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Dopaminergic Correlates of Metabolic Network Activity in Parkinson's Disease

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Abstract: Parkinson's disease (PD) is associated with distinct metabolic covariance patterns that relate to the motor and cognitive manifestations of the disorder. It is not known, however, how the expression of these patterns relates to measurements of nigrostriatal dopaminergic activity from the same individuals. To explore these associations, we studied 106 PD subjects who underwent cerebral PET with both ^{18}F-fluorodeoxyglucose (FDG) and ^{18}F-fluoro-L-dopa (FDOPA). Expression values for the PD motor- and cognition-related metabolic patterns (PDRP and PDCP, respectively) were computed for each subject; these measures were correlated with FDOPA uptake on a voxel-by-voxel basis. To explore the relationship between dopaminergic function and local metabolic activity, caudate and putamen FDOPA PET signal was correlated voxel-wise with FDG uptake over the entire brain. PDRP expression correlated with FDOPA uptake in caudate and putamen ($P < 0.001$), while PDCP expression correlated

Additional Supporting Information may be found in the online version of this article.

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with uptake in the anterior striatum ($P < 0.001$). While statistically significant, the correlations were only of modest size, accounting for less than 20% of the overall variation in these measures. After controlling for PDCP expression, PDRP correlations were significant only in the posterior putamen. Of note, voxel-wise correlations between caudate/putamen FDOPA uptake and whole-brain FDG uptake were significant almost exclusively in PDRP regions. Overall, the data indicate that PDRP and PDCP expression correlates significantly with PET indices of presynaptic dopaminergic functioning obtained in the same individuals. Even so, the modest size of these correlations suggests that in PD patients, individual differences in network activity cannot be explained solely by nigrostriatal dopamine loss. *Hum Brain Mapp 36:3575–3585, 2015.*

Key words: brain networks; dopamine; FDOPA; Parkinson's disease; PET

INTRODUCTION

While to date the diagnosis of idiopathic Parkinson's disease (PD) relies on the clinical exam, neuroimaging has substantially contributed to characterizing and better understanding the brain pathology underlying the motor and cognitive manifestations of this disorder. The hallmark of the disease, the loss of nigral dopaminergic projections to the striatum, with concomitantly reduced dopamine levels in the latter structure, can be accurately assessed using PET and single photon emission tomography imaging with radiotracers such as ^{18}F-fluoro-L-dopa (FDOPA) and ^{18}F-fluoropropyl-β-CIT (FPCIT). Dopaminergic imaging in PD patients has revealed consistent reductions in striatal tracer uptake, involving mainly the motor-related posterior putamen [Jokinen et al., 2009; O'Brien et al., 2004]. By contrast, radiotracer uptake is relatively preserved in the cognition-related anterior striatum, most notably in the caudate nucleus [Carbon et al., 2004; Polito et al., 2012; van Beilen et al., 2008]. Nonetheless, brain dysfunction in PD is not limited to dopamine loss in the basal ganglia. Apart from distinct regional changes in the basal ganglia [Eggers et al., 2009], spatial covariance analysis has revealed specific large-scale metabolic brain networks associated with motor and cognitive disease features [Eidelberg, 2009; Holtbernd and Eidelberg, 2012]. The PD motor-related pattern (PDRP) is characterized (Fig. 1, *left*) by metabolic increases in the globus pallidus internus, thalamus, pons, cerebellum, and sensorimotor cortex, associated with relative reductions in posterior parietal and premotor cortices [Ma et al., 2007]. This metabolic network is highly specific for PD, and unlike imaging measures of nigrostriatal dopamine loss, the PDRP is not expressed in patients with atypical parkinsonism [Niethammer and Eidelberg, 2012; Tang et al., 2010b]. Conversely, the topographically distinct PD cognition-related pattern (PDCP) is characterized (Fig. 1, *right*) by metabolic reductions in the medial prefrontal and rostral supplementary motor regions, and in superior medial parietal association cortex, which co-vary with relative increases in the cerebellar deep nuclei and pons [Huang et al., 2007a]. PDRP and PDCP subject scores, denoting expression levels for each pattern in a given individual [Spetsieris and Eidelberg, 2011; Spetsieris et al., 2013], have been found to correlate consistently with clinical measures of motor and cognitive dysfunction in PD patients [Eidelberg, 2009; Huang et al., 2007b; Niethammer and Eidelberg, 2012; Tang et al., 2010a]. Nonetheless, information is scant concerning the precise relationship between PDRP and PDCP expression on one hand, and caudate and putamen dopaminergic integrity on the other [Niethammer et al., 2013]. In the current study, we systematically examined the relationship between these measures at the voxel, regional, and network-wide levels in a cohort of over 100 PD patients who underwent dual tracer PET imaging for the combined assessment of presynaptic nigrostriatal dopaminergic function (FDOPA) and resting glucose metabolism (^{18}F-fluorodeoxyglucose [FDG]) in the same individuals.

MATERIALS AND METHODS

Subjects

We studied 106 PD subjects (age 57.0 ± 11.3 [mean ± SD] years, 38 female/68 male, Hoehn and Yahr stage 2.4 ± 1.1) recruited at the Department of Neurology at Cologne University Hospital. All subjects underwent dual tracer PET imaging with both FDG and FDOPA. Because of the retrospective nature of the study, an ethical vote was not mandatory according to German federal laws. However, the ethics committee of the Medical Faculty of the University of Cologne approved the protocol on request. Patients were not asked for informed consent as case records were anonymized and deidentified prior to analysis. The subjects were diagnosed with PD according to the UK Brain Bank Criteria [Hughes et al., 1992]. We excluded subjects without any clinical response to levodopa treatment, signs and symptoms of dementia, or past history of stroke or brain surgery. Detailed demographical data are displayed in Table I. Two separate groups of healthy subjects served as controls for comparison with the PD measurements. The first cohort was comprised of 19 subjects (age 42.3 ± 13.9 years, 6 female/13 male) who were scanned with FDG PET; the second cohort was comprised of 10 subjects (age 48.1 ± 12.2 years, 4 female/6 male) scanned with FDOPA PET.

