

veloping brain with early bilateral periventricular damage. Overall, the present findings bridge the gap between behavioral deficits and recording of functional cortical activity offering new insights into the functional pathology of PVL.

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## The Human Immunodeficiency Virus Reduces Network Capacity: Acoustic Noise Effect

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**Objective:** Increased acoustic noise (AN) during working memory leads to increased brain activation in healthy individuals and may have greater impact in human immunodeficiency virus (HIV) patients. **Results:** Compared with control subjects, HIV patients showed reduced AN activation and lower neuronal marker *N*-acetylaspartate in prefrontal and parietal cortices. Competing use of the working memory network between AN and cognitive load showed lower dynamic range of the hemodynamic responses in prefrontal and parietal cortices in HIV patients. **Interpretation:** These findings suggest that reduced reserve capacity of the working memory network in HIV patients and additional stress (eg, AN) might exhaust the impaired network for more demanding tasks.

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Patients with human immunodeficiency virus (HIV)–associated dementia commonly have slower psychomotor and motor speed, and deficits in attention and memory<sup>1</sup>; in particular, working memory (WM) is affected.<sup>2–4</sup> Abnormal patterns of brain activation on functional magnetic resonance imaging (fMRI) during WM tasks have been detected in HIV patients with mild dementia,<sup>5</sup> as well as in HIV patients with normal cognitive performance on neuropsychological

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tests.<sup>6</sup> Similarly, altered brain activation patterns suggesting neuroadaptation in the brains of HIV patients with or without cognitive deficits were detected on fMRI during visual attention tasks.<sup>7</sup> These studies demonstrate that fMRI can detect changes due to HIV brain injury even during the asymptomatic stage of the disease and suggest an increased usage of brain reserve to maintain cognitive performance as a compensatory response. However, these fMRI studies did not consider how acoustic noise (AN) during fMRI might additionally interfere with cognitive function or brain activation. The intrinsically high sound pressure levels (90–130dB) produced by the scanner may interfere with cognitive tasks and change brain activation differentially for patients and control subjects.<sup>8</sup> We recently demonstrated that increased scanner noise increased brain activation in healthy subjects.<sup>9</sup> This study evaluates the effect of AN on WM processing in men infected with HIV.

### Subjects and Methods

Ten HIV-positive men (age,  $37.1 \pm 2.7$  years; education,  $15.0 \pm 1.0$  years) and 15 HIV-seronegative men (age,  $34.4 \pm 2.3$  years; education,  $15.8 \pm 0.6$  years) participated in this fMRI study performed on a 4-tesla Varian MRI System (Varian Inc., Palo Alto, CA). All subjects were screened carefully by a neuropsychiatric examination to ensure they fulfilled study criteria that included only HIV patients with CD4 less than  $500/\text{mm}^3$  and normal range of hearing on audiometry, and excluded other brain disorders, drug dependence, head trauma, or any other contraindications for MRI. All subjects also had screening blood tests (including HIV tests in the control subjects) and urine toxicology, as well as a battery of neuropsychological tests. The subjects performed two sessions of verbal WM tasks with graded levels of difficulty<sup>5,10</sup> (0-, 1-, and 2-back) under two different sound pressure levels (“Quiet”: 92dB; “Loud”: 104dB) using the same fMRI protocol as reported previously.<sup>9</sup> Half the studies started with the Quiet session; the remaining studies started with the Loud session to control for practice effects.<sup>11</sup> Localized proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) was additionally performed in the left superior prefrontal (SPF) and right superior parietal (SP) lobes to determine whether brain injury due to HIV contributed to abnormal activation on fMRI. The statistical analyses of the fMRI data sets were performed as reported previously<sup>9</sup> using the Statistical Parametric Mapping package SPM99 (Wellcome Department of Cognitive Neurology, London, United Kingdom). The MRS data sets were analyzed with the commercial LC model program.<sup>12</sup> We used our absolute quantitation approach into the linear combination model (LC Model) program to determine the metabolite concentrations (corrected for cerebrospinal fluid content).<sup>13,14</sup>

