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REVIEW

Neuroimaging studies of the aging HIV-1-infected brain

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Abstract Highly active antiretroviral therapy (HAART) has increased life expectancy among HIV-infected individuals, and by 2015, at least half of all HIV-infected individuals will be over 50 years of age. Neurodegenerative processes associated with aging may be facilitated by HIV-1 infection, resulting in premature brain aging. This review will highlight brain abnormalities in HIV patients in the setting of aging, focusing on recent neuroimaging studies of the structural, physiological, functional and neurochemical changes. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy studies performed during the pre-HAART era or on antiretroviral-naive subjects suggest an accelerated aging process, while those on HAART-treated subjects suggest premature brain atrophy. Diffusion tensor imaging studies yielded conflicting findings on the relationship between HIV and age in neuroasymptomatic individuals. Functional MRI studies found evidence of premature or accelerated aging processes in the brains of HIV subjects. Lastly, many age-related illnesses such as diabetes, stroke, and depression, as well as comorbid substance abuse, may further exacerbate the aging process in the HIV-infected brain, leading to premature or accelerated age-related brain changes. Given the different pathologic or physiologic changes in the brain assessed by the different neuroimaging techniques, using a multimodal approach in longitudinal follow-up studies is recommended for future studies.

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Introduction

Highly active antiretroviral therapy (HAART) has increased life expectancy among HIV-infected individuals, and hence, by 2015, at least half of all HIV-infected individuals will be over 50 years of age (Smith 2005). However, HIV and HAART combined may exacerbate many comorbidities (e.g., cardiovascular diseases, diabetes, etc.) associated with normal aging (Effros et al. 2008), and HIV patients exceed the expected risk for the development of these complications (Deeks 2011). HIV-1 infection may also facilitate the neurodegenerative processes associated with aging, which ultimately could result in premature aging (Brew et al. 2009) (i.e., due to HIV-associated brain injury, changes occur earlier than, but may be parallel to, the normal aging process) or accelerated aging (i.e., due to interaction between HIV and aging, changes progress at a faster rate than in normal aging). The increased life expectancy and progressive neurodegeneration associated with HIV may contribute to the development of HIV-1-associated neurocognitive disorders (HAND) in as many as 50 % of HIV-1-infected individuals. HAND includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and the most severe form, HIV-1-associated dementia (HAD). While the prevalence of HAD has decreased to <7 %, the incidence of both ANI and MND have been on the rise over the past decade (Antinori et al. 2007; Woods et al. 2009). HAND persists among HIV-infected individuals despite the decreased morbidity and mortality with the advent of HAART. The current higher prevalence of the milder form of HAND coincides with the aging population of HIV-infected individuals; therefore, aging may be an important risk factor for HAND.

In seronegative (SN) individuals, aging results in global increases in immune activation, even in the central nervous system (CNS). The number of microglia increases with increasing age, but these "aging" microglia are less functional in terms of neuroprotection (Streit and Xue 2010), resulting in a less-than-optimal inflammatory environment in the brain (Schuitemaker et al. 2012). In patients with HIV-1 infection, HIV-infected monocytes traverse the blood–brain barrier, disseminate the virus, and induce a proinflammatory environment that further propagates HIV-1 infection in the CNS (Haase 1986). HIV-induced glial activation may lead to neuronal dysfunction and greater reactive neuroinflammation, and the dystrophic microglia in the aging brain may not provide the necessary repair or neuroprotection, which ultimately results in premature aging in HIV-1-infected individuals. With recent technical advances, various neuroimaging techniques are available for assessing the effects of HIV-1 on the living, aging brain.

Neuroimaging techniques are widely used in clinical and research settings to aid in the diagnosis and delineation of neurological disorders or to assess neurological sequelae. They can be divided broadly into four categories based on what they characterize, these include: brain structures, neurochemistry, neurophysiology, and brain activation networks. Several different techniques are available in each of these categories. Structural neuroimaging includes X-ray computed tomography (CT), structural magnetic resonance imaging (MRI), and diffusion MRI. Neurochemicals or neurometabolites can be measured by magnetic resonance spectroscopy (MRS) and with positron emission tomography (PET) using radiotracers. Techniques that allow for imaging of physiology, such as blood flow, can be assessed with perfusion (or arterial spin labeling [ASL]) MRI and glucose metabolism with fluorodeoxyglucose PET. Carbon 11-labeled Pittsburgh compound B was also used to assess fibrillary amyloid plaque binding in HIV patients, which might detect preclinical Alzheimer's disease (Ances et al. 2012a). Lastly, brain activation networks are studied using functional MRI (fMRI) by employing blood oxygen level-dependent (BOLD) imaging and ASL. Each of these techniques has provided insights in the brain changes associated HIV-1 infection, including those that occur during aging.

Many factors contribute to brain changes in aging individuals and may further exacerbate changes in the HIV-1-infected brain, either by the disease or by some HAART regimens. Examples of these comorbid factors include hypertension, diabetes, stroke, depression, and particular host genetic factors. Many of these risk factors are further affected by the administration of HAART, which is known to have toxic side effects at the cellular level (e.g., mitochondrial toxicity), the vasculature (e.g., increasing lipids and atherosclerosis), and ultimately, on the nervous system. This review will highlight brain abnormalities in HIV patients in the setting of aging, focusing on recent neuroimaging studies that contributed to our understanding of the structural, physiological, functional, and chemical alterations in the HIV-infected brain.

