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Novel Neuroimaging Methods to Understand How HIV Affects the Brain

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Abstract

In much of the developed world, the HIV epidemic has largely been controlled by anti-retroviral treatment. Even so, there is growing concern that HIV-infected individuals may be at risk for accelerated brain aging, and a range of cognitive impairments. What promotes or resists these changes is largely unknown. There is also interest in discovering factors that promote resilience to HIV, and combat its adverse effects in children. Here we review recent developments in brain imaging that reveal how the virus affects the brain. We relate these brain changes to changes in blood markers, cognitive function, and other patient outcomes or symptoms, such as apathy or neuropathic pain. We focus on new and emerging techniques, including new variants of brain MRI. Diffusion tensor imaging, for example, can map the brain's structural connections while fMRI can uncover functional connections. Finally, we suggest how large-scale global research alliances, such as ENIGMA, may resolve controversies over effects where evidence is now lacking. These efforts pool scans from tens of thousands of individuals, and offer a source of power not previously imaginable for brain imaging studies.

Keywords

Neuroimaging; MRI; Brain connectivity; Atrophy; cortical thinning

Introduction

Neuroimaging in HIV

A broad range of evidence relates HIV infection to behavioral or cognitive changes in children and adults, across the human lifespan. Yet for many years, the diversity in the populations of infected individuals, and different viral clades, led to inconsistent findings regarding neuropsychiatric changes and ongoing structural and functional brain changes.

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Conflict of Interest

Paul Thompson and Neda Jahanshad declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Today, new initiatives are bringing together researchers from all over the world, vastly increasing the power and scope of brain imaging studies. This new source of insight into the diversity of HIV-infected populations should begin to resolve several key questions regarding the HIV epidemic, and how it affects brain health, brain aging, and what can be done to resist it. These efforts may also serve to disentangle the effects of numerous confounds and comorbidities that have made HIV risks to the brain harder to understand.

In this review, we explain how imaging is used to study HIV effects on the brain. The past decade has seen a revolution in brain mapping techniques. These methods track subtle changes in brain structure and function, and patterns of connectivity as the brain matures and ages. This has greatly enhanced clinical research, and reveals how brain structure and function may differ in people living with HIV.

The first set of questions - that brain imaging can address - concerns how HIV-infected people's brains differ functionally and structurally from matched healthy controls. A vast range of brain imaging studies have assessed this; here we review some of the most recent studies, describing areas of consensus as well as disagreement. Brain scans with standard structural MRI show subtle but significant patterns of atrophy (regional tissue loss), on average, in people with HIV [1, 2]. Clearly, there is great practical value in knowing how these patterns relate to future outcomes for patients, such as cognitive decline. These brain changes may also depend on treatment regimes, and they are related to blood markers of patients' health in the past and in the future. In addition, it is important to determine whether brain atrophy is progressive, and if so, what factors promote or resist ongoing brain changes.

Clinical research also aims to determine any factors - in the genome or environment - that might increase resilience to HIV, or its adverse effects on the brain [3]. HIV exposure may affect the developing brain, and emerging methods in brain imaging can visualize how treatments may modulate or restore brain growth [4]. If treatment effects on brain aging or development could be verified in cohorts worldwide, there would be important implications for global health.

A worldwide movement in brain imaging is creating very large-scale consortia to address questions that no single researcher could resolve on his or her own. In clinical neurology, many major brain diseases - such as Alzheimer's, Parkinson's disease, frontotemporal dementia, and multiple sclerosis - have characteristic radiological signatures that help in differential diagnosis. These differences, seen in brain scans, can also help to evaluate treatment response. In HIV/AIDS however, there is less of a consensus on the brain regions and even neuropsychological functions affected (see Wendelken and Valcour for a review [5]). The pooling and comparison of brain scans from many cohorts across the world may help sort out whether there is a characteristic profile of brain changes, and what are their primary modulators.

In fact, some groups argue that brain scanning has little value for HIV-infected patients, if they do not show any neurological symptoms. Nishijima et al. [6] studied 485 HIV+ patients who underwent MRI screening between 2001 and 2013. For patients with CD4 counts below

200/μl, intracranial deficits were detected in only 3 (3%) of 144 asymptomatic patients, compared to 46 (32%) of 113 symptomatic patients ($p<0.01$).

