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Differential involvement of striato- and cerebello-thalamo-cortical pathways in tremor-and akinetic/rigid-predominant Parkinson's disease

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Abstract

Parkinson's disease (PD) presents clinically with varying degrees of resting tremor, rigidity, and bradykinesia. For decades, striatal-thalamo-cortical (STC) dysfunction has been implied in

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Specific Contributions of Authors

Mechelle M. Lewis: Data acquisition, analysis, and interpretation; obtaining funding for the study, administrative support for the study; primary drafting and critical revision of the manuscript.

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bradykinesia and rigidity, but does not explain resting tremor in PD. To understand the roles of cerebello-thalamo-cortical (CTC) and STC circuits in the pathophysiology of the heterogeneous clinical presentation of PD, we collected functional magnetic resonance imaging (fMRI) data from 17 right-handed PD patients [nine tremor predominant (PD_T) and eight akinetic-rigidity predominant (PD_{AR})] and 14 right-handed Controls while they performed internally-guided (IG) sequential finger tapping tasks. The percentage of voxels activated in regions constituting the STC and CTC [divided as cerebellar hemisphere-thalamo-cortical (C_HTC) and vermis-thalamo-cortical (C_VTC)] circuits was calculated. Multivariate analysis of variance compared the activation patterns of these circuits between study groups. Compared to Controls, both PD_{AR} and PD_T subjects displayed an overall increase in the percentage of voxels activated in both STC and CTC circuits. These increases reached statistical significance in contralateral STC and CTC circuits for PD_T subjects, and in contralateral CTC pathways for PD_{AR} subjects. Comparison of PD_{AR} and PD_T subjects revealed significant differences in ipsilateral STC ($p=0.005$) and CTC ($p=0.043$ for C_HTC and $p=0.003$ for C_VTC) circuits. These data support the differential involvement of STC and CTC circuits in PD subtypes, and help explain the heterogeneous presentation of PD symptoms. These findings underscore the importance of integrating CTC circuits in understanding PD and other disorders of the basal ganglia.

Keywords

Parkinson's disease; motor pathways; cerebellum; striatum; fMRI

Parkinson's disease (PD)¹ is characterized by resting tremor, rigidity, bradykinesia, and gait disorder, each expressed in varying proportions and progressing in a highly individual manner. Hoehn and Yahr (1967) first described the marked clinical diversity exhibited in PD, and later studies (Jankovic et al., 1990; Spiegel et al., 2007) provided empirical support for PD subgroup differences. Patients may have either primary rigidity and bradykinesia with minimal tremor (akinetic/rigidity predominant, PD_{AR}), or tremor with minimal rigidity, bradykinesia and other symptoms (tremor-predominant, PD_T).

Several lines of evidence suggest PD tremor may have different underlying pathophysiology processes from those of bradykinesia and rigidity [see Zaidel et al. (2009) for a recent review]. For example: factor analysis of PD signs shows rest tremor is relatively independent of other cardinal signs of PD (Zetuskus et al., 1985), is less reliably responsive to dopaminergic modulation (Marjama-Lyons and Koller, 2000), and does not worsen at the same rate as bradykinesia and rigidity (Zetuskus et al., 1985; Louis et al., 1999; Jankovic and Kapadia, 2001). Recent PD imaging studies suggest dopamine transporter levels and myocardial sympathetic degeneration correlate with hypokinesia/rigidity but not tremor (Spiegel et al., 2007). Finally, there is no correlation between rest tremor and striatal ¹⁸F-fluorodopa uptake in PD patients (Vingerhoets et al., 1997).

The pathological hallmark of PD is dopamine neuron loss in the substantia nigra pars compacta (SNc) of the basal ganglia (BG). For decades, a classic model emphasized the role of the BG in modulating cortical function through striatal-thalamo-cortical (STC) circuits (DeLong et al., 1984; Alexander et al., 1986; Albin et al., 1989), the dysfunction of which may lead to bradykinesia and rigidity. This model does not, however, explain PD resting tremor. Emerging evidence suggests the necessity of incorporating cerebello-thalamo-cortical (CTC) circuitry into discussions of motor function in both normal (Kelly et al., 2009) and dysfunctional (Deiber et al., 1993; Neychev et al., 2008; Argyelan et al., 2009; Benninger et al., 2009; Zaidel et al., 2009) states. CTC dysfunction is implied in tremorgenesis in PD_T, as

¹Please see Appendix Cover Page for summary of all abbreviations used in this Application.

