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Dynamic changes in cerebello-thalamo-cortical motor circuitry during progression of Parkinson's disease

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Abstract

Both the basal ganglia and cerebellum are known to influence cortical motor and motor-associated areas via the thalamus. Whereas striato-thalamo-cortical (STC) motor circuit dysfunction has been implicated clearly in Parkinson's disease (PD), the role of the cerebello-thalamo-cortical (CTC) motor circuit has not been well defined. Functional magnetic resonance imaging (fMRI) is a convenient tool for studying the role of the CTC *in vivo* in PD patients, but large inter-individual differences in fMRI activation patterns require very large numbers of subjects in order to interpret data from cross-sectional, case control studies. To understand the role of the CTC during PD progression, we obtained *longitudinal* fMRI two years apart from five PD (57 ± 8 yr) and five Controls (57 ± 9 yr) performing either externally- (EG) or internally-guided (IG) sequential finger movements. All PD subjects had unilateral motor symptoms at baseline, but developed bilateral symptoms at follow-up. Within-group analyses were performed by comparing fMRI activation patterns between baseline and follow-up scans. Between-group comparisons were made by contrasting fMRI activation patterns generated by the more-affected and less-affected hands of PD subjects with the dominant and non-dominant hands of Controls, respectively. *Compared to baseline*, Controls showed changes in CTC circuits, but PD subjects had increased recruitment of both cortical motor-associated and cerebellar areas. *Compared to Controls*, PD subjects demonstrated augmented recruitment of CTC circuits over time that was statistically significant when the IG task was performed by the hand that transitioned from non-symptomatic to symptomatic. This *longitudinal* fMRI study demonstrates increased recruitment of the CTC motor circuit concomitant with PD progression, suggesting a role of the CTC circuit in accommodation to, or pathophysiology of, PD.

Keywords

Parkinson's disease; Longitudinal; FMRI; Cerebellum; Neurocircuits; Motor Control

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Parkinson's disease (PD) is a progressive, neurodegenerative disorder characterized by asymmetrical onset of motor symptoms such as bradykinesia, rigidity, and tremor. The principal pathology in PD is the loss of dopamine neurons in the substantia nigra *pars compacta*, but the exact pathophysiology of all PD motor symptoms is unclear. Much of the current understanding of motor control is guided by an elegant model of basal ganglia (BG) function first developed nearly two decades ago (Albin et al., 1989; Alexander et al., 1990; Alexander et al., 1986; DeLong et al., 1984). In this classic model, the BG was suggested to affect motor control by modulating cortical function through striato-thalamo-cortical motor circuits (STC). Although this model provides an adequate explanation for bradykinesia, it does not address many other aspects of PD motor symptoms including compensation that occurs during PD progression.

The cerebellum also is an important component in motor control, and is known to influence cerebral cortical activity via cerebello-thalamo-cortical (CTC) circuits (Afifi and Bergman, 1998). These CTC circuits have been implicated in somatosensory integration (Manzoni, 2007) and information updating (Bonnefoi-Kyriacou et al., 1998). The role of the cerebellum in PD pathophysiology, however, is not well understood.

The motor deficits of PD are primarily related to volitional initiation of movement that has been termed internally-guided (IG). The internal motor deficits in PD subjects can be overcome by external visual or auditory cues (Chuma et al., 2006; Jahanshahi et al., 1995; Nowak et al., 2006). Recent functional magnetic resonance imaging (fMRI) studies suggested a role for the cerebellar circuit in externally-guided (EG) tasks (Debaere et al., 2003; Taniwaki et al., 2003; Taniwaki et al., 2006). It has been postulated that the CTC circuit may provide a potential compensatory mechanism in PD to overcome the deficits in the STC circuit, an hypothesis supported by several recent fMRI studies (Cerasa et al., 2006; Lewis et al., 2007; Taniwaki et al., 2006). These latter studies, however, were done using cross-sectional designs. The large inter-individual differences in fMRI activation patterns make it difficult to study temporal changes in neurocircuitry during PD progression using a cross-sectional, case control design.

