Selective defect of *in vivo* glycolysis in early Huntington's disease striatum

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Activity of complexes II, III, and IV of the mitochondrial electron transport system (ETS) is reduced in postmortem Huntington's disease (HD) striatum, suggesting that reduced cerebral oxidative phosphorylation may be important in the pathogenesis of neuronal death. We investigated mitochondrial oxidative metabolism *in vivo* in the striatum of 20 participants with early, genetically proven HD and 15 age-matched normal controls by direct measurements of the molar ratio of cerebral oxygen metabolism to cerebral glucose metabolism ($CMRO_2$/CMRglc) with positron emission tomography. There was a significant increase in striatal $CMRO_2$/CMRglc in HD rather than the decrease characteristic of defects in mitochondrial oxidative metabolism (6.0 ± 1.6 vs. 5.1 ± 0.9, $P = 0.04$). $CMRO_2$ was not different from controls (126 ± 37 vs. 134 ± 31 μmol 100 g^{-1} min^{-1}, $P = 0.49$), whereas CMRglc was decreased (21.6 ± 6.1 vs. 26.4 ± 4.6 μmol 100 g^{-1} min^{-1}, $P = 0.01$). Striatal volume was decreased as well (13.9 ± 3.5 vs. 17.6 ± 2.0 ml, $P = 0.001$). Increased striatal $CMRO_2$/CMRglc with unchanged $CMRO_2$ is inconsistent with a defect in mitochondrial oxidative phosphorylation due to reduced activity of the mitochondrial ETS. Because HD pathology was already manifest by striatal atrophy, deficient energy production due to a reduced activity of the mitochondrial ETS is not important in the mechanism of neuronal death in early HD. Because glycolytic metabolism is predominantly astrocytic, the selective reduction in striatal CMRglc raises the possibility that astrocyte dysfunction may be involved in the pathogenesis of HD.

cerebral metabolism | mitochondria | oxidative phosphorylation | basal ganglia

Huntington's disease (HD) is a degenerative neurological disease that is manifested by abnormal involuntary movements, psychiatric disorders, and dementia. It has a variable age at onset and progresses slowly to death 15–25 years after symptoms develop. HD is neuropathologically characterized by early selective loss of medium spiny neurons in striatum (caudate and putamen) with later neuronal loss in cortex, globus pallidus, and other structures. Although it is now known that an expansion of the triple repeat CAG in the IT15 gene on chromosome 4 leads to production of an abnormal polyglutamine string on the huntingtin protein, it is still unclear how this leads to selective neuronal cell death (1). In postmortem specimens from the striatum of patients with HD, reduced activity of the mitochondrial electron transport system (ETS) (29–76% decreases in complexes II and III and 30–62% decreases in complex IV) has been measured *in vitro*, although these findings have not been universal (2–6). These findings and the correlative effects of mitochondrial toxins in producing striatal neuronal loss in animal models suggest that excitotoxicity triggered by reduced ATP production as a consequence of impaired mitochondrial oxidative phosphorylation may be an important mechanism for neuronal death in HD (7). Alternatively, these mitochondrial changes may be a consequence, not a cause, of the pathologic mechanisms underlying neuronal loss in HD (8). The relationship between reductions in mitochondrial ETS complex activity and defects in oxidative metabolism and ATP generation is not straightforward. *In vitro*, a threshold effect has been described such that acute inhibition of 60–80% of complexes III and IV is required before oxygen consumption and ATP production are reduced (9). However, a recent study indicates that *in vitro* inhibition of complex I insufficient to reduce ATP production acutely may do so after a period of several days (10).

These observations demonstrate the considerable uncertainty in translating *in vitro* postmortem measurements of ETS activity to *in vivo* levels of mitochondrial oxidative phosphorylation. Previous studies of cerebral metabolism *in vivo* in HD have not addressed this issue. They have almost exclusively concentrated on measurements of glycolytic, not oxidative, metabolism, reporting early reductions in both the caudate and putamen (11–14). Only a single case study has reported measurements of striatal oxidative metabolism (15). If a defect in mitochondrial oxidative phosphorylation is important in the pathogenesis of neuronal loss in HD, it will be present early in the course of the disease when neuronal loss has just begun. To test this hypothesis, we directly measured the cerebral metabolic rate of oxygen ($CMRO_2$) and the cerebral metabolic rate of glucose (CMRglc) *in vivo* with positron emission tomography (PET) and compared striatal $CMRO_2$/CMRglc molar ratios between participants with HD and age-matched normal controls. A defect in mitochondrial oxidative phosphorylation will reduce $CMRO_2$. However, because the brain regulates metabolism to match energy demand, both $CMRO_2$ and CMRglc are reduced under any condition with diminished energy demand, such as barbiturate anesthesia (16). Specific defects in mitochondrial oxidative phosphorylation decrease $CMRO_2$ proportionately more than CMRglc (fewer moles of oxygen consumed per mole of glucose metabolized), thereby producing a reduction in the $CMRO_2$/CMRglc ratio below the normal value of 5.6 (17, 18).

