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Neural correlates of attention and working memory deficits in HIV patients

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Article abstract—*Objectives:* To evaluate the neural correlates of attention and working memory deficits in patients with HIV-1. *Method:* fMRI was used to evaluate brain activity in 11 patients with HIV and 11 age-, sex-, education-, and handedness-matched seronegative subjects, while performing a battery of tasks that required different levels of attention for working memory. *Results:* Patients with HIV showed greater brain activation (blood oxygenation level dependent signal changes) in some regions compared with control subjects while performing the same tasks. For the simpler tasks, patients with HIV showed greater activation in the parietal regions. However, with more difficult tasks, patients with HIV showed greater activation additionally in the frontal lobes. Reaction times during these tasks were slower but accuracy was similar in the patients with HIV compared with control subjects. *Conclusion:* Injury to the neural substrate caused by HIV infection may necessitate greater attentional modulation of the neural circuits, hence a greater use of the brain reserve; additional activation of the frontal lobes is required to perform the more complex tasks. The task-dependent increased frontal activation in patients with HIV suggests that the neural correlate of attentional deficits may be excessive attentional modulation as a result of frontostriatal brain injury.

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Cognitive abnormalities commonly occur in patients with HIV infection.[1] Among otherwise healthy HIV-positive patients, cognitive deficits are thought to be infrequent,[2] but 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 less than 100 cells/μL, approximately 20% of patients may develop a more disabling dementia syndrome directly related to HIV infection[4]; this syndrome has been termed HIV cognitive motor complex.[5] Early diagnosis and treatment of HIV dementia is especially important because patients with early stages of the dementia may show reversal of their cognitive deficits and neurochemistry abnormalities after treatment.[6]

Typical neuropsychological deficits in HIV patients include decreased sustained attention, mental flexibility, general motor speed, and memory.[7,8] In particular, working memory may be affected in these patients.[9-12] However, the underlying neuroanatomic substrate for these neuropsychological deficits is unknown. A variety of functional neuroimaging techniques, including PET,[13] SPECT,[14,15] and MRS,[16-18] have been applied to evaluate physiologic changes in the brains of patients with HIV. Such functional neuroimaging studies found alterations in cerebral blood flow and metabolism, and invariably evaluated the brain function at rest.

In this study, fMRI, using the blood oxygenation level dependent (BOLD) contrast, was obtained in subjects performing tasks that required increasing cognitive load of attention and working memory.

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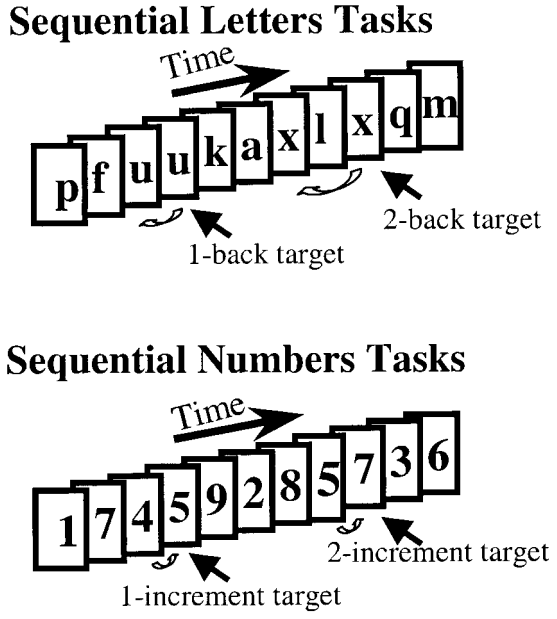

Figure 1. Schematic diagrams show the sequential letter tasks and the sequential number tasks.

This allows us to correlate neuroimaging information with behavioral performance and, thus, to identify the neuroanatomic substrate of specific cognitive impairments. fMRI is an ideal technique to study cerebral activation because it is noninvasive and nonradioactive; therefore, it can be performed repeatedly. Our aim in this preliminary study was to explore neurophysiologic correlates of deficits in attention and working memory in patients with HIV by using fMRI. Ideally, the extent of physiologic abnormalities showed by fMRI will predict the degree to which cognitive performance is reduced in these patients.