Two recent positron emission tomography (PET) studies reported longitudinal changes in PD subjects in cortical, BG, and cerebellar structures. Huang et al. (Huang et al., 2007) measured dopamine transporter binding and cortical/subcortical glucose metabolism changes in PD subjects over time, but their imaging protocol did not involve a motor task. In another study, Carbon et al. (Carbon et al., 2007) assessed both brain activation and motor performance during an externally-cued motor paradigm in PD and control subjects. Although the changes in brain activation in PD subjects over time were compared, there were no comparisons made to changes in Controls (Carbon et al., 2007). The current study investigates the changes in the recruitment patterns in STC and CTC motor circuits in both EG and IG tasks during the progression of PD as compared to changes over a similar time period in age-matched Controls. Our data show clearly that function of the CTC circuit changes with progression of PD.

Experimental procedures

Subjects

Five newly diagnosed PD subjects (57 ± 8 yrs) with unilateral motor symptoms and five healthy control subjects (57 ± 9 yrs) were recruited from a movement disorder specialty clinic. All subjects were strongly right-handed as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971). Three of five PD subjects started with right-hand symptoms, whereas the other two started with left-hand symptoms. Each PD subject was diagnosed by a movement disorders specialist (XH) based on previously published criteria (Gibb and Lees, 1988). All subjects were scanned twice approximately two years apart (21.6 ± 4.5 months for PD, and

20.0 $\pm$ 2.4 months for Controls). All PD subjects had unilateral motor symptoms at baseline, but developed bilateral symptoms at follow-up. Prior to each fMRI scan, PD subjects were asked to withhold their antiparkinson medication for approximately 12 hours, and all subjects were asked not to imbibe any caffeinated or alcoholic beverages for 24 hours prior to the scan (Table 2). Controls were found free of any signs of other neurological and psychological deficits, and were not taking any drugs with psychoactive properties. Subjects in both groups were negative for hypothyroidism, vitamin B₁₂ or folate deficiency, and were free of kidney or liver disease. The study protocol followed the Helsinki principles, and was reviewed and approved by the University of North Carolina Institutional Review Board. Written informed consent was obtained from all subjects who participated in the study.

FMRI data acquisition

Images were acquired on a 3.0 Tesla Siemens scanner (Siemens, Erlangen, Germany) with a birdcage-type standard quadrature head coil and an advanced nuclear magnetic resonance echoplanar system. The head was positioned along the canthomeatal line and foam padding was used to limit head motion. High-resolution T1 weighted anatomical images (3D SPGR, TR=7.7 ms, TE=14 ms, flip angle=25°, voxel dimensions 1.0×1.0×1.0 mm, 176×256 voxels, 160 slices) were acquired for co-registration and normalization of functional images. A total of 49 co-planar functional images were acquired using a gradient echoplanar sequence (TR=3000 ms, TE=30 ms, flip angle=80°, NEX=1, voxel dimensions 3.0×3.0×3.0 mm, imaging matrix 64×64 voxels). Two radio frequency excitations were performed prior to image acquisition to achieve steady-state transverse relaxation.

FMRI Activation Paradigm

This study used a modified activation paradigm based on previous studies in control and PD subjects (Lewis et al., 2007; Sabatini et al., 2000). Briefly, the paradigm consisted of sequential finger-tapping movements (SFM) at 0.5 tap/sec using either the right or the left hand. The sequences were presented with instructions either to follow the hands on the screen (EG task) or to continue the finger-tapping sequence (IG task). Each SFM block was 60 seconds long, and each block was preceded and followed by a 30 second rest (R) period. Each run consisted of four blocks of rest, EG, and IG tasks (total 10 minutes, Figure 1). The finger-tapping sequences of each block were alternated to prevent memorization from previous blocks (see Table 1). In order to obtain adequate performance on the tasks, all subjects practiced the task for about 20 min prior to scanning session, demonstrating greater than 90% accuracy. Two runs of fMRI data from each subject were included in the analysis.

FMRI Image pre-processing

The fMRI data was preprocessed using SPM5 software (Wellcome Trust Center for Neuroimaging, London, UK) for spatial realignment and motion correction. The spatial smoothing of functional time series was performed with a Gaussian smoothing kernel with full width at half maximum (FWHM) = 6 mm×6 mm×6 mm.