Results

Participants. Twenty-five subjects with HD were initially enrolled. Complete studies were carried out in 20. Five did not successfully complete PET and MR studies because of technical problems.

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Abbreviations: CBV, cerebral blood volume; CMRglc, cerebral metabolic rate of glucose; $CMRO_2$, cerebral metabolic rate of oxygen; CSF, cerebrospinal fluid; ETS, electron transport system; ^{18}FDG, [^{18}F]fluorodeoxyglucose; HD, Huntington's disease; LC, lumped constant; PET, positron emission tomography; CBF, cerebral blood flow; OEF, oxygen extraction fraction.

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Table 1. Striatal metabolism and volume in early Huntington's disease and age-matched controls

Participant	*n*	$CMRO_2$/CMRglc	$CMRO_2$	CMRglc	Volume, ml	CBF	OEF
Normal controls	15	5.1 ± 0.9	134 ± 31	26.4 ± 4.7	17.6 ± 2.0	49 ± 8	0.37 ± 0.08
All HD	20	6.0 ± 1.6	126 ± 37	21.6 ± 6.1	13.9 ± 3.5	42 ± 11	0.40 ± 13
Pre-symptomatic HD	9	5.8 ± 1.6	143 ± 30	25.3 ± 3.3	15.5 ± 2.4	41 ± 14	0.48 ± 0.14
Early symptomatic HD	11	6.2 ± 1.7	111 ± 37	18.5 ± 6.3	12.7 ± 3.8	42 ± 9	0.33 ± 0.08
Control vs. all HD, *t* test		$P = 0.044$*	$P = 0.502$	$P = 0.016$	$P = 0.001$	$P = 0.052$	$P = 0.51$

$CMRO_2$ in μmol 100 g^{-1} min^{-1}; CMRglc in μmol 100 g^{-1} min^{-1}; CBF in ml 100 g^{-1} min^{-1}.
*Primary analysis.

The 20 participants with HD were ages 32–52 (mean 42). The number of CAG repeats was 39–52. There were 13 men and 7 women. Neurological evaluation revealed that 9 were without symptoms and 11 had had symptoms for 12–72 months. Thirty-three normal control subjects were initially enrolled in a combined study of HD and Parkinson's disease (see *Methods*). Ten did not successfully complete PET and MR studies: eight because of technical problems, one had an abnormal MR scan, and one withdrew after MR. From the 23 who successfully completed PET and MR studies, 15 were matched by age to the 20 participants with HD without reference to any PET or MR data. Their ages were 23–59 (mean 43) years. There were nine men and six women.

Mitochondrial Oxidative Metabolism. The primary analysis showed a statistically significant 17% increase in the striatal $CMRO_2$/CMRglc molar ratio in HD (Table 1). This increase is the opposite direction expected for defects in mitochondrial oxidative phosphorylation. Striatal $CMRO_2$ was not different between the two groups, whereas both striatal CMRglc and striatal volume were reduced by 20% in HD. Cerebral blood flow (CBF) and oxygen extraction fraction (OEF) were not different. Separate data for the presymptomatic ($n = 9$) and early symptomatic ($n = 11$) participants with HD are provided but should be interpreted with caution because of the smaller numbers involved.

Systemic physiological measurements were comparable between the participants with HD and the controls: pCO_2, 36 ± 3 vs. 36 ± 4 mmHg (1 mmHg = 133 Pa) ($P = 0.848$); pO_2, 91 ± 11 vs. 89 ± 16 mmHg ($P = 0.653$); arterial oxygen content, 17.9 ± 1.8 vs. 16.9 ± 1.8 ml 100 ml^{-1} ($P = 0.138$); and arterial plasma glucose, 4.71 ± 0.37 vs. 4.65 ± 0.34 μmol/ml ($P = 0.618$).