Regardless of the utility of brain MRI for routine clinical evaluations, there are many large multi-site neuroimaging studies such as COBRA (http://fp7-cobra.eu/) in the European Union, and - in the United States - CHARTER [7, 8], the Multi-Cohort AIDS Study [9] (MACS) and the HIV Neuroimaging Consortium, or HIVNC [10]. Global neuroimaging consortia, such as Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA, http://enigma.ini.usc.edu/) [11], are pooling brain scan and clinical data from over 30 countries. These efforts are beginning to identify what brain changes there are in HIV/AIDS patients, what promotes and resists them, and their typical clinical correlates. In fact, we are only just beginning to understand the many demographic, lifestyle, genetic, and treatment related factors that influence the extent and progress of HIV-related brain dysfunction (see a recent review by Masters and Ances, 2014, [12]).

Conventional Brain Morphometry and the Mapping of Brain Abnormalities

Anatomical MRI is the mainstay of clinical diagnosis for many brain disorders - from the degenerative dementias to white matter demyelinating disorders, such as multiple sclerosis and ALS. Standard MRI shows the brain's structural anatomy in detail, including the major gray matter nuclei, white matter, and the gyral and sulcal anatomy of the cortex. Early in the HIV epidemic, CT (computed tomography) or T2-weighted brain MRI were often used radiologically to screen for encephalitis, white matter damage, and vascular lesions due to secondary infections. Imaging was also used to monitor any progression in brain lesions, to assess their likely impact on behavior and cognition.

More recently, at least in the developed world, the HIV epidemic has been largely controlled, as combined antiretroviral therapy became widely used. It is now relatively uncommon for a HIV+ person who is stable on treatment, to show severe brain atrophy – at the level of a patient with Alzheimer's disease, for example. However, some evidence points to consistent patterns of atrophy in the cortex and basal ganglia, and in some regions of the cerebellum, such as the vermis.

For decades, it was the manual delineation of brain structures on MRI scans that pointed to atrophy in these regions and thinning of the corpus callosum and expansion of the lateral ventricles in people with HIV/AIDS [13, 14]. Hand-tracing methods have been largely superseded by automated computer programs to measure the volumes of key brain regions, such as the caudate nucleus, hippocampus, and the thickness of the cerebral cortex [15, 16]. Defining these patterns and what affects them has involved the aggregation of clinical and neuroimaging data from multiple patients and controls, and high-throughput methods to analyze them.

The last 3 years have seen the automatic computation of brain measures on a previously unimaginable scale - the ENIGMA consortium, for example, screened 30,000 brain MRI scans from people in 33 countries, and found 8 genetic loci that appear to affect the size of key brain regions [17]. On average, each single genetic locus may have less than half a percent effect on the volumes of brain structures, the power of large imaging consortia to

detect subtle effects on the brain is clear. Now, we can quickly test for statistical associations between brain measures and clinical data, including cognitive performance, duration and course of illness, clinical history and medications, and current or previously collected blood serum markers. This has led to a surge in statistical studies of HIV/AIDS and other disorders that seek clinical correlates of brain atrophy or brain decline [18].

Figure 1 summarizes a study of cortical gray matter thickness in a group of HIV+ people, compared to a group of matched seronegative controls of the same age and sex (adapted from Thompson et al., 2005 [1]). Each group was scanned with conventional anatomical MRI. On average, the HIV+ group had thinner cortex in sensorimotor regions of the brain, and in some supplementary motor areas in the frontal lobes. The degree of gray matter deficit was also correlated with neurocognitive performance in the patients, assessed using the neuropsychological z-score "NPZ" scale, which averages normalized scores across multiple test batteries and is sensitive to subtle differences in motor processing speed. In this and other studies, the degree of gray matter reduction was also associated with the patients' nadir CD4+ T-cell counts - meaning the lowest recorded CD4 counts for each patient. As in many HIV studies, the nadir CD4 is a marker of early disease burden that is often correlated with later losses of tissue on brain MRI [19].

In a finer-scale analysis of what might affect the level of brain atrophy, Kallianpur and colleagues [20] studied PBMC HIV DNA detectability in a cohort of HIV+ subjects. Relative to the HIV+ group with undetectable HIV DNA, people with detectable HIV DNA had lower volumes of cerebellar (-14%) and total subcortical (-10%) gray matter. The authors concluded that the inability to clear peripheral blood of HIV DNA may be associated with regional brain atrophy, even in controlled HIV infection. Consequently, peripheral as well as central viral reservoirs may promote brain dysfunction in HIV+ people.