Structural magnetic resonance imaging studies in HIV and aging

MRI can easily assess structural changes that occur during normal aging, which include shrinkage of almost all brain regions. For example, with advancing age, the hippocampi, entorhinal cortices, inferior temporal cortices, and prefrontal white matter (WM) show volume loss (Raz et al. 2005). Similarly, the gray matter (GM) shows age-dependent decreases in density (Sowell et al. 2004), while the ventricles increase in size with age (Sowell et al. 2003). Despite the widespread structural changes that occur during aging, many functions are still preserved, in part due to restructuring of the circuitry and reassigning or shared functions between regions (Tyler et al. 2010). Such reallocation of neural resources might lead to limited cognitive reserve capacity in the normal aging brain. However, in the aging HIV-infected brain, both structural and cognitive reserve may be even more limited.

Neuronal and myelin loss in the HIV-infected brain have been well documented on neuropathology (Bell 1998), which may be related to the cortical atrophy seen and measured on MRI (Archibald et al. 2004; Ghafouri et al. 2006). Morphometric analyses of MRI have shown volumetric loss in the caudate, amygdala and hippocampus (Archibald et al. 2004; Chang et al. 2011; Chiang et al. 2007; Harezlak et al. 2011; Lepore et al. 2008), and corpus callosum (Chiang et al. 2007; Dewey et al. 2010) in HIV-infected individuals.

Several studies evaluated gross structural brain volume or GM density changes in the aging, HIV-infected brain (Table 1). Two cross-sectional studies utilizing voxel-based morphometry (VBM), a technique that measures the brain volumes at each voxel independently, reported age-related GM changes that were distinct from HIV infection-related GM atrophy. Towgood et al. (2011) found that despite similarly normal cognitive performance between cognitively asymptomatic HIV subjects and controls, the younger HIV subjects had an area of smaller GM in the medial and superior frontal area and the older subjects had smaller GM in the superior frontal gyrus than their respective age-matched control group. They also found significant aging effects in the frontotemporal GM and WM, independent of the effect of HIV. Becker et al. (2011) reported similar age effects in the frontal and temporal regions, but more extensive atrophy in HIV subjects than SN controls in the frontal GM and inferior and posterior temporal, parietal, and

Table 1 Brain changes associated with HIV and aging: MRI and DTI studies

Reference	Subjects	ARVs in HIV subjects	Brain regions evaluated	Findings	Aging effect(s) in HIV
Structural MRI studies					
Pfefferbaum et al., Biol Psychiatry 2012	59 HIV+ (45.3±8.6 years); 65 HIV+/alcohol (45.3± 8.6 years); 110 alcohol (48.1±9.4 years); 108 SN (46.2±11.8 years)	88; 86 %	ROIs: lateral and medial frontal, temporal, parietal, calcarine, occipital, insula, anterior cingulate, posterior cingulate, precuneus, caudate, putamen, globus pallidus, hippocampus/amygdala, thalamus	Age regressions performed in HIV+ subjects with and without alcohol use. In HIV+ subjects without alcohol use, estimated age of infection and age at MRI were both predictive of reduced anterior cingulate volume. However, the age of infection contributed more to the brain atrophy.	No comparison with SN controls
Ances et al., J Acquir Immune Defic Syndr 2012b	26 HIV+/HAART+ (40±12 years); 26 HIV+/ HAART− (37±13 years); 26 SN (34±11 years)	100; 0 %	Amygdala, caudate, thalamus, hippocampus, putamen, corpus callosum	No volumetric differences between HAART+ and HAART−. Compared to SN, the combined HIV+ group had significant reductions in caudate volume as a function of HIV (6 %/decade) and age (4 %/decade). Amygdala volumes decreased as a function of HIV (7 %/decade).	Premature
Chang et al., Neuroimage 2011	22 HIV+ APOEe4+ (48.3±2.7 years); 47 HIV+ APOEe4− (47.0±1.2 years); 16 SN APOEe4+ (46.0± 3.2 years); 54 SN APOEe4− (45.8±1.8 years); 81–94 % male across all groups	79 %	Total brain volume cerebral WM, cerebellum, hippocampus, amygdala, thalamus, pallidus, caudate, putamen	Compared to SN, HIV+ subjects had smaller global cerebral volume. HIV+ APOEe4+ subjects had the smallest brain volumes, while SN APOEe4+ subjects had the largest volumes. APOEe4 was associated with smaller volumes in older SN, but larger volumes in younger SN subjects. Conversely, APOEe4 was associated with smaller brain volumes in younger subjects, but not older HIV subjects.	Premature
Towgood et al., Cortex 2011	20 HIV+ young (20–40 years); 20 HIV+ older (50–75 years); 20 SN young (20–40 years); 20 SN older (50–75 years); 100 % male in all groups	100 %	WM volume, GM volume	Age-related atrophy of frontal, insula, temporal lobes. Age-related increase in thalamus volume relative to whole brain. HIV-related GM atrophy in medial and superior frontal gyri.	Premature
Becker et al., Neuroradiology 2011	81 HIV+ (56.3±3.9 years); 67 SN (57.7±6.3 years); 100 % male in both groups	100 %	WM volume, GM volume	Age-related atrophy of superior temporal and inferior frontal GM. Age-related WM loss primarily periventricular and frontal. HIV-related GM atrophy in posterior and inferior temporal lobe, parietal lobe, and cerebellum. HIV-related WM atrophy existed, but much less than age-related WM atrophy.	Aging and HIV have independent effects
Cardenas et al., J NeuroVirology 2009	39 HIV+ (45.0±6.7 years); 30 SN (42.3±9.1 years); 100 % male in both groups	100 %	CSF volume, WM volume, GM volume, global volume	ROI analyses showed that, over a 2-year period, HIV+ subjects had greater rates of loss in WM than SN subjects. VBM analyses revealed that HIV+ subjects with detectable viral loads had the greatest rates of GM and WM loss.	Accelerated
Stout et al., Arch Neurol 1998	86 HIV+ (3 CDC stage A; 19 CDC stage B; 34 CDC stage C); 23 SN; 100 % male in both groups	Not stated	Cortical GM, subcortical GM, WM, sulcal CSF, ventricular CSF	Compared to SN, all three HIV groups had greater losses in CSF, WM, and caudate nucleus. Greater losses were associated with more advanced disease and rate of decline of CD4 count.	Accelerated
DTI studies					
Chang et al., J Neuroimmune Pharmacol 2008b	39 HIV (28–67 years); 32 SN (21–71 years)	100 %	Frontal WM, parietal WM, caudate, splenium, genu, putamen, globus Pallidus, thalamus	At baseline, HIV+ subjects had higher frontal WM MD and lower parietal FA. After 1 year, HIV+ individuals showed increased MD in frontal and parietal WM, putamen, and genu. HIV subjects had greater than normal age-related increased diffusion in genu after 1 year. Normal age-related MD changes in frontal WM and normal age-related FA in genu and putamen were not observed in HIV subjects.	Premature aging of genu and putamen
Towgood et al., Cortex 2011	20 HIV young (20–40 years); 20 HIV older (50–75 years); 20 SN young (20–40 years); 20 SN older (50–75 years); 100 % male in all groups	100 %	WM	Age-related reduction in FA and increased MD in frontal and temporal WM. No significant effect of HIV on either FA or MD.	No difference from SN subjects
Gongvatana et al., J Neurovirology 2011	85 HIV, (23–65 years, 67 % male)	81 %	29 cerebral WM regions	Older age in HIV subjects was associated with lower FA in WM of frontal, temporal, and parietal lobes, but higher MD only in occipital WM.	No comparison with SN controls