PET studies indicate increased regional cerebral blood flow (rCBF) in the vermis, whereas stimulation of the thalamic Vim nucleus (site of cerebellar output) can capture and ameliorate PD tremor (Deiber et al., 1993). Several recent imaging studies suggest altered/compensatory activity in cerebellar pathways in PD (Cerasa et al., 2006; Yu et al., 2007; Sen et al., 2009) and its progression (Sen et al., 2009).

To understand the clinical heterogeneity of PD presentation, and the role of STC and CTC circuits in PD pathophysiology, we compared functional magnetic resonance imaging (fMRI) activation patterns in STC and CTC pathways of PD_{AR} and PD_T subjects to Controls and to each other. In the past, numerous fMRI studies have investigated brain activation in PD (Haslinger et al., 2001; Buhmann et al., 2003; Cerasa et al., 2006; Yu et al., 2007; Tinaz et al., 2008; Helmich et al., 2009) that involved PD_{AR} subjects or subjects with mixed symptoms. To our knowledge, no study has either investigated the fMRI activation pattern in PD_T subjects compared to Controls, or directly compared PD_{AR} and PD_T subjects to each other.

Experimental Procedures

Subjects

Seventeen PD subjects (nine PD_T and eight PD_{AR}) were recruited for this study from a tertiary movement disorders clinic (see Table 1 for demographic information). Each PD subject was diagnosed by a movement disorders specialist (XH) based on previously published criteria (Gibb and Lees, 1988). Twelve PD subjects (six PD_{AR} and six PD_T) had right side predominant symptoms. Most subjects were early in their disease course (see Table 1), with a mean ($\pm$ SD) disease duration for PD_{AR} subjects of 16.0 ± 23.8 mon (range 0.23-72.3 mon) and PD_T subjects 4.1 ± 5.2 mon (range 0-12.2 mon). All PD subjects were free of other neurological illnesses, psychosis, and cognitive decline. Fourteen Control subjects were recruited from IRB-approved advertisements on campus and in the surrounding community. On-going psychiatric or neurological illnesses were an exclusion criterion for the Controls. All subjects were free of hypothyroidism, vitamin B12 or folate deficiency, and free of kidney or liver disease. In addition, all subjects (PDs and Controls) were strongly right handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

Unified Parkinson's Disease Rating part III motor (UPDRS-III) and Hoehn and Yahr scores were obtained for each PD subject after withholding all PD medication overnight (~12 hr) before fMRI scans (Table 1). In addition, levodopa equivalent dosages (LEDs) were calculated for each PD subject. For PD_{AR} subjects, three subjects were not taking any PD-related medications at the time of the study, three were on Sinemet, and two were taking Mirapex. In the PD_T group, six subjects were not taking any medications at the time of the study, one was on Sinemet, and one was taking Requip.

PD subjects were classified as either PD_{AR} or PD_T using the modified ratio developed by Schiess et al. (2000) based on the UPDRS-III. Namely, a numerical ratio was derived from a patient's mean tremor score and mean akinetic-rigidity score. Tremor was assessed using a nine-item scale that included history of left or right tremor (two items), rest tremor of the face/lips/chin and each limb (five items), as well as postural tremor of the right and left upper extremities (two items). The 12-item akinetic-rigidity scale assessed passive range of motion rigidity of the neck and each extremity (five items), rapid opening/closing of hands (one item), finger tapping (one item), rising from a chair (one item), posture and postural instability (two items), gait (one item), and body bradykinesia (one item). Each item was rated 0-4 with 0 representing absence of the symptom or normal activity and 4 significant presence of the symptom or impairment. The mean of each scale was calculated and then the

ratio (tremor/akinetic-rigidity score) determined. Using this method, PD_{AR} subjects will have a ratio <0.8, whereas PD_T subjects will have a ratio >1.0. In the current study, the average ratio for PD_{AR} subjects was 0.20 ± 0.31 (range 0-0.71) and for PD_T subjects 3.02 ± 2.41 (range 1.07-8.00; Table 1). 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.

