

Chapter 6

Human Brain Imaging in HIV and NeuroAIDS

Mona A. Mohamed

Keywords HIV • NeuroAIDS • HAND • Brain • Imaging • MRI • MRS • DTI • PET • Biomarkers

Core Imaging Modalities

Structural changes in HIV

fMRI and brain connectivity in HIV

MRS at work: a lens of brain metabolites changes in HIV

DTI: white matter fibers integrity in HIV

Imaging cerebral blood flow in HIV

PET and SPECT in HIV

6.1 Introduction

More than 25 years have passed since the description of neurological dysfunction, HIV-associated dementia. A plethora of research done before and after the era of combined antiretroviral therapy (cART) focused on the role of immune responses and their neurotoxic effects on cognition in HIV infection. However, more work is still ahead of us to explain unanswered questions regarding the pathogenesis of NeuroAIDS.

HIV infection usually progresses to AIDS. Barely a few percent of infected patients can control the infection without treatment due to a diminishing T cell response during infection. cART suppresses viremia; however, chronic activation of

M.A. Mohamed, MD, PhD, MEHP, MPH (✉)
Russell H. Morgan Department of Radiology and Radiological Sciences, Neuroradiology
Division, Johns Hopkins University School of Medicine,
Park 367G, 600 N. Wolfe Street, Baltimore, MD 21287, USA
e-mail: mnourel1@jhmi.edu

the immune system is the major factor behind the progression of the disease and not the HIV replication [1].

Postmortem brain tissue studies suggest trafficking of bone marrow-derived monocytes into the deep white matter during late stage of infection [2].

The pathogenesis of AIDS dementia complex is still not well understood. Once HIV-infected monocytes and macrophages cross the blood–brain barrier, mediators and neurotoxins are released with development of neurological dysfunction. Brain macrophages, neurons, astrocytes, and glial cells act as chronic HIV reservoirs [3].

Neurocognitive deficits in motor, reaction time (speed), visuospatial reconstruction, memory encoding, attention, and executive functions are common symptoms in NeuroAIDS. Ruling out other causes of dementia can be challenging to the clinician as there are no clinical markers for HIV-associated cognitive impairment. Neurocognitive deficits are measured by neuropsychological tests using either the Memorial Sloan Kettering (MSK) AIDS Dementia Scale [4–6] or more commonly today using the Frascati criteria [7]. HAND diagnosis is based on neuropsychometric testing and includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive impairment (MCI), and the most severe form, HIV-associated dementia (HAD) [7]. Correlation of neurocognitive tests with imaging markers is a common tool used to help understand the pathogenesis of NeuroAIDS.

Currently, there is significant reduction of HIV-associated brain disease, specifically HIV encephalitis and CNS opportunistic infections, due to effective combination antiretroviral therapy (cART) [8].

An emerging body of evidence from neuroimaging, clinical, and pathological studies suggests that despite remarkable advances in treatment, central nervous system dysfunction in the context of chronic and stable HIV persists despite successful systemic therapy [9].

Little was known about the anatomical and structural alteration caused by HIV infection. Currently, with advanced neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET), using different brain radioligands, the structural, functional, and metabolic brain changes in the brains of HIV patients are being unveiled. These alterations, described in the literature, although nonspecific, are considered new lenses, which help understanding the pathogenesis of NeuroAIDS. This technology ultimately helps monitor disease progression, treatment effect, and development of new means of therapy [10].

6.2 Brain Imaging

Brain imaging techniques include those which show brain structure (structural imaging) and those which show function or brain metabolism (functional imaging) of the regions of interest in normal and pathological conditions. Structural techniques include X-rays (including angiography), computed tomography (CT), and magnetic resonance imaging (MRI). Functional procedures include functional MRI (fMRI), magnetoencephalography (MEG), magnetic resonance spectroscopy (MRS), magnetic resonance spectroscopic imaging (MRSI), positron emission

tomography (PET), electroencephalography (EEG), and single-photon emission computed tomography (SPECT).