Bihemispheric measurements were comparable between the participants with HD and the controls: $CMRO_2$/CMRglc, 5.5 ± 1.2 vs. 5.5 ± 1.2 ($P = 0.925$); $CMRO_2$, 126 ± 28 vs. 125 ± 24 μmol 100 g^{-1} min^{-1} ($P = 0.925$); CMRglc, 23.1 ± 3.0 vs. 23.0 ± 4.2 μmol 100 g^{-1} min^{-1} ($P = 0.958$); and brain volume, 1,053 ± 116 vs. 1,063 ± 103 ml ($P = 0.802$).

Discussion

The hypothesis that patients with early HD have a defect in mitochondrial oxidative phosphorylation was tested by comparison of striatal $CMRO_2$/CMRglc molar ratios between participants with HD and age-matched normal controls. In addition to increased specificity for defects in mitochondrial function, the use of the $CMRO_2$/CMRglc ratio also removes any residual differences in measurements between the two groups due to partial volume effects from striatal atrophy in HD. We used a method that corrects for artifactual reductions in PET measurements due to partial volume effects from increases in ventricular and sulcal cerebrospinal fluid (CSF) volume in HD. It will thus produce accurate bihemispheric PET measurements in HD and will correct for the artifactual reduction in striatal PET measurements due to enlarged ventricles adjacent to atrophic caudate nuclei. The method does not correct for partial volume effects on the caudate and putamen from surrounding white matter (19, 20). These white matter effects will worsen with caudate and putaminal atrophy and, thus, could potentially result in a measured reduction in striatal $CMRO_2$ in HD when none actually exists. However, because the partial volume effect of surrounding white matter will be the same for $CMRO_2$ and CMRglc, the use of the ratio eliminates this problem. The $CMRO_2$ method that we have used has been validated for quantitative accuracy in nonhuman primates across a wide range of $CMRO_2$ (21, 22). Included in these validation studies were measurements during intraaortic sodium cyanide infusion, specifically demonstrating the accuracy of this technique to accurately measure a reduction in $CMRO_2$ under conditions of reduced mitochondrial ETS activity (22). In measuring CMRglc with [^{18}F]fluorodeoxyglucose (^{18}FDG), we explicitly assumed that the lumped constant (LC) value is the same for HD as it is for normal controls. In adults, the LC has been shown to change appreciably only in tumors or under conditions in which glucose delivery becomes rate limiting for glucose metabolism, e.g., during ischemia and hypoglycemia (23–26). In our participants with HD, neither ischemia nor hypoglycemia was present. Striatal CBF, OEF, blood-to-brain glucose transport (as measured by the rate constant k_1), and plasma glucose were all not different from controls. Thus, our assumption that the LC value is the same for HD as it is for normal controls is reasonable.

We measured a statistically significant 17% increase in the striatal $CMRO_2$/CMRglc ratio in early HD due to a 20% reduction in CMRglc with no detectable change in $CMRO_2$. An increase in striatal $CMRO_2$/CMRglc with unchanged $CMRO_2$ is inconsistent with a defect in mitochondrial oxidative phosphorylation because of reduced ETS activity. These results are unexpected in light of the reports of reduced mitochondrial ETS activity in postmortem striatal tissue from patients with HD. These postmortem studies measured reduced activity of mitochondrial ETS activity in gross tissue samples from both caudate and putamen indicating that, even if these defects are restricted to only a certain fraction of striatal cells, they are of sufficient magnitude to be detected in assays of the structures as a whole (2–5, 27). Our finding of preserved mitochondrial oxidative metabolism early in HD when neuronal loss is already manifest by striatal atrophy indicates that any defects in ATP production due to striatal ETS activity are either insufficient to impair oxidative phosphorylation or are not present early in the course of the disease (6, 9).

We did not measure any changes in bihemispheric CMRglc or volume as others have reported, most probably because of our intentional selection of patients early in the course of their disease (28). A single case study in a subject with clinically diagnosed hereditary HD who had had symptoms for 5 years reported reduced striatal $CMRO_2$ and CMRglc and $CMRO_2$/CMRGlc of 5.6 in the striatum (15). In this study, there were no control subjects with $CMRO_2$/CMRglc for comparison.