Functional MRI Acquisition

Images were acquired using 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. PD subjects were scanned in a practically defined 'off' state (>12 hr off PD medications). The subject's head was positioned along the canthomeatal line. Foam padding was used to minimize head motion within the coil. High-resolution T1-weighted anatomical images (3D SPGR, TR=14 ms, TE=7.7 ms, flip angle=25°, voxel dimensions 1.0×1.0×1.0mm, 176×256 voxels, 160 slices) were acquired for co-registration of functional images. A total of 49 co-planar functional images were acquired using a gradient echoplanar sequence (TR=3000ms, TE=30ms, flip angle=80°, NEX=1, voxel dimensions 3.0×3.0×3.0 mm, imaging matrix 64×64 voxels). Functional runs consisted of 200 time points, and two radio frequency excitations were performed prior to image acquisition to achieve steady-state transverse relaxation.

Activation paradigm – sequential finger-tapping movements

This study used a modified activation paradigm based on previous studies in control and PD subjects (Sabatini et al., 2000; Lewis et al., 2007; Sen et al., 2009). Briefly, the paradigm consists of sequential finger-tapping movements (SFM) at 0.5 tap/sec using either the right or left hands. The sequences were presented with instructions that first asked the subject to follow the finger sequence presented on the screen during an externally guided training session, and then asked the subject to continue the finger-tapping sequence (internally guided 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, externally guided training, and internally guided tasks (total 10 minutes, Figure 1). The finger-tapping sequences of each block were alternated to prevent memorization from previous blocks (see Table 2). All subjects practiced the task with both hands for about 20 minutes prior to scanning in order to obtain adequate performance on the tasks. For this manuscript, we present the data from the internally guided task performed by the right (dominant) hand, as previous studies have suggested that PD mainly affects internally rather than externally guided tasks (Jahanshahi et al., 1995; Chuma et al., 2006; Nowak et al., 2006), and the non-dominant hand displays a more complicated pattern of neurocircuitry recruitment [(Mattay et al., 1998) and unpublished data from our lab]. Two runs of fMRI data from each subject were included for 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.

Generation of first level fMRI activation maps

The spatial transformation into a common coordinate space that is traditionally done for most fMRI studies deemphasizes inherent anatomical variability of the human brain, factors

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 using SPM5 comparing the activation pattern of the IG task performed by the right hand to rest. The anatomic region of interest (ROI) based-multivariate analysis of fMRI activation pattern then was applied as described below.

Obtaining the fMRI activation level in each ROI constituting the STC and CTC circuits

The anatomical regions of interest (ROIs) were defined on high resolution T1 images using automatic segmentation software [AutoSeg, Neuro Image Research and Analysis Laboratories, University of North Carolina at Chapel Hill, NC; (Joshi et al., 2004; Gouttard et al., 2007)] 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 $p = 0.05$) was calculated for each ROI in the bilateral STC [lentiform nucleus (Lent), thalamus (Th), supplementary motor area (SMA), and primary motor cortex (PMC)] and CTC circuits. For the purpose of this study, the CTC pathway was divided into C_HTC [cerebellar hemisphere, Th, lateral premotor cortex (PrMC), and somatosensory cortex (SMC)] and C_VTC [vermis/paravermis including bilateral dentate nuclei (Vm), Th, PrMC 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).