cerebellar regions. Overall, they concluded that, in the post-HAART era, HIV infection is still linked to GM and WM volume loss, independent of age effects. A third cross-sectional study found that the estimated age at the time of HIV infection and the subjects' age at the time of the scan independently and significantly correlated with smaller anterior cingulate volumes in HIV+ subjects but not in HIV+ subjects with an alcohol abuse or dependence history. Furthermore, a multiple regression revealed that age at HIV infection was a unique predictor, over age, of anterior cingulate volume (Pfefferbaum et al. 2012).

A longitudinal study performed during the pre-HAART era found greater loss of WM and caudate, with greater enlarged cerebrospinal fluid (CSF) space in HIV subjects than SN controls over a 2-year follow-up period, especially in HIV subjects who were medically symptomatic or had lower CD4 counts (Stout et al. 1998). A more recent study of HIV subjects maintained on more potent antiretroviral (ARV) regimens still found that, over a 24-month period, WM loss was greater in HIV subjects than SN controls (Cardenas et al. 2009). Recent morphometry studies, using an automated image segmentation technique, found that both HIV and aging independently contributed to volume reductions in many brain regions (Ances et al. 2012b; Chang et al. 2011). While atrophy in the amygdala was associated with aging, reductions in the corpus callosum were associated with HIV in a small study (Ances et al. 2012b). In addition, HIV subjects with apolipoprotein E (APOE)-ε4 genotype showed premature brain atrophy (in subjects <50 years), especially in the WM and bilateral putamen (Chang et al. 2011) (Fig. 1a).

In summary, HIV infection is associated with greater than age-related brain atrophy, beyond that found with normal aging in the frontal and temporal regions, as well as the basal ganglia (BG), parietal, and cerebellar regions. HIV-infected individuals with genetic risk factors, such as APOEe4, may have even greater risk for premature age-related brain atrophy.

Diffusion tensor imaging studies in HIV and aging

Diffusion tensor imaging (DTI) is another MR technique that measures the molecular motion of water molecules, which reflects changes in the microstructural environment of the brain. Since neuroinflammation is associated with increased brain water, DTI is sensitive to changes in WM and inflammatory changes associated with HIV infection (Chang et al. 2008a). Two common measures are fractional anisotropy (FA), which reflects the organization or integrity of WM fibers and the movement of water molecules along them, and mean diffusion (MD), which reflects the averaged diffusion from both diffusion along the axons (axial diffusion) and diffusion perpendicular to axonal fibers (radial diffusion). WM pallor suggestive of myelin loss is apparent soon after HIV infection (Gray et al. 1996). DTI quantitatively assesses WM integrity (Lim and Helpern 2002) and has detected WM abnormalities in HIV-infected subjects who had normal-appearing MRI images (Pomara et al. 2001). Multiple DTI studies have documented higher diffusion and lower FA in many brain regions in HIV subjects compared to controls; however, only three studies evaluated HIV subjects in relation to age.