Data Analysis

First level statistical analysis—Spatial transformation into a common coordinate space as traditionally done for most fMRI studies deemphasizes inherent anatomical variability of the human brain that may be amplified by aging and neurodegenerative processes. In addition, covarying regions are often of great importance, but are not included in the group methods described in traditional SPM analyses. To circumvent these problems, we carried out first level statistical analyses in native space, and generated individual T-maps comparing the activation patterns of each task to rest (i.e., EG vs. rest and IG vs. Rest).

The anatomical regions of interest (ROIs) were defined on high resolution T1 images using automatic segmentation software [AutoSeg, NeuroImage Research and Analysis Laboratories, University of North Carolina at Chapel Hill, NC; (Gouttard et al., 2007; Joshi et al., 2004)] for each subject. This permits statistical comparisons of similar brain areas across subjects without warping (“normalizing”) the brain. The percent of voxels activated with a t value > 1.96 (corresponding to a $p = 0.05$) were calculated for each ROI in the bilateral STC [putamen/globus pallidus (BG), thalamus (Th), supplementary motor area (SMA), and primary motor cortex (PMC)] and CTC circuits. For the purpose of this study the CTC circuit was divided into C_HTC [cerebellar hemisphere (CB), Th, lateral premotor cortex (PreMC), and somatosensory cortex (SMC)] and C_VTC [vermis/paravermis including bilateral dentate nuclei (Vm), Th, PreMC and SMC] circuits. We divided the cerebellum into three segments of two lateral hemispheres and one midline vermis/paravermis because these regions have been suggested to subserve different functions (Afifi and Bergman, 1998). A statistical method that compared multiple ROIs together, namely multivariate analysis of variance (MANOVA), was employed to compare the neurocircuitry changes within and between groups as described below.

Within group comparisons between follow-up and baseline scans—Collective values of percentage of voxels activated in ROIs that constitute each of the bilateral STC, C_HTC , and C_VTC circuits were treated as multivariate dependent variables. For each group (PD or Control), a randomized block design procedure (a special case of two-way MANOVA) was employed to compare the fMRI activation differences between baseline and follow-up scans. This is a multivariate version of the paired t -test for univariate response settings. The analysis was carried out using SAS PROC GLM, option MANOVA with two factors: SUBJECT (1 through 5 treated as blocks) and TIME (0 for baseline and 1 for follow-up). The blocking effect (SUBJECT) is introduced to eliminate the subject-to-subject variations, and our objective is to test the TIME effect (i.e., the difference between baseline and follow-up scans). Analyses were conducted independently for both EG and IG tasks within each group.

Between group comparison of PD and Controls—Since two of the five PD subjects had left-sided symptoms, both the more-affected and less-affected sides of PD subjects were compared to an averaged activity of the dominant and non-dominant hands of Controls. ROIs that constitute the bilateral STC, C_HTC , and C_VTC circuits were treated as co-multivariate response variables. In this analysis, the change in percent activation over time in the ROIs of these circuits in each subject was the multivariate dependent variable, whereas the independent variable was PD status (1=PD vs. 0=Controls). Task (EG or IG) and PD status (PD or Controls) were “dummy-coded” as either 1 or 0.

All comparisons were conducted by utilizing multiple MANOVAs using the PROC GLM command with option MANOVA in SAS (System 9.1, SAS Inc., Cary, NC). The significance of a given structure in a circuit was probed by a simple t -test.

Results

Within group comparison between baseline and follow-up

As described in the methods, the ROI approach permits statistical comparison of similar brain areas across subjects without warping (“normalizing”) the brain. In addition, MANOVA allows comparison of collective values from multiple ROIs between groups. The results of this combined ROI and MANOVA approach are described below.

PD group—PD subjects did not show statistically significant changes in recruitment of STC and CTC circuits during either the EG or IG tasks over time when using their less-affected

hand. When using their more-affected hand, however, PD subjects had increased recruitment over time of the contralateral STC circuit during the IG task ($p=0.045$, Table 3, Figure 2A) and the ipsilateral C_HTC circuit during the EG task ($p=0.001$, Table 3, Figure 2B).