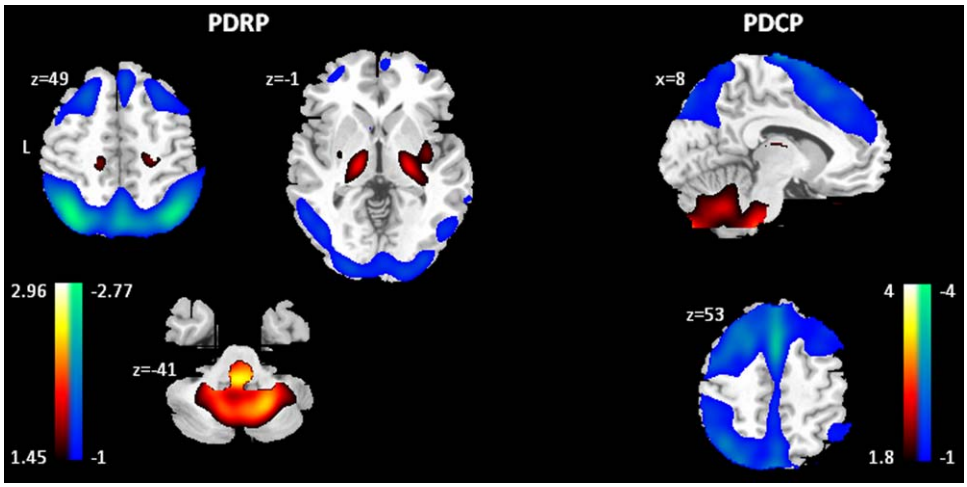

Figure 1.

Left, Parkinson's disease motor-related pattern (PDRP) characterized by relative metabolic increases (*red*) in the pons, cerebellum, globus pallidus internus, thalamus and sensori-motor cortex, accompanied by relative metabolic decreases (*blue*) in premotor and posterior parietal cortices [adapted from Ma et al., 2007]. *Right*, Parkinson's disease cognitive pattern (PDCP) characterized by relative hypermetabolism (*red*) in the cerebellum/dentate nuclei and relative metabolic decreases (*blue*) in the dorsolateral prefrontal cortex, rostral supplementary motor areas and superior parietal cortices [adapted from "Metabolic brain networks associated with cognitive function in Parkinson's disease," 34, Huang et al., pp. 714–723, Copyright (2007), with Permission from Elsevier]. [Voxels with positive region weights (metabolic increases) are color-coded red and those with negative region weights (metabolic decreases) are color-coded blue. Display was superimposed on a standard single subject T1 template. Coordinates are displayed in Montreal Neurological Institute standard space. Color stripes indicate the z-score range.].

Positron Emission Tomography

Similar PET imaging procedures were performed for the PD and the two healthy control groups [Ghaemi et al., 2002]. Scans were performed using a 24 detector ring scanner (ECAT EXACT HR, Siemens CTI, Knoxville, TN). During scanning, subjects lay comfortably in a supine position in a room with dimmed lighting and low background noise. All anti-parkinsonian medication was stopped at least 16 h before starting PET registration. Data were acquired in a 3-D mode, subsequently reconstructed, including a correction for random coincidences, attenuation, and scatter. PET scans were registered on consecutive days with a delay of no longer than 14 days between scans. For metabolic imaging, cerebral glucose metabolism representing the regional metabolic activity at rest was measured after the injection of 370 MBq of FDG. Scans were acquired in four dynamic 10-min frames between 20 and 60 min. For dopaminergic imaging, 100 mg of carbidopa was administered orally to the subjects before the intravenous injection of 370 MBq FDOPA. Patients were scanned for 90 min, recording a dynamic series of nine 10-min frames.

Data Processing

Preprocessing of scan data was performed using SPM 5 (Wellcome Trust Center for Neuroimaging, London, UK) implemented in MATLAB (Mathworks, Sherborn, MA). FDG PET images were spatially normalized and smoothed (FWHM 10 × 10 × 10 mm). Subject scores for the PDRP and PDCP spatial covariance patterns, reflecting whole-brain network expression in each individual, were computed using ScAnVP software (freely available at www.feinsteinneuroscience.org) as described previously [Spetsieris and Eidelberg, 2011; Spetsieris et al., 2013]. To standardize the subject scores computed in the PD patients, PDRP and PDCP expression values were separately quantified in the FDG PET scans that were acquired in the 19 normal controls. The resulting control values were used to *z*-transform the subject scores from the entire sample ($n = 125$: 106 PD patients + 19 normal controls) such that in the healthy group, the mean for each pattern was zero with a standard deviation of one [Spetsieris and Eidelberg, 2011; Spetsieris et al., 2013]. PDRP and PDCP expression values increase slightly during healthy aging [Eidelberg, 2009]. To account for the significantly younger age in normal controls compared to PD (mean difference 14.7 years), we computed the average annual increase in

TABLE I. Demographics for Parkinson's disease patients

Age	57.0 ± 11.3 (30–83)
Gender	38 female/68 male
H&Y	2.4 ± 1.1 (1–4)
Age at onset	49.9 ± 11.3 (26–78)
Duration (years)	7.1 ± 6.3 (0.1–24)
LEDD (mg)	440.4 ± 439.7 (0–1900.0)

Values are presented as mean ± SD (range). H&Y = Stage according to the Hoehn and Yahr scale; LEDD = Levodopa equivalent daily dosage.