Methods. *Patients.* Eleven men seropositive for HIV-1 (mean age, 41 ± 4.8 years; education, 14 ± 2.1 years; 1 left-handed and 10 right-handed) and 11 healthy seronegative men matched for age, education, and handedness (mean age, 38 ± 4.8 years; education, 16.4 ± 3.3 years; 1 left-handed and 10 right-handed) were scanned with fMRI while performing a set of working memory tasks with varying degrees of difficulty. All patients with HIV were recruited from a Los Angeles County hospital, and all seronegative control subjects were recruited from the local community by advertisements or were friends or relatives of the patients. Before the study, each patient underwent a screening neuropsychiatric evaluation, including evaluation with the HIV dementia scale devised by Power,[19] the Karnofsky score,[20] and the Memorial Sloan–Kettering system for AIDS dementia staging.[21] The screening evaluation also included routine chemistry, thyroid panel, syphilis serology, CD4 cell count, and plasma viral load. Patients were enrolled only if they fulfilled the inclusion criteria: HIV-1 seropositive status, history of CD4 cell count <500/mL, negative urine toxicology screen, no other chronic medical or psychiatric illnesses, and MRI without structural abnormalities. Patients were excluded if they had a history of drug dependence, focal brain lesions, head trauma with loss of consciousness for more than 30 minutes, seizure disorders, hypertension, diabetes, or history of neurosyphilis. Control subjects additionally were seronegative and taking no medications. Before the study, each patient signed a written consent form approved by the Institutional Review Board at Harbor-UCLA Research and Education Institute.

Activation paradigms. The stimulation paradigms were modeled after tasks on the California Computerized Assessment Package.[22] A battery of five tasks was presented twice in the same order for each participant. The first was a simple reaction task: a number was flashed for 500 milliseconds at random times, with fixation, 10 times per 30 seconds. The 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. This task was followed by four working memory tasks. For the two sequential letter tasks, random alphabetical letters were presented sequentially at a rate of 1 per second (figure 1). The subjects were instructed to push a button as quickly as possible when the current letter was the same as the one before (one-back task) or two before (two-back task). For the two sequential number tasks, single digit numbers were sequentially displayed instead (see figure 1). The participants were instructed to respond when the number was one or two higher (one-increment or two-increment tasks) than the previous number. During each task period of 30 seconds, five targets were presented at random times. During the rest period (30 seconds), nonsense characters of the same size were randomly displayed at the same rate and luminance, and the participants 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. Participant motion was minimized using extensive cushioning and a bite-bar. The reaction times and accuracy were recorded during the scans for all the tasks, except for the two-back tasks because of a technical error. Visual stimuli were generated on a Hewlett Packard workstation (Palo Alto, CA) and displayed on a 20-inch monitor that was visible through 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 caused by the magnetic field.

Functional MRI scans. Scans were performed on a 1.5-T system (SIGNA 5.7; General Electric, Milwaukee, WI) with fast gradients (SR 120), using a quadrature head coil. After obtaining an anatomic scan (fast inversion recovery, repetition time, 4500 milliseconds; echo time, 32 milliseconds; inversion time, 120 milliseconds; 36 slices, resolution 0.9 ×0.9 × 3.5 mm), functional MRI was performed using a single-shot gradient-echo echo-planar imaging sequence (relaxation time, 2500 milliseconds; echo time, 60 milliseconds; 16 axial slices, resolution 3 × 3 × 8 mm; 10 seconds dummy scans).