6.2.1 Structural Imaging

Although computed tomography (CT) involves ionizing radiation, it is still often used for many clinical HIV brain imaging studies, as it is more commonly available in hospitals, and it is less costly than magnetic resonance imaging (MRI). Besides being safe and nonionizing, MRI is a better imaging modality for anatomical and structural mapping, with great tissue resolution and contrast. The MR signal is from water and fat which are of different precession frequencies and have different T1 relaxation times. Chemical shift is the difference between water and fat magnetic moment or spin frequency of the atom or energy level (in Hz per pixel). Clinically, 1.5 and 3 Tesla (T) machines are used. High magnetic fields such as 7 T are used for research studies. MRI is based on nuclear magnetic resonance in which, by using head coils, radiofrequency pulses are sent to the examined organ. The protons from the various types of tissues (from water content to fat content with different relaxation times) will absorb radiofrequency and will then spin. When the radiofrequency pulse is turned off, relaxation of tissues at different rates will emit radio wave energy indicators that are captured as MRI signals.

Structural changes are sometimes better enhanced when chemical agents such as gadolinium are injected to improve tissue contrast. Using T1 images, findings include increased post-contrast enhancement on contrast-enhanced magnetic resonance imaging (CE-MRI), which can reflect breakdown of the microvascular integrity of the BBB in HIV neuronal inflammation [11]. This measure can be correlated with viral load and neurocognitive impairment and can predict progression of HIV-positive patients and the development of HIV-associated dementia [12].

Diffuse cortical and subcortical brain atrophy in HIV infection is well known even before the cART era [13]. Example of HIV brain atrophy is shown in Fig. 6.1.

Corresponding T2 and FLAIR sequence nonspecific hyperintense focal lesions may be seen in the frontal and parietal white matter, suggestive of gliosis [14, 15]. Voxel-based morphometry (VBM) is an MRI technique, which measures brain region volumes. VBM is associated with changes mainly frontal white matter, subcortical, and striatal regions including the basal ganglia. Structural MRI shows significant reduction in volume of the frontal white matter with dilation of the ventricles due to atrophy. This cortical atrophy is usually progressive even if the HIV patients are under treatment [16].

Although age-related GM atrophy is primarily seen in the superior temporal and inferior frontal regions, HIV-related GM loss includes the posterior and inferior temporal lobes, parietal lobes, and cerebellum. The interaction of age and HIV status has a significant effect on brain volume [17, 18].

New imaging techniques using multiatlas-based segmentation of multiple brain areas according to patient age group [19–22]. Example of automated multiatlas brain segmentation is shown in Fig. 6.2.

Immunodeficiency is a risk factor for opportunistic infections in NeuroAIDS. Using computerized tomography (CT) and MRI, especially in T1, T2, and FLAIR images, HIV-1 and AIDS-associated CNS pathologies are visualized. These neuropathologies include encephalitis, primary CNS lymphoma (enhancing parenchymal nodular lesions in the frontal lobe and basal ganglia with perilesional edema, and restricted diffusion [23]), cerebral toxoplasmosis (single or multiple focal brain lesions with ring enhancement and possible “eccentric target sign”),

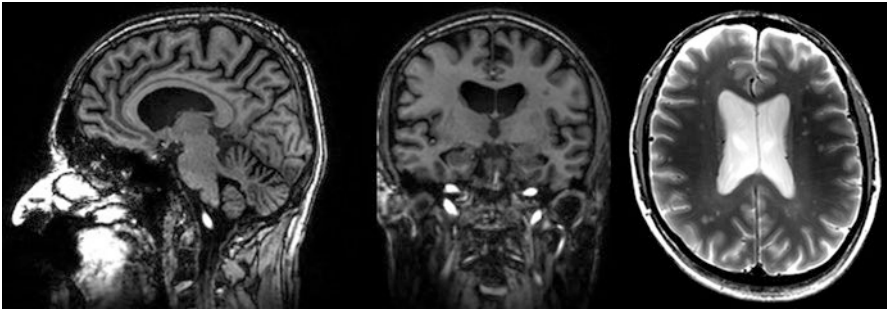
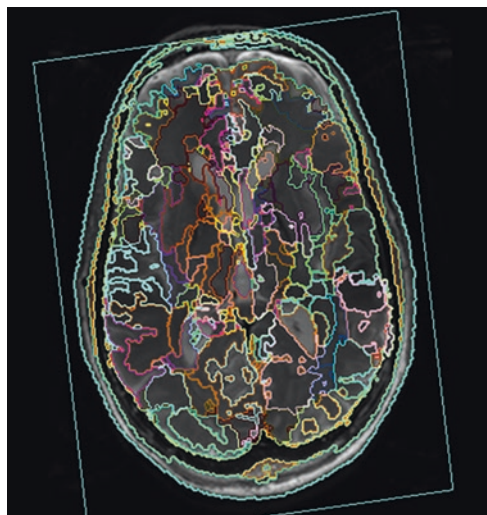


