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# The Relationship of Quantitative Brain Magnetic Resonance Imaging Measures to Neuropathologic Indexes of Human Immunodeficiency Virus Infection

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**Objective:** To directly examine the relationship between magnetic resonance imaging (MRI) abnormalities and neuropathologic changes in the brains of patients with the acquired immunodeficiency syndrome.

**Design:** A total of 17 brains from patients with acquired immunodeficiency syndrome for which postmortem MRI scans were available were used in this study. Volumes of cortical gray matter, deep gray matter, and abnormal white matter were estimated from the MRIs of the left hemispheres of the formalin-fixed brains from patients with acquired immunodeficiency syndrome using quantitative morphometric techniques. Quantitative estimates of human immunodeficiency virus, gliosis, and neocortical synaptic and dendritic density were obtained from the corresponding right hemispheres. Quantification of human immunodeficiency virus and gliosis was performed on all 17 specimens, while quantification of synaptic and dendritic density was performed on 10 of the 17 specimens.

**Setting:** All specimens were obtained from patients with

the acquired immunodeficiency syndrome who underwent autopsy between 1990 and 1992 at the University of California–San Diego Medical Center and the San Diego (Calif) Department of Veterans Affairs Hospital.

**Results:** No association was found between MRI volumes and gliosis, a nonspecific marker of central nervous system damage. Significant and regionally specific relationships were obtained, however, between the severity of central nervous system human immunodeficiency virus infection and the MRI volume estimates of gray matter and abnormal white matter. In addition, a significant association was observed between cortical gray matter volumes and cortical synaptic density.

**Conclusion:** These findings indicate that the quantitative morphometric analysis of MRIs in patients may provide sensitive in vivo markers of neuropathologic changes associated with human immunodeficiency virus infection of the brain.

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**A**QUIRED immunodeficiency syndrome (AIDS) has been associated with a variety of neurologic complications,<sup>1</sup> including a constellation of cognitive, motor, and behavioral deficits termed the *AIDS dementia complex*.<sup>2</sup> Although neurologic disturbances in patients with AIDS can result from a number of opportunistic infections and neoplasms, the AIDS dementia complex has been particularly associated with a subacute encephalitis caused by primary human immunodeficiency virus (HIV) infection of the brain.<sup>3,4</sup> Human immunodeficiency virus has repeatedly been detected within multinucleated giant cells and macrophages in the brains of patients with AIDS.<sup>5-7</sup> Consistent with the "subcortical" nature of the cognitive deficits seen in the AIDS dementia complex, HIV and gliosis have been localized most

frequently in the white matter and deep gray matter (DGM) regions of the brain. Neocortical damage has also been demonstrated in AIDS brains,<sup>8,9</sup> with loss of neurons and synapses related to the amount of HIV in the brain.<sup>10</sup>

Cranial magnetic resonance imaging (MRI) of patients with AIDS has demonstrated patterns of brain abnormalities that correspond to neuropathologic changes seen at autopsy.<sup>11-13</sup> Both white matter lesions and cerebral atrophy (ie, sulcal and ventricular enlargement) have been noted on the MRIs of neurologically symptomatic HIV-infected patients. Primary HIV infection appears to be associated with large, bilateral

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See Materials and Methods  
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## MATERIALS AND METHODS

A total of 17 brains with postmortem MRI scans were available for this study (**Table 1**). All specimens were obtained from patients with AIDS who underwent autopsy between 1990 and 1992 at the University of California–San Diego Medical Center and the San Diego Department of Veterans Affairs Hospital. Five of the patients were also participants in the University of California–San Diego HIV Neurobehavioral Research Center. Each brain was bisected sagittally into left and right hemispheres. The left half was fixed for 1 to 2 weeks in 20% formalin before MRI analysis. The right hemisphere was dissected and portions were fixed in 2% paraformaldehyde; the remainder was used for neuropathologic analyses.<sup>10</sup>

### PATHOLOGIC ANALYSIS

#### Quantification of HIV and Gliosis

After fixation, blocks of tissue from midfrontal and temporal CGM, cortical white matter (CWM), and DGM (including inner and outer globus pallidus and putamen) were embedded in paraffin and studied for the presence of gliosis and HIV. Gliosis was assessed by immunocytochemical staining for glial fibrillary acidic protein (GFAP) (Dako Corp, Carpinteria, Calif) and scored from 0 through 3 as follows: 0, no difference in immunocytochemical staining from seronegative controls; 1, thin glial processes dispersed among a histologically unremarkable neuropil; 2, glial cells with well-defined processes stained for GFAP; and 3, glial cells with abundant somal GFAP staining and thick and abundant processes within a histologically perturbed neuropil. Only areas without evidence of other opportunistic infections were assessed for gliosis. Levels of HIV antigen expression were assessed with an immunocy-

tochemical technique for HIV envelope protein gp41 (mouse monoclonal antibody from Genetic Systems, Seattle, Wash), and were scored on a scale from 0 through 2 as follows: 0, no cells stained for gp41; 1, fewer than two cells stained for gp41 in an average of five  $\times$ 20 fields; and 2, more than two cells stained for gp41 in an average of five  $\times$ 20 fields. This compressed scale was chosen to ensure maximum interobserver reliability. All assessments were done blindly and independently by two authors (C.L.A. and C.A.W.), followed by simultaneous viewing and resolution of any discrepancies.

#### Quantification of Neocortical Dendritic and Synaptic Damage

Sensitive neurohistologic assessment using laser confocal immunomicroscopy for synaptic and dendritic markers requires that autopsy brains be removed less than 24 hours after death and that tissue blocks be immediately dissected and fixed in 2% paraformaldehyde. Using these inclusion criteria, 10 of the 17 brains were available for this analysis. Forty-micron-thick sections of the frontal cortex were double immunolabeled with a polyclonal antibody against the dendritic marker anti-microtubule-associated protein 2 (MAP-2) (Sigma Chemical Co, St Louis, Mo) and the monoclonal antibody against the synaptic marker synaptophysin (Boehringer Mannheim Corp, Indianapolis, Ind) as previously described.<sup>10</sup> Double-immunolabeled sections were imaged with a laser scanning confocal microscope (MRC 600, BioRad, Watford, England). Digitized images (0.5  $\mu$ m thick) were transferred to a microcomputer (Macintosh IICI), running the public domain program of Wayne Rasband (Image 1.2.3). The threshold of immunolabeled dendritic and presynaptic areas was set, and areas were quantified and expressed as a percentage of the total image area. Four optical sections in each of three

areas of diffuse deep white matter (DWM) abnormality (seen as regions of high-signal intensity on T<sub>2</sub>-weighted images) along with smaller lesions in the basal ganglia. Focal lesions on MRIs, in contrast, are more often associated with toxoplasmosis or other nonviral infections and lymphoma. In a study comparing postmortem MRIs of formalin-fixed brains with the neuropathologic changes seen at autopsy, Grafe et al<sup>14</sup> concluded that while MRI was insensitive to HIV-infected microglial nodules (eg, the primary pathologic features of HIV) because of their microscopic size, MRI was capable of detecting the secondary changes (eg, cerebral atrophy and abnormal white matter [AWM]) associated with HIV infection. Although most studies have relied on subjective clinical ratings to assess MRI abnormalities in patients with AIDS, a recent investigation using a quantitative morphometric analysis of MRIs<sup>15</sup> was able to demonstrate significant reductions in cerebral gray and white matter volumes (along with a corresponding increase in cerebrospinal fluid [CSF] volume) in medically symptomatic HIV-infected patients compared with asymptomatic patients and low-risk noninfected control subjects.

In the present investigation, quantitative brain MRI morphometric techniques and quantitative immunocytochemical analyses were combined for direct examination of the relationship between MRI abnormalities and

neuropathologic changes in patients with AIDS. Volumes of cortical gray matter (CGM), DGM, and AWM were estimated from the postmortem MRIs of the left hemispheres of formalin-fixed AIDS brains, while quantitative estimates of HIV, gliosis, and neocortical synaptic and dendritic density were obtained from the corresponding right hemispheres. If HIV infection is directly involved in the formation of the MRI abnormalities in patients with AIDS, then the level of HIV in the brain should be significantly associated with the quantitative MRI measures, particularly those involving the white matter and DGM regions. In addition, if the CGM volume reduction observed on MRI<sup>15</sup> reflects the neocortical damage observed at autopsy,<sup>10</sup> then decreased CGM volume should also be significantly related to decreases in neocortical synaptic or dendritic density.

## RESULTS

### NEUROPATHOLOGIC FINDINGS

As an estimate of total cerebral damage, a composite gliosis score was computed by summing the individual GFAP scores across the three cerebral regions (ie, CGM, CWM, and DGM). Total cerebral damage was considered

vibratome sections were analyzed, for a total of 12 measurements for each case. Standardized immunocytochemical, immunocytochemical, and immunoelectron microscopic quantitative assays for detection of synaptophysin,<sup>16-18</sup> in combination with experimental studies in the denervated rat,<sup>19,20</sup> validated these techniques as fast and highly reproducible alternatives to estimate synaptic populations in the human and rodent brain.

## IMAGE ANALYSIS

After fixation, each specimen was drained of formalin and then scanned using a standardized imaging protocol. Magnetic resonance imaging was performed on a 1.5-T superconducting magnet (Signa, General Electric, Milwaukee, Wis) at the University of California–San Diego/American Medical International Magnetic Resonance Institute. Two spatially registered images (**Figure 1**) were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (repetition time, 3000 milliseconds; echo times, 30 and 80 milliseconds) to obtain images of the entire hemisphere. The contiguous sections were 4 mm thick, and a 256×256 matrix and a 24-cm field of view were used. For the following discussion of image analysis, the term *pixel* will be used to refer to a single picture element (or signal value) from the image matrix. The term *voxel* will be used to refer to the corresponding three-dimensional volume from which the signal value for a pixel arises.

The formalin-fixed hemispheres were analyzed with the same quantitative morphometric techniques previously developed for use with *in vivo* brain MRIs.<sup>21-24</sup> Briefly, each pixel location within a section of the imaged brain is classified on the basis of its signal values in both original images (echo times, 30 and 80 milliseconds) as most resembling CSF, gray matter, white matter, or signal hyperintensity. (Although no CSF was present in these fixed speci-

mens, the signal characteristics of residual formalin resembled those of either CSF or signal hyperintensities.) This classification is accomplished in two steps. First, two new linear combinations of the pixel values are computed to optimize tissue contrast (CSF/brain and gray/white). Classification criteria, adjusted separately for each section based on white matter tissue values, are then applied to these computed values. The full series of images is analyzed to sample the entire hemisphere. Trained operators then use a stylus-controlled cursor on these "pixel-classified" images to manually delineate the following DGM structures: caudate nuclei, lenticular nuclei, and diencephalon.

Volume of the fixed hemisphere was estimated by summing all gray matter, white matter, and tissue hyperintensity voxels over all sections. Formalin voxels (ie, voxels that were classified either as CSF or as nontissue hyperintensities) were not included in the volume estimate. Cortical gray matter volume, caudate volume, lenticular volume, and diencephalic volume were each estimated by summing the gray voxels pertaining to each structure over all sections. Deep gray matter volume was estimated by combining the caudate, lenticular, and diencephalic volumes. Finally, an index of signal alterations in the white matter was constructed by summing voxels within the white matter regions having signal characteristics meeting criteria for gray matter or for signal hyperintensities (ie, having longer T<sub>2</sub> values).

## STATISTICS

Relationships between the quantitative MRI volumetric and neuropathologic measures were examined using Pearson product-moment correlations.<sup>25</sup> Relationships between regional MRI indexes and regional neuropathologic measures were examined using multiple linear regression analyses.<sup>25</sup>

minimal when these composite scores ranged from 0 through 1, moderate when scores ranged from 2 through 4, and severe when scores ranged from 5 through 9. Fifteen (18%) of the 17 specimens demonstrated moderate to severe cerebral damage (**Figure 2**). An examination of the regional GFAP scores indicated that this damage was primarily localized to the CWM and DGM regions, with over 75% of the brains displaying little or no gliosis reactivity in the CGM region.

A similar composite score for the presence of HIV was estimated by summing the individual gp41 scores across the three cerebral regions. Human immunodeficiency virus was considered absent or minimal with scores ranging from 0 through 1, moderate with scores ranging from 2 through 3, and severe with scores ranging from 4 through 6. The severity of HIV infection among the 17 specimens covered the spectrum of minimal, moderate, and severe (**Figure 3**). As with the estimates of gliosis, HIV was found to be primarily localized within the CWM and DGM regions, with the majority (ie, 70%) of the specimens displaying no HIV in the CGM.

The total presence of HIV, summed across the three cerebral regions, was found to be significantly correlated with the amount of total cerebral gliosis ( $r=.51$ ,  $P<.05$ ). Regional analyses revealed significant associa-

tions between the presence of HIV in the CWM and the severity of gliosis in the CWM ( $r=.53$ ,  $P<.05$ ), and between HIV in the DGM and severity of gliosis in the DGM ( $r=.62$ ,  $P=.01$ ). No significant correlation was observed between the presence of HIV in the CGM and the severity of gliosis in the CGM.

Neocortical dendritic and synaptic (ie, presynaptic terminal) densities were estimated by computing the percent of the neocortical area immunostained for MAP-2 and antisynaptophysin, respectively, in all 10 of the 17 specimens with 24 hours or less of postmortem autolysis. Decreased dendritic, but not synaptic, density was found to be significantly associated with greater HIV infection in the CGM ( $r=.70$ ,  $P<.05$ ). Neither dendritic nor synaptic density was significantly associated with severity of gliosis in the CGM. Surprisingly, dendritic density and synaptic density were not found to be significantly associated with each other within this small sample.<sup>10</sup>

## Relationships Between MRI and Pathologic Measures

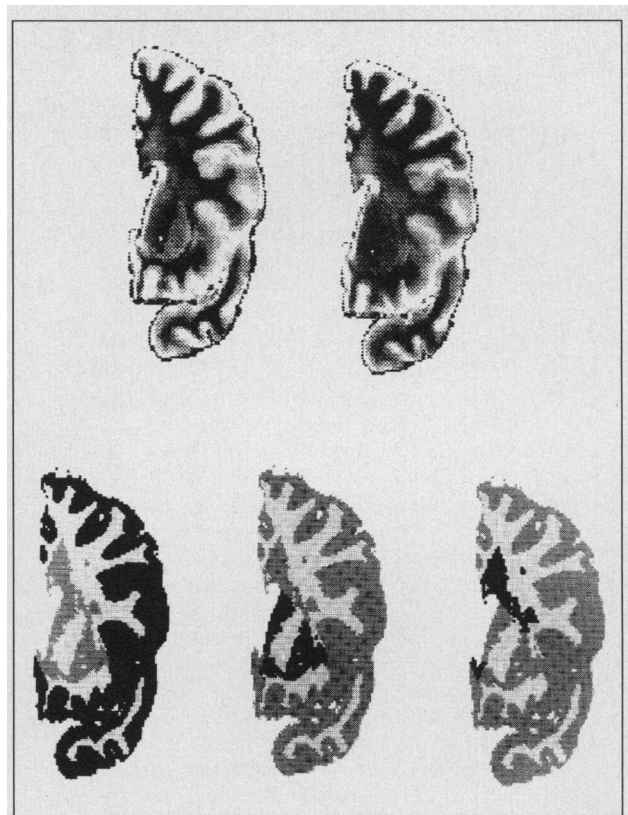
Estimates of total hemisphere volume, CGM volume, AWM volume, and DGM volume were computed from the postmortem MRIs of all 17 left hemisphere speci-

**Table 1. Neuropathologic Findings and Length of Time Between Death and Postmortem Examination of the Brains of 17 Patients With Acquired Immunodeficiency Syndrome**

Case No.	Neuropathologic Findings	Postmortem Time, h
1	Myelinopathy	36
2	Microglial nodule encephalitis	24
3	Microglial nodule encephalitis	11
4	Subacute encephalitis without nodules, occasional microscopic white matter infarcts	11
5	Chronic meningitis	10
6	Chronic meningitis, mild vacuolar myelopathy	15
7	Cryptomeningitis and cerebellar cryptococcoma	36
8	History of central nervous system lymphoma with several basal ganglia and hippocampal lesions, no tumor seen	48
9	Chronic meningitis, microglial nodule encephalitis with multinucleated giant cells	12
10	Chronic meningitis	17
11	Acute pontine infarct	57
12	Cytomegalovirus ventriculitis	41
13	Herpes simplex encephalitis	20
14	None	18
15	None	16
16	Acute hippocampal sclerosis	50
17	Progressive multifocal leukoencephalopathy	52

mens using the previously described quantitative morphometric techniques.<sup>21</sup> As expected, total left hemisphere volume was found to be highly significantly correlated with the fixed weight of the corresponding right hemisphere ( $r=.92$ ,  $P<.0001$ ) in the 11 specimens for which fixed weight was available. To adjust for individual differences in brain size, estimates of the CGM, AWM, and DGM structures were computed as proportions of this total hemispheric volume.

The presence of HIV was found to be significantly associated with both decreased DGM proportion ( $r=-.54$ ,  $P<.05$ ) and increased AWM ( $r=.52$ ,  $P<.05$ ), but was not significantly associated with CGM proportion (**Figure 4**). The severity of damage (as assessed by the composite GFAP score) was not significantly associated with any of the left hemisphere gray matter measures, although the association between gliosis and AWM did approach significance ( $r=.45$ ,  $P=.07$ ). To examine the relationship between the regional MRI indexes and the regional neuropathologic measures, multiple regression analyses were used to estimate the magnitudes of the independent effects of the left hemisphere CGM proportion, DGM proportion, and AWM proportion on the right hemisphere CGM, DGM, and CWM scores for gp41 and GFAP. The results of these regressions are shown in **Table 2**. Independent effects of both CGM and AWM proportion but not DGM proportion were found on CGM HIV. In contrast, increased DGM HIV was significantly associated only with decreased DGM proportion, but not with CGM or AWM. The presence of HIV in the CWM region was not significantly associated with any MRI struc-



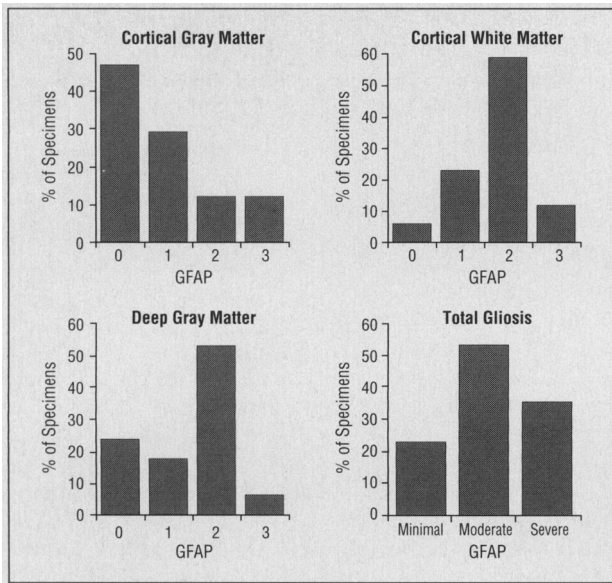
**Figure 1.** Representative images from the magnetic resonance imaging protocol. Top, Filtered images (echo times, 30 and 80 milliseconds; repetition time, 3000 milliseconds). Sections are 4 mm thick and interleaved. A 24-cm field of view and a 256×256 matrix were used. Bottom, Fully processed images with regions of interest highlighted in black. The regions include cortical gray matter, deep gray matter, and abnormal tissue.

tural measure. The severity of gliosis in the CGM region was significantly associated with increased AWM, but not with the two gray matter proportions. Gliosis in the CWM and DGM regions was not significantly associated with any MRI measure.

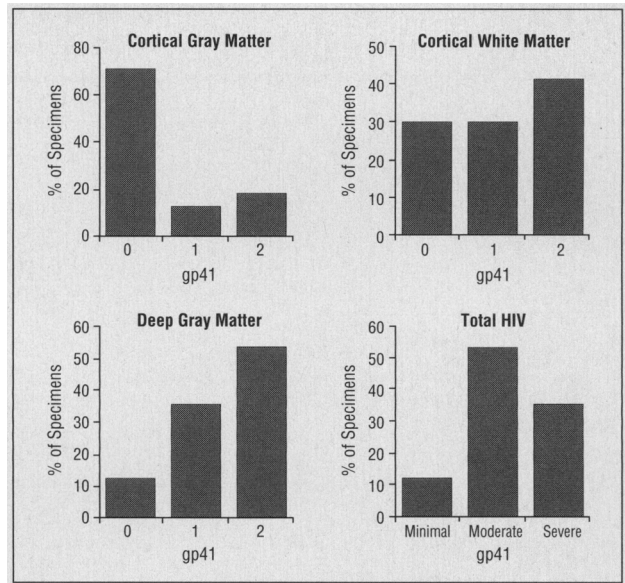
Finally, correlational analyses were used to examine the relationship between left hemisphere CGM proportion and neocortical dendritic and synaptic density in 10 of the 17 specimens (**Figure 5**). Decreased CGM volume was found to be highly significantly associated with decreased synaptic density ( $r=.83$ ,  $P=.003$ ), but the relationship between cortical volume and dendritic density did not reach significance ( $r=.57$ ,  $P=.08$ ).

#### COMMENT

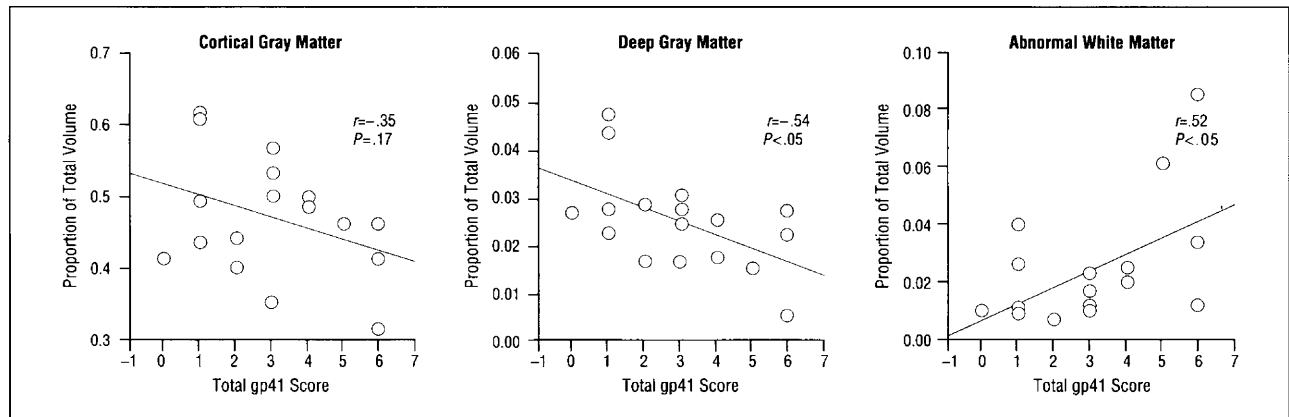
Previous MRI studies have demonstrated changes in the brains of patients with AIDS that seem to correspond to the pathologic changes observed at autopsy. To our knowledge, the present study is the first to directly demonstrate significant associations between quantitative measures of MRI and neuropathologic changes in patients with AIDS. As shown in previous studies, moderate to high levels of both HIV and gliosis were observed primarily (but not exclusively) in the CWM and DGM of the AIDS brains. More importantly, the severity of central nervous system HIV infection, but not gliosis, was found to



**Figure 2.** Regional and total gliosis scores for the 17 specimens. Regional quantification of immunostaining for glial fibrillary acidic protein (GFAP) on a scale of 0 through 3 was performed as described in the "Materials and Methods" section. Total gliosis was defined as a composite score by summing the scores from the three regions. Those brains with composite scores of 0 through 1 were classified as minimal; those with composite scores of 2 through 4, as moderate; and those with composite scores of 5 through 9, as severe.



**Figure 3.** Regional and total human immunodeficiency virus (HIV) scores for the 17 specimens. Regional quantification of immunostaining for the transmembrane envelope protein of HIV (gp41) on a scale of 0 through 2 was performed as described in the "Materials and Methods" section. Total HIV was defined as a composite score by summing the scores from the three regions. Those brains with composite scores of 0 through 1 were classified as minimal; those with composite scores of 2 through 3, as moderate; and those with composite scores of 4 through 6, as severe.



**Figure 4.** Magnetic resonance imaging estimates of the volume of left hemisphere cortical gray matter, deep gray matter, and abnormal white matter (computed as proportions of total left hemisphere volume) plotted as a function of total human immunodeficiency virus infection (ie, total gp41 score) in the corresponding right hemisphere.

be significantly correlated with the quantitative MRI estimates of the volumes (expressed as proportions of total hemispheric volume) of DGM and AWM. Specifically, increased levels of HIV were significantly associated with decreased DGM volume and increased AWM volume. Multiple linear regression analyses further revealed regional specificities in the associations between MRI changes and HIV: the severity of HIV in CGM was associated with MRI volume changes in CGM and AWM but not in DGM, whereas the severity of HIV in DGM was associated with MRI volume change in DGM but not in CGM or AWM. Taken together, these results indicate that quantitative MRI measures are sensitive to regional quantitative measures of neuropathologic changes observed in patients with AIDS, and that some of these MRI changes may be directly attributable to primary HIV in-

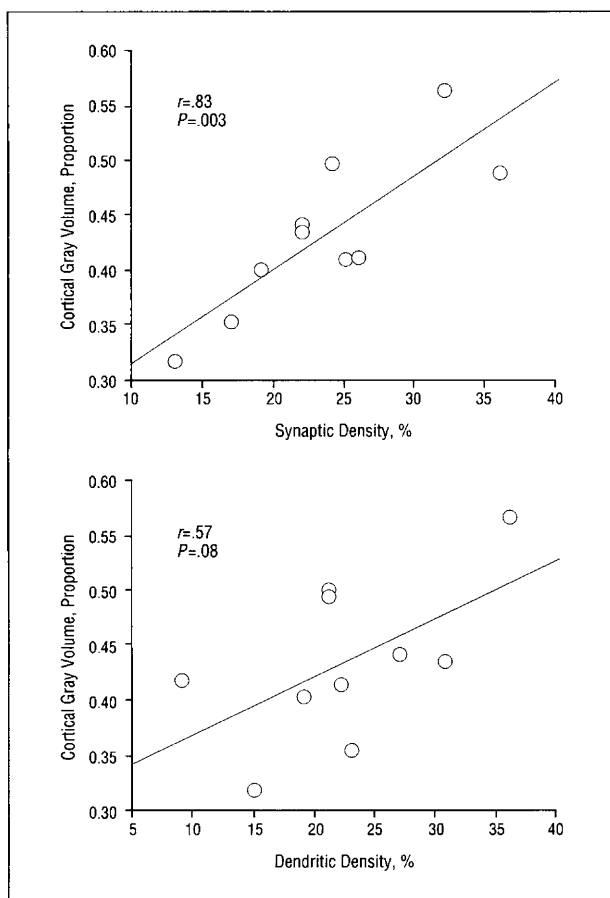
fection of the brain rather than to neuropathologic damage in general (ie, gliosis). These findings are consistent with those of a recent postmortem computed tomographic study<sup>26</sup> that demonstrated an increased frequency of cerebral atrophy (as reflected in increased cerebrospinal spaces) in brains with HIV-associated histopathologic changes.

Estimates of neocortical dendritic and synaptic density were derived from the percentages of neuropil area in the frontal cortex that were immunostained for MAP-2 and synaptophysin, respectively. Increased levels of HIV in the CGM were found to be significantly correlated with decreased dendritic density. Similar correlations with the presynaptic marker synaptophysin did not achieve statistical significance. In contrast, decreased CGM volume estimates taken from the MRIs were found to be more

**Table 2. Multiple Regression of Neuropathologic Variables and Quantitative Magnetic Resonance Imaging (MRI)\***

	MRI Structural Measures					
	Cortical Gray		Deep Gray		Abnormal Tissue	
	$\beta$	P	$\beta$	P	$\beta$	P
CGM HIV	-0.755	.013	0.155	.562	0.638	.002
DGM HIV	0.365	.317	-0.792	.040	0.215	.357
CWM HIV	0.213	.578	-0.503	.197	0.383	.133
CGM GFAP	-0.411	.300	-0.464	.240	0.548	.043
DGM GFAP	0.007	.986	-0.371	.338	0.526	.043
CWM GFAP	-0.205	.621	0.063	.878	0.456	.103

\*CGM indicates cortical gray matter; DGM, deep gray matter; CWM, cortical white matter; HIV, human immunodeficiency virus; and GFAP, glial fibrillary acidic protein.



**Figure 5.** Magnetic resonance imaging estimate of left hemisphere cortical gray matter volume (computed as a proportion of total left hemisphere volume) plotted as a function of cortical synaptic density and dendritic density of the corresponding right hemisphere.

highly correlated with decreased synaptic rather than dendritic density. It is therefore interesting to speculate from this pattern of results that the neurotoxic effects of HIV may be primarily postsynaptic (possibly mediated via N-methyl-D-aspartate receptors distributed on dendritic membranes), but that synaptic loss must occur before neocortical volume changes are observed on MRI. This interpretation must be treated cautiously, however, both because of the relatively small number of specimens for which dendritic and synaptic density esti-

mates were available and because of the surprising finding that the tight association between synaptic and dendritic damage seen previously<sup>10</sup> was not observed in the present study.

Neurologic studies of dementia in AIDS, unlike those of illnesses such as Alzheimer's disease, are complicated by the presence of abundant opportunistic infections and neoplasms that plague this population. In this initial study, four of the 17 patients (including one of the 10 patients available for synaptic and dendritic measurements) had opportunistic diseases that could potentially affect the brain volume estimates obtained from the MRIs. An expanded version of this study in which patients with confounding neuropathologic changes are excluded is currently in progress. It seems likely, however, that the exclusion of such subjects would strengthen rather than weaken the observed correlations between the MRI volume estimates and the measures of HIV and synaptic density.

A further complication in the present study concerns the general difficulty in interpreting correlations (or lack of correlations) between the presence of any virus and fixed neurologic damage. For example, in the case of polio where anterior horn motoneurons are lytically infected, correlation of neuronal damage and viral infection is only possible during acute infection. At later stages when neurons are lost and there is a fixed neurologic deficit, the spinal cord anterior horn regions are atrophic despite the lack of virus. The potential for a similar problem exists in the case of a chronic viral infection such as HIV encephalitis: neurologic damage can become fixed while presence of HIV can be either waxing or waning. This problem is further exacerbated by the advent of drug therapy with which the temporal arrest of viral replication is possible. Despite these potential confounding changes, we have been able to discern significant relationships between the presence of HIV and both neuropathologic<sup>9</sup> and, in the present study, neuroradiologic evidence of atrophy.

Although MRI has become an increasingly important tool in the neurologic evaluation of patients with AIDS, interpretive problems still exist in linking these MRI findings to patients' underlying neuropathologic changes. The results of the present study demonstrate that the quantitative morphometric analysis of MRIs can provide measures of brain structural changes that are sensitive to specific neuropathologic changes seen at autopsy. In particular, these measures have been shown to

be sensitive to both the level and the regional distribution of HIV in the brain, as well as to estimates of neocortical synaptic density. The ability to obtain sensitive in vivo markers of the underlying neuropathologic changes associated with HIV infection is critical for investigations concerned with the pathogenesis and longitudinal progression of neurologic disturbances in patients with AIDS.

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