Data processing. Data were processed on an SGI workstation (Silicon Graphics, Inc., Mountain View, CA) using the Statistical Parametric Mapping package (SPM99b). The first processing step was motion correction.[23] Only data sets with less than 0.8 mm maximal displacement and less than 1° rotation during an entire scan were used. Two of the patients with HIV and one control subject had

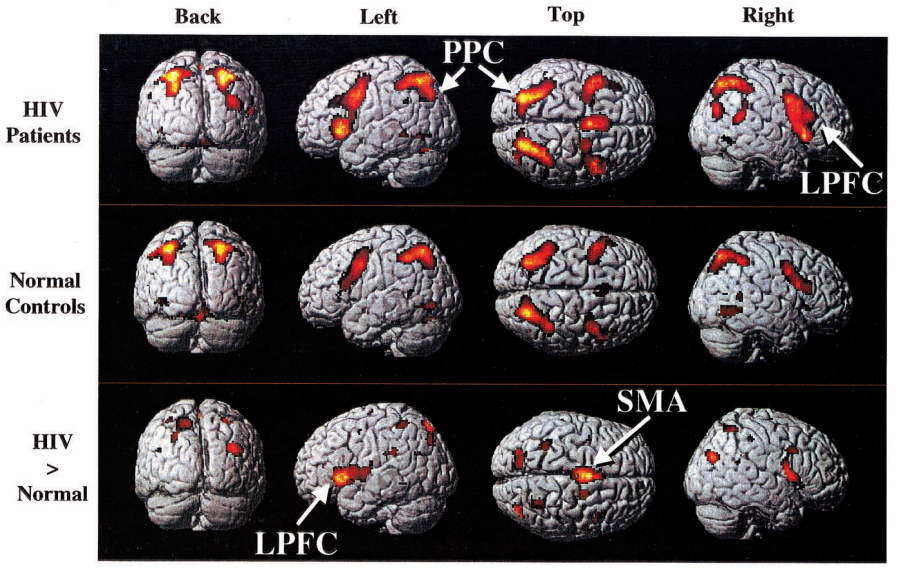

Figure 2. Group activation data for the one-increment task in patients with HIV (top row) and seronegative control subjects (middle row). Note the significantly greater activation in some brain regions of the patients with HIV compared with the control subjects (bottom row). The color scale indicates T-scores; only activated areas with a threshold ($T \geq 3.1$, p = 0.001) are displayed on the surface views. LPFC = lateral prefrontal cortex; PPC = posterior parietal cortex; SMA = supplementary motor area.

excess motion and their data were discarded. However, three additional subjects fulfilling the same criteria were recruited for the study; therefore, all 22 subjects included in the data analyses fulfilled these criteria. Next, the echo-planar images were coregistered to the high-resolution scans[24] and transformed into Talairach space, using a full affine transformation and 4 × 5 × 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.[25] The design matrix was generated with a 6-second 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).

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). To evaluate for possible relationships between the BOLD signal changes and task performance, we performed linear regression analyses, separately for the posterior parietal cortex (PPC) and lateral prefrontal cortex (LPFC), using the individual percentage signal change values as independent variable and the individual reaction times and performance as dependent variables.

Results. *Patients clinical characteristics.* The patients with HIV had the following clinical characteristics: CD4 cell count, 329 ± 197/mL; nadir CD4 cell count, 170 ± 126/mL; plasma viral load, 30,959 ± 36,549 copies/mL; Karnofsky score, 88 ± 9 (normal function, 100); HIV dementia scale score, 13.0 ± 3.4 (maximum, 16); and AIDS dementia complex (ADC) stage, 0.5 ± 0.1. Four patients with HIV had minor cognitive motor disorder (ADC stage 0.5); three had mild HIV dementia (ADC stage 1); and four were asymptomatic for cognitive deficits (ADC stage 0). All except one patient with HIV were taking antiretroviral medications. Two patients were taking two antiretroviral medications (didanosine [ddI] and stavudine [d4T]; d4T and lamivudine [3TC]); four patients were taking three antiretroviral medications (3TC, zidovudine [AZT], and indinavir [IDV]; IDV, 3TC, and d4T; IDV, AZT, and 3TC; d4T, nelfinavir [NFV], and nevirapine [NVP]); one patient was taking four antiretroviral medications (ritonavir [RIT], saquinavir [SQV], d4T, and 3TC); and three patients were taking five antiretroviral medications (ddI, RIT, IDV,