PDRP and PDCP expression in a separate cohort comprised of 73 healthy subjects (age 51.0 ± 17.6 years, range: 20.3–79.6 years) who have been previously scanned with FDG PET at The Feinstein Institute for Medical Research (Manhasset, NY). Regression analyses showed that the rates of increase in PDRP and PDCP scores with age in this normal cohort was 0.032/year ($P < 0.001$) and 0.028/year ($P < 0.001$) (z-score scale), respectively. Next, a correction term (group age difference * progression rate) was calculated to adjust individual PDRP and PDCP scores in the 19 normal subjects.

For FDOPA PET quantification, specific uptake ratio was measured using previously validated analytical protocols [Dhawan et al., 2002; Ma et al., 2010]. Dynamic frames were realigned from 0 to 90 min to create a mean count image and transformed into Montreal Neurological Institute standard space using the mean count image and a custom-made FDOPA PET template. Occipital counts of FDOPA uptake were computed in a manually placed region-of-interest (ROI) delineated on the last frame of each scan reflecting tracer uptake from minutes 80 to 90. The last frame of each scan was then divided by the corresponding occipital ROI value and subtracted by one to generate whole-brain FDOPA uptake ratio maps. Ratio maps were smoothed using a 10 mm FWHM kernel and entered into SPM analysis.

PDRP and PDCP expression values were correlated with whole-brain FDOPA uptake at the voxel-level using a regression model implemented in SPM [Niethammer et al., 2013]. Subject scores for the PD-related patterns were additionally correlated with FDOPA uptake ratio values for the caudate and putamen measured using standardized anatomical ROIs placed bilaterally on the maps of FDOPA uptake ratio. ROI placement was adjusted manually to obtain the best fit in the individual scans. Left and right ROI values were averaged for each structure; total striatal uptake was computed by averaging uptake values from the caudate and putaminal ROIs. Lastly, the anterior–posterior striatal uptake gradient was computed by subtracting putaminal from caudate uptake values.

FDOPA uptake ratio values for the caudate, putamen, and for the whole striatum, were entered as covariates in an SPM regression model against normalized FDG uptake over the entire brain volume. Subject age was entered as a covariate of no interest in all analyses. The voxel threshold was set at $P < 0.001$, corrected for false discovery rate at $P < 0.05$. For voxel-wise correlation analyses against normalized FDG uptake, individual differences in globally normalized regional FDG uptake values were inspected post hoc in spherical (radius = 5 mm) volumes-of-interest (VOIs) centered on the peak voxels of the significant SPM clusters.

Statistical Analysis

Statistical analyses were performed using SPSS (SPSS, Chicago, IL). Group comparisons of network scores and regional FDOPA uptake between PD patients and healthy controls were performed using the Student's t-test for independent samples. Post hoc correlations of regional FDOPA uptake with network expression and between FDOPA uptake and the regional cerebral metabolic rate of glucose were performed using the Pearson correlation coefficient. Results were assumed significant for $P < 0.05$.

RESULTS

PDRP and PDCP expression values (Fig. 2A) were abnormally elevated in PD patients compared to healthy controls ($P < 0.001$ for both patterns). Of note, PDRP and PDCP expression values (Fig. 2B) were closely intercorrelated ($r = 0.865$, $P < 0.0001$). A similar relationship between network expression values was observed in the healthy control cohort ($r = 0.830$, $P < 0.0001$). Pattern expression values for the two metabolic networks correlated with age in the disease group (PDRP: $r = 0.549$; PDCP: $r = 0.512$; $P < 0.0001$ for both patterns).

FDOPA uptake in the caudate nucleus and putamen (Fig. 2C) was reduced in PD patients compared to healthy controls ($P < 0.0001$ for both). Specifically, dopaminergic depletion was pronounced in the putamen, and consequently the anterior–posterior gradient was significantly greater in the PD group compared to healthy subjects (0.32 ± 0.10 vs. 0.16 ± 0.09, $P < 0.0001$). Of note, caudate and putaminal ROI values were intercorrelated in the PD ($r = 0.914$, $P < 0.0001$; Fig. 2D) and normal control ($r = 0.723$, $P = 0.018$) groups. Striatal FDOPA uptake did not correlate with subject age in either group ($P > 0.05$).

Correlation of PDRP and PDCP Expression Levels with Local Dopaminergic Integrity

Voxel-wise regression of PDRP subject scores against whole-brain FDOPA uptake (Fig. 3, *left*) revealed a strong negative correlation localized to the entire striatum. A similar correlation was seen between PDCP values and striatal FDOPA uptake (Fig. 3, *middle*), but of substantially smaller extent than for the PDRP. Indeed, this correlation was strictly limited to the most anterior portion of the striatum. Interestingly, once adjustment was made for individual differences in PDCP expression, the dopaminergic correlation with PDRP scores (Fig. 3, *right*) was limited mainly to the posterior putamen. That said, voxel-wise FDOPA correlations with PDCP values did not reach significance after adjustment for individual differences in PDRP expression. No positive correlations were evident between PDRP/PDCP network expression levels and local measures of presynaptic dopaminergic function.