Fig. 6.1 Sagittal T1, coronal T1, and axial T2 images of the brain of an asymptomatic neurocognitive impairment (ANI) HIV+ patient showing signs of brain atrophy (dilated lateral ventricles and wide *sulci*). Multiple small T2 hyperintensities are seen in the periventricular white matter bilaterally

Fig. 6.2 Atlas-guided brain MRI segmentation of 286 regions of interest (ROIs) of an HIV+ subject's brain using BrainGPS: A multiatlas cloud-based processing pipeline



cytomegalovirus (CMV) and Epstein-Barr (EB) virus encephalitis [24], progressive multifocal leukoencephalopathy (PML) (as ill-defined hyperintense edge and hypointense core on diffusion-weighted imaging (DWI) in the white matter and U fibers) [25], tuberculoma (focal brain lesions), neurocysticercosis, and CNS fungal diseases, which include cryptococcal meningitis, aspergillosis, and mucormycosis [26, 27]. Toxoplasmosis may be difficult to distinguish from cerebral lymphoma [28]. Associated hydrocephalus or ophthalmic involvement with the various opportunistic CNS infections and inflammations can also be detected using CT or MRI. These opportunistic infections and pathologies were more prevalent before the cART era compared with today. Example of opportunistic infections (toxoplasmosis and herpes) and PML in HIV brain are shown in Figs. 6.3, 6.4, and 6.5.

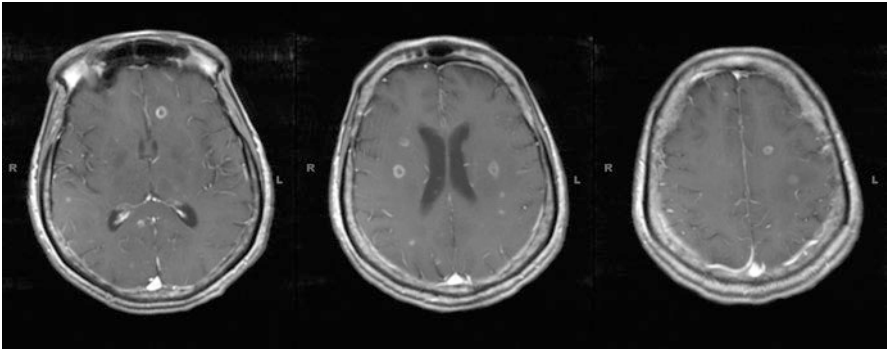


Fig. 6.3 T1W image showing bilateral, multiple ring enhancing lesions in the periventricular region consistent with toxoplasmosis in an HIV+ immunocompromised patient (Images are the property of Dr. Haris Sair and the Johns Hopkins School of Medicine Neuroradiology teaching file)

