RESEARCH ARTICLE

Rate of 6-[18F]Fluorodopa Uptake Decline in Striatal Subregions in Parkinson's Disease

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ABSTRACT: Background: Rate of decline in 6-L-[18F]fluorodopa (FDOPA) uptake within the striatum has been reported as showing regional differences in Parkinson's disease (PD).

Methods: We acquired longitudinal brain FDOPA positron emission tomography (PET) studies in 26 PD subjects and 11 controls over 4.5 years. We analyzed both spatially normalized voxel-wise maps of radiotracer influx (Kocc) and average Kocc values for six non-overlapping volumes of interest (VOIs) encompassing the striatum.

Results: The voxel-wise analysis showed that in PD, FDOPA Kocc decline spanned the striatum but was greatest in the posterior putamen ipsilateral and anterior putamen contralateral to initial symptoms. The VOI approached showed that absolute rates of Kocc decline were significantly greater in PD than control subjects, but that the slope of decline did not differ between subregions. In PD, ratios of uptake between subregions did not change during the study with the exception of the ipsilateral putamen/caudate ratio. Decline rates were marginally greater during earlier time segments. Both male gender and advancing age were associated with lower baseline FDOPA uptake, but no difference in decline rates. VOI Kocc values were significantly correlated with disease duration, but only moderately correlated with clinical measures.

Discussion: We conclude that FDOPA uptake in subregions of the striatum is strongly correlated with disease duration and age, and declines approximately equally from symptom onset in PD. This implies that in idiopathic PD, relative preservation of uptake in the anterior striatum reflects a delay in pathologic involvement of nigrostriatal projections to this region. © 2011 *Movement Disorder Society*

Key Words: Parkinson's disease; Fluorodopa positron emission tomography; disease progression; aging; gender

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Rate of decline in side-to-side averaged striatal 6-L-[18F]-fluorodopa (FDOPA) uptake, imaged using positron emission tomography (PET), has been used as a surrogate for disease progression in Parkinson's disease (PD).[1,2] Therefore, understanding the evolution of changes in this biomarker is of utmost importance to interpreting intervention studies. The PET hallmarks of PD are abnormal cerebral hemispheric, caudal to rostral (putamen to caudate), and dorsal to ventral gradients in striatal FDOPA uptake,[3] with

most severely compromised uptake in the dorsal posterior putamen contralateral (CL) to the initially symptomatic limbs.[4–7] The caudal-rostral gradient is attributed to predominant involvement of the ventrolateral portion of the substantia nigra (SN) that projects to the putamen, with relative preservation of the dorsomedial SN that projects to the caudate.[8,9] The annual rate of FDOPA uptake decline is greatest in early PD,[10,11] and has been quantified as 8.3 to 12.5% of baseline for the putamen and 3.5 to 9.5% for the caudate,[1,10,12,13] in contrast to less than 1% in normal aging.[12,14] These observations suggest that the rate of decline should differ between striatal subregions, depending on length of disease involvement. The aim of this study was to compare the rate of change in FDOPA uptake between striatal subregions in PD, and to investigate the evolution of left-right and caudal-rostral gradients.

Patients and Methods

Subjects

Twenty-six subjects with idiopathic PD by UK Brain Bank criteria[15] (aged 56 ± 11 years; 15 male, 11 female), and 11 controls (aged 61 ± 12 years; 5 male, 6 female) completed a protocol approved by the local Institutional Review Board. At enrollment, 14 PD subjects were Hoehn and Yahr (HY) stage I, 11 HY II, and 1 HY III. The date and location of earliest motor symptoms were used to calculate disease duration (mean 3.2 years) and to designate onset laterality. At enrollment, 15 PD subjects were taking levodopa, 11 selegiline and/or pramipexole, and none catechol-*o*-methyltransferase inhibitors. One additional subject began taking levodopa between study sessions 2 and 3. Mean mini mental state examination scores were 28/30 for PD subjects and 29.7/30 for controls.