Findings from the voxel-wise searches were confirmed using prespecified anatomically defined VOIs (see Methods). FDOPA uptake values measured in the caudate VOI (Fig. 4A,B) correlated with PDRP and PDCP expression ($r = -0.439$, $P < 0.0001$, and $r = -0.338$, $P < 0.001$, respectively). FDOPA uptake values measured in the putamen (Fig. 4C) correlated ($r = -0.361$, $P < 0.001$) with PDRP expression. In contrast to the voxel-wise results, a weak correlation ($r = -0.225$, $P = 0.020$) was also discerned between

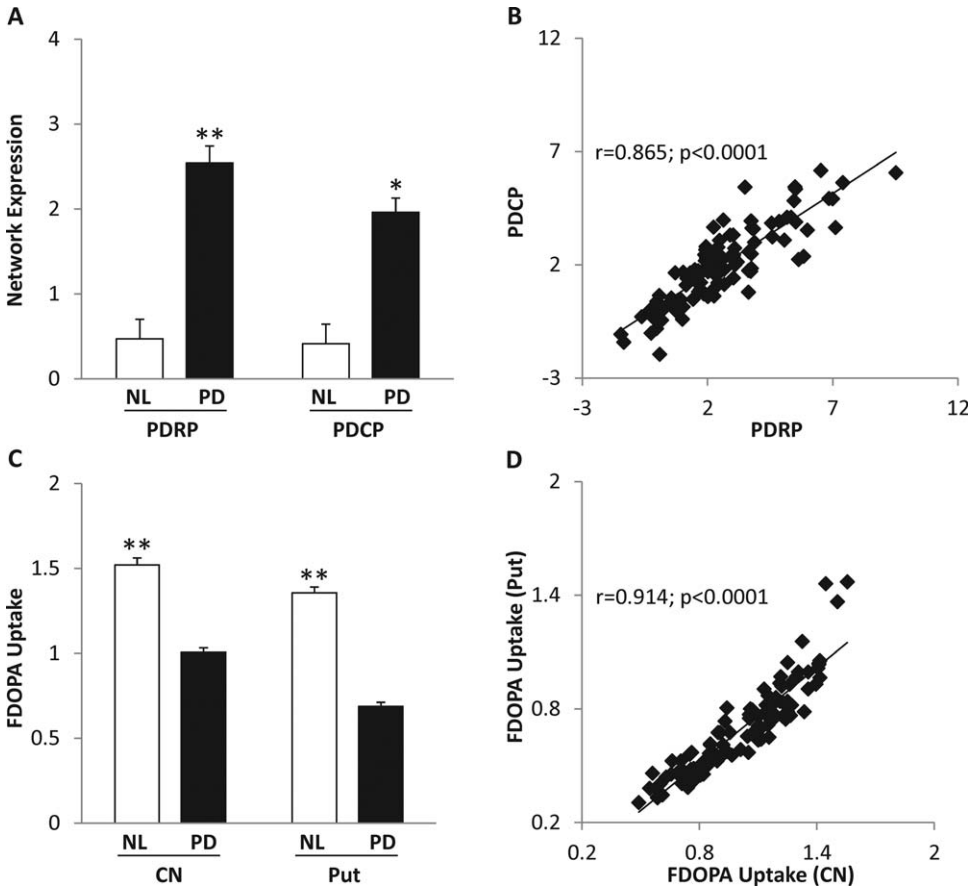

Figure 2.

(**A**) PDRP and PDCP expression were elevated to abnormal levels in patients with Parkinson's disease (PD, *black bars*) compared to healthy controls (NL, *white bars*). (**B**) PDRP and PDCP scores exhibited a strong intercorrelation in the Parkinson's disease group. (**C**) FDOPA uptake was reduced in the caudate nucleus (CN) and putamen (Put) of Parkinson's disease patients compared to controls. (**D**) FDOPA uptake values in the caudate and putamen of Parkinson's disease patients showed a strong intercorrelation. [The error bars represent the SEM. $^{**}P < 0.0001$, $^{*}P < 0.001$, Student's *t*-test.].

FDOPA uptake in this region and PDCP expression values. Nonetheless, putaminal FDOPA uptake did not remain a significant predictor of PDCP expression after controlling for individual differences in PDRP expression ($P > 0.05$, step-wise multiple regression model). Conversely, the correlation between PDRP expression and putamen FDOPA uptake remained significant ($P < 0.001$) after controlling for individual differences in PDCP expression.

Correlation of Regional Brain Metabolism with Striatal Dopaminergic Integrity

To assess the relationship between nigrostriatal dopaminergic integrity and regional metabolic activity, caudate and putamen FDOPA uptake values were correlated with globally normalized FDG activity on a voxel-by-voxel basis. The spatial distribution of voxels significantly correlating with metabolic activity closely resembled the PDRP topography; loss of caudate and putamen FDOPA uptake correlated with reductions in metabolic activity bilaterally in the caudate and anterior putamen, in parietal association regions (Brodmann area [BA] 39/40) including the cuneus (BA 17/18) and in premotor/prefrontal cortex (BA 8/9). Inverse correlations (Fig. 5) with caudate and putamen FDOPA uptake were evident in the cerebellum and pons, and bilaterally in sensorimotor cortex (BA 4/6). Correlations were confirmed by post hoc VOI analysis (Fig. 6A–F; Table II). Similar metabolic correlations were observed using either caudate or putamen FDOPA uptake as the regressing variable in the correlation analysis (Supporting Information Fig. S1).

DISCUSSION

Few studies to date have systematically explored the relationship between presynaptic nigrostriatal dopaminergic

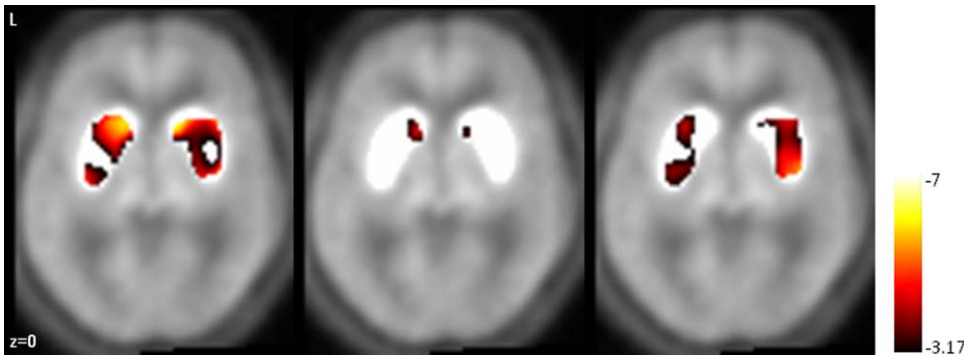

Figure 3.

