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Disrupted cerebral metabolite levels and lower nadir CD4 + counts are linked to brain volume deficits in 210 HIV-infected patients on stable treatment

Xue Hua [a], Christina P. Boyle [a], Jaroslaw Harezlak [b], David F. Tate [c], Constantin T. Yiannoutsos [b], Ron Cohen [d,e], Giovanni Schifitto [f], Assawin Gongvatana [e], Jianhui Zhong [g], Tong Zhu [g], Michael J. Taylor [h], Thomas B. Campbell [i], Eric S. Daar [j], Jeffry R. Alger [k], Elyse Singer [k], Steve Buchthal [l], Arthur W. Toga [a], Bradford Navia [m], Paul M. Thompson [a,*], the HIV Neuroimaging Consortium

[a] Imaging Genetics Center, Laboratory of Neuro Imaging, Dept. of Neurology, UCLA School of Medicine, Los Angeles, CA, USA
[b] Indiana University Fairbanks School of Public Health, Indianapolis, IN, USA
[c] Henry M. Jackson Foundation for the Advancement of Military Medicine Contractor, San Antonio Military Medical Center, San Antonio, TX, USA
[d] Centers for Behavioral and Preventive Medicine, The Miriam Hospital, Providence, RI, USA
[e] Department of Psychiatry and Human Behavior, the Warren Alpert Medical School of Brown University, Providence, RI, USA
[f] Department of Neurology, University of Rochester, Rochester, NY, USA
[g] Department of Imaging Sciences, University of Rochester, Rochester, NY, USA
[h] Department of Psychiatry, University of California, San Diego, CA, USA
[i] University of Colorado Denver, Aurora, CO, USA
[j] Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, University of California, Los Angeles, CA, USA
[k] David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[l] Department of Medicine, JABSOM, University of Hawaii, Honolulu, HI, USA
[m] Department of Public Health, Infection Unit, Tufts University School of Medicine, Boston, MA, USA

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ABSTRACT

Cognitive impairment and brain injury are common in people with HIV/AIDS, even when viral replication is effectively suppressed with combined antiretroviral therapies (cART). Metabolic and structural abnormalities may promote cognitive decline, but we know little about how these measures relate in people on stable cART. Here we used tensor-based morphometry (TBM) to reveal the 3D profile of regional brain volume variations in 210 HIV+ patients scanned with whole-brain MRI at 1.5 T (mean age: 48.6 ± 8.4 years; all receiving cART). We identified brain regions where the degree of atrophy was related to HIV clinical measures and cerebral metabolite levels assessed with magnetic resonance spectroscopy (MRS). Regional brain volume reduction was linked to lower nadir CD4+ count, with a 1–2% white matter volume reduction for each 25-point reduction in nadir CD4+. Even so, brain volume measured by TBM showed no detectable association with current CD4+ count, AIDS Dementia Complex (ADC) stage, HIV RNA load in plasma or cerebrospinal fluid (CSF), duration of HIV infection, antiretroviral CNS penetration-effectiveness (CPE) scores, or years on cART, after controlling for demographic factors, and for multiple comparisons. Elevated glutamate and glutamine (Glx) and lower *N*-acetylaspartate (NAA) in the frontal white matter, basal ganglia, and mid frontal cortex — were associated with lower white matter, putamen and thalamus volumes, and ventricular and CSF space expansion. Reductions in brain volumes in the setting of chronic and stable disease are strongly linked to a history of immunosuppression, suggesting that delays in initiating cART may result in imminent and irreversible brain damage.

1. Introduction

Since the introduction of combined antiretroviral therapies (cART), opportunistic infections and HIV-associated dementia are much less common, resulting in marked improvements in life expectancy and quality of life for people living with HIV (Antinori et al., 2007; Palella et al., 1998; Schouten et al., 2011). Even so, the incidence of mild to moderate cognitive dysfunction is increasing in HIV+ cohorts (Ances

* Corresponding author at: Imaging Genetics Center, Laboratory of Neuro Imaging, Dept. of Neurology, UCLA School of Medicine, Neuroscience Research Building 225E, 635 Charles Young Drive, Los Angeles, CA 90095-1769, USA. Tel.: +1 310 206 2101; fax: +1 310 206 5518.
E-mail address: thompson@loni.ucla.edu (P.M. Thompson).