Procedures

Each study session included administration of the Unified Parkinson's Disease Rating Scale (UPDRS) by one of three movement disorders neurologists and FDOPA PET scanning. Over the 4-year span, 19 PD subjects and 11 controls completed three sessions, and the remaining seven PD subjects completed two sessions. The mean interval between sessions was 1.8 years. UPDRS scores for the maximally affected side were 15.7 ± 8.4, 16.4 ± 7.7, and 20.3 ± 11.8 for the three sessions consecutively.

Ninety-minute 3D dynamic PET images were acquired on the same Advance scanner (General Electric Medical Systems, Waukesha, WI) after the IV administration of 204 to 284 MBq (5.5–7.7 mCi) of FDOPA.[16] Subjects were off anti-Parkinson medication for 18 hours before scanning, and ingested 100 mg of carbidopa 30 minutes before

radiotracer injection. Brain MRI scans, obtained on a 1.5 Tesla scanner (General Electric Medical Systems, Waukesha, WI) that included a 124-section axial spoiled-gradient readout sequence (repetition time 29 ms, echo time 13 ms, flip angle = 35°, FOV = 220 mm; slice thickness = 1.2 mm), available for all but four subjects, were coregistered to PET for anatomic specificity.

Image Analysis

PET and MRI images were realigned, within-subject, using FSL/FLIRT (http://fmrib.ox.ac.uk/fsl), then spatially normalized and resampled to 2 mm cubic voxels. Using an in-house software package (http://brainimaging.waisman.wisc.edu/~oakes/spam), volumes of interest (VOIs) encompassing the head and body of caudate nucleus, putamen, posterior $1/2$ of putamen by volume, and a 900 to 1,000 voxel occipital cortex reference region, were defined manually over each subject's normalized MRI scan by one rater (CLG). The caudate and putamen were divided ventrally along the plane of internal capsular fibers visible on coronal views. This technique allowed for individual differences in the location of subcortical structures, and applied the same subject-specific VOI's to repeat PET scans. For four subjects with missing MRI scan data, VOI's were drawn on the spatially normalized PET sum image. Once drawn, all VOI volumes were reinspected and revised if inaccurate. Average radiotracer influx (K_{occ}) values for each VOI, and voxel-wise parametric maps, were computed from 30 to 90 minute PET frames using multiple-time graphical analysis method (MTGA) with occipital cortex (tissue) input function.[17,18] For the purpose of the voxel-wise analysis, the initially affected hemispheres of PD subjects were aligned on the left.

Statistical Analysis

To define regions of significant change between sessions, an exploratory analysis was conducted in Statistical Parametric Mapping 5 (SPM5; http://www.fil.ion.ucl.ac.uk/spm). Realigned K_{occ} images from first and last sessions were entered into a repeated measures analysis of variance (without global normalization), masked exclusively to basal ganglia, that included as factors subject, group (PD/control), and session. For analysis of the VOI data, K_{occ} values for the putamen, caudate nucleus, and posterior putamen were divided into pools according to their anatomic relationship as ipsilateral (IL) or contralateral (CL) to the initially symptomatic limbs. Data from PD subjects were compared with the corresponding side in control subjects. Caudal-rostral (putamen K_{occ}/caudate K_{occ})[19] and hemispheric (CL putamen K_{occ}/IL putamen K_{occ}) ratios were generated. Several linear mixed effects models, in which a response variable (UPDRS
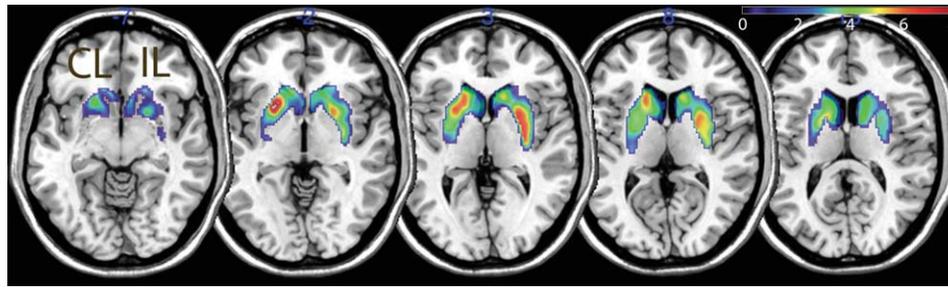
FIG. 1. In PD, decline in FDOPA uptake between the first and last PET sessions spanned the striatum, with local maxima in the posterior putamen ipsilateral (IL) and anterior putamen contralateral (CL) to initial symptoms ($P < 0.05$ FWE, analysis restricted to basal ganglia). The colored scale bar indicates the voxel-level t statistic.