In a 1-year follow-up study (Chang et al. 2008a), a group of neuroasymptomatic (NAS) HIV subjects had significantly higher MD in the frontal WM and lower FA in the parietal WM than SN controls at baseline. After 1 year, these HIV subjects showed increases in MD in the frontal and parietal WM, putamen, and genu; HIV subjects also showed greater increased genu diffusion than SN controls. These changes in MD in the genu and FA in the parietal and frontal WM and putamen correlated with changes in global cognitive deficit scores. Therefore, the greater than normal age-related inflammatory changes in the genu of these HIV patients might have contributed to the cognitive deficits. Furthermore, although the age-dependent changes in mean diffusivity and FA were not significantly different between HIV subjects and SN controls, the younger HIV subjects tended to show elevated diffusion and lower FA, suggesting greater neuroinflammation than the younger SN subjects (Chang et al. 2008a) (Fig. 1b).

Similarly, a cross-sectional DTI study also found only normal age-dependent changes in FA and MD in a group of NAS HIV subjects, but no HIV effect or HIV status-by-age interaction on their diffusion measures. The investigators attributed these normal DTI findings to their exceptional cohort of HIV subjects who had relatively high premorbid intelligence quotients, no comorbid disorders or substance abuse, and well-suppressed viral load (Towgood et al. 2011). Another recent study that evaluated various clinical variables on diffusion measures in 85 HIV subjects found that, in addition to the age-dependent decreases in FA in most WM regions, especially the frontal regions, those with a common coinfection, hepatitis C, also had lower frontal WM FA and higher diffusion primarily in the parietal and occipital WM regions (Gongvatana et al. 2011). The authors suggested that since different comorbid conditions may contribute differentially to brain changes, future DTI studies of HIV patients should evaluate the entire brain.

Proton magnetic resonance spectroscopy studies in HIV and aging

HIV infection causes glial activation and neuronal injury (Everall et al. 1993; Navia et al. 1986). Proton MRS is a sensitive method for detecting brain metabolites that reflect

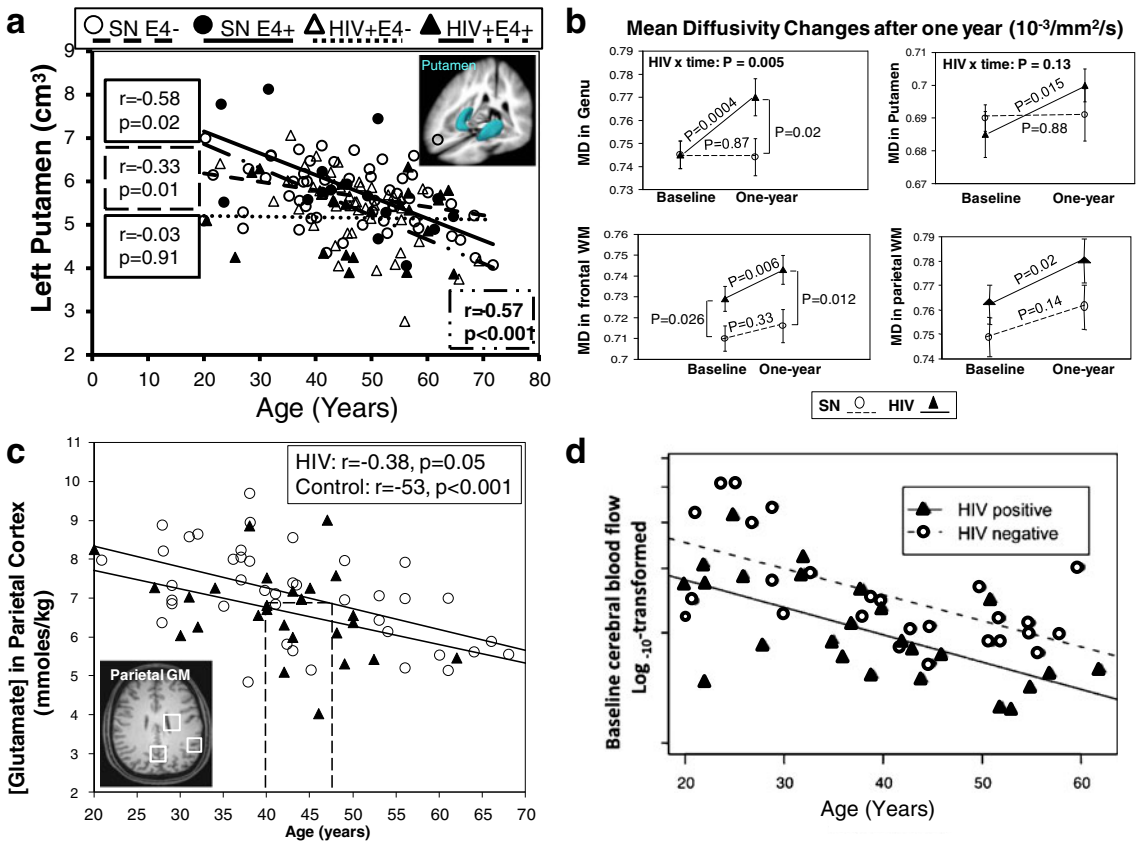

Fig. 1 **a** Left Putamen volume, **b** Mean Diffusivity in four brain regions, **c** Glutamate concentration in parietal cortex, **d** baseline rCBF, in the brains of HIV-1-infected subjects (see next for details and references)