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and Ellis, 2007; Heaton et al., 2010, 2011). 15–50% of patients who have received long-term treatment show some cognitive impairment (Cysique et al., 2004; Simioni et al., 2010), suggesting continued central nervous system (CNS) involvement despite viral suppression and immune reconstitution.

Neuroimaging studies have provided useful insights into the pattern and extent of CNS damage associated with HIV infection (Jernigan et al., 1993; Tucker et al., 2004). The HIV Neuroimaging Consortium (HIVNC) was formed in 2005 to map the course of structural brain injury over time, and to relate brain changes to cognitive impairment in a prospective cohort of HIV+ subjects with a history of chronic disease on stable cART. Multimodal neuroimaging data was collected to assess the HIV+ brain in terms of: (1) cellular injury and inflammatory response measured by proton magnetic resonance spectroscopy (^{1}H-MRS) (Cohen et al., 2010a; Harezlak et al., 2011), and (2) structural brain atrophy measured from standard anatomical magnetic resonance imaging (MRI) (Cohen et al., 2010a, 2010b).

To date, neuroimaging studies of HIV+ populations have found important associations between CNS structural abnormalities, immunological markers, and neural injury reflected by brain metabolite disruption. Reduced cortical and subcortical volumes in addition to metabolite abnormalities persist in HIV patients receiving cART, and are associated with advanced disease stage and cognitive impairment (Chiang et al., 2007; Cohen et al., 2010a, 2010b; Harezlak et al., 2011; Patel et al., 2003; Paul et al., 2002, 2008; Tate et al., 2009, 2011). Among structural brain abnormalities, atrophy in the basal ganglia and frontal white matter, as well as abnormalities in periventricular white matter are most commonly observed, suggesting a primary involvement of the frontal–striatal networks (Dal Pan et al., 1992; Navia et al., 1986a; Tate et al., 2009). White matter atrophy is common in both pre- and post-cART HIV+ cohorts and is strongly associated with disturbances in cognitive function (Gongvatana et al., 2009; Navia et al., 1986a; Schouten et al., 2011). Abnormalities previously reported in the basal ganglia structures include either hypertrophy (an increase in volume) (Castelo et al., 2007) or hypotrophy (a deficit in volume) (Jernigan et al., 2005) in HIV+ patients, possibly due to the different stages of infection and response to treatment. Methamphetamine use may also cause hypertrophy of the white matter (perhaps due to inflammation); although the cause and consistency of the white matter effects of meth are not well-understood, some cohorts deliberately assess HIV participants with co-morbid IV drug use, where the balance of effects tends to reflect a combination of viral effects and those of chronic drug use. Recent evidence for white matter changes in HIV+ participants includes faster rates of white matter volume loss in HIV+ patients on stable cART with viral suppression (Cardenas et al., 2009), lower white matter fractional anisotropy as well as greater brain network deficits measured by diffusion tensor imaging (Chen et al., 2009; Jahanshad et al., 2012; Nir et al., 2013; Pfefferbaum et al., 2007; Pfefferbaum et al., 2009; Ragin et al., 2004; Tate et al., 2010; Wu et al., 2006). In the HIVNC cohort and a separate cohort named CNS HIV Antiretroviral Therapy Effects Research (CHARTER), nadir CD4+ count has been associated with lower total white matter and subcortical gray matter volumes (Cohen et al., 2010b; Jernigan et al., 2011), as well as lower corpus callosum volumes (Tate et al., 2011).