Display of age-corrected correlations between PDRP and PDCP network scores with whole-brain FDOPA uptake. PDRP scores were correlated with FDOPA uptake in the entire striatum (*left*), whereas individual PDCP expression was associated with dopaminergic function in the anterior striatum only (*middle*). When correcting for PDCP expression, the correlation of PDRP scores was localized to the posterior putamen only (*right*). [Display was superimposed on a custom-made FDOPA template. The color stripe indicates the *t*-value; voxel threshold $P < 0.001$. Coordinates are displayed in Montreal Neurological Institute standard space.].

function and cerebral metabolism in PD patients using a dual tracer design. The large number of subjects scanned with both FDOPA and FDG PET, as well as the measurement of metabolic activity at both the regional and network levels, provide important data concerning the relationship of localized dopamine loss and the activity of the abnormal brain networks that characterize this disorder.

Loss of Dopaminergic Function and Increased Network Activity in Parkinson's Disease

In line with prior studies, we observed an overall reduction of presynaptic nigrostriatal dopaminergic function in PD patients. As typically observed in PD [Jokinen et al., 2009; O'Brien et al., 2004], loss of dopaminergic innervation was most severe in the posterior putamen, whereas dopaminergic afferents to the caudate and anterior putamen were relatively preserved, albeit at levels lower than in healthy subjects. Also in good agreement with prior findings [Eidelberg, 2009; Spetsieris and Eidelberg, 2011], PD patients exhibited abnormal increases in both PDRP and PDCP expression values. Of note, the magnitude of network elevation was higher for the motor-related PDRP topography as compared to its cognitive counterpart. In this vein, we previously reported that in PD, abnormal elevations in PDRP expression develop earlier and exceed PDCP values measured in the same individuals [Huang

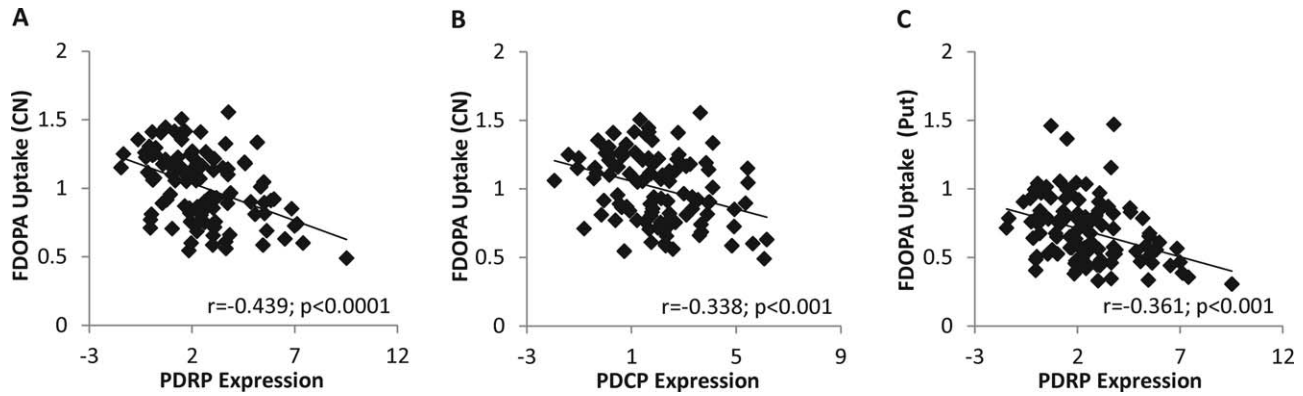

Figure 4.

Post hoc region-of-interest (ROI) validation of voxel-wise correlations between PDRP and PDCP subject scores with striatal FDOPA uptake. FDOPA uptake was measured in prespecified anatomical ROIs in the caudate nucleus (CN) and putamen (Put) (see Methods). FDOPA uptake in the CN was correlated with both PDRP (**A**) and PDCP (**B**) expression. In contrast, FDOPA uptake in the Put was correlated to PDRP expression only (**C**).

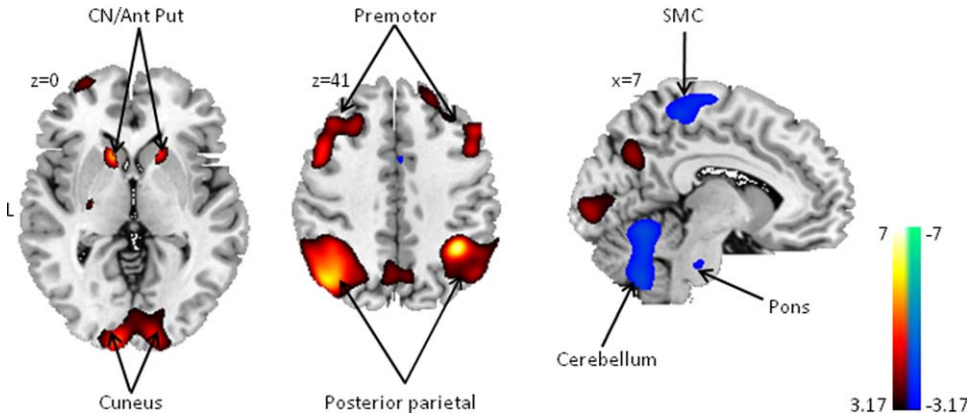

Figure 5.

