Published in final edited form as:
Neuroscience. 2007 June 15; 147(1): 224–235.

Task specific influences of Parkinson's disease on the striato-thalamo-cortical and cerebello-thalamo-cortical motor circuitries

Mechelle M. Lewis[1], **Cara G. Slagle**[1], **Drew B. Smith**[1], **Young Truong**[4], **Ping Bai**[5], **Martin McKeown**[6], **Richard Mailman**[1,2,3,4], **Aysenil Belger**[2], and **Xuemei Huang**[1]

1 *Department of Neurology, University of North Carolina, Chapel Hill, NC 27599-7125*

2 *Department of Psychiatry, University of North Carolina, Chapel Hill, NC 27599-7125*

3 *Department of Pharmacology, Medicinal Chemistry, University of North Carolina, Chapel Hill, NC 27599-7125*

4 *Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27599-7125*

5 *Department of Statistics, University of North Carolina, Chapel Hill, NC 27599-7125*

6 *Department of Medicine (Neurology), Pacific Parkinson's Research Centre, University of British Columbia (UBC), University Hospital, Vancouver, BC, Canada V6T 2B5*

Abstract

The motor deficits in Parkinson's disease (PD) have been primarily associated with internally guided (IG), but not externally guided (EG), tasks. This study investigated the functional mechanisms underlying this phenomenon using genetically-matched twins. Functional magnetic resonance images were obtained from a monozygotic twin pair discordant for clinical PD. Single-photon emission computed tomography neuroimaging using [^{123}I](−)-2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane confirmed their disease-discordant status by demonstrating a severe loss of transporter binding in the PD-twin, whereas the non-PD-twin was normal. Six runs of fMRI data were acquired from each twin performing EG and IG right-hand finger sequential tasks. The percentage of voxels activated in each of several regions of interest (ROI) was calculated. Multiple analysis of variance was used to compare each twin's activity in ROIs constituting the striato-thalamo-cortical motor circuits [basal ganglia (BG)-cortical circuitry, but including the globus pallidus/putamen, thalamus, supplementary motor area, and primary motor cortex] and cerebello-thalamo-cortical circuits (referred to as the cerebellar–cortical circuitry, including the cerebellum, thalamus, somatosensory cortex, and lateral premotor cortex). During the EG task, there were no significant differences between the twins in bilateral BG-cortical pathways, either basally or after levodopa, whereas the PD-twin had relatively increased activity in the cerebellar-cortical pathways basally that was normalized by levodopa. During the IG task, the PD-twin had less activation than the non-PD-twin in ROIs of the bilateral BG-cortical and cerebellar-cortical pathways. Levodopa

Corresponding author Xuemei Huang MD, PhD, Division of Movement Disorders, Department of Neurology, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27599-7025, Voice: 919-966-5549, Fax: 919-966-2922, Email: xuemei@med.unc.edu

Disclosure Drs. Huang and Mailman have an equity interest in BioValve Technologies, the licensee from the University of North Carolina of a series of dopamine D_1 agonists that have been proposed to have utility for Parkinson's therapy. The current manuscript focuses only on levodopa, however, and should not affect the perceived value of D_1 agonists. Nonetheless, all opinions represent those of the authors, and not of BioValve Technologies or the authors' employers.

 (XH), MH058251 (AB), RR00046 (GCRC), a Parkinson's fellowship grant from His Excellency Sheik Abdulmohsin Al-Sheikh (MML), a National Parkinson's Foundation Center of Excellence grant (MJM), and the Foundation of Hope (AB, XH).

normalized the hypoactivation in the contralateral BG-cortical pathway, but “over-corrected” the activation in the ipsilateral BG-cortical and bilateral cerebellar-cortical pathways. In this first fMRI study of twins discordant for PD, the data support the hypothesis that BG-cortical and cerebellar-cortical pathways are task-specifically influenced by PD. The levodopa-induced “over-activation” of BG-cortical and cerebellar-cortical pathways, and its relevance to both compensatory changes in PD and the long-term effects of levodopa in PD, merit further exploration.

Keywords

fMRI; basal ganglia; cerebellum; twins; externally guided; internally guided

Parkinson’s disease (PD) presents primarily with motor dysfunction (resting tremor, bradykinesia, rigidity, and postural instability), the principal pathophysiology of which is the loss of dopaminergic neurons in the substantia nigra pars compacta of the basal ganglia (BG). The classic model of BG function (DeLong et al., 1984;Alexander et al., 1986;Albin et al., 1989;Alexander et al., 1990) suggests that the BG affects motor control by modulating cortical function through striato-thalamo-cortical motor circuits (hereafter referred to as BG-cortical circuitry). According to this model, dopamine deficiency in PD causes BG dysfunction via excessive thalamic inhibition of cortical function, resulting in bradykinesia and rigidity. Although this classic model provides an excellent starting point in understanding the pathophysiology of PD, some aspects of PD (e.g., tremor genesis) are explained inadequately.

The motor deficits of PD are related primarily to volitional initiation of movement that has been termed internally guided (IG), and thus it has been postulated that BG-cortical circuits play an essential role in IG motor tasks. One of the fascinating clinical phenomena in PD is that these IG motor deficits can be overcome by external visual or auditory cues (Jahanshahi et al., 1995;Chuma et al., 2006;Nowak et al., 2006). A classic clinical scenario is that a PD patient experiencing difficulty in initiating gait (i.e., freezing) will begin to walk if a clinician places a foot in front of the patient, thus providing visual guidance. Although paradoxical, a visual cue (going through a door way) may also initiate a freezing event, the exact cause of which is unclear but might involve a patient’s emotional state (Bartels et al., 2003;Lieberman, 2006). Nevertheless, physical therapy using a strategy of either visual or auditory external cues is known to be beneficial for the gait and balance of PD patients (Morris, 2000;Protas et al., 2005). Although these effects of EG cues are well-known clinical phenomena, the underlying neural mechanisms are unknown. The cerebellum is another important component in motor control, and is known to influence cerebral cortical activity via the cerebello-thalamo-cortical circuits (hereafter referred to as the cerebellar circuit; see p. 325 in Afifi and Bergman, 1998)]. This cerebellar-cortical circuit has been implicated in somatosensory integration (Manzoni, 2007) and information updating (Bonnefoi-Kyriacou et al., 1998). Recent fMRI studies also support the role of the cerebellar circuit in EG tasks (Debaere et al., 2003;Taniwaki et al., 2003;Taniwaki et al., 2006).

Functional magnetic resonance imaging (fMRI) has been utilized to investigate the brain activation patterns of PD patients using either an externally- (Haslinger et al., 2001;Buhmann et al., 2003;Cerasa et al., 2006), or an internally- (Sabatini et al., 2000;Cerasa et al., 2006) cued activation paradigm. An activation paradigm involving both EG and IG motor tasks, however, is essential to test the hypothesis that the functional activity in the BG and cerebellar pathways are task-specifically modulated by PD. A challenge in such fMRI studies has been the large interindividual variability in activation patterns (Deiber et al., 1999), a major source of which may be genetic (Styner et al., 2005;Toga and Thompson, 2005). For example, Meyer-Lindenberg and colleagues have recently reported the significant impact of a complex genetic variation on fMRI activation patterns in healthy subjects (Meyer-Lindenberg et al., 2006).

None of the published case-controlled fMRI studies in PD are genetically matched (Sabatini et al., 2000;Haslinger et al., 2001;Rowe et al., 2002;Mattay et al., 2002;Buhmann et al., 2003). Indeed, comparing PD subjects to healthy controls failed to detect differential neurocircuitry involvement between EG and IG rhythmic tasks (Cerasa et al., 2006). In this report, we addressed these issues by studying a set of monozygotic twins discordant for PD, using a finger-sequential paradigm to explore both IG- and EG-cued activation.

Experimental Procedures

Identical twin pair discordant for PD

A 37-year-old identical twin pair was identified through a tertiary-care movement disorders clinic. The life histories of the twins were remarkably similar in terms of upbringing, education, and occupation. Neither had smoked, but both drank alcohol occasionally, and drank coffee (regularly for non-PD-twin, occasionally for PD-twin).

Two years prior to this study, the PD-twin developed right-hand resting tremor and rigidity, the latter attenuated by pramipexole. The PD-twin also had been treated with venlafaxine for anxiety/depression for three years prior to the PD diagnosis. The non-PD-twin was perceived as healthy, was not taking any medication, and showed no motor signs of PD. No other family members had been diagnosed with PD. The PD-twin was strongly right handed, whereas the non-PD-twin was ambidextrous according to the modified Edinburgh Handedness Inventory (Oldfield, 1971).

Zygosity was confirmed by DNA profiles of 14 genetic markers (GeneTree DNA testing center, Salt Lake City, UT). Both twins were negative for hypothyroidism, vitamin B_{12} 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 the twins.

