PET Scan Investigations of Huntington’s Disease: Cerebral Metabolic Correlates of Neurological Features and Functional Decline

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Fifteen drug-free patients with early to midstage Huntington’s disease were evaluated with quantitative neurological examinations, scales for functional capacity, computed tomographic (CT) scans, and positron emission tomographic (PET) scans of $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$F-FDG) uptake. All patients had abnormal indices of caudate metabolism on PET scanning, whereas in patients with early disease indices of putamen metabolism and CT measures of caudate atrophy were normal. Indices of caudate metabolism correlated highly with the patients’ overall functional capacity ($r = 0.906; p < 0.001$) and bradykinesia/rigidity ($r = -0.692; p < 0.01$). Indices of putamen metabolism correlated highly with motor functions: chorea ($r = -0.841; p < 0.01$), oculomotor abnormalities ($r = -0.849; p < 0.01$), and fine motor coordination ($r = -0.866; p < 0.01$). Indices of thalamic metabolism correlated positively with dystonia ($r = 0.559; p < 0.05$). The data suggest that PET scanning with $^{18}$F-FDG is a sensitive measure of brain dysfunction in Huntington’s disease and that basal ganglia metabolism is highly correlated with the overall functional capacity of individual patients and with the degree of their motor abnormalities.


Huntington’s disease (HD) is a dominantly inherited neurodegenerative disorder characterized by progressive cognitive and motor deterioration. The clinical features and natural history of the disease have been carefully evaluated and defined. Early neurological signs include chorea, decreased fine motor coordination, and slowed saccadic eye movements [7, 11, 16, 26–29, 35]. Later signs include dysarthria, rigidity, bradykinesia, and dystonia [7, 11, 26–28, 35]. With progression, the patient’s ability to perform activities of daily living declines [4, 5, 26, 27, 29]. A number of standardized rating scales have been designed to quantify the motor and functional capacities in this disorder [7, 26, 27, 29, 35].

Pathologically, HD is characterized by marked neuronal loss in the caudate nucleus and putamen, with coexistent gliosis and astrocytic proliferation [3, 15, 33]. Little or no cortical abnormality has been observed [33]. The globus pallidus and thalamus are mildly affected as is the cerebellum [3, 6, 15].

With the advent of positron emission tomographic (PET) techniques for studying brain metabolism, it has been possible to investigate HD patients at various stages of their illness to determine the relationship between brain metabolism and the neurological features of the disease [12–14, 23]. Studies with PET have shown a marked reduction of caudate metabolism in patients with early HD who exhibit little or no atrophy as measured by computed tomography (CT) [13]. These earlier studies investigated patients treated with various pharmacological agents and did not attempt to correlate specific neurological and behavioral findings with brain glucose metabolism. We observed 15 unmedicated HD patients who were evaluated carefully by clinical and neuropsychological testing. We present here our findings on the physiological aspects of the illness. Another report on the results of neuropsychological testing is in preparation [2].

Methods

Fifteen patients with adult-onset HD, as determined by family history and physical examination, were examined at least
1 month after discontinuation of any medications. Over a 2-
day period, patients received: (1) a quantitative neurological
evaluation conducted by two or more investigators using a
previously designed scale [35]; (2) an evaluation of func-
tional capacity according to the Shoulson and Fahn scale
[29]; and (3) neuropsychometric testing (results to be
reported separately [2]). In addition, each patient had a CT
scan and PET scan using $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$F-
FDG).

The 15 HD patients (ages 25 to 60 years; average ± SEM:
40 ± 3 years) were compared with 14 normal controls (ages
25 to 65 years; average ± SEM: 37 ± 3 years). Patients
were in stages I, II, or III of the disease as defined by the
Shoulson and Fahn scale, a total functional capacity (TFC)
which assesses the patient's ability to be gainfully em-
ployed, to handle financial and domestic responsibilities, to
perform activities of daily living, and to be cared for at home
[29]. It is a 13-point scale with 13 indicating normal and 0
referring to patients who require total care. It is further sub-
divided into five stages: stage I (TFC 13–11), stage II (TFC
10–7), stage III (TFC 6–3), stage IV (TFC 2–1), and stage V
(TFC 0).