glial and neuronal changes. For example, myoinositol (MI) and choline compounds (CHO) are elevated in brain disorders with chronic inflammation and glial activation, while the neuronal marker *N*-acetylaspartate (NAA) is decreased in later or more severe stages of HIV dementia (Chang et al. 2012). With normal aging, the glial marker MI and, to a lesser extent, total creatine (tCr) and CHO increase linearly with age (Chang et al. 1996). MRS has also proven useful in identifying subtle changes associated with cognitive decline; for example, the MI/tCr ratio has been used to discriminate healthy subjects from those with mild cognitive impairment (Catani et al. 2001). Similarly, in ARV-naïve HIV subjects, elevated levels of MI in the frontal WM was associated with poorer performance on tasks that require executive function (Stroop interference task), as well as lower CD4 count and higher viral load, while elevated CHO in the same brain region correlated with slower performance on a working memory task (Chang et al. 2002). Numerous MRS studies have been applied to evaluate HIV patients with and without HAND; some studies also demonstrated that MRS may be a useful biomarker to monitor the effects of HAART (Chang et al. 2012).

Among the many MRS studies, only four reports specifically evaluated the effects of HIV in relation to age (Table 2). In a group of relatively young (mean age, 36 years) ARV-naïve HIV subjects, accelerated age-associated metabolite changes were observed. Only HIV subjects showed age-related decline in NAA (−3.7 %/decade) and tCr (−4 %/decade) in the BG, suggesting neurodegeneration in this brain region. The HIV subjects also showed greater than age-related increases in MI (+12 % instead of 3 %/decade) and CHO (+10 % instead of 2 %/decade), suggesting greater neuroinflammation in the frontal WM (Ernst and Chang 2004). A multicenter MRS consortium also found evidence of premature age-associated brain metabolite abnormalities in primarily HAART-treated HIV-infected individuals. Those with AIDS dementia complex (ADC) or Memorial Sloan–Kettering (MSK) stage 1 (equivalent to the MND) and MSK stages 2 and 3 (equivalent to HAD) had the highest level of the MI/tCr and CHO/tCr in the WM and BG and higher but parallel elevations of Cho/tCr and MI/tCr in their BG across the age groups compared to the NAS subjects. The BG of the NAS group, even the younger HIV subjects (<40 years of age), showed higher MI/tCr and CHO/tCr than the younger SN subjects, at levels similar to the older SN subjects. In contrast, the NA/tCr levels were lower in the ADC (HAND) group, even in the younger subjects, and decreased further with age in both the

Table 2 Brain changes associated with HIV and aging: MRS and fMRI studies

Reference	Subjects	ARV therapy	Brain regions or network evaluated	Findings	Aging effect(s)
MRS studies					
Ernst and Chang, AIDS 2004	46 HIV+ (92 % male); mean age, 36.1 (18–58 years); 58 SN (28 % male); mean age, 51.5 (19–78 years)	Naïve	Frontal WM, frontal GM, BG	Compared with SN controls, HIV subjects showed additional and marked increases in the concentration of glial markers, CHO (SN, +2 %/decade; HIV, +10 %/decade) and MI (SN, +3 %/decade; HIV, +12 %/decade), with aging in the frontal WM. In the BG, NA and tCr decreased with age only in HIV patients (NA, −3.7 %/decade; tCr, −4 %/decade).	Accelerated aging
Chang et al., Neuroimage 2004a	39 HIV+ NAS (87 % male, 19–51 years); 61 HIV+ ADC (89 % male, 31–63 years); 37 SN (49 % male, 19–58 years)	82; 98 %	Frontal WM, parietal GM, BG	HIV infection and aging had additive effects on elevated Cho/Cr and MI/Cr in the BG and WM. Younger (<40 years) HIV subjects showed lower NAA/tCr than younger SN in frontal WM, which may reflect greater inflammatory response in younger subjects, leading to enhanced neuronal injury.	Premature aging
Ernst et al., JMRI 2010	27 HIV+ NC (96 % male, 46.7±1.9 years); 18 HIV+ HAND (89 % male, 44.9±2.5 years); 45 SN (80 % male, age 43.3±1.8 years)	Not specified	Parietal GM, frontal WM, frontal GM, BG	GLU levels in HIV+ subjects were equivalent to those of SN subjects approximately 10 years older.	Premature aging
Harezlak et al., AIDS 2011	124 HIV+ NAS (83 % male, 44.5 years); 66 HIV+ ADC 0.5 (85 % male, 48.5 years); 50 HIV+ ADC >1 (90 % male, 47.9 years); 28 SN (36 % male, 53.0 years); all subjects (ages 30–70 years)	100 %	Frontal WM, frontal GM, BG	HIV effect: HIV subjects had higher MI/Cr Cho/Cr in all brain regions, lower Glx/tCr in the frontal WM only in the NAS group, and lower NA/tCr only in the ADC group. Age-dependent decrease in NA/tCr medial frontal cortex and age-dependent decline in Glx/tCr in the frontal WM (HIV subjects at age 30 years equivalent to SN subject at age 56 years). MI/Cr in frontal WM increased with age in NAS and ADC 0.5 subjects, but decreased with age for ADC >1.	Premature aging
Brain network studies					
Ernst et al., Ann Neurol 2009	31 HIV+ (97 % male, 49.6±1.5 years); 32 SN (87 % male, 46.9±2.3 years)	100 %	Visual attention	Over 1 year, HIV patients showed no change in their neurocognitive status or in task performance during fMRI. However, HIV patients showed significant 1-year increases in fMRI signals in the prefrontal and posterior parietal cortices for the more difficult tasks, whereas SN control participants showed only decreases in brain activation in these regions.	Premature aging
Ances et al., J. Infect Dis 2010	26 HIV+ (77 % male, 39 years); 25 SN (56 % male, 41 years); age range, 20–62 years	60 %	Primary visual stimulation	HIV+ had lower baseline CBF, but no interaction between HIV and age. HIV+ equivalent to SN plus 15 years. HIV+ had greater functional CBF increases, as did age, but no interaction. HIV+ equal to SN plus 21 years. HIV+ had reduced BOLD, as did age, but no interaction. HIV+ equivalent to SN plus 15 years.	Premature aging