Striatal FDOPA uptake correlated (*red*) with the normalized regional cerebral metabolic rate of glucose (rCMRglc) in the bilateral premotor and posterior parietal cortex including the cuneus, and the anterior putamen (Ant Put) and caudate nucleus (CN). Negative correlations (*blue*) between FDOPA uptake and normalized rCMRglc were observed in the pons, cerebellum and bilateral sensorimotor cortex (SMC). [Positive correlations are displayed in red, negative correlations in blue. The color stripe indicates the t-value; voxel threshold $P < 0.001$. Coordinates are displayed in Montreal Neurological Institute standard space.].

et al., 2007b]. Indeed, abnormal PDRP levels are observed in hemispheres contralateral to the clinically affected limbs of hemi-PD patients and in "prodromal" parkinsonian states such as rapid eye movement sleep behavior disorder [Holtbernd et al., 2014; Tang et al., 2010a; Wu et al., 2014]. The increase in PDCP expression seen with advancing disease tends to be smaller by contrast, lagging behind the PDRP by several years [Huang et al., 2007b; Tang et al., 2010a]. Although the current data set is cross-sectional, the finding of consistently lower PDCP scores in the individual subjects accords well with the slower rate of progression posited for this network [Eidelberg, 2009].

Parkinson's Disease Network Expression Correlates with but is Not Equivalent to Nigrostriatal Dopamine Denervation

In a previous longitudinal study of 15 early stage PD subjects scanned with FPCIT and FDG PET, we found a significant correlation between declining dopamine transporter binding in the caudate and putamen and increasing PDRP expression over time [Huang et al., 2007b]. Similarly, in a cross-sectional dual tracer study of 17 PD subjects, a significant relationship was seen between increases in PDCP expression and individual reductions in caudate dopamine transporter binding [Niethammer et al., 2013]. In both studies, the observed correlations were of modest size accounting for only 30–40% of the variance in these measures. In the current study of a much larger cross-sectional patient cohort, we found highly significant, but similarly modest correlations (R^2 ~10–20%) between these variables. In contrast to the weak correlation of PDRP expression with nigrostriatal dopaminergic innervations, a more intimate relationship was observed in PD between the activity of this network and subthalamic nucleus firing rates [Lin et al., 2008]. Thus, the abnormal PDRP elevations seen in these subjects are more indicative of disease-related changes in basal ganglia efferent activity, which is modulated by the subthalamic nucleus [Parent and Hazrati, 1995], as opposed to differences in striatal dopaminergic input. The emergence of elevations in PDCP activity may be attributable in part to alterations in other neurotransmitter systems, most importantly in cholinergic pathways [Hilker et al., 2005; Klein et al., 2010]. Moreover, the widespread alterations in cortical metabolism that characterize the PDCP topography may additionally reflect the development of Lewy body pathology in key network regions [Braak et al., 2003]. Taken together, these findings indicate that expression values for both PDRP and PDCP are correlated—but not interchangeable with simultaneously acquired measures of nigrostriatal dopaminergic function. Rather, the data suggest that these abnormal brain networks incorporate pathophysiological aspects of the disease that are not captured by presynaptic dopaminergic imaging alone [Niethammer and Eidelberg, 2012].

PDRP and PDCP Show Topographically Distinct Correlations with Striatal FDOPA Uptake

Correlations between PDCP values and presynaptic FDOPA uptake were most prominent in the "nonmotor" anterior striatum, particularly the caudate nucleus. By contrast, relationships with PDRP values were less well localized, with significant correlations in the anterior and posterior putamen, as well as the caudate. Nonetheless, when controlling for individual differences in PDCP expression, voxel-wise relationships with PDRP values