Both twins were scanned with single-photon emission computed tomography (SPECT) neuroimaging using [^{123}I](−)-2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane (β-CIT) to assess the integrity of the nigrostriatal dopamine system. The results of the SPECT imaging of [^{123}I]-β-CIT demonstrated a severe loss of transporter binding in the PD-twin, whereas the non-PD-twin was normal (unpublished data, available upon request).

Functional MRI

Subject preparation—To eliminate the effect of drugs on the fMRI studies, the PD-twin was tapered off venlafaxine and amantidine for three weeks, and pramipexole for one week, prior to the fMRI studies. Carbidopa/levodopa 25/100 was used to keep the PD-twin comfortable until it also was discontinued 24 hours prior to the fMRI studies. After the studies, the PD-twin resumed prior PD medication under the guidance of a movement disorder specialist (X.H.). Both twins were instructed not to drink alcohol or coffee 24 hours prior to the study, and to eat a light breakfast (to avoid being overly full) in the morning prior to the scan. All fMRI studies in this report were obtained on the same morning for both twins with the following scan sequence: PD-twin pre-drug, non-PD-twin, and PD-twin post-drug. Fruit, other snacks, and fluid were offered to the twins throughout the morning between their scans.

Functional MRI 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. Foam padding was used to limit head motion. High-resolution T_1 weighted anatomical images (3D SPGR, TR=14

ms, TE=7700 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.

Activation paradigm—We used a modified activation paradigm based on one that has been used previously to study PD patients (Sabatini et al., 2000) (see Figure 1). Our paradigm consisted of three different finger-tapping movements (see Table 1) performed using the right hand. For sequential task number 1, subjects tapped in the order of the index, middle, ring and little finger; for sequence 2, the order was index, ring, middle and little fingers; and for sequence 3, the order was middle, little, index, and ring fingers. Each sequence was followed by an opening and closing of the fist twice, and then the sequence was repeated in reverse, followed by a second opening and closing of the fist twice. The sequences were presented with instructions to follow the hands on the screen (EG task) or to continue the finger tapping sequence (IG task, Figure 1). The two consecutive conditions were preceded and followed by a rest (R) period. Each block was 30 s and tapping frequency was 1 Hz (Figure 1). Both twins practiced the task for about 20 min prior to the scanning session, demonstrating greater than 95% accuracy. There were a total of six runs for each experiment, and each run consisted of four blocks of rest, EG and IG task, respectively. Each twin was videotaped during each run, which then was used to score accuracy and compliance with the task. There were no significant differences between the twins' abilities to perform the task, or in the PD twin following levodopa.

fMRI Image Pre-processing

The fMRI data was preprocessed for time realignment, motion correction, and smoothing using standard Statistical Parameter Map SPM-2 software. The time series of functional images was aligned for each slice, and spatial filtering of functional time series was performed by convolution of each EPI—image with a two-dimensional Gaussian smoothing kernel with full width at half maximum (FWHM)=2.8 mm×2.8 mm. Temporal filtering of functional time series included removal of the linear drifts of the signal with respect to time from the time-course of each voxel, and low-pass filtering of the time-course of each voxel with a one-dimensional Gaussian filter with FWHM=6s.

Generation of statistical activation maps: first level analysis

Following preprocessing, each volume (time point) was coded as a particular type of task (such as rest, EG-task, IG-task). A t-test was done on each voxel based on contrasting two different tasks (i.e., EG-tasks vs. rest or IG-tasks vs. rest) to generate the first level statistical activation map (t-map) for each run. The percent of voxels activated with a t value > 1.96 (corresponding to a $p = 0.05$) were calculated for each region of interest (ROI) in the bilateral BG-cortical [putamen/globus pallidus, thalamus, supplementary motor area (SMA), and primary motor cortex (PMC)] and cerebellar-cortical [cerebellum, thalamus, lateral premotor cortex (PreMC), and somatosensory cortex (SMC)] circuitries. Each ROI was drawn manually by the same trained research associate with assistance from multiple publicly available on-line atlases. The rater reliability of the ROI drawn was demonstrated by the high degree correlation on pre-and post- ROIs on the PD-twin ($r = 0.99$). The functional t-map consisting of all six runs then was overlaid onto each twin's individual anatomical scans as demonstrated in Figures 2 and 4.

Comparison between twins: second level analysis

A statistical method that compared multiple ROIs together, namely multiple analysis of variance (MANOVA), was employed to compare the twins. ROIs that constitute the bilateral BG and cerebellar pathways were treated as covariables. Percent of activation in ROIs of these pathways was the dependent variable, whereas the independent variable was PD status (the PD-twin vs. the non-PD-twin, or the PD-twin prior to and after levodopa). Task (EG or IG) and Drug (on or off) were dummy coded as either 0 or 1. For ease, the non-PD-twin was considered 'on' drug. An array of three comparisons was set up as follows: comparison of the non-PD-twin to the PD-twin prior to levodopa administration; comparison of the non-PD-twin to the PD-twin following levodopa administration; and comparison of the PD-twin prior to and after levodopa administration. PD status was compared in the EG or IG task in the four different pathways by conducting multiple MANOVAs using the PROC GLM command with option MANOVA in SAS (System 9.1, SAS Inc., Cary, NC; see Table 2). Significance in a pathway was probed by a simple t-test.

The validity of this method can be justified provided: (A) the runs are independent trials; (B) the variability for runs between groups is approximately the same; and (C) ROI values are multivariate normal. For (A), since the runs are separated by more than 30 sec, we assume that they are independent although it is conceivable that they may not be. In principle, the effect of dependence on the ANOVA results can be addressed either by extending the number of runs (using Durbin-Watson for testing serial correlation), or recruiting more identical twins discordant for PD (using one run for each twin pair). These approaches are impractical at the moment. To address (B), we applied Levene's test to compare the variance homogeneity between the twins, and the results were not significant. This confirms that the variability of the responses between the twins is approximately the same. Lastly, since we are taking the percentage of voxels activated in each ROI, (C) can be relaxed by appealing to the central limit theorem [(CLT), (see p. 273 in Johnson and Wichern, 2002). Based on the above, we felt justified to carry out the MANOVA to obtain comparative results for the BG and cerebellar pathways for these twins. If results from MANOVA indicated significant (i.e., $p < 0.05$) differences in BG and cerebellar pathways for a specific task (i.e. EG or IG) between the twins, we also carried out a t-test to yield preliminary results on the differences in each ROI in the BG and cerebellar pathways for that specific task (i.e., EG or IG).

Results

Externally Guided Task

Representative functional t-maps for the twin subjects performing the EG task at three axial levels are shown in Figure 2. The twins displayed similar neural activation patterns, except that the PD-twin displayed relatively lower activation in subcortical structures and relatively heightened activity in cerebellum and PreMC areas.

Multivariate analysis indicated that there were no significant differences in bilateral BG-cortical pathways during the EG task between the twins prior to levodopa administration, nor did levodopa have any influence on either pathway (see Table 2, columns A and B, and Figure 3). In addition, comparison of the PD-twin before and after levodopa revealed no significant differences in the BG-cortical or cerebellar-cortical pathways during the EG task (Table 2, column C). In contrast, multivariate analysis indicated a significant difference between the twins in the activation of bilateral cerebellar-cortical pathways prior to levodopa administration, with relatively increased activation in PreMC and cerebellum areas (Table 2, column A, and Figure 4). After levodopa, there was no longer a significant difference between the twins in the cerebellar-cortical pathways, although there was still a trend towards significance in the contralateral cerebellar-cortical pathway (Table 2, column B).

Internally Guided Task

The functional t-maps at three axial levels for the twin subjects performing the IG task are shown in Figure 5. Compared to the EG task (Figure 2), the non-PD-twin displayed considerably more fMRI activation at cortical and subcortical levels during the IG task.

Multivariate analysis (Table 2) indicated that there were significant differences between the twins in the activation of both bilateral BG-cortical and ipsilateral cerebellar-cortical pathways prior to levodopa administration, with ***lower*** activity in most ROIs in the PD-twin relative to the non-PD-twin (Table 2, column A, and Figures 6 and 7). There was a trend towards significance in the contralateral cerebellar-cortical pathway. Levodopa administration significantly changed the contralateral BG-cortical and cerebellar-cortical pathways (Table 2, column C), with a trend towards a significant change in the ipsilateral BG-cortical and cerebellar-cortical pathways in the PD-twin (Table 2, column C). As a result, there was no longer a significant difference between the twins in the contralateral BG-cortical pathway. There remained, however, a significant difference in the ipsilateral BG-cortical and bilateral cerebellar-cortical pathways (Table 2, column B). Interestingly, the differences in the ipsilateral BG-cortical and cerebellar-cortical pathways were due to ***higher*** activity in most ROIs in the PD-twin relative to the non-PD-twin (Figures 6 and 7).