Statistical comparison of fMRI activation patterns in STC and CTC circuits between groups

A statistical method that compared multiple ROIs together, namely multivariate analysis of variance (MANOVA), was employed to compare the fMRI activation patterns between groups in ROIs of the neurocircuitry described above. ROIs that constitute the bilateral STC, C_HTC , and C_VTC circuits were treated as co-multivariate response variables. The number of ROIs included in each pathway was limited to four based on the sample size in each PD group ($n=8$ or 9). Specifically, it is required in the MANOVA procedure that the number of ROIs plus the number of groups will have to be less than the sample size (Johnson and Wichern, 2002). The percent activation in the ROIs of these pathways in each subject was the multivariate dependent variable, whereas the independent variable was PD status ($2=Control$, $1=PD_T$, $0=PD_{AR}$). Activity in STC and CTC circuits was compared between Controls and PD_{AR} or PD_T subjects. PD_{AR} and PD_T subjects also were compared directly. All comparisons were conducted by utilizing multiple MANOVAs with adjustment of age using the PROC GLM command with option MANOVA in SAS (System 9.1, SAS Inc., Cary, NC). In addition, when PD_{AR} and PD_T subjects were compared we also included side of symptom onset as a factor in the analysis. Significant MANOVA results were probed with a Student's t -test. P values less than 0.05 were considered to represent significant differences between groups.

Results

Demographic data

Although PD_T subjects appeared on average to be slightly older than Control and PD_{AR} subjects, there were no significant differences in age among the groups (Table 1). For PD subtypes, there were no significant differences in disease duration, total UPRDS, or Hoehn and Yahr scores. PD_{AR} subjects had a higher LED compared to PD_T subjects. As expected, the two subtypes showed significant differences in the tremor/AR ratio (Table 1).

PD_{AR} versus Control subjects

In all ROIs comprising the bilateral STC and CTC circuits, PD_{AR} subjects displayed increased activity relative to Controls (see Figure 2). Direct comparison of PD_{AR} and Controls revealed significant differences in all STC and CTC circuits, with contralateral CTC pathways having p values <0.0001 , ipsilateral CTC circuits 0.01, and those for the contralateral and ipsilateral STC pathways 0.0002 and 0.0012, respectively. After adjusting for age, however, only the contralateral CTC circuits remained significant (C_{HTC} $p=0.0113$, C_{VTC} $p=0.0169$), with a trend towards significance in the bilateral STC pathways (p values ~ 0.09 , see Table 3). Post-hoc t -tests within the significant CTC pathways revealed no statistical significance for any of the ROIs.

PD_T versus Control subjects

In bilateral STC and CTC pathways, PD_T subjects displayed increased activity relative to Controls in most ROIs comprising these circuits, although they demonstrated decreased activity in contralateral PMC and bilateral lentiform nucleus. Direct comparison of PD_T and Controls demonstrated significant differences in all STC and CTC circuits except the ipsilateral C_{VTC} circuit ($p=0.0565$). All contralateral pathways had p values <0.0002 , whereas those for the ipsilateral STC and C_{HTC} circuits were 0.0094 and 0.0299, respectively. These statistically significant differences remained only in contralateral STC ($p=0.0089$) and CTC (C_{HTC} $p=0.0404$ and C_{VTC} $p=0.0472$) pathways after adjusting for age (Table 3), although none of the ROIs reached significance by post-hoc t -test.

PD_{AR} versus PD_T subjects

As shown in Figure 4, PD_{AR} subjects displayed more activity in almost all cortical and subcortical ROIs relative to PD_T subjects, whereas PD_T subjects showed more activity in the vermis, contralateral cerebellar hemisphere, and ipsilateral thalamus. Direct comparison between PD_{AR} and PD_T subject revealed statistically significant difference in all STC and CTC circuits (p values ranging from 0.0031-0.0255) except for the ipsilateral STC ($p=0.0582$). Most of the statistical differences disappeared after individual adjustment for age or side of symptom onset in PD subjects. Yet there was an even stronger significant difference between the subtypes in ipsilateral STC ($p=0.005$) and CTC ($p=0.043$ for C_{HTC} and $p=0.003$ for C_{VTC}) circuits after adjustment for both factors (see Table 3). None of the individual ROIs, however, reached significance when probed with a t -test.

