K. Role for supplementary motor area cells in planning several movements ahead. Nature 1994;371:413–416. [PubMed: 8090219]

Thach WT. A role for the cerebellum in learning and movement coordination. Neurobiol. Learn Mem 1998;70:177–188. [PubMed: 9753595]

Toni I, Krams M, Turner R, Passingham RE. The time course of changes during motor sequence learning: a whole-brain fMRI study. Neuroimage 1998;8:50–61. [PubMed: 9698575]

Toni I, Rowe J, Stephan KE, Passingham RE. Changes of cortico-striatal effective connectivity during visuomotor learning. Cereb. Cortex 2002;12:1040–1047. [PubMed: 12217967]

Wu T, Chan P, Hallett M. Modifications of the interactions in the motor network when a movement becomes automatic. J Physiol 2008;586:4295–4304. [PubMed: 18617569]

Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain 2005;128:2250–2259. [PubMed: 15958505]

Wu T, Hallett M. The influence of normal human ageing on automatic movements. J Physiol 2005;562:605–615. [PubMed: 15513939]

Wu T, Kansaku K, Hallett M. How self-initiated memorized movements become automatic: a fMRI study. J Neurophysiol 2004;91:1690–1698. [PubMed: 14645385]

Wu T, Wang L, Chen Y, Zhao C, Li K, Chan P. Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. Neurosci Lett 2009;460:6–10. [PubMed: 19463891]