Control group—When using their dominant hand, Control subjects did not show any significant changes in recruitment patterns of the STC and CTC circuits during either the EG or IG tasks over time. When using their non-dominant hand, however, Control subjects had greater activation of the ipsilateral C_HTC circuit during the EG task ($p=0.016$, Table 4, Figure 3B) and contralateral C_VTC circuit during both the EG and IG tasks ($p=0.036$ and $p=0.042$, respectively; Table 4, Figure 3B).

Between groups neurocircuitry analysis: comparing longitudinal changes between PD and Controls

When using the less-affected hand that transitioned from non-symptomatic to symptomatic during the study, PD subjects showed significantly increased recruitment of the ipsilateral C_VTC circuit over time during IG tasks compared to Controls ($p=0.043$, Table 5, Figure 4). In addition, there was a trend toward significant increased recruitment of the ipsilateral C_HTC circuit over time during IG tasks in PD subjects compared to Controls ($p=0.083$, Table 5, Figure 4). There were no statistically significant differences (or trends towards significance) in the recruitment of motor circuits between PD and Controls during the EG task (Table 5). When using the more-affected hand that was already symptomatic at baseline, PD subjects did not demonstrate significant differences in the recruitment of motor circuits from that of Controls during either EG or IG tasks (Table 5).

Discussion

Both the BG and cerebellum are known to influence cortical motor and associated areas via the thalamus, yet only the STC circuit has been implicated clearly in the pathophysiology of PD. Whereas previous cross-sectional studies using fMRI have demonstrated increased activity in cerebellum (Cerasa et al., 2006; Eckert et al., 2006) and numerous cortical areas (Eckert et al., 2006; Haslinger et al., 2001; Sabatini et al., 2000) in PD, we believe this is the first longitudinal fMRI study to assess the temporal changes in STC and CTC circuits during PD progression. The results from the current study are consistent with the hypothesis that CTC motor circuits are involved in PD progression.

As noted earlier, longitudinal PET imaging studies of PD subjects found increased activation in cortical, BG, and cerebellar structures over time (Carbon et al., 2007; Huang et al., 2007). The current fMRI data show a similarly increased activation over time in the STC, as well as CTC, circuits in PD subjects. Collectively, these studies suggest that there are decreases in the efficiency (i.e., the need for more recruitment) of structures in STC and CTC circuits used to perform the same motor tasks during PD progression.

Interestingly, control subjects also showed statistically significant changes in the CTC circuit (see Tables 4, and Figure 3), emphasizing the importance of using Controls for this type of study. The biological relevance of time-dependent CTC changes in Controls is unclear, but may reflect an age-related alteration of this circuit as previously reported (Alexander et al., 2008; Onozuka et al., 2003). Nevertheless, PD subjects clearly demonstrated augmented recruitment of CTC circuits compared to those of normal aging Controls (Table 5), implicating the CTC circuit in accommodation to, or progression of, PD above and beyond normal aging.

Earlier, we had proposed a model that integrated the role of the CTC circuit into PD pathophysiology (Lewis et al., 2007) that may assimilate some of the seemingly divergent basic and clinical results in PD that cannot be explained only by dysfunction of the STC circuit

(Buhmann et al., 2003; Cerasa et al., 2006; Haslinger et al., 2001; Mattay et al., 2002; Sabatini et al., 2000). As we discuss below, we now suggest a modification of this model to account for the dynamical changes in both STC and CTC circuits during PD progression (Figure 5).

Increased CTC recruitment occurs during the non-symptomatic to symptomatic transition in PD motor progression

The increased CTC recruitment in PD subjects was significantly different from Controls only when the hand that transitioned from non-symptomatic to symptomatic performed the tasks. This result suggests that changes in the CTC motor circuit play a role in the emergence of PD motor symptoms. The lack of significant changes in CTC circuits for the hand that was symptomatic at baseline may reflect an already established compensatory pattern of CTC activity at baseline without an additional increase in compensatory activity over time.

Increased CTC recruitment may represent compensation for inadequate STC function

The significant differences in augmented CTC activity between PD and Controls over time were seen only during the IG, but not EG, task (Figure 4). This is not surprising since IG tasks are thought primarily to be encoded in the STC circuit, whereas EG tasks are thought to be processed through the CTC circuit (*see* Figure 5, upper panel) (Lewis et al., 2007; Taniwaki et al., 2006). Thus, the current data suggest that the emergence of symptoms on the less-affected side during PD progression may be related to a decompensation of the initially functional STC circuit. This then leads to the compensatory recruitment of the CTC circuit that permits proper execution of IG motor tasks (*see* Figure 5 lower panel).