Discussion

In doing the first fMRI study that has compared Control, PD_{AR}, and PD_T subjects, we have shown that there is differential involvement of STC and CTC pathways for the two different PD clinical presentations (or subtypes). The results indicate first, that PD_{AR} and PD_T subjects both display overall increased recruitment of STC and CTC neurocircuitry compared to Controls during this internally guided motor task. Second, the pattern of the recruitment of STC and CTC circuits was different for PD_{AR} and PD_T subjects. Namely, PD_{AR} subjects showed significantly increased activity in contralateral CTC circuits with trends toward significant differences in bilateral STC pathways, whereas PD_T subjects displayed significant changes in contralateral STC and CTC pathways. Third, the direct comparison of PD_{AR} and PD_T subjects supports significant differences in STC and CTC circuits between these PD subtypes. PD_{AR} subjects displayed increased activity relative to PD_T subjects, notably in areas related to the primary pathology in PD (lentiform nucleus of the basal ganglia), whereas PD_T subjects demonstrated higher activity in cerebellar and thalamic regions suggested to be involved in tremorgenesis. These results help contribute to understanding the pathophysiology and clinical heterogeneity of PD presentation.

PD_{AR} and PD_T subjects displayed an overall increase in activity in bilateral motor areas relative to Controls, consistent with previous functional imaging studies in PD (Rascol et al., 1997; Haslinger et al., 2001; Cerasa et al., 2006; Yu et al., 2007). Although the exact meaning of blood oxygen level dependent (BOLD) changes measured by fMRI is still controversial, the increase in BOLD signal changes during tasks may indirectly reflect increased activity or oxygenation demands in these brain regions (Heeger et al., 2000; Rees et al., 2000; Logothetis et al., 2001). The increased recruitment of STC and CTC motor areas demonstrated in the current fMRI study suggests compensatory activation or an overall decrease in efficiency of these brain regions to drive the same motor task in the pathological state of PD. These results are consistent with previous studies in PD subjects that suggest simple tasks recruit brain regions that are normally associated with more complex tasks (Carbon et al., 2007; Moraschi et al., 2010).

Consistent with previous studies demonstrating increased activity in cerebellum and lateral premotor areas (Rascol et al., 1997; Sabatini et al., 2000; Thobois et al., 2004; Wu and Hallett, 2005), PD_{AR} subjects showed significantly increased activity in CTC pathways. PD_{AR} subjects also displayed a trend toward significant increases in bilateral STC pathways compared to Controls, suggesting a possible increased recruitment (decreased efficiency) in these circuits as well. These results are consistent with previous studies that demonstrated increased activation in regions comprising the STC circuits in PD_{AR} subjects (Haslinger et al., 2001; Cerasa et al., 2006). Moreover, the current study echoes recent studies in dystonic patients (Neychev et al., 2008; Argyelan et al., 2009), where traditional views have placed responsibility for motor dysfunction on BG circuitry. In each case, there is emerging evidence that in addition to BG circuit dysfunction, cerebellar circuits also are involved (Cerasa et al., 2006; Yu et al., 2007; Neychev et al., 2008; Argyelan et al., 2009; Benninger et al., 2009; Sen et al., 2009).

In comparing PD_T subjects to Controls, we found that PD_T subjects showed a pattern of activation similar to PD_{AR} subjects in CTC pathways. Within the contralateral STC pathway, however, PD_T subjects displayed differential activity relative to Controls. Namely, PD_T subjects had increased activity in contralateral SMA and thalamus but decreased activity in PMC and lentiform nucleus, which may imply less compensatory activity (or more efficient activity) in the STC circuits of PD_T subjects. The present results are complimentary to studies that have reported pathologically increased oscillations in contralateral STC and CTC circuits in PD_T subjects (Timmermann et al., 2003; Pollok et al., 2009).