Discussion

The results of this study support directly the hypothesis that, in PD, a deficit in the BG-cortical pathway occurs in a task-specific manner (i.e., for the IG task only). This finding provides a functional mechanism underlying the clinical phenomenon that motor deficits in PD have been associated primarily with IG tasks that can be overcome by external visual or auditory cues (Jahanshahi et al., 1995;Chuma et al., 2006;Nowak et al., 2006). In addition, this study identified a potential alternative or compensatory pathway (the cerebellar-cortical pathway) by which EG tasks may be processed in PD. Further understanding of the functional interactions between BG-cortical and cerebellar-cortical pathways may provide invaluable guidance and insight into their functional mechanism(s) and their relevance in the treatment of PD, such as how externally cued motor activities (e.g., a treadmill) may influence PD.

Basal ganglia-cortical and cerebellar-cortical pathways in EG and IG tasks

Our results favor the preferential involvement of the BG-cortical pathway in the IG task, consistent with studies done in normal subjects (Debaere et al., 2003;Taniwaki et al., 2003;Taniwaki et al., 2006), but at odds with a recent study in PD patients (Cerasa et al., 2006). The discrepancy between our results and those of Cerasa et al. (2006) may relate to differences in data analysis (MANOVA vs. SPM), and/or the subjects used (genetically matched subjects vs. 10 PD and 11 control subjects). In addition, finger sequencing tasks similar to the current study may be encoded more in BG, whereas a timing task used by Cerasa et al. (2006) may be encoded in both BG and cerebellum.

It is important to emphasize that our data demonstrate that the BG-cortical circuitry is involved in both EG and IG tasks, as both tasks elicit BG-cortical functional activity. It appears, however, that this pathway is essential only for IG tasks. Indeed, the fact that the activation in the BG-cortical pathway (particularly at the cortical level) is nearly normal in the PD-twin during the EG task (both before and after levodopa) supports the hypothesis that there may be an alternate pathway through which EG tasks can be processed. It is very possible that this alternate pathway contains structures in cerebellar-cortical pathways that are known to be involved in EG movement, and which rely heavily on somatosensory integration, including structures such as the cerebellum (Debaere et al., 2003), SMC (Taniwaki et al., 2003), and PreMC (Elsinger et al., 2006). Interestingly, previous studies have observed increased activity in each of these

regions in PD patients (Samuel et al., 1997;Sabatini et al., 2000;Haslinger et al., 2001). It is possible that recruitment of these structures can compensate for decreases in BG structures. Indeed, the near-normal SMC activity, and increased activity in the cerebellum and PreMC, in the PD-twin during the EG task support this hypothesis.

Effect of levodopa on the basal ganglia-cortical and cerebellar-cortical pathways

Another novel observation of our study is related to the role of levodopa in the treatment of PD. Namely, we found that levodopa "over-corrected" the deficits observed in some ROIs in the BG-cortical and cerebellar-cortical pathways during the IG task. Levodopa has been the gold standard for treating PD via its repletion of the dopamine that is lost due to degeneration of nigral neurons (albeit with the clear risk that long-term use may cause dyskinesias). One possible explanation for such over-activation is the down–regulation of dopamine transporters (DATs), a finding that has been associated with treatment of PD (Lee et al., 2000). This transporter down-regulation may lead to a lessening of the normally tight regulation in the dopamine system, resulting in "over-flooding" of the system after levodopa administration. This is consistent with a recently proposed hypothesis that the down-regulation of DATs may be associated with dyskinesia (Sossi et al., 2006). This hypothesis must be addressed cautiously, however, as it has been shown that chronic levodopa administration to the unilateral 6-OHDA dopamine-lesioned rat actually caused an up-regulation of DATs on the lesioned side (Ferrario et al., 2004).

The role of MZ twin pair discordant for PD in FMRI studies

This first fMRI study on a pair of identical twins currently discordant for PD offered a unique opportunity to examine, *in vivo*, the neurocircuity underlying the disease and its therapy. One underlying hypothesis was that such a discordant twin pair would minimize much of the large inter-individual differences that can confound such studies. The remarkable similarity can be seen visually in the structural features of these sibling's brains (Figures 2 and 5), as well as in the patterns of brain activation between the non-PD-twin and PD-twin after levodopa (Figures 2 and 5). This provided an unusually stable baseline that permitted us to generate robust data testing the hypothesis of a task-specific influence of PD and levodopa on the BG-cortical and cerebellar-cortical circuitry in this one pair of twins. Moreover, we feel these data suggest that intensive fMRI studies in other MZ twins discordant for PD is likely to be an extremely important direction to pursue.

It has been reported that there is a high degree of concordance for PD in MZ twin pairs, especially with those having young onset of PD (Tanner et al., 1999). Normal density of dopamine transporters using SPECT imaging with [^{123}I]-β-CIT in the non-PD-twin confirmed that the twin had a completely intact nigrostriatal dopamine system, whereas the PD-twin had the expected large deficit (unpublished data, available upon request).

A new model of functionally related basal ganglia-cortical and cerebellar-cortical pathways

We recognize that the current findings need to be explored in other discordant twin pairs, and also that covariant ROI analysis using MANOVA may not fully reflect important neuronal networks. Nonetheless, it is not premature to place these data in the context of a new model of BG function in motor control (see Figure 8). This model integrates the two partially segregated (see Hoshi et al., 2005, however), but functionally-related, loops of the BG-cortical and cerebellar-cortical circuits. Whereas previous studies using fMRI have demonstrated decreased activity in BG structures (Holden et al., 2006), or increased activity in cerebellar (Cerasa et al., 2006;Eckert et al., 2006) or numerous cortical (Sabatini et al., 2000;Haslinger et al., 2001;Eckert et al., 2006) areas in PD, we believe this is the first study to test these structures combined into functional circuits. This model seems to be able to explain much of the seemingly divergent basic and clinical results in PD (e.g., Sabatini et al., 2000;Haslinger et al.,

2001;Mattay et al., 2002;Buhmann et al., 2003;Cerasa et al., 2006), with the following inherent implications and hypotheses.

First, in the normal condition, EG tasks are primarily processed through cerebellar-cortical circuitry, with the recruitment of the BG-cortical circuitry (Panel A), whereas IG tasks are primarily encoded in the BG-cortical pathway, with the recruitment of cerebellar-cortical circuitry (Panel B). Second, in PD, EG tasks also are processed primarily via the cerebellar-cortical pathway, though with enhanced activity in this circuit, particularly in cerebellulm and PreMC areas (Panel C). IG tasks in PD, however, neither adequately activate the BG-cortical pathway (its primary processing center), nor cause adequate recruitment of the cerebellar-cortical pathway. As a result, both pathways display decreased activity (Panel D). Third, levodopa restores normal cerebellar-cortical activity during the EG task after adequate BG-cortical activation (Panel E, compare to Panel A). In the IG task, levodopa administration increases functional activity in both BG-cortical and cerebellar-cortical pathways, significantly "over-correcting" both circuits (Panel F). The model emphasizes that the two pathways are functionally related, despite the fact that there may be some degree of segregation. This last assumption is important for the model because it provides a functional compensatory model in PD.

In conclusion, the current results support the hypothesis that the BG-cortical and cerebellar-cortical pathways are functionally-related circuits and task-specifically influenced by PD. The results supported a new working model of motor control with integration of these two functionally related circuitries, and the finding of levodopa "over-activation" of some structures in the BG-cortical and cerebellar-cortical pathways in PD is clearly worthy of further exploration. Above and beyond the current data, there appears to be great potential utility of functional studies of discordant identical twin pairs in PD.

Acknowledgements

We want to thank the twin pair who participated in our studies. We want to recognize the assistance of Peter Chen, Colleen A. Hanlon, Jennifer Woodward, Jennifer Simmons, and Anna Dow, support from the UNC fMRI Center and General Clinical Research Center, and the computational consulting of Josh Bizzell of UNC-Duke Brain Imaging and Analysis Center (BIAC). This work was supported in part by NIH grants AG21491

References

Afifi, AK.; Bergman, RA. Functional Neuroanatomy: Text and Altas. New York; McGraw-Hill: 1998.

