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The human immunodeficiency virus reduces network capacity: acoustic noise effect

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Abstract

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

Introduction

Patients with human immunodeficiency virus (HIV)-associated dementia commonly have slower psychomotor and motor speed, and deficits in attention and memory¹; in particular, working memory (WM) is affected.^{2–4} Abnormal patterns of brain activation on fMRI during working memory tasks have been detected in HIV patients with mild dementia⁵, as well as in HIV patients with normal cognitive performance on neuropsychological tests.⁶ Similarly, altered brain activation patterns suggesting neuroadaptation in the brains of HIV patients with or without cognitive deficits were detected during visual attention tasks on fMRI.⁷ 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 (*spl*: 90–130 dB) produced by the scanner may interfere with cognitive tasks and change brain activation differentially for patients and control subjects.⁸ We recently demonstrated that increased scanner noise increased brain activation in healthy subjects.⁹ The present study evaluates the effect of AN on WM processing in men infected with HIV.

Methods

Ten HIV-positive men (age = 37.1 ± 2.7 years; education = 15.0 ± 1.0 years) and 15 HIV-seronegative men (age = 34.4 ± 2.3 years; education = 15.8 ± 0.6 years) participated in this fMRI study performed on a 4 Tesla Varian MRI System. All subjects were carefully screened by a neuropsychiatric examination to ensure they fulfilled study criteria that included only HIV

subjects with $CD4 < 500/mm^3$ 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 controls) 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^{5, 10} (0-, 1-, and 2-back) under two different *spl* (“Quiet”: 92 dB; “Loud”: 104 dB) using the same fMRI protocol as reported previously.⁹ Half the studies started with the “Quiet” session; the remaining studies started with the “Loud” session to control for practice effects.¹¹ Localized proton magnetic resonance spectroscopy (¹H-MRS) was additionally performed in the left superior prefrontal (SPF), and right superior parietal (SP) lobes to determine if brain injury due to HIV contributed to abnormal activation on fMRI. The statistical analyses of the fMRI datasets were performed as reported previously⁹ using the statistical parametric mapping package SPM99 (Wellcome Department of Cognitive Neurology, London UK). The MRS datasets were analyzed with the commercial LC model program.¹² We used our absolute quantitation approach into the LC model program to determine the metabolite concentrations (corrected for CSF content).^{13, 14}

Results

HIV patients had $CD4$ count of $320 \pm 50/mm^3$, and a plasma viral load of $5,720 \pm 3,390$ copies/ml. Two HIV patients were not taking antiretroviral medications, 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 score¹⁵ of 93.0 ± 2.7 , performed well on the HIV dementia scale¹⁶ (14.8 ± 0.3), and were slower on two of the reaction time tasks that required working memory (choice reaction time, 50 ms slower, $p = 0.036$; one-back cued reaction time, 73 ms slower, $p = 0.047$). Performance accuracy and reaction times during fMRI were similar for HIV and control subjects, and not affected by increased acoustic noise (Fig 1A). All HIV patients and control subjects had normal hearing and similar auditory bandwidth (HIV: mean $\pm$ SD: 6655 ± 2186 Hz; control subjects: 6667 ± 1800 Hz). The concentration of N-acetylaspartate (NAA) was lower for the HIV group in the SPF ($p = 0.02$), and SP ($p = 0.003$) regions (Fig 1C), in agreement with previous MRS studies.¹⁷

For control subjects, “Loud” scans produced larger BOLD responses than “Quiet” scans in the cerebellum (CER, $p_{corrected} < 0.0005$, corrected for multiple comparisons), and the middle (MFG), medial (medFG), and lingual (LG) gyri ($p_{corrected} < 0.029$; Fig 2, Upper left panel). For HIV-positive men, louder acoustic noise increased fMRI signals only in the CER and LG ($p_{corrected} < 0.0005$), but decreased fMRI signals in the superior parietal cortex (SPC; Fig 2, Upper right panel, green regions). With increased noise level, HIV patients activated less compared to the effects in controls in the CER ($p_{corrected} = 0.045$), SPC ($p_{corrected} < 0.0005$), and medFG ($p_{corrected} = 0.028$) (Fig 2, Bottom left panel).

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 CER (correlation factor, $-0.47 > R > -0.82$; $p < 0.04$; Fig 2, bottom panel). The intercept of the regression lines with the y-axis (WM-load) was significantly higher for controls than for HIV subjects in three regions (SPC: $p = 0.001$, medFG: $p = 0.03$; CER: $p = 0.04$).

Discussion

This study has two major findings. First, acoustic noise has differential effects on brain activation in HIV-patients compared to control subjects. Second, the load- and AN-responses correlated negatively in the medFG, parietal cortices, and cerebellum for both groups; but the intercept of the linear regression in these regions was lower for HIV subjects than for controls.

These findings suggest that louder noise is associated with differential increased usage of brain reserves in controls and in HIV subjects. If HIV subjects have brain injury that leads to a diminished reserve network capacity, this capacity may be saturated more easily with increased acoustic noise, which in turn would decrease their ability to perform at higher working memory load.

Evidence for brain injury in these HIV subjects is demonstrated by lower neuronal marker NAA in the superior prefrontal and parietal lobes. These findings are consistent with prior MRS studies that suggest neuronal injury is associated with cognitive impairment in HIV patients.¹⁷ These HIV subjects, however, had relatively mild cognitive deficits with slower performance on two of the reaction time tasks that required working memory, but relatively normal performance on other neuropsychological tests.

Consistent with prior observations⁹, “Loud” scans produced larger BOLD responses during working memory 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.⁹ Differential AN-effects for control and HIV men are consistent with previous results from auditory event-related potential (ERP) studies that found lower wave amplitudes¹⁸ and longer wave latencies¹⁹ in HIV-positive compared to 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 subjects also suggests that they have decreased capacity to modulate the working memory network to perform the more difficult task.

The negative correlations between the WM-load effect and the AN-effect in the SPFC and the SPC 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 working memory network is a limited capacity system.²⁰ The y-intercept of the regression lines, which represents the average dynamic range of hemodynamic responses in the network, was higher for controls than for HIV men in the SPC and the SPFC (Fig 2). This finding further suggests that the maximum network capacity may be reduced in HIV patients. The 2-back task demands high level of attention and sustained working memory; 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 increases from 530 to 630 ms from 1-back to 2-back (Fig 1A). Therefore, with increased acoustic noise the lower reserve capacity in HIV patients may be exhausted sooner for more demanding cognitive processing (i.e. further increased WM-load or cued reaction time tasks). These findings suggest that HIV patients might require low noise environment in order 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 since most suffer from high frequency sensorineural hearing loss.²¹

Lastly, since 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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Figure 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 region of interest) for Quiet and Loud scans. (C) Representative proton magnetic resonance (1H-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).

Figure 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).