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ORIGINAL RESEARCH

Arterial spin labeling reveals relationships between resting cerebral perfusion and motor learning in Parkinson's disease

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Abstract

Parkinson's disease (PD) is an age-related neurodegenerative disease that produces changes in movement, cognition, sleep, and autonomic function. Motor learning involves acquisition of new motor skills through practice, and is affected by PD. The purpose of the present study was to evaluate regional differences in resting cerebral blood flow (rCBF), measured using arterial spin labeling (ASL) MRI, during a finger-typing task of motor skill acquisition in PD patients compared to age- and gender-matched controls. Voxel-wise multiple linear regression models were used to examine the relationship between rCBF and several task variables, including initial speed, proficiency gain, and accuracy. In these models, a task-by-disease group interaction term was included to investigate where the relationship between rCBF and task performance was influenced by PD. At baseline, perfusion was lower in PD subjects than controls in the right occipital cortex. The task-by-disease group interaction for initial speed was significantly related to rCBF ($p < 0.05$, corrected) in several brain regions involved in motor learning, including the occipital, parietal, and temporal cortices, cerebellum, anterior cingulate, and the superior and middle frontal gyri. In these regions, PD patients showed higher rCBF, and controls lower rCBF, with improved performance. Within the control group, proficiency gain over 12 typing trials was related to greater rCBF in cerebellar, occipital, and temporal cortices. These results suggest that higher rCBF within networks involved in motor learning enable PD patients to compensate for disease-related deficits.

Keywords Parkinson's disease · Motor1 · ASL · Basal ganglia · Substantia nigra · Thalamus · Imaging · Brain mapping · Cerebral cortex · Blood flow

Introduction

Motor learning involves the acquisition, automation, and consolidation of new physical skills through practice. Motor skill acquisition has been divided into an initial fast phase that requires cognitive input, an associative stage during which skills are refined, and an autonomous stage that requires little cognitive input and during which the organism can continue the learned skill in spite of distraction (Fitts and Posner 1967). Motor learning involves motor and premotor cortical regions, the striatum, cerebellum, premotor cortex and supplementary motor area, anterior cingulate, dorsolateral prefrontal cortex (DLPFC), and parietal cortex (Floyer-Lea and Matthews 2005; Dayan and Cohen 2011), as well as the hippocampus (Schendan et al. 2003). During the initial rapid phase of motor skill acquisition, the associative striatum along with attentional and limbic networks are activated; with consolidation, there is a shift from the associative to the sensorimotor striatum and motor

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cortical regions, as well as a shift from cerebellar cortex to deep nuclei (Doyon et al. 2009). In the later stages of skill refinement, motor cortical regions and striatum are involved, whereas the cerebellum participates mainly in motor adaptation.

Brain regions involved in motor skill acquisition are also members of cortico-striatal and cortico-cerebellar networks that are known to be affected by Parkinson's disease (Alexander et al. 1986). Although the majority of studies in PD report motor learning deficits (Sommer et al. 1999; Stefanova et al. 2000; Ghilardi et al. 2003; Smith and McDowall 2006) that worsen with disease progression (Doyon et al. 1997; Stephan et al. 2011), a few find that PD patients perform similarly to controls (Mentis et al. 2003; Mallol et al. 2007), especially during less complex tasks (Mentis et al. 2003). PD-related motor deficits are most evident during internally cued, or self-paced, tasks (Siegert et al. 2002; Michely et al. 2012), such as choice reaction time tasks (Hocherman et al. 2004; Michely et al. 2012). For this study, we chose a self-paced motor learning task that was likely to demonstrate deficits in PD.

Arterial spin labeling (ASL) is a non-invasive MRI technique that magnetically labels water protons in arterial blood to measure cerebral perfusion. ASL eliminates potentially harmful radioactive materials that have typically been used to study cerebral blood flow, as well as the need for long preparation times (Alsop et al. 2010; Melzer et al. 2011). Previous studies measuring CBF in PD using ASL have reported perfusion changes in various cortical regions including the occipital cortex, posterior parietal cortex, posterior cingulate, cuneus, precuneus, dorsal premotor cortex and pre-SMA, prefrontal cortex, precentral gyrus, and superior and middle frontal gyri (Ma et al. 2010; Melzer et al. 2011; Kamagata et al. 2011; Fernández-Seara et al. 2012; Al-Bachari et al. 2014; Madhyastha et al. 2015; Syrimi et al. 2017). Therefore, several regions showing perfusion differences in PD are also known to participate in motor learning networks. The primary goal of the present study was to map differences in resting cerebral blood flow (rCBF) in relation to motor skill acquisition in PD patients compared to controls using ASL. Based on previous literature, we hypothesized we would see an abnormal resting cerebral perfusion pattern in PD patients. Moreover, we hypothesized that rCBF within networks known to be involved in motor learning would show different relationships to task performance in PD patients compared to controls.