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–375. [PubMed: 2479133]

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 1990;85:119–146. [PubMed: 2094891]

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381. [PubMed: 3085570]

Bartels AL, Balash Y, Gurevich T, Schaafsma JD, Hausdorff JM, Giladi N. Relationship between freezing of gait (FOG) and other features of Parkinson's: FOG is not correlated with bradykinesia. J Clin Neurosci 2003;10:584–588. [PubMed: 12948464]

Bonnefoi-Kyriacou B, Legallet E, Lee RG, Trouche E. Spatio-temporal and kinematic analysis of pointing movements performed by cerebellar patients with limb ataxia. Exp Brain Res 1998;119:460–466. [PubMed: 9588780]

Buhmann C, Glauche V, Sturenburg HJ, Oechsner M, Weiller C, Buchel C. Pharmacologically modulated fMRI--cortical responsiveness to levodopa in drug-naive hemiparkinsonian patients. Brain 2003;126:451–461. [PubMed: 12538411]

Cerasa A, Hagberg GE, Peppe A, Bianciardi M, Gioia MC, Costa A, Castriota-Scanderbeg A, Caltagirone C, Sabatini U. Functional changes in the activity of cerebellum and frontostriatal regions during

externally and internally timed movement in Parkinson's disease. Brain Res Bull 2006;71:259–269. [PubMed: 17113955]

Chuma T, Faruque RM, Ikoma K, Mano Y. Motor learning of hands with auditory cue in patients with Parkinson's disease. J Neural Transm 2006;113:175–185. [PubMed: 15959849]

Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Internal vs external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. Neuroimage 2003;19:764–776. [PubMed: 12880805]

Deiber MP, Honda M, Ibanez V, Sadato N, Hallett M. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: Effect of movement type and rate. Journal of Neurophysiology 1999;81:3065–3077. [PubMed: 10368421]

DeLong MR, Alexander GE, Georgopoulos AP, Crutcher MD, Mitchell SJ, Richardson RT. Role of basal ganglia in limb movements. Hum Neurobiol 1984;2:235–244. [PubMed: 6715208]

Eckert T, Peschel T, Heinze HJ, Rotte M. Increased pre-SMA activation in early PD patients during simple self-initiated hand movements. J Neurol 2006;253:199–207. [PubMed: 16222427]

Elsinger CL, Harrington DL, Rao SM. From preparation to online control: reappraisal of neural circuitry mediating internally generated and externally guided actions. Neuroimage 2006;31:1177–1187. [PubMed: 16540347]

Ferrario JE, Taravini IR, Mourlevat S, Stefano A, Delfino MA, Raisman-Vozari R, Murer MG, Ruberg M, Gershanik O. Differential gene expression induced by chronic levodopa treatment in the striatum of rats with lesions of the nigrostriatal system. J Neurochem 2004;90:1348–1358. [PubMed: 15341519]

Haslinger B, Erhard P, Kampfe N, Boecker H, Rummeny E, Schwaiger M, Conrad B, Ceballos-Baumann AO. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 2001;124:558–570. [PubMed: 11222456]

Holden A, Wilman A, Wieler M, Martin WR. Basal ganglia activation in Parkinson's disease. Parkinsonism Relat Disord 2006;12:73–77. [PubMed: 16458037]

Hoshi E, Tremblay L, Feger J, Carras PL, Strick PL. The cerebellum communicates with the basal ganglia. Nat Neurosci 2005;8:1491–1493. [PubMed: 16205719]

Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 1995;118 (Pt 4):913–933. [PubMed: 7655888]

Johnson, RA.; Wichern, DW. Applied Multivariate Statistical Analysis. Prentice Hall: 2002.

Lee CS, Samii A, Sossi V, Ruth TJ, Schulzer M, Holden JE, Wudel J, Pal PK, del F-F, Calne DB, Stoessl AJ. In vivo positron emission tomographic evidence for compensatory changes in presynaptic dopaminergic nerve terminals in Parkinson's disease. Ann Neurol 2000;47:493–503. [PubMed: 10762161]

Lieberman A. Are freezing of gait (FOG) and panic related? J Neurol Sci 2006;248:219–222. [PubMed: 16797596]

Manzoni D. The cerebellum and sensorimotor coupling: Looking at the problem from the perspective of vestibular reflexes. Cerebellum 2007;6:24–37. [PubMed: 17366264]

Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, Hyde TM, Weinberger DR. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 2002;51:156–164. [PubMed: 11835371]

Meyer-Lindenberg A, Nichols T, Callicott JH, Ding J, Kolachana B, Buckholtz J, Mattay VS, Egan M, Weinberger DR. Impact of complex genetic variation in COMT on human brain function. Mol Psychiatry 2006;11:867–77. 797. [PubMed: 16786032]

Morris ME. Movement disorders in people with Parkinson disease: a model for physical therapy. Phys Ther 2000;80:578–597. [PubMed: 10842411]

Nowak DA, Tisch S, Hariz M, Limousin P, Topka H, Rothwell JC. Sensory timing cues improve akinesia of grasping movements in Parkinson's disease: a comparison to the effects of subthalamic nucleus stimulation. Mov Disord 2006;21:166–172. [PubMed: 16161152]

Oldfield RC. Ambidexterity in Surgeons. Lancet 1971;1:655. [PubMed: 4101266]

Protas EJ, Mitchell K, Williams A, Qureshy H, Caroline K, Lai EC. Gait and step training to reduce falls in Parkinson's disease. NeuroRehabilitation 2005;20:183–190. [PubMed: 16340099]

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]

Sabatini U, Boulanouar K, Fabre N, Martin F, Carel C, Colonnese C, Bozzao L, Berry I, Montastruc JL, Chollet F, Rascol O. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. Brain 2000;123 (Pt 2):394–403. [PubMed: 10648446]

Samuel M, Ceballos-Baumann AO, Blin J, Uema T, Boecker H, Passingham RE, Brooks DJ. Evidence for lateral premotor and parietal overactivity in Parkinson's disease during sequential and bimanual movements. A PET study. Brain 1997;120 (Pt 6):963–976. [PubMed: 9217681]

Sossi V, de la Fuente-Fernandez R, Schulzer M, Troiano A, Stoessl AJ, Ruth TJ. Role of DAT in synaptic dopamine oscillations in Parkinson's disease: a PET study. Mov Disord 2006;21:S587–S588.

Styner M, Lieberman JA, McClure RK, Weinberger DR, Jones DW, Gerig G. Morphometric analysis of lateral ventricles in schizophrenia and healthy controls regarding genetic and disease-specific factors. Proc Natl Acad Sci U S A 2005;102:4872–4877. [PubMed: 15772166]

Taniwaki T, Okayama A, Yoshiura T, Nakamura Y, Goto Y, Kira J, Tobimatsu S. Reappraisal of the motor role of basal ganglia: a functional magnetic resonance image study. J Neurosci 2003;23:3432–3438. [PubMed: 12716951]

Taniwaki T, Okayama A, Yoshiura T, Togao O, Nakamura Y, Yamasaki T, Ogata K, Shigeto H, Ohyagi Y, Kira JI, Tobimatsu S. Functional network of the basal ganglia and cerebellar motor loops in vivo: Different activation patterns between self-initiated and externally triggered movements. Neuroimage. 2006

Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, Langston JW. Parkinson disease in twins: an etiologic study. JAMA 1999;281:341–346. [PubMed: 9929087]

Toga AW, Thompson PM. Genetics of brain structure and intelligence. Annu Rev Neurosci 2005;28:1–23. [PubMed: 15651931]