### Results

HIV patients had a CD4 count of  $320 \pm 50/\text{mm}^3$  and a plasma viral load of  $5,720 \pm 3,390$  copies/ml. Two HIV patients were not taking antiretroviral medica-

tions, three patients were on stable regimens of two antiretroviral medications, and five patients were taking stable potent antiretroviral regimens. The patients had minimal symptoms, with an average Karnofsky score of  $93.0 \pm 2.7$ , performed well on the HIV dementia scale<sup>15</sup> ( $14.8 \pm 0.3$ ), and were slower on two of the reaction time tasks that required WM (choice reaction time, 50 milliseconds slower,  $p = 0.036$ ; one-back cued reaction time, 73 milliseconds slower,  $p = 0.047$ ). Performance accuracy and reaction times during fMRI were similar for HIV patients and control subjects and were not affected by increased AN (Fig 1A). All HIV patients and control subjects had normal hearing and similar auditory bandwidth (HIV patients: mean  $\pm$  standard deviation,  $6,655 \pm 2,186\text{Hz}$ ; control subjects:  $6,667 \pm 1,800\text{Hz}$ ). The concentration of *N*-acetylaspartate was lower for the HIV group in the SPF ( $p = 0.02$ ) and SP ( $p = 0.003$ ) regions (see Fig 1C), in agreement with previous MRS studies.<sup>16</sup>

For control subjects, Loud scans produced larger blood oxygen level dependent responses than Quiet scans in the cerebellum ( $p_{\text{corrected}} < 0.0005$ , corrected for multiple comparisons) and the middle, medial (medFG), and lingual (LG) gyri ( $p_{\text{corrected}} < 0.029$ ; Fig 2, top left). For HIV-positive men, louder AN increased fMRI signals only in the cerebellum and LG ( $p_{\text{corrected}} < 0.0005$ ), but decreased fMRI signals in the superior parietal cortex (SPC; see Fig 2, top right, green regions).

With increased noise level, HIV patients activated less compared with the effects in control subjects in the cerebellum ( $p_{\text{corrected}} = 0.045$ ), SPC ( $p_{\text{corrected}} < 0.0005$ ), and medFG ( $p_{\text{corrected}} = 0.028$ ) (see Fig 2, bottom left).

Across subjects in both groups, the load responses during Quiet scans (2-back minus 1-back) correlated negatively with the AN responses during the 2-back task in the medFG, SPC, and the cerebellum (correlation factor,  $-0.47 > R > -0.82$ ;  $p < 0.04$ ; see Fig 2, bottom). The intercept of the regression lines with the *y*-axis (WM load) was significantly higher for control subjects than for HIV patients in three regions (SPC:  $p = 0.001$ ; medFG:  $p = 0.03$ ; cerebellum:  $p = 0.04$ ).

### Discussion

This study has two major findings. First, AN has differential effects on brain activation in HIV patients compared with control subjects. Second, the load and AN responses correlated negatively in the medFG, parietal cortices, and cerebellum for both groups; however, the intercept of the linear regression in these regions was lower for HIV patients than for control subjects. These findings suggest that louder noise is associated with differential increased usage of brain reserves in control subjects and HIV patients. If HIV patients have brain injury that leads to a diminished

reserve network capacity, this capacity may be saturated more easily with increased AN, which, in turn, would decrease their ability to perform at higher WM load.

Evidence for brain injury in these HIV patients is demonstrated by lower neuronal marker *N*-acetylaspartate in the SPF and SP lobes. These findings are consistent with prior MRS studies that suggest neuronal injury is associated with cognitive impairment in HIV patients.<sup>16</sup> The HIV patients in this study, however, had relatively mild cognitive deficits with slower performance on two of the reaction time tasks that required WM, but relatively normal performance on other neuropsychological tests.

Consistent with prior observations,<sup>9</sup> Loud scans produced larger blood oxygen level dependent responses during WM tasks than Quiet scans in the cerebellum, the LG, and the PFC in the control subjects. This finding suggests that louder scanner noise leads to increased attentional requirement to perform a given task, leading to increases in fMRI signals.<sup>9</sup> Differential

AN effects for control and HIV-positive men are consistent with previous results from auditory event-related potential studies that found lower wave amplitudes<sup>17</sup> and longer wave latencies<sup>18</sup> in HIV-positive patients compared with control subjects. The findings suggest reduced network capacity for attention processing as a result of HIV-associated brain injury. Decreased WM load activation in HIV patients also suggests that they have decreased capacity to modulate the WM network to perform the more difficult task.

The negative correlations between the WM load effect and the AN effect in the SPF and SP cortices demonstrate that subjects who showed the largest increases in brain activation with louder scans showed the least attentional modulation with the WM load, and vice versa. This finding supports the theoretical notion that the WM network is a limited capacity system.<sup>19</sup> The *y* intercept of the regression lines, which represents the average dynamic range of hemodynamic responses in the network, was higher for control subjects than for