Methods

Subjects

Participants were recruited through the William S. Middleton VA and University of Wisconsin neurology clinics, the Wisconsin Alzheimer's Disease Research Center (ADRC) Recruitment Registry Database, and community organizations associated with PD. Of 85 participants, 14 were excluded from the analyses due to ASL sequence instability following an MRI scanner upgrade, and 10 were excluded due to inadequate motor task data. The remaining 61 participants (30 PD patients and 31 age-and gender- matched controls) had both motor task and MRI data meeting quality control criteria for analysis. Quality control criteria included completing 11 or more motor task blocks as well as having good quality ASL data. Group demographics along with disease characteristics for these participants are shown in Table 1. PD participants

Table 1 Demographic, neuropsychological, and clinical characteristics of participants

	PD ($n = 30$) Mean (SD)	Control ($n = 31$) Mean (SD)	*t-value*
Demographics			
Age (years)	66.14 (8.97)	67.48 (8.31)	0.60
Gender (M:F)	24:6	25:6	−0.06
Formal education (years)	15.47 (2.84)	17.81 (2.54)	3.39*
Handedness (R:L:A)	27:3:0	29:1:1	
Neuropsychological Data†			
Executive composite	−0.388 (1.02)	−0.014 (0.723)	1.65
Memory composite	−0.786 (1.27)	−0.132 (0.998)	−2.24
Language composite	−0.144 (1.08)	0.079 (0.831)	−0.91
Disease-specific characteristics			
Age at diagnosis (years)	62.23 (8.48)	n/a	
Disease duration (years)	6.14 (3.90)	n/a	
Motor subtype (TD:PIGD)	22:8	n/a	
Laterality of motor onset (R:L:S)	18:8:4	n/a	
Hoehn & Yahr stage	1.75 (0.70)	0 (0)	−13.84*
UPDRS III OFF	20.25 (10.59)	1.45 (1.52)	−10.65*

*P < 0.001 by independent samples t-test

† = mean of Z scores for selected tests; for details see *Cognitive Assessments*

A Ambidextrous; *S* Symmetrical; *UPDRS III OFF* Unified Parkinson's disease rating scale motor sub score while off anti-parkinson's medication

PD Parkinson's disease; *PIGD* Postural instability and gait disorder; *TD* Tremor-dominant

were at least 45 years of age at symptom onset and met UK brain bank criteria for idiopathic Parkinson's disease (Hughes et al. 1992). All participants had Mini-Mental Status Examination (MMSE; Folstein et al. 1983) scores between 27 and 30. For PD participants, exclusion criteria included signs of an "atypical" Parkinsonian syndrome, dementia, other significant neurologic or psychiatric disease, and a family history of PD in two or more first-degree relatives. All participants were examined by a movement disorders specialist (CG) and imaged while off anti-Parkinson's medication for a minimum of 12 hours. To quantify the severity of PD symptoms, right limb, left limb, and axial "off" scores were summed from the Motor Section of the Unified Parkinson's Disease Rating Scale (UPDRS-III; Fahn and Elton 1987). Disease stage was assigned based on clinical signs using the Hoehn and Yahr scale (Hoehn and Yahr 1967); disease duration (y) was defined as the time from initial motor symptoms to time of imaging. On the Hoehn and Yahr scale, patients with motor signs on one side of the body are stage 1; on both sides, stage 2; and with various degrees of postural instability and immobility, stage 3–5. This study was approved by the University of Wisconsin IRB and endorsed by the William S. Middleton VA R&D Committee. Each participant provided informed written consent before participation in the study.

Motor sequence task

A finger-typing motor sequence task (MST, Tucker et al. 2011), was used to quantify motor skill acquisition. This task was completed in the off-medication state within 2 h of the MRI scan. Subjects were instructed to press a sequence of 5 keys (4–1–3-2-4) on a laptop keyboard that were labeled with the numbers 1,2,3,4, with their left hand, as quickly and accurately as possible. Each task block consisted of a 30-s typing phase followed by a 30-s rest. Each participant completed 12 blocks, without feedback for errors. During each block, custom software recorded the number of correct sequences typed as well as the total number of keys pressed.

For the purpose of analysis, several variables were generated: (1) *initial speed*, defined as the number of correct sequences typed during the first block; (2) *plateau speed*, or mean number of correct sequences typed per block during blocks 4–12; (3) *proficiency gain*, defined as the mean number of correct sequences typed during each of the last three blocks minus the number typed during the initial block; and (4) *accuracy*, or the total number of correct sequences typed over the 12 blocks divided by the number of correct sequences that would have been typed had all keystrokes registered been correct. Since PD patients have bradykinesia, or movement slowing, we compared the number of correct sequences typed during each block between PD and control groups (Fig. 1) using an independent samples t-test (Table 2). Additionally, since participants completed the task with their left hand, we analyzed within-group characteristics for PD based on side of onset (right vs. left) and disease stage (Hoehn & Yahr I vs. Hoehn & Yahr II and above) to determine if these factors influenced motor task performance. Except for 4 individuals who were not able to complete 1 of the 12 blocks (these blocks were not included in any of the main outcome measures), all participants completed all blocks.

Cognitive assessments

Subjects completed a cognitive test battery that was designed to assess intellectual ability, psychomotor speed, language, verbal memory, and executive function. They also completed evaluations of mood and daytime sleepiness using the Epworth Sleepiness Scale (Johns 1991). Neuropsychological testing was conducted immediately prior to the brain MRI, with PD participants in the off-medication state. For analysis, Z scores were generated for each of the individual neuropsychological tests using the control group mean and SD. Then

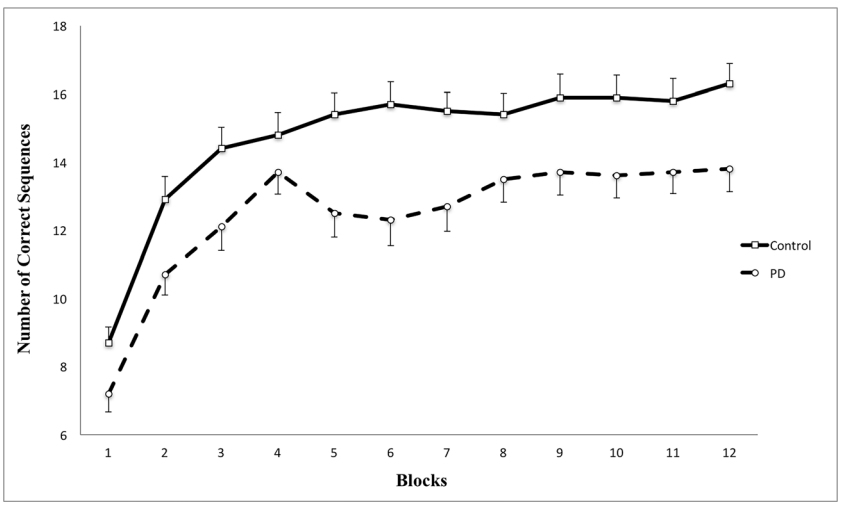

Fig. 1 Means and standard errors (SEM, bars) for the number of correct sequences typed during each of the 12 motor sequence task blocks are shown for the Parkinson's (PD) and control groups

Table 2 Motor sequence task performance

Task Variable	PD M (SD)	Control M (SD)	*t*-value
Initial speed (correct sequences/block)	7.23 (4.1)	8.65 (3.6)	1.45
Plateau speed (correct sequences/block)	13.26 (5.1)	15.66 (4.6)	1.92
Proficiency gain (correct sequences/block)	6.46 (4.1)	7.38 (3.3)	0.97
Accuracy (correct/all keystrokes)	0.91 (0.06)	0.94 (0.04)	2.41*

*P < 0.05 by independent samples t-test

M Mean; *PD* Parkinson's disease; *SD* Standard deviation

these individual Z scores were combined into composite scores representing several cognitive domains in agreement with previous assessments of mild cognitive impairment in PD (Morrison et al. 2000; Litvan et al. 2012): Executive composite = {Category Fluency (Benton and Hamsher 1976) + Stroop task (Golden 1975) color-word score – [Trails B – A] time difference (Reitan 1992) – Wisconsin Card Sort perseverative errors score}/4; Memory composite = {Hopkins verbal learning test delayed recall + total recall scores (Benedict et al. 1998)}/2; Language composite = {Phonemic Fluency score (Barry et al. 2008) + Boston Naming Test (Kaplan et al. 1983) score}/2. Relationships between the motor task variables and domain-specific cognitive composite scores were examined for each group separately using multiple regressions controlled for age, gender, and education in SPSS (Version 22.0, 2013).

Neuroimaging protocol

Participants were scanned on a GE 750 Discovery 3 T MRI scanner (General Electric, Waukesha, WI) with an 8-channel phased array head coil. Participants fasted for at least 4 h prior to the scan and withheld any medications with vasoactive properties (such as nitrates) on the day of the scan. PD participants also withheld anti-Parkinson medications for 12–18 h prior to the scan. Three-dimensional T_1-weighted inversion recovery-prepared spoiled gradient echo scans were collected using the following parameters: inversion time (T1)/echo time (TE)/repetition time (TR) = 450 ms/3.2 ms/8.2 ms, flip angle = 12°, slice thickness = 1 mm no gap, field of view (FOV) = 256, matrix = 256 × 256. rCBF assessments were obtained using background suppressed pseudocontinuous ASL (pcASL; Ye et al. 2000; Dai et al. 2008), which has been shown to have excellent test-retest reliability ($r > 0.95$) at our center (Xu et al. 2010). This sequence is a 3-D fast spin echo spiral sequence that utilizes a stack of variable-density spiral 4-ms readout and 8 interleaves with multislice spin labeling to eliminate off-resonance errors (Garcia et al. 2005). The pcASL scan parameters included TE/TR = 10.5 ms/4.9 ms, slice thickness = 4 mm with no gap, matrix = 512 × 8, labeling radiofrequency amplitude of 0.24 mG, and post-labeling delay of 2025 ms. Three pcASL acquisitions (NEX = 3) were averaged to improve signal-to-noise ratio. The pcASL sequence also included a fluid-suppressed proton density acquisition with the same image dimensions as the pcASL but without RF-labeling, for CBF quantitation and image registration. The entire pcASL sequence – all 3 excitations plus proton density scan - lasts 4 min and 44 s.

Image preprocessing

Quality checks were performed on raw images to ensure the scan did not contain motion or other artifacts. All 61 participants included in the final analyses had high quality ASL image data. As described in Okonkwo et al. (2014), ASL data were then processed to yield spatially normalized maps of rCBF (in mL/min/100 g) according to a lab standard in SPM12 (www.fil.ion.ucl.ac.uk/spm). Briefly, each participant's proton density image was co-registered to their T1 volume, and individual T1 volumes to MNI space; spatial transforms were concatenated to bring the CBF image to the Montreal Neurological Institute (MNI) template, with resampling to a $2 \times 2 \times 2$ mm^3 voxel size. The normalized CBF maps were then smoothed using an 8-mm full-width at half-maximum Gaussian kernel.

Voxel-wise analysis of ASL scans

To account for inter-subject variability in CBF, normalized and smoothed CBF images were proportionally scaled in SPM12 by mean whole-brain CBF. We applied an *a priori* gray matter mask from SPM12 (gray matter probability >0.4) to exclude white matter and extracranial voxels. Group (PD versus control) differences in rCBF were evaluated in a voxel-wise regression model with age, gender, and education as covariates. Then, group differences in the relationship between CBF and task performance were evaluated in four voxel-wise linear regression models (one for each task variable of initial speed, plateau speed, proficiency gain, and accuracy). In each of these models, the independent variable of interest was a task-by-disease group interaction term, generated by multiplying the group term (0 for control, 1 for PD) by the task performance variable; rCBF maps were the voxel-wise dependent, while task performance, group, age, gender,

and years of formal education were covariates. In addition, the effect of task performance on rCBF was evaluated separately within each group, in case a similar relationship between rCBF and task in both groups obscured an interaction effect. Cluster-based methods were used for multiple comparisons correction; only clusters with a minimum number of 110 contiguous voxels (2-sided thresholding) and a P_{voxel} of <0.001 were deemed significant at a cluster-extent threshold of $P < 0.05$. This threshold was derived via Monte Carlo simulations (3dClustSim in AFNI; http://afni.nimh.nih.gov).

Results

Subject characteristics

Demographic characteristics of the 61 study participants by group are listed in Table 1. The age of participants ranged from 48 to 83 (Mean = 66.82, SD = 8.59) and varied in years of formal education from 12 to 20 years (Mean = 16.66, SD = 2.91). Mean education was lower in the PD group (t[df] = 3.39[59], $p < 0.001$). The study included 5 left-handed subjects – 2 controls (1 pure left-handed, 1 ambidextrous) and 3 PD participants (3 pure left-handed). For PD participants, disease-specific characteristics such as age of diagnosis, UPDRS-III scores, and Hoehn & Yahr staging are also shown in Table 1. The range of H&Y stages for the PD patients was 1–3.

Motor sequence task performance

The majority of motor learning occurred during the first three task blocks with subsequent plateau in performance in both PD and control subjects. Table 2 shows descriptive statistics and group comparisons by independent-samples t-tests. Mean performance was non-significantly slower in PD participants across all stages of skill acquisition (Fig. 1); however, accuracy was significantly lower in PD (t[df] = 2.41[59], $p = 0.019$). Of the 30 PD subjects, 9 were stage HY I right limb symptom onset and performed the motor task with their unaffected left hand. Thus, the majority of subjects (2 HY I, left onset; 11 HY II; and 8 HY III) were performing the task with their disease-affected hand. Amongst PD subjects, we found a non-significant trend towards worse performance in those using their disease-affected hand (t[df] = 1.02[28], $p = 0.16$).

Relationship between motor task performance and cognitive measures

Multiple regression analyses controlling for age, gender, and education (β is the standardized regression coefficient) showed relationships between the task measures (Table 3). In both groups, initial speed was related to plateau speed (β = 0.771–0.872, $p \leq 0.002$), reflecting individual variation in typing speed, as well as negatively related to proficiency gain (β = −0.633-0.387, $p < 0.05$). Task performance was related to age (β = −0.719 –0.379, $p \leq 0.040$), but not to level of education in either group. In addition, several relationships between cognitive and task measures were seen in the PD group but not the control group (Table 3). In PD, higher executive composite scores were related to greater initial (β = 0.857, $p = 0.001$) and plateau (β = 0.417, $p < 0.05$) speed; memory composite scores were related to both proficiency gain (β = −0.460, $p < 0.05$) and plateau speed (β = −0.326, $p < 0.05$); and language composite scores were related to initial speed (β = 0.425, $p < 0.05$). Of interest, in the control group, a lower Epworth Sleepiness Scale score was associated with greater accuracy (β = −0.450, $p = 0.015$). Disease-specific measures in PD showed UPDRS-III scores were moderately correlated with disease duration (β = 0.444, $p < 0.05$), but not with the motor task variables.

Table 3 Standardized beta coefficients from multiple regression models showing the relationship between motor task variables with cognitive and task measures

	PD (n = 30)				Control (n = 31)			
	Initial Speed	Proficiency Gain	Accuracy	Plateau Speed	Initial Speed	Proficiency Gain	Accuracy	Plateau Speed
Cognitive Measures								
Executive composite	0.857*	−0.364	0.221	0.417*	−0.160	−0.008	−0.014	−0.210
Memory composite	0.125	−0.460*	−0.233	−0.326*	−0.026	0.267	0.161	0.033
Language composite	0.425*	−0.127	0.333	0.228	−0.007	0.231	0.098	0.140
ESS	−0.062	0.073	−0.195	0.021	−0.049	0.013	−0.450*	0.004
Motor Task Measures								
Initial speed	–	−0.633*	0.235	0.771*	–	−0.387*	0.318	0.872*
Proficiency gain	–	–	−0.013	0.421	–	–	−0.104	0.369
Accuracy	–	–	–	0.380	–	–	–	0.221

*P < 0.05

PD Parkinson's disease; *ESS* Epworth sleepiness scale

Disease group differences in rCBF and rCBF-task interactions

Compared to controls, PD patients showed hypoperfusion in a large right occipital region ($T_{peak} = 4.19$, MNI peak coordinates 10, −84, −2, $n = 758$ voxels; Fig. 2); there were no significant clusters in which PD group perfusion exceeded that of controls. With regard to the task-by-group interaction analyses, initial speed (number of correct sequences typed during the first block) was differently related to rCBF in PD versus control subjects in several regions that included parts of occipital cortex and cerebellum, bilateral anterior cingulate cortex, right superior and middle frontal gyri, and right parietal-occipital cortex (Table 4, Fig. 3). Completing a larger number of correct sequences during the first block was positively correlated with rCBF in these regions in PD subjects and negatively correlated with rCBF in controls (Fig. 3). There were no significant clusters for the opposite contrast. The plateau speed, proficiency gain, and accuracy analyses did not yield significant effects for task-by-group interaction.

The within-group analyses supported an interaction effect for initial speed, showing within the control group, lower rCBF in the right caudate nucleus, left occipital lobe and cerebellum, and right medial temporal-occipital junction was associated with completing a larger number of correct sequences during the first block (Table 5). There were no significant clusters for the effect of initial speed on rCBF within the PD group. Analysis of proficiency gain within the control group showed a positive correlation, i.e. greater proficiency gain over the twelve trials was related to greater rCBF in a large cluster within the right occipital cortex and cerebellum, as well as two smaller clusters in the left cerebellar hemisphere (Table 5, Fig. 4). The opposite contrast yielded no significant clusters. Within the PD group, there were no significant clusters associated with proficiency gain. The plateau speed and accuracy analyses did not yield significant within-group effects for either control or PD.

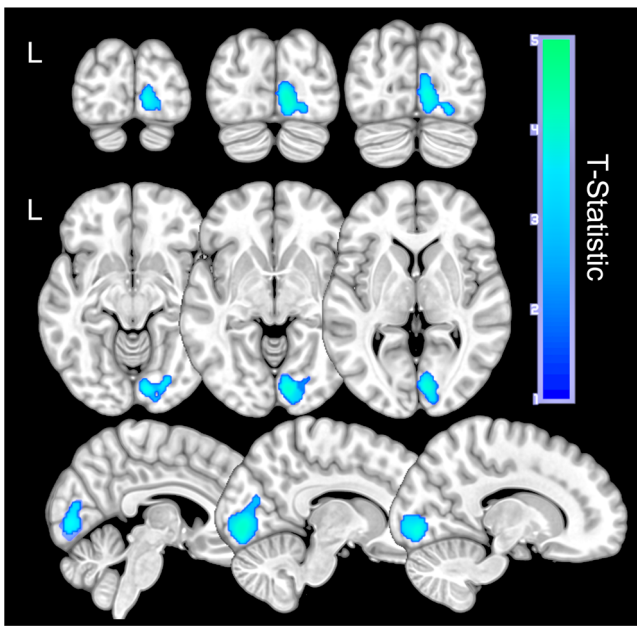

Fig. 2 Coronal, axial, and sagittal views of the right occipital cluster showing lower rCBF in Parkinson's patients compared with controls ($p < 0.05$, cluster-corrected)

Discussion

This study analyzed the relationship between resting cerebral blood flow and motor sequence learning among Parkinson's disease patients and age- and gender-matched controls. In agreement with previous studies, we found that PD subjects had lower rCBF in posterior cortical regions, specifically the occipital cortex, relative to controls (Melzer et al. 2011; Kamagata et al. 2011; Fernandez-Seara et al. 2012; Madhyastha et al. 2015). Spatial covariance analysis of both metabolic and blood flow-based imaging have shown abnormalities of resting networks in PD patients, with relatively increased metabolism in the pallidum, thalamus, cerebellum, and motor cortex, along with decreased metabolism in the premotor cortex, SMA, and parietal association areas (Ma et al. 2007). The mechanism for occipital hypoperfusion in PD is unknown, although it may be related to loss of dopaminergic neurons in the retina (Kamagata et al. 2011).

We also found that PD participants showed a different relationship than controls between rCBF and task performance within a network of brain regions (cerebellum, anterior cingulate, parietal, and prefrontal cortices) known to participate in motor learning (Doyon et al. 2009; Floyer-Lea and Matthews 2005). Specifically, higher rCBF in these regions was related to greater initial speed in PD, and lower initial speed in controls (Table 4). Although it is possible that the initial speed variable actually provided an index of disease severity (i.e. bradykinesia), rather motor learning, the strong correlation between this measure and the executive cognitive composite (Table 3) suggests that the task variable is related to cognitive processing speed. The early phases of motor sequence learning are known to depend on executive functions of attention, processing speed, and working memory (Ghilardi et al. 2003).

In this study, some relationships between rCBF and task performance that were seen in the control group were not evident in the PD group. In controls, greater initial speed was related to lower rCBF in the left occipital cortex and cerebellum, right caudate nucleus, and right medial temporal-occipital junction, whereas proficiency gain was related to higher rCBF in the cerebellum, left temporal, and right occipital cortices. The finding of a predominantly right cortical and striatal relationship to task performance in the control group makes

Table 4 Brain regions in which different relationships between rCBF and initial speed were observed in Parkinson's versus control subjects

Anatomic Location	MNI Coordinates:			T-Statistic (peak)	Size (mm^3)
	X	Y	Z		
Left Occipital Cortex and Cerebellum	−46	−76	−26	4.77	1359
Right Occipital Cortex and Cerebellum	42	−72	−18	4.06	672
Bilateral Anterior Cingulate	−2	32	28	4.22	518
Left Cerebellum	−14	−78	−54	4.18	288
Right Parietal-occipital Cortex	34	−60	38	4.03	221
Right Superior and Middle Frontal Gyri	24	32	34	4.02	219
Right Parietal Cortex	60	−46	24	3.78	138
Right Parietal-occipital Cortex	44	−70	24	3.56	127

Shown are the anatomic location, MNI coordinates, t-statistic, and cluster extent in number of voxels for regions in which the effect of task-by-group interaction was significant for initial speed. The relationship was positive for PD, and negative for controls. Results are cluster-corrected at $P < 0.05$

sense on the basis of neuroanatomical considerations, since participants were using their left hand to perform the task. Furthermore, the lack of relationship between proficiency gain and rCBF in the PD group may reflect physiologic deficits in the function of motor learning networks related to the disease process.

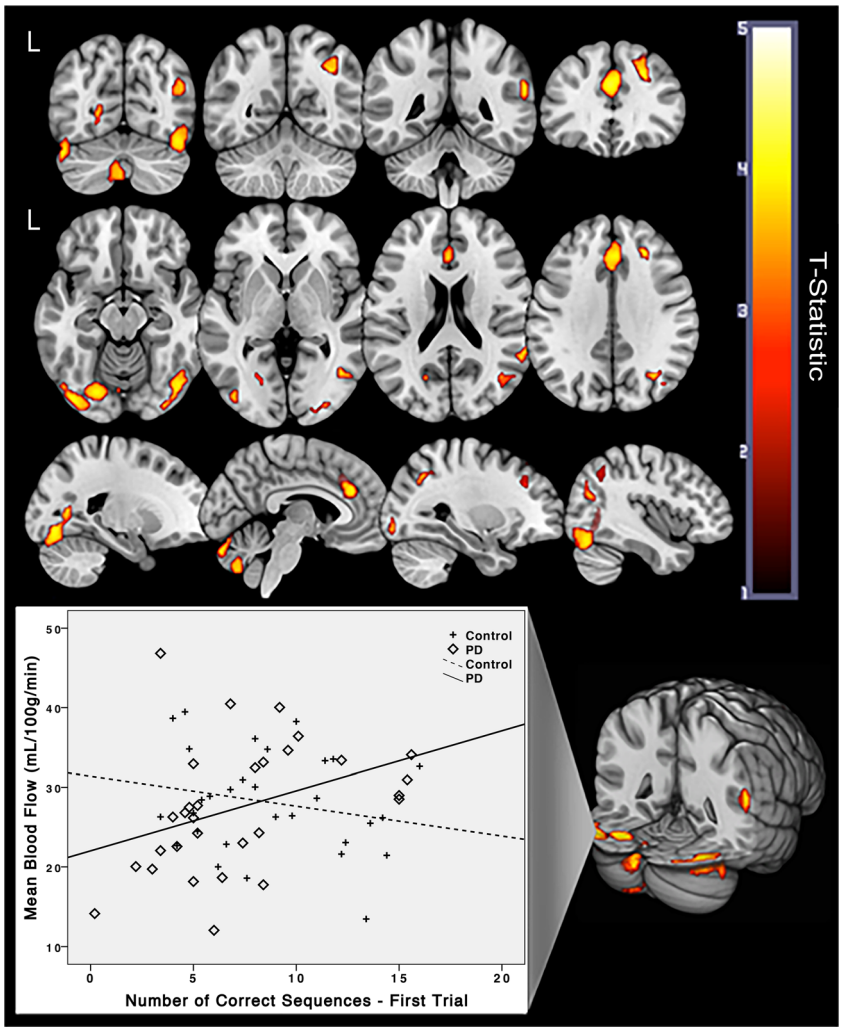

Fig. 3 Coronal, axial, and sagittal views of clusters in which a significant task-by-group interaction was seen for initial speed ($p < 0.05$, cluster-corrected), or number of correct sequences typed during the first task block. To illustrate the task-by-group interaction, mean resting blood flow (in mL/100 g/min) extracted from a cluster in the left occipital lobe and cerebellum (cutout) is plotted against task performance (inset graph). In PD, greater initial speed was related to higher rCBF, whereas greater initial speed was related to lower rCBF in controls

Table 5 Brain regions in which motor learning was related to rCBF in the individual groups

Task Variable	Anatomic Location	MNI Coordinates:			T-Statistic (peak)	Size (mm^3)
		X	Y	Z		
Initial Speed	Left Occipital Cortex and Cerebellum	−38	−86	−20	4.55	811
	Right Caudate Nucleus	6	4	4	4.77	418
	Right Medial Temporal-Occipital Junction	28	−50	−6	4.13	137
Proficiency Gain	Right Occipital Cortex and Cerebellum	24	−74	−18	4.88	2241
	Left Temporal Cortex and Cerebellum	−44	−38	−16	3.97	176
	Left Cerebellum and Pons	−16	−30	−26	4.01	143

Shown are the anatomic location, MNI coordinates, t-statistic, and cluster extent (number of voxels) for regions in which the effect of rCBF was negatively correlated with initial speed and positively correlated with proficiency gain in controls. Results are cluster-corrected at $P < 0.05$

We hypothesize that our findings fit with the concept of compensation versus reserve. In this framework, persons who are more agile in performing a task use less brain reserve (and in our study, have lower rCBF within task-based networks), whereas those who require greater effort to compensate for imperfect brain function (such as diseased or elderly) have higher or more extensive activity. Functional MRI studies conducted during sequential motor tasks have shown that PD patients have decreased activation of the rostral supplementary motor area (SMA) and dorsolateral prefrontal cortex, but increased activation of anterior cingulate, primary sensorimotor, other premotor, and parietal cortices (Sabatini et al. 2000). Furthermore, task-based activation does not attenuate normally during the automatic phase of motor learning in PD subjects (Wu and Hallett 2005). In general, $H_2{}^{15}O$ Positron Emission Tomography (PET) studies have shown that during finger sequence learning, PD patients utilize greater volumes of tissue within similar primary and premotor regions as controls, as well as recruiting additional regions such as parietal cortex and cerebellum (Mentis et al. 2003; Catalan et al. 1999; Nakamura et al. 2001; Samuel et al. 1997; Thobois et al. 2000). In one study, the relationship between task performance and cortical activation was reported as opposite in PD patients (greater correct movements with lower activation) in comparison to controls (greater correct movements with greater activation) – which bears resemblance to our (opposite) results from resting data (Mentis et al. 2003). It should not be assumed, of course, that the results of resting CBF studies will be analogous to those of activation studies. In fact, the few studies that have investigated the relationship between rCBF and task-based CBF change suggest a potentially complex relationship that is influenced by subject factors. For example, a study that utilized both ASL at rest and fMRI during task in adolescents with traumatic brain injury (TBI) showed that the relationship of activation to rCBF differed between TBI and control groups (Newsome et al. 2012).

Our observation of greater rCBF in the cerebellum being associated with more normal task performance in PD suggests that the degree to which PD subjects use cerebellar circuits in response to striatal deficits determines their ability to overcome disease related cognitive-motor problems. The basal ganglia and cerebellum participate in a system of (mostly) segregated loops that intersect anatomically at the level of the motor cortex, thalamus, and subthalamic nucleus (Caligiore et al. 2017). Although how interactions between these networks influences motor control is not fully understood, striatal circuits are thought to "learn opportune goals" while the cerebellum "generates and refines intentions" through motor adaptation (Caligiore et al. 2017). Feed forward models of motor control have theorized that the cerebellum compares internal models of sensory outcomes to ongoing movements to produce real time adjustments; delays in this

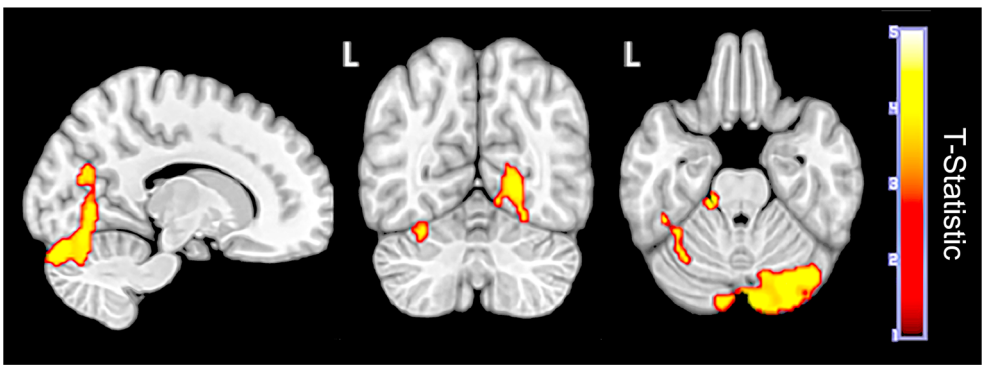

Fig. 4 Voxel-wise maps of regions showing significant positive relationship between proficiency gain over the 12 task blocks and rCBF in the control group ($p < 0.05$, cluster-corrected)

system produce critical inelegance and lack of efficiency (Shadmehr et al. 2010). Both basal ganglia and cerebellar circuits appear to be involved in PD resting tremor, as modulation of either circuit via DBS can abolish tremor (Benabid et al. 1991; Krack et al. 2003).

This study had several limitations. Motor task data and rCBF data were not gathered simultaneously, so inferences from the results are indirect. In addition, the subject groups were not ideally matched for level of formal education, which could affect motor learning during a typing task. However, regression analyses revealed no relationships between education and task performance in either group. To avoid confounding effects, we included education in all regression models used to evaluate rCBF relationships. Additional technical factors should be considered: In ASL acquisition, the use of multiple post-labeling delays has been advocated as a way to prevent variance related to arterial transit time (Qin et al. 2014). For this study, we used a standard protocol that averaged 3 post-labeling acquisitions (NEX) to reduce signal-to-noise. In addition, we did not correct the ASL data for cortical atrophy, which may influence blood flow quantification. However, PD is generally not associated with regional atrophy except in Parkinson's disease dementia (Melzer et al. 2012), which was an exclusion criterion for this study.

Conclusions

The present study identified decreased perfusion in posterior cortical regions in PD compared to controls, coinciding with findings from previous PD ASL studies. Moreover, we demonstrated that different relationships between rCBF and task performance can be measured in PD patients relative to controls using ASL. We hypothesize that the different relationships between rCBF and task performance within these networks in PD reflects the degree to which PD patients are able to compensate for dysfunction of striatal networks by adjustments in cerebellar networks. Further work measuring perfusion simultaneously with activation using fMRI might be the next logical step.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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