ABBREVIATIONS

6-OHDA
6-hydroxydopamine

BG
Basal ganglia

Cereb
Cerebellum

CLT
Central limit theorem

DAT
Dopamine transporter

EG
Externally guided

fMRI
Functional magnetic resonance imaging

FWHM
Full width at half maximum

GP/Put
Globus pallidus/putamen

IG
Internally guided

MANOVA
Multiple analysis of variance

MZ
Monozygotic

NEX
Number of excitations

PD
Parkinson's disease

PMC
Primary motor cortex

PreMC
Lateral premotor cortex

ROI
Region of interest

SMA
Supplementary motor area

SMC
Somatosensory cortex

SPECT
Single-photon emission computed tomography

SPM
Statistical parametric mapping

TE
Excitation time

Thal
Thalamus

TR
Relaxation time

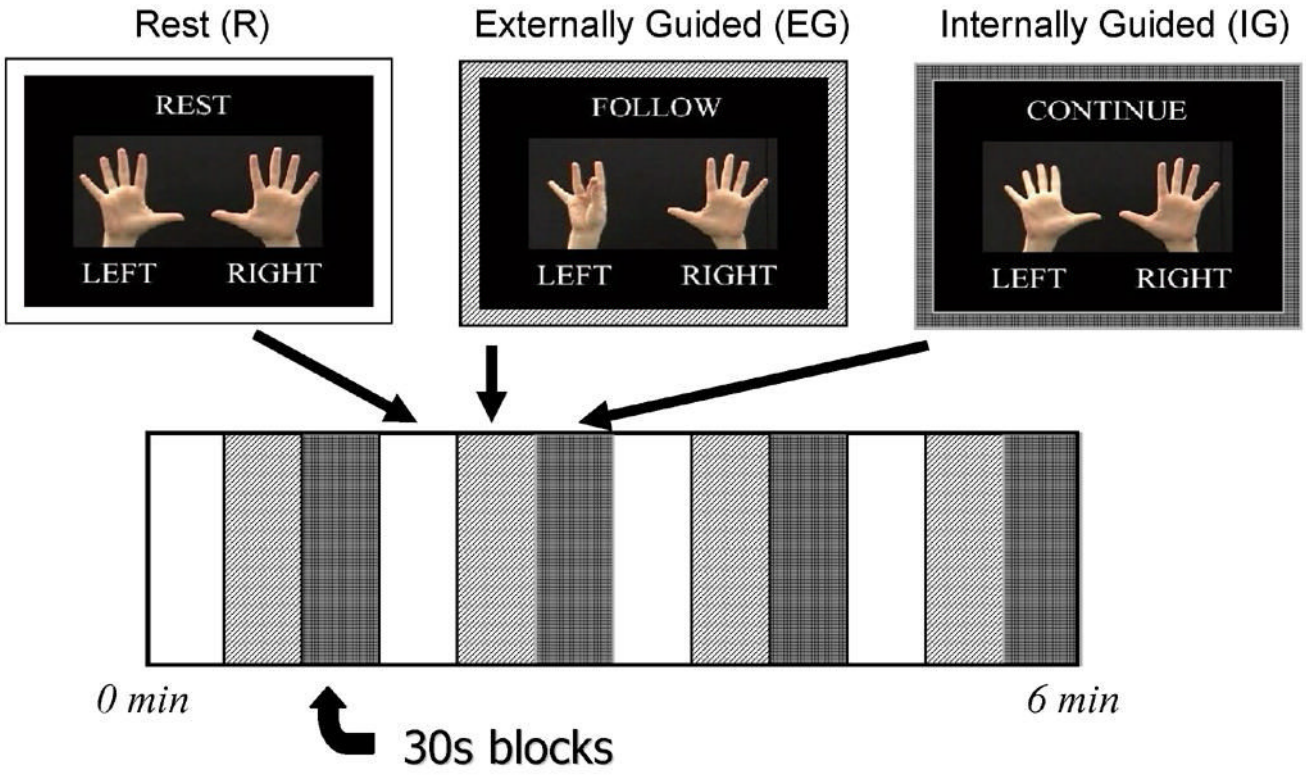

Figure 1.

Activation paradigm for fMRI motor task. A block design paradigm was used wherein subjects held their right hand at rest, followed the sequence on the screen (EG task), or generated the previous sequence internally (IG task). The specific sequence is listed in Table 1. Each block was 30 seconds in duration and the rate was 1 Hz. paradigm. Open block represent Rest, Hatched blocks represent EG periods, and Gray block represent IG.

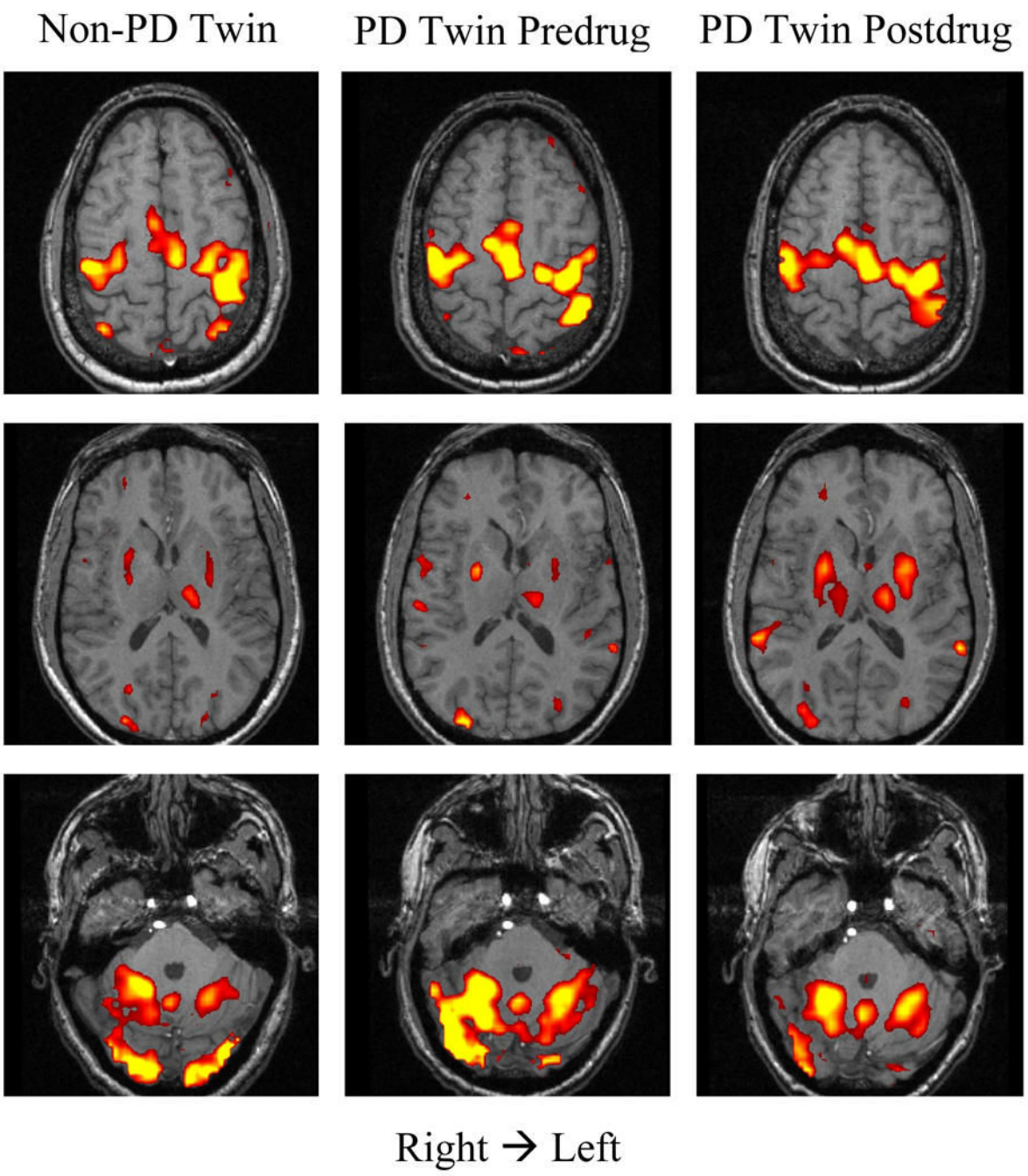

Figure 2.
T-maps of the non-PD and PD-twin during completion of an externally guided (EG) right handed task. The images were created using t-map contrasts of right handed EG task vs. Rest overlaid onto each subjects' anatomical scan (see Methods for details) using a t-threshold of 1.96. The three sets of scans represent images at the cortical, basal ganglia, and cerebellar levels (top to bottom, respectively).