frontal WM and the parietal cortex, but the NAS subjects showed only mild decreases of NA/tCr in the WM which did not decline with age. Therefore, the higher CHO/tCr and MI/tCr in the BG and WM of the NAS (no HAND or ANI) and ADC (HAND) subjects and the lower NA/tCr in the WM and parietal cortex in the ADC (HAND) subjects, which were already present in the younger HIV subjects, indicate a premature aging process (Chang et al. 2004a).

A more recent multicenter study of slightly older (median ages, 45–49 years) HAART-treated HIV-infected individuals continued to show elevated MI/tCr and CHO/tCr throughout the brain, with decreased NAA/tCr in the frontal WM only in ADC (MSK stage $\geq$0.5 or HAND) subjects and decreased glutamate+ glutamine (Glx)/tCr in NAS (MSK stage 0, no HAND diagnosis or ANI) subjects in the frontal WM (Harezlak et al. 2011). This study also found that, while the glial metabolite ratio MI/tCr increased with age in NAS subjects and those with ADC 0.5 (equivalent to MND), MI/tCr decreased with age in subjects with ADC (HAND). These finding may reflect the age-related increase in microglia cells in the subjects with NAS or ADC 0.5 but a premature age-related microglial senescence process in those with ADC (HAND).

Another study that specifically evaluated brain glutamate (GLU) using a special MRS technique (TE-averaged PRESS) found that HIV subjects with HAND had lower parietal GLU levels, but those without HAND had higher BG GLU. Additionally, although HIV subjects showed similar rates of age-related decline in brain GLU levels, their GLU levels were already lower in the younger subjects, equivalent to those of SN subjects who were approximately 10 years older, again suggesting premature aging (Ernst et al. 2010) (Fig. 1c).

MRS has proven to be a valuable technique for studying age-related brain changes associated with HAND and can measure region-specific changes in brain metabolites that reflect glial activation and neuronal injury or loss. The few studies that evaluated age-related changes suggest that ARV-naïve HIV subjects show accelerated age-dependent changes in glial activation or neuronal injury; however, HAART-treated HIV subjects show only a premature aging process, especially those with HAND. All of these studies were done cross-sectionally, which may suffer biases from intersubject variability; longitudinal studies are needed to validate these cross-sectional findings.

Functional neuroimaging studies in HIV and aging

Although HIV does not infect neurons directly, it is believed that viral proteins released by infected macrophages and microglia leads to neuronal apoptosis and ongoing aberrant neuroinflammation, which contribute to the development of HAND (Kaul et al. 2005). The BOLD contrast on fMRI is an indirect measure of neuronal function (Arthurs and Boniface 2002) and detects brain activity while subjects are resting or while they are engaged in cognitive or motor tasks that do not involve head motion. Several fMRI studies evaluated brain function in HIV-infected individuals. The major findings included decreased activation in the normal attention network (Chang et al. 2004b), but greater activation in adjacent or contralateral brain regions, suggesting greater usage of the reserve brain networks (Chang et al. 2001, 2004b). The need to use the reserve brain network, with greater activation, in order to maintain normal cognitive performance was also demonstrated in NAS HIV patients (Ernst et al. 2002). However, the reserve network has a limited capacity, especially in HIV subjects, which may not provide sufficient reserve for the more difficult tasks or during competing brain activities (e.g., simultaneous visual and auditory functions) that would interfere with the attention network(Tomasi et al. 2006). Furthermore, neuroinflammation, as demonstrated by the elevated glial metabolites (MI, CHO, and tCr) in HIV-infected individuals, may lead to greater BOLD signals, suggesting a greater requirement for usage of the brain reserve (Ernst et al. 2003). Since both HIV and aging may lead to greater neuroinflammation, additive effects on brain activation and the usage of the reserve network would be expected. Lastly, since some ARVs, such as the nucleoside reverse transcriptase inhibitors (NRTIs), might be neurotoxic (Dagan et al. 2002), long-term treatment with HAART in aging HIV patients might also lead to further decreases in the brain network capacity. A study that evaluated the effects of ARVs on brain function found that HIV subjects who were taking ARVs with NRTIs required greater brain activation during a set of parametric attention tasks than those without ARVs (Chang et al. 2008b).

To date, only two fMRI studies evaluated brain activation or perfusion in relation to age. A longitudinal fMRI study of cognitively unimpaired HIV and SN control subjects showed greater BOLD activation at baseline in the occipital, cerebellar, and right prefrontal regions of HIV subjects during performance of the most difficult level of a visual attention task. After 1 year, although there were no changes in task performance for either group, HIV subjects had significantly increased BOLD activation, primarily in the prefrontal and parietal regions, for all three levels of the task. Conversely, SN participants showed only decreased BOLD signals, consistent with practice effects (Ernst et al. 2009) (see Fig. 1). These finding are consistent with a premature aging model, since older healthy individuals showed greater activation on a visual attention task than younger individuals (Madden et al. 2007). Further evidence of premature aging in HIV-infected individuals is shown in a study that utilized ASL, which evaluated resting cerebral

blood flow (CBF) as well as CBF changes in response to visual stimulation. Similar to the other MR studies in HAART-treated HIV patients, HIV+ subjects had lower CBF across the age span, equivalent to that in SN subjects who were 15 years older, and also lower brain activation during visual stimulation across the age span, equivalent to that of SN subjects who were 21 years older (Ances et al. 2010) (Fig. 1d).

These fMRI studies suggest that HIV-associated brain injury leads to a less efficient network, with lower resting CBF like older individuals that require greater usage of neural resources to maintain cognition, and the aging HIV infected brain will have an even lower cognitive reserve that may not provide sufficient capacity to maintain cognition. Hence, the prematurely aged brains of HIV patients will likely suffer the development of HAND as they age. Again, longitudinal studies are needed to validate these hypotheses.

Common comorbidities with aging in HIV

Many comorbidities are common in the aging population, which may further affect the aging HIV-infected brain. Aging is associated with increased incidence of cardiovascular diseases, including hypertension and stroke (Gorelick et al. 2011), as well as diabetes (McBean et al. 2004) and depression (Vink et al. 2009). In addition, particular genotypes (e.g., APOEe4 allele) may further prevent the normal repair processes needed for the aging brain and HIV-associated neurodegeneration (Chang et al. 2011). Furthermore, substance abuse, which is prevalent among HIV-infected individuals, may lead to additive effects on brain injury (Chang et al. 2005b, 2006), especially in the aging brains of HIV patients. Other coinfections, such as hepatitis C, can also lead to brain inflammation and injury, which might further impact the aging process. Few studies have evaluated how these comorbid conditions affect the HIV-infected brain, especially in the setting of the aging brain, and even fewer have applied neuroimaging to evaluate comorbid conditions in the HIV aging brain. We will briefly review a few neuroimaging studies of these potential contributing factors to the aging process in HIV-infected individuals.

Diabetic complications in the aging HAART-treated HIV-infected brain

Multiple studies have shown that HAART significantly increases the prevalence of diabetes mellitus in HIV-infected individuals, with 13–14 % having insulin resistance (Brown et al. 2005; Palacios et al. 2006). In particular, protease inhibitors are associated with increased incidence of insulin resistance and new-onset diabetes (Carr et al. 1999; Dever et al. 2000; Palacios et al. 2006; Walli et al. 1998). Neuroimaging studies have shown significant brain pathologies in diabetic patients. Specifically, MRI showed atrophy throughout the brains of diabetic patients, with smaller cortical and subcortical volumes (Tiehuis et al. 2008), as well as smaller hippocampi and amygdalae (den Heijer et al. 2003). Furthermore, patients with type 2 diabetes have increased WM hyperintensities associated with neuroinflammation and more lacunar infarcts from the small vessel disease (Tiehuis et al. 2008). In diabetic patients, increased WM lesions are evident even with CT (Gorelick et al. 2011). In the aging HIV-infected brain, the neuropathology associated with diabetes would likely exacerbate those already found in HIV and aging, leading to additional brain atrophy, WM inflammation, and increased likelihood for cerebral infarcts.

Increased prevalence of strokes in HIV-infected individuals

Approximately one third to half of older people have had infarcts; many of whom do not show cognitive deficits (Schneider et al. 2009), probably due to their cognitive reserve. HIV infection is also associated with an increased risk of stroke (Cole et al. 2004; Qureshi et al. 1997), up by 60 % between 1997 and 2006 in stroke patients with the coexisting diagnosis of HIV (Ovbiagele and Nath 2011). Treatment with protease inhibitors may further increase the incidence of vascular events. Therefore, strokes may occur in younger HIV-infected individuals, as shown in a recent study that the majority of HIV-infected stroke patients were under 46 years of age (Tipping et al. 2007). These younger patients did not have the typical risk factors for strokes, but 20 % had HIV vasculopathy. Therefore, co-occurrence of HIV and strokes will likely decrease the cognitive reserve and lead to greater prevalence of HAND.

