Huntington disease (HD) is an autosomal dominant disorder caused by an expansion of the CAG repeat in the IT15 gene, leading to progressive impairments in motor, cognitive, and psychiatric domains after a preclinical period. Mutation carriers are exposed to mutant huntingtin from conception, but in previous studies no evidence was found of caudate nucleus atrophy on pathologic examination1 or to distinguish the receptor state and function of some preclinical mutation carriers (PMC) from healthy controls.2 Knowledge of the time course of neuronal impairment and clinical disease is lacking and a biologic marker of this process could facilitate testing putative neuroprotective strategies.3

In this imaging study, part of an ongoing longitudinal program, we characterize in vivo striatal biochemical and structural changes in PMC.

Methods. Subjects who had been presymptomatically tested for the HD mutation at Groningen or Leiden University Medical Center were asked to participate. Mutation carriers were defined as having 36 or more CAG repeats in the IT15 gene. Those with a normal test result could participate as controls. To improve statistical power, mutation carriers were overrepresented among eligible study subjects. Inclusion criteria were: age 18 years or older and classified to be free of HD signs as indicated by a score of 0 or 1 (meaning no or nonspecific motor abnormalities or soft signs) on the Unified Huntington’s Disease Rating Scale (UHDRS) scale of clinical confidence.4 We excluded five subjects with signs of CNS disease, use of neuroleptics, pregnancy, or contraindications for MRI; three withdrew without giving a reason. Twenty-seven PMC and 14 controls were enrolled (table 1). The institutional ethics committee approved the study and all subjects gave written informed consent. The principal investigators (JCHvO, KLL) were blinded to the results of genetic testing and scans were anonymized before analysis.

MRI studies were performed on a 1.5 Tesla MRI scanner, acquiring three-dimensional gradient echo (three-dimensional MP-RAGE) images with 1.5-mm contiguous slices of the entire brain. A single trained investigator (JCHvO) identified contours of putamen and caudate nucleus on each transversal slice. Approximate structure volumes were then calculated.

Subjects were scanned with one Siemens ECAT Exact HR+.scanner (Siemens Erlangen, Germany) and data were processed using the SPM99 software package (Wellcome Department of Cog- nitive Neuroscience, London, UK). After spatial normalization to whole brain of the dynamic scans, we aligned the later frames and placed regions of interest (ROI) bilaterally on caudate, putamen, cerebellum, and multiple regions throughout the brain using an automated template. The same ROI template was applied to both racipride (RAC) and fluorodesoxyglucose (FDG). For RAC-PET, binding potentials (BP) were computed with the cerebellum as a reference region. For each striatal ROI, we calculated relative glucose metabolic index (GMI) with the mean of all regions as a reference. We used blood samples and multiple time graphic analysis (Gjedde-Patlik) to compute “absolute” striatal cerebral metabolic rates of glucose (rCMRglu) for these regions.

Please see appendix E-1 for additional information on methods and statistics (available on the Neurology Web site at www.neurology.org).

Results. Data of 41 PMC (27 PMC, 14 controls) were available for analysis, but were incomplete for 11 scans (four FDG, four MRI, three RAC) in 10 subjects. None of the study subjects revealed the result of genetic testing. PMC had significantly reduced values for GMI, volume, and RAC-BP of putamen and caudate. We defined normal imaging results as within mean –2 SD in controls and found normal striatal values for MRI in 88%, for FDG in 67%, and for RAC in 50% (figure 1, and table E-1). The absolute striatal cerebral metabolic rate of glucose was 31.1 in PMC and 34.7 in controls (p = 0.09).

The chance of any mutation carrier to develop HD in the near future increases with age and CAG repeat length; the product of these factors (AGE × CAG) predicts striatal damage in HD.5

Striatal RAC-BP markedly decreased as a function of AGE × CAG in PMC (R² = 0.52, p < 0.0001 (table 2 and figure E-1). Striatal GMI did not decrease (p = 0.09) with increasing AGE × CAG. Although striatal volume did decrease with mounting AGE × CAG, this was also seen in controls. We found a decrease in striatal volumes with age, both in PMC (R² = 0.20, p = 0.027, slope for linear fit −0.079) and in controls (R² = 0.49, p = 0.0077, slope −0.084).

From the Movement Disorder Unit, Department of Neurology, (Drs. Van Oostrom, Maguire, and Leenders, L. Veenma-Van Der Duin), Department of Clinical Genetics (Dr. Verschuuren-Bemelmans), and PET Center (Dr. Pruim), Groningen University Medical Center, Groningen; and Department of Neurology (Dr. Roos), Leiden University Medical Center, Leiden, The Netherlands.

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Address correspondence and reprint requests to Dr. K.L. Leenders, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands; e-mail: k.l.leenders@neuro.umcg.nl

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We calculated the ratio of striatal RAC-BP over FDG-GMI and over volumetry values. We then related these ratios to the AGE/H11003CAG product. With increasing AGE/H11003CAG, we found decreasing RAC-BP/GMI ratios (R2 = 0.46, p < 0.0005) and RAC-BP/volume ratios (R2 = 0.22, p = 0.03; figure E-2). Thus, reductions in RAC-BP turn out to outweigh those in FDG-GMI or volume with rising AGE/H11003CAG.