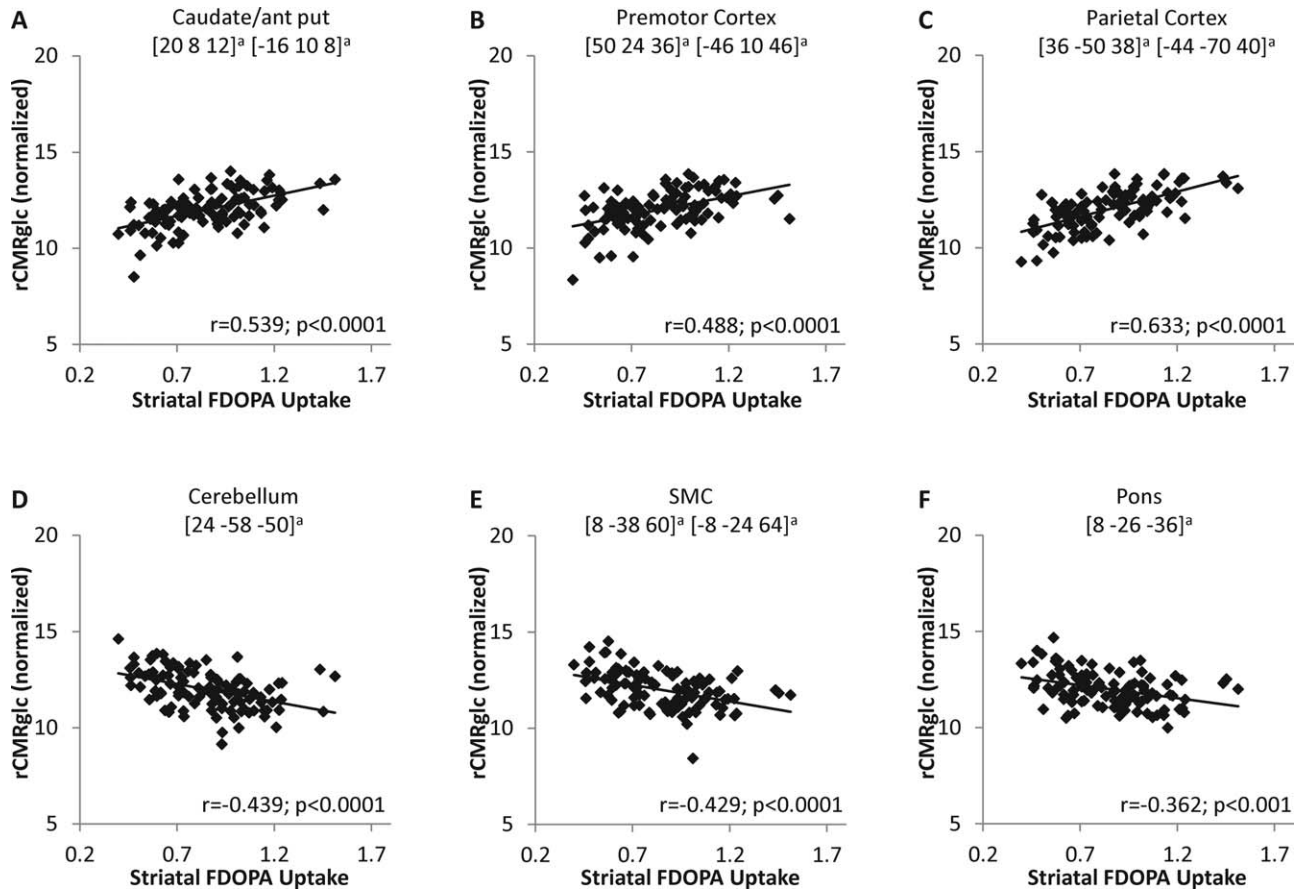

Figure 6.

For post hoc validation of correlational analyses between striatal FDOPA uptake, 5 mm spherical volumes-of-interest (VOIs) were placed, centered at the peak voxel of the major correlating clusters (see Fig. 5). For symmetric correlations, values of the normalized regional cerebral metabolic rate of glucose (rCMRglc) were extracted from the left and right VOIs and averaged. Significant correlations were confirmed at each cluster. [[a]Coordinates are displayed in Montreal Neurological Institute standard space.].

became more specific, with localization to the motor-related posterior putamen. These findings are in good agreement with published studies showing consistent correlations between cognitive dysfunction in nondemented PD subjects and caudate dopaminergic denervation [e.g., Carbon et al., 2004; Polito et al., 2012; van Beilen et al., 2008]. By contrast, motor impairment has been primarily associated with loss of putaminal dopaminergic function [Rinne et al., 2000; Weder et al., 1999]. Of note, the topography of the dopaminergic correlates of PDCP expression strikingly resembled analogous findings from a correlative FPCIT PET dopamine transporter binding study [Niethammer et al., 2013]. In that study, however, no correlation was observed between PDRP values and striatal dopaminergic integrity. This disparity was likely attributable to the incipient floor effect in the putamen seen with this radiotracer [Tang et al., 2010a] as well as the relatively narrow range of PDRP values evident in this small cohort [Niethammer et al., 2013]. By contrast, in addition to involving more subjects, the current PD sample was characterized by a broader range of putaminal FDOPA uptake values than prior PET studies. This was particularly evident in patients with early stage disease, in whom a relationship could now be discerned between PDRP expression and dopaminergic integrity of the posterior putamen.

Of further note, we did not observe significant relationships between PDRP/PDCP expression and presynaptic dopaminergic function outside the basal ganglia. FDOPA PET measures activity of the aromatic amino acid decarboxylase (AADC) responsible for the decarboxylation of L-dopa to dopamine. Thus, AADC is typically enriched in brain regions predominantly containing dopaminergic neurons such as the striatum. In these regions, FDOPA uptake provides accurate information about the integrity of the dopaminergic system. However, AADC is also

TABLE II. Brain regions exhibiting a significant correlation between striatal FDOPA uptake and regional brain metabolism

Correlation	Region	Cluster extend[a]	T max	Coordinates[b]
Positive	L CN/ant put	338	6.03	−16 10 8
	R CN/ant put	253	6.31	20 8 12
	L premotor (BA 8)	2117	5.09	−46 10 46
	R premotor (BA 9)	775	4.55	50 24 36
	L parietal (BA 39)	4019	5.98	−44 −70 40
	R parietal (BA 40)	1658	6.79	36 −50 38
	L cuneus (BA 17)	1595	5.09	−10 −100 −2
	R cuneus (BA 18)	[c]	[c]	14 −98 −4
Negative	Pons	30	3.32	6 −26 −36
	Cerebellum	2140	4.62	24 −58 −50
	L SMC (BA 6)	1054	4.30	−8 −24 64
	R SMC (BA 4)	[c]	[c]	8 −38 60
	R temporal (BA 22)	61	4.22	46 −16 −10
	R ACC (BA 24)	10	3.44	2 6 38

CN = caudate nucleus; ant put = anterior putamen; SMC = sensorimotor cortex; ACC = anterior cingulate cortex.
[a]The extend of each cluster is given as the number of voxels with the size of each voxel equalling $2 \times 2 \times 2$ mm^3.
[b]Coordinates are displayed in Montreal Neurological Institute standard space.
[c]Left and right sides were part of a single cluster.

enriched in brain regions containing serotonergic and noradrenergic terminals. Indeed, FDOPA PET can be used to accurately assess integrity of the serotonergic system in PD [Pavese et al., 2012]. Longitudinal FDOPA PET studies have also shown that serotonergic pathway integrity progressively declines in PD patients, and that change occurs independently of concurrent presynaptic dopaminergic terminal loss [Pavese et al., 2011]. Substantially lower AADC expression in cortical regions with concomitantly lower PET signal may explain why correlations were not found in these areas even after lowering the voxel threshold to a minimum ($P < 0.05$, uncorrected). Similarly, low cortical signal may be an important reason why prior efforts to quantify extra-striatal FDOPA uptake have relied almost exclusively on regional (ROI/VOI) as opposed to voxel-based methods [Gallagher et al., 2014; Kumakura et al., 2010; Pavese et al., 2011, 2012]. Thus, it may be predictive to use ROI-based methods to study relationships between network activity and FDOPA uptake in regions rich in serotonergic terminals.