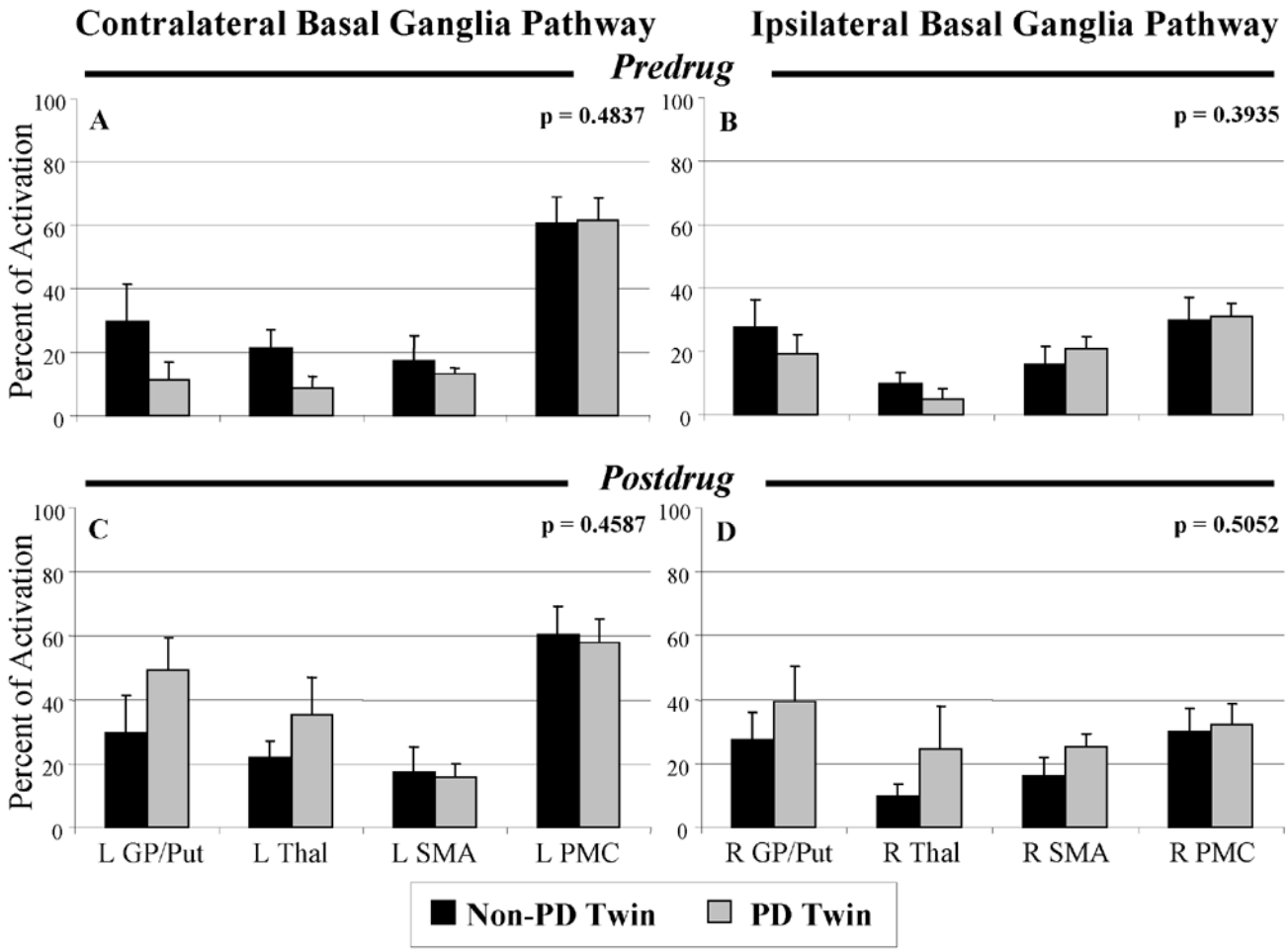

Figure 3.

Percent of activation values for ROIs in the BG-cortical pathways during the EG task in the non-PD-twin (black bars) and PD-twin (gray bars) before (A and B) and after levodopa (C and D). Data represent the mean ± standard error of a given ROI over the six runs each twin completed. P values from multivariate analysis on the BG-cortical pathways between twins are given in the upper right corner of each graph. GP/Put: globus pallidus/putamen; Thal: thalamus; SMA: supplementary motor area; PMC: primary motor cortex.

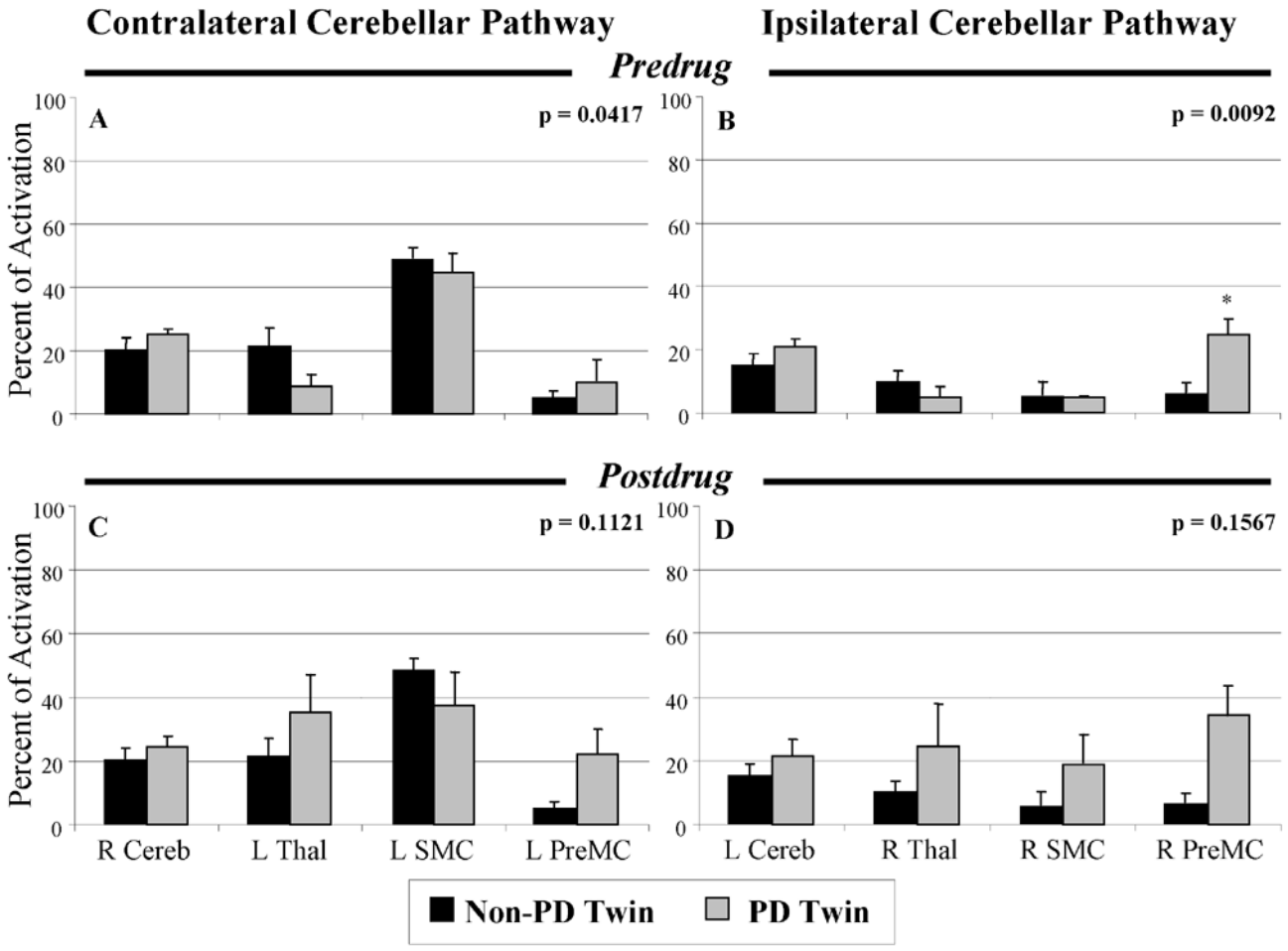

Figure 4.

Percent of activation values for ROIs in the cerebellar-cortical pathways during the EG task in the non-PD-twin (black bars) and PD-twin (gray bars) before (A and B) and after levodopa (C and D). Data represent the mean ± standard error of a given ROI over the six runs each twin completed. P values from multivariate analysis on the cerebellar-cortical pathways between twins are given in the upper right corner of each graph. *Indicates significant difference between twins with $p < 0.05$ by simple t-test. Cereb: cerebellum; Thal: thalamus; SMC: somatosensory cortex; PreMC: lateral premotor cortex.

