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Lower cognitive reserve in the aging human immunodeficiency virus-infected brain

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Abstract

More HIV-infected individuals are living longer; however, how their brain function is affected by aging is not well understood. One hundred twenty-two men (56 seronegative control [SN] subjects, 37 HIV subjects with normal cognition [HIV+NC], 29 with HIV-associated neurocognitive disorder [HAND]) performed neuropsychological tests and had acceptable functional magnetic resonance imaging scans at 3 Tesla during tasks with increasing attentional load. With older age, SN and HIV+NC subjects showed increased activation in the left posterior (reserve, “bottom-up”) attention network for low attentional-load tasks, and further increased activation in the left posterior and anterior (“top-down”) attention network on intermediate (HIV+NC only) and high attentional-load tasks. HAND subjects had only age-dependent decreases in activation. Age-dependent changes in brain activation differed between the 3 groups, primarily in the left frontal regions (despite similar brain atrophy). HIV and aging act synergistically or interactively to exacerbate brain activation abnormalities in different brain regions, suggestive of a neuroadaptive mechanism in the attention network to compensate for declined neural efficiency. While the SN and HIV+NC subjects compensated for their declining attention with age by using reserve and “top-down” attentional networks, older HAND subjects were unable to compensate which resulted in cognitive decline.

Keywords

Aging; Attention; Brain reserve; fMRI; HIV

1. Introduction

HIV-infected individuals are living longer because of effective combination antiretroviral therapy (cART); hence, half of the HIV-infected population in the United States will be older than 50 years by 2015 (Kirk and Goetz, 2009). Chronic HIV infection is associated with neuroinflammation, glial activation, and neuronal apoptosis (Gray et al., 2001; Kaul et al., 2001), which might lead to HIV-associated neurocognitive disorders (HAND) (Antinori

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Disclosure statement

The authors have no actual or potential conflicts of interest.

All study participants completed the protocol after signing a written consent form approved by our institution.

Appendix A. Supplementary data

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et al., 2007). Despite viral suppression with cART, HIV patients continue to show ongoing neuroinflammation, with increased diffusivity on diffusion tensor imaging over time (Chang et al., 2008b).

With cART, HIV-associated dementia decreased from 7% to 1%, but the milder forms of HAND, including asymptomatic neurocognitive impairment and mild neurocognitive disorder, remain common—up to 50% (Heaton et al., 2011; McArthur et al., 2010). HAND subjects show deficits in attention, executive function, fluency, learning, memory, and slower psychomotor or motor speed (Heaton et al., 2011). Similarly, normal brain aging is associated with glial activation (Terry et al., 1987) and decline in the same cognitive domains (Goh et al., 2012; Mazaux et al., 1995). These cognitive changes might be related partly to decline in dopaminergic function that occurs with HIV-infection (Berger et al., 1994, 2000; Chang et al., 2008a) and aging (Volkow et al., 1996, 1998; Wang et al., 2004). In addition, structural brain changes occur with normal aging throughout the brain, but HIV-infected individuals showed either premature or accelerated age-related brain atrophy particularly in the subcortical brain regions, although the brain regions affected by aging and HIV-infection might be distinct (Holt et al., 2012). These structural brain changes might contribute to cognitive deficits in HIV subjects. Therefore, aging might lead to additional or exacerbated cognitive deficits in HIV-infected subjects.

HIV patients with normal cognition (HIV+NC) or mild dementia showed hypoactivation of the normal attention network but increased usage of reserve brain regions (adjacent or contralateral to the normal network) during attention-requiring tasks, such as those that require working memory (Chang et al., 2001; Ernst et al., 2002; Melrose et al., 2008), tracking moving targets (Chang et al., 2004b; Ernst et al., 2009), mental rotation (Schweinsburg et al., 2012), and even for memory encoding (Castelo et al., 2006). However, despite stable cART, HIV+NC subjects showed further increased brain activation during visual attention over 1 year, suggesting increased usage of brain reserve (Ernst et al., 2009). HIV patients also showed lower than normal resting cerebral blood flow across the age span (Ances et al., 2010), slower than normal return to baseline hemodynamic response function (HRF) (Juengst et al., 2007), and lesser functional connectivity between the striatal and frontal regions (Melrose et al., 2008).

Changes in brain activation also occur with normal aging. For example, older age is associated with increased hippocampal activation (Adler et al., 2001; Laurienti et al., 2002) and decreased parietal and prefrontal activation (Grossman et al., 2002; Rypma and D'Esposito 2000) during working memory tasks. However, older subjects who performed better on a category learning task had greater parietal activation (Fera et al., 2005). In addition, greater hippocampal atrophy was associated with greater activation of the right prefrontal cortex (Persson et al., 2006). Furthermore, age-related decline in cognitive abilities might result in dedifferentiation, difficulty in recruiting specialized cognitive networks leading to activation of nonspecific neuronal resources (Li and Lindenberger 1999; Voss et al., 2008), or compensation and recruitment of additional cognitive reserves to counteract cognitive decline (Cabeza et al., 2002). This is further demonstrated by the findings that only older adults with higher performance show evidence of compensation, and those with lower performance show no evidence of compensation and inefficient use of recruited networks (Cabeza et al., 2002). Therefore, these variable brain activation changes associated with normal aging might also be seen in the aging HIV-infected individuals.

Whether age and HIV interact on brain activation during attention-requiring tasks is unknown, and was evaluated in this study. To assess how the normal aging brain or the HIV-infected aging brain might differ in terms of their cognitive reserve capacity, we employed a well validated visual attention tasks with increasing task difficulty or attentional

load (tracking 2 balls, 3 balls, and 4 balls). These tasks require both bottom-up visual attention (primarily in the inferior parietal regions, to detect the balls which are salient stimuli), as well as top-down control attention (in the dorsal parietal and prefrontal regions, to track the moving balls) (Jovicich et al., 2001). Previous studies showed that HIV-infected subjects showed greater load-dependent activation of the top-down attention network than seronegative (SN) healthy control subjects (Chang et al., 2004b). Based on the aforementioned studies, we hypothesized that, compared with SN subjects, HIV+NC subjects would show greater than normal age-dependent increases in activation of the reserve bottom-up network (parietal regions) on the simpler task, and additional increased activation of the top-down network (dorsal parietal and prefrontal regions) with increasing attentional load, whereas subjects with HAND would be unable to compensate, especially with higher attentional load, and show steeper age-dependent decreases in activation in both attention networks (prefrontal and parietal regions).