For PET studies, patients had an arterial line placed in the
radial artery of one arm and an intravenous line in the other
arm. $^{18}$F-FDG (5 to 10 mCi) was injected as an intravenous bolus while the patient was in a quiet, dimly lit room with minimal background noise, with eyes blindfolded and ears unplugged. Although sensory deprivation is known to affect glucose metabolism in normal subjects [18], these conditions were chosen because they were considered to provide the most reproducible scanning conditions among subjects. Plasma $^{18}$F-FDG curves were determined for each patient. Repeated 0.5-ml arterial samples were drawn over the first 45 minutes after injection according to the following proto-
ocol: injection to 2 minutes, one sample every 5 seconds,
then samples at 3, 4, 5, 6, 7, 12, 17, 22, 37, and 45 minutes.

The scans were obtained on a Cyclotron Corporation PET
4600A Scanner, which is a three-ring (2.2-cm center-to-
center spacing), five-slice, 96-detector ring tomograph. The
spatial resolution is 11 mm in the X-Y plane (within a trans-
axial slice) and 8.8 mm in the Z plane (along the central axis
of the scanner). Ten transaxial slices separated by approxi-
mately 5.5 mm with an orientation parallel to the cantho-
metal plane were obtained from the base of the cerebellum to
the top of the caudate nucleus. An additional five slices sepa-
rated by 11 mm were acquired to image the next 5 cm of
brain. The local glucose metabolic rate (ICMRglc) for each
region of brain was calculated according to previously de-
scribed methods [22, 31] using updated rate constants
[Mazzotta JC, personal communication, 1984].

Data from each scan were analyzed by a standard tech-
nique as described below. The slice corresponding to the 0-
degree Section, No. 8 or No. 9 from the CT atlas of Matsui
and Hirano [17], was analyzed in detail from each patient.
Cross-sectional histograms through (1) the caudate nucleus
(halfway between the rostral edge of the thalamus and the
frontal cortex anterior to the ventricles); (2) the putamen
(halfway between the caudate cross-section and the rostral
edge of the thalamus); and (3) the middle of the thalamus
(Fig 1). By inspection of the cross-sectional histograms, the
maximum glucose metabolic rate over the head of the cau-
date was observed in all the normal controls and in most of
the HD patients. Although caudate metabolism in some of
the HD patients was quite low, the location of the shoulder
on the cross-sectional histogram could be determined by cal-
culating the second derivative of the curve (Fig 2). Although
this method of determining caudate metabolism cannot cor-
rect for alterations in partial volume, it was found to be more
reproducible than values obtained from simple, visually
guided region-of-interest (ROI) measurements. This method
was also considered to be more accurate than the use of
standardized ROI programs, which do not correct for the
underlying caudate atrophy in HD. Values of caudate, puta-
men, and thalamus metabolic activity were taken as an aver-
age of data from a 1 × 3 pixel ROI (ROI = $\sum_{i=1}^{3} I_{CMRglc}$)
on a 64 × 64 pixel matrix reconstruction of the PET scan
data. Raw data from right and left cortex, caudate, putamen,
and thalamus were averaged in 10 patients and 10 controls
(Table 1). (Data from the first 5 HD patients and first 4
controls were not included in this latter analysis because they
were scanned prior to a series of modifications in our scanner
that affected absolute but not relative measures of glucose
metabolism.) The lack of metabolic change in HD cortex
compared with controls suggested that normalization of the
values of caudate, putamen, and thalamus to cortex at the
same levels was valid for subsequent analyses. Normalization
is frequently used in PET studies because it reduces the
overall variability of the measures [13, 14, 23]. Absolute
measures of metabolism from caudate, putamen, and
thalamus were normalized to the peak cortical activity (a 1 × 3
pixel [11 mm$^2$] ROI) determined on the same cross-
sectional histogram (see Fig 1). The normalized values will be
referred to as indices of metabolism. The ratio of caudate met-
abolism to putamen metabolism was also calculated for each
patient.

In this study, CT scans were evaluated using previously
described techniques [1, 25, 30, 32]. Both the frontal horn/
bicaudate diameter ratios (FH/CC) and the bicaudate diame-
ter/outer table diameter ratios (CC/OT) at the level of the
caudate were calculated as depicted in Figure 1.