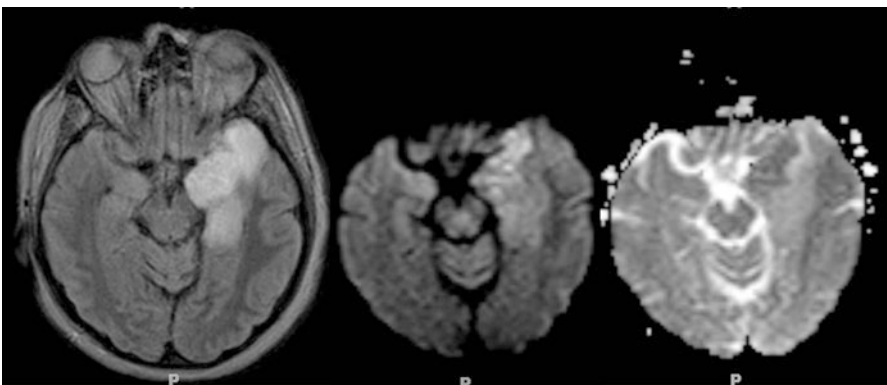


Fig. 6.4 T2-FLAIR image (*left*) demonstrating edema in the left anterior and mesial temporal lobe. DWI-trace and ADC images (*middle* and *right*) demonstrate areas of restricted diffusion consistent with Herpes infection in HIV+ patient (Images are the property of Dr. Haris Sair and the Johns Hopkins School of Medicine Neuroradiology teaching file)

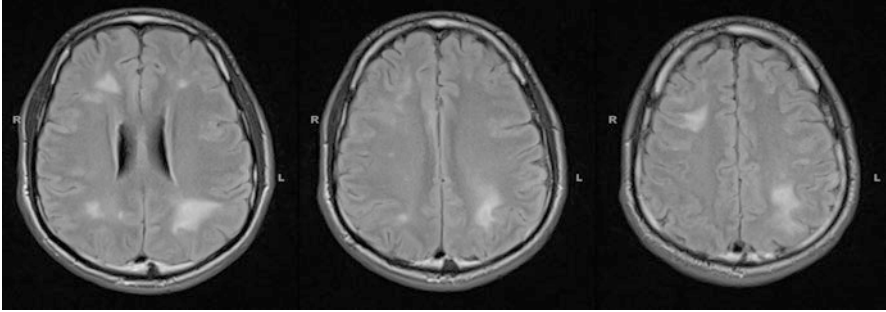


Fig. 6.5 Multifocal confluent T2-FLAIR hyperintense white matter lesions including the subcortical U fibers consistent with progressive multifocal leukoencephalopathy (PML) (Images are the property of Dr. Haris Sair and the Johns Hopkins school of medicine neuroradiology teaching file)

6.2.2 Functional Neuroimaging

6.2.2.1 Magnetic Resonance Spectroscopy (MRS) and Magnetic Resonance Spectroscopic Imaging (MRSI)

HIV has been extensively studied using magnetic resonance spectroscopy (MRS) at field strengths of 1.5 and 3.0 Tesla (T) [29, 30]. Proton magnetic resonance spectroscopy (MRS) is a noninvasive and safe imaging modality that profiles brain metabolism at a molecular level. It allows mapping of the chemical composition of the tissue. It can therefore give information on the human brain pathophysiology, which may appear normal to the neuroradiologist through measurement of these brain metabolite levels that may show neuronal or glial impairment [31]. It utilizes a continuous band of radiofrequencies that excite hydrogen atoms in different chemical compounds other than water, thus, allowing an understanding of chemical changes of the brain at the molecular level. The tissue chemical composition determines the frequency of the metabolic peak on the MRS spectrum. It is a spectrum of the amount of metabolite peak concentration against the chemical shift or frequency (in ppm). This enables identifying the metabolites in a voxel (large voxel ranging from 1 to 10 cm³) on the spectrum as well as quantifying it. In MRS, the chemical shift is the difference between metabolites spin, the magnetic moments in part per million (PPM) which is the Hz multiplied by million since the frequency difference is very small. PPM is a locator number on the spectrum that reflects the spin difference and thus gives the information about the molecular group carrying the proton. MRS can, therefore, help identify metabolites, which is measured to help early detection, progression, and in monitoring responses to therapeutic interventions.