Our findings of reduced striatal CMRglc and atrophy agree well with previous reports (11–14, 28, 29). The measured reduc-

tion in striatal CMRglc cannot be due simply to residual uncorrected partial volume effects from white matter because it was not present to the same degree in the striatal $CMRO_2$ measurement. The reduction in CMRglc with preserved $CMRO_2$ indicates that there is a selective impairment of striatal glycolytic metabolism. In the brain, glycolysis is predominantly an astrocytic metabolic process, whereas oxidation is primarily neuronal (30, 31). Thus, a selective impairment of cerebral glycolysis suggests astrocytic dysfunction or death. Experimental animal systems have demonstrated a link between astrocytic dysfunction and excitotoxic neuronal death. Astrocytes play a prominent role regulating glutamate hemostasis by taking up synaptic glutamate. Dysfunction of astrocyte glutamate transport systems can lead to excitotoxic cell death due to excess extracellular glutamate (32). In the R6 transgenic mouse models of HD, mutant huntingtin accumulates in glial cells in association with reduced expression of glutamate transporters, decreased glutamate uptake, and excitotoxic neuronal death (33, 34).

The striatal $CMRO_2$/CMRglc in HD was 6.0, equivalent to the molar ratio for complete oxidation of glucose, whereas the ratio in the brain as a whole was normal. Under the normal resting conditions of this study, the $CMRO_2$/CMRglc ratio is 5.6 (35). ≈90–95% of glucose is completely oxidized and the rest is metabolized only as far as lactate (35). Thus, the mitochondria in HD striatum may be oxidizing a higher fraction than normal of metabolized glucose in the face of a reduced overall glucose metabolic rate, serving to maintain the absolute rate of oxidative glycolysis. This increase in fractional striatal glucose oxidation rate may be a compensatory response to maintain ATP levels. Alternatively, mitochondria my be oxidizing the normal 90–95% of the reduced amount of glucose that enters the glycolytic pathway with the remaining oxygen consumed by either uncoupling of oxidative phosphorylation or oxidation of another substrate.

Materials and Methods

Participants. ***HD.*** Participants with HD were recruited from the Washington University Movement Disorders Center and through the Huntington's Disease Society of America.

Inclusion criteria were:

1. Previous gene testing with more than 38 CAG repeats of one allele for IT15.
2. Self-reported symptoms either absent or present for duration of less than 4 years.

Exclusion criteria were:

1. Younger than 18 years old.
2. Major neurological or psychiatric disease other than HD or clinically significant lesions on brain imaging that was done before enrollment in the study.
3. Regular treatment or exposure in the last 6 months to neuroleptics, metoclopramide, alphamethyldopa, clozapine, olanzapine, quetiapine, flunarizine, cinnarizine, reserpine, amphetamines, MAO inhibitors, or other medications that might interfere with mitochondrial metabolism.
4. Currently taking chloramphenicol or valproic acid.
5. Ever having taken dopaminergic medications.
6. Anticholinergics, amantadine, CoQ10, selegiline, and Vitamins E and C must be discontinued for 30 days before entry into the study.
7. Diabetes mellitus treated by medications.
8. Pregnancy.

All underwent clinical neurological evaluation by movement disorder specialists and were assigned a duration of symptoms based on this examination.

Normal controls. Normal controls were recruited contemporaneously by public advertisement and from friends and spouses of patients. All underwent clinical neurological evaluation by a neurologist.

Inclusion criteria were:

1. Disease free by subject's own history including no history of migraine, childhood febrile seizures, or head trauma with loss of consciousness.
2. Taking no medication by subject's own history.
3. No signs or symptoms of neurological disease other than mild distal sensory loss in the legs consistent with age.
4. No pathological lesions on MR scan done for this study (see below). Mild atrophy and punctate asymptomatic white matter abnormalities were not considered pathological.

Exclusion criteria were the same as for the participants with HD.

Normal controls were recruited as part of a larger study including patients with Parkinson's disease and then retrospectively age matched to the patients with HD without reference to PET or striatal volume measurements.

Image Acquisition. High-resolution T1-weighted MR images were acquired with a Siemens Magnetom SONATA 1.5T scanner (Siemens Medical Solutions USA, Malvern, PA). A midsagittal scout spin-echo sequence was used to position the subject, and then a 3D MPRAGE sequence was acquired (TR/TE/TI = 1,900/3.93/1,100 ms, flip angle = 8°, 7:07 min, 128 × 256 × 256 matrix 1.25 × 1 × 1 mm voxels).