Related work by HIV researchers in Thailand [21] studied HIV effects on brain structure in HIV-infected individuals with and without HIV-associated neurocognitive disorders (HAND), to determine whether brain scans can reliably differentiate people with cognitive impairment. When young HIV+ adults started on combination antiretroviral therapy (cART), their CD4 lymphocyte counts were associated with total and subcortical gray matter volumes but not with cognitive measures. The authors concluded that brain atrophy may not be a sensitive measure of HAND in patients, except in those who have advanced immunosuppression. Even so, some aspects of brain aging may be accelerated in at least some HIV+ people. Cysique and Brew (2014) [22] noted that as HIV+ persons are aging, there may also be a greater incidence of age-associated diseases (see also Pfefferbaum et al., 2014, [23]). Even so, these brain-aging effects are not as dramatic as in the primary dementias, requiring some skill in study design to detect and understand. Brain aging in HIV + patients is an active area of research, as with treatment, these individuals are living much longer and otherwise normal lives.

Neuroanatomy and HIV

Perhaps the first surprise from the neuroimaging studies of HIV/AIDS is that brain atrophy from an infectious illness should be localized at all in the brain. Based on autopsy studies, the virus is known to enter the brain within the first weeks post-infection, and many early

anti-retroviral treatments had limited ability to penetrate the blood brain barrier. As such, the notion of an “HIV reservoir” in the brain led to studies of viral propagation, and even lineages being constructed based on active viral changes in the living brain [24].

One explanation for the pattern of brain atrophy is that the virus may enter the brain primarily via the CSF or fluid-filled spaces, such as the lateral ventricles. Greatest atrophy is often seen in the basal ganglia, along with mild but significant sulcal widening - a sign of cortical atrophy. A better understanding of this gray matter atrophy is crucial: Keltner (2014) [8] reported that smaller total cerebral cortical gray matter volume was associated with the severity of distal neuropathic pain (DNP) - one of the most prevalent, disabling, and treatment-resistant complications of HIV disease. Over half of the 241 HIV-infected participants in the Keltner study reported DNP symptoms, and these may have their origins in CNS regions affected by HIV.

Figure 2 shows the results of a “tensor-based morphometry” study of HIV/AIDS, adapted from Chiang et al. [2]. Red colors show white matter areas with deficits in brain tissue volume, on average, compared to matched regions in healthy seronegative controls of the same age and sex, with similar demographics. As in the cortical studies (Figure 1), premotor and frontal atrophy are detected. Similar studies of the cerebellum implicated the cerebellar vermis as especially atrophied in HIV/AIDS [25], but the mechanism for this is unclear.

Tensor-based morphometry has been used in several studies to visualize patterns of brain changes in HIV+ patients [2, 26, 27]. In these morphometric analyses, groups of standard anatomical scans from patients and controls are aligned digitally into the same coordinate space - computer programs are used align brain scans to a standard, or “average” template of the brain. Nonlinear image registration, or “warping”, methods are used to elastically stretch or compress the brain scans, in three dimensions (3D), to match the brain template. These transformations are then analyzed mathematically to determine the relative sizes of each part of the brain in each person. Such methods provide automated pixel-by-pixel assessments of associations between brain atrophy and HIV status, treatment, and possible modulators of disease. Research is underway to pool evidence from such studies across multiple cohorts worldwide, in a voxel-based meta-analysis [28].

MRI spectroscopy (MRS) is a variant of anatomical MRI that measures the concentration of key brain metabolites in the living brain tissue. Anatomical MRI typically measures the nuclear magnetic resonance signal from hydrogen atoms (protons) in water and lipids in the brain, but the MRI scanner can also be programmed to detect levels of key cellular metabolites, such as *N*-acetylaspartate, a widely-used marker of neuronal integrity [29]. Based on data from MRS studies, blood-based markers of inflammation and immune activation, in particular MCP-1 and sCD14, can predict metabolic disturbance in chronically HIV-infected subjects [30].