The current study, however, did not demonstrate significant differences in the recruitment of STC circuits in PD subjects compared to Controls over time. Although this might seem unexpected at first, it very well may reflect a residual drug effect. Antiparkinson medication has been shown to reduce activity in the STC circuit in PD subjects (Asanuma et al., 2006). The fMRI scans for PD subjects in the current study were obtained when subjects were “off” all PD medications for more than 12 hours. Although this “off” stage for PD subjects has been used frequently (Langston et al., 1992), there well may be residual drug effects on STC circuits (Fahn, 2005). Indeed all of our subjects, except for one, were on some form of dopamine agonist (Table 2).

At this point it worth mentioning that the main limitation of this study is the variability in the data between PD and Control groups. In comparing PD vs. Controls, our two-sample test used the Hotelling’s T^2 -statistic that includes the variability of the pooled samples, which is larger than the non-pooled sample variance of each group alone. A loss of significance can result from small increases in variability, and we believe this affected our analyses, particularly when comparing the significant changes observed with the more-affected hand in PD subjects to changes in Controls performing the same task. Future studies with increased sample sizes are needed to test our hypothesis further.

Implications for a striato/cerebello-thalamocortical model in PD

The hypothesis that the STC and CTC circuits are functionally related circuits that are influenced by PD (summarized in Figure 5) offers a more comprehensive view of motor control that leads to a variety of testable hypotheses. First, in the normal condition, EG tasks are primarily processed through the CTC circuit, with the recruitment of the STC circuit (Figure 5, Panel A); whereas IG tasks are primarily encoded in the STC circuit, with recruitment of the CTC circuit (Figure 5, Panel B). Second, in PD EG tasks also are processed primarily via the CTC circuit throughout the course of the disease (Figure 5, Panel C). Finally, in PD IG tasks inadequately activate the STC circuit (its primary processing center) leading to compensatory recruitment of CTC circuits (Figure 5, Panel D). Future studies that test such

hypotheses and validate or modify this striato/cerebello-thalamocortical model of PD should assist in understanding many unexplained aspects of PD motor symptomatology, as well as shedding light on the function of these circuits in the normal brain.

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Abbreviations

PD	Parkinson's disease
fMRI	Functional Magnetic Resonance Imaging
SFM	Sequential finger movement
EG	Externally Guided
IG	Internally Guided
STC	Striato-thalamo-cortical
CTC	Cerebello-thalamo-cortical
ROI	Region of interest
PMC	Primary motor cortex
SMA	Supplementary motor area
SMC	Somatosensory cortex
PreMC	Pre-motor cortex
CB	Cerebellum
Vm	Vermis/Paravermis (including bilateral dentate nuclei)
Th	Thalamus
BG	Basal Ganglia (Putamen and Globus Pallidus)
MANOVA	Multivariate Analysis of Variance

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Functional MRI activation paradigm. Subjects performed finger-tapping sequences in the following order: Rest, EG-guided, and IG-guided, alternating between their two hands. Each run consisted of 4 blocks of EG-tasks and 4 blocks of IG-tasks lasting 60 seconds per block with 30-second rest blocks.

Figure 2.

Comparison of percent activation changes in (a) STC and (b) CTC circuits over time within PD subjects using the more affected hand. P values for each circuit were deduced from MANOVA comparison between baseline and follow-up of the collective percent activation changes within ROIs composing each circuit (see Materials and Methods). Bars in the figures represent mean $\pm$ SEM of percent activation changes within a given ROI for PD subjects for simple visualization (not for MANOVA calculation). Circuits are defined as listed in the legend of Table 2.

Figure 3.

Comparison of percent activation changes in (a) STC and (b) CTC circuits over time within Controls using the non-dominant hand. P values for each circuit were deduced from MANOVA comparison between baseline and follow-up of the collective percent activation changes within ROIs composing each circuit (see Materials and Methods). Bars in the figures represent mean $\pm$ SEM of percent activation changes within a given ROI for PD subjects for simple visualization (not for MANOVA calculation). Circuits are defined as listed in the legend of Table 3.