Substance abuse and HIV on the aging brain

Substance abuse is another common comorbid condition among HIV-infected individuals, and little or no data exist regarding how drug use might further impact the aging brain. Stimulants, such as methamphetamine, may lead to more severe microglia activation and more pronounced loss of synaptophysin in HIV-associated encephalitis (Langford et al. 2003). Methamphetamine abuse also may lead to greater than age-related cortical volume reductions (Nakama et al. 2011) but larger subcortical volumes (Chang et al. 2005a; Jernigan et al. 2005). Furthermore, additive or interactive effects between HIV and methamphetamine usage were observed on brain morphometry (Jernigan et al. 2005), alterations in WM integrity (Thames et al. 2011), additive effects on neuronal and glial metabolites (Chang et al. 2005b; Taylor et al. 2004), as well as possible additive

effect on lower resting CBF and greater CBF changes in response to brain activation (Ances et al. 2011). Similarly, HIV+ cocaine users also had greater reductions in dopamine transporter density and D2 receptors than HIV subjects without drug use (Chang et al. 2008a). Since dopamine receptors decline with age, cocaine abuse in HIV subjects could exacerbate their age-associated dopaminergic receptor loss (Chang et al. 2008a). Furthermore, a growing number of HIV patients are identified to have alcohol use problems (Bonacini 2011), which is well known to contribute to the aging process in the brain (Pfefferbaum et al. 2012). Alcohol abuse appears to contribute to additional brain changes in HIV patients who had greater brain atrophy with larger ventricular volumes (Pfefferbaum et al. 2006), decreased neuronal marker NAA (Pfefferbaum et al. 2005), and greater diffusion abnormalities with lower FA and higher MD (Pfefferbaum et al. 2007). Lastly, despite the high prevalence of marijuana use by the HIV-infected population, for both therapeutic and recreational purposes (Prentiss et al. 2004), virtually no data is available regarding how marijuana might influence brain aging in these individuals. Only one paper evaluated the independent and combined effects of HIV and marijuana use on brain metabolites (Chang et al. 2006). While few studies have examined the combined or interactive effects of HIV and substance abuse on the aging brain, the limited data suggest that comorbid substance abuse may have negative impact in the aging brains of HIV patients.

Summary and conclusion

A variety of neuroimaging techniques have been applied to evaluate possible additive or interactive effects of age and HIV infection on the brain. The neuroimaging studies reviewed evaluated anatomical (MRI) or microstructural changes (DTI), neurochemical alterations (MRS), and brain activation (fMRI) in HIV-infected individuals. Because these techniques evaluated different pathophysiological aspects of HIV-associated brain injury and had differential sensitivities for detecting brain changes, we found differences in the rate of brain degeneration. For example, while the fMRI studies found accelerated aging, the structural MRI studies found premature aging. Similarly, brain activation measured by fMRI (unpublished data) and cognitive performance may be different across subjects with or without HAND despite similar volume loss detected by structural MRI (Chang et al. 2011). Most importantly, the majority of these studies were performed cross-sectionally in a small number of subjects, which may be affected by intersubject variability or biases in subject selections. Therefore, cross-sectional studies are limited in differentiating between premature aging and accelerated aging.

Earlier MRI and MRS studies from the pre-HAART era or in ARV-naive subjects suggest an accelerated aging process, with greater than normal age-dependent brain atrophy and brain metabolite abnormalities. However, more recent studies of HIV subjects maintained on HAART demonstrate premature brain atrophy, with earlier brain changes that may then parallel the aging process. With chronic long-term HIV infection, those with and without HAND may show similar degrees of brain atrophy; however, those with APOE-ε4 allele(s) may have the greatest brain atrophy and early onset brain atrophy. Although HIV subjects with minimal cognitive deficits may show higher than normal levels of MI across the age span, MI appears to decline with age in those with HAND, suggesting a decline in glial function.

DTI studies yielded conflicting findings on the relationship between HIV and age in NAS individuals. One study found similar age-related changes in both SN and HIV subjects (Towgood et al. 2011), while another study found greater than normal age-related changes in diffusion after 1-year, especially in the genu (Chang et al. 2008a). This discrepancy may result from differences in the image-processing techniques, brain regions evaluated, and the research designs (e.g., cross-sectional vs. longitudinal).

fMRI studies found evidence of premature or accelerated aging processes in the brains of HIV subjects. Lesser CBF changes and BOLD activation were found across the age span of HIV subjects during a simple visual stimulation task (Ances et al. 2010). However, increased activation, rather than the normal decreased activation (practice effects), were seen during attention-requiring tasks after 1 year in cognitively normal HIV subjects (Ernst et al. 2009). These studies demonstrate that BOLD fMRI, especially with tasks that require attention (or cognitive "stress"), may be the most sensitive technique for assessing the decline of neural efficiency and the aging effects of the HIV-infected brain.

Lastly, many age-related illnesses such as diabetes, stroke, and depression may further exacerbate the combined or interactive effects of HIV and aging on the brain, leading to premature or accelerated age-related brain changes. However, only a few small neuroimaging studies have evaluated these comorbid issues in HIV patients but did not assess these effects on the aging process. Other concurrent issues, such as the potential direct or indirect neurotoxic effects of particular ARV medications (e.g., NRTIs or protease inhibitors) and the greater prevalence of substance abuse (Ostrow 1994) and nicotine smoking among HIV subjects (Reynolds 2009), could also impact the HIV-infected aging brain. Future studies evaluating the independent and combined effects of these comorbid issues in HIV patients are needed.

Since the different neuroimaging techniques assess different pathologic or physiologic changes in the brain, using a multimodal approach in longitudinal follow-up studies would lead to a better understanding of the relationships

between structural, chemical, and functional changes in the aging brains of HIV patients.

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