Magnetic resonance spectroscopic imaging (MRSI) is similar to MRS in measuring brain metabolites; however, despite requiring a longer scan time, it has the advantage of mapping the metabolic profile of the whole brain, i.e., exploring regional metabolic variations in one session. It acquires data from small voxels ranging from 1 to 4 cm³ covering the whole brain. Factor analysis is one statistical

technique, which looks at multiple-dependent variables and reducing them to fewer factors to evaluate the metabolite levels across several brain regions. One study showed identified “NAA factor” that differentiated between patients with HIV dementia from those without dementia and correlated best with psychomotor and executive function tests. The “Cr factor” was increased in HIV dementia. The Cr factor correlated with the patients’ CSF monocyte chemoattractant protein-1 levels. Both NAA and Cr factor scores were strongly weighted to white matter neuronal impairment in HIV dementia. Regional Cho elevations reflected glial turnover early in the disease differentiating HIV+ from HIV- [32].

Measuring brain metabolites can reflect neuronal integrity and gliosis in early and late stages of HIV and HIV-associated dementia (HAND). These metabolites can be used as biomarkers for seroconversion as well as neurocognitive impairment. In HIV, infected host immune cells cross the BBB early in the early stage of infection activating microglia and infect other immune cells adding to the spread of infection. Neuronal toxicity and inflammation lead to neuronal and glial dysfunction and further disruption of the BBB [12]. Previous MRS studies showed previous brain magnetic resonance spectroscopy (MRS) studies at 1.5 and 3 T that have shown alterations in the neurometabolic profile in HIV+ patients. One study showed impaired neuronal integrity across the white and gray matter regions as reflected by the decreased NAA/Cr and Glu/Cr in HIV patients with symptomatic cognitive impairment which correlate with neuropsychiatric tests [31, 33]. Example of single voxel brain spectrum is shown in Fig. 6.6.

Other MRS studies showed improvement of MRS values after treatment suggesting neuroprotective value of cART in HIV infection [34]. Another study, case control study using 3 T MRS, showed that increased Glx in FWM may suggest excitotoxicity in HIV-positive patients [35].

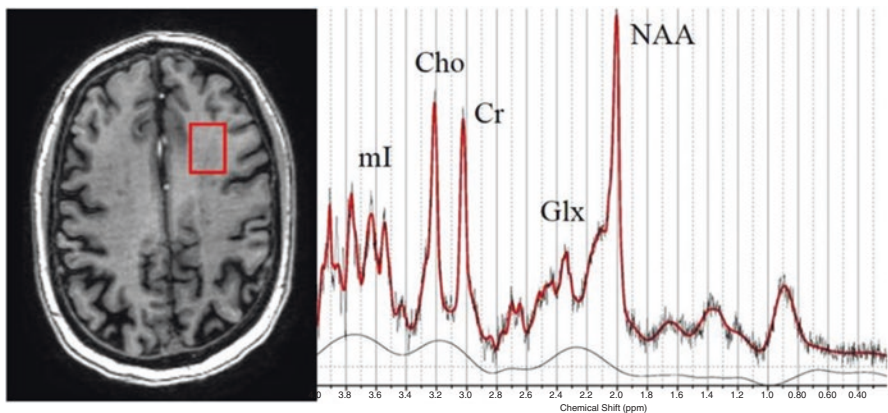


Fig. 6.6 Left frontal white matter (FWM) magnetic resonance spectroscopy (MRS) voxel (*red box*) and its corresponding spectrum in a 55 years old white HIV+ male patient with asymptomatic neurocognitive impairment (ANI)

6.2.3 MRS Metabolites

6.2.3.1 N-Acetyl Acetate (NAA)

NAA is only found in the neurons. Its concentration is about 7.8 millimolar (mM). They provide a measure of neuronal integrity. NAA decreases in neuronal and axonal loss as well as decreased neuronal function. The concentration also decreases in case of brain edema. Mitochondrial energy correlates with the synthesis of NAA in the neurons and axons. Decreased NAA concentration represents loss of neuronal integrity and is therefore a marker for neuronal dysfunction in NeuroAIDS [36].