Figure 4.

Comparison of percent activation changes in CTC circuits over time between PD and Controls during EG and IG tasks. P values for each circuit were deduced from MANOVA comparison between PD subjects using the less-affected hand (*) and Controls [average of dominant and non-dominant hands (■)] of the collective values of percent activation changes within ROIs composing each circuit. Bars in the figures represent mean±SEM of percent activation changes within a given ROI for simple visualization (not for MANOVA calculation). Circuits are defined as listed in the legend of Table 4.

Figure 5.

Revised striato/cerebello-thalamocortical model for Parkinson's disease. In the normal condition, **(A)** *EG tasks* are primarily processed through the CTC circuit with recruitment of the STC circuit, whereas **(B)** *IG tasks* are primarily encoded in the STC circuit with recruitment of the CTC circuit. In PD subjects, **(C)** *EG tasks* also are processed through the CTC circuit (its primary processing center), whereas **(D)** *IG tasks* inadequately activate the STC circuit (its primary processing center) leading to compensatory recruitment of the CTC circuit.

Table 1

Finger sequences used in the fMRI paradigm.

Paradigm	Description of sequences
Slow Sequence Number 1	Thumb to digit 2 → 3 → 4 → 5 → open and close fists twice → Repeat → Return to beginning of sequence
Slow Sequence Number 2	Thumb to digit 3 → 5 → 2 → 4 → open and close fists twice → Repeat → Return to beginning of sequence

Table 2

Demographics of Parkinson's disease subjects in this study

Subject #	Age at baseline (yr)	Handed-ness	Presenting symptoms	Scan interval (mo)	UPDRS-III scores in "off" stage		Antiparkinson drugs at baseline*	Antiparkinson drugs at follow-up
					Baseline	Follow-up		
1	52	Right	Decreased arm swing and left hand dexterity	22	2	3	Pramipexole 1.5 tid	Carbidopa/Levodopa/Entacapone 50 tid Pramipexole 1 tid Selegiline 5 bid
2	58	Right	Tenseness and decreased left hand dexterity.	21	3	3	Carbidopa/Levodopa 25/100 tid	Carbidopa/Levodopa 25/100 tid; 37.5/150 qam
3	50	Right	Postural tremor of right hand.	27	4	4.5	Pramipexole 0.5 tid	Pramipexole 0.5 tid Selegiline 5 bid
4	55	Right	Stiffness and decreased right hand dexterity.	20	6	7.5	Pramipexole 1.5 tid	Pramipexole 1.5 tid Selegiline 5 bid
5	71	Right	Right hand resting tremor.	24	7	10.5	Carbidopa/Levodopa/Entacapone 50 tid Pramipexole 0.375 tid	Pramipexole 1.5 i.i.d Selegiline 5 bid

* Doses are in mg except as noted; qam=every morning; bid = twice a day; tid = three times a day

Table 3

MANOVA results comparing longitudinal changes in STC and CTC motor circuits between baseline and follow-up in PD subjects.

Follow-up vs. Baseline				
	PD (less-affected)		PD (more-affected)	
	EG	IG	EG	IG
Ipsilateral STC[†]	0.851	0.935	0.738	0.496
Ipsilateral C_HTC^{††}	0.930	0.307	0.001*	0.501
Ipsilateral C_VTC^{†††}	0.692	0.341	0.094	0.646
Contralateral STC[‡]	0.731	0.130	0.863	0.045*
Contralateral C_HTC^{‡‡}	0.433	0.596	0.369	0.795
Contralateral C_VTC^{‡‡‡}	0.249	0.389	0.168	0.865

The percent of voxels activated with a *t* value > 1.96 (corresponding to a *p* = 0.05) were calculated for each ROI in the STC (BG, Th, SMA, and PMC), C_HTC (CB, Th, PreMC, and SMC), and C_VTC (Vm, Th, PreMC and SMC) circuits. Network analyses were performed using MANOVA with the changes in percent activation of individual ROIs as the dependent variables.