score, K_{occ} value, or ratio) was regressed against explanatory variables of time (age, disease duration, or time from baseline session), gender, group, and time-by-group interaction, were used to model the main effects of these covariates, and the strength of interactions (http://www.math.mcgill.ca/keith/surfstat). Then, using the subgroup of 19 PD subjects who had completed three sessions, both annualized raw decline rates [(K_{occ} earlier-K_{occ} later) min^{-1}/years between] and annualized percent decline rates for the session 1-2 and session 1-3 intervals were compared using paired samples t tests in SPSS 16 (SPSS, Inc., Chicago, IL).[20]

Results

Exploratory Voxel-Wise Analysis

A contrast comparing the first and last PET scan sessions in all 26 PD subjects (corrected for false discovery rate [FDR] at a threshold of $P < 0.05$) showed two significant clusters spanning the basal ganglia, with local maxima in the IL posterior putamen (MNI coordinates 30, −8, 2, voxel-level $T = 6.62$) and CL anterior putamen (−24, 12, −2, $T = 7.63$) (Fig. 1). A similar contrast produced no significant clusters in the control group. Since this statistical model did not take into account variation in time interval between sessions, we proceeded to mixed effects analysis of the the manually-drawn VOIs.

Group Differences at Baseline

As expected, an anterior–posterior gradient, with decreasing K_{occ} values in whole putamen compared with caudate nucleus, and in posterior putamen compared with whole putamen, was present in the PD group but not the control group. IL and CL putamen, caudate, and posterior putamen K_{occ}, and hemispheric putamen, and putamen/caudate ratios were significantly different between the PD and control groups ($P < 0.005$). CL putamen and posterior putamen K_{occ} values did not overlap between groups. In the PD group, uptake in all structures, was higher in women ($t[df]$, $P = −2.2[26], 0.035$), while mean disease duration was 3.2 years for both genders. This gender effect was most significant for the CL caudate nucleus ($t[df]$, $P = −3.7[26], 0.001$). Caudate nucleus (mean 420 voxels) and putamen (mean 675 voxels) VOI volumes did not differ by group or gender (Table 1).

Within Subject Longitudinal Data Stability

For the control group, the average absolute scan-to-scan difference in VOI K_{occ} measurements was 0.0008 min^{-1} for the caudate and 0.0009 min^{-1} for the putamen, representing 7% of baseline for both structures.

Linear Mixed Effects Analysis

Models evaluating the main effects of group (PD versus control), gender, and age on FDOPA uptake

TABLE 1. Subregional baseline values and mean raw annual decline rates

Subregion		Parkinson's group			Control group		
		Mean K_{occ} (min^{-1})	SD (min^{-1})	Annual decline (min^{-1})	Mean K_{occ} (min^{-1})	SD (min^{-1})	Annual decline (min^{-1})
Contralateral	Caudate	0.0100	0.0015	0.0005	0.0117	0.0011	0.0001
	Putamen	0.0072	0.0015	0.0005	0.0137	0.0014	0.0001
	Post. putamen	0.0052	0.0016	0.0004	0.0135	0.0010	0.0002
Ipsilateral	Caudate	0.0106	0.0017	0.0006	0.0122	0.0015	0.0002
	Putamen	0.0083	0.0023	0.0006	0.0136	0.0011	0.0001
	Post. putamen	0.0065	0.0022	0.0006	0.0131	0.0018	0.0001

Baseline means, standard deviations, and linear regression decline rate estimates for K_{occ} values derived from striatal subregions.
SD, standard deviation; K_{occ}, uptake rate constant for FDOPA; CL, contralateral to initially symptomatic limbs; IL, ipsilateral to initially symptomatic limbs; Post., posterior.