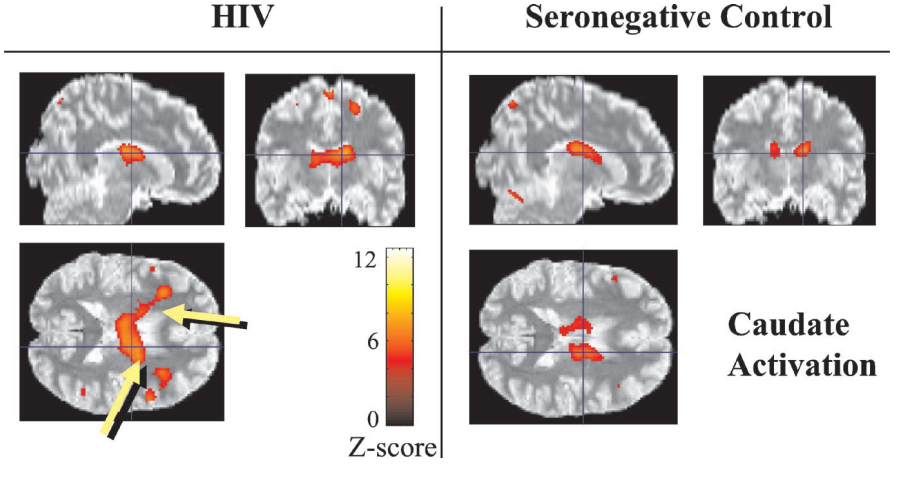

Figure 3. Group activation data for the one-increment task in patients with HIV and seronegative control subjects showed in the cross-sectional views (sagittal, axial, and coronal). Note activation in the caudate brain regions bilaterally in the control subjects (right) but that greater activation is observed in the head of the caudate (arrows) and the subcortical frontal regions of the patients with HIV (left). The color scale indicates T-scores; only activated areas with a threshold $T \geq 3.1$, p = 0.001, are shown.