[†] Ipsilateral STC was defined as ipsilateral BG, Th, SMA, and PMC;

^{††} Ipsilateral C_HTC was defined as contralateral CB and ipsilateral Th, PreMC, and SMC;

^{†††} Ipsilateral C_VTC was defined as Vm and ipsilateral Th, PreMC, and SMC;

[‡] Contralateral STC was defined as contralateral BG, Th, SMA, and PMC;

^{‡‡} Contralateral C_HTC was defined as ipsilateral CB and contralateral Th, PreMC, and SMC;

^{‡‡‡} Contralateral C_VTC was defined as Vm and contralateral Th, PreMC, and SMC.

Table 4

MANOVA results comparing longitudinal changes in STC and CTC motor circuits between baseline and follow-up in Controls.

Follow-up vs. Baseline				
	Controls (Non-dominant hand)		Controls (Dominant hand)	
	EG	IG	EG	IG
Ipsilateral STC[†]	0.734	0.517	0.529	0.269
Ipsilateral C_HTC^{††}	0.016*	0.575	0.913	0.757
Ipsilateral C_VTC^{†††}	0.212	0.438	0.744	0.749
Contralateral STC[‡]	0.811	0.420	0.251	0.330
Contralateral C_HTC^{‡‡}	0.126	0.212	0.139	0.552
Contralateral C_VTC^{‡‡‡}	0.036*	0.042*	0.115	0.457

The percent of voxels activated with a *t* value > 1.96 (corresponding to a *p* = 0.05) were calculated for each ROI in the STC (BG, Th, SMA, and PMC), C_HTC (CB, Th, PreMC, and SMC), and C_VTC (Vm, Th, PreMC and SMC) circuits. Network analyses were performed using MANOVA with the changes in percent activation of individual ROIs as the dependent variables.

[†] Ipsilateral STC was defined as ipsilateral BG, Th, SMA, and PMC;

^{††} Ipsilateral C_HTC was defined as contralateral CB and ipsilateral Th, PreMC, and SMC;

^{†††} Ipsilateral C_VTC was defined as Vm and ipsilateral Th, PreMC, and SMC;

[‡] Contralateral STC was defined as contralateral BG, Th, SMA, and PMC;

^{‡‡} Contralateral C_HTC was defined as ipsilateral CB and contralateral Th, PreMC, and SMC;

^{‡‡‡} Contralateral C_VTC was defined as Vm and contralateral Th, PreMC, and SMC.

Table 5

MANOVA results comparing longitudinal changes in STC and CTC motor circuits between PD and Control subjects.

	PD (less-affected) vs. Control		PD (more-affected) vs. Control	
	EG	IG	EG	IG
Ipsilateral STC[†]	0.879	0.703	0.477	0.744
Ipsilateral C_HTC^{††}	0.364	0.083	0.699	0.678
Ipsilateral C_VTC^{†††}	0.419	0.043*	0.710	0.767
Contralateral STC[‡]	0.529	0.731	0.613	0.279
Contralateral C_HTC^{‡‡}	0.654	0.406	0.611	0.603
Contralateral C_VTC^{‡‡‡}	0.455	0.277	0.647	0.645

The percent of voxels activated with a *t* value > 1.96 (corresponding to a *p* = 0.05) were calculated for each ROI in the STC (BG, Th, SMA, and PMC), C_HTC (CB, Th, PreMC, and SMC), and C_VTC (Vm, Th, PreMC and SMC) circuits. Network analyses were performed using MANOVA with the changes in percent activation of individual ROIs over time as the dependent variables and PD status (PD vs. Control) as the independent variable.

[†] Ipsilateral STC was defined as ipsilateral BG, Th, SMA, and PMC;

^{††} Ipsilateral C_HTC was defined as contralateral CB and ipsilateral Th, PreMC, and SMC;

^{†††} Ipsilateral C_VTC was defined as Vm and ipsilateral Th, PreMC, and SMC;

[‡] Contralateral STC was defined as contralateral BG, Th, SMA, and PMC;

^{‡‡} Contralateral C_HTC was defined as ipsilateral CB and contralateral Th, PreMC, and SMC;

^{‡‡‡} Contralateral C_VTC was defined as Vm and contralateral Th, PreMC, and SMC.