

- neurodevelopmental disorders with cognitive deficits. *Brain Res* 1997;760:68–73.
39. Koczyk D. Differential response of microtubule-associated protein 2 (MAP-2) in rat hippocampus after exposure to trimethyltin (TMT): an immunocytochemical study. *Acta Neurobiol Exp* 1994;54:55–58.
40. Galea LA, McEwen BS, Tanapat P, et al. Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. *Neuroscience* 1997;81:689–697.
41. Varvel SA, Hamm RJ, Martin BR, et al. Differential effects of delta9-THC on spatial reference and working memory in mice. *Psychopharmacology* 2001;157:142–150.
42. O'Leary DS, Block RI, Flaum M, et al. Acute marijuana effects on rCBF and cognition: a PET study. *NeuroReport* 2000;11:3835–3841.
43. Block RI, O'Leary DS, Hichwa RD, et al. Cerebellar hypoactivity in frequent marijuana users. *NeuroReport* 2000;11:749–753.

Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients

T. Ernst, PhD; L. Chang, MD; J. Jovicich, PhD; N. Ames, BA; and S. Arnold, MS

Abstract—Background/Objectives: A previous fMRI study demonstrated increased brain activation during working memory tasks in patients with HIV with mild dementia. The current study aims to determine whether patients who are HIV-1 positive and have normal cognitive function also show increased brain activation on fMRI. **Methods:** Blood oxygenation level-dependent (BOLD) fMRI was performed in 10 patients with HIV (CD <500) and 10 age-, sex-, education-, and handedness-matched seronegative subjects. Each subject performed a battery of neuropsychological tests and fMRI with three tasks (0-back, 1-back, and 2-back) that required different levels of attention for working memory. **Results:** Compared with control subjects, patients with HIV showed greater magnitude of brain activation (BOLD signal intensity changes, $p \leq 0.001$) in the lateral prefrontal cortex, with normal performance during fMRI and on a battery of neuropsychological tests. The patients with HIV also showed increased activated brain volume in the lateral prefrontal cortex ($p = 0.007$) but not in other activated regions, including the posterior parietal cortex, supplementary motor area, thalamus, caudate, and occipital cortex. The increase in activated brain volume was independent of task difficulty. **Conclusion:** Increased brain activation in subjects who are positive for HIV precedes clinical signs or deficits on cognitive tests. Early injury to the neural substrate may necessitate increased usage of brain reserve to maintain normal cognitive function. BOLD fMRI appears to be more sensitive than clinical and neuropsychological evaluations for detecting early HIV-associated brain injury.

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Cognitive abnormalities commonly occur in patients with HIV-1 infection.¹ Among healthy individuals who are seropositive for HIV, cognitive deficits are thought to be infrequent²; however, some investigators suggest that more sensitive measures may be needed to detect the mild cognitive decline during the asymptomatic stage.³ In later stages of HIV disease, with CD4 counts <100 cells/ μ L, approximately 20% of patients may develop a more disabling dementia syndrome directly related to HIV infection⁴; this syndrome has been termed HIV cognitive motor complex (CMC).⁵ Early diagnosis and treatment of HIV dementia are especially important because patients with early stages of the dementia may show

reversal of their cognitive deficits and neurochemical abnormalities after treatment.^{6,7}

Typical neuropsychological deficits in patients with HIV include decreased sustained attention, mental flexibility, general motor speed, and memory^{8,9}; in particular, working memory may be affected.^{10–13} However, little is known about the neuroanatomic substrate underlying these neuropsychological deficits. A variety of functional neuroimaging techniques, including PET,¹⁴ SPECT,^{15,16} and MRS,^{17–19} found alterations in cerebral blood flow and metabolism in the brains of individuals infected with HIV. Although the majority of these studies were performed in patients with HIV with cognitive impairment or de-

From the Medical Department (Drs. Ernst and Chang, and S. Arnold) and Chemistry Department (Dr. Ernst), Brookhaven National Laboratory, Upton, NY; Department of Brain and Cognitive Sciences (Dr. Jovicich), Massachusetts Institute of Technology, Cambridge; and Department of Neurology (N. Ames), Harbor–University of California, Los Angeles Medical Center, Torrance.

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Address correspondence and reprint requests to Dr. Thomas Ernst, Medical Department, Brookhaven National Laboratory, Bldg. 490, Upton, NY, 11973-5000; e-mail: TErnst@bnl.gov

mentia, several MRS studies demonstrated neurochemical abnormalities even in patients without cognitive deficits or with minor cognitive motor disorder.¹⁹⁻²¹

One of the disadvantages of prior imaging studies is that brain function was evaluated at rest. In contrast, fMRI, using the blood oxygenation level-dependent (BOLD) contrast, allows the direct, noninvasive observation of brain activation while subjects are performing cognitive tasks. This approach is analogous to performing a “stress test” for the brain. In a previous study, we observed pronounced differences (increases) in brain activation on fMRI during working memory in patients with early HIV CMC when compared with control subjects negative for HIV.²² Because the initial findings indicated that neural abnormalities may precede functional deficits in patients with HIV, probably due to the “reserve capacity” of the brain, we hypothesized that increased brain activation on fMRI may be present even in patients with normal cognitive function. Therefore, we evaluated two groups of subjects, control subjects negative for HIV and patients positive for HIV, with neuropsychological tests (to ensure normal cognitive function) and fMRI using tasks that required increasing cognitive load of attention and working memory.