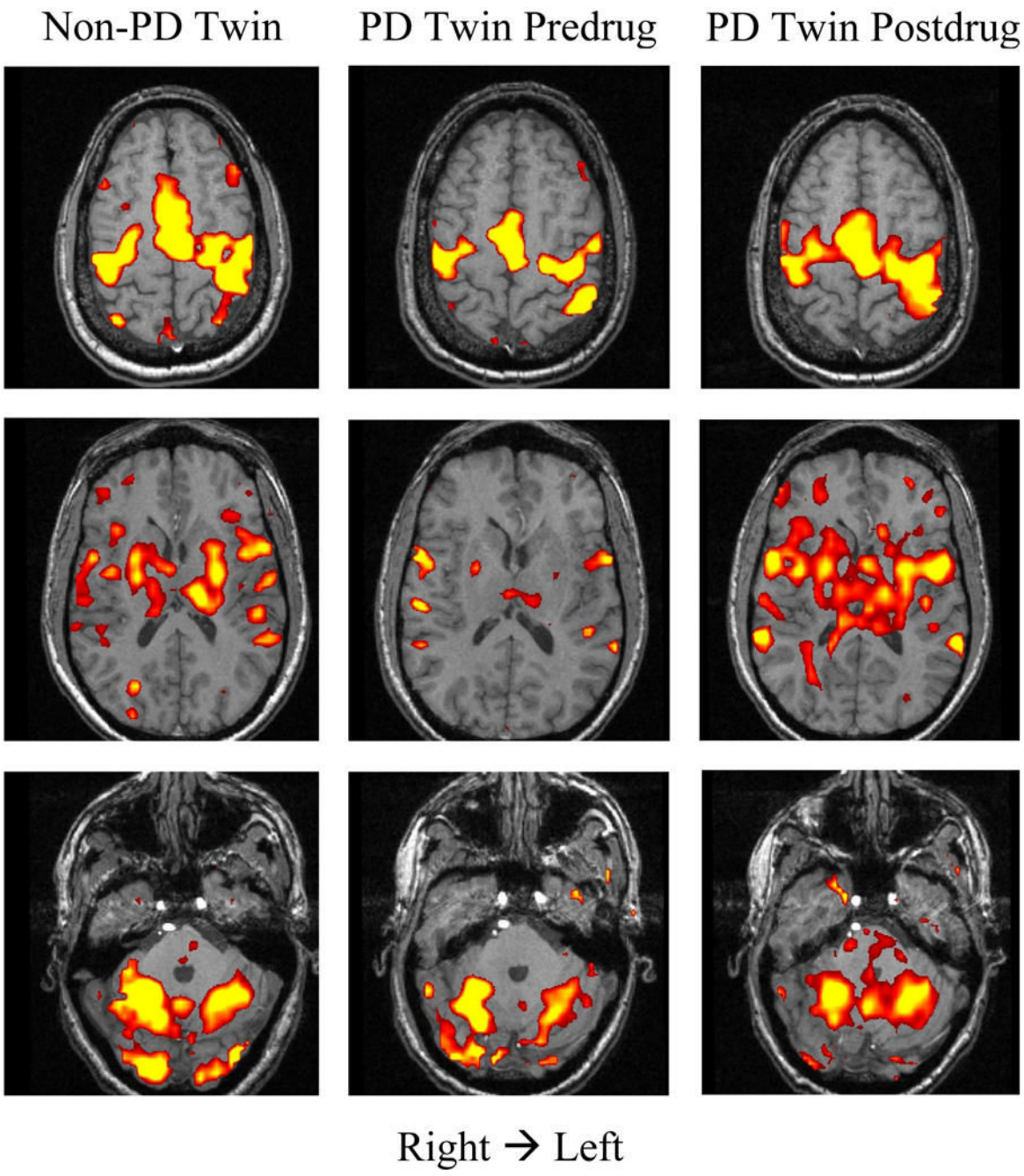

Figure 5.
T-maps of the non-PD- and PD-twin during completion of an internally guided (IG) right handed task. The images were created using t-map contrasts of right handed IG task vs. Rest overlaid onto each subjects' anatomical scan (see Methods for details) using a t-threshold of 1.96. The three sets of scans represent images at the cortical, basal ganglia, and cerebellar levels (top to bottom, respectively).

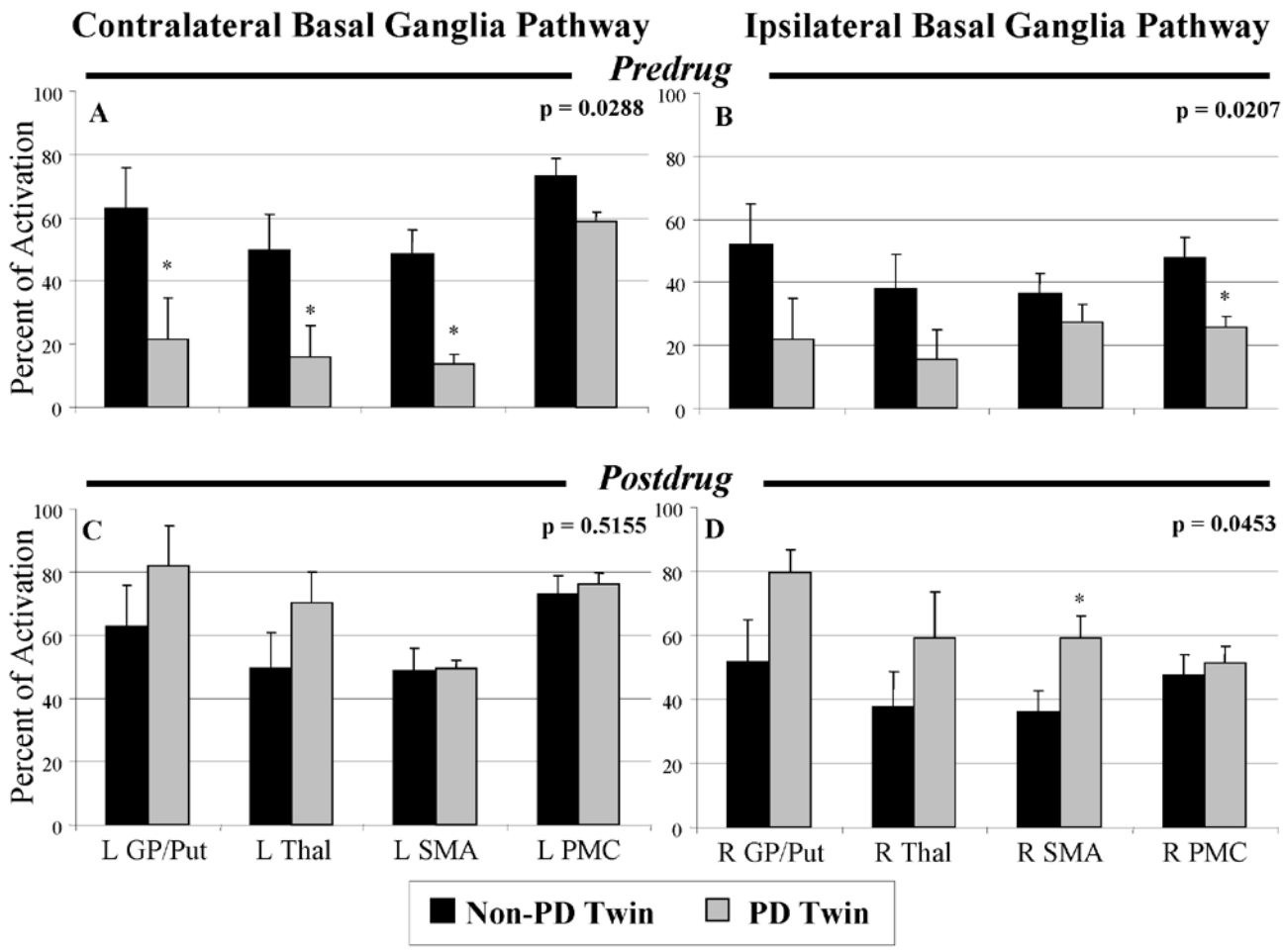

Figure 6.

Percent of activation values for ROIs in the BG-cortical pathways during the IG task in the non-PD-twin (black bars) and PD-twin (gray bars) before (A and B) and after levodopa (C and D). Data represent the mean ± standard error of a given ROI over the six runs each twin completed. P values from multivariate analysis on the BG-cortical pathways between twins are given in the upper right corner of each graph. *Indicates significant difference between twins with $p < 0.05$ by simple t-test. GP/Put: globus pallidus/putamen; Thal: thalamus; SMA: supplementary motor area; PMC: primary motor cortex.

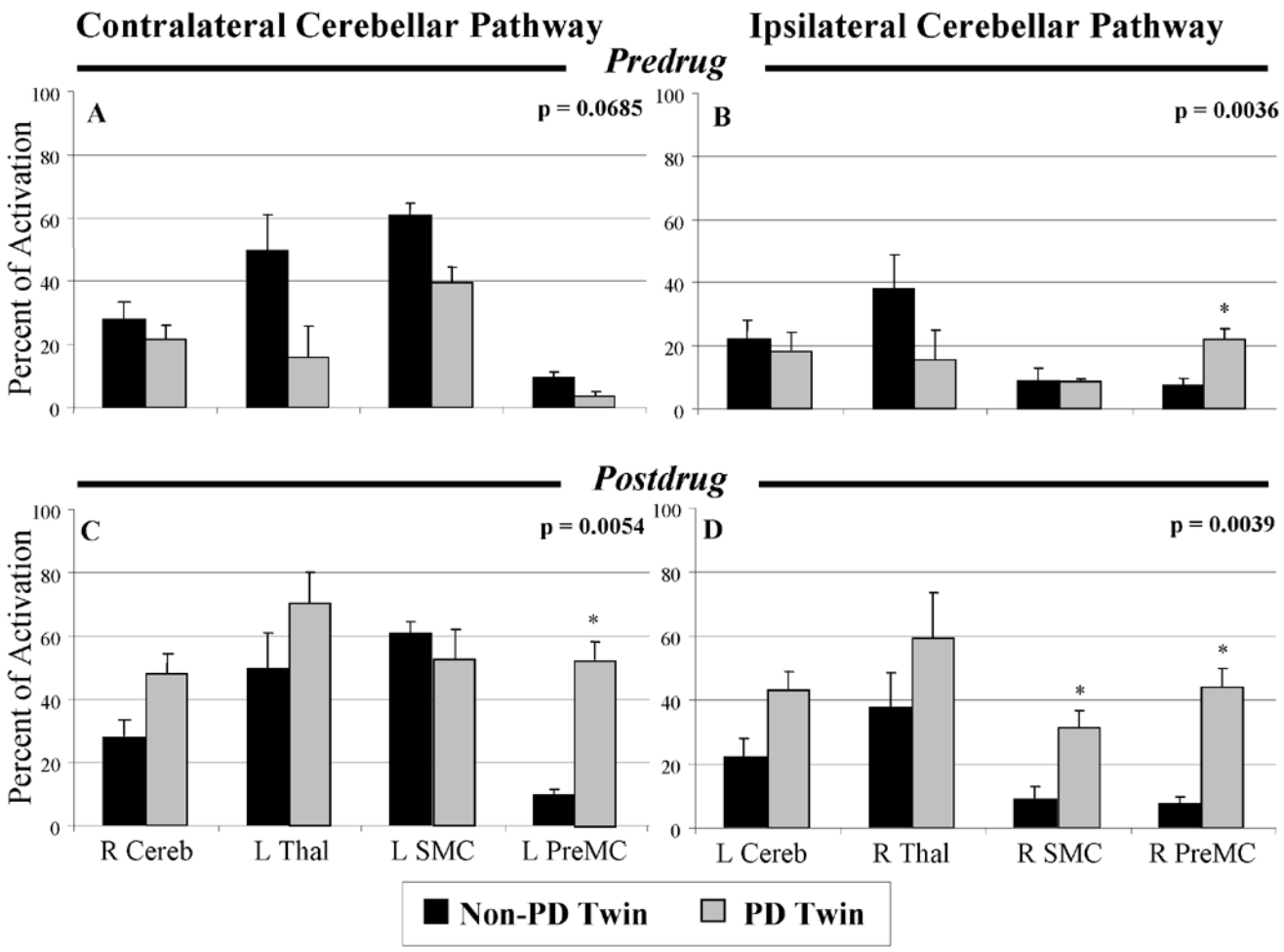

Figure 7.