TABLE 2. Group, age, gender, and time effects in mixed models of striatal subregional uptake

Response variable		Age (df = 100)	Group (df = 100)	Gender (df = 100)	Time*Group (df = 99)	Duration in PD (df = 68)
				Effects		
Contralateral	Caudate	−2.5/0.005*	−4.5/9x10^{-6}*	1.1/0.15	−4.3/2×10^{-5}*	−7.4/1×10^{-10}*
	Putamen	−1.5/0.06	−16.7/0.006*	1.7/0.04*	−4.1/3×10^{-5}*	−7.5/×10^{-11}*
	Post. putamen	−0.8/0.20	−22.7/1 x10^{-41}*	2.1/0.02*	−1.6/0.05*	−2.2/0.01*
	Putamen/caudate	0.9/0.18	−12.7/6x10^{-23}*	1.2/0.11	−0.7/0.53	−0.5/−0.31
Ipsilateral	Caudate	−2.7/0.004*	−2.6/0.006*	1.8/0.04*	−3.4/6×10^{-4}*	−7.4/1×10^{-10}*
	Putamen	−3.4/5x10^{-4}*	−10.1/3x10^{-17}*	1.3/0.10	−5.3/2×10^{-7}*	−9.3/5×10^{-14}*
	Post. putamen	−1.8/0.03*	−12.3/4x10^{-22}*	2.0/0.03*	−3.1/0.001*	−5.1/1×10^{-6}*
	Putamen/caudate	−1.1/0.14	−11.2/2x10^{-19}*	0.14/0.44	−2.5/0.008*	−1.9/0.03*
Hemispheric	Putamen ratio	2.6/0.006*	−3.8/1x10^{-4}*	−0.2/0.43	0.3/0.38	0.6/0.26

Significance values (*t* statistic/*P* value) for main effects (columns 2–4,6) and interactions (5) from the mixed effects analyses (random effects are reported).
df, degrees of freedom; Post., posterior.
*significant *P* value (<0.05).

identified group effects for all subregions, and for caudal-rostral, and hemispheric putamen ratios, age effects for all subregions except the CL posterior putamen, and gender effects for several subregions (Table 2). When the small control group was analyzed separately, the effect of age on putamen K_{occ} was marginal ($P < 0.06$), and the decline rate estimated by linear regression (Table 1) as 0.0001 to 0.0002 min^{-1}, or 0.7 to 1.5% of baseline uptake annually, did not reach significance. Models evaluating the rate of decline difference between groups, or time-by-group interactions, showed significant differences for all substructures and for the IL putamen/caudate ratio. Subtle differences in the slopes of linear regression lines fitted to the data from each substructure by group were not significant (Fig. 2). Also, gender differences in the rate of decline were not significant. In the PD group, disease duration affected uptake in all substructures (Table 2). Intercept values for the disease duration models, which represent the projected K_{occ} at symptom onset, were 0.0114 (caudate nucleus), 0.0092 (putamen), 0.0072 (posterior putamen) for the IL brain and 0.0106 (caudate nucleus), 0.0075 (putamen), 0.0053 (posterior putamen) for the CL brain (compared with mean baseline control K_{occ} of 0.0136 for putamen and 0.0120 for the caudate nucleus). When similar models were applied to the PD group using total UPDRS scores as the outcome variable, age was a strong contributor (*t*[df], $P = 2.92[68], 0.002$) and FDOPA uptake in all substructures a weak contributor (*t*[df], $P = 1.5[68], 0.05$) to clinical outcome. Total UPDRS scores were not significantly related to time or to disease duration. At session 1, HY I PD subjects had smaller mean hemispheric putamen ratio than HYII/III subjects (*t*[df], $P = 2.8[24], 0.01$); however, this ratio did not change significantly as HYI subjects transitioned to HYII.