PET and CT scan data were obtained and recorded sepa-
ately from the clinical information. Data from scans and the
clinical evaluations were entered into a computer for analy-
sis. The scan measurements were then compared between
the controls and HD patients using t tests. The non-
parametric clinical data were analyzed and compared to scan
data and to each other using Spearman rank correlation
coefficients. Parametric scan data were compared to other
scan data using Pearson product-moment correlation
coefficients. Data analysis was done using the Biomedical
Program Statistical Software (Alphaville, CA).

Results
All HD patients had demonstrable PET abnormalities
(Figs 2, 3). There were 5 stage I patients, 9 stage II
patients, and 1 stage III patient. Measurement of corti-
cal metabolism at the level of the caudate, putamen,
and thalamus in the HD patients did not differ
significantly from that in controls (see Table 1). In HD
patients as a population, the caudate and putamen met-
abolic activity was significantly decreased compared

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with controls. The thalamic metabolism in HD patients was not significantly different from control values, but when normalized to cortex as in Figure 1, thalamic/cortex ratios were significantly higher in HD patients than they were in controls (1.06 ± 0.14 standard deviations [SD] versus 0.94 ± 0.12 SD; p < 0.02, Student's independent t test).

Caudate and putamen indices of metabolism were highly correlated with the TFC of the patient (see Fig 3, Table 2). In the earliest stages of the disease, the caudate index in the HD patients fell just below the lowest index of the control group, and as a group, the stage I patients (TFC = 13–11) had significantly lower caudate indices than did the control group (p < 0.01). Putamen indices had a strong correlation with TFC, but in stage I patients the putamen indices did not differ significantly from those of the control group. Putamen indices for the stage II patients (TFC = 10–7) were clearly lower than those of controls (p < 0.01). The PET measures of caudate and putamen were correlated very highly with each other, but not with the thalamic indices. There was also no correlation between TFC and the thalamic indices of metabolism.

The quantitative neurological measures (chorea, both at rest and during stress), dysdiadochokinesia (evaluated by rapid finger tapping as well as alternating supination and pronation of the hands), abnormalities of saccadic eye movements, bradykinesia/rigidity, and dystonia were analyzed in detail (Table 3). Motor abnormalities were highly correlated with each other, ex-

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**Fig 1. Summary of positron emission tomographic and computed tomographic (CT) measures. Histograms of cross-sectional metabolic data (A) were obtained through the caudate (B), putamen (C), and thalamus (D). Indices of caudate, putamen, and thalamic metabolism were calculated by determining the peak values of metabolic data through the structures in question (open circles) normalized to the peak cortical activity at the same level (open triangles). (E) CT measures were also made: CC = the intercaudate distance; OT = the distance between the outer tables of the skull at the level of the caudate; and FH = the distance between the tips of the frontal horns at the level of the caudate. (LCMRG = local cerebral metabolic rate for glucose; CD = caudate; CX = cortex; PU = putamen; TH = thalamus.)**

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**Fig 2. Examples of computed tomographic (CT) (left) and positron emission tomographic (PET) (middle) scans on a series of cases ranging from normal (A) to stage III Huntington's disease (D). The CT and PET scans were taken at a level midway through the caudate and putamen. To the right of each PET scan is the cross-sectional histogram of metabolic data taken through the caudate (see legend for Figure 1 for method) as shown by the arrows on the PET scans. Note the decrease in caudate metabolism as the disease advances. (LCMRG = local cerebral metabolic rate for glucose; TFC = total functional capacity, see text for description of staging.)**
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Table 1. Glucose Metabolism in Cortex, Basal Ganglia, and Thalamus of Huntington's Disease Patients and Age-Matched Controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Controls</th>
<th>Huntington's Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At level of caudate</td>
<td>7.1 ± 1.8</td>
<td>6.5 ± 1.5</td>
</tr>
<tr>
<td>At level of putamen</td>
<td>6.5 ± 1.8</td>
<td>6.3 ± 1.4</td>
</tr>
<tr>
<td>At level of thalamus</td>
<td>6.6 ± 1.4</td>
<td>6.5 ± 1.2</td>
</tr>
<tr>
<td>Caudate</td>
<td>7.1 ± 1.2</td>
<td>2.8 ± 1.6</td>
</tr>
<tr>
<td>Putamen</td>
<td>7.1 ± 1.8</td>
<td>3.7 ± 1.7</td>
</tr>
<tr>
<td>Thalamus</td>
<td>6.1 ± 1.7</td>
<td>7.0 ± 1.2</td>
</tr>
</tbody>
</table>

*Values are from 10 controls and 10 Huntington's disease patients. Values from each area represent the raw data obtained from 1 × 3 pixel (11 mm²) regions of interest as described in Figure 1. p < 0.001 by two-tailed independent Student's t test.