Inflammation may contribute to brain pathology in HIV+ individuals. Even so, Zahr and colleagues [31] advised caution in interpreting HIV infection as the primary driver of brain metabolite abnormalities related to inflammation. They found that having an acquired immune deficiency syndrome (AIDS)-defining event or hepatitis C was associated with

higher levels of choline in the brain; lower choline levels, however, were associated with low thiamine levels and with the use of highly active antiretroviral HIV treatment (HAART). Higher levels of myoinositol were related to greater lifetime alcohol consumed, and the use of HAART treatment itself was associated with lower myoinositol levels. These often complex networks of predictors necessitate caution in epidemiological studies. The vast number of confounds - measured and unmeasured - suggest that we need to replicate findings across multiple diverse cohorts to reliably identify the primary contributors to brain dysfunction. This is especially important as complex networks of plasma and blood markers also interact [32, 33]. Statistical methods combining many, potentially unrelated, sources of information [34] are being applied to neuroimaging research to improve power to identify affected pathways.

Mapping Rates of Brain Growth and Tissue Loss

A related type of study maps tissue loss rates in a given patient over time, or the rate of brain growth during development. Figure 3 shows “norms” for childhood brain growth, much like the growth charts for height and weight used in child health clinics worldwide. Growth rate maps can be computed from repeatedly collected brain MRI data, with the “tensor-based morphometry” method [35, 36]. This approach can map how the brain changes over time, when a patient, or a group of patients, is scanned longitudinally over a period of months to years. The PREDICT study in Thailand, for example, assesses brain growth in HIV+ children, including those whose treatment with antiretroviral therapy is deferred, versus given immediately. A key goal in scanning these cohorts is to establish growth rate “norms” based on as much statistical data as possible. Despite the large effect sizes for structural brain differences in elderly cohorts with HIV [37], brain differences between HIV+ and HIV- children have been more difficult to identify [38].

Connectomics

A major line of work in brain mapping is “connectomics”, which uses new techniques to study the brain’s connections. The overt loss of neural tissue in HIV is thought to be accompanied by a Wallerian degeneration of axons. Loss of anatomical connections may contribute to brain dysfunction, by impairing information transfer and integration in the brain’s neural networks. Figure 4 shows the pattern of neural pathways identified with a variant of brain MRI, called diffusion tensor imaging or DTI (we review the use of DTI in neurology in Thomason and Thompson 2011 [40]). Water diffusion in the brain is directionally constrained along axons, and more so in heavily myelinated neural pathways. DTI uses this principle to map the physical connectivity of brain regions, and the integrity of the axons. In one study [39], the integrity of connections in the brain’s anatomical network was lower in HIV+ patients versus controls, and was further disrupted in people with prolonged HIV exposure and with the *APOE4* genotype. A finer scale analysis of specific brain regions implicated motor areas that consistently showed atrophy in prior studies of cortical gray matter thickness.

Perhaps related to this, in a separate cohort, Wilson et al. [41] reported abnormal magneto encephalography (MEG) responses - spatially coincident with reduced gray matter volume - in HIV-infected patients.

Effects of Genotype

Diversity in the viral genome may impact the degree of HIV-associated neurological deficits [42]. Additionally, a person's own genome may interact with the virus and affect the relative degree of brain abnormalities [43]. In the connectivity study [39], deficits were greater in HIV+ people who carried the *APOE4* risk haplotype (see Figure 4), a common genetic variation associated with a 3–4-fold increased risk for late-onset Alzheimer's disease. In their studies of brain metabolites with MR spectroscopy, Chang and colleagues [44, 45] also noted that carrying *APOE4* may exacerbate the effects of HIV infection to lead to greater cognitive deficits, especially in those with greater neuroinflammation. The ability to detect not just the HIV effect on the brain, but genetic factors that resist or worsen it, is a major goal of neuroimaging research. This has led to vast studies combining imaging and genetic data (see ENIGMA below).

Diffusion-Weighted MRI

As well as mapping patterns of anatomical connectivity, diffusion imaging can also quantify white matter damage [37]. In a series of studies of vertically-infected HIV+ children, a research group in South Africa reported a possible association of first-line treatment failure with white matter brain dysfunction in pediatric neuro-HIV [46].

In 50 cART-treated children aged 6 to 15, white matter integrity was related to a number of clinical variables. Lower fractional anisotropy (FA) or higher mean diffusivity (MD), potential indicators of abnormalities in neuronal development or axonal damage, were associated with being on second-line cART, increased viral load and with lower key blood measures like hemoglobin and albumin.

