Putamen Hypertrophy in Nondemented Patients With Human Immunodeficiency Virus Infection and Cognitive Compromise

J. Mimi Boer Castelo, MA; Maureen G. Courtney, MA; Rebecca J. Melrose, MA; Chantal E. Stern, DPhil

Background: Documented death and dysfunction of basal ganglia cells in patients seropositive for human immunodeficiency virus (HIV) suggest that the virus may cause structural compromise to these regions.

Objectives: To examine subcortical volumes in nondemented patients seropositive for HIV (HIV+) by means of a novel automated neuroanatomic morphometric analysis tool, and to investigate relationships among cognitive function, immune health, and subcortical volumes.

Design and Setting: Cross-sectional study of subcortical morphometry and cognitive function conducted at the Boston University Center for Memory and Brain and the Massachusetts General Hospital Athinoula A. Martinos Center for Biomedical Imaging.

Patients: Twenty-two nondemented HIV+ patients and 22 age- and education-matched healthy control participants.

Main Outcome Measures: Subcortical segmentation volumes, neuropsychological performance, and immunological variables.

Results: Nondemented HIV+ patients demonstrated relative and isolated putamen hypertrophy compared with control participants. Putamen volume enlargement in HIV+ patients was related to motor slowing and immune status, such that higher CD4 lymphocyte levels were associated with larger putamen volumes. There were no other subcortical volume differences between the groups.

Conclusions: This study suggests that basal ganglia hypertrophy accompanies HIV-related mild cognitive compromise. These findings may represent a structural imaging parallel to functional imaging studies demonstrating basal ganglia hypermetabolism in HIV+ patients with mild cognitive compromise and early HIV-associated brain disease.

Arch Neurol. 2007;64(9):1275-1280

The basal ganglia (BG) and hippocampus are selectively vulnerable to the human immunodeficiency virus (HIV). Several studies document BG atrophy in late-stage HIV infection and patients with HIV dementia, but the patterns of subcortical volume change in early stages of the illness remain unclear. Although there is evidence of BG atrophy in nondemented patients with HIV, other studies of patients who are seropositive for HIV (HIV+ patients) in asymptomatic disease stages and with motor dysfunction fail to replicate these findings. The variability in cognitive assessment methods of HIV+ patients and definition of neuroanatomic regions of interest (ROIs) contributes to the inconsistency of the findings across studies.

The purposes of this study were to examine whether subcortical regions undergo volumetric changes in HIV+ patients without dementia and to expand on previous studies in 3 ways. First, we sought to examine the structural integrity of the hippocampus and BG with higher spatial resolution than many of the previous studies (1- vs 3- to 5-mm section thickness). Second, participants were screened for HIV-associated dementia and HIV-related opportunistic infections to enable examination of subcortical structures in the absence of clinically confounding conditions. Third, volumetric analyses were implemented using an automated neuroanatomic labeling tool not previously applied in HIV populations that relies on magnetic resonance imaging (MRI) signal intensity and spatial positioning of sub-cortical regions.
cortical structures compared against a probabilistic atlas.9 Furthermore, this method enables segmentation of the hippocampus, putamen, caudate nucleus, and globus pallidus separately to examine structural changes specific to individual structures (Figure 1) and has been validated as a tool sensitive to anatomic variability that may exist in clinical populations.9 We conducted neuropsychological testing and correlated the results with volumes to examine relationships between cognitive and structural change.

We predicted that volumetric change would be evident in the hippocampus and BG regions, based on their vulnerability to HIV-related neuropathologic features and evidence suggesting that striatal structures show structural compromise in HIV.4-6 In addition, we predicted that volume changes would correlate with neuropsychological performance in HIV+ patients.

METHODS

PARTICIPANTS

Twenty-two HIV+ patients (HIV group) and 22 healthy control participants seronegative for HIV (control group) were recruited from clinical centers in the Boston area. Exclusionary criteria for all subjects included a history of head injury with loss of consciousness, neurological illness, psychiatric illness other than depression or anxiety disorders, history of substance abuse or use within the past month, and history of intravenous drug use. Past drug use was assessed through participant self-report and was equated across the groups, with 11 of 22 controls and 10 of 22 HIV+ patients reporting past recreational drug use. Additional exclusionary criteria for the HIV group included any opportunistic infections of the central nervous system or a score on the HIV Dementia Screening Scale indicative of dementia.10 Seventeen HIV+ patients were receiving stable antiretroviral medication, 2 were not currently taking antiretroviral medication, and medication status was unavailable for 3. Five HIV+ patients and 1 control participant were taking psychotropic medications. The Centers for Disease Control and Prevention staging system was implemented to characterize severity of HIV disease in our patients.11 The CD4 lymphocyte counts and the presence of specific HIV-related conditions were recorded to determine the Centers for Disease Control and Prevention disease stage. The immunological characterization for both groups is given in Table 1.