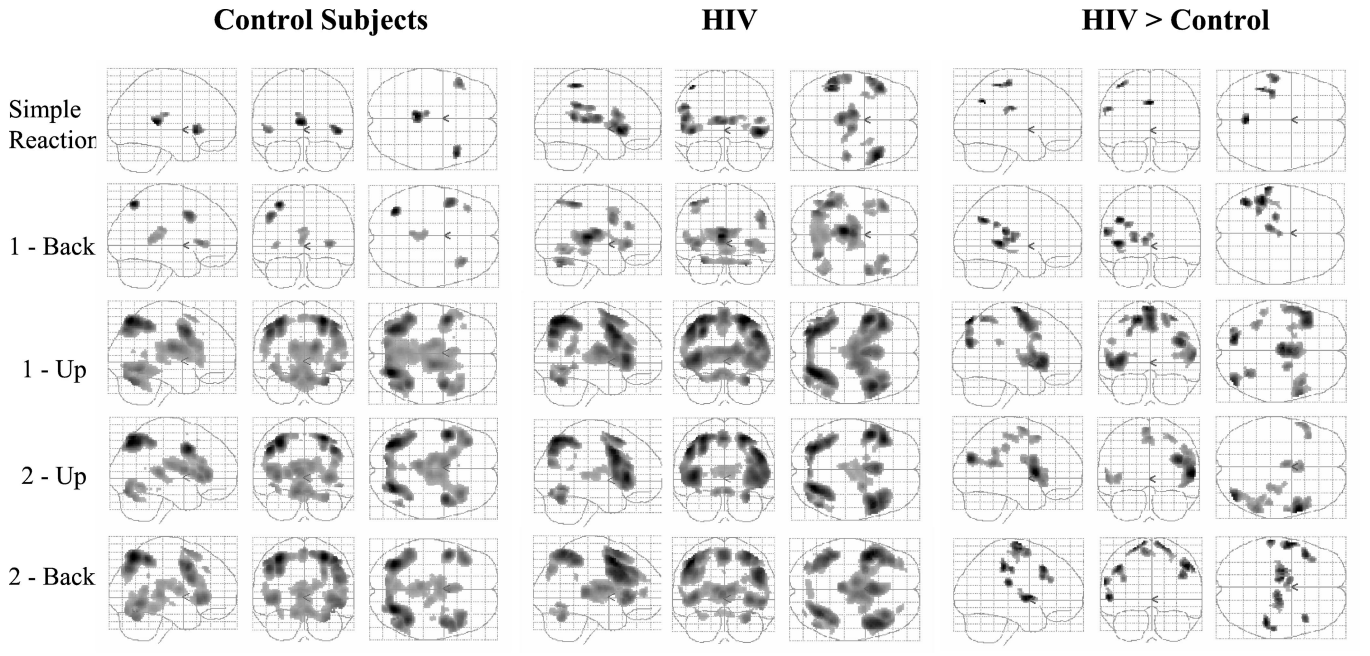

Figure 4. Glass brain views of Statistical Parametric Mapping package (SPM99b) maps of brain activation in control subjects (left column) and patients with HIV (middle column), and the difference maps (patients with HIV > control subjects) for simple reaction task and sequential letter tasks. The left and middle columns represent significant differences between activated state and resting state. The right column represents significantly greater activation (BOLD signal change) in patients with HIV compared with that in the control subjects. All maps are shown at the same threshold T-score of 3.1 ($p < 0.001$*, cluster size >40, representing pixels consistently activated across all subjects). For the simpler tasks (simple reaction and one-back), patients with HIV showed greater activation in the parietal regions. However, with more difficult tasks, patients with HIV showed greater activation additionally in the frontal lobes.*

d4T, and SQV; 3TC, IDV, NVP, 3TC, and NVP; NFV, NVP, RIT, abacavir, and d4T). No cerebral atrophy or brain lesions were observed in any of the subjects.

fMRI results. All participants showed similar patterns of activation with each task. With the simple reaction task and the four working memory tasks, all participants showed activation consistently in the LPFC (Talairach coordinates, ±45, 0, 45), PPC (±30, −70, 55), and caudate (±7, −15, 20) bilaterally. In addition, the supplementary motor area (SMA) (0, 0, 65) was activated consistently for the working memory tasks; however, at the threshold of 3.1, the SMA is visible on the group data only for the two-back task in the patients with HIV more than the control subjects, and on the sequential number tasks only in the patients with HIV. The brain regions activated during the one-increment task were mapped on the brain surface (figure 2) and on cross-sections through the caudate (figure 3). Compared with the control subjects, patients with HIV showed significantly greater BOLD activation predominantly in the frontal regions, inferior LPFC, and the SMA (see figure 2, arrows).

Patients with HIV showed greater brain activation (BOLD signal changes) in some brain regions compared with the control subjects for each tasks (figure 4). Regional comparisons show that compared with control subjects, patients with HIV activate significantly more in the left and middle parietal regions for the simple reaction and the one-back tasks (see figure 4, right columns), but significantly more in the frontal regions (LPFC and SMA) for the more difficult tasks, sequential numbers, and two-back tasks (see figure 4, right columns). These regions with greater activation in the patients with HIV were typically in the periphery of, or adjacent to, the corresponding regions activated in the control subjects. In contrast, brain regions activated in the control subjects typically also were activated in the patients with HIV; there were no differences in the BOLD signals in the regions that were activated in both groups (see figure 2).

Performance during fMRI. All participants performed more slowly and less accurately as the tasks required increasing load on working memory and attention (table). The increasing order of task difficulty was confirmed by the increasing reaction times on these tasks (analysis of variance, $p < 0.0001$); post hoc analyses showed significant differences in reaction times between all the tasks (ranging from $p = 0.006$ to $p < 0.0001$), except for those between one-increment and one-back, which had similar reaction times. Compared with the control subjects, the patients with HIV showed no significant difference in accuracy, but were slower in performing these tasks (analysis of variance, $p = 0.05$; see the table). The patients' reaction time was slowest (−23%) and least accurate (−11%) for the most difficult task in the table (two-increment). In the patients with HIV, but not in the control subjects, the percentage of signal change in most of the activated brain regions correlated with the performance on the sequential number tasks (positively with reaction times and negatively with percentage of accuracy), but not on the simple reaction time or one-back task because almost all subjects performed at 100% (see the table).

