**Supplemental Data**

**Supplemental Methods**

**Subjects**

We studied 28 PD subjects (20 men and 8 women; age 61.0 ± 9.6 (mean ± SD) years; duration 8.7 ± 9.6 years; baseline off-state Unified Parkinson's Disease Rating Scale (UPDRS) motor ratings 24.6 ± 6.8). The diagnosis of PD was made according to the United Kingdom (UK) Brain Bank Criteria for idiopathic PD (1). All subjects exhibited greater than 20% improvement in UPDRS motor ratings following a single oral dose of levodopa/carbidopa administered at the time of enrollment.

The PD subjects were divided into two groups based on whether dyskinesias were seen during the infusion. The NLID group comprised 14 subjects (10 men and 4 women; age 60.0 ± 9.9 years; duration 6.1 ± 5.0 years; UPDRS motor ratings 22.3 ± 7.8) who had stable responses to levodopa infusion (0.61 ± 0.25 mg/kg/h) that improved motor symptoms (change in UPDRS motor ratings 9.4 ± 4.6; 43.6 ± 19.0%) without dyskinesia. The LID group comprised the remaining 14 subjects (10 men and 4 women; age 62.0 ± 9.6 years; duration 13.1 ± 8.4 years; UPDRS motor ratings 26.9 ± 4.9), in whom levodopa infusion (0.83 ± 0.47 mg/kg/h) improved motor symptoms (change in UPDRS motor ratings 11.1 ± 4.2; 42.1 ± 16.8%) but produced sustained dyskinesias. The clinical characteristics of the LID and NLID subjects are summarized in **Supplemental Table 1**. The two groups did not differ significantly in age, gender, or baseline UPDRS motor ratings. Differences in estimated disease duration obtained from the subject directly or from the physician record were, however, significant ($p<0.02$; Student's *t*-test). The levodopa infusion rate and the mean change in UPDRS motor ratings during the infusion did not differ between groups ($p>0.15$).

Treatment-mediated CBF and CMR changes during levodopa infusion were compared to corresponding differences recorded in an independent control group consisting of eight PD subjects (4 men and 4 women; age 65.1 ± 9.1 years; UPDRS motor ratings 29.6 ± 13.8) who were scanned in two repeat PET sessions in a test-retest (TRT) paradigm. In each session, the subjects underwent dual-tracer PET imaging in which maps of CBF and CMR were concurrently acquired following their usual morning

dose of oral levodopa/carbidopa, without dyskinesia. The test and retest imaging sessions for each subject were separated by eight weeks.

For each PD group (LID, NLID, TRT), CBF and CMR values were compared to corresponding measurements from 14 healthy subjects (10 men and 4 women; age 60.7 ± 8.2 years) who underwent dual-tracer [$^{15}$O]-water ($H_2{}^{15}O$) and FDG PET in a single session. Limited data from 11 (8 NLID and 3 LID) of the 28 levodopa infusion subjects and from the TRT group have appeared previously (2).

**Positron emission tomography**

Infusion subjects fasted overnight and were off antiparkinsonian medications for at least 12 hours before undergoing dual-tracer imaging with $H_2{}^{15}O$ and FDG PET to map CBF and CMR at baseline (OFF) and during levodopa treatment (ON) in separate randomly ordered sessions over a two-day period (2). UPDRS motor ratings were obtained for each subject immediately prior to imaging. In each study, the levodopa infusion was individually titrated (mean infusion rate 0.72 ± 0.38 mg/kg/h) to maximal motor improvement for each subject (change in UPDRS motor ratings 10.8 ± 4.5; 44.8 ± 18.3%).

The scans were acquired in 3D mode using the GE Advance Tomograph (General Electric, Milwaukee, WI, USA) at The Feinstein Institute for Medical Research, Manhasset, NY, USA. Image processing was performed using SPM5 (Wellcome Department of Cognitive Neurology, University College, London, UK) implemented in Matlab 7.0.1 (MathWorks, Sherborn, MA, USA). The scans from each subject were realigned separately, spatially normalized, and smoothed with an isotropic Gaussian kernel (full width at half maximum (FWHM) 15 mm for $H_2{}^{15}O$ PET and 10 mm for FDG PET) to improve the signal-to-noise ratio.

**The Cologne Sample: Relationship between regional changes and local dopaminergic input**

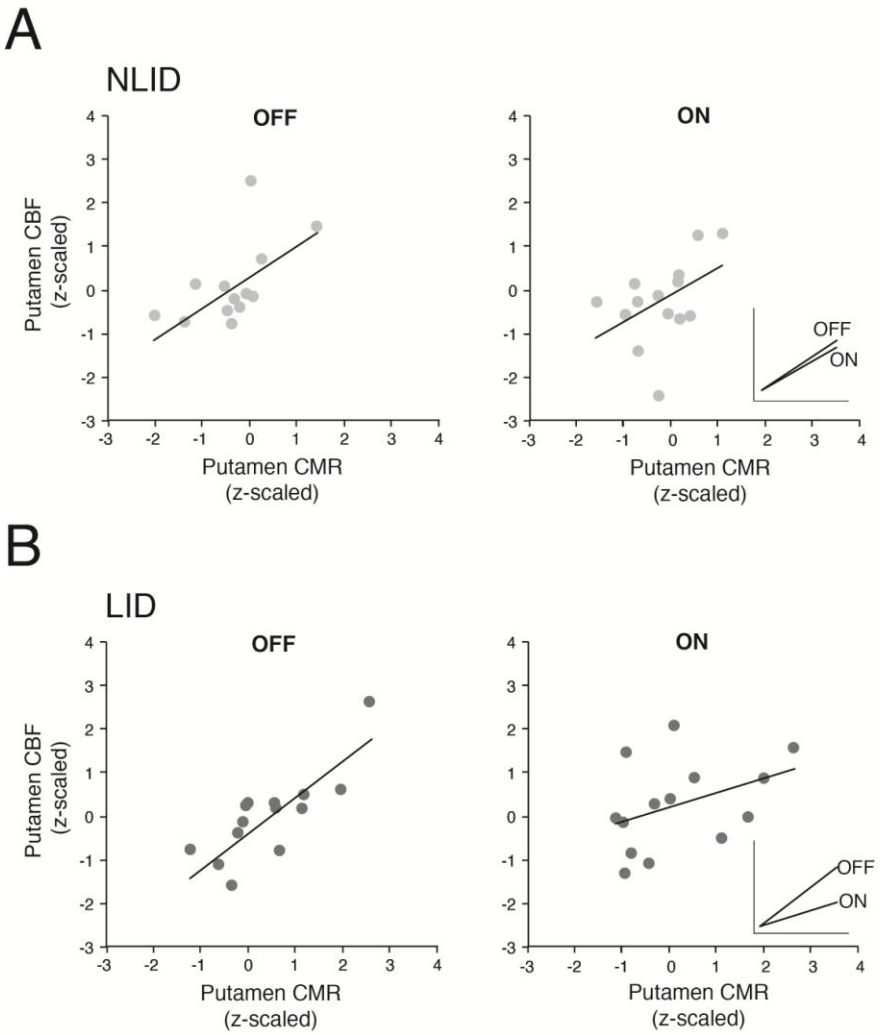
Because of radiation dosimetry constraints, it was not possible to perform additional imaging with FDOPA PET in the current patient sample. It was, however, possible to define VOIs corresponding to the areas identified as having significant levodopa-mediated CBF/CMR dissociation or significant baseline differences in these subjects and transfer the regions to co-registered FDOPA PET slices from a separate,

although clinically and demographically very similar, group of patients. To this end, we analyzed scans from 106 PD patients (68 men and 38 women; age 57.0 ± 11.3 years) who were studied with both FDOPA and FDG PET in the medication-free baseline state at Cologne University Hospital, Cologne, Germany. The details of the imaging studies in this group are provided in Supplemental Methods and elsewhere (3).

The PD subjects in the Cologne sample were divided into mild (Hoehn and Yahr stages 1-2; n=59: 38 men and 21 women; age 53.7 ± 11.4 years; duration 3.3 ± 2.8 years) and moderately advanced (Hoehn and Yahr stages 3-4; n=47: 30 men and 17 women; age 61.1 ± 9.7; duration 11.9 ± 6.2 years) groups. The clinical characteristics of the subjects in these groups are summarized in **Supplemental Table 2**. VOIs corresponding to the putamen, the region with the greatest levodopa-mediated dissociation effect in the Feinstein Institute sample, and the SMC, the region with the largest baseline difference between the Feinstein Institute LID and NLID subjects, were placed on co-registered FDOPA and FDG PET scans from the Cologne testing subjects. Radiotracer uptake values from this sample (3) were computed for the mild and moderately advanced PD patients, and for a group of healthy control subjects (FDOPA, n=10: 6 men and 4 women; age 48.1 ± 12.2 years; FDG, n=19: 13 men and 6 women; age 42.3 ± 13.9 years) scanned on the same tomograph.

For each region, local FDOPA uptake and CMR of the subjects in the mild and moderately advanced PD groups were each compared to corresponding healthy control subjects using Student's *t*-test. Differences between the mild and moderately advanced PD groups were also compared separately for the two regions using Student's *t*-test.

**Supplemental Figure**




**Supplemental Figure 1. Coupling and uncoupling: effects of levodopa on the relationship between cerebral blood flow and glucose metabolism in the putamen.** The relationship between cerebral blood flow (CBF) and cerebral metabolic rate for glucose (CMR) was assessed in the putamen dissociation region (Figure 1A) in the baseline unmedicated condition (*left*) and during levodopa infusion (*right*). (**A**) The NLID group showed a significant correlation (coupling) between putamen CBF and CMR values at baseline ($R^2$=0.31, p<0.04; Pearson correlation). The magnitude of this correlation ($R^2$=0.19, p=0.12) was reduced by treatment, with modest uncoupling of regional CBF and CMR values ($F_{(2,24)}$=3.84, p<0.04; Chow test) as reflected by the small change in the regression slope (*inset*). (**B**) In the LID group, putamen CBF and CMR values exhibited a strong baseline correlation ($R^2$=0.64, p<0.0007), which was attenuated by levodopa ($R^2$=0.16, p=0.16). Levodopa-mediated uncoupling was more pronounced in this group ($F_{(2,24)}$=12.40, p<0.0003; Chow test), as indicated by the flattening of the regression line during treatment (*inset*). [Putamen CBF and CMR values for each group were *z*-scored in the two treatment conditions. For standardized values, the slope of the regression line is proportional to the Pearson product-moment correlation coefficient. Thus, for each group, the magnitude of levodopa-mediated uncoupling is represented graphically by the change in the regression slope induced by treatment (*insets*).]

**Supplemental Tables**

**Supplemental Table 1. Demographic and clinical data: PD subjects (Feinstein Institute)**

| | NLID (±SD) | LID (±SD) |
|---|---|---|
| Age | 60.0 (9.9) | 62.0 (9.6) |
| Gender | 10M, 4F | 10M, 4F |
| Duration (years) | 6.1 (5.0) | 13.1 (8.4)* |
| UPDRS (motor), off-state | 22.3 (7.8) | 26.9 (4.9) |
| ΔUPDRS [%] | 43.6 (19.0) | 42.1 (16.8) |
| H&Y, off-state | 2.0 (0.7) | 2.3 (0.4) |
| LDD (mg/d) | 600.0 (274.7) | 472.9 (167.0) |
| LDD(w) (mg/kg/d) | 6.264 (2.62) | 6.382 (2.44) |
| LEDD (mg/d) | 752.1 (309.4) | 800.8 (294.6) |
| LEDD(w) (mg/kg/d) | 7.803 (2.79) | 10.628 (3.84) |

*$p<0.05$; Student's *t*-tests for comparison of LID vs. NLID.
LID: subjects with levodopa-induced dyskinesia
NLID: subjects without LID
UPDRS (motor): Unified Parkinson's Disease Rating Scale motor (Part III, off-state) (1)
H&Y: Hoehn and Yahr stage
LDD: levodopa daily dose
LDD(w): weight-corrected levodopa daily dose
LEDD: levodopa equivalent daily dose (4)
LEDD(w): weight-corrected levodopa equivalent daily dose

**Supplemental Table 2. Demographic and clinical data: PD subjects (Cologne University Hospital)**

| | Mild (±SD) | Advanced (±SD) |
|---|---|---|
| Age | 53.7 (11.4) | 61.1 (9.7)*** |
| Gender | 38M, 21F | 30M, 17F |
| Duration (years) | 3.3 (2.8) | 11.9 (6.2)*** |
| H&Y, off-state | 1.5 (0.5) | 3.5 (0.5)*** |
| LEDD (mg/d) | 308.9 (301.5) | 803.2 (376.3)*** |

***$p<0.001$; Student's *t*-tests for comparison of Mild vs. Advanced.
H&Y: Hoehn and Yahr stage
LEDD: levodopa equivalent daily dose (4)

**Supplemental References**

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