In adults, abnormalities on DTI may also be promoted by other cerebrovascular risk factors and a longer duration of illness [47]. Wright et al. [48] studied white matter abnormalities in acutely and chronically-infected people with HIV, and standard DTI metrics in recently-infected individuals (a median of 4.1 months after estimated infection) were similar to HIV-participants but were correlated with disruptions in the blood-brain barrier (indicated by CSF/plasma albumin ratio and CSF protein). By contrast, chronically-infected patients had significant loss of white matter integrity that correlated with biomarkers of infection and inflammation (blood viral load, CD4 T-cell count, neopterin, and CSF white blood cell counts).

Other efforts with DTI seek specific behavioral correlates of white matter abnormalities. In Kamat et al. [49], the patient's level of *apathy* - measured using the Frontal Systems Behavioral Scale - was associated with white matter abnormalities in anterior, medial brain regions in persons infected with HIV, particularly in the setting of lower current immune functioning, which may have implications for antiretroviral therapy.

Functional MRI

Measurement of regional cerebral blood flow has been a major goal of functional brain mapping since the 1980s. Temporal fluctuations in brain activity are easily measured with functional MRI, which infers neural activation from the coupled blood flow fluctuations that

affect the MRI signal. Most published fMRI studies scan a person's brain as they perform a task (such as watching a visual stimulus, processing language, or making a decision). Task-based fMRI can also monitor changes in the neuropsychiatric function of patients, compared to HIV-negative controls [50]. In one study, Ernst and colleagues found no overall difference in neurocognitive status or task performance, but did observe localized increases in fMRI signal in the prefrontal and posterior parietal cortices for certain more difficult tasks. They suggested that patients may show increased usage of the attention network, perhaps compensating for ongoing brain changes in order to remain clinically stable.

By contrast, resting state fMRI measures temporal correlations in brain activation, in different parts of the brain, over a period of around 10 minutes. This scan is done while a participant lies still in the scanner, not performing a task. Statistical analysis of these patterns of synchronized activity has identified brain networks that tend to be more active at rest than when performing a cognitive task, and *vice versa* [51].

Resting-state measures show promise for clinical research - drug companies designing clinical trials have been interested in whether rs-fMRI signals may respond to interventions more quickly than brain structure or measures of anatomical connectivity. Thomas et al. [52] investigated connectivity patterns in resting-state fMRI activation in five functional brain networks including the default mode, control, and salience networks. All of these had lower intra-network correlations in HIV+ individuals. However, they found no differences between the sensorimotor or dorsal attention networks in HIV patients, compared to controls. As the default mode and salience networks were also found to show decreased connectivity with aging in the same study, they suggested that HIV and aging may both independently decrease brain function. As with structural imaging studies, there is an implication that HIV infection may lead to an accelerated aging effect in the brain.

In general, in the neuroimaging of HIV+ cohorts, there is a move towards multi-modal imaging, i.e., scanning the brain with multiple methods. This should help define more reliable biomarkers in the brain data that offer better diagnostic sensitivity for HIV-associated cognitive impairment, or better prognostic value.

ENIGMA

One frustrating barrier in the field of neuroimaging has been the relatively small cohorts of patients scanned consistently with MRI at various sites around the world. There is no doubt that brain differences are consistently identifiable in HIV+ cohorts, using modalities as diverse as structural MRI, MR spectroscopy, functional MRI, and even PET [53].

Even so, large cohorts are needed to disentangle HIV effects on the brain from other confounders, such as the effects of drug use, mode of infection, and key modulators such as duration of illness or treatment, medication compliance, and other key factors, known or unknown, in the genome or environment.

Another related concern is that many brain imaging studies report associations that are not later replicated, and it is hard to tell why. Studies may lack statistical power to conclusively rule out effects or pick up subtle effects. Due to the vast cost of collecting large amounts of

scan data, there is a reluctance to fund multiple studies with the same design. Learning from the work of multi-site studies such as the Alzheimer's Disease Neuroimaging Initiative [54, 55] which studied around 1000 elderly people in North America, the ENIGMA Consortium combines MRI data - and clinical and genomic data - from over 30,000 persons worldwide [11, 17, 56, 57]. ENIGMA's studies of schizophrenia, depression, and bipolar illness reveal treatment effects (of antipsychotics, antidepressants, and neuroleptics) and appear to distinguish them from the primary effects of those disorders on the brain [58–60].

HIV effects on the brain depend on many factors, confounded with numerous risk factors, known and unknown. Global alliances and research consortia are offering new leads in understanding how to resist damaging effects of HIV on the brain. Recently, an ENIGMA-HIV working group was formed to determine consistent patterns of brain differences in HIV + cohorts worldwide [61]. The accumulation and comparison of this aggregated data is vital for accurate modeling of important confounders and modulators such as demographics, ethnic background, and duration, timing, and compliance with treatment.

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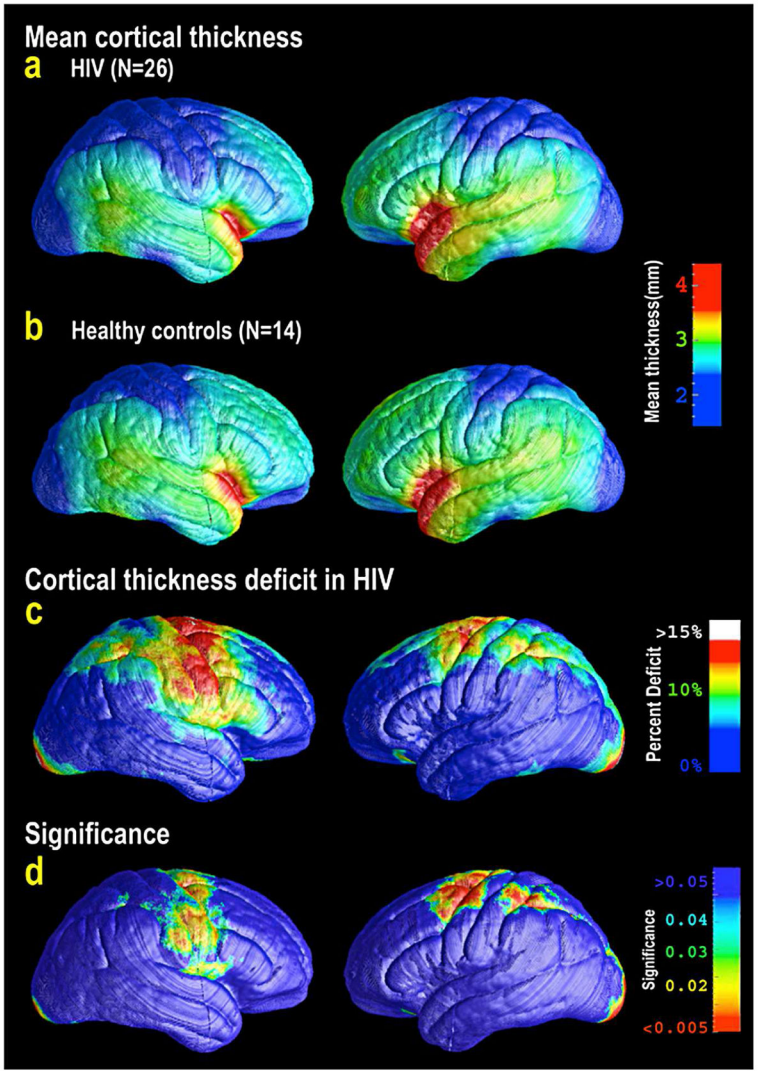

Figure 1.

Cortical gray matter thinning has been shown in HIV+ patients, compared to age- and sex-matched seronegative controls (adapted from Thompson et al., 2005 [1]).

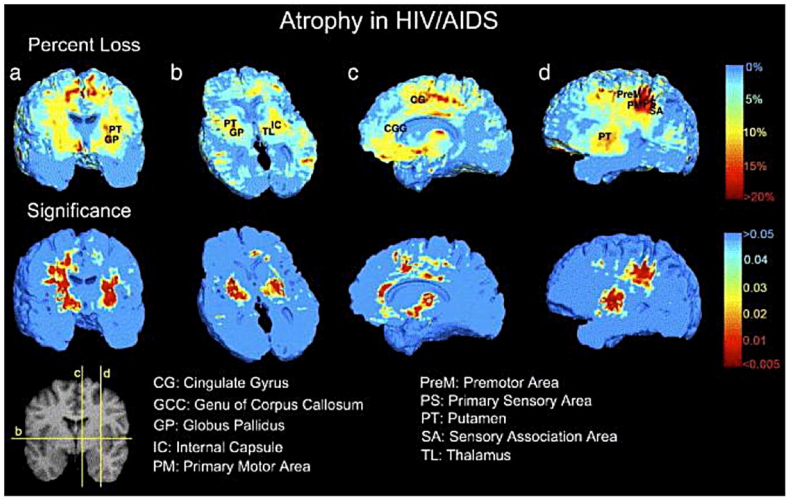

Figure 2.

Morphometric studies of brain MRI scans compare volume differences between HIV+ patients and HIV-negative individuals on a voxel-by-voxel, or point-by-point level. This figure, adapted from Chiang et al., [2] shows white matter regions with reduced volume in patients compared to demographically matched seronegative controls.

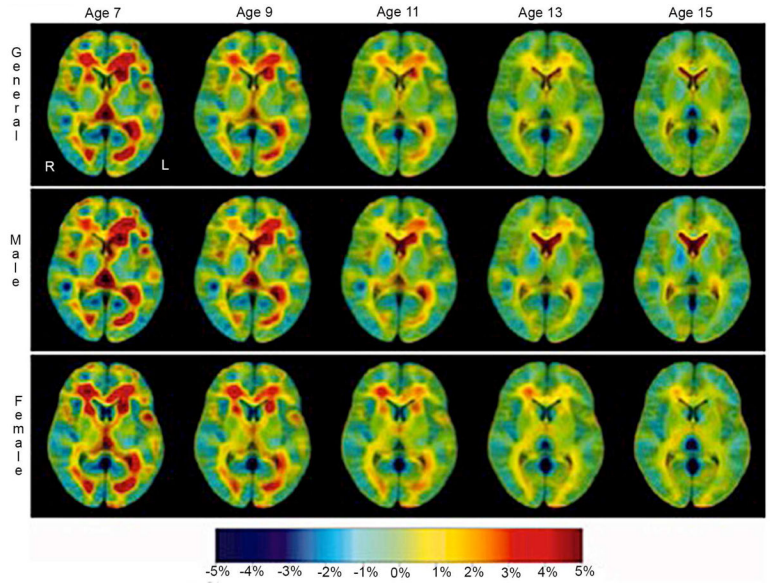

Figure 3.

Adapted from Hua et al. [35], serial MRI scanning of children at different ages can map tissue-specific growth rates throughout the various stages of brain development.

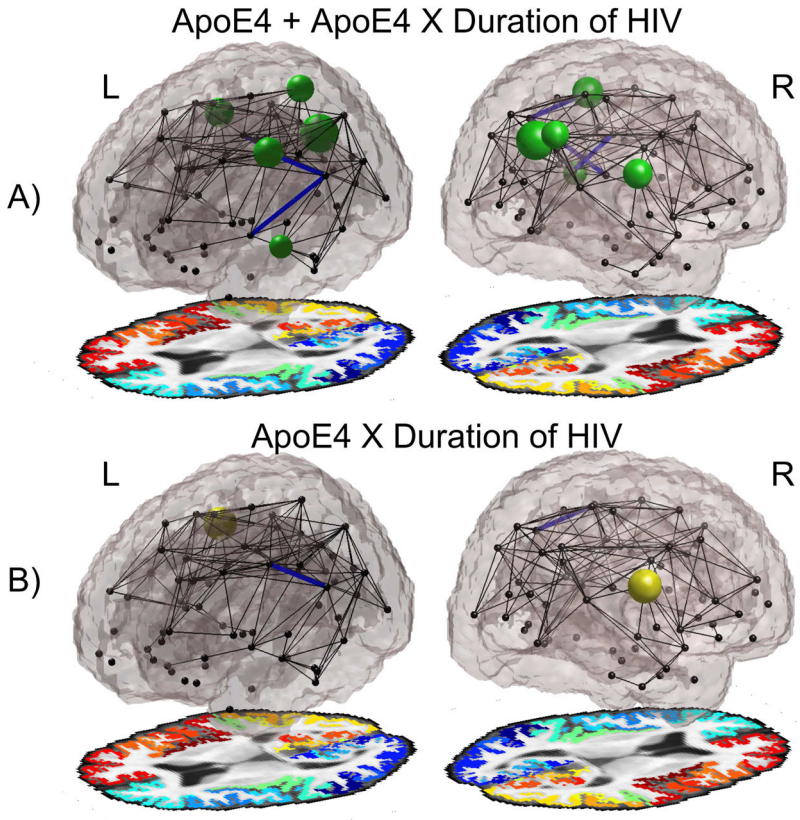

Figure 4.

Adapted from Jahanshad et al. [39], this image shows structural connections in the brain that show greater age-related reductions in density in HIV-infected individuals over age 60, who carry the ApoE4 genotype.