All participants were administered a neuropsychological battery (Table 1). Measures that are sensitive in detecting early HIV-related cognitive impairments were administered to examine attention, memory, processing speed, and motor speed12; performance on the National Adult Reading Test was used to estimate verbal intelligence.13 The following 4 cognitive composite scores were computed for this analysis: attention and executive functioning (Trail Making Test B and FAS verbal fluency), psychomotor speed (Trail Making Test A and Wechsler Adult Intelligence Scale III processing speed index), memory (California Verbal Learning Test I learning trials 1-5, immediate and delayed recall; Wechsler Memory Scale III verbal paired associates learning trials 1-5 and delayed recall), and motor speed (dominant and nondominant grooved pegboard and finger tapping tasks).

Structural imaging was conducted at the Massachusetts General Hospital Athinoula A. Martinos Center for Biomedical Imaging in Charlestown, and neuropsychological data were collected on the Boston University campus. Before participation in the study, subjects signed consent forms approved by the Partners Human Research Committee (which oversees human research at the Athinoula A. Martinos Center for Biomedical Imaging) and the Boston University institutional review board.

MAGNETIC RESONANCE IMAGING

Anatomical data were acquired on a 3.0-T scanner (Siemens Trio; Siemens, New York, New York). Two high-resolution T1-weighted magnetization-prepared rapid gradient echo images...
were obtained from each participant (resolution, 1.3×1.3×1 mm; echo time, 3.45 milliseconds; repetition time, 2530 milliseconds; inversion time, 1000 milliseconds; flip angle, 7°; field of view, 256×256 mm; matrix, 192×256). These settings were empirically optimized for high gray matter–white matter and gray matter–cerebrospinal fluid contrast.

MRI ANALYSIS

The methods for attaining volumetric measures of subcortical brain structures have been published previously.9 Two high-resolution anatomic images were motion corrected, averaged, and intensity normalized to create a single high-signal, high-contrast volume for each participant. After registration to a Talairach atlas to calculate intracranial volume, the skull was stripped and a brain mask was created in which the labeling occurred. The specific labels were created using an automated subcortical labeling algorithm based on a probabilistic atlas derived from a manually labeled training set.9 This analysis method automatically assigns a neuroanatomic label to each voxel in an MRI volume based on signal intensity information, as well as relative spatial positioning of the voxel, as determined by comparison with a manually derived probabilistic brain atlas. This technique is superior in sensitivity and accuracy of neuroanatomic labeling to methods that rely solely on tissue signal intensity information. Because there is significant overlap in signal intensities between different tissue classes (cortical gray matter and white matter overlap by more than 12%), relying on not only tissue signal but also spatial information contributes to the sensitivity and accuracy of tissue classification and structure determination.9 The normalization and registration techniques have been validated as sensitive to anatomic variability and ventricular enlargement that may accompany neurological disease and aging.9,14 Motion correction, the averaging of 2 high-resolution anatomic images per participant, and visual inspection of all labeled volumes ensured accurate segmentations. Subcortical volumes were corrected for total brain volume.

STATISTICAL ANALYSES

Four ROIs were examined: the hippocampus, caudate nucleus, putamen, and globus pallidus. To correct for multiple comparisons, a statistical threshold equal to P≤.013 (.05 divided by 4) was enforced. We conducted independent-sample t tests to examine between-group differences in subcortical volumes, corrected for brain volume, and neuropsychological performance (Table 1). Stepwise linear regressions were implemented to examine the extent to which immunological health (CD4 lymphocyte count per microliter), cognitive function, age, and education affected subcortical volume changes in HIV+ patients. Regression models were only implemented to examine these relationships for subcortical volumes that differed significantly between groups. Cognitive composite scores (attention/executive function, psychomotor speed, motor speed, and memory) were computed in the following manner. First, all raw scores were computed to z scores based on published normative data. The z scores for the tests in a given cognitive category were then averaged to compute 1 composite score per person. To avoid potential colinearity among the cognitive variables, all composite scores were included in the stepwise regression models simultaneously. This ensured that shared variance between cognitive composite scores was accounted for within a single statistical model. The subcortical ROIs were entered as dependent variables, and each of the 4 composite cognitive scores, age, education, and CD4 lymphocyte count were submitted as independent variables in the stepwise linear regression model. Statistical analyses were performed using SPSS, version 11.0.4 statistical analysis software for Macintosh (SPSS Inc, Chicago, Illinois).

RESULTS

BEHAVIORAL RESULTS

The results of independent t tests to examine group differences in neuropsychological performance and demographic variables are given in Table 1. Age, education, and estimated premorbid verbal intelligence (as determined by the mean±SD National Adult Reading Test score; control group, 117.9±5.7; HIV group, 117.3±7.0) did not differ between groups. The HIV group demonstrated a lower performance on the following measures: Wechsler Adult Intelligence Scale III processing speed index (t = 2.31 [P = .03]), semantic fluency (animal naming; t = 2.08 [P = .04]), and finger tapping (nondominant hand; t = 2.6 [P = .01]). There was a trend toward attentional compromise in the HIV group, as assessed by the Brief Test of Attention (t = 1.9 [P = .07]). Once the individual neuropsychological tests were z transformed and averaged to compute the 4 cognitive composite scores, only the motor speed composite score was significantly lower in the HIV group (t = 2.3 [P = .03]), and there was a trend toward slower processing speed in the HIV group (t = 1.9 [P = .07]).
MRI RESULTS

Brain volume did not differ between groups ($t=0.55 \ [P= .59]$) and therefore permitted a valid group comparison using brain volume–corrected subcortical volumes. The results of independent $t$ tests to examine group differences in subcortical ROI volumes are given in Table 2. The only ROI that demonstrated a significant between-group difference was the putamen, which was larger in the HIV group relative to the control group. When corrected for multiple comparisons, only the hypertrophy of the right putamen in the HIV group maintained significance, with the left putamen hypertrophy considered a statistical trend (right, $t=-2.6 \ [P=.01]$; left, $t=-2.0 \ [P=.05]$). There were no significant between-group differences in volumes of the hippocampus, caudate nucleus, or globus pallidus. There were no subcortical volume differences in individuals with past drug use compared with those with no past drug use, both collapsed across HIV status and in the HIV group only (data not shown).

Table 2. Subcortical Volume Measures

<table>
<thead>
<tr>
<th>Region</th>
<th>Volume, mm$^3$</th>
<th>Control Group</th>
<th>HIV Group</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1145 845</td>
<td>11 120 934</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>(124 592)</td>
<td>(174 687)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>1 562 761</td>
<td>1 571 541</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>(29 956)</td>
<td>(35 408)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>3540 (654)</td>
<td>3556 (408)</td>
<td>.30</td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>1794 (129)</td>
<td>1753 (188)</td>
<td>.93</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>4012 (550)</td>
<td>4070 (468)</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>5346 (534)</td>
<td>5504 (638)</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>3586 (603)</td>
<td>3665 (456)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>1819 (187)</td>
<td>1894 (304)</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>4223 (616)</td>
<td>4242 (440)</td>
<td>.35</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>5046 (812)</td>
<td>5310 (578)</td>
<td>.01</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviation: HIV, human immunodeficiency virus.

*Based on results of independent-sample $t$ tests after volumes were corrected for brain volume.

To assess the extent to which immunological health (CD4 lymphocyte count), cognitive function, age, and education affected subcortical volume changes in the HIV group, we conducted planned stepwise linear regression analyses. In the first model, age, education, CD4 lymphocyte count, and the 4 cognitive composite scores (attention/executive function, psychomotor speed, motor speed, and memory) were submitted as independent variables, and left putamen volume was the dependent variable. The overall model was statistically significant ($R^2=0.31 \ [F=8.12; \ P=.01]$). The CD4 lymphocyte count was the only variable that entered the regression model ($\beta=0.56 \ [P=.01]$). The $\beta$ weight indicates that, in the HIV group, hypertrophy of the left putamen is associated with higher CD4 lymphocyte levels (Figure 2). The same analysis was conducted with right putamen volume as the dependent variable, and this regression model was also significant ($R^2=0.25 \ [F=6.10; \ P=.02]$). The motor speed cognitive composite score was the only variable that entered the regression model ($\beta=−0.50 \ [P=.02]$). The $\beta$ weight indicates that, in the HIV group, hypertrophy of the right putamen is associated with lower scores on neuropsychological measures of motor speed (ie, motor slowing; Figure 2).

COMMENT

The goal of this study was to use precise and sensitive morphological segmentation techniques to examine subcortical volumes in nondemented HIV+ patients. Use of a segmentation procedure that not only relies on MRI signal intensity information but also compares spatial information of brain voxels$^5$ showed that nondemented HIV+ patients with motor slowing demonstrate hypertrophy of the putamen compared with age- and education-matched control participants. There were no other significant subcortical volume differences between the groups.

The present findings may reflect a structural imaging parallel to early positron emission tomography studies$^{15-16}$ that documented hypermetabolic processes in nond-
demented HIV+ patients. Basal ganglia hypermetabolism is evident in HIV+ patients with subclinical neurological dysfunction or mild cognitive impairment. As HIV disease progresses into a state of severe cognitive impairment or HIV dementia, BG hypometabolism is observed. These functional imaging studies provide support for the interpretation that putamen hypertrophy reflects HIV-mediated processes in the BG during a period of mild cognitive compromise, characterized only by motor slowing. Although we did not examine patients in later disease stages, previous studies suggest that, as disease states progress, BG atrophy may be evident. Although the exact etiology of enlarged putamen volumes observed in HIV+ patients remains unclear, a few possible mechanisms may be discussed. First, putamen hypertrophy may be a result of inflammation in the BG. The neuropathogenesis of HIV is characterized by brain inflammation instigated by HIV viral proteins. In vitro studies demonstrate that expression of inflammatory markers are directly involved in the neuropathogenesis of HIV dementia and that, even after the introduction of highly active antiretroviral therapy, there is ongoing detectable neuroinflammation in BG. Inflammatory activity in the BG may be a marker of neurological progression from asymptomatic to symptomatic disease stages in HIV.

The observed putamen hypertrophy in HIV+ patients may also be related to dysfunction of dopaminergic systems caused by HIV. Striatal enlargement has been observed in other clinical populations with dopaminergic system dysfunction, including schizophrenic patients undergoing long-term treatment with neuroleptic medications and abusers of cocaine and methamphetamine. A dopaminergic-based mechanism may elucidate why BG volumetric changes were observed, but hippocampal volumes did not differ between groups. Further investigation between BG volumes and dopaminergic function is warranted to confirm such a relationship.

We observed that motor slowing and higher CD4 levels in HIV+ patients were associated with enlarged putamen volumes. The relationship between altered BG structural integrity and motor slowing is well documented, supporting the interpretation that the underlying mechanisms of putamen hypertrophy may also mediate motor slowing. The paradoxical relationship between CD4 counts and putamen volume is more difficult to interpret because higher CD4 counts signal stronger immune health. Antiretroviral medications can have neurotoxic effects, which may explain why HIV+ patients with higher CD4 lymphocyte counts and motor slowing. These findings may represent a structural imaging parallel to functional imaging studies demonstrating BG hypermetabolism in HIV+ patients with mild cognitive compromise and early HIV-associated brain disease that becomes hypometabolic with disease progression.

We used a new segmentation technique to observe enlarged bilateral putamen volumes in a group of non-demented HIV+ patients with cognitive compromise. Putamen hypertrophy was associated with higher CD4 lymphocyte counts and motor slowing. These findings may represent a structural imaging parallel to functional imaging studies demonstrating BG hypermetabolism in HIV+ patients with mild cognitive compromise and early HIV-associated brain disease that becomes hypometabolic with disease progression.

Accepted for Publication: April 11, 2007.
Correspondence: J. Mimi Boer Castelo, MA, Center for Memory and Brain, Boston University, 2 Cummington St, Room 109, Boston, MA 02215 (mboer@bu.edu).

Author Contributions: Study concept and design: Castelo, Courtney, Melrose, and Stern. Acquisition of data: Castelo, Courtney, and Melrose. Analysis and interpretation of data: Castelo, Courtney, Melrose, and Stern. Drafting of the manuscript: Castelo and Stern. Critical review of the manuscript for important intellectual content: Castelo, Courtney, Melrose, and Stern. Statistical analysis: Castelo and Courtney. Obtained funding: Castelo, Melrose, and Stern. Administrative, technical, and material support: Stern. Study supervision: Stern.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants F31 NS054570, F31 NS052126, and R01 NS40239 from the National Institutes of Health, grant RR14075 from the National Center for Research Resources, and grant P50 MH071702 from the National Institute of Mental Health.

Additional Contributions: Members of the Boston University Cognitive Neuroimaging Laboratory, especially Alex Oleinik, BA, and Karin Schon, PhD, provided helpful assistance in data analysis. Members of the Athinoula A. Martinos Center for Biomedical Imaging, especially Bruce Fischl, PhD, and Jenni Pacheco, MA, provided development of and assistance with the methods used in this study. We thank our subjects for their participation.

REFERENCES


©2007 American Medical Association. All rights reserved.


Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of Archives of Dermatology (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.