6.2.3.2 Creatine (Cr)

Cellular oxidative metabolism is represented by the spectral resonance of Cr and phosphocreatine (PCr). It reflects the energy metabolism. The concentration of Cr is about 4.5 mM and is generally stable in the healthy brain. Thus, constant cellular metabolism in the healthy brain is reflected in the stability of the concentration of Cr. Stability in the concentration of Cr indicates constant cellular energy metabolism; therefore, it is used as a reference or control metabolite when assessing other brain metabolites level. Besides measuring the metabolites concentrations, calculating the ratios of brain metabolites to Cr is another common measure used by researchers to assess brain metabolites. In the brain, reductions in the concentration of Cr indicate deficient cellular energy metabolism [37]. Cr may decrease if the HIV patient has an associated hepatic encephalopathy.

6.2.3.3 Choline (Cho)

Phosphoryl choline and glycerophosphoryl choline, components of the manufacture and the breakdown of cellular membranes, make up the largest part of the total Cho resonance. It is about 1.3 mM of concentration. Increments in Cho likely represent a greater cell growth or cellular proliferation and gliosis. Thus, Cho is a marker of cell membrane turnover. Increase in its concentration indicates active myelin breakdown [37, 38]. Choline (Cho) concentrations and ratios to creatine (Cr) in the basal ganglia are found to be elevated early in HIV infection but then stabilize after treatment [34]. One study showed that when cART is started during chronic HIV, it was associated with reduced neuronal glia and inflammatory markers. Alterations in Cho were noted among individuals who remain cognitively impaired after 12 months of cART as compared with those without HIV-associated neurocognitive disorders (HAND) [39].

6.2.3.4 Myoinositol (MI)

MI is a cerebral osmolyte, which regulates osmolar states and cellular volume. Its concentration in the brain is about 3.8 mM. It represents gliosis in demyelination and in AIDS dementia. Additionally, MI takes part in the second-messenger system of phosphoinositide [37]. Myoinositol (MI) is a surrogate marker of glial activation as measured by magnetic resonance spectroscopy (MRS) [12].

One study showed that the ratio of myo-inositol to creatine is increased in white matter of HIV+ patients early in the disease compared with normal controls, which then normalizes. In AIDS dementia complex, MI is at normal levels, whereas NAA levels decrease [40].

6.2.3.5 Glutamate (Glu), Glutamine (Gln), and Glx

Glutamate receptor stimulation is one mechanism by which gp120 and TAT exert their neurotoxic events through glutamate receptor stimulation. Glutamate excitotoxicity plays a role in TAT-induced toxicity and peroxy-nitrite, nitric oxide, and reactive nitrogen species [41–44] which causes inflammation and neuronal damage can be a target for therapeutic approaches targeting glutamate receptors [45], other report that glutamate is protective to neurons [46]. TAT-induced neurotoxicity is also induced via the dopaminergic system in the striatum [47].

Reduced Glu uptake has previously been demonstrated to occur in vitro in astrocytes exposed to HIV possibly through reduced expression of the glutamate transporter, excitatory amino acid transporter 2 (EAAT2) [48]. Using 3 T MRI scanner, one MRS study showed decreased frontal white matter (FWM) Glu and Glx (the summation of Glu and glutamine) in HIV-associated dementia (HAD) patients compared with HIV patients with mild cognitive impairment group (MCI) and normal controls (NC). Their findings were positively associated with impaired performance in neurocognitive domains, such as fine motor, executive functioning, working memory, and attention [31].

6.2.3.6 Lactate (Lac)

Lactate is usually not normally detected in the brain tissue due to its very low concentration. If detected, it is usually increased in anaerobic nonoxidative glycolysis indicating ischemia.

6.2.3.7 Glutathione (GSH)

Glutathione (GSH) is a protective antioxidant against the increased reactive oxygen and nitrogen species which occurs in HIV infection. Oxidative stress is usually measured by invasive technologies [49]. Due to its very low concentration, it is difficult

to detect GSH by conventional MRS. Today, novel MEGA PRESS MRS techniques can detect GSH. Low GSH concentration reflects oxidative stress. In HIV, activated macrophages release free radicals which cause disruption of the blood–brain barrier and neuronal synapses [46], leading to functional impairment in the brain of individuals with HIV [50]. GSH can, therefore, be a predictive marker in identifying individuals at risk of oxidative stress in HIV dementia.