2. Methods

2.1. Research participants

A group of 128 men fulfilling study criteria completed the protocol after signing a written consent form approved by our institution. Only men were studied because brain activation on attention tasks varies with sex (Speck et al., 2000). Sixty-nine HIV-infected individuals [39 HIV+NC, 30 HAND] and 59 SN control subjects with similar age ranges and education were evaluated with detailed clinical assessments, including neuro-psychological tests. Three SN control subjects and 2 HIV+NC subjects who did not meet the performance criterion and 1 HAND subject who did not meet performance and movement criteria during the functional magnetic resonance imaging (fMRI) scan were excluded from subsequent analyses. The final sample included 122 subjects (56 SN controls, 37 HIV+NC, and 29 HAND subjects). The data from a subset of these subjects (32 SN and 31 HIV subjects) who had normal cognitive function on neuropsychological testing, were stable on antiretroviral medications for the HIV subjects, and additionally had 1-year follow-up scans were reported previously as part of the longitudinal study (Ernst et al., 2009). SN controls were included if they: (1) were men age 18 years; (2) had negative urine toxicology for common drugs of abuse (see previous report, Ernst et al., 2009); and (3) were HIV-seronegative. HIV subjects were included if they fulfilled criteria 1 and 2, and were (3) HIV positive, either medication naive or stable and taking antiretroviral agents for >6 months; (4) with or without HAND; (5) able to provide informed consent; and (6) had a nadir CD4 <500/mm³. Exclusion criteria for both subject groups were: (1) chronic medical or neuropsychiatric illnesses that might confound the study; (2) abnormal laboratory studies that might confound the outcome measures (e.g., hematocrit <37%, severe abnormalities on liver enzyme or renal function tests, abnormal electrocardiogram indicating cardiovascular disease); (3) history of head trauma with loss of consciousness >30 minutes; (4) history of drug dependence according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, except for nicotine; and (5) contraindications for magnetic resonance imaging (MRI).

2.2. Neuropsychological testing and HAND classifications

Each participant performed a battery of neuropsychological tests that evaluated the 7 cognitive domains required to assess HAND (Table 1). For each subject and cognitive domain, a Z-score normalized to data from 342 seronegative healthy subjects (adjusted for age and education) was calculated, as well as a global Z-score. Depressive symptoms were assessed using the Center for Epidemiological Studies-depression scale. We also estimated intellectual functioning with the New Adult Reading Test-Revised.

Each HIV subject was classified according to the “Updated Research Nosology for HAND” (Antinori et al., 2007): 37 HIV subjects had normal cognition on neuropsychological testing (HIV+NC group) and 29 HIV subjects showed signs of neurocognitive disorders (HAND) on neuropsychological testing. All subjects were further assessed using the Functional Activities Questionnaire, the Instrumental Activities of Daily Living scale (Pfeffer et al., 1982) and by clinical evaluations. Based on these assessments, the 29 HAND subjects were further classified to 13 with asymptomatic neurocognitive impairment, 14 with mild neurocognitive disorder, and 2 with HIV-associated dementia (Antinori et al., 2007).

2.3. Structural MRI and automated morphometry

All subjects performed structural MRI and fMRI studies of visual attention on a 3 Tesla Siemens Trio scanner. MRI included a 3-plane localizer (repetition time/echo time (TR/TE) = 20/5 ms; 1 average), a sagittal 3-D magnetization-prepared rapid gradient-echo (TR/TE/inversion time = 2200/4.91/1000 ms; 1 average; $208 \times 256 \times 144$ matrix), and an axial fluid attenuated inversion recovery sequence (TR/TE = 10,000/85 ms; 1 average; $205 \times 320 \times 28$ matrix) to rule out focal brain abnormalities. Automated morphometric analyses to determine subcortical and global brain volumes were performed on the magnetization-prepared rapid gradient-echo images using FreeSurfer 4.3.1 (<http://surfer.nmr.mgh.harvard.edu>). After brain extraction, the images were registered to an existing template before automated cortical, subcortical, and white matter structure segmentation, and then each was normalized to the estimated total intracranial volumes, as described previously (Chang et al., 2011).

2.4. fMRI data acquisition

Before fMRI, subjects had a brief training session outside the scanner. fMRI was performed using 3 single-shot gradient-echo echo planar imaging time series (TE/TR = 30/3000 ms, 3 mm slices, typically 46 axial slices, 64^2 matrix, 19.2 cm field of view, 126 time points), 1 per condition (2, 3, or 4 balls). An MRI trigger pulse was used to synchronize the stimulus software with the magnetic resonance (MR) acquisition. The fMRI tasks required mental tracking of multiple targets (2, 3, or 4 target balls) that were highlighted briefly among 10 balls moving randomly and colliding with each other (Jovicich et al., 2001; Pylyshyn and Storm 1988). For each condition (2, 3, or 4 balls), subjects performed 3 blocks, each comprising 60 seconds of active tracking (5 trials) alternating with 60 seconds of passive viewing (5 trials). At the beginning of each trial, an instruction indicated (for 2 seconds) whether subjects had to track actively (“TRACK”) or view passively (“DO NOT TRACK”). Next, 10 balls were displayed at random positions, in addition to a central fixation cross. Subjects were asked to fixate throughout the entire trial. In active-tracking trials, the 2–4 target balls to be tracked were highlighted briefly (3 seconds) with white squares, whereas the balls remained motionless for 3 seconds during passive-viewing trials. After this cue period, the balls started moving (simulated Brownian motion). After 8 seconds, the balls stopped moving; 2, 3, or 4 balls (equal to the number of target balls) that were either the same or different from the original target balls were briefly highlighted (for 1 second), and the subjects responded with a button press only if the balls were the same as the original targets. The subject's responses therefore provided an objective measure of tracking performance, with chance being, on average, 50%. Only scans with task performance accuracy >70% and motion <1 mm and <1° were accepted. Distortion (Zaitsev et al., 2004) corrections were performed during image reconstruction.

2.5. fMRI data analyses

fMRI time series were analyzed with the SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). Images were spatially normalized to the MNI152 atlas and spatially smoothed with an 8 mm full width at half maximum (FWHM) isotropic kernel.

Brain activation maps were calculated for each subject and task, using a fixed-effects model. Each subject's output from the fixed-effects analysis (t-images) were included in a subsequent random-effects multiple regression analysis, using each subject's age as a covariate, to test for positive and negative age correlations within each group for each task. Within-group binary masks, including all voxels exceeding the peak-level threshold, were created and then combined (e.g., SN plus HIV+NC) to constrain each subsequent random effects multiple regression, again using age as a covariate, that examined aging effects between the 3 groups (i.e., interactions). Statistical thresholds for analyses were a cluster-wise extent of >100 contiguous voxels that exceeded $p < 0.05$ family-wise error-corrected peak-level. SPM8 findings were illustrated using extracted regional % change in blood oxygenation level-dependent (BOLD) signal from each significant cluster (0.729 cm^3 centered at cluster maximum). To assess the contribution of age-related volumetric reductions, the multiple regression analyses were repeated with age-corrected intracranial volumes entered as a regressor.

2.6. Statistical analyses

Statistical analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC, USA). One-way analysis of variance (ANOVA), t test, or Fisher's exact test, were used to compare clinical characteristics, cognitive domains, and subcortical brain volumes between SN controls and HIV groups. Simes correction was used for subcortical brain volume comparisons. Repeated measures ANOVA was used to compare ball-tracking performance and reaction time with task difficulty (low, medium, high load) as the within-subject factor, and group (SN, HIV+NC, HAND) as the between-subject factor. Post hoc paired t tests were performed. Relationships between continuous variables were examined using Pearson correlations. Parametric tests were used because the data were normally distributed. P values < 0.05 were considered significant. Effect sizes using Cohen's d , Cohen's f^2 (for ANOVA), and odds ratio (for binary variables) are reported.