**Discussion.** Blinded for genetic test results, we studied 27 PMC without signs of clinical motor disease and 14 controls. We found indications of lower striatal dopamine D2 receptor availability (with RAC-BP), glucose metabolism (with FDG-GMI), and anatomic MRI volumes in PMC. However, the majority of PMC still showed normal imaging results. This is evidence against a gradual decline of imaging variables from birth on and suggests a nonlinear or biphasic course of HD activity, as noted previously in studies with PET and MRI.6

RAC-BP was the most sensitive imaging modality with 50% of PMC showing decreased values; it also showed the highest correlation with AGE × CAG, a measure of cumulative disease load. Moreover, changes in dopamine D2 receptor availability with increasing AGE × CAG are relatively larger than those in glucose metabolism or volume, indicating that changes in function as measured by BP-RAC exceed the changes caused by atrophy as measured by brain volume.

Controls were older than PMC (45 vs 39 years, p = 0.08 by rank sum test). Because many imaging variables decrease with aging,7 any age-related bias would lead us to underestimate differences between both groups.

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**Table 1 Demographic and genetic characteristics of study subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preclinical mutation carriers</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>39 ± 6.6 (29–56)</td>
<td>45 ± 11.6 (26–64)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>CAG repeats (range)</td>
<td>43 ± 2.4 (40–47)</td>
<td>20 ± 4.5 (17–34)</td>
</tr>
</tbody>
</table>

Values are means ± SD, unless indicated otherwise.

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**Table 2 Correlation of imaging data with the product of age and CAG repeat in preclinical Huntington disease mutation carriers**

<table>
<thead>
<tr>
<th>Imaging variable</th>
<th>Correlation with AGE × CAG (R²)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG-GMI putamen</td>
<td>0.13</td>
<td>0.09</td>
</tr>
<tr>
<td>FDG-GMI caudate</td>
<td>0.059</td>
<td>0.25</td>
</tr>
<tr>
<td>FDG-GMI striatum</td>
<td>0.099</td>
<td>0.14</td>
</tr>
<tr>
<td>RAC-BP putamen</td>
<td>0.43</td>
<td>0.0005</td>
</tr>
<tr>
<td>RAC-BP caudate</td>
<td>0.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RAC-BP striatum</td>
<td>0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Volume putamen</td>
<td>0.26</td>
<td>0.011</td>
</tr>
<tr>
<td>Volume caudate</td>
<td>0.16</td>
<td>0.050</td>
</tr>
<tr>
<td>Volume striatum</td>
<td>0.26</td>
<td>0.012</td>
</tr>
</tbody>
</table>

R² for linear fit, with analysis of variance. Values for putamen and caudate are calculated means of left and right regional values. Striatal RAC and FDG is the calculated mean of putamen and caudate; striatal volume is sum of putamen and caudate volume.

AGE × CAG = product of age and CAG repeat length; FDG = fluorodeoxyglucose; GMI = glucose metabolic index; RAC = 11C-raclopride; BP = binding potential.

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**Figure.** Preclinical carriers of the HD mutation show decreased striatal glucose metabolism (A), dopamine D2 receptor availability (B), and volumes (C). Dashed line indicates mean –2 SD in controls. Volumes in milliliters.
We used manually determined measures of MRI volumes. Possibly, computer-driven methods for MRI volumetry are more sensitive, but to our knowledge these methods have not been compared.

Both RAC-BP and FDG-GMI are corrected for uptake in reference regions and thus are insensitive to global changes affecting the brain (e.g., aging). Changes in our striatal volumes (which represent absolute measures of space) may reflect “normal” brain atrophy with increasing age. This could explain the negative correlation of striatal volumes with AGE × CAG in controls (figure E-1).

HD remains an incurable disease, but testing in animal models may suggest new disease modifying substances. A reliable biomarker would greatly facilitate judging their value in humans, both in terms of duration and size of trials. PET scanning with $^{11}$C-raclopride gives an indication of dopamine D2 receptor availability and is considered to reflect progressive changes in striatopallidal projection neurons in both presymptomatic and clinical HD. Neuropathological examination shows a reduction of D2-positive cells from the earliest stage on. We found RAC to be a more sensitive detector of changes in brain of PMC than FDG or volumetry. RAC-BP/GMI ratio decreased significantly with increasing exposure to mutant huntingtin, supporting superiority of RAC as an indicator of neuronal dysfunction in PMC subjects. This gap between relatively preserved glucose metabolism as opposed to reduction of D2 receptor availability in preclinical HD striatum may reflect selective depletion of a small subpopulation of D2 receptor bearing cells, whereas the effect on total striatal glucose consumption is small. Alternatively, these findings may indicate neuronal dysfunction preceding cell death. This would imply reversal of some of the dysfunction is possible, as an animal model suggested.

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