Table *Performance data (reaction times and % accuracy),* p *values, and correlations with % signal changes in LPFC and PPC*

Reaction	Seronegative control subjects	Patients with HIV	% Differences	*p* Value	Correlation with % signal change in LPFC in patients with HIV		Correlation with % signal change in PPC in patients with HIV	
					Left	Right	Left	Right
Simple reaction								
Time, ms	331 ± 47	384 ± 117	+16%	NS	NS	NS	NS	NS
% Accuracy	99.9 ± 0.4	98 ± 2.8	−2%	NS	NS	NS	NS	NS
1-Back								
Time, ms	471 ± 49	548 ± 82	+16%	0.03	NS	NS	NS	NS
% Accuracy	99.5 ± 1.6	96 ± 6	−3.5%	NS	NS	NS	NS	NS
1-Increment								
Time, ms	491 ± 53	593 ± 119	+21%	0.03	$r = 0.65$	$r = 0.76$	$r = 0.60$	NS
					$p = 0.02$	$p = 0.003$	$p = 0.03$	
% Accuracy	83 ± 9.6	84 ± 7	−1%	NS	NS	$r = -0.74$	NS	NS
						$p = 0.004$		
2-Increment								
Time, ms	573 ± 136	703 ± 217	+23%	0.08	$r = 0.64$	NS	$r = 0.62$	$r = 0.56$
					$p = 0.02$		$p = 0.02$	$p = 0.05$
% Accuracy	73 ± 12	65 ± 18	−11%	NS	$r = -0.49$	$r = -0.66$	$r = -0.64$	$r = -0.56$
					NS	$p = 0.01$	$p = 0.02$	$p = 0.05$

Because of technical errors, data for 2-back were lost.

p Values of ≤0.05 are considered significant.

NS = not significant; LPFC = lateral prefrontal cortex; PPC = posterior parietal cortex.

Discussion. This preliminary study compares brain activation in patients with HIV with that in 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.[26] The fMRI activation paradigms used in this study produced robust and consistent activation of the LPFC, the PPC, and the SMA across participants, as observed in previous studies of working memory.[27-31] We also observed caudate activation associated with the working memory tasks.[26] In the control subjects and the patients with HIV, brain activation increased with task difficulty, from simple reaction to sequential letters or numbers. Similar results of increased brain activation with increased task difficulty have been reported.[26,32,33] These findings imply a relationship between the cognitive load and the signal changes on fMRI, probably because of task-related attentional modulation of neuronal activity or, alternatively, recruitment of the neuronal reserve capacity to solve the more complicated tasks. For this discussion, we define attentional modulation as the influence of attention on brain function, as measured by the changes on fMRI signals, and neuronal reserve capacity is defined as the additional capacity of a neural network to perform a certain function.

The patients with HIV showed greater activation (BOLD signal changes) in some brain regions compared with control subjects while performing each of these tasks. The greater activation in the patients with HIV often occurred in the periphery of or adjacent to the corresponding activated brain regions in the control subjects, but typically not in the regions already activated in the control subjects. This outward extension of the brain activation pattern suggests a saturation of the neural activity in the normally activated regions and a need to recruit adjacent neural substrate, and it supports the hypothesis that the reserve system of the neuronal network is being used.

Injury to the neural substrate attributable to the HIV infection appears to necessitate greater attentional modulation of the neural circuits, hence a greater use of the neuronal reserve, to maintain performance on the simpler tasks (simple reaction and one-back), with little or minimal reserve left for the more complex tasks. This hypothesis is partly supported by the trend that on the simple reaction task, patients with HIV were able to maintain their performance accuracy (−2%) despite being 16% slower compared with the seronegative control subjects. The slower performance may reflect increased time required for additional neural processing. However, the patients were 23% slower on the most difficult task (two-increment) and were least accurate (−11%) (see the table). Therefore, with the more difficult tasks, if little or no brain reserve is left, performance might not be maintained.