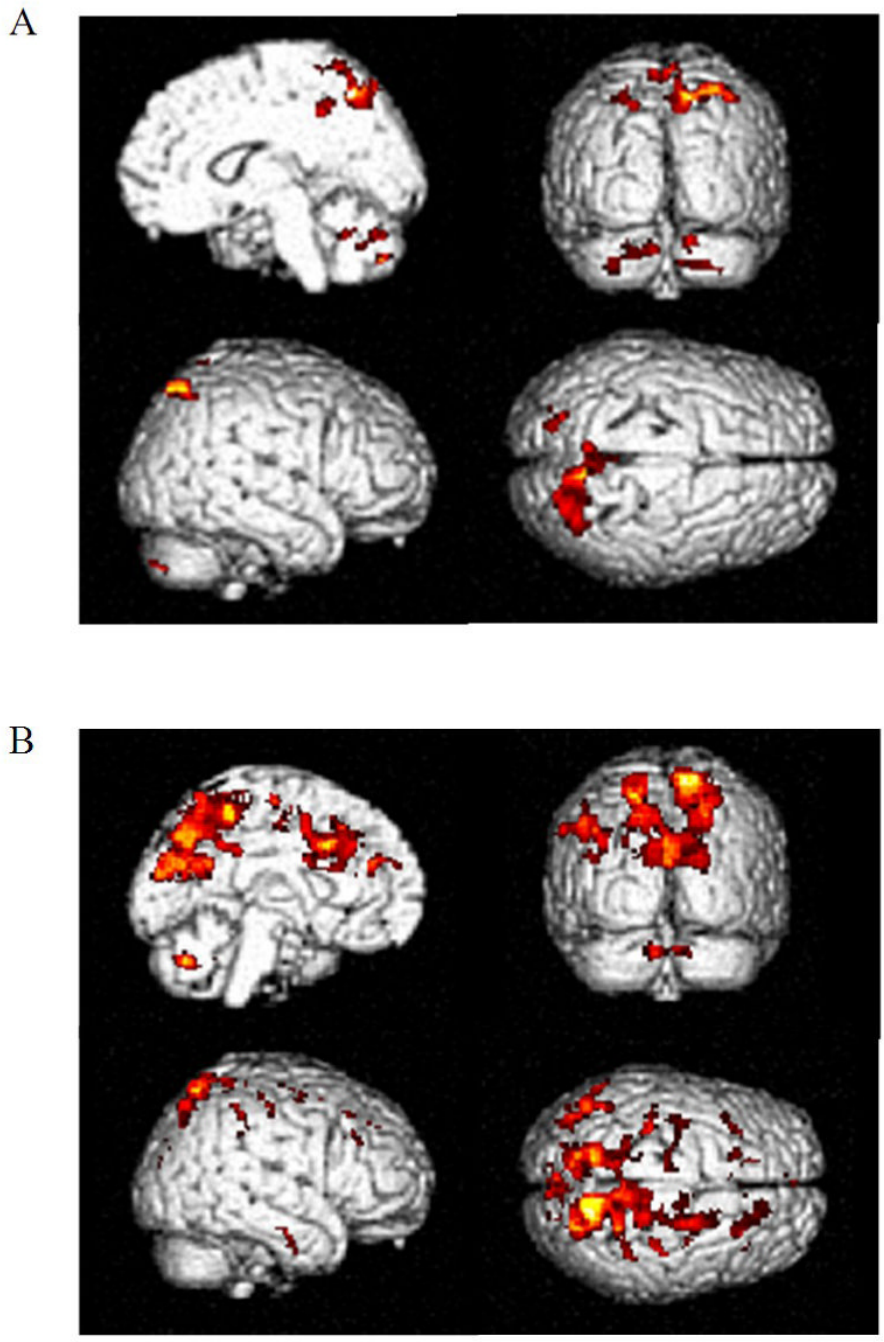

Figure 1.
Psychophysiological interaction (PPI) results from the rostral supplementary motor area (pre-SMA) in Parkinson's disease (PD) patients (A) and normal controls (B). Brain regions are shown that receive significantly more influence from the pre-SMA at the automatic stage compared to the novel stage ($p < 0.05$, FWE corrected).

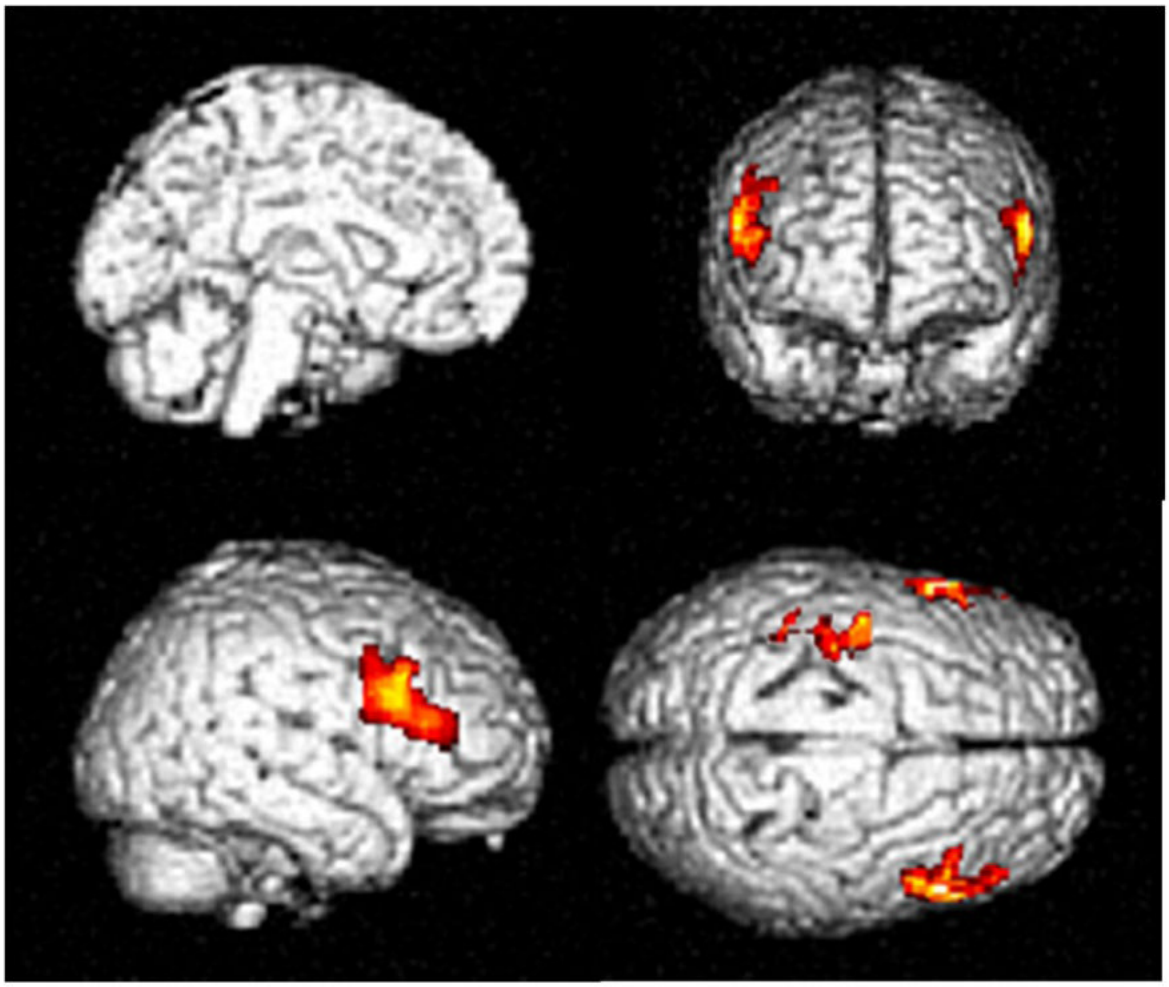

Figure 2.
PPI results from the left dorsal lateral prefrontal cortex (DLPFC) in normal subjects. Brain regions are shown that receive significantly more influence from the left DLPFC at the novel stage compared to the automatic stage ($p < 0.05$, FWE corrected).

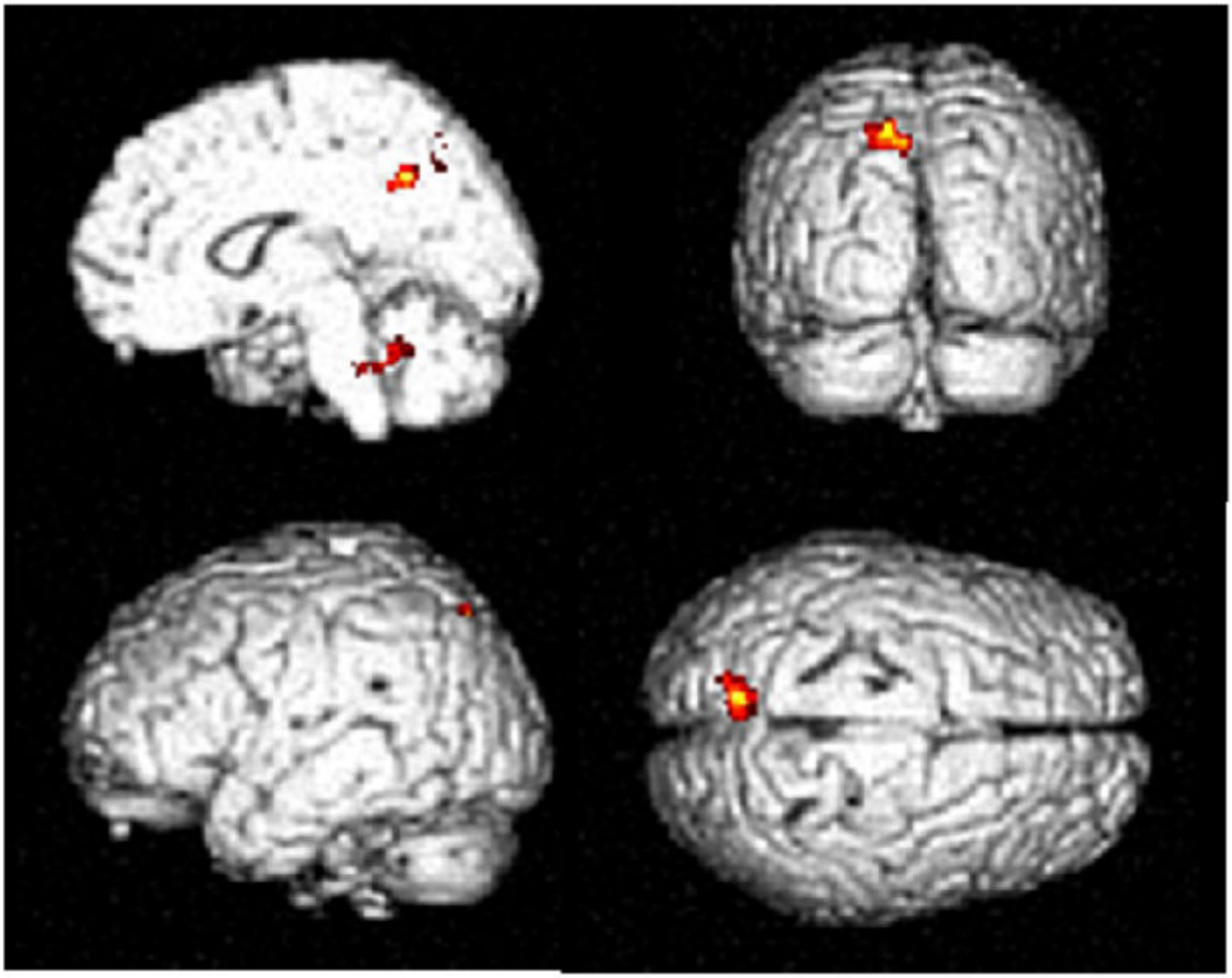

Figure 3.
Results of correlation analysis between the UPDRS (Unified Parkinson's Disease Rating Scale) and PPI results in the pre-SMA in PD patients ($p < 0.05$, FWE corrected). Brain regions are shown that have negative correlation between PPI results and UPDRS.

Table 1

Results of correlation analysis between the UPDRS (Unified Parkinson's Disease Rating Scale) and PPI results in the pre-SMA in patients with Parkinson's disease

Index Area	Areas Receiving Stronger Influence	Brodmann area	Cluster Size	Coordinates			Z-value
				x	y	z	
Pre-SMA	R Precuneus	7	566	12	−58	53	17.21
	L Superior Parietal Lobule	7	684	−20	−67	57	8.64
	R Cingulate	31	125	6	−41	42	5.09
	L Cerebellum, Posterior Lobe, Pyramis		117	−6	−79	−25	7.96
	R Cerebellum, Posterior Lobe, Declive		168	14	−73	−18	6.16
LCB	L Frontal Lobe, Medial Frontal Gyrus	10	96	−4	57	10	6.00
	R Frontal Lobe	13	138	30	11	22	4.52
	L Frontal Lobe, Superior Frontal Gyrus	10	83	−22	62	2	5.01
	L Precentral Gyrus	6	291	−44	−4	46	4.80
	L Caudate		102	−6	4	0	5.77
CMA	R Superior Parietal Lobule	7	298	34	−61	55	8.25
	L Precuneus	7	60	−10	−50	47	7.40
	L Frontal Lobe, Middle Frontal Gyrus	8	83	−42	20	43	7.02
	L Frontal Lobe, Medial Frontal Gyrus	6	73	−4	−3	54	6.64
	R Cingulate	32	89	6	16	40	4.64

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 $P < 0.05$, FWE corrected. Abbreviations: L: left; R: right; CB: cerebellum; CMA: cingulate motor area; Pre-SMA: pre-supplementary motor area.

Table 2

Brain areas receiving significant automaticity-process dependent influences from the index areas in normal subjects

Index Area	Areas Receiving Stronger Influence	Brodmann area	Cluster Size	Coordinates			Z-value
				x	y	z	
Pre-SMA	R Frontal Lobe, Paracentral Lobule	4	2123	8	−36	63	12.08
	R Medial Frontal Gyrus	9	167	2	42	20	8.29
	R Middle Frontal Gyrus	9	133	36	27	30	7.16
	L Parietal Lobe, Supramarginal Gyrus	40	108	−55	−54	36	6.81
	L Inferior Parietal Lobule	40	134	−46	−60	38	6.42
	L Cingulate Gyrus	32	1147	−8	11	34	6.38
	R Postcentral Gyrus	3	108	38	−19	47	5.97
	R Middle Temporal Gyrus	39	131	55	−65	24	5.87
	R Cingulate Gyrus	32	89	4	19	34	5.30
	L Precentral Gyrus	6	112	−34	−5	50	5.22
	L Cerebellum, Posterior Lobe, Pyramis		313	−6	−67	−25	5.56
	R Cerebellum, Posterior Lobe, Pyramis		198	18	−64	−27	5.52
LCB	L Medial Frontal Gyrus	6	1288	−8	4	52	7.86
	L Precentral Gyrus	6	176	−40	−9	48	7.14
	L Cingulate Gyrus	24	299	−4	−10	30	6.63
	L Frontal Lobe, Paracentral lobule	5	249	−10	−32	54	5.84
	R Middle Temporal Gyrus	20	83	50	−30	−14	5.68
	R Cingulate	32	168	6	25	32	5.47
	R Caudate Nucleus		150	8	12	4	6.87
	R Cerebellum, Posterior Lobe, Uvula		128	24	−67	−25	6.37
RCB	R Middle Frontal Gyrus	8	164	36	23	41	6.18
	L Cingulate	32	188	−8	21	32	5.55
	L Temporal Lobe, Fusiform Gyrus	20	94	−42	−28	−16	5.48
	L Postcentral Gyrus	3	162	−22	−32	56	5.14
	R Precuneus	7	286	31	−48	52	4.90
	L Superior Parietal Lobule	7	109	−31	−62	58	4.87

Index Area	Areas Receiving Stronger Influence	Brodmann area	Cluster Size	Coordinates			Z-value
				x	y	z	
	L Cerebellum, Anterior Lobe, Culmen		458	−15	−32	−14	6.59
CMA	L Cingulate Gyrus	24	910	−12	2	42	8.12
	R Precuneus	7	331	6	−65	40	6.76
	L Posterior Cingulate	31	1284	−22	−63	14	6.42
	L Middle Temporal Gyrus	19	121	−40	−77	22	6.31
	R Precentral Gyrus	6	80	46	−7	8	6.02
	R Precentral Gyrus	4	126	24	−22	52	5.98
	R Cingulate Gyrus	24	139	16	−5	46	5.86
	R Superior Frontal Gyrus	11	235	20	52	−13	5.29
	L Inferior Parietal Lobule	40	186	−42	−49	37	4.98
	R Parahippocampal Gyrus		188	27	−31	−7	5.73
	L Cerebellum, Anterior Lobe, Culmen		288	−4	−42	−21	6.99
	R Cerebellum, Posterior Lobe, Tonsil		192	−22	−60	−32	6.26
	Putamen L Postcentral Gyrus	3	73	−26	−32	60	7.11
	R Precentral Gyrus	4	612	34	−20	54	6.25
	L Cingulate	31	270	−10	−37	33	5.86
	R Superior Frontal Gyrus	11	118	30	52	−13	5.53
	R Cingulate	24	78	4	−2	41	5.30
	L Insula	13	119	−38	14	−1	5.17
	L Cerebellium, Posterior Lobe, Declive		114	−8	−79	−21	6.01

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 $P < 0.05$, FWE corrected. Abbreviations: L: left; R: right; CB: cerebellum; CMA: cingulate motor area; Pre-SMA: pre-supplementary motor area.

Table 3

Brain areas receiving more significant automaticity-process dependent influences from the index areas in normal subjects compared to PD patients

Index Area	Areas Receiving Stronger Influence	Brodmann area	Cluster Size	Coordinates			Z-value
				x	y	z	
Pre-SMA	L Cingulate Gyrus	32	223	−8	19	36	5.78
	R Middle Temporal Gyrus	19	167	40	−78	24	5.59
	L Precuneus	7	86	−8	−55	58	5.18
	L Middle Temporal Gyrus	19	109	−38	−80	22	5.10
	R Cerebellum, Posterior Lobe, Declive		146	36	−73	−16	5.26
LCB	L Precentral Gyrus	6	106	−40	−7	46	5.14
	L Paracentral Lobule	31	69	−10	−13	47	5.13
	L Cingulate Gyrus	24	118	−14	6	36	5.07
	R Caudate Nucleus		98	12	12	−2	5.86
CMA	L Cingulate Gyrus	32	210	−8	23	34	6.14
	R Anterior Cingulate	32	171	20	30	22	5.64
	L Cingulate Gyrus	24	84	−12	−12	37	5.51
	R Precentral Gyrus	4	58	20	−28	53	5.12
	L Thalamus		61	−14	−5	11	5.32
	L Cerebellum, Posterior Lobe, Uvula		102	−16	−67	−24	5.94
	R Cerebellum, Posterior Lobe, Pyramis		92	12	−73	−23	5.87

The results are the comparison between PD patients and controls (two sample t-test, $p < 0.05$, FWE corrected). The coordinates are given as stereotaxic coordinates referring to the atlas of Talairach and Tournoux. Cluster size is the number of voxels. Abbreviations: L: left; R: right; CB: cerebellum; CMA: cingulate motor area; Pre-SMA: pre-supplementary motor area.

Table 4

Results of correlation analysis between the UPDRS (Unified Parkinson's Disease Rating Scale) and PPI results in the pre-SMA, left cerebellum, and CMA in patients with Parkinson's disease

Index Area	Areas	Brodmann area	Cluster Size	Coordinates			Z-value
				x	y	z	
Pre-SMA	L Precuneus	7	139	−10	−62	51	10.40
	R Precuneus	7	70	12	−52	38	7.37
	R Cerebellum, Posterior Lobe, Tonsil		83	24	−34	−34	8.19
LCB	L Frontal Lobe, Medial Frontal Gyrus	10	78	−10	59	12	7.85
	L Precentral Gyrus	4	73	−28	−15	47	6.20
	L Caudate		62	−16	1	26	7.05
CMA	L Precuneus	7	128	−12	−51	36	8.48
	R Cingulate	30	281	−8	−60	14	7.08

The results are shown that have negatively correlation between PPI results and UPDRS in each index area. 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 $P < 0.05$, FWE corrected. Abbreviations: L: left; R: right; CB: cerebellum; CMA: cingulate motor area; Pre-SMA: pre-supplementary motor area.