ICMRglc = local cerebral metabolic rate for glucose; SD = standard deviation.

Discussion

Our data indicate that basal ganglia metabolism is clearly abnormal in HD and that the degree of metabolic abnormality is correlated both with the patients' overall TFC as well as with their neurological signs and symptoms. The TFC scale used in this study has been validated in prior studies of CT measures \([26, 27, 35]\) and in studies of the clinical progression of the disease \([26, 27, 35]\). This scale seems to be very sensitive to measures of early progression in the illness. Our study confirms previous CT studies of HD \([25, 30, 32]\) and provides evidence that metabolic measures in caudate are even more sensitive in early disease than are CT measures. Caudate metabolism is particularly sensitive to functional decline since even patients with the earliest forms of the disease had caudate metabolism below that of the lowest normal subject examined. In these patients with early HD, CT measures were normal. The presence of a relationship between functional capacity and caudate metabolism is further established by the strong correlation between TFC and verbal learning and memory, cognitive efficiency, and years.
Table 2. Spearman Rank Correlation Coefficients for the Relationships between Neurological Signs, PET Measures of ICMRglc, and CT Measures of Atrophy

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>PET Measure</th>
<th>CT Measure (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caudate</td>
<td>Putamen</td>
</tr>
<tr>
<td>Total functional capacity (n = 15)</td>
<td>0.906c</td>
<td>0.836c</td>
</tr>
<tr>
<td>Chorea at rest (n = 15)</td>
<td>-0.761c</td>
<td>-0.841c</td>
</tr>
<tr>
<td>Chorea with stress (n = 15)</td>
<td>-0.635a</td>
<td>-0.798b</td>
</tr>
<tr>
<td>Dysdiadochokinesia (n = 15)</td>
<td>-0.776c</td>
<td>-0.866b</td>
</tr>
<tr>
<td>Slowed saccades (n = 12)</td>
<td>-0.745b</td>
<td>-0.849b</td>
</tr>
<tr>
<td>Dystonia (n = 15)</td>
<td>-0.235</td>
<td>-0.497</td>
</tr>
<tr>
<td>Bradykinesia/rigidity (n = 15)</td>
<td>-0.592b</td>
<td>-0.690b</td>
</tr>
<tr>
<td>Age (n = 15)</td>
<td>-0.018</td>
<td>0.098</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.002.

PET = positron emission tomography; ICMRglc = local cerebral metabolic rate for glucose; CT = computed tomography; CC/OT = bicaudate diameter/outer table diameter ratio; FH/CC = frontal horn/bicaudate diameter ratio.

Table 3. Spearman Rank Correlation Coefficients for the Relationships between Various Motor Signs and Total Functional Capacity

<table>
<thead>
<tr>
<th>Motor Signs</th>
<th>Chorea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Rest</td>
</tr>
<tr>
<td>Total functional capacity</td>
<td>-0.841b</td>
</tr>
<tr>
<td>Chorea at rest</td>
<td>0.938b</td>
</tr>
<tr>
<td>Chorea with stress</td>
<td>0.696a</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0.656</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.002.

Table 4. Pearson Product-Moment Correlation Coefficients for the Relationships between Various Positron Emission Tomographic and Computed Tomographic Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Putamen</th>
<th>Thalamus</th>
<th>CC/OT</th>
<th>FH/CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate metabolism</td>
<td>0.786b</td>
<td>0.373</td>
<td>-0.863b</td>
<td>0.656a</td>
</tr>
<tr>
<td>Putamen metabolism</td>
<td>-0.018</td>
<td>-0.660a</td>
<td>0.378</td>
<td></td>
</tr>
<tr>
<td>Thalamus metabolism</td>
<td></td>
<td>-0.436</td>
<td>0.640a</td>
<td></td>
</tr>
<tr>
<td>CC/OTcc</td>
<td>-0.817b</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05.