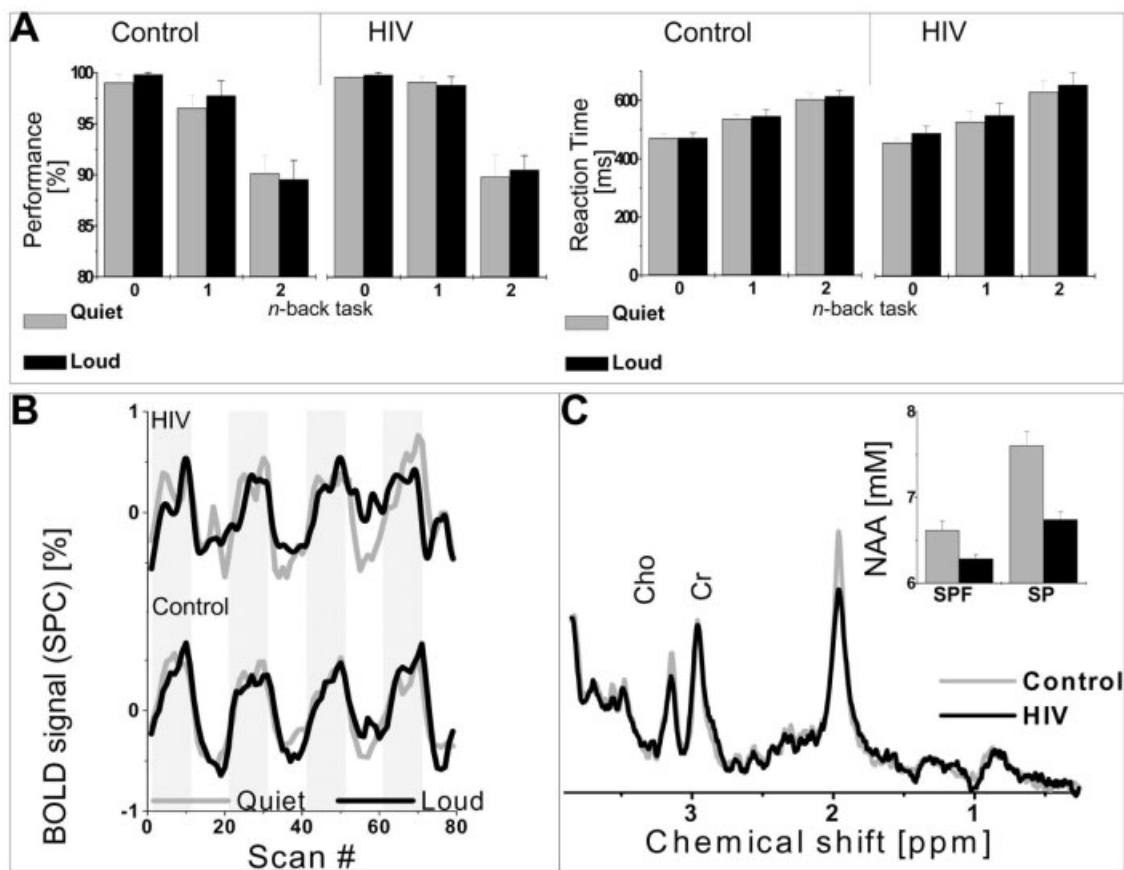


Fig 1. (A) Subjects' performance accuracy (left) and reaction times (right) during the functional magnetic resonance imaging tasks for "Quiet" and "Loud" scans. (B) Average time courses of blood oxygen level dependent (BOLD) responses across subjects in the superior parietal cortex (SPC; 0.73cc<sup>3</sup> region of interest) for Quiet and Loud scans. (C) Representative proton magnetic resonance (<sup>1</sup>H-MR) spectra for control and human immunodeficiency virus (HIV)-positive men. The concentration of *N*-acetylaspartate (NAA), a neuronal cell marker, was lower for HIV patients in the superior prefrontal (SPF; *p* = 0.02) and superior parietal (SP; *p* = 0.003) white matter regions (bar plot).