3. Results

3.1. Subject characteristics and cognitive function

Table 1 shows that SN and the 2 HIV groups were similar in age and age range, and had similar hematocrit (which might affect BOLD signals) (Levin et al., 2001). However, the HIV subjects had more depressive symptoms (on Center for Epidemiological Studies-depression scale) than SN control subjects. The 2 HIV groups had similar HIV disease severity, as assessed by CD4 count, nadir CD4 count, plasma viral load, and similar proportion of subjects with undetectable viral loads, duration of HIV infection, and were maintained with antiretroviral medications.

The subject groups had similar educational attainment, but estimated verbal IQs were lower in both HIV subject groups than the SN control subjects, with the lowest level in the HAND group. As expected, the HAND subjects had lower HIV-dementia scale than the HIV+NC subjects, and minimally lower scores on the Folstein Mini Mental State Examination than both HIV+NC and SN subjects. Also by definition, the HAND subjects performed worse than the SN and HIV+NC subjects on neuropsychological tests across all domains.

All subjects performed the fMRI ball-tracking tasks at relatively high accuracy (>88%; Fig. 1). Increasing task difficulty had an overall effect on accuracy across the 3 groups in repeated measures analysis ($F(2,235) = 6.91$; $p = 0.001$). The SN subjects showed a trend for declined accuracy with increasing task difficulty, and the HIV+NC group showed a decline only with the most difficult task (tracking 4 balls), whereas the HAND group showed decreased performance accuracy when the task became slightly more difficult

(tracking 3 balls) and on the most difficult (tracking 4 balls). Reaction time was slightly affected by increasing task difficulty ($F(2,232) = 2.79$; $p = 0.06$). However, this was because of the slower reaction times in HAND subjects only during the most difficult task (4 balls) (Fig. 1), which was associated with lower accuracy on this task ($r = -0.41$; $p = 0.04$). No overall group effects or group-by-task interactions were seen on accuracy or reaction time.

3.2. Age-dependent changes in brain activation during fMRI

Based on visual inspection and conjunction analyses, all groups showed similar activation patterns during the attention tasks (Supplementary Fig. 1 and Fig. 2), including bilateral superior and inferior parietal regions (right > left), bilateral frontal regions (right > left), and bilateral thalami and cerebellum (data not shown), consistent with previous fMRI studies on attention network performed on 3 Tesla and 4 Tesla MR scanners (Chang et al., 2004b; Ernst et al., 2009; Tomasi et al., 2006b, 2007).

Although fMRI task performance was high, the patterns of age-dependent changes in brain activation differed among the 3 groups. SN subjects showed age-dependent increases in BOLD signals in the left temporal and parietal cortices on the simplest 2-ball task (primarily a bottom-up attention network), no age-dependent increase in activation with the 3-ball task (perhaps because of practice effect). However, on the most difficult 4-ball task, greater age-dependent increased activation was found in the parietal and occipital regions (bottom-up network) and the frontal regions (top-down network) (Table 2, Fig. 2, left column). For the HIV+NC subjects, age-dependent increases in brain activation were observed for all 3 tasks, including extensive bilateral increases in both hemispheres for the intermediate (3 balls) and most difficult (4 balls) tasks (Table 2, Fig. 2, right column), to include the top-down network even on the 3-ball task. These findings remained significant even when the 2 youngest and the 1 oldest participant were removed from the analyses. Although age correlated with duration of HIV infection ($r = 0.29$; $p = 0.02$), covarying for the duration of HIV did not change the findings significantly. Conversely, subjects with HAND showed no significant BOLD signal increases with age after correcting for multiple comparisons, but some age-dependent decreases primarily in the left hemisphere (Figs. 4 and 5).

3.3. Group differences in age-dependence of brain activation

Several interactions between age and HIV group status were found. On the 3-ball task, HIV+NC subjects showed greater age-related increases in brain activation compared with SN subjects in the right parietal regions and cerebellar vermis (declive) (cluster-corrected $p < 0.0001$; Table 3; interaction $p = 0.001$ – 0.0005 at cluster maxima; Fig. 3A). Likewise, while tracking 4 balls, the HIV+NC, but not SN, subjects showed age-dependent increases in brain activation in the right parietal, cingulate, and paracentral regions (cluster-corrected $p = 0.006$; Table 3; interaction $p = 0.01$ – 0.0007 ; Fig. 3B). In contrast, age-dependent decreases in activation in HAND subjects, but increases in the SN subjects, were found in the left frontal, temporal, and occipital regions while tracking 4 balls (cluster-corrected $p = 0.009$; Table 3; interaction $p = 0.003$ – 0.0002 ; Fig. 4). Findings remained significant even when the 2 oldest participants were removed from the analyses (Fig. 3) or when the youngest participant was removed (Fig. 4). Therefore, interactions were observed in the left frontal (top-down control) regions between the HIV+NC (age-dependent increases) and HAND subjects (age-dependent decreases) while tracking 3 balls (Table 3, Fig. 5A) and 4 balls (Table 3, Fig. 5B).

3.4. Group differences in load-dependence of brain activation independent of age

When subject groups were compared for differences in brain activation in terms of task difficulty (load effects), using a repeated measures ANOVA, HIV+NC subjects showed load-dependent decreased activation and SN subjects showed load-dependent increase in the

right temporal region (cluster maximum: 45, -34, -17, Brodmann's area [BA] 20, fusiform gyrus; cluster level family-wise error-corrected $p = 0.020$, cluster size 1361 voxels), which included 2 subclusters (cluster maxima: 51, -28, -17; and 42, 11, -20, fusiform gyrus, BA 20, and superior temporal gyrus, BA 38); see Fig. 6. Two-way ANOVA or 2-way analysis of covariance from the extracted region of interest validated the SPM8 analyses ($p < 0.0001$, without covariation for age; $p < 0.0001$, covaried for age). However, HAND subjects showed only nonsignificantly load-dependent decreased activation compared with the other subject groups. These findings also validate the visual interpretations of the brain activation patterns reported in Supplementary Fig. 1.

3.5. Group differences in age-dependence of cognitive performance

Motor function declined with age across all subject groups, but the learning and memory domains showed a differential age effect among groups (Fig. 7). Specifically, HAND subjects, but not the other 2 groups, showed an age-dependent decline in learning domain (HIV+NC vs. HAND: interaction $p = 0.03$). Likewise, HAND subjects, but not HIV+NC or SN control subjects, showed age-dependent declines in memory (HIV+NC vs. HAND: interaction $p = 0.02$).

3.6. Relationship between BOLD activation and global cognitive Z-scores

Brain activation during the ball tracking tasks of HIV subjects and SN controls were evaluated in relation to the global Z-score, using age as a covariate. We found significant group differences on the relationship between BOLD activation in a large cluster in the right hemisphere (p family-wise error-corrected < 0.0001 ; $k = 3245$) and global Z-score during the tracking of 4-ball task only. BOLD signals extracted from region of interest centered on the 3 subcluster maxima are shown in Fig. 8, left column. While the HIV subjects showed decreased BOLD signals in all 3 brain regions as they approached or were below the global Z-score of -1, the SN control subjects showed a U-shaped curve with greater BOLD signals in 2 of the subregions, in those who were able to compensate and perform better (+0.5 to +1 Z-score) or those who could not compensate (-0.5 to -1.0). A trend for group difference in brain activation during the 3-ball task and global Z-score was found in a cluster in the right superior parietal region (p family-wise error-corrected = 0.076; $k = 1232$).

We further evaluated brain activation during the ball tracking tasks that might show a threshold effect in relation to the global Z-scores across all HIV subjects, and found this to occur only during the 4-ball task (data extracted from regions of interest centered around the 3 subcluster maxima are shown in Fig. 8, right column). In these 3 brain regions, HIV subjects who performed poorer than -1.0, only those with HAND showed lesser brain activation while HIV+NC and SN subjects showed relatively stable level of brain activation across the range of global cognitive Z-scores.

3.7. BOLD activation and brain volumes

Although the HIV subjects as a group showed smaller volumes than SN subjects in all brain regions measured, brain atrophy did not differ between HIV+NC and HAND subjects (Table 4), and the effect of age-corrected brain volumes on all analyses was minimal and did not change the results.

4. Discussion

This study found: (1) healthy SN control subjects showed age-dependent increases in activation primarily in the left temporal and parietal (bottom-up attention) regions with low attentional load but additionally required the left frontal (top-down attention) region for high attentional load. (2) HIV+NC subjects had age-dependent increases in activation primarily

in the left attention network during the 2-ball task, but showed load-dependent decrease rather than the normal increased activation with increasing task difficulty in the right temporal lobe region. Their inability to activate further with increasing attentional load led to their performance decline on the high attentional load task suggesting an exhausted reserve capacity. (3) As HAND subjects age, they showed no further reserve brain capacity to compensate with increasing attentional load despite their mild degrees of cognitive impairment. Therefore, the HIV-infected brain showed a complex response with aging. While HIV+NC subjects show age-dependent decreases in the brain regions that normally would activate more with increasing load (normal reserve region) but increased activation of an altered reserve network with aging, to compensate and maintain performance on the simplest task, older HAND subjects show age-dependent decline activation because of diminished reserve capacity, and hence have deficits on standard neuropsychological testing.

4.1. Age and load-dependent increases in activation in seronegative control subjects

In SN subjects, age-dependent increased activation in the left temporoparietal regions while tracking 2 balls, were extended into the left frontal (top-down attention) brain regions while tracking 4 balls. Because the visual attention network typically involves the right more than the left hemisphere (Chang et al., 2004b), the shift to left hemisphere activation with increasing age suggests that older SN subjects had to use their reserve network to maintain performance. In contrast, no age-dependent increased activation was seen on the 3-ball task, suggesting a preserved practice effect on this intermediate load task (Tomasi et al., 2004), even in the older subjects. These findings indicate that normal aging is associated with reduced neural efficiency in the attentional network, requiring additional recruitment of the left prefrontal executive attentional network as the attentional load increases.

Similarly, previous fMRI studies of healthy subjects reported age-dependent increased BOLD signals, predominantly in the frontal lobe and/or bilateral hemisphere (Cabeza et al., 1997; Fera et al., 2005; Gazzaley and D'Esposito, 2007; Park and Reuter-Lorenz, 2009; Reuter-Lorenz et al., 2000). This increased activation is interpreted as “scaffolding” or compensation of the “adaptive brain” in response to reduced neural efficiency with aging (Park and Reuter-Lorenz, 2009). Additionally, older healthy subjects showed altered “top-down” modulation of neural activity predominantly in their ability to suppress interfering stimuli (Gazzaley and D'Esposito, 2007), and hence poorer working memory performance.

4.2. Greater than normal age-dependent increases in brain activation in HIV+NC subjects

Like SN subjects, older HIV+NC subjects used their left (reserve) attention network to maintain performance, but on tasks that required only low and intermediate attentional load. However, this reserve capacity was exhausted in the older HIV+NC subjects during the high attentional load (4 balls) task because they performed worse on this task despite greater than normal age-dependent increased activation in the left parietal and cerebellar regions (bottom-up network). The inability to compensate for increasing task difficulty in the HIV+NC subjects was further demonstrated by the opposite load-dependent changes in brain activation in the left temporal lobe (fusiform) region compared with the SN control subjects.

4.3. Age-dependent decreases in activation in HAND subjects

The HAND subjects, despite their relatively mild cognitive deficits, showed only age-dependent decreased activation in the left (reserve and top-down) frontal regions, in contrast to the increased activation in these brain regions with age in the SN and HIV+NC subjects. The resulting interactions between HAND status and aging in the left frontal regions suggest that older HAND subjects had no further reserve to compensate, and hence had poorer performance during the intermediate and high attentional load tasks, and on many cognitive domains with neuropsychological testing. Therefore, the attention network in HAND

subjects appears to deteriorate with older age, resulting in lesser activation in the older subjects.

We further demonstrated that HIV subjects, especially those with global cognitive Z-scores at or below -1 , which comprise most of those with HAND, showed a threshold effect with lesser brain activation during the most difficult task (tracking 4 balls) in the right superior frontal region, extending to the left anterior cingulate cortex. This suggests that those with HAND could not use these brain regions to compensate or maintain cognitive function. In addition, the HAND subjects showed a differential relationship between the brain activation and cognitive performance compared with the SN control subjects in the right hemisphere, which are near the brain regions that the HIV+NC subjects activated more than the SN subjects to maintain performance.

The age-related decline in brain activation in the HAND subjects might be due to brain atrophy, which could lead to attenuation of the BOLD signals because of more cerebrospinal fluid within each voxel. However, automated brain morphometry demonstrated similar degrees of brain atrophy between the 2 HIV groups. Other factors, such as the apolipoprotein E-epsilon4 (*APOE-ε4*) genotype, also might play an important role in brain atrophy and cognitive dysfunction in these aging individuals (Chang et al., 2011). However, the current study does not have sufficient sample size for individuals with the $\epsilon 4$ genotype for such an analysis.

4.4. Brain reserve capacity

The concept of using reserve capacity to compensate in HIV-positive individuals is consistent with previous studies. For instance, younger HIV (Chang et al., 2001) and HIV +NC subjects (Ernst et al., 2002) showed increased brain activation compared with SN subjects on attention-requiring working memory tasks. HIV subjects also showed lower and limited reserve capacity on a paradigm that involved acoustic interference during working memory tasks (Tomasi et al., 2006a). Furthermore, in a longitudinal study, HIV+NC subjects maintained normal task performance and cognition but showed increased activation over 1 year, suggesting declined neural efficiency, whereas SN subjects had decreased brain activation, suggesting practice effects (Ernst et al., 2009). Therefore, further age-associated declines in neural efficiency might require HIV subjects to compensate even when they perform tasks with low attentional load, as observed in the current study.

Interestingly, the pattern of compensation in our HIV+NC subjects parallels that in patients with mild cognitive impairment, who show “paradoxical” greater activation on memory tasks (associative encoding) compared with control subjects and Alzheimer's disease patients (Sperling, 2007). Similarly, healthy seniors are more likely than healthy young adults to show overactivations at lower memory loads, and underactivations at higher memory loads (Cappell et al., 2010). Together, these findings suggest that compensation using the reserve network might be a common mechanism to maintain performance during mild stages of brain injury or in premature aging such as that seen in our HIV+NC subjects. However, when compensatory resources are exhausted such as that seen in our HIV+NC and HAND subjects during the higher attentional loads, cognitive decline ensues.

4.5. Possible pathophysiology for the age-dependent brain activation changes

These age-dependent brain activation changes in our subjects might be related to age-associated decline in dopaminergic function (Volkow et al., 1996, 1998), or neuroinflammation and glial activation (Conde and Streit, 2006; Terry et al., 1987). Dopaminergic transmission is essential for attention-requiring tasks. However, aging is associated with declines in presynaptic dopaminergic transporters (-6% per decade)

(Volkow et al., 1996) and post-synaptic dopamine D2 receptors (−4 to −6% per decade) (Rinne et al., 1993), which is associated with psychomotor slowing (Volkow et al., 1998). Similarly, HIV patients show reduced brain dopamine transporters (8%–17%) (Wang et al., 2004) and age-related decline in D2 receptors in the caudate (Chang et al., 2008a). In HIV subjects, lower dopamine transporter availability was associated with poorer performance on motor, psychomotor, attention, and working memory function. Likewise, lower binding for D2 receptors, associated with nicotine use, contributed to slower motor function in HIV patients (Chang et al., 2008a).

The relationship between neuroinflammation and cognitive function in the aging HIV population is not well studied. However, even serum inflammatory markers, such as haptoglobin levels and C-reactive protein, are associated with poorer cognitive outcome in the healthy aging population (Teunissen et al., 2003). HIV and aging showed additive effects on glial markers on MR spectroscopy (Chang et al., 2004a). Overall, both dopaminergic deficits and glial activation might reduce the efficiency of neural processing in the aging HIV-infected brain, requiring compensatory increases in brain activation to maintain cognitive performance.

Conversely, our HAND subjects showed age-dependent decreases in brain activation and cognitive performance, suggesting an inability to compensate or lack of further reserve capacity with age. HAND subjects might have even lower dopaminergic function, greater oxidative-stress mediated neuronal loss (Lipton, 1996), or microglial immunosenescence (Streit and Xue, 2010). Neuronal injury in HAND subjects was shown by elevated cerebrospinal fluid neurofilament proteins (Abdulle et al., 2007; Gisslen et al., 2007), lower neuronal marker N-acetylaspartate levels in the frontal white matter (Chang et al., 1999; Mohamed et al., 2010), and steeper than normal age-related declines in intracellular glutamate (Ernst et al., 2010) and N-acetylaspartate/total creatine (Harezlak et al., 2011).

Although we do not know the exact etiologies for the different compensatory responses between the 2 HIV subject groups, it is likely that the combination of greater dopaminergic deficits and neuronal injury in those with HAND than in HIV+NC, played important roles in these different patterns of activation with aging. Specifically, the frontostriatal circuit, which is involved in the “top-down” attentional modulation, might remain intact only in HIV subjects who still had sufficient dopaminergic function but not in the HAND subjects who likely had dopaminergic deficits. Future studies evaluating dopaminergic function or neuronal integrity in the frontal cortex in relation to cortical activation in HIV patients are needed.

The current study included a relatively large number of well screened and characterized subjects, and the groups were well-matched by age, education, and hematocrit, and by HIV disease severity between the HIV subgroups. We also applied strict criteria to ensure acceptable subject motion during fMRI. The parametric fMRI paradigm also proved important, because both age and HIV-related BOLD signal alterations are dependent on the attentional load. However, several limitations should be noted. First, the aging process might be variable across subjects; factors such as changes in vasculature with age might affect the HRF (Samanez-Larkin and D'Esposito, 2008), which might be altered by HIV infection (Juengst et al., 2007). Therefore, longitudinal evaluations are needed to validate whether the same patterns of age-related changes occur consistently over time, and the HRF needs to be included as a regressor from a different task for each subject in the group comparisons (Samanez-Larkin and D'Esposito, 2008). Second, because only men and few individuals older than age 65 years were studied, these findings might not be generalizable to the aging effects in HIV-infected women or in elderly HIV individuals. Third, although brain atrophy was not different between the 2 HIV groups, *APOE-ε4* genotype, which might lead to age-

by-HIV-status interactions (Chang et al., 2011), should be included as a covariate in future studies with equal proportion of participants with and without *APOE*- ϵ 4. Last, the present analysis was based on a general linear model approach, i.e., evaluation of main effects of aging and HIV status, and interactions between the 2, on brain activation. However, considering the variable patterns of compensatory brain activations across the different subject groups and tasks, broader network modeling approaches, such as structural equation models or other latent variable methods, might provide further insight into the relationships between aging, HIV infection, and regional brain activation, and its relation to compensation.

In conclusion, this study confirms our working hypothesis that HIV and aging act synergistically to exacerbate brain activation abnormalities on BOLD fMRI. Though the SN and HIV+NC subjects were able to compensate for declining neural efficiency with age, by using the left (reserve) temporoparietal and frontal (“top-down”) attentional network, older HAND subjects were unable to fully compensate or activate the reserve network, resulting in declined cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Performance accuracy (% correct $\pm$ standard error) and reaction times during the functional magnetic resonance imaging ball tracking task for each subject group. All groups showed a progressive decline in performance accuracy (in %) with increasing task difficulty. Although the decline was not significant in the seronegative (SN) subjects, the HIV subjects with normal cognition (HIV+NC) performed significantly poorer on the task with high attentional load (tracking 4 balls), and the HIV-associated neurocognitive disorder (HAND) group performed significantly poorer on the tasks with medium (tracking 3 balls) and high attentional load (tracking 4 balls). Only the HAND subjects showed slower reaction times with the most difficult task (tracking 4 balls).

Fig. 2.

Surface views of brain regions with age-dependent changes in blood oxygen level dependent signal during the visual attention (ball tracking) tasks in seronegative (SN) and HIV with normal cognition (HIV+NC) subject groups. Left panel: SN subjects show age-dependent increases in brain activation within the attention network, primarily in the left posterior cortex during low attentional load (2 balls), nonsignificant increase in activation during the medium attentional load (tracking 3 balls), and more extensive age-dependent increases in activation involving the left (L) frontal regions during the high attentional load (tracking 4 balls). Right panel: HIV+NC subjects show similar age-dependent increases in activation as the SN subjects in the L posterior attention network during the low attentional load (tracking 2 balls), but extensive age-related increases in activation throughout the attention network during the 3-ball and 4-ball tasks. Please see Table 2 for cluster maximum coordinates, size, corrected *p* values and *t* scores. Maps were created using $t > 2.0$ and cluster size > 750 voxels. Abbreviation: R, right.

Fig. 3.

Images showing brain regions with significant age by HIV status (seronegative [SN] subjects vs. subjects with HIV and normal cognition [HIV+NC]) interaction on blood oxygen level-dependent (BOLD) signals for the 3-ball task (A, cluster corrected $p < 0.0001$) and the 4-ball task (B, cluster corrected $p = 0.006$); see also Table 3. The scatter plots validated the interactions found on SPM8, showing dependence of BOLD signals extracted (from regions of interest centered at the cluster maxima) on subject age. The HIV+NC subjects (black circles and regression lines) show significant increases in BOLD signals with age (3 balls: $r = 0.46$ – 0.59 ; 4 balls: $r = 0.50$ – 0.55), and the SN subjects (green circles and regression lines) show relatively flat or slightly declining slopes of the BOLD responses across the age span (3 balls: $r = -0.06$ to -0.27 ; 4 balls: $r = -0.18$ to 0.23). Abbreviations: BA, Brodmann area; L, left; R, right.