Using MRS and MRSI, predictive models for the associated predictors of CNS injury are useful in identifying human risk factors and their interaction in the progression of HIV. For instance, risk factors such as age, race, and gender; disease-specific factors such as HIV RNA concentration, ADC stage, duration of HIV infection, nadir CD4, current CD4 count, plasma RNA, and treatment-specific factors such as CNS penetration and effectiveness of cART can all be in the same predictive model. Using MRS, one study scanned 260 HIV+ subjects with various neurological stages and looked at all these risk factors. They measured and calculated 12 MRS brain metabolites ratios in 3 brain regions: the basal ganglia, the frontal white matter, and gray matter (MFC = midfrontal cortex). Their study showed that in chronic HIV, the host and viral factors which are related to both the current and past HIV statuses contribute to persisting abnormalities in the cerebral metabolite levels [9].

One study sought to investigate premature aging and cardiovascular disease (CVD) as two risk factors to HIV-associated neurocognitive disorder (HAND) in virally suppressed clinically stable HIV-infected adults. They aimed to know if brain MRS metabolites abnormalities in HIV adults involve only the frontal white matter (FWM) and caudate (the two typically affected brain regions) or do they extend to other brain region affected in pathological aging such as the posterior cingulate cortex and wanted to assess age and CVD as additional independent risk factors of brain injury in HIV+ adults. They also looked at immune recovery (measured by CD4), HIV duration, and inflammatory markers (CSF B2 microglobulin and neopterin) and its association with brain neurochemical injury (measured by metabolites abnormalities using MRS) in HIV adults, and if MRS are predictive of lower neuropsychiatric (NP) performance and if age, CVD and HIV status may moderate this relationship. They included 92 HIV-positive patients and 30 HIV-negative individuals in their study. They showed that (1) CDV risk factors were associated with lower NAA in PCG and *caudate*, (2) past acute events were associated with increased MI in PCG, (3) HIV duration was also associated with lower NAA in caudate, (4) high CNS cART penetration efficiency was associated with lower MI in PCG, (5) the degree of immune recovery on cART was associated with higher NAA in FWM, and (6) CSF neopterin was associated with high MI in PCG and FWM, (7) HIV and age interaction was associated with lower FWM NAA and (8) the increased Cho/NAA ratio was associated with decreased NP performance. The authors concluded that in long term virally suppressed, clinically stable HIV-infected adults, HIV duration, age, and CVD (past or recent events) are independent risk factors for brain inflammation [51].

MRS provides quantitative estimates of the concentration of cerebral metabolites in the various regions of the brain. Furthermore, normal cerebral metabolism is

characterized by the ratios of the concentrations of specific metabolites including NAA/Cho, NAA/Cr, Cho/Cr, and MI/Cr. The normal values for individuals at specific ages and gender provide guidelines to assess deviations from the normal and healthy concentrations and ratios.

6.3 MRS Protocols

Magnets of 1.5 T and 3.0 T are common clinical scanners. Scanners of 3.0 T provide a higher resolution. Magnet of 7.0 T is used for HIV research and not in the clinic. Using a head coil, the subject is scanned in the supine position. Structural imaging typically includes T1, T2, and fluid attenuation inversion recovery (FLAIR) in sagittal, oblique coronal, and oblique axial planes. Spectroscopic data are acquired with a single voxel technique (MRS) or multiple voxel imaging (MRSI) techniques. The signals are obtained for specific regions of interests (ROIs). In HIV, frontal white matter (FWM), basal ganglia (BG), anterior cingulate (ACG), posterior cingulate gyrus (PG), and hippocampus (if researchers are interested in aging studies in HIV) are the commonly used ROIs.