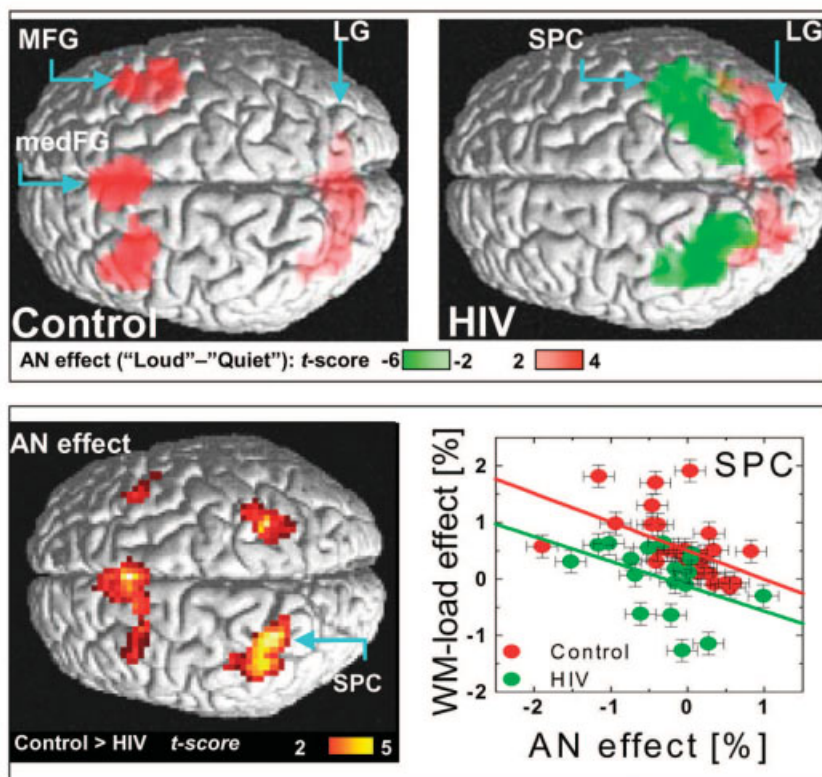


Fig 2. (Top) Group analyses of differential “Loud” minus “Quiet” activation during the working memory (WM) tasks (1-back and 2-back, combined); louder scans produced increased brain activation in the lingual (LG; both groups), middle (MFG), and medial gyri (medFG) in control subjects, but reduced activation in the superior parietal cortex (SPC) in human immunodeficiency virus (HIV) patients. (Bottom left) Brain regions where acoustic noise (AN) activation was lower in HIV men than in control men. (Bottom right) The WM load (“2-back” – “1-back”; “Quiet”) and the AN (“Loud” – “Quiet”; “2-back”) effects correlated negatively in the WM network; for HIV patients (green), the intercept of the linear regression line with the y-axis (dashed line) was lower than for control subjects (red) in the superior parietal (SP) and superior prefrontal (SPF) cortices (not shown).

HIV men in the SP and SPF cortices (see Fig 2). This finding further suggests that the maximum network capacity may be reduced in HIV patients. The 2-back task demands a high level of attention and sustained WM; therefore, some subjects may require the use of near-full network capacity to perform well on the task. The behavioral data during the study demonstrate that performance accuracy dropped from 99 to 90%, and reaction time increased from 530 to 630 milliseconds from 1-back to 2-back (see Fig 1A). Therefore, with increased AN, the lower reserve capacity in HIV patients may be exhausted sooner for more demanding cognitive processing (ie, further increased WM load or cued reaction time tasks). These findings suggest that HIV patients might require a low-noise environment to maintain normal daily activity. The HIV patients in this study had normal hearing; however, HIV/AIDS patients frequently have auditory dysfunction. We anticipate that most background and ambient noise (low-to-medium frequencies) would have similar interfering effects on attention in most HIV patients because most suffer from high-frequency sensorineural hearing loss.<sup>20</sup>

Lastly, because increased scanner noise can affect healthy and injured brains differently, comparison of brain activation patterns of a particular disorder across different fMRI studies should take into account the effect of scanner noise, which might vary with field strength and different fMRI sequences.

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# Periodic Electroencephalogram Complexes in a Patient with Variant Creutzfeldt–Jakob Disease

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**Objective:** Based on the current criteria, the diagnosis of “possible” or “probable” variant Creutzfeldt–Jakob disease (vCJD) implies the absence of periodic sharp wave complexes (PSWCs) in the electroencephalogram (EEG). To verify this point, we investigated the development of the EEG changes along the course of the disease in a patient with vCJD. **Methods:** Long-lasting EEG-polygraphic recordings were performed once a month during the last year of illness. **Results:** We found the occurrence of a typical EEG periodic pattern in the late clinical stage of the vCJD patient. **Interpretation:** In the light of our finding, the diagnostic criteria for vCJD should be amended to include the possibility of a typical periodic EEG in advanced stages of disease in cases with long survival.

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Variant Creutzfeldt–Jakob disease (vCJD) was first described in 1996 as a novel form of human spongiform encephalopathy<sup>1</sup> and subsequently was found to be causally linked to bovine spongiform encephalopathy (BSE).<sup>2,3</sup> With respect to sporadic CJD (sCJD), distinguishing features of vCJD include young age of onset, predominantly psychiatric presentation, relatively long duration, and presence of large numbers of amyloid deposits in form of “florid” plaques in the cerebral cortex and cerebellum<sup>1</sup> made up of a distinct type of the disease-associated prion protein (PrP<sup>res</sup>) termed type 4 PrP<sup>res</sup> (Collinge’s classification)<sup>2</sup> or type 2B PrP<sup>res</sup> (Parchi’s classification).<sup>4</sup> Based on the analysis of a series of patients with pathologically confirmed vCJD and cases referred as suspect vCJD in which the diag-

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