Evaluation of Annual Rate of Change Between Time Intervals

A within-subject comparison of time intervals for PD subjects who completed three sessions showed that decline rates were not uniform across sessions. For the session 1-2 interval, annual decline rates were 9.6 (IL putamen), 7.8 (CL putamen), 7.4 (CL caudate), and 3.8 (IL caudate) percent of baseline, and for the session 1-3 interval, 6.6 (IL putamen), 6.0 (CL putamen), 4.9 (CL caudate), and 3.8 (IL caudate) percent. Raw annual rates of decline were different between time intervals for the IL putamen (*t*[df], $P = 2.4[18], 0.03$) and CL caudate (*t*[df], $P = 2.2[18], 0.04$) (Fig. 3).

The Effect of Pharmacotherapy

Annual decline rates for PD subjects taking pramipexole and/or selegiline were greater than those taking carbidopa/levodopa; however, use of carbidopa/levodopa was also correlated with disease duration ($r = 0.66, P < 0.001$).

Discussion

Studies that have used annual rates of change in striatal FDOPA uptake as a surrogate outcome measure have averaged side-to-side differences to improve scan-to-scan reproducibility.[1] We addressed the question of whether rates of FDOPA uptake decline show regional differences within the striatum in PD. We first used an exploratory voxel-wise approach that suggested the regions of most significant change between sessions to be the CL anterior dorsal and IL posterior putamen. Previous voxel-based analyses have localized the region of greatest PD-related FDOPA decline to the anterior striatum,[21] and to the IL posterior putamen.[12] We then used a detailed VOI selection technique to comprehensively sample FDOPA uptake in striatal subregions. This technique yielded a favorable
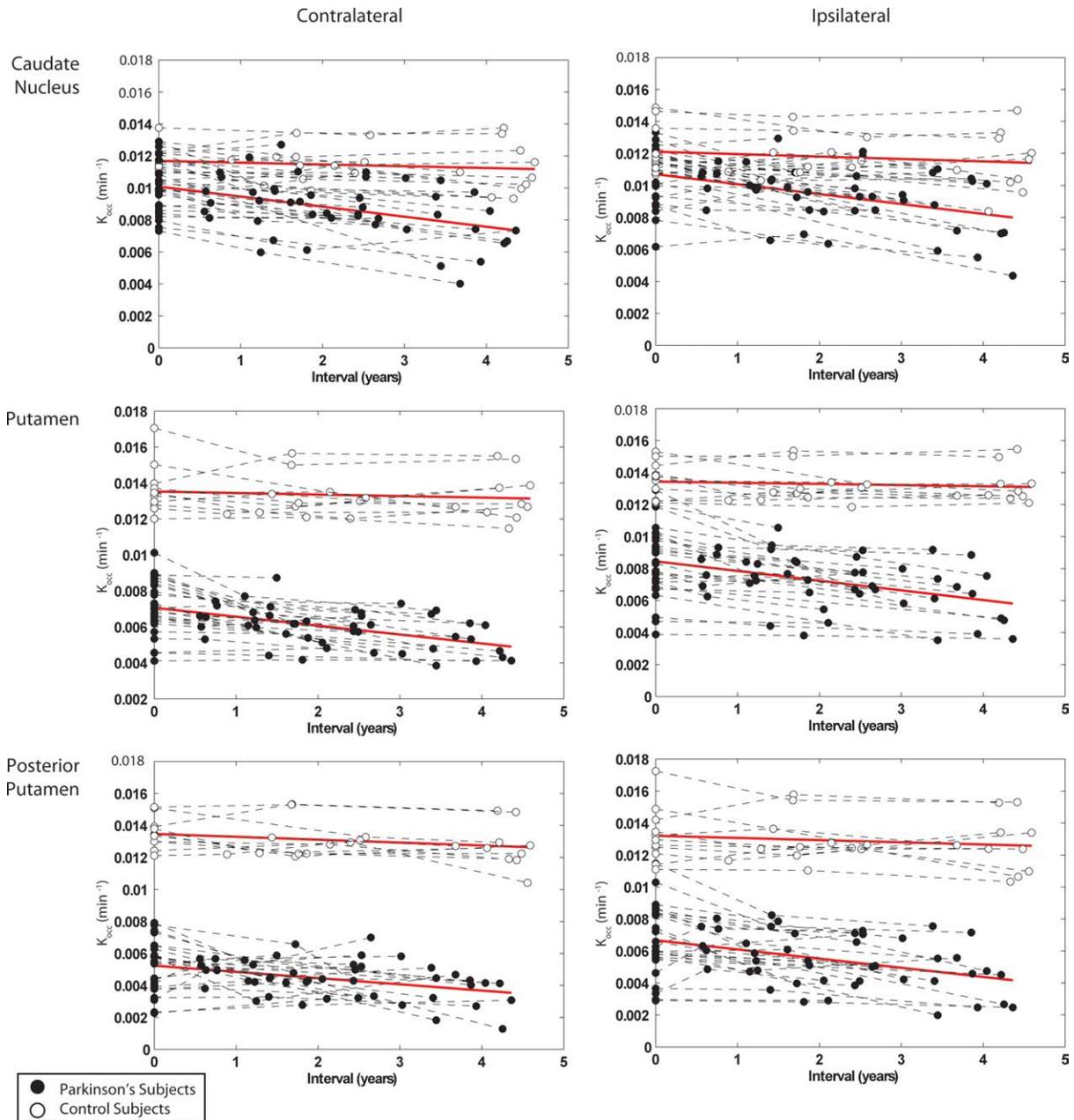
FIG. 2. The slopes of regression lines fitted to sequential K_{occ} measurements did not differ significantly between subregions. Within-subject measurements are connected by dashed lines.