**p < 0.002.

CC/OT = bicaudate diameter/outer table diameter ratio correlation coefficient; FH/CC = frontal horn/bicaudate diameter ratio.

after diagnosis. Also, there is a strong correlation between caudate metabolism and learning and memory [2].

The fact that in early HD caudate metabolism is affected more dramatically than is putamen metabolism reinforces the pathological information on patients with early disease that the disorder begins in the caudate nucleus (specifically the dorsal medial areas of caudate) and then progresses to the putamen [33]. Putamen metabolism is not as sensitive since there was overlap between stage I patients and the control group in this measure. That caudate and putamen metabolism were only mildly reduced in patients with early disease suggests that either the symptoms of HD begin soon after the onset of neuronal damage or that compensatory properties maintain or even increase metabolic activity in the remaining basal ganglia neurons.

Caudate metabolism was not as significantly cor-
related with motor abnormalities as was putamen metabolism. However, caudate metabolism was correlated very highly with putamen metabolism ($r = +0.786; p < 0.002$), and so the relative contributions of each are difficult to discern. Since the caudate nucleus receives its major inputs from association cortex and not from primary motor and sensory cortex [8], the lower correlations of caudate metabolism with motor variables are noteworthy. Thus, decreased caudate metabolism would likely reflect primarily impairment of cognitive and integrative functions and be less indicative of pure motor dysfunction. The high correlation of caudate indices of metabolism with TFC suggests that the cognitive dysfunction in HD influences TFC to a major extent. The disturbance in cognition may subserve a lowering of TFC. New learning correlated highly with both TFC and caudate metabolism [2]. However, there was a lack of correlation between cognitive and motor measurements [2]. Furthermore, multiple linear regression analyses suggest that caudate metabolism was the most important feature in determining TFC.

The high correlation of putamen metabolism with motor abnormalities may reflect the fact that the putamen receives input from sensory and motor cortex [8]. Multiple regression analyses further support this conclusion since putamen indices explained most of the variability in the motor features except for dystonia and bradykinesia/rigidity. Thus, dysfunction of putamen neurons would likely lead to poor motor coordination.

Thalamic activity was correlated with dystonia, and it is of interest that metabolic activity in this area was increased in the HD patients as a group compared with controls. Neuroanatomical and neurochemical information suggests that the caudate and putamen output cells project to the medial and lateral globus pallidus and substantia nigra pars reticulata [8]. These projections are primarily inhibitory and γ-aminobutyric acid–ergic (GABAergic) [20, 34]. The medial globus pallidus and substantia nigra pars reticulata neurons are also inhibitory and GABAergic, and project to the thalamus [20, 34]. Thus the increased thalamic metabolism in HD patients may represent a disinhibition of pallidothalamic and nigrothalamic pathways. Our data would suggest that excessive input to the thalamus from the globus pallidus and substantia nigra pars reticulata may contribute to dystonic motor abnormalities. We plan a future study of rigid and dystonic juvenile patients.

There have been other studies of PET scanning in HD [12–14, 19, 21, 23]. As previously described, we found a significant decrease in the glucose metabolic rate in the basal ganglia of patients with early disease while there was little or no caudate atrophy observed on CT scans. However, unlike previous authors [12, 14], we found less difference between the glucose metabolic rate of our patients with early disease and that of controls. In addition, we observed strong direct correlations between metabolic indices and the degree of functional or motor abnormalities in the patients. Others have studied at-risk persons and found altered metabolism in about one half of the subjects [12, 13]. Some of these patients have gone on to develop HD [12]. We are currently studying 40 at-risk persons prospectively but have found only minimal caudate changes to date. The studies in at-risk persons will help define further the relationship between the earliest metabolic changes and motor and cognitive decline.

In summary, PET measures of basal ganglia metabolism have reinforced our knowledge of basal ganglia anatomy, physiology, and pathology and suggest that such measures will be useful indicators of functional and clinical decline in HD patients. If subsequent at-risk studies confirm that there are significant metabolic changes before the onset of symptoms, then prophylactic therapy in conjunction with PET scanning may provide a useful measure of therapeutic agents. Such measures will be particularly important since the new data describing a DNA marker linked to the HD gene will soon allow the diagnosis of HD in presymptomatic patients [9, 10].

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References