To minimize the artifacts of blood and cerebrospinal fluid (CSF), VOIs commonly exclude vasculature structures containing CSF. A point-resolved spectroscopy sequence with long and short echo times of short or long TE is usually obtained after shimming, fat, and water suppression. Sequences are run to estimate the concentrations of relevant metabolites and pertinent metabolic ratios, particularly NAA, Cho, and Cr. Ratios to Cr or to Cho can also be calculated: NAA/Cho, NAA/Cr, and Cho/Cr. The estimation of metabolites with a small brain concentration is facilitated with sequences with short echo times. MEGA-point-resolved spectroscopy (PRESS) editing (MEGA PRESS) techniques are novel techniques, which can detect brain metabolites which are difficult to resolve, such as GSH, N-acetyl aspartate glutamate (NAAG), or gamma amino butyric acid (GABA) [52–57]. Recently, novel MRS MEGA PRESS editing techniques are now available to measure multiple brain metabolites in one session, thus, decreasing the scan time especially if the patients cannot tolerate long scan times inside the MR machine [57–59].

6.3.1 Functional MRI (fMRI)

Assessment of the functional connectivity of brain regions is one area that was unveiled by functional MRI (fMRI). It examines the network dysfunction and coordination between the different parts of the brain needed for complex tasks done through fMRI experiments inside the magnet. These tasks can be correlated with tasks done outside the magnet as well as serological and neuropsychiatric tests and reaction times to investigate the level of neurocognitive impairment.

In HIV, it is known that there is injury and structural changes in the subcortical and *frontostriatal* brain regions; therefore, exploring the association of HIV serological and neurocognitive status with structural and functional resting stated fMRI data is of great importance [60–63]. One study suggested that HIV-associated dopaminergic abnormalities could be related to impaired frontostriatal connectivity which can be explored using PET imaging modality [62]. Another fMRI study showed that HIV+ showed reduced connectivity in the left caudate and the ventral prefrontal cortex and global pallidus as compared with seronegative controls which explained the impaired sequencing task in HIV+ patients [63]. Another fMRI study showed that HIV+ scored worse in facial recognition task as compared with seronegative controls which also correlated to brain volume reduction in HIV+ patients [60, 61].

6.3.2 Diffusion Tensor Imaging and DWI

The introduction of diffusion-weighted imaging had led to fiber tracking which helps the clinicians and surgeons to see damaged or displaced brain tissue.

The technique depends on measuring the molecular diffusion of water molecules in the brain tissue depicting macro- and microscopic anatomies of the various brain regions [64]. This anatomy can be disrupted in pathological conditions. Quantification of the degree of white matter (WM) abnormalities in chronic and virally suppressed HIV-infected (HIV+) persons can be achieved. Increased mean diffusivity reflects increased neuroinflammation which can be used to follow up progression of the disease [65]. White matter DTI measures like fractional anisotropy (FA) can be normal except for patients with longer HIV disease duration and who developed neurocognitive impairment [66]. Furthermore, restricted diffusion within the brain lesion on diffusion-weighted sequences was especially seen in focal lesions in HIV opportunistic infections or primary lymphoma.

6.3.3 Perfusion-Weighted Imaging (PWI) and Arterial Spin Labeling (ASL)

Perfusion-weighted imaging (PWI) technique using intravenous contrast injection allows mapping of hemodynamic changes based on the perfusion of the injected contrast material. This technique is used if there is suspicion of stroke in HIV patients.

Arterial spin labeling (ASL) is a safe MRI technique which provides a rapid, noninvasive, and quantitative measure of the cerebral blood flow (CBF) in various brain regions without intravenous injection. It can be used as a biomarker of the effects of HIV on the brain perfusion. Studies showed that the CBF is reduced in the early stages of HIV seroconversion even before they show neuropsychological impairment [67, 68].

6.3.4 *Quantitative Susceptibility Mapping (QSM) and Susceptibility-Weighted Imaging (SWI)*

Three-dimensional gradient echo (GRE) is a novel MRI-based sequence mainly used for susceptibility-weighted imaging (SWI) and quantitative susceptibility mapping (QSM) [69]. Quantitative susceptibility mapping (QSM) relies on the magnetic field distribution estimates of the examined brain tissue [70].

T2 GRE and SWI hypointensities can be seen in the frontal white matter and the U fibers and cortex adjacent to the white matter lesions in the demyelinating progressive multifocal leukoencephalopathy (PML) [71].

6.3.5 *Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT)*

PET is an imