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ORIGINAL RESEARCH

A longitudinal study of motor performance and striatal [18F] fluorodopa uptake in Parkinson's disease

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Abstract Although [^{18}F]fluoro-L-dopa [FDOPA] positron emission tomography (PET) has been used as a surrogate outcome measure in Parkinson's disease therapeutic trials, this biomarker has not been proven to reflect clinical status longitudinally. We completed a retrospective analysis of relationships between computerized sampling of motor performance, FDOPA PET, and clinical outcome scales, repeated over 4 years, in 26 Parkinson's disease (PD) patients and 11 healthy controls. Mixed effects analyses showed that movement time and tongue strength best differentiated PD from control subjects. In the treated PD cohort, motor performance measures changed gradually in contrast to a steady decline in striatal FDOPA uptake. Prolonged reaction and movement time were related to lower caudate nucleus FDOPA uptake, and abnormalities in hand fine force control were related to mean striatal FDOPA uptake. These findings provide evidence that regional loss of nigrostriatal inputs to frontostriatal networks affects specific aspects of motor function.

Keywords Fluorodopa · Motor control · Parkinson's disease · Positron emission tomography · Ageing · Tongue/*physiopathology · Facial Muscles/*physiopathology

Abbreviations

D	Dominant side
FDOPA	[^{18}F]fluoro-L-dopa
MRI	Magnetic resonance imaging

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ND	Non-dominant side
PD	Parkinson's disease
PET	Positron emission tomography
UPDRS	Unified Parkinson's Disease Rating Scale
VOI	Volume of interest

Introduction

Parkinson's disease (PD) is the second most common late-life neurodegenerative disease, with a lifetime risk of 4% (Elbaz et al. 2002). In PD, the onset of motor symptoms (muscle rigidity, slow movements, and tremor) coincides with death of dopaminergic neurons in the substantia nigra pars compacta that project to the striatum (Braak et al. 2003). The specific mechanism by which this lesion causes motor symptoms remains an area of active investigation through motor performance, functional imaging, and neurophysiologic studies. Asymmetric onset of motor symptoms is present in 85% of cases of idiopathic PD (Yust-Katz et al. 2008). Progression from unilateral to bilateral symptoms is one basis for the clinical staging system (Hoehn and Yahr 1967).

Motor performance testing has been used to quantify motor abnormalities in PD. Untreated PD patients have prolonged simple reaction time (Evarts et al. 1981) that is shortened by anti-Parkinson medications (Montgomery et al. 1991). Parkinson's disease patients are unable to adequately increase movement velocity with increasing reach distances, unlike healthy control subjects (Draper and Johns 1964; Flowers 1975). During force matching tasks, PD patients show a slower rate of force development, but similar ability to maintain isometric force, in comparison with elderly control subjects (Stelmach et al. 1989). Aging also affects reaction time, movement velocity, and bulbar strength (Crow and Ship 1996).

[^{18}F]fluoro-L-dopa [FDOPA] positron emission tomography (PET), which measures uptake and trapping of dopamine precursors in nigrostriatal projections, has been used as a surrogate outcome measure for disease progression in clinical trials (Whone et al. 2003). A number of cross-sectional analyses have correlated examiner-dependent ratings of clinical signs in PD with striatal uptake of dopamine transporter radiotracers (Seibyl et al. 1995) or FDOPA (Morrish et al. 1996a; Nagasawa et al. 1993; Vingerhoets et al. 1997). Pathological investigations have also shown that the severity of bradykinesia is correlated with the degree of dopamine depletion in the putamen (Bernheimer et al. 1973). However, the rate of change in striatal radiotracer uptake does not correlate with clinical change in individual patients studies longitudinally with dopamine transporter ligands (Marek et al. 2001; Pirker 2003) or [18F]FDOPA (Morrish et al. 1996b). In this study we used automated measurement systems to acquire measures of reaction time and movement velocity over different reach distances, and to measure maximum forces and isometric force control in both limb and bulbar muscles. The baseline motor testing was acquired while patients were off anti-Parkinson medication; subsequent testing was performed on medication. Therefore, the effects of medication were not controlled and therefore the measures we evaluated may represent optimized motor function in PD. However, few studies have measured as many parameters, have measured them serially, or have compared them with PET. We hypothesized that in spite of ongoing treatment, the effects of disease on motor performance and the rate of change in motor performance would be distinguishable from the effects of aging. We hypothesized that specific relationships would be discovered between the motor performance measures, striatal FDOPA uptake, and clinical disability as measured by the Unified Parkinson's Disease Rating Scale Score (UPDRS) (Fahn et al. 1987).

Methods: subjects

We performed a retrospective analysis of PET, motor performance, and clinical data gathered as research between 1993 and 1999. PD patients and age-matched normal controls were recruited through regional neurology clinics. Thirty patients who initially met UK Parkinson's Disease Society Brain Bank criteria (Gibb and Lees 1988) for idiopathic PD were originally enrolled. Data from four PD patients were subsequently excluded based on clinical or pathological findings of atypical Parkinsonism (1), early age of onset (1), missing data (1), or dropout (1). Twenty-six PD patients (age 56±11 years; 15 male, 11 female) and 11 healthy control subjects (age 61±12 years; 6 male, 5 female) had data sufficient for analysis. At enrollment, mean disease duration for the PD group was 3.2 years (SD 2.1), and mean duration of pharmacotherapy for Parkinson's disease was 1.0 year. All PD patients were treated: 18 with carbidopa/levodopa; 19 with selegiline; 2 with dopamine agonists (pergolide or pramipexole); and one with trihexyphenidyl. Six additional PD patients were started on carbidopa/levodopa during the study interval. Precise medication doses were not uniformly recorded. 14 subjects were Hoehn and Yahr (HY) stage I, 11 HY II, and 1 HY III. During the study, 6 PD patients experienced disease progression to a higher HY stage. Mean total UPDRS scores taken from the maximally affected limbs were 15.7 +/− 8.4, 16.4 +/− 7.7, and 20.3 +/− 11.8 for the three sessions consecutively. At enrollment, mean Mini Mental State Examination (MMSE) scores were 28/30 for PD patients and 29.7/30 for control subjects. The protocol was approved by the local Institutional Review Board, and written informed consent was obtained from all participants.

Procedures

Each session included administration of the UPDRS by a movement disorders neurologist, 6-L-[^{18}F]-fluorodopa (FDOPA) PET scanning, and motor performance testing (S.D.). A total of 19 PD patients and 11 control subjects completed three study sessions; the remaining 7 PD patients completed two sessions. The mean interval between sessions was 1.8 years, and the mean interval between PET imaging and motor testing was 0.11 years. Baseline motor performance testing was conducted off anti-Parkinson medication; subsequent testing was conducted without alteration of PD patients' usual medication regimen.

PET acquisition and quantification

PET data consisted of 90-minute, three-dimensional dynamic PET images acquired on the same Advance scanner (General Electric Medical Systems, Waukesha, WI) after intravenous administration of 204–284 MBq (5.5–7.7 mCi) of FDOPA (Brown et al. 1999). PD patients were off medication for 18 h prior to scanning, and all subjects ingested 100 mg of carbidopa 30 min before radiotracer injection. A 124-section axial spoiled-gradient recalled (SPGR) volume (repetition time 29 ms, echo time 13 ms, flip angle=35°, FOV= 220 mm; slice thickness=1.2 mm), obtained on a 1.5-T magnetic resonance (MRI) scanner (General Electric Medical Systems, Waukesha, WI), was available for coregistration to PET in all but four subjects.

Within-subject realignment of PET sum images (time frames from 5 to 30 min post-injection) to MRI using FSL/FLIRT (http://www.fmrib.ox.ac.uk/analysis/research/flirt/) was followed by spatial normalization of the MRI to Montreal Neurological Institute (MNI) space, and application of these spatial transforms to the PET sum image and its aligned dynamic frames. As part of the normalization process, the PET and MRI volumes were resampled to 2-mm cubic voxels, and then visually inspected for misregistration. Using an in-house software package (http://brainimaging.waisman.wisc.edu/~oakes/spam), five volumes of interest (VOIs), encompassing each putamen, and head and body of the caudate nucleus, and an occipital cortex reference region of 900–1000 voxels, were manually drawn over each subject's normalized MRI scan by one rater (C.G.). This technique allowed for individual differences in the location of subcortical structures, while applying the same subject-specific VOIs to repeat PET scans. For the four subjects with missing MRI data, VOIs were drawn on a normalized PET sum image. Once drawn, all VOI volumes were compared, and cases that represented outliers (±2 standard deviations from mean volume) were redrawn if inaccurate. Average radiotracer influx (K_{occ}) values for each VOI were computed from 30- to 90-minute PET frames using a standard multiple-time graphical analysis method (MTGA) with occipital cortex (tissue) input function (Patlak and Blasberg 1985). For statistical analysis, caudate and putamen K_{occ} values were averaged between brain hemispheres.

Motor testing

The motor testing protocol used computer-cued tasks to measure simple reaction time, maximum instantaneous movement velocity, time from movement initiation to maximum movement velocity, pinch strength, and fine force control, for each hand. Intraoral force transducers were used to measure tongue strength.

Reaction and movement times

Subjects were seated comfortably, facing an apparatus with a depressible base and three elevated targets 3, 6, and 9 in. (approximately 7.6, 15.2, and 22.9 cm) from the base. An accelerometer was attached to the back of the active hand; the subject placed this hand on the base (which, when depressed, completed a circuit) and then, when cued by a tone, touched the first target as quickly as possible. The cuing tone, generated at random intervals by a computer, was repeated three times for each target. For each movement, simple reaction time was recorded from the cuing tone to interruption of the base circuit, and an average of these nine trials (RT) for each hand, was used for analysis. Accelerometer output was used to derive time from interruption of the base circuit to peak velocity (movement time, MT), and maximum instantaneous movement velocity. This method of measuring MT was chosen because at times tremor and overshoot made it difficult to reliably determine from the accelerometer signal when the target was reached. The average MT of the three trials reaching to the most distant target (MT9) was used for analysis. The VMx for the 3-inch target (~7.6 cm) was subtracted from that for the 9-inch (~22.9 cm) target to generate an index of peak velocity scaling (VMx93).

Because of bradykinesia, PD patients are expected to take a longer time to generate peak movement velocity (longer MT) and, because of abnormalities in motor planning, PD patients are expected to be unable to scale reach speed to anticipated movement length, and therefore to have smaller values for VMx93.

Maximum force measurements

Isometric pinch grip force (PinMx) was measured by asking the subject to grasp and hold with maximum effort a force transducer between the pad of the thumb and side of the index finger; at steady state, the force generated in grams was recorded (Wing 1988). A lingual strain gauge was used

to measure maximum tongue protrusion force (TongMx) according to techniques described previously (Barlow and Abbs 1984).

Force control measures

While gripping the pinch force transducer, subjects were asked to generate and maintain a target force of 200 g for 5 s. A cursor representing the target force level was displayed on an oscilloscope at slow sweep speed (500 ms/division); a cursor reflecting the subject's force output was provided and the subject was directed to match the target line as closely as possible. Three seconds of force signal at steady state (after at least 1 s on task) was computer digitized (300 samples/s), and the mean and standard deviation of these 900 samples recorded as pinch force control (Pin200) and standard deviation (Pin200SD).

Statistical analysis

We analyzed the motor data according to side of hand dominance, rather than to side of symptom onset (in PD subjects), so that limbs with a similar level of dexterity were compared between groups. To evaluate the relationship between repeated PET, motor performance, and UPDRS measures, we used general linear mixed effects models that are explicitly designed for modeling longitudinal data (http://www.math.mcgill.ca/keith/surfstat). The main difference between these longitudinal and cross-sectional models is that they specifically incorporate the dependence of repeated measurements taken in the same individual. For each subject, the number of variables entered into the model is equal to the number of observations/sessions. Each model has both fixed effect (age, group, gender, motor variables) and a random effect (subject) terms, with associated error. Within-subject variability is typically smaller than the between-subject variability. Correction for multiple comparisons is not required in this statistical approach because each set of variables is evaluated in a separate model. The three types of such models that were used are described below.

Type 1: Motor Performance Variable=1+Group+Age+Gender+Random (subject)+I

To evaluate the effects of diagnostic group on motor performance, a separate mixed effects model was constructed for each motor measurement in which this measurement was regressed against group (PD versus control), age, and gender covariates. A contrast was then applied to yield a t-statistic and P-value describing the significance level for each covariate's contribution to the model.

Type 2: Motor or PET variable=1+Group+Gender+Time+Time*Group+Random (subject)+I

We hypothesized that even in treated PD patients, motor variables would change at a greater rate than in control subjects. To test this hypothesis, we constructed a separate model for each motor performance and PET measurement, in which this dependent variable was regressed against group, gender, time from session 1, and a time-by-group interaction term. If the time-by-group interaction is significant, the rate of change in the disease group is different than would occur due to normal aging. Age was not included in these models because it is collinear with the time variable.

Type 3: PET variable or UPDRS total score=1+Motor variable+Age+Gender+Random (subject)+I

To test the hypothesis that the motor performance measures would be related to striatal FDOPA uptake in the PD group, three mixed effects models were constructed for each motor performance variable, with age and gender as covariates. The dependent variables for each of the three models were mean caudate nucleus K_{occ}, mean putamen K_{occ}, and total UPDRS score. Significant relationships were plotted in Matlab (version R2009a). If these relationships were based on outlying values, these values were replaced with the mean plus or minus twice the standard deviation.

Results

At baseline, the PD and control groups did not differ significantly in gender, hand dominance, or age, but did differ in years of education (PD mean, 14.3 years vs. control mean, 17.7 years; P=0.02). Mean baseline K_{occ} (±SD) for caudate nuclei/putamina were 0.012 (±0.001)/0.014 (±0.001) min^{-1} in control subjects and 0.010 (±0.002)/0.008 (±0.002) min^{-1} in PD subjects.

Group effects

Parkinson's disease patients had prolonged non-dominant hand reaction time (RT), prolonged bilateral hand movement time (MT9), and lower dominant hand force control (Pin200) than control subjects (Table 1). Tongue strength (TongMx) was lower in PD, while hand strength was equal to controls. Age had highly significant effects on several motor performance variables, including reaction time (t[df] >3.4[104], P<0.0001), peak velocity scaling (t[df]<−2.6[104], P<0.01), movement time (t[df] <2.0[104], P<0.05), maximum pinch

Table 1 Group differences and baseline values

	RT (ms		VMx93 (m/s)		MT9 (ms)		Pin200 (g)		Pin200SD (g)		PinMx (kg)		TongMx (kg)
	D	ND	D	ND	D	ND	D	ND	D	ND	D	ND	
Baseline mean (SD)													
Control	246 (46)	240 (47)	0.63 (.22)	0.56 (.14)	180 (44)	169 (70)	206 (7.5)	204 (5.4)	7	5	6.1 (1.5)	6.2 (1.6)	1.3 (0.5)
PD	236 (67)	257 (73)	0.62 (.21)	0.61 (.21)	222 (106)	234 (79)	199 (9)	202 (13)	11	8	6.9 (2.0)	6.9 (2.0)	0.9 (0.3)
Group Effect													
t	1.20	2.34	0.12	−1.00	2.70	−3.20	−2.40	−0.70	0.80	1.00	0.53	0.37	−3.31
P	0.12	0.01	0.45	0.15	0.004	<0.0001	0.01	0.24	0.20	0.13	0.47	0.35	<0.0001
		*			**	***	*						***

Model type 1: Motor variable=1+Group+Age+Gender+Age*Group+Random(Subject)+*1*. Outcome variables are listed across the top. After building each model, a contrast for the covariate of interest (group, age, or gender) was applied to derive the *t*-statistics and *P*-values; degrees of freedom=104. * P=0.01–0.05; ** P=0.001–0.009; *** P<0.001

Abbreviations and variables: D dominant hand; MT9, time from movement onset to peak velocity when reaching to the 9-inch target; ND, non-dominant hand; Pin200, mean force accuracy for 200 g target; Pin200SD, measured standard deviation in Pin200; PinMx, maximum pinch strength; RT, reaction time; TongMx, maximum tongue protrusion strength; VMx93, maximum instantaneous movement velocity scaling to reach distance (peak velocity for 9-inch reach [~22.9 cm] − peak velocity for 3-inch reach [~7.6 cm])

(t[df]<−2.7[104], P<0.005) and tongue strength (t[df]<−3.5 [104], P<0.0005). Age-by-group interactions were present for reaction time and movement time (−t|[df] >1.8 [104], P<0.05).

Time effects

Time-by-group interactions, indicating that the rate of change in PD was significantly greater than would be expected due to aging, were present for non-dominant hand reaction time (t [df]=2.08 [104], P<0.05) and dominant hand MT (t [df]= 1.8[104], P<0.05). However, the significance of the interaction term was greatest for striatal FDOPA K_{occ} (t [df] < −4.0 [104], $P<3\times10^{-5}$). Longitudinal changes in movement time, reaction time, and FDOPA uptake over the study interval are presented in Figure 1. The effect of time on UPDRS scores was not significant in the PD subject group (t [df]=1.3[68], P=0.13).

Relationship of motor performance measures to PET

We then hypothesized that the mixed effects models, which are designed to evaluate repeated within-subject measurements, would show relationships between the PET and motor variables. Non-dominant hand reaction time (RT) and dominant hand movement time (MT) were inversely related to caudate nucleus FDOPA uptake (Table 2, Figure 2). Higher caudate nucleus and putamen K_{occ} was related to greater increases in dominant hand peak movement velocity in response to increasing reach distance (VMx93), and to higher mean target forces during the fine force control task. Greater variation in non-dominant hand fine force control (Pin200SD) was also related to lower striatal FDOPA uptake. The incorporation of disease duration instead of age into the model did not significantly improve the significance of these relationships, although striatal FDOPA K_{occ}, as expected, was strongly related to disease duration (t[df]<−7.8[67], $P<1\times10^{-11}$).

When UPDRS scores, rather than striatal FDOPA uptake, were modeled as the dependent variable, greater variability in force levels (Pin200SD), lower tongue strength (TongMx), and impaired velocity scaling (VMx93) predicted higher (more impaired) UPDRS scores (Figure 3). UPDRS scores were not significant contributors to models of caudate or putamen FDOPA K_{occ}. The effect of age was significant (t [df] >3 [67], P<0.005) in all of the models, and tended to overwhelm the effects of other covariates.

Discussion

This study presents a retrospective analysis of longitudinal motor performance, clinical, and FDOPA PET data. We used

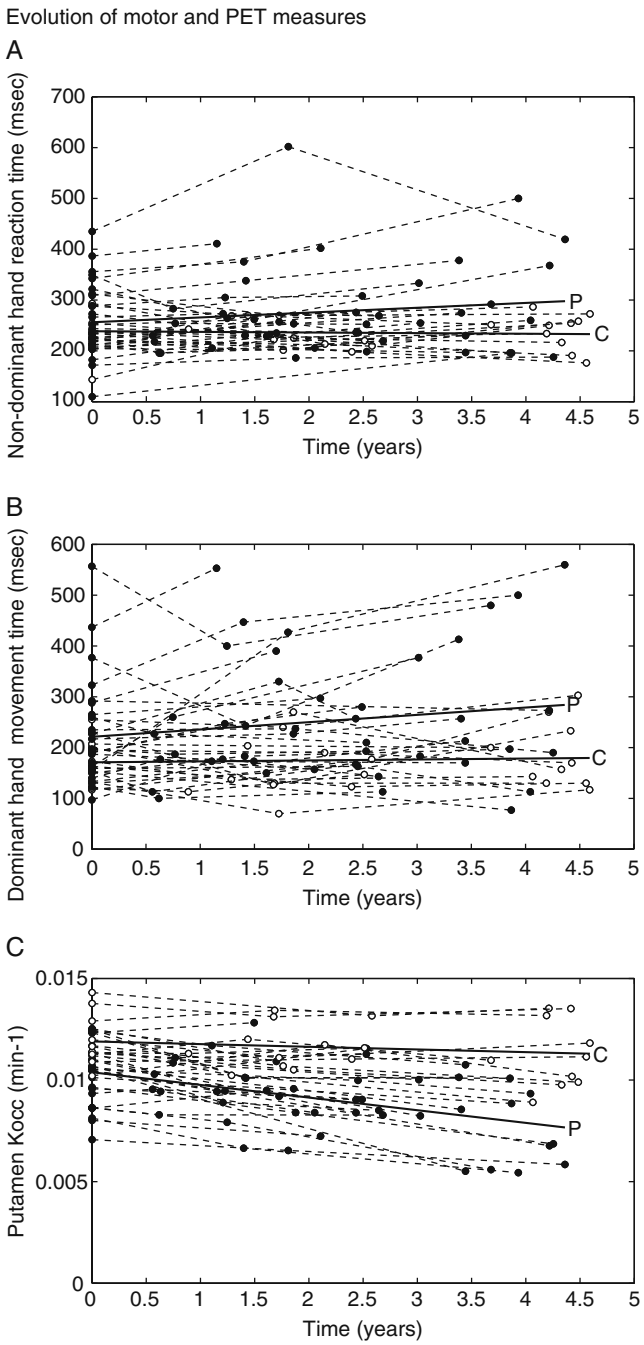

Fig. 1 Evolution of motor and PET measures. Non-dominant hand reaction time **a**, dominant hand movement time **b**, and mean putamen FDOPA K_{occ} **c** for PD patients (*filled circles*, regression line indicated by P) and control subjects (*unfilled circles*, regression line indicated by C) are plotted against timing of visits over the study interval. Within-subject measurements are connected by dashed lines. The time effect is of greatest significance for putamen K_{occ} (t [df]=−8.7 [104], $P<10^{-13}$) in contrast to motor measures (t [df] >1.8 [104], $P<0.04$)

mixed effects models to separate the effects of demographic covariates from disease effects, but could not control for the effects of pharmacotherapy since PD subjects' medication regimens were not altered for motor testing, and precise medication doses were not recorded. Consistent with previous investigations, we found disease (group) effects on reaction time (Hallett and Khoshbin 1980; Montgomery et al. 1991), movement time, hand fine force control (Stelmach et al. 1989), and tongue strength (O'Day et al. 2005; Solomon et al. 1995). Among the motor performance variables tested, the most robust disease indicators were prolonged movement time and reduced tongue strength. Therefore, these measures may be useful as disease biomarkers.

Disease group differences were overshadowed by the significant effects of age on motor performance, which were accentuated in the PD group. Evidence of an interaction between aging and clinical symptom severity in PD is abundant, but has not been specifically quantified using motor performance testing. In PD, advanced age is a risk for faster progression of motor disability (Diederich et al. 2003), gait and postural impairment (Levy et al. 2005), dementia (Aarsland and Kurz 2009), and failure to benefit from standard therapies (Russmann et al. 2004).

Time-by-group interactions, indicating a greater rate of change in the PD group than would occur due to normal aging, were observed for simple reaction time and movement time. Rate of change in the motor performance measures was subtle in comparison to the rate of decline in striatal FDOPA uptake; however, ongoing treatment may have reduced the significance level for motor abnormalities in the PD group. Using a complex motor task during [^{15}O] H_2O PET, Carbon et al. showed movement onset and velocity to be relatively prolonged in PD, to lengthen over time, and to correspond to increased blood flow in the right dorsal premotor and dorsolateral prefrontal cortex (Carbon et al. 2007).

Non-human primate studies have shown that parallel networks connect distinct striatal regions with frontal cortical regions, and prefrontal cortex with the cerebellum (Alexander et al. 1986). These functional networks participate in motor planning, attention, motivation, timing, and adjustment of ongoing movements. They are essential to the initiation of accurate preprogrammed hand movements (Desmurget et al. 2003), and to regulation of ongoing movements through submovements (Tunik et al. 2009). PD subjects underestimate the required force to accomplish motor tasks, and require additional adjustments to ongoing movements in comparison to controls (Hallett and Khoshbin 1980). We found that indices of motor planning (velocity scaling), force estimation (mean fine force accuracy), and submovements (standard deviation in fine force accuracy) were related to striatal FDOPA uptake. These findings help to confirm that insufficient nigrostriatal dopamine input contributes the diverse motor control problems observed in PD.

The caudate nucleus has been considered part of the "spatial" or "oculomotor" circuit, receiving projections for

Table 2 Relationship of imaging and clinical measures to motor performance in PD (model type 3)

Motor variable:	RT (ms)		VMx93 (m/s)		MT9 (m/s)		Pin200 (g)		Pin200SD (g)		TongMx (kg)
Outcome:	D	ND	D	ND	D	ND	D	ND	D	ND	
Caudate K_{occ} (min^{-1})											
t	−1.27	−1.90	−3.27	−2.18	−2.04	−1.49	4.67	1.61	−0.89	−2.18	1.10
P	0.10	0.03 *	<0.001 **	0.02 *	0.03 *	0.07	<0.001 **	0.06	0.18	0.01 *	0.13
Putamen K_{occ} (min^{-1})											
t	−0.45	−1.20	−3.10	−1.52	0.79	−1.47	3.8	1.05	−0.15	−1.90	0.90
P	0.32	0.11	0.001 **	0.07	0.22	0.07	<0.001 **	0.15	0.43	0.02 *	0.18
UPDRS Total											
t	0.82	−0.67	0.14	−1.80	0.12	0.28	1.20	0.06	1.00	2.90	−2.05
P	0.20	0.25	0.44	0.04 *	0.12	0.39	0.11	0.47	0.16	0.002 **	0.02 *

Model type 3: Outcome=1+Motor Variable+Age+Gender+random(Subject)+*I*; degrees of freedom=67 (PD patients only). Dependent variables (left side of equation) are mean caudate FDOPA K_{occ} (averaged between brain hemispheres), mean putamen FDOPA K_{occ}, and total UPDRS scores. Motor variables (right side of the equation), modeled separately for the dominant (D) and non-dominant (ND) hand, were RT, VMx93, MT9, Pin200, and Pin200SD. The significance of contribution of each motor variable to the model is tested using a contrast that yields a *t*-statistic and *P*-value. **P*=0.01–0.05; ***P*=0.001–0.009; ****P*<0.001

Abbreviations and variables: D dominant hand; *FDOPA* [^{18}F]fluoro-L-dopa; K_{occ}, uptake of FDOPA; *MT9* movement time to achieve peak velocity during the longest movement; *ND* non-dominant hand; *Pin200* mean force accuracy for 200 g target (Pin200); *Pin200SD* standard deviation in force accuracy at 200 g; *RT* simple reaction time; *TongMx* maximum tongue protrusion strength; *UPDRS* Unified Parkinson's Disease Rating Scale total score; *VMx93* maximum instantaneous movement velocity scaling to reach distance (peak velocity for 9-inch reach [~22.9 cm] − peak velocity for 3-inch reach [~7.6 cm])

the dorsolateral prefrontal cortex and posterior parietal cortex. We found that prolonged reaction time and movement time were each related to lower caudate nucleus FDOPA uptake. In a study of healthy elderly subjects, lower dopamine transporter binding in either caudate nucleus or putamen was equally correlated with longer simple reaction time (Van Dyck et al. 2008). Since FDOPA uptake declines throughout the striatum in PD, with relative preservation of anterior and ventral regions, caudate nucleus uptake may be an indicator of the overall severity of dopamine synthesis and storage insufficiency (Bruck et al. 2006). However, animal studies suggest that lesions of the dorsomedial striatum selectively prolong simple reaction time, possibly due to effects on attentional control (Hauber and Schmidt 1994). Caudate nucleus K_{occ} is correlated with performance in attention-demanding tasks such as the Stroop interference task (Rinne et al. 2000).

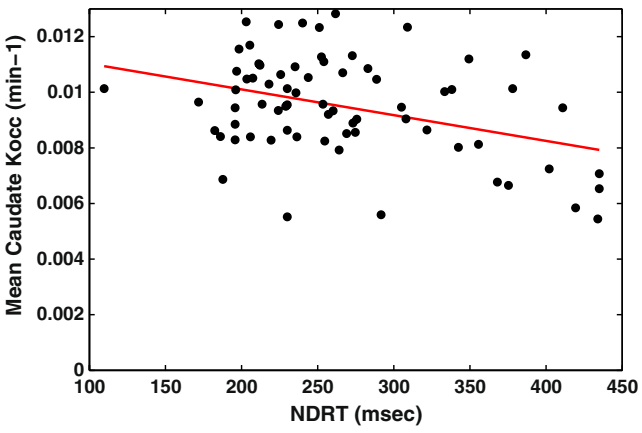

Fig. 2 Reaction time versus caudate nucleus FDOPA uptake. In the Parkinson's group, non-dominant hand reaction time (NDRT) was significantly related to lower caudate nucleus K_{occ} averaged between brain hemispheres (t [df]=−1.90 [67], *P*=0.03)

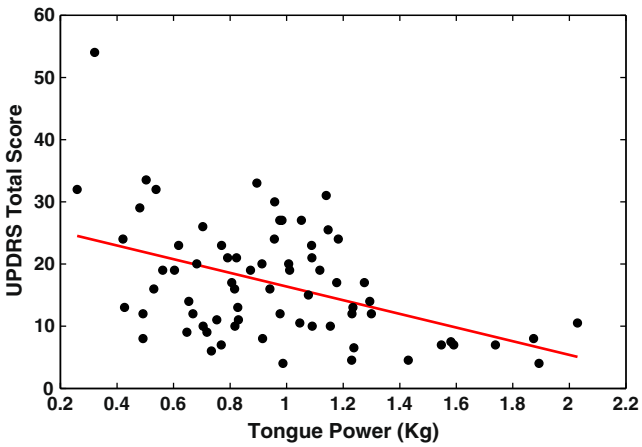

Fig. 3 Tongue power versus UPDRS total score. In the Parkinson's group, lower tongue strength was significantly related to higher (more impaired) UPDRS scores (t [df]=−2.05, [67], *P*=0.02)

Huntington's disease patients, who show various oculomotor abnormalities attributed to this circuit, have prolonged saccadic latency (i.e. visual reaction time) (Lasker and Zee 1997). FDOPA uptake in the right (non dominant hemisphere) caudate nucleus has also been correlated with performance of bimanual tasks (de la Fuente-Fernandez et al. 2000).

In our data, greater standard deviation in non-dominant hand fine force control and reduced maximum tongue strength predicted greater impairment on the UPDRS scale. These results are particularly encouraging, because effective interventions are available to improve tongue and pharyngeal function both in aging and in PD (Connor et al. 2009; El Sharkawi et al. 2002), and exercise programs are known to improve UPDRS scores (Nocera et al. 2009; Yousefi et al. 2009); occupational therapy to improve fine motor control might also improve function in activities of daily living. Tongue strength can be improved by treatments that improve motor function in PD, specifically subthalamic nucleus deep brain stimulation (Gentil et al. 1999).

Limitations

The retrospective aspect of this data analysis produced significant limitations. To determine the severity of disease-related motor changes, motor testing should have been conducted while subjects were off anti-Parkinson medication for at least 12 h. Also, since the precise doses of medication were not known for all participants, levodopa-equivalent doses could not be incorporated as covariates into the statistical models. Therefore, any relationships between PET and motor function discovered in this exploratory analysis should be interpreted with caution. Because the disease group and control group were not ideally matched for years of education, we cannot exclude a contribution of education to motor performance differences between the groups. All cuing and recording of results from the motor performance testing was automated, but those administering the tests (S.D.) were not blinded to the clinical condition of research subjects. There was also variability in the frequency of administration of the motor test battery, with some PD patients being tested multiple times; control subjects were tested a maximum of three times. Practice effects, however, would be expected to reduce the difference between groups.

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