Relative to PD_T subjects, PD_{AR} subjects demonstrated increased recruitment of most ROIs comprising the STC and CTC pathways. This increased recruitment, however, was only significant in the ipsilateral STC and CTC circuits. The exact mechanism for this observation is unclear at this moment. Bilateral recruitment of motor areas with unilateral motor tasks, indeed, has been reported previously (Cincotta et al., 2006; Moraschi et al., 2010), and was suggested to be reflective of underlying neuropathological mechanisms. Mirror movements (MM) in unused hands have been reported in PD (Vidal et al., 2003; Espay et al., 2005; Espay et al., 2006; Li et al., 2007), and are particularly associated with rigidity (Espay et al., 2005). Transcranial magnetic stimulation and PET activation studies have demonstrated enhanced facilitation and increased rCBF in the ipsilateral motor cortex of primary MM syndromes (Kanouchi et al., 1997). Furthermore, recent fMRI studies have indicated significant recruitment of ipsilateral brain regions during a simple motor task in PD (Moraschi et al., 2010). Together, these data lead to the hypothesis that both PD_{AR} and PD_T subjects may have maximized the recruitment of contralateral structures that normally are used for performing IG motor tasks (Rascol et al., 1997; Mattay et al., 1998; Elsinger et al., 2003). Conversely, PD_{AR} subjects may require increased recruitment of additional brain

structures (even from ipsilateral hemispheres) to compensate for the functions usually carried out by these contralateral structures. These results lend support to the notion that PD_{AR} may represent a more advanced stage of the pathophysiological process occurring during PD (Jellinger, 1991; Jellinger and Paulus, 1992).

Most interestingly, PD_{AR} and PD_T subjects demonstrated different patterns of activity in basal ganglia and cerebellar regions, areas linked to the primary pathology of PD and tremorgenesis, respectively. Namely, PD_{AR} subjects displayed higher activity in the lentiform nucleus whereas PD_T subjects showed increased activity in vermis, cerebellar hemisphere, and thalamus of the ipsilateral pathways. These results suggest different degrees of pathological changes in these regions in the different subtypes of PD (Zaidel et al., 2009). If the higher activity does imply increased pathology (less efficient brain regions), these results are consistent with previous studies demonstrating increased neuronal loss in the basal ganglia in PD_{AR} subjects (Jellinger, 1991; Jellinger and Paulus, 1992), as well as increased cerebral blood flow in the vermis (Deiber et al., 1993) and decreased gray matter volume in the declive of the cerebellum (Benninger et al., 2009) in PD_T subjects. Together, the current results also support the greater involvement of the cerebellum in tremorgenesis in PD (Poirier et al., 1975; Pechadre et al., 1976; Deiber et al., 1993; Duffau et al., 1996; Zaidel et al., 2009).

There are several limitations for our study. First, the sample size limited our ability to study additional regions of interest in a more detailed manner (such as subdividing the lentiform nucleus into its independent components, the putamen and GP); Second, although PD subjects were imaged in the practically defined 'off drug' state, we cannot rule out potential residual effects of dopaminergic medications on the neurocircuits. Also, it is well known that tremor in PD generally is less responsive to dopaminergic modulation than bradykinesia and rigidity (Marjama-Lyons and Koller, 2000). The current study did not address the effect of levodopa on STC and CTC circuitry in the different PD subtypes. Third, the behavioral assessments were subjective, relying on the demonstrated proficiency immediately prior to the fMRI session and not reflecting the exact performance during fMRI data collection. Future studies with a larger sample size, drug naïve patients, better behavioral data recording, and subject response to levodopa would be useful.

In the nearly two decades since its description, the classic model of motor control emphasized the role of the BG in influencing cortical function (DeLong et al., 1984; Alexander et al., 1986; Albin et al., 1989), and elegantly posited an explanation for rigidity and bradykinesia. The model, however, was not able to explain resting tremor in PD. In both normal (Kelly et al., 2009; Hoshi et al., 2005; Bostan et al., 2010) and disease conditions (Cerasa et al., 2006; Yu et al., 2007; Neychev et al., 2008; Argyelan et al., 2009; Sen et al., 2009), increasing evidence suggests the necessity of incorporating cerebellar function/dysfunction into a comprehensive view of motor control and tremorgenesis in PD (Deiber et al., 1993; Benninger et al., 2009). The current study provides further evidence that there is differential involvement of striato- and cerebello-thalamo-cortical circuits in PD_T and PD_{AR} subtypes.