Furthermore, the BOLD signal change in the LPFC correlated with the performance (reaction time and accuracy) on the sequential number tasks. Patients with HIV and higher BOLD signal changes were slower and less accurate. Together, these findings indicate that the neural substrate for cognitive deficits in patients with HIV-associated brain injury is increased requirement for attentional modulation.

The regional difference in brain activation between the patients with HIV and the control subjects provides further insight into the processes underlying the cognitive deficits. With the simpler tasks (simple reaction and one-back), the PPC were activated more in the patients with HIV than in the control subjects. In contrast, the more complex tasks (two-back, one-up, and two-up) caused relatively more activation in the frontal brain regions (LPFC and SMA) of the patients with HIV. The SMA, in particular, is observable in the group data for one-up and two-up tasks only in the patients with HIV, but not in the control subjects, and more in the two-back task in the patients with HIV than in the control subjects. These findings suggest a shift of neural processing with increased cognitive load from the parietal to the frontal brain regions in the patients with HIV compared with the control subjects. Two factors may contribute to this regional shift in attentional modulation with task difficulty.

First, attention-requiring tasks are associated with greater activation in the frontal cortices than the parietal cortices, even in healthy subjects. This has been shown in an fMRI study of visual attention in healthy subjects, in which moderate attentional modulation (moderate increase of the fMRI signal) was observed in the PPC, but strong modulation (larger increase of fMRI signal) was found in the LPFC and SMA.[34] Second, injury in the frontostriatal system may necessitate even greater attentional modulation, with recruitment of additional neural processes and greater frontal activation in the patients with HIV than in the control subjects, to perform these working memory tasks. The frontostriatal system is often most severely affected in patients with HIV dementia based on neuropathologic and neuroimaging studies.[16,35-37] In particular, the dopaminergic system, which has a major role in regulating working memory function in the prefrontal cortices,[38] may be affected in HIV dementia.[39,40]

Working memory deficits have been reported and observed in patients with HIV dementia,[9-11] but patients with HIV who were asymptomatic were found to have normal working memory.[12] Although the accuracy on the working memory tasks in our patients with HIV was not different from that in the control subjects, increased task-dependent brain activation, especially in the frontal lobes, was observed in the patients with HIV. Therefore, fMRI may be more sensitive than clinical evaluations for detecting working memory deficits associated with HIV brain injury.

Increases in brain activation in selected brain regions also have been reported in other brain disorders, including children with attention deficit disorder,[41] adults with mild traumatic brain injury[42] or schizophrenia,[43] and people at risk for AD.[44] Therefore, the concept that brain injury leads to increased use of brain reserve capacity may be further supported from fMRI studies of other brain disorders.

One potential confound in the current study is that all patients but one were taking antiretroviral medications. The BOLD fMRI signal may be affected by medications, as has been observed in schizophrenic patients who were taking typical antipsychotic medications.[45] Unlike typical antipsychotic medications that affect the dopaminergic system and, therefore, indirectly affect the microvasculature, antiretroviral medications are not known to affect cerebral perfusion. Previous studies in patients with HIV, however, have shown alterations in cerebral perfusion,[15,46] which also may contribute to the abnormal BOLD signals. The relationship between altered cerebral perfusion and BOLD signal changes is unknown. However, the current study showed task-dependent activation changes in patients with HIV that are difficult to explain based solely on vascular abnormalities. Nevertheless, future fMRI studies should evaluate perfusion and BOLD signal changes in the same patients with HIV before and during antiretroviral treatment to understand the relationship between perfusion abnormalities and BOLD signal changes and to exclude the possibility that these medications might affect cerebral perfusion or the BOLD signal.

The task-dependent increased frontal activation in the patients with HIV suggests that the neural correlate of attentional deficits may be excessive attentional modulation as a result of frontostriatal brain injury. The presence of abnormalities in the fMRI response in the patients with HIV, even with the simpler tasks, indicates that fMRI is exquisitely sensitive for detecting injury to the neural substrate in patients with HIV. Future studies will determine whether these fMRI techniques can be used to monitor the efficacy of antiretroviral medications.

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