Striatal Dopaminergic Depletion is Related to Metabolism in PDRP Regions

Although several studies have used dual tracer dopaminergic and metabolic imaging in PD, few directly explored the metabolic correlates of nigrostriatal denervation in PD at the voxel level [Berti et al., 2010; Kaasinen et al., 2006]. We observed a positive correlation between diminution in striatal FDOPA uptake and reduced metabolic activity in frontal and parieto-occipital association cortex and in the anterior putamen and caudate. By contrast, inverse relationships with striatal FDOPA reductions were observed in the ponto-cerebellar region and in the sensorimotor cortex bilaterally. In line with our findings, a correlation between decreased putaminal dopamine transporter binding and reduced prefrontal metabolic activity has been previously noted [Berti et al., 2010]. Interestingly, Polito and colleagues observed a similar association of frontal hypometabolism and caudate dopamine loss [Polito et al., 2012]. Of note, we found similar correlations between regional metabolism and caudate and putamen dopaminergic functioning, as would be predicted by the close correlation that was seen between uptake values in the two regions [Huang et al., 2007a].

Of note, we found that metabolic correlations with striatal FDOPA uptake were not restricted to frontal areas as previously reported [Berti et al., 2010; Polito et al., 2012]. Indeed, the overall spatial distribution of regions with significant correlations was strikingly similar to that of the PDRP topography. Interestingly, brain regions showing a positive metabolic correlation with striatal FDOPA uptake overlapped with underactive (blue) PDRP nodes while the regions with significant inverse correlations corresponded to the active (red) network regions. That said, there were also important differences between the pattern of regional correlations observed in the current study and the previously characterized PDRP topography. For example, significant correlations were evident between loss of striatal dopaminergic terminals and reduced metabolic activity in the caudate and anterior putamen—areas not generally considered to be part of the PDRP. That said, the posterior putamen/globus pallidus internus and ventrolateral thalamus, which correspond to major zones of metabolic overactivity within the PDRP, did not correlate (positively or negatively) with caudate or putamen dopaminergic function in the current dataset. It is likely that univariate voxel-based correlations, such as those identified with SPM and related methods, are most sensitive to monosynaptic relationships [Lin et al., 2008]. Thus, the metabolic concomitant of presynaptic loss of nigrostriatal dopamine projections would be most pronounced in target regions such as the striatum. Such voxel-wise correlations can be sensitive to the dispersion of the data, with reductions in the magnitude of correlation as one or the other measured variable approaches a limiting value. In PD, presynaptic dopaminergic markers have been found to exhibit incipient floor effects even at early disease stages with progressive declines in the dispersion of the measure as values approach the lower bound [Huang et al., 2007b]. Interestingly, significant correlations with increasing PDRP expression may paradoxically be discerned only in those parts of the striatum with relatively intact dopaminergic innervations (i.e., the caudate and anterior putamen) in which FDOPA uptake is typically far from the floor values. By contrast, less consistent univariate voxel-wise

correlations were observed between caudate/putamen dopaminergic denervation with local metabolic activity in downstream regions. As previously noted in a study of metabolic correlations with intraoperative subthalamic nucleus firing rate measures [Lin et al., 2008], such relationships are readily demonstrated for monosynaptic effects, but become progressively attenuated over multiple synapses. The absence of a significant correlation between caudate or putamen FDOPA uptake and metabolic activity in globus pallidus internus or thalamus is compatible with this idea. Indeed, as with correlations with subthalamic nucleus firing rate, the most robust relationships were with measurements of overall network activity as opposed to individual regional values.

Strengths and Limitations

A major strength of the study is the unique size of the study population, which allowed for the detection of subtle effects that may not have been observed in smaller samples. In this study, specific brain FDOPA signal was determined by the uptake ratio from a single frame [Jokinen et al., 2009; Ma et al., 2010], a simple parameter that performs similarly to rate constant estimates derived from graphical analysis of dynamic scan data [Dhawan et al., 2002].

That said, several methodological issues are noteworthy. Quantitative ratings of motor and cognitive dysfunction were not obtained systematically in members of this cohort. Thus, the data could not be used to evaluate relationships between the imaging measurements and the duration, severity, and subtype (e.g., predominance of akinesia-rigidity, tremor, or posture-gait disturbance) of clinical manifestations in a given PD subject. Moreover, patients and control subjects were not matched for age. In keeping with early observations [Eidelberg et al., 1993; Ishikawa et al., 1996], significant correlations between caudate/putamen FDOPA uptake and age were not seen in the current healthy volunteer group. That said, weak correlations between PD-related network expression and age have been noted previously in normal subjects [Moeller and Eidelberg, 1997; Tang et al., 2008].

To account for potential effects of healthy aging on PDRP expression in the current study population, we implemented an age correction based upon metabolic scans from a large, independent normal sample (see text). Notably, the major findings were not influenced by group differences in age or other demographic measures. Indeed, the findings remained highly significant whether or not PDRP values were adjusted for subject age.

CONCLUSION

In summary, the findings of this study substantially extend our knowledge on the relationship of dopaminergic and metabolic brain function in PD. In a uniquely large cohort of PD patients, we demonstrated a robust association between nigrostriatal dopaminergic loss and the activity of previously validated disease-related metabolic brain networks. Indeed, presynaptic dopaminergic dysfunction in the putamen correlated specifically with increased expression of the motor-related PDRP network. By contrast, in the anterior striatum, dopaminergic measures correlated with increased expression of this pattern as well as the cognition-related PDCP network. Separate voxel-wise correlations of striatal FDOPA uptake with metabolic activity over the whole brain disclosed a set of regions with significant positive and negative correlations that overlapped substantially with the PDRP topography. The modest magnitude of the observed correlations suggest that in PD, metabolic brain changes relate to nigrostriatal dopamine loss, as well as dysfunction in other transmitter systems.

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