Collectively, this evidence suggests that the classic model should be modified with integration of cerebellum influences if the clinical heterogeneity of PD (and the "unexplained" tremor) are to be better understood. Elegant work by Strick and colleagues previously demonstrated that the basal ganglia and cerebellum project to and influence similar cortical regions [summarized in (Middleton and Strick, 2000)], but the need for a revised model is accentuated by recent findings that the striatum and cerebellum also may communicate and/or influence each others' functions at the subcortical level through di- and trisynaptic connections (Hoshi et al., 2005; Bostan et al., 2010). Figure 5 provides a

hypothetical schematic in which STC and CTC circuits are integrated. In this model, both the striatum and cerebellum influence cortical motor functions through parallel or complementary STC and CTC circuits, with both structures also modulating each other at the subcortical level [Figure 5, long dash and small dotted arrows, respectively; (Hoshi et al., 2005; Bostan et al., 2010)]. The primary dysfunction (decreased efficiency with over activation) in the STC circuit (Figure 5, light gray structures connected with dashed arrows) may lead to bradykinesia and rigidity observed in PD_{AR} subjects. In contrast, primary dysfunction in the CTC circuit (Figure 5, dark gray structures connected with solid arrows), particularly the vermis/paravermis region, may be responsible for the occurrence of resting tremor in PD_T. The different degrees of functional deficits of the STC and CTC circuits may assist in understanding the observed clinical heterogeneity of PD motor symptoms. Future studies exploring such hypotheses, with detail understanding role of subnuclei of BG, cerebellums and related structures, may not only shed light on PD pathophysiology, but also help elucidate the function of these circuits in other disorders as well as the healthy brain.

Research Highlights

- PD_{AR} & PD_T subjects show more activity in STC and CTC circuits compared to Controls
- PD_T subjects show significant changes from Controls in contralateral STC and CTC
- PD_{AR} subjects only show significance in contralateral CTC compared to Controls
- Comparing PD_T & PD_{AR} subjects shows significant differences in ipsilateral STC and CTC

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Abbreviations

BG	Basal ganglia
CTC	Cerebello-thalamo-cortical
C_HTC	Cerebellar hemisphere-thalamo-cortical
C_VTC	Cerebellar vermis-thalamo-cortical
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
Lent	Lentiform nucleus
MANOVA	Multiple analysis of variance
NEX	Number of excitations
PD	Parkinson's disease
PD_{AR}	Akinetic/rigidity predominant Parkinson's disease
PD_T	Tremor predominant Parkinson's disease

PMC	Primary motor cortex
PrMC	Lateral premotor cortex
ROI	Region of interest
SFM	Sequential finger tapping movements
SMA	Supplementary motor area
SMC	Somatosensory cortex
SNc	Substantia nigra pars compacta
SPGR	Spoiled gradient recall
TE	Echo time
Th	Thalamus
TR	Repeat time
Vim	Ventral intermediate nucleus of the thalamus
Vla	Ventral lateral anterior of the thalamus

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Figure 1.
Schematic of paradigm.

Figure 2.

Comparison of percent activation changes in STC and CTC circuits in Control and PD_{AR} subjects. Control (black bars) and PD_{AR} (gray bars) subjects performed the finger tapping task with their right hand. P values for each circuit were deduced from MANOVA comparison 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 within a given ROI for simple visualization (not for MANOVA calculation). Circuits are defined as listed in the legend of Table 3.

Figure 3.

Comparison of percent activation changes in STC and CTC circuits in Control and PD_T subjects. Control (black bars) and PD_T (gray bars) subjects performed the finger tapping task with their right hand. P values for each circuit were deduced from MANOVA comparison 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 within a given ROI 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 STC and CTC circuits in PD_{AR} and PD_T subjects. PD_{AR} (black bars) and PD_T (gray bars) subjects performed the finger tapping task with their right hand. P values for each circuit were deduced from MANOVA comparison of the collective percent activation 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 simple visualization (not for MANOVA calculation). Circuits are defined as listed in the legend of Table 3.

Figure 5.