PET images were obtained in the 2D acquisition mode with a Siemens/CTI ECAT EXACT HR 47 PET scanner with participants lying supine in a quiet dark room. One radial arterial and one peripheral venous catheter were placed for arterial blood sampling and i.v. injection of radiotracers. Individual attenuation measurements were made with ^{68}Ga-^{68}Ge rotating rod sources. All PET measurements were made at rest with eyes closed. CBF data were acquired with a 40-sec emission scan after rapid injection of 50 mCi $H_2{}^{15}O$ in saline (36). Cerebral blood volume (CBV) data were acquired with a 5-min emission scan beginning 2 min after brief inhalation of 75 mCi of $C^{15}O$ (37). $CMRO_2$ and OEF data were acquired with a 40-sec emission scan after brief inhalation of 75 mCi of $O^{15}O$ (21). During these ^{15}O studies, arterial blood was withdrawn at 5 ml/min from the radial artery through narrow bore tubing to a lead shielded scintillation detector that measures positron emissions with 1-sec temporal resolution. These arterial blood radioactivity measurements were corrected for delay and dispersion in the tubing using previously determined parameters. The time shift between arrival of radioactivity in the sampled arterial blood and in the brain was determined during the $H_2{}^{15}O$ scan by the sudden increase in total coincidence events in the field-of-view as recorded at 1-sec intervals by the scanner. Arterial blood samples for measurement of pCO_2, pO_2, and oxygen content were collected and analyzed (Instrumentation Laboratory, Lexington, MA). Data for measurement of the cerebral metabolic rate of glucose were obtained after slow i.v. injection of 10 mCi of ^{18}FDG over 10–20 sec. Dynamic PET acquisition began with injection and continued for 60 min according to the following scheme: 16 30-sec frames, 8 1-min frames, 16 2-min frames, and 4 3-min frames. During this period, blood samples were frequently hand drawn from the arterial catheter and counted in a well counter. Arterial samples for plasma glucose determination were obtained just before, at the midpoint during, and at the end of the scan. The scanner was calibrated to the well counter for conversion of PET counts to quantitative radiotracer concentrations by using a cylindrical phantom. All PET emission scans were reconstructed with filtered back projection using the individual attenuation measurements and scatter correction with

a ramp filter cutoff at the Nyquist frequency, producing images with a resolution of 4.3 mm full width at half maximum.

Image Analysis. The MR image was segmented by first plotting histograms of the voxel intensities of cortical gray matter and ventricular CSF. The threshold intensity separating brain from CSF was chosen as the midpoint between gray matter and CSF peaks. Removal of voxels below this intensity and voxels not connected in 3-dimensions to a seed point within each brain removed most nonbrain voxels. Manual editing was required to remove external tissue where there was insufficient CSF to separate the brain (near sinuses, temporal lobes, eyes, and brainstem), and a single erosion followed by conditional dilation completed the tissue segmentation. The MR image was then edited manually to generate a region of interest encompassing both cerebral hemispheres by removing the cerebellum and brainstem. The brainstem was sectioned along a plane connecting the posterior commissure and the most inferior point of the interpeduncular fossa (38). The bihemispheric volume was determined from the number of voxels and the voxel volume size.

For each participant, the caudate and putamen regions of interest were outlined on the MR image. The following anatomic rules for identification of these regions were used. Medially and anteriorly, the putamen was defined on the coronal view. Where separation from caudate or nucleus accumbens by white matter was not clear, an arbitrary straight line was drawn laterally and inferiorly following the direction of the internal capsule on this section. Laterally, the claustrum was excluded whenever the external capsule could be partially or completely visualized. The tail of the caudate was excluded by reference to sagittal views. Medially and anteriorly, the caudate was defined on the coronal view. The medial border was defined by the edge of the lateral ventricle. Where separation from putamen by white matter was not clear, an arbitrary straight line was drawn laterally and inferiorly following the direction of the internal capsule on this section. In all cases, an investigator who was blinded to participant diagnosis manually traced these regions. The volume of each caudate and putamen for each participant was determined from the number of voxels within each structure and the voxel volume size. The sum of these four structures was calculated to yield a combined striatal anatomic volume.

The original segmented MR image plus the three ^{15}O PET images were coregistered to a composite 40–60 min ^{18}FDG PET image by using Automated Image Registration software (AIR; Roger Woods, University of California, Los Angeles, CA) (39). A binary tissue image was created from the original segmented MR image (voxel values of 1 representing brain and 0 representing nonbrain) and convolved to the 3D resolution of the PET images. This convolved tissue image defines the fractional tissue contribution for the measured PET activity in each voxel and was used to correct the radioactivity measurement in each PET image for partial volume effects due to nonbrain structures including CSF (20). Partial volume corrected mean counts were generated for the bihemispheric and combined striatal regions of interest for each of the three ^{15}O PET images and for the dynamic ^{18}FDG PET images. Corrected mean counts were converted to quantitative CBF, OEF, or $CMRO_2$ by using described methods (40).