Fig. 4.

Statistical parametric maps showing significant interactions between age and cognitive status on brain activation (tracking 4 balls) for the seronegative (SN) and HIV-associated neurocognitive disorder (HAND) groups (cluster corrected $p = 0.009$). Top row: magnetic resonance imaging scans showing brain regions with significant interactions in 3 subclusters (see also Table 3). Bottom row: the scatter plots show opposite slopes in HAND and SN subjects on their age-dependent changes in blood oxygen level-dependent (BOLD) signals in these 3 brain regions (HAND subjects: red circles and regression lines, $r = -0.34$ to -0.58 ; SN subjects: green circles and regression line, $r = 0.17$ – 0.38). Abbreviations: BA, Brodmann area; L, left.

Fig. 5. Subjects with HIV and normal cognition (HIV+NC) and HIV-associated neurocognitive disorder (HAND) subjects show opposite relationships on their age-dependent changes in blood oxygen level-dependent (BOLD) signals while tracking 3 balls (A) and 4 balls (B). Magnetic resonance imaging scans in each panel show brain regions with significant interactions in the subclusters (see also Table 3) and the corresponding scatter plots show opposite slopes in HAND and HIV+NC subjects on their age-dependent changes in BOLD signals in each of the subclusters (HAND: red circles and regression lines; HIV+NC subjects: black circles and regression lines). Abbreviations: BA, Brodmann area; L, left; R, right.

Fig. 6.

Brain regions that show differences in load-dependent changes in blood oxygen level-dependent (BOLD) signals between subjects with HIV and normal cognition (HIV+NC) and control subjects include the fusiform gyrus (Brodmann area [BA] 20) and the superior temporal gyrus (BA 38). Though seronegative (SN) subjects showed load-dependent increases in activation in these regions, HIV+NC subjects showed load-dependent decreases in these brain regions. No age effects were seen in these regions, and the findings remained unchanged when age was added as a covariate. The surface maps are generated with $t > 1.67$, cluster size > 1000 voxels. Abbreviations: ANCOVA, analysis of covariance; FWE, family-wise error.

Fig. 7.

Scatter plots showing the motor, learning, and memory Z-scores in each subject in relation to age. The Z-scores are normalized to a database of 342 healthy seronegative (SN) subjects evaluated using the same tests, and adjusted for age and education. All subjects showed age-dependent decline in motor function. Note steepest age-dependent decline in memory ($r = -0.25$; $p = 0.20$) and learning ($r = -0.36$; $p = 0.06$) in the HIV-associated neurocognitive disorder (HAND) subjects. Abbreviation: HIV+NC, subjects with HIV and normal cognition.

Brain Activation (tracking 4-balls) in Relation to Global Cognitive Z-score

Fig. 8.

Left, brain regions activated during tracking of 4 balls in relation to global cognitive Z-scores that showed significant group differences, covaried for age (cluster level p (family-wise error)-corrected <0.0001 , $k > 1000$ voxels and T -threshold > 3.5). Percentage of blood oxygen level-dependent (BOLD) signals extracted from region of interest surrounding the 3 subcluster maxima are shown: right superior parietal lobule (Brodmann area [BA] 7: 36, -49, 67), right parahippocampal gyrus (BA 19: 39, -46, -2) and right medial frontal gyrus (BA 6: 15, 2, 27). While the HIV subjects showed decreased BOLD signals as they approached or were below global Z-score of -1 in all 3 regions, the SN healthy controls showed a U-shaped curve with greater BOLD signals in those who were able to compensate and perform better (+0.5 to +1 Z-score) or those who could not compensate (-0.5 to -1.0) for 2 of these subregions. Right, subclusters from the frontal brain regions where the HIV subjects showed a threshold effect on their brain activation during the tracking of 4 balls in relation to global Z-score (covaried for age, cluster level, p (family-wise error)-corrected $p < 0.001$, $k = 2451$ voxels, $T > 3.0$). HIV subjects that performed poorer than -1 Z-score, primarily HIV-associated neurocognitive disorder (HAND) subjects, showed progressively lesser activation in the right superior frontal gyrus (BA 6: -15, 38, 7 and 15, 14, 49) and the left anterior cingulate (BA 32: 15, -4, 67).

Table 1

Subject characteristics, HIV disease severity, and cognitive assessments

	SN (<i>n</i> = 56)	HIV+NC (<i>n</i> = 37)	HAND (<i>n</i> = 29)	ANOVA/Fisher's exact (ES, <i>p</i> value)	HIV+NC vs. SN (ES, <i>p</i> value)	HAND vs. SN (ES, <i>p</i> value)	HAND vs. HIV+NC (ES, <i>p</i> value)
Age (range), y	45.7 ± 1.7 (22–72)	47.6 ± 1.5 (23–65)	46.6 ± 1.5 (20–61)	$\chi^2 = 0.006, p = 0.71$	$d = 0.17, p = 0.44$	$d = 0.08, p = 0.74$	$d = -0.11, p = 0.65$
Hematocrit (%)	44.4 ± 0.3	45.0 ± 0.6	43.9 ± 0.8	$\chi^2 = 0.02, p = 0.39$	$d = 0.19, p = 0.36$	$d = -0.16, p = 0.44$	$d = -0.28, p = 0.25$
Depression score (CES-D)	7.2 ± 0.8	10.1 ± 1.6	13.0 ± 1.9	$\chi^2 = 0.08, p = 0.009$	$d = 0.36, p = 0.07$	$d = 0.71, p = 0.001$	$d = 0.29, p = 0.24$
CD4 (<i>n</i> per mm ³)	407.2 ± 37.5	407.2 ± 37.5	394.7 ± 35.8				$d = -0.06, p = 0.81$
Nadir CD4 (<i>n</i> per mm ³)	167.6 ± 22.6	167.6 ± 22.6	146.6 ± 22.3				$d = -0.16, p = 0.52$
Plasma viral load (copies per mL)	10,773 ± 3,280	10,773 ± 3,280	31,956 ± 11,786				$d = 0.45, p = 0.06$
Log plasma viral load	2.8 ± 0.2	2.8 ± 0.2	2.7 ± 0.3				$d = -0.002, p = 0.99$
Undetectable viral load, <i>n</i> (%)	18 (49)	18 (49)	16 (55)				OR = 1.30, <i>p</i> = 0.63
Antiretroviral therapy, <i>n</i> (%)	28 (76)	28 (76)	26 (90)				OR = 2.79, <i>p</i> = 0.20
Karnofsky score (0–100)	93.2 ± 1.5	93.2 ± 1.5	89.3 ± 1.4				$d = -0.49, p = 0.06$
Duration of HIV (mo)	142.9 ± 12.9	142.9 ± 12.9	145.9 ± 16.1				$d = 0.04, p = 0.88$
Education and clinical assessment of cognitive function							
Education (y)	14.8 ± 0.3	14.7 ± 0.4	14.6 ± 0.4	$\chi^2 = 0.001, p = 0.95$	$d = -0.03, p = 0.86$	$d = -0.07, p = 0.73$	$d = -0.03, p = 0.90$
MMSE (0–30)	29.0 ± 0.1	29.1 ± 0.1	28.5 ± 0.2	$\chi^2 = 0.07, p = 0.02$	$d = 0.10, p = 0.64$	$d = -0.54, p = 0.02$	$d = -0.62, p = 0.01$
Estimated verbal IQ ^a	112.7 ± 1.2	109.8 ± 1.5	101.7 ± 2.3	$\chi^2 = 0.20, p < 0.0001$	$d = -0.33, p = 0.12$	$d = -1.01, p < 0.0001$	$d = -0.75, p = 0.003$
HIV dementia scale (0–16)	15.0 ± 0.2	15.0 ± 0.2	13.6 ± 0.4				$d = -0.89, p = 0.0005$
MSK AIDS dementia stage (0–4)	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.1				$d = 0.41, p = 0.11$
Cognitive domain Z-scores ^b							
Motor skills ^c	-0.09 ± 0.10	-0.03 ± 0.13	-0.76 ± 0.19	$\chi^2 = 0.13, p = 0.001$	$d = 0.08, p = 0.71$	$d = -0.74, p = 0.001$	$d = -0.79, p = 0.002$
Fluency ^d	0.25 ± 0.09	0.38 ± 0.11	-0.58 ± 0.12	$\chi^2 = 0.32, p < 0.0001$	$d = 0.19, p = 0.38$	$d = -1.21, p < 0.0001$	$d = -1.45, p < 0.0001$
Executive function ^e	-0.01 ± 0.11	0.35 ± 0.14	-0.69 ± 0.15	$\chi^2 = 0.21, p < 0.0001$	$d = 0.43, p = 0.05$	$d = -0.82, p = 0.0007$	$d = -1.28, p < 0.0001$
Attention/working memory ^f	0.07 ± 0.10	-0.08 ± 0.12	-1.08 ± 0.10	$\chi^2 = 0.47, p < 0.0001$	$d = -0.22, p = 0.32$	$d = -1.75, p < 0.0001$	$d = -1.57, p < 0.0001$
Speed of information processing ^g	-0.05 ± 0.10	0.16 ± 0.09	-0.57 ± 0.10	$\chi^2 = 0.20, p < 0.0001$	$d = 0.33, p = 0.13$	$d = -0.82, p = 0.0008$	$d = -1.35, p < 0.0001$

	SN (<i>n</i> = 56)	HIV+NC (<i>n</i> = 37)	HAND (<i>n</i> = 29)	ANOVA/Fisher's exact (ES, <i>p</i> value)	HIV+NC vs. SN (ES, <i>p</i> value)	HAND vs. SN (ES, <i>p</i> value)	HAND vs. HIV+NC (ES, <i>p</i> value)
Learning ^h	0.21 ± 0.09	0.27 ± 0.09	-0.83 ± 0.17	$\chi^2 = 0.40, p < 0.0001$	$d = 0.09, p = 0.69$	$d = -1.29, p < 0.0001$	$d = -1.47, p < 0.0001$
Memory ⁱ	0.22 ± 0.09	0.16 ± 0.08	-0.68 ± 0.15	$\chi^2 = 0.33, p < 0.0001$	$d = -0.10, p = 0.63$	$d = -1.19, p < 0.0001$	$d = -1.25, p < 0.0001$
Global	0.09 ± 0.07	0.17 ± 0.06	-0.74 ± 0.07	$\chi^2 = 0.73, p < 0.0001$	$d = 0.19, p = 0.38$	$d = -1.89, p < 0.0001$	$d = -2.53, p < 0.0001$

Data are presented as mean ± standard error, except where otherwise noted.

Key: ANOVA, analysis of variance; CES-D, Center for Epidemiological Studies-depression scale; ES, effect size; HAND, HIV-associated neurocognitive disorder; HIV+NC, HIV subjects with normal cognition; MMSE, Mini Mental State Examination; MSK, Memorial Sloan-Kettering; OR, odds ratio; SN, seronegative control subjects.

^aEstimated verbal intelligence quotient is derived from the National Adult Reading Test.

^bZ-scores are normalized to 342 SN, evaluated with the same tests scripted for the administration (and adjusted for age and education).

^cMotor skills: Grooved Pegboard, dominant and nondominant hands.

^dFluency: Ruff Figural Fluency Test and Verbal Fluency (with letters FAS).

^eExecutive Function: Stroop Interference and Trail Making Test B.

^fAttention/working memory: Wechsler Adult Intelligence Scale-III Digit Span Backward, Letter-Number Sequencing, Arithmetic and Paced Auditory Serial Addition Test 1.

^gSpeed of information processing: Symbol Digit, Trail Making Test A, Stroop Color Naming, and California Computerized Assessment Package Simple Reaction Time.

^hLearning: Rey Auditory Verbal Learning Test Trial 5 and Rey-Osterrieth Complex Figure Test (Immediate Recall).

ⁱMemory: Rey Auditory Verbal Learning Test Delayed Recall (Trial 7) and Rey Complex Figure Delayed Recall.

Table 2

Brain regions showing significant age-dependent changes (increases) in brain activation in SN and HIV+NC subjects (see also Fig. 2)

Brain region(s) in cluster	Talairach coordinate at center of cluster	Cluster level		Voxel level
	x, y, z (mm)	Corrected <i>p</i> value	Voxels, <i>n</i>	T-score
SN (tracking 2 balls)				
Left inferior parietal lobule (BA 40)	−54, −49, 52	0.021	1950	5.08
Left superior temporal gyrus (BA 39)	−42, −52, 31			4.55
Left interior temporal gyrus (BA 20)	−54, −49, −11			3.84
SN (tracking 4 balls)				
Left middle occipital gyrus (BA 18)	−24, −100, 10	<0.001	2641	4.52
Left middle occipital gyrus (BA 19)	−48, −82, 10			4.12
Left postcentral gyrus (BA 2)	−66, −22, 31			3.83
Left inferior frontal gyrus (BA 47)	−27, 29, −11	0.012	1547	4.06
Left superior frontal gyrus (BA 10)	−18, 56, 16			3.87
Right anterior cingulate (BA 32)	6, 47, 4			3.85
HIV+NC (tracking 2 balls)				
Left middle temporal gyrus (BA 20)	−54, −40, −11	0.016	1566	4.42
Left lingual gyrus (BA 18)	−6, −91, −11			4.32
Right fusiform gyrus (BA 18)	21, −94, −14			3.46
Left superior parietal lobule (BA 7)	−30, −70, 46	0.054	1213	3.30
Left precentral gyrus (BA 4)	−27, −25, 61			3.13
Left middle frontal gyrus (BA 8)	−51, 11, 40			3.02
HIV+NC (tracking 3 balls)				
Right superior temporal gyrus (BA 39)	33, −52, 31	<0.001	12011	5.07
Left precentral gyrus (BA 4)	−39, −16, 49			4.87
Right cerebellum, declive	24, −85, −20			4.34
HIV+NC (tracking 4 balls)				
Left lingual gyrus (BA 17)	−9, −94, −8	<0.001	7634	5.04
Left middle frontal gyrus (BA 8)	−30, 11, 37			4.64
Right fusiform gyrus (BA 18)	24, −94, −14			4.46

Key: BA, Brodmann area; HIV+NC, HIV subjects with normal cognition; SN, seronegative control subjects.

Table 3

Brain regions showing significant interaction between age-dependent changes (increase or decrease) in brain activation between the subject groups (see also Figs. 3 and 4)

Brain region(s) in cluster	Talairach coordinates at local maxima of the clusters	Cluster level		Voxel level
	x, y, z (mm)	Corrected <i>p</i> value	Voxels, <i>n</i>	T-score
HIV+NC > SN (tracking 3 balls)				
R parietal angular gyrus (BA 39)	42, −55, 25	<0.0001	7539	3.69
R cerebellum, declive	3, −79, −20			3.65
R inferior parietal lobule (BA 40)	33, −49, 34			3.65
HIV+NC > SN (tracking 4 balls)				
R parietal angular gyrus (BA 39)	45, −55, 28	0.006	1719	3.61
R cingulate gyrus (BA 31)	15, −19, 37			3.59
R paracentral lobule (BA 31)	6, −28, 46			3.12
HAND < SN (tracking 4 balls)				
L middle frontal gyrus (BA 6)	−21, 2, 43	0.009	1767	4.29
L middle occipital gyrus (BA 19)	−27, −88, 7			3.56
L temporal lobe subgyral	−39, −55, 4			3.50
HAND < HIV+NC (tracking 3 balls)				
L middle frontal gyrus (BA 8)	−27, 8, 34	<0.0001	7873	3.92
L cingulate gyrus (BA 24)	−21, 5, 43			3.91
R sublobar insula (BA 13)	36, 8, 16			3.87
HAND < HIV+NC (tracking 4 balls)				
L frontal subgyral	−27, −1, 31	<0.0001	5312	5.42
L cingulate gyrus (BA 24)	−18, 5, 43			5.07
L frontal subgyral	−24, 11, 31			4.70

Key: BA, Brodmann area; HAND, HIV-associated neurocognitive disorder; HIV+NC, HIV subjects with normal cognition; L, left; R, right; SN, seronegative control subjects.

Table 4

Automatically segmented brain volumes

Brain region		SN (<i>n</i> = 56)	HIV+NC (<i>n</i> = 37)	HAND (<i>n</i> = 28)	HAND vs. HIV+NC (ES, <i>p</i> value)	All HIV subjects vs. SN (ES, <i>p</i> value)
Amygdala	L	1.86 ± 0.04	1.74 ± 0.04	1.76 ± 0.03	<i>d</i> = 0.11, <i>p</i> = 0.67	<i>d</i> = -0.43, <i>p</i> = 0.02
	R	1.78 ± 0.03	1.68 ± 0.04	1.69 ± 0.04	<i>d</i> = 0.04, <i>p</i> = 0.88	<i>d</i> = -0.39, <i>p</i> = 0.03
Caudate	L	3.94 ± 0.07	3.73 ± 0.09	3.58 ± 0.09	<i>d</i> = -0.29, <i>p</i> = 0.26	<i>d</i> = -0.52, <i>p</i> = 0.005 ^a
	R	3.82 ± 0.07	3.68 ± 0.08	3.54 ± 0.08	<i>d</i> = -0.31, <i>p</i> = 0.23	<i>d</i> = -0.41, <i>p</i> = 0.03
Hippocampus	L	4.42 ± 0.06	4.25 ± 0.07	4.26 ± 0.09	<i>d</i> = 0.03, <i>p</i> = 0.91	<i>d</i> = -0.39, <i>p</i> = 0.04
	R	4.57 ± 0.07	4.38 ± 0.06	4.37 ± 0.09	<i>d</i> = -0.03, <i>p</i> = 0.92	<i>d</i> = -0.42, <i>p</i> = 0.02
Pallidum	L	2.12 ± 0.04	1.97 ± 0.06	1.88 ± 0.05	<i>d</i> = -0.27, <i>p</i> = 0.30	<i>d</i> = -0.61, <i>p</i> = 0.001 ^a
	R	1.83 ± 0.03	1.73 ± 0.05	1.72 ± 0.04	<i>d</i> = -0.05, <i>p</i> = 0.83	<i>d</i> = -0.42, <i>p</i> = 0.03
Putamen	L	5.83 ± 0.11	5.42 ± 0.13	5.19 ± 0.13	<i>d</i> = -0.31, <i>p</i> = 0.23	<i>d</i> = -0.64, <i>p</i> = <0.001 ^a
	R	5.70 ± 0.10	5.38 ± 0.12	5.19 ± 0.12	<i>d</i> = -0.27, <i>p</i> = 0.28	<i>d</i> = -0.56, <i>p</i> = 0.003 ^a
Thalamus	L	7.78 ± 0.15	7.31 ± 0.16	7.02 ± 0.19	<i>d</i> = -0.29, <i>p</i> = 0.25	<i>d</i> = -0.55, <i>p</i> = 0.003 ^a
	R	7.78 ± 0.14	7.35 ± 0.15	7.03 ± 0.20	<i>d</i> = -0.32, <i>p</i> = 0.20	<i>d</i> = -0.57, <i>p</i> = 0.002 ^a
Cerebellar white matter	L	15.1 ± 0.29	14.9 ± 0.38	14.8 ± 0.44	<i>d</i> = -0.01, <i>p</i> = 0.96	<i>d</i> = -0.11, <i>p</i> = 0.54
	R	14.0 ± 0.23	13.8 ± 0.34	13.8 ± 0.37	<i>d</i> = -0.02, <i>p</i> = 0.93	<i>d</i> = -0.08, <i>p</i> = 0.67
Cerebellar cortex	L	55.0 ± 0.74	53.7 ± 0.92	51.6 ± 1.0	<i>d</i> = -0.38, <i>p</i> = 0.14	<i>d</i> = -0.40, <i>p</i> = 0.03
	R	56.3 ± 0.78	54.7 ± 0.90	52.7 ± 0.97	<i>d</i> = -0.38, <i>p</i> = 0.14	<i>d</i> = -0.43, <i>p</i> = 0.02
Global cerebral white matter	L	277 ± 4.5	266 ± 5.2	262 ± 5.1	<i>d</i> = -0.13, <i>p</i> = 0.60	<i>d</i> = -0.40, <i>p</i> = 0.03
	R	288 ± 4.8	275 ± 5.8	273 ± 5.58	<i>d</i> = -0.06, <i>p</i> = 0.82	<i>d</i> = -0.42, <i>p</i> = 0.02
Global cerebral cortex	L	251 ± 3.8	242 ± 4.2	234 ± 4.6	<i>d</i> = -0.33, <i>p</i> = 0.20	<i>d</i> = -0.46, <i>p</i> = 0.01 ^a
	R	249 ± 3.7	241 ± 3.80	232 ± 4.25	<i>d</i> = -0.36, <i>p</i> = 0.16	<i>d</i> = -0.47, <i>p</i> = 0.01 ^a
Global cerebral volume		1120 ± 16.4	1076 ± 18.7	1053 ± 18.0	<i>d</i> = -0.22, <i>p</i> = 0.39	<i>d</i> = -0.47, <i>p</i> = 0.01 ^a

Volumes are cm³, mean ± standard error.

Key: ES, effect size; HAND, HIV-associated neurocognitive disorder; HIV+NC, HIV subjects with normal cognition; L, left; R, right; SN, seronegative control subjects.

^aSignificant *p* values after Simes correction.