New model integrating STC and CTC circuits. Neuroanatomical evidence indicates that for the STC circuit (light gray structures connected with dashed arrows) the output nucleus of the striatum, the internal segment of the GP, projects to the ventral lateral anterior nucleus of the thalamus, up to the SMA and then PMC, with reciprocal projections back to the striatum. For the CTC circuit (dark gray structures with solid arrows), the cerebellum projects to the ventral intermediate nucleus of the thalamus, up to the premotor cortex and then over to the SMC. The cortex then sends projections back to the cerebellum. In addition, we hypothesize that the PrMC and SMC also send fibers to the finally motor endpoint, the PMC. Recent evidence suggests that the basal ganglia (Bostan et al., 2010) and cerebellum (Hoshi et al., 2005) communicate and/or influence each other's functions at the subcortical level. These connections are indicated using dashed-arrows (basal ganglia to cerebellum) and small-dotted arrows (cerebellum to basal ganglia). BG: basal ganglia, GP: globus pallidus, PMC: primary motor cortex, PN: pontine nuclei, PrMC: lateral premotor cortex, SMA: supplementary motor area, SMC: somatosensory cortex, STN: subthalamic nucleus, Vla: ventrolateral anterior nucleus of the thalamus, Vim: ventral intermediate nucleus of the thalamus

Table 1

Subject demographic data

	Controls (n = 14)	PD_{AR} (n = 8)	PD_T (n = 9)	P value
Age (mean $\pm$ SD, yrs)	51.4 $\pm$ 14.5	51.3 $\pm$ 10.2	59.3 $\pm$ 6.6	>0.05 [*]
Disease duration (mean $\pm$ SD, mon)	NA	16.0 $\pm$ 23.8	4.1 $\pm$ 5.2	0.280 ^{**}
Total UPDRS	NA	9.5 $\pm$ 3.9	9.2 $\pm$ 3.2	0.884 ^{**}
Hoehn & Yahr score	NA	1.3 $\pm$ 0.5	1.3 $\pm$ 0.4	0.657 ^{**}
Levodopa equivalent dosage (LED), mg	NA	225 $\pm$ 192	67.5 $\pm$ 130	0.050 ^{**}
Tremor/AR ratio	NA	0.20 $\pm$ 0.31	3.02 $\pm$ 2.41	0.005 ^{**}
Right side symptom onset	NA	6	6	NA
Handedness	Right	Right	Right	NA

Summary of demographic information for Control, PD_{AR}, and PD_T subjects included in the study. Age, disease duration, total UPDRS, Hoehn & Yahr score, LED, and Tremor/AR ratio were compared using a two-tailed t-test. PD_{AR} – akinetic/rigid predominant PD, PD_T – tremor predominant PD, NA – not applicable, mon – months, tremor/AR ratio – tremor/akinetic-rigidity ratio.

^{*} Comparison of age for Controls and PD_{AR} subjects p=0.990, Controls and PD_T subjects p=0.139, and for PD_{AR} and PD_T subjects p=0.066.

^{**} P value reflects the comparison between PD_{AR} and PD_T subjects.

Table 2

Finger sequences used in the fMRI paradigm.

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

Table 3MANOVA comparisons among Controls, PD_{AR} and PD_T subjects.

	Control vs PD _{AR}	Control vs. PD _T	PD _{AR} vs. PD _T
Contralateral STC [†]	0.0909	0.0089	0.8999
Contralateral ChTC ^{††}	0.0113	0.0404	0.8483
Contralateral CvTC ^{†††}	0.0169	0.0472	0.7433
Ipsilateral STC [†]	0.0959	0.1940	0.0048
Ipsilateral ChTC ^{††}	0.2690	0.3085	0.0438
Ipsilateral CvTC ^{†††}	0.3518	0.4176	0.0030

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 (Lent, Th, SMA, and PMC), ChTC (CB, Th, PreMC, and SMC), and CvTC (Vm, Th, PreMC and SMC) circuits. Network analyses were performed using MANOVA with percent activation of individual ROIs as the dependent variables. All p values have been adjusted for age.

[†] Contralateral STC was defined as contralateral Lent, Th, SMA, and PMC

^{††} Contralateral ChTC was defined as ipsilateral CB and contralateral Th, PreMC, and SMC

^{†††} Contralateral CvTC was defined as Vm and contralateral Th, PreMC, and SMC

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

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

^{†††} Ipsilateral CvTC was defined as Vm and ipsilateral Th, PreMC, and SMC.