Brain MRS shows regional metabolite disturbances, including increases in choline and myoinistol, along with decreases in N-acetyl aspartate, reflecting inflammation and neuronal injury, respectively, in the frontal white matter and subcortical nuclei (Chang et al., 2004; Harezlak et al., 2011; Sacktor et al., 2005; Yiannoutsos et al., 2004). A recent HIVNC study of 240 HIV+ patients showed a persistence of these abnormalities in the setting of stable disease and cART (Harezlak et al., 2011). Although cerebral metabolite abnormalities were associated with cortical and subcortical gray matter deficits in the HIVNC cohort, significant relationships with white matter volume have not yet been detected (Cohen et al., 2010a). Here we set out to use a sensitive MRI analysis technique called tensor-based morphometry (TBM) to relate clinical markers of HIV infection and brain metabolites to differences in regional brain volume. TBM is a nonlinear registration based approach designed to detect regional differences in brain volume in a cohort, and study factors that affect them (Chiang et al., 2007; Chung et al., 2001; Davatzikos, 1996; Fox et al., 2001; Hua et al., 2013; Shen and Davatzikos, 2003; Studholme et al., 2001; Thompson et al., 2000). Multivariate TBM has been recently applied to study structural abnormalities (Lepore et al., 2008) and lateral ventricular surface differences (Wang et al., 2010) associated with HIV/AIDS. Unlike traditional ROI-based volumetric methods, TBM provides a whole brain voxel-based analysis without requiring any prior anatomical hypothesis about where differences should be found. It is a helpful method to study the profile of white matter atrophy on anatomical MRI, which lacks detectable anatomical landmarks to parcellate white matter in a consistent way.

Here we mapped the 3D pattern of brain abnormalities in a large cohort of HIV-infected patients on stable cART, as part of the HIVNC study. Regional brain volume variations in 210 HIV-infected patients – both cognitively asymptomatic and symptomatic – were examined for relationships with MRS cerebral metabolite levels and HIV clinical indices such as nadir and current CD4+ levels, HIV RNA concentrations and duration of known HIV infection. We hypothesized that the level of atrophy in frontal brain regions, particularly the white matter, and the basal ganglia, would relate to metabolic markers of neuronal injury, and to nadir CD4+ count, a marker of immune function and a major risk factor for neurocognitive impairment (Heaton et al., 2011).

2. Materials and methods

2.1. Subjects

We studied 210 HIV-infected patients (mean age 48.6 ± 8.4 years; 175 men and 35 women) enrolled in the HIVNC during the years 2003–2009. Subjects were recruited from seven sites across the United States including Colorado (N = 36), UCLA (N = 42), UCLA-Harbor (N = 54), UCSD (N = 11), Rochester (N = 49), Stanford (N = 15), and Pittsburgh (N = 3). Subjects of various ethnicities were enrolled, including Caucasians (N = 148; 70% of the cohort), African-Americans (N = 54; 26%), Asians (N = 2; 1%) and Native Americans and American Indians (N = 6; 3%). Inclusion criteria included nadir CD4+ cell count less than 200 cells/mm^3; stable antiretroviral regimen with any Food and Drug Administration (FDA)-approved therapy for at least 12 consecutive weeks prior to the study; hemoglobin greater than 9.0 g/dl; serum creatinine less than three times the upper limit of normal (ULN); aspartate aminotransferase (serum glutamic-oxaloacetic transaminase) [AST (SGOT)], alanine transaminase (serum glutamic–pyruvic transaminase) [ALT (SGPT)], and alkaline phosphatase of three times the ULN or less.

Exclusion criteria included severe premorbid or comorbid psychiatric disorders, confounding neurologic disorders such as chronic seizures, stroke, head trauma resulting in loss of consciousness of more than 30 min, multiple sclerosis, brain infection (except for HIV), or brain neoplasms, including CNS lymphoma and active alcohol and drug abuse or related medical complications within 6 months of study. All procedures were reviewed and approved by local institutional review boards (IRBs). All participants gave written informed consent.

2.2. Clinical characteristics

Clinical measures included the AIDS Dementia Complex (ADC) stage (Navia et al., 1986a, 1986b; Price and Brew, 1988), current CD4+ counts, nadir CD4+ counts (lowest cell counts prior to treatment), HIV RNA viral load in plasma and cerebrospinal fluid (CSF), duration of HIV infection or duration of known infection when patient was first tested, antiretroviral CNS penetration-effectiveness (CPE) scores, and years on cART. Although 210 participants were available for study,