scan-rescan reproducibility in the control group,[13] but also averaged uptake over fairly large volumes and was therefore expected to be less sensitive to small regional changes than the voxel-wise approach. Commensurate with the voxel-wise findings, the VOI analysis showed a slight decline in the IL caudal-rostral gradient (putamen K_{occ}/caudate K_{occ}), and a slightly greater decline rate in the IL putamen (Fig. 3) that might reach statistical significance in a larger sample. Although different in techniques of image sampling and radiopharmacology, a study using a dopamine transporter ligand did demonstrate significantly faster PD-related decline in the IL putamen.[22] Although the linear random effects analyses demon-

strated significant differences in the rate of decline between PD and control groups (significant time-by-group interaction) for all subregions, we found no significant within-group differences in the decline rate between the selected VOIs. The roughly parallel regional decline trajectories was further supported by lack of change over the study interval in the hemispheric putamen ratio (CL/IL putamen K_{occ}) and CL caudal-rostral gradient, and the linear relationship of uptake in all subregions to disease duration. The hemispheric putamen ratio was smaller for subjects who entered the study at HYI than for subjects of HYII/III, but did not change at later sessions as HYI subjects transitioned clinically to HYII. These conclusions are
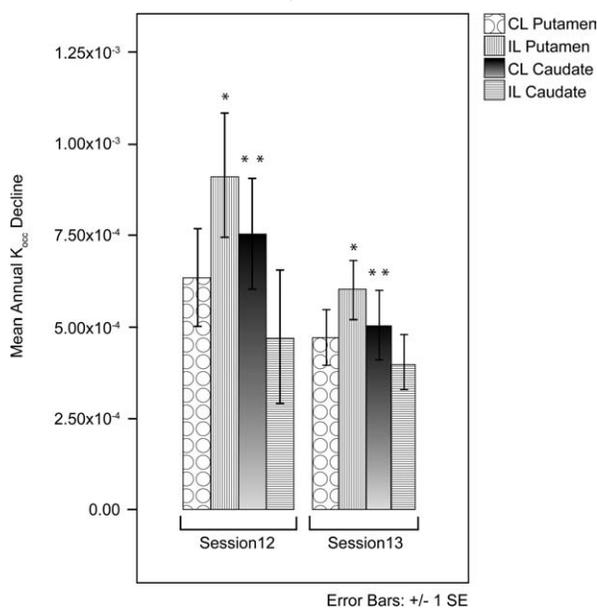
FIG. 3. Raw annualized rates of decline from baseline Kocc (min^{-1}) were compared by subregion between the session 1 to 2 and 1 to 3 intervals. Abbreviations: CL, contralateral; IL, ipsilateral; *, **, rates differ by paired t test ($P < 0.05$).

commensurate with two previous studies that found no difference in the rate of decline between striatal subregions in 31 PD subjects over 2 years,[23] and in 21 PD subjects over 5 years.[12] The advantage of our study in confirming this observation is lack of potentially confounding medication changes, as only 1/26 of our subjects began taking levodopa during the study interval, whereas 27/31 and 10/21 began taking levodopa in the former studies. The finding of equivalent decline rates is at odds with previous studies using FDOPA[2,10] that have described different rates of change for the caudate nucleus and putamen. Whereas the rate of change expressed as a percentage of baseline uptake may differ between striatal subregions, our analysis suggests the raw rate of change in K_{occ} is roughly equivalent when averaged over relatively large volumes.

Age and Gender Effects

We found increasing age to be associated with reduced FDOPA uptake in the PD group, with a marginal effect in the control group, and a trivial decline rate 0.7 to 1.5% per annum in the control group, consistent with one previous investigation.[12] Female gender also had a moderate effect on FDOPA uptake in all structures, especially the IL caudate nucleus. Higher striatal, especially caudate, FDOPA uptake in women has been described in both normal and PD groups controlled for disease duration.[24] Since the incidence of PD is higher in men, it is possible that women are partially protected by higher baseline striatal dopaminergic function.[25]

Deceleration of FDOPA Uptake Loss Over Time

This study provides a within-subject comparison of the slope of FDOPA uptake decline between sequential time intervals. The results support previous hypotheses, based on single time intervals, that FDOPA uptake loss is greater in earlier than later stages of disease.[10,11] However, the significance of our findings ($P = 0.03–0.05$) would not withstand correction for multiple comparisons, and greater statistical power might have been achieved had subjects representing a greater spectrum of disease stages been enrolled. A slower rate of decline in more depleted structures suggests that regions in which the disease is more advanced may be experiencing a slower rate of cell loss.[21] However, the relationship between FDOPA uptake decline and cell loss is uncertain,[26] partially because factors that cannot be estimated from 90-minute dynamic FDOPA PET data, specifically dopamine turnover, vary with disease stage and influence the K_{occ} value.[27,28] Although small doses of levodopa do not have short-term effects on quantification of striatal FDOPA uptake in PD,[29] measured rates of decline are influenced by chronic treatment.[1] In this sample, the apparent slower progression rate in subjects treated with selegiline/pramipexole in comparison to those treated with levodopa may reflect greater disease duration in the levodopa-treated group rather than an effect of pharmacotherapy.

Conclusions

In this study, PET scan measurements were more consistently correlated with time and disease duration than were UPDRS scores. However, time may not be the most valuable surrogate for disease progression in a heterogeneous clinical population. A surrogate outcome measure should be "used as a substitute for a clinically meaningful end point that measures directly how the patient feels, functions, or survives."[30] An uncertain relationship between imaging measures and clinical outcomes has plagued many drug development trials.[31] This study brings to light two issues related to using PET as a surrogate outcome measure in PD. First, age, disease duration, and gender influence FDOPA uptake and should continue to be matched between groups in studies that use PET as a surrogate outcome measure.[1,11] Second, the use of relative normalization methods in an effort to control for individual differences (in this case, normalizing annual rates of change to baseline FDOPA uptake), may contribute to uncertainty about how a biomarker reflects pathology.[32] We found that striatal structures experience a largely parallel average rate of FDOPA loss in PD, such that rostrocaudal and hemispheric gradients do not change significantly over time. Our findings imply

that all striatonigral projections are similarly affected from symptom onset, but that striatal subregions are involved sequentially with the disease process. Therefore, estimates of the "preclinical" period for these subregions will differ.[10] ∎

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