Percent of activation values for ROIs in the cerebellar-cortical pathways during the IG task in the non-PD-twin (black bars) and PD-twin (gray bars) before (A and B) and after levodopa (C and D). Data represent the mean ± standard error of a given ROI over the six runs each twin completed. P values from multivariate analysis on the cerebellar pathways between twins are given in the upper right corner of each graph. *Indicates significant difference between twins with $p < 0.05$ by simple t-test. Cereb: cerebellum; Thal: thalamus; SMC: somatosensory cortex; PreMC: lateral premotor cortex.

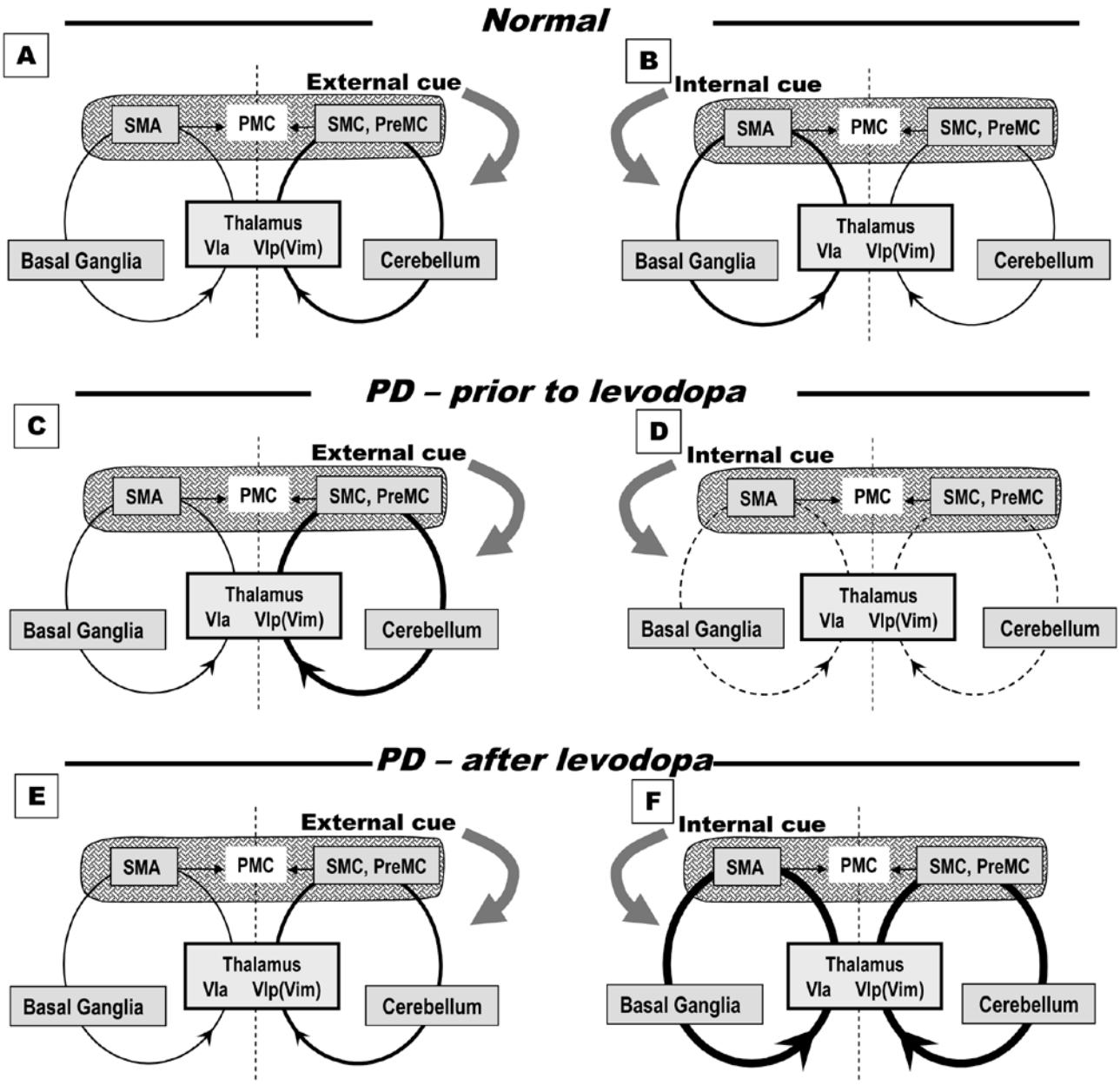

Figure 8.

The proposed model for the segregated, but functionally related, basal ganglia-thalamo-cortical and cerebello-thalamo-cortical circuits. Normally, EG tasks are primarily processed through cerebellar-cortical circuitry, with the recruitment of the BG-cortical circuitry (Panel A), whereas IG tasks are primarily encoded in the BG-cortical pathway, with the recruitment of cerebellar-cortical circuitry (Panel B). In PD, EG tasks also are processed primarily via the cerebellar-cortical pathway, though with enhanced activity in this circuit, particularly in cerebellulm and PreMC areas (Panel C). IG tasks in PD, however, neither adequately activate the BG-cortical pathway (its primary processing center), nor cause adequate recruitment of the cerebellar-cortical pathway. As a result, both pathways display decreased activity (Panel D). Levodopa restores normal cerebellar-cortical activity during the EG task after adequate BG-cortical activation (Panel E, compare to Panel A). In the IG task, levodopa administration

increases functional activity in both BG-cortical and cerebellar-cortical pathways, significantly "over-correcting" both circuits (Panel F). The thickness of the lines in each pathway reflects the level of activity within that circuit. Abbreviations are as follows: PMC: primary motor cortex; PreMC: lateral premotor area; SMA: Supplemental Motor Area; SMC; Sensorimotor Cortex; STN; Vla; Ventralis lateralis anterior thalamus; VLp: Ventralis lateralis posterior thalamus, also know as ventralis intermedius (Vim).

Table 1

Three different finger sequences used in the fMRI paradigm.

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

Digit 1: thumb; digit 2: index finger; digit 3; middle finger; digit 4: ring finger; digit 5: little finger.

Table 2

Multivariate analysis results of percentage of activation of ROIs in bilateral BG-cortical and cerebellar-cortical pathways.

	Column A Non-PD vs. PD-Twin Predrug (p value)		Column B Non-PD vs. PD-Twin Postdrug (p value)		Column C PD-twin: Predrug vs. Postdrug (p value)	
Pathway	**EG**	**IG**	**EG**	**IG**	**EG**	**IG**
Contralateral BG-Cortical Pathway	0.4837	0.0288	0.4587	0.5155	0.1187	0.0076
Ipsilateral BG-Cortical Pathway	0.3935	0.0207	0.5052	0.0453	0.6398	0.0654
Contralateral Cerebellar-Cortical Pathway[*]	0.0417	0.0685	0.1121	0.0054	0.1085	0.0084
Ipsilateral Cerebellar-Cortical Pathway[**]	0.0092	0.0036	0.1567	0.0039	0.5360	0.0591

EG = Externally Guided; IG = Internally Guided

The BG-cortical pathways include the GP/Put, thalamus, SMA, and PMC.

[*] In the contralateral cerebellar-cortical pathway, ‘contralateral’ refers to cortical and subcortical areas and includes the ipsilateral cerebellum with the contralteral thalamus, SMC, and PreMC.

[**] In the ipsilateral cerebellar-cortical pathway, ‘ipsilateral’ refers to cortical and and subcortical areas and includes the contralateral cerebellum with the ipsilateral thalamus, SMC, and PreMC.

Values in the table represent the p value for a particular analysis.