Subjects and methods. *Subjects.* Ten men seropositive for HIV-1 (age 36.3 ± 7.9 years; education 14.8 ± 2.0 years, one left-handed and nine right-handed) and 10 healthy seronegative men matched for age, education, and handedness (age 36.1 ± 6.8 years; education 15.6 ± 2.6 years; one left-handed and nine right-handed) were scanned with fMRI while they performed a set of working memory tasks with varying degrees of difficulty. All patients with HIV were recruited from the Los Angeles area, and all seronegative control subjects were recruited from the local community by advertisements or were friends or partners of the patients. Prior to the study, each patient underwent a screening neuropsychiatric evaluation, including the HIV Dementia Scale,²³ Karnofsky score,²⁴ and the Memorial Sloan-Kettering system for AIDS dementia staging.^{25,26} The screening evaluation also included routine chemistry, thyroid panel, syphilis serology, CD4 count, and plasma viral load. Patients were enrolled only if they fulfilled the inclusion criteria: HIV-1 seropositivity; history of CD4 < 500/mL; negative urine toxicology screen (for cocaine, cannabis, amphetamines, benzodiazepines, and opiates); no other chronic medical or psychiatric illnesses; vision 20/20; native English speaking; and MRI without structural abnormalities. Subjects were excluded if they had a history of illicit drug or alcohol dependence, focal brain lesions, head trauma with loss of consciousness for >30 minutes, seizure disorders, hypertension, diabetes, or history of neurosyphilis. Smokers were asked not to smoke within a 24-hour period prior to the fMRI scan. Control subjects additionally were seronegative and on no medications. Prior to the study, each subject signed a written consent form approved by the Institutional Review Board at Harbor-University of California, Los Angeles, Research and Education Institute.

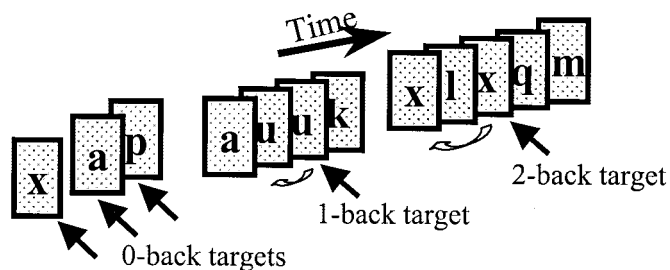


Figure 1. The sequential letter tasks (0-back, 1-back, and 2-back tasks).

To ensure normal cognitive function, all subjects were evaluated with a battery of neuropsychological tests that was designed to include measures most sensitive to functional deficits associated with injury to the frontal lobe and the striatum. The battery included measures of gross motor functioning: timed gait; fine motor speed: grooved pegboard²⁷; psychomotor speed: Trail Making Test²⁸ and Symbol Digit Modalities²⁹; verbal memory: Rey Auditory Verbal Learning Test³⁰; executive function: Stroop Color Interference Test³¹; mood: Center for Epidemiologic Studies-Depression Scale³²; estimated verbal intelligence: New Adult Reading Test-Revised.³³ Additionally, a customized computerized test for psychomotor speed and reaction times, the California Computerized Assessment Package (CalCAP, customized expanded version), was performed.³⁴

Activation paradigms. The stimulation paradigms were modeled after tasks on the CalCAP.³⁵ A battery of three tasks was presented twice in the same order for each subject. The first was a simple reaction (0-back) task: a letter was flashed for 500 ms at random times, with fixation, 10 times per 30 seconds. The subjects' task was to push a low-resistance button as soon as a number appeared on the screen. During the control periods of 30 seconds, only a fixation cross was displayed. For the two working memory tasks (sequential letter tasks), random alphabetical letters were presented sequentially at a rate of one per second (figure 1). The subjects were instructed to press the button as fast as possible when the current letter was the same as the one before (1-back task) or two before (2-back task). During each 30-second task period, five targets were presented at random time points. During the rest period (30 seconds), nonsense characters were randomly displayed at the same size, rate, and luminance, and the subjects were instructed not to respond but to maintain fixation at the center cross.

Each task was performed during two scans; each scan consisted of four stimulation and four resting intervals. Subject motion was minimized using extensive foam support. The reaction times and accuracy were recorded during the scans for all the tasks. Visual stimuli were generated on a Hewlett Packard workstation (Palo Alto, CA) and displayed on a 20-inch monitor that was visible via a mirror mounted on the head coil inside the scanner. The monitor was placed at the end of the patient table and magnetically shielded to avoid geometric or chromatic distortions due to the magnetic field.

fMRI scans. Scans were performed on a 1.5-T system (General Electric, SIGNA 5.8, Milwaukee, WI) with fast gradients (SR 120), using a quadrature head coil. After

obtaining an anatomic scan (fast inversion recovery, repetition time 4,500 ms, echo time 32 ms, inversion time 120 ms, 36 slices, resolution $0.9 \times 0.9 \times 3.5 \text{ mm}^3$), fMRI was performed using a single-shot gradient-echo echo-planar imaging sequence (relaxation time 2,500 ms, echo time 60 ms, 16 axial slices, resolution $3.125 \times 3.125 \times 8 \text{ mm}^3$; 10-second dummy scans).

Data processing. fMRI data were processed on a Compaq XP1000 workstation (Compaq Computer Corp., Houston, TX) using the Statistical Parametric Mapping package (SPM99b, London, UK, available at: <http://www.fil.ion.ucl.ac.uk/spm>). The first processing step was motion correction.³⁶ Only data sets with $<0.8 \text{ mm}$ maximal displacement and $<1^\circ$ rotation during an entire scan were used. One of the patients with HIV had excess motion and his data were discarded. Next, the echo-planar images were coregistered to the high-resolution scans³⁷ and transformed into Talairach space, using a full affine transformation and $4 \times 5 \times 4$ spatial cosine transformations and spatial smoothing with a 10-mm Gaussian filter.

Activation maps were calculated for each paradigm and group using the general linear model with fixed-effect analysis.³⁸ The design matrix was generated with a 6 seconds' delayed boxcar reference function, a high-pass filter (cutoff 1/120 Hz), and intersubject scaling. The resulting activation maps reflect the probability (*t*-score) of a region to be activated (increased BOLD signal intensity) during the task (minimum threshold $T \geq 3.1$, or $p \leq 0.001$; cluster size ≥ 40 voxels). In addition, SPM difference maps comparing BOLD signal differences between patients with HIV and control subjects were calculated (also with $T \geq 3.1$, cluster size ≥ 40 voxels).

To determine regional activated brain volumes in the individual subjects, single-subject analyses were performed with SPM. For each individual, eight spherical volumes of interest of 25-mm radius were defined at the center of group activation in the left and right lateral prefrontal cortex (LPFC; Talairach coordinates: ± 50 ; 14; 20), left and right posterior parietal cortex (PPC; ± 36 ; -50 ; 48), caudate (0; -15 , 20), midline thalamus (0; -20 , 8), supplementary motor area (SMA) (0; 10; 50), and the occipital cortex (0; -65 ; -20). For each subject, the number of activated fMRI voxels above a *T*-threshold of 2.33 was then determined in each volume of interest. For each region, the effect of HIV infection on the activated volumes was assessed with repeated-measures analysis of variance (ANOVA), using task difficulty and hemisphere (when appropriate) as "within" measures, and HIV serostatus as "between" measure. To explore the relationship between fMRI activation and clinical variables in the patients with HIV, simple linear regression analyses were performed between activated volumes in regions showing a significant HIV effect on the ANOVA, and CD4 counts, and the log plasma and log CSF viral loads. For ANOVA main effects and the regression analyses, statistical significance was defined as $p \leq 0.05$ (double-sided); for the post hoc tests, significance was defined as $p \leq 0.05$ (single-sided increases).

Results. *Subject characteristics.* Although the subjects were all native English speakers, they represented a variable ethnic distribution: patients with HIV (five white, three Hispanic, two African-American) and seronegative

controls (seven white, one Hispanic, one Asian, and one African-American). The patients with HIV had the following clinical characteristics (mean \pm SD): CD4 count $375 \pm 187/\text{mL}$; nadir CD4 $241 \pm 145/\text{mL}$; log plasma HIV viral load 3.36 ± 1.3 copies/mL; log CSF HIV viral load 2.92 ± 1.2 copies/mL; Karnofsky score 93 ± 5 (normal function = 100); HIV Dementia Scale 15.6 ± 0.6 (maximum 16). All patients with HIV had normal cognitive function, i.e., AIDS Dementia Complex (ADC) stage 0. On the battery of neuropsychological tests sensitive to HIV CMC,⁸ there were no significant differences between patients with HIV and control subjects in any of the tasks. Patients with HIV performed faster on the form discrimination task (617 ms vs 714 ms; $p = 0.04$), but the difference was not significant after correction for multiple comparisons.

All patients with HIV were on stable antiretroviral medications (no change in medications within 2 months of the fMRI study), except for one patient who was naive to antiretroviral medications. Of the nine medicated patients, four subjects were on four antiretroviral medications [three were on stavudine (D4T) + lamivudine (3TC) + lopinavir + ritonavir; one was on nelfinavir + nevirapine + stavudine + ritonavir]; and five subjects were on three antiretroviral medications [two of these were on d4T + 3TC + nelfinavir; one was on D4T + ritonavir + saquinavir; one was on zidovudine + 3TC + Capravirine; one was on zidovudine + 3TC + indinavir]. Three subjects who were HIV positive and two who were seronegative had a history of smoking. No cerebral atrophy or brain lesions were observed in any of the subjects.

fMRI results. During the fMRI scans, all subjects performed slower as the tasks required increasing load on working memory and attention (0-back: 334 ms; 1-back: 1,476 ms; 2-back: 2,468 ms). The increasing task difficulty was confirmed by the increasing reaction times on these tasks (repeated-measures ANOVA, $p < 0.0001$); post hoc analyses showed significant differences in reaction times between all three tasks ($p < 0.0001$ for all contrasts). Subjects in both groups performed the 0-back and 1-back tasks with high accuracy ($>98\%$); accuracy on the more difficult 2-back task was slightly lower but still very high (approximately 90%). Compared with control subjects, patients with HIV showed no significant differences in accuracy or reaction time while performing these tasks (0-back: control 337 ms, 99.9%, HIV+ 331 ms, 99.3%; 1-back: control 1,481 ms, 99.7%, HIV+ 1,471 ms, 98.9%; 2-back: control 2,532 ms, 88.3%, HIV+ 2,404 ms, 92.6%).

On the fMRI group analyses, the subjects showed similar patterns of activation with each task. With both the 0-back and the two working memory tasks, all subjects showed activation in the LPFC, PPC, caudate, thalamus, SMA, and also the occipital cortex. On the SPM group analyses, patients with HIV showed significantly greater BOLD activation (percent signal changes) compared with the control subjects predominantly in the LPFC (figure 2 for surface rendering of activation on the 1-back task).

The increase in brain activation on the group analyses was supported by the findings of the volumetric single-subject analyses, which are summarized in the table. In the LPFC, the subjects who were positive for HIV showed significantly increased activated brain volume in comparison with the control subjects ($p = 0.007$; HIV effect on repeated-measures ANOVA; figure 3). This increase was

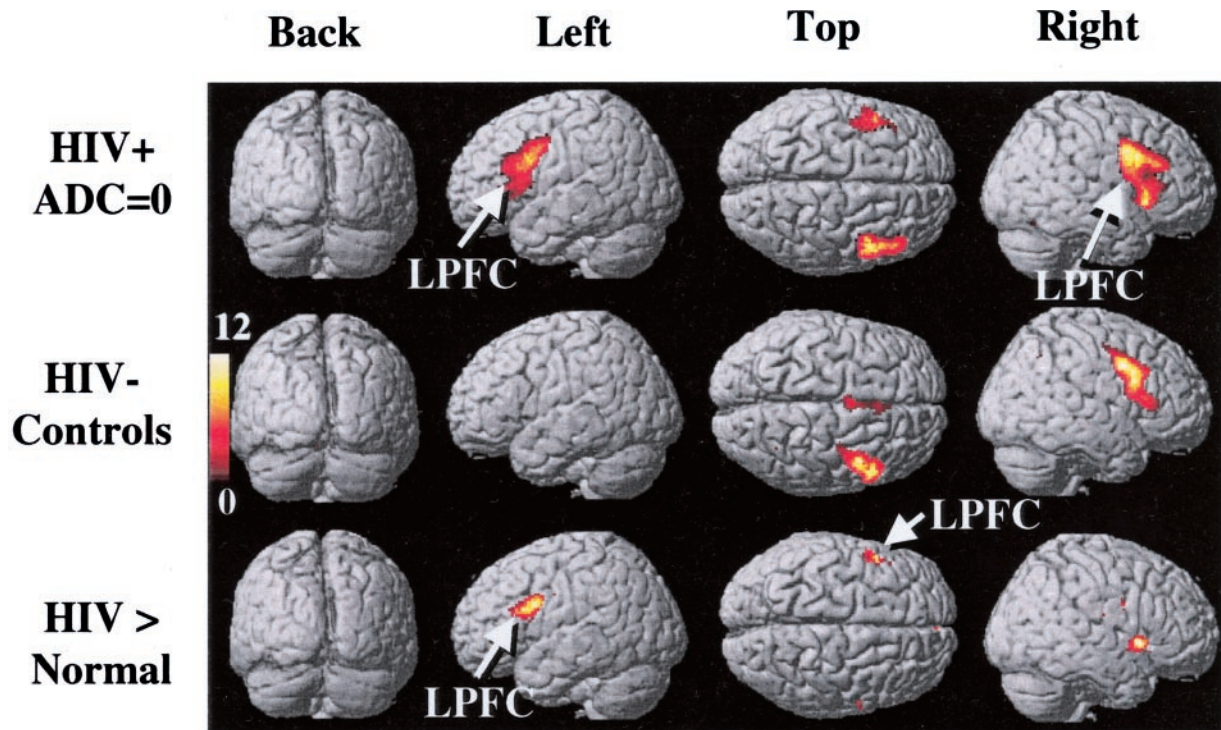


Figure 2. Group activation data (T-score maps) for the 1-back task in patients with HIV (top row) and seronegative control subjects (middle row). Note significantly greater activation in the lateral prefrontal cortex (LPFC) of the patients with HIV compared with the control subjects in the direct statistical parametric mapping (SPM) group comparison (bottom row). The color scale indicates T-scores; only activated areas with a threshold $T \geq 3.1$ ($p = 0.001$) are displayed on the surface views.

independent of task or hemisphere, because there was no significant interaction between group status and task difficulty or hemisphere. In contrast, the other brain regions (PPC, caudate, thalamus, SMA, and occipital) showed no main effects of HIV serostatus on the activated volumes or interactions of HIV status with the other variables (hemisphere or task difficulty). In the patients with HIV, the left LPFC volume activated during the 1-back task showed a trend for correlation with the log plasma viral load ($r =$

$+0.73$; $p = 0.06$) but not with the CSF viral load ($r = +0.56$, $p = 0.25$). In addition, there was a trend for correlation between the CD4 count and the right LPFC activation during the 0-back task ($r = -0.61$; $p = 0.08$).

The volumetric single-subject analyses also revealed main effects in several variables other than HIV serostatus. Increasing task difficulty was associated with significantly increased activated brain volumes (subjects with HIV and control subjects combined) in the PPC ($p = 0.007$;

Table Activated brain volumes and the logarithm of the number of activated voxels on fMRI in HIV-seropositive subjects ($ADC = 0$) and healthy control subjects

HIV status	PPC		LPFC		Caudate	Thalamus	SMA	Occipital
	Left	Right	Left	Right				
Positive								
0-back	0.52/1.81 \pm 0.33	0.82/2.01 \pm 0.30	0.87*/2.04 \pm 0.24	1.16‡/2.16 \pm 0.37	0.06/0.88 \pm 0.41	0.08/1.02 \pm 0.39	0.41/1.71 \pm 0.40	0.12/1.17 \pm 0.39
1-back	0.75/1.97 \pm 0.31	1.01/2.10 \pm 0.23	1.31†/2.22 \pm 0.36	2.35/2.47 \pm 0.34	1.26/2.20 \pm 0.32	1.03/2.11 \pm 0.33	0.27/1.52 \pm 0.47	0.46/1.76 \pm 0.43
2-back	2.05/2.41 \pm 0.32	4.31/2.73 \pm 0.11	3.58‡/2.65 \pm 0.18	3.17/2.60 \pm 0.31	0.37/1.66 \pm 0.43	0.30/1.58 \pm 0.44	3.23/2.61 \pm 0.18	0.27/1.54 \pm 0.39
Negative								
0-back	0.23/1.46 \pm 0.37	0.21/1.42 \pm 0.39	0.08/1.01 \pm 0.28	0.11/1.13 \pm 0.38	0.03/0.56 \pm 0.34	0.03/0.61 \pm 0.33	0.33/1.62 \pm 0.44	0.07/0.96 \pm 0.31
1-back	0.20/1.39 \pm 0.36	1.19/2.17 \pm 0.32	0.13/1.22 \pm 0.28	1.06/2.12 \pm 0.31	0.09/1.06 \pm 0.48	0.15/1.29 \pm 0.45	0.45/1.75 \pm 0.47	0.22/1.44 \pm 0.44
2-back	0.85/2.02 \pm 0.33	1.59/2.30 \pm 0.33	0.70/1.94 \pm 0.33	1.30/2.21 \pm 0.25	0.50/1.80 \pm 0.41	0.32/1.61 \pm 0.43	0.30/1.57 \pm 0.51	0.83/2.02 \pm 0.42

Values are expressed as activated brain volumes (mL)/logarithm of the no. of activated voxels \pm SE.

* $p = 0.007$ (HIV+ vs control subjects; single-sided).

† $p = 0.02$ (HIV+ vs control subjects; single-sided).

‡ $p < 0.05$ (HIV+ vs control subjects; single-sided).

PPC = posterior parietal cortex; LPFC = lateral prefrontal cortex; SMA = supplementary motor area.

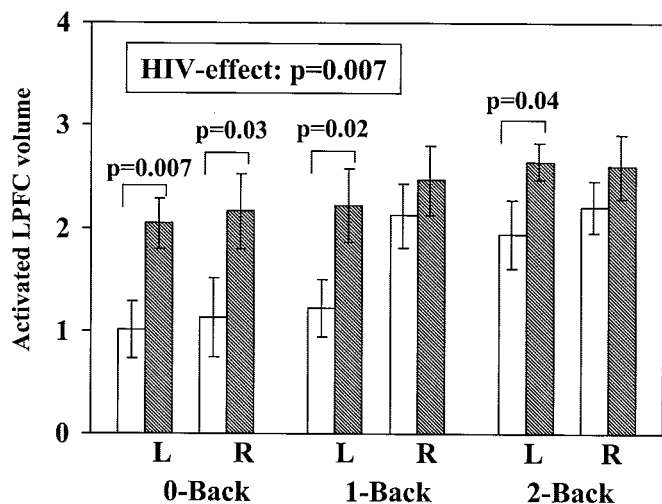


Figure 3. Activated brain volumes (log of number of activated voxels) on fMRI in the left and right lateral prefrontal cortices (LPFC) of subjects positive for HIV (shaded bars) and subjects who were seronegative (open bars). The patients with HIV show increased activated volume throughout the n-back tasks ($p = 0.007$ on analysis of variance). The p values above the individual columns indicate significant increases between patients and control subjects on post hoc tests (single sided). There was no significant interaction between HIV status and hemisphere or task difficulty.

main effect of task difficulty on repeated-measures ANOVA), the LPFC ($p = 0.01$), the thalamus ($p = 0.01$), and the caudate ($p = 0.002$). Furthermore, across both subject groups, the PPC as well as the LPFC showed greater activated volumes in the right ($p = 0.01$) as compared with the left hemisphere (main effect on ANOVA).

Discussion. This preliminary study compares brain activation in patients positive for HIV without cognitive deficits to that in healthy seronegative control subjects. The two groups were carefully matched for age, education, handedness, and sex, because each of these variables might cause differences in the pattern and extent of brain activation.³⁹⁻⁴¹ As with previous fMRI studies of working memory, the fMRI activation paradigms used in this study produced robust and consistent activation of the LPFC, the PPC, and the SMA,⁴²⁻⁴⁶ as well as caudate activation³⁹ across subjects. In both the control subjects and the patients with HIV, brain activation increased with task difficulty, from 0-back to the 2-back task. Similar results of increased brain activation with increased task difficulty have been reported.^{39,47,48} These findings imply a relationship between the cognitive load and the signal changes on fMRI, probably due to task-related attentional modulation of neuronal activity, i.e., the influence of attention on brain function.

The patients with HIV showed greater brain activation (BOLD signal changes) compared with control subjects while performing these tasks, most notably in the LPFC, where the activated volume was also larger in the patients. Our study also indicates a

trend that poorer immune status (higher viral loads and lower CD4) may be associated with increased activation in some brain regions. Due to a relatively large intersubject variability on fMRI brain activation, a larger sample size will be needed to further evaluate these relationships. Increased brain activation in the patients with HIV may be surprising considering the patients demonstrated normal cognitive function on a battery of neuropsychological tests shown to be sensitive for early cognitive abnormalities in patients with HIV.⁸ Additionally, the performance (reaction times and accuracy) of the seropositive subjects during fMRI was indistinguishable from that of the control subjects. Working memory deficits have been reported and observed in patients with HIV dementia¹⁰⁻¹²; however, as observed in the current study, patients with HIV who were asymptomatic were found to have normal working memory.¹³ Therefore, the increased brain activation in the patients with HIV may be interpreted as increased usage of brain reserve capacity in order to maintain normal working memory and other cognitive functions. Our findings also suggest that the injury due to HIV in the neural substrate may have to reach a threshold before cognitive abnormalities can be detected clinically or on cognitive testing. Furthermore, our data indicate that fMRI may be more sensitive than clinical evaluations for detecting early neural deficits associated with HIV brain injury.

This study suggests increased neural processing in the frontal brain regions of the patients with HIV compared with the control subjects. Two factors may contribute to this regional increase in neural processing. First, attention-requiring tasks are associated with greater activation in the frontal cortex compared with the parietal cortex even in healthy subjects. This has been demonstrated in an fMRI study of visual attention in healthy subjects, in which moderate attentional modulation (moderate increase of the fMRI signal with greater attentional load) was observed in the PPC, but very strong modulation (large increase of fMRI signal) was found in the LPFC and SMA.^{49,50} Second, injury to the frontostriatal circuits in the patients with HIV may necessitate greater attentional modulation of these circuits, with recruitment of additional neural processes and greater frontal activation in the patients compared with control subjects, to perform these working memory tasks. The frontostriatal brain regions are often most severely affected in patients with HIV dementia based on neuropathologic and neuroimaging studies.^{17,51-53} In particular, the dopaminergic system, which has a major role in regulating working memory function in the prefrontal cortices,⁵⁴ may be affected in HIV dementia.^{55,56}

The fMRI abnormalities in this study generally resemble those we previously observed in a group of 11 subjects positive for HIV with mild cognitive abnormalities (mean ADC 0.5).²² Compared with seronegative individuals, those patients had greater

activation in the parietal regions on the 0-back task (on SPM group analyses), but with the more difficult tasks, they had greater activation additionally in the frontal lobes. Overall, increases in brain activation in the patient group appeared to be larger in the previous study (mean ADC = 0.5) compared with this study (ADC = 0); therefore, fMRI abnormalities may reflect disease severity. However, activated brain volumes were not analyzed in the previous study. Increases in brain activation on fMRI have also been reported in other brain disorders, including children with attention deficit disorder,⁵⁷ adults with mild traumatic brain injury,⁵⁸ patients with PD,⁵⁹ and people at risk for AD.⁶⁰ Therefore, the concept that brain injury leads to increased usage of brain reserve capacity appears to be supported by fMRI studies of other brain disorders.

One potential confound in the current study is that all but one of the patients were on antiretroviral medications. The BOLD fMRI signal may be affected by medications, as has been observed in patients with schizophrenia who were placed on typical antipsychotic medications.⁶¹ However, unlike typical antipsychotic medications that affect the dopaminergic system, antiretroviral medications are not known to affect cerebral perfusion. Another potential confound is that altered cerebral blood flow might influence the BOLD response. Prior studies in patients with HIV have demonstrated alterations in cerebral perfusion at rest,^{16,62,63} which may contribute to the abnormal BOLD signals. However, the relationship between altered cerebral perfusion and BOLD signal changes is unknown. Therefore, future fMRI studies should evaluate both perfusion and BOLD signal changes in patients with HIV before and during antiretroviral treatment in order to understand the relationships between perfusion abnormalities and BOLD signal changes and to exclude the possibility that these medications might affect cerebral perfusion or the BOLD signal.

The presence of brain activation abnormalities in patients with HIV with normal cognitive function indicates that fMRI is exquisitely sensitive for detecting injury to the neural substrate in patients with HIV. Future studies in a different cohort are needed to validate this study and to determine whether fMRI can be used to monitor the efficacy of antiretroviral medications.

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References

1. McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. *Neurology* 1993;43:2245–2252.
2. McArthur JC, Cohen BA, Selnes OA, et al. Low prevalence of neurological and neuropsychological abnormalities in otherwise healthy HIV-1 infected individuals: results from the Multicenter AIDS Cohort Study. *Ann Neurol* 1989;26:601–611.
3. Heaton R, Grant I, Butters N, et al. The HNRC 500: neuropsychology of HIV infection at different stages. *HIV Neurobehav-*

- ioral Research Center. *J Int Neuropsychol Soc* 1995;1:231–251.
4. Qureshi A, Hanson D, Jones J, Janssen R. Estimation of the temporal probability of the human immunodeficiency virus (HIV) dementia after risk stratification for HIV-infected persons. *Neurology* 1998;50:392–397.
5. American Academy of Neurology AIDS Task Force Working Group. Report of a Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type-1. *Neurology* 1991;41:778–785.
6. Sacktor NC, Lyles R, Skolasky R, et al. Combination antiretroviral therapy improves psychomotor speed performance in HIV-seropositive homosexual men. Multicenter AIDS Cohort Study (MACS). *Neurology* 1999;52:1640–1647.
7. Chang L, Ernst T, Leonido-Yee M, et al. Highly active antiretroviral therapy reverses brain metabolite abnormalities in mild HIV dementia. *Neurology* 1999;53:782–789.
8. Miller EN, Selnes OA, McArthur JC, et al. Neuropsychological performance in HIV-1 infected homosexual men: the Multicenter AIDS Cohort Study (MACS). *Neurology* 1990;40:197–203.
9. Selnes OA, Miller EN. Development of a screening battery for the HIV-related cognitive impairment: the MACS experience. In: Grant I, Martin A, eds. *Neuropsychology of HIV infection*. New York: Oxford University Press, 1994:176–187.
10. Law WA, Martin A, Mapou RL, et al. Working memory in individuals with HIV infection. *J Clin Exp Neuropsychol* 1994;16:173–182.
11. Martin E, Pitrak D, Pursell K, Mullane K, Novak R. Delayed recognition memory span in HIV-1 infection. *J Int Neuropsychol Soc* 1995;1:575–80.
12. Hinkin CH, van Gorp WG, Satz P, et al. Actual versus self-reported cognitive dysfunction in HIV-1 infection: memory-metamemory dissociations. *J Clin Exp Neuropsychol* 1996;18:431–443.
13. Grassi B, Graghentini G, Campana A, et al. Spatial working memory in asymptomatic HIV-infected subjects. *J Neuropsychiatry Clin Neurosci* 1999;11:387–391.
14. Rottenberg DA, Sidtis JJ, Strother SC, et al. Abnormal cerebral glucose metabolism in HIV-1 seropositive subjects with and without dementia. *J Nucl Med* 1996;37:1133–1141.
15. Rosci MA, Pignorini F, Bernabei A, et al. Methods for detecting early signs of AIDS dementia complex in asymptomatic subjects: a quantitative tomography study of 18 cases. *AIDS* 1996;6:1309–1316.
16. Harris GJ, Pearlson GD, McArthur JC, Zeger S, LaFrance ND. Altered cortical blood flow in HIV-seropositive individuals with and without dementia: a single photon emission computed tomography study. *AIDS* 1994;8:495–499.
17. Barker PB, Lee RR, McArthur JC. AIDS dementia complex: evaluation with proton MR spectroscopic imaging. *Radiology* 1995;195:58–64.
18. Lopez-Villegas D, Lenkinski RE, Frank I. Biochemical changes in the frontal lobe of HIV-infected individuals detected by magnetic resonance spectroscopy. *Proc Natl Acad Sci USA* 1997;94:9854–9859.
19. Chang L, Ernst T, Leonido-Yee M, Walot I, Singer E. Cerebral metabolite abnormalities correlate with clinical severity of HIV-cognitive motor complex. *Neurology* 1999;52:100–108.
20. Meyerhoff D, Bloomer C, Cardenas V, Norman D, Weiner M, Fein G. Elevated subcortical choline metabolites in cognitively and clinically asymptomatic HIV+ patients. *Neurology* 1999;52:995–1003.
21. Suwanwela N, Phanuphak P, Phanthumchinda K, et al. Magnetic resonance spectroscopy of the brain in neurologically asymptomatic HIV-infected patients. *Magn Reson Imaging* 2000;18:859–865.
22. Chang L, Speck O, Miller E, et al. Neural correlates of attention and working memory deficits in HIV patients. *Neurology* 2001;57:1001–1007.
23. Power C, Johnson RT. HIV-1 associated dementia: clinical features and pathogenesis. *Can J Neurol Sci* 1995;22:92–100.
24. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. *New York: Columbia University Press, 1949:199–205.*

25. Aronow HA, Brew BJ, Price RW. The management of the neurological complications of HIV infection and AIDS. *AIDS* 1988;2:151–159.
26. The Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders. Clinical confirmation of the American Academy of Neurology algorithm for HIV-1-associated cognitive/motor disorder. *Neurology* 1996;47:1247–1253.
27. Kløve H. Clinical neuropsychology. *Med Clin North Am* 1963;46:110–125.
28. Army individual test battery: manual of directions and scoring. Washington, DC: War Department, Adjutant General's Office, 1944.
29. Smith A. Symbol Digit Modalities Test. Los Angeles, CA Western Psychological Services, 1982.
30. Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Arch Psychol* 1941;28:286–340.
31. Stroop J. Studies of interference in serial verbal reaction. *J Exp Psychol* 1935;18:643–662.
32. Radloff LL. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401.
33. Blair J, Spreen O. The new adult reading test—revised manual. Victoria, Canada: University of Victoria, 1989.
34. Miller EN. California computerized assessment package, custom edition. Los Angeles: Norland Software, 1990.
35. Miller EN, Satz P, Visscher BR. Computerized and conventional neuropsychological assessment of HIV-1 infected homosexual men. *Neurology* 1991;41:1608–1616.
36. Friston KJ, Ashburner J, Poline JB, Frith CD, Frackowiak RSJ. Spatial realignment and normalization of images. *Hum Brain Mapp* 1995;2:165–189.
37. Itti L, Chang L, Mangin JF, Darcourt J, Ernst T. Robust multimodality registration for brain mapping. *Hum Brain Mapp* 1997;5:3–17.
38. Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general approach. *Hum Brain Map* 1995;2:189–210.
39. Speck O, Ernst T, Braun J, Koch C, Miller E, Chang L. Gender differences in the functional organization of the brain for working memory. *Neuroreport* 2000;11:1–5.
40. Ross MH, Yurgelun-Todd DA, Renshaw PF, et al. Age-related reduction in functional MRI response to photic stimulation. *Neurology* 1997;48:173–176.
41. Peres M, Van De Moortele PF, Pierard C, et al. Functional magnetic resonance imaging of mental strategy in a simulated aviation performance task. *Aviat Space Environ Med* 2000;71:1218–1231.
42. Cohen JD, Perlstein WM, Braver TS, et al. Temporal dynamics of brain activation during a working memory task. *Nature* 1997;386:604–608.
43. Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. An area specialized for spatial working memory in human frontal cortex. *Science* 1998;279:1347–1351.
44. D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neuronal basis of the central executive system of working memory. *Nature* 1995;378:279–281.
45. McCarthy G, Blamire AM, Purce A, et al. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proc Natl Acad Sci USA* 1994;91:8690–8694.
46. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. *Science* 1999;283:1657–1661.
47. Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 1997;35:1373–1380.
48. Manoach DS, Schlag G, Siewert B, et al. Prefrontal cortex fMRI signal changes are correlated with working memory load. *Neuroreport* 1997;8:545–549.
49. Culham JC, Brandt SA, Cavanagh P, Kanwisher NG, Dale AM, Tootell RBH. Cortical fMRI activation produced by attentive tracking of moving targets. *J Neurophysiol* 1998;80:2657–2670.
50. Jovicich J, Peters RJ, Koch C, Braun J, Chang L, Ernst T. Brain areas specific for attentional load in a motion tracking task. *J Cogn Neurosci* 2001;13:1048–1058.
51. Kure K, Weidenheim KM, Lyman WD, Dickson DW. Morphology and distribution of HIV-1 gp41-positive microglia in sub-acute AIDS encephalitis. *Acta Neuropathol (Berl)* 1990;80:393–400.
52. Power C, Kong PA, Crawford TO, et al. Cerebral white matter changes in acquired immunodeficiency syndrome dementia: alterations of the blood-brain barrier. *Ann Neurol* 1993;34:339–350.
53. Rottenberg DA, Moeller JR, Strother SC, et al. The metabolic pathology of the AIDS dementia complex. *Ann Neurol* 1987;22:700–706.
54. Goldman-Rakic P. Regional and cellular fractionation of working memory. *Proc Natl Acad Sci USA* 1996;93:13473–13480.
55. Berger JR, Kumar M, Kumar A, Fernandez J, Levin B. Cerebrospinal fluid dopamine in HIV-1 infection. *AIDS* 1994;8:67–71.
56. Lopez O, Smith G, Meltzer C, Becker J. Dopamine systems in human immunodeficiency virus-associated dementia. *Neuropsychiatry Neuropsychol Behav Neurol* 1999;12:184–192.
57. Vaidya CJ, Austin G, Kirkorian G, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc Natl Acad Sci USA* 1998;95:14494–14499.
58. McAllister TW, Sparling MB, Flashman LA, Guerin SJ, Mamourian AC, Saykin AJ. Differential working memory load effects after mild traumatic brain injury. *Neuroimage* 2001;14:1004–1012.
59. Mattay V, Tessitore A, Callicott J, et al. Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Ann Neurol* 2002;51:156–164.
60. Bookheimer SY, Strojwas MH, Cohen MS, et al. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med* 2000;343:450–456.
61. Honey G, Bullmore E, Soni W, Varatheesan M, Williams S, Sharma T. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. *Proc Natl Acad Sci USA* 1999;96:13432–13437.
62. Tracey I, Hamberg LM, Guimaraes AR, et al. Increased cerebral blood volume in HIV-positive patients detected by functional MRI. *Neurology* 1998;50:1821–1826.
63. Chang L, Ernst T, Leonido-Yee M, Speck O. Perfusion MRI detects rCBF abnormalities in early stages of HIV-cognitive motor complex. *Neurology* 2000;54:389–396.