For ^{18}FDG, a modified Marquardt parameter estimation routine was used to derive bihemispheric rate constants for each participant by using the partial volume corrected dynamic PET counts and arterial whole blood time–radioactivity curves. We used the standard three-compartment ^{18}FDG model (41). Five parameters were estimated: four rate constants (k_1, k_2, k_3, and k_4) and the time shift (T_0). The flux from compartment 2 to compartment 1 was treated mathematically as direct egress from the field of view. The value for the time shift between arrival of radioactivity in the sampled arterial blood and in the brain measured from the $H_2{}^{15}O$ scan was used as the starting value for this parameter. The volume of compartment 1 was fixed equal to the measured regional CBV. Bihemispheric ^{18}FDG uptake was calculated as $(Glc_{wb}/LC)[(K_1 \times k_3)/(k_2 + k_3)]$, where Glc_{wb} is the whole blood glucose concentration (μmol/ml) and $K_1 = CBV \times k_1$ (41, 42). Because the parameter estimation was based on whole blood time–radioactivity data, we used glucose concentrations of whole blood calculated as the plasma concentration $\times$ [1 $-$ (0.30 $\times$ hematocrit)] (42).

Fluorodeoxyglucose is an analog of glucose that is transported across the blood–brain barrier by the glucose transporter, initially metabolized by hexokinase and then not metabolized further. Because glucose and fluorodeoxyglucose are transported and metabolized to different degrees, it is necessary to apply a correction factor called the LC to convert ^{18}FDG uptake to CMRglc (41). Reported LC values range from 0.42 to 0.89 and are dependent on the actual methods used to compute ^{18}FDG uptake and CMRglc (43). For this study, we computed the LC that yielded a mean bihemispheric value for $CMRO_2$/CMRglc equal to the value of 5.6 that has been directly measured from arterial and jugular venous samples in normal adults ages 21–69 (44). For this calculation, we used our entire series of 23 normal control subjects ages 26–70 and calculated an LC = 0.64.

For calculation of striatal CMRglc, we used a different strategy designed to minimize measurement variability from methodological causes to maximize the ability to detect intergroup differences. The smaller size of the striatum increases the variability measuring its radioactivity compared with the hemispheres. As a result, the estimates of the rate constants derived from parameter estimation are subject to greater error. An alternative method for calculating regional CMRglc from ^{18}FDG uptake data is to use mean ^{18}FDG counts integrated from 40 to 60 min postinjection and a single set of rate constants (K_1, k_2, k_3, and k_4). By this time, most of the radioactivity is in the form of metabolized ^{18}FDG-6-phosphate, and the value for ^{18}FDG uptake is only slightly influenced by the rate constants used (45–47). We compared the four rate constants derived from bihemispheric parameter estimation in the 20 participants with HD and the 15 age-matched normal controls (see below) and found no difference (all $P > 0.4$). We therefore used the following mean values for the rate constants derived from all 35 participants in the calculation of striatal CMRglc: $k_1 = 2.36$, $k_2 = 0.25$, $k_3 = 0.16$, $k_4 = 0.012$ (all min^{-1}), and calculated $K_1 = CBV \times k_1$ by using the individual striatal measured regional CBV for each participant.

Statistical Analysis. The null hypothesis of no difference in striatal mitochondrial oxidative phosphorylation in patients with early HD was tested by comparison of striatal $CMRO_2$/CMRglc ratios between participants with HD and age-matched normal controls by two-sided unpaired t test with the criterion for statistical significance set at $P < 0.05$ (SPSS 12.0 for Windows; SPSS, Chicago, IL). We also performed secondary analyses of striatal $CMRO_2$, CMRglc, CBF, OEF, and striatal volume. These data, along with measurements of systemic physiology and bihemispheric PET and MR measurements, are presented with P values from two-sided unpaired t tests that are uncorrected for multiple comparisons. Assigning formal statistical significance to any differences is not possible, and these results have only been used to provide data for further interpretation of any changes in the striatal $CMRO_2$/CMRglc ratio. None of the data sets deviated significantly from the normal distribution (Kolmogorov–Smirnov test, all $P > 0.27$). Data are presented as mean $\pm$ SD unless otherwise noted.

This protocol received prior approval by the Washington University Human Studies Committee (Institutional Review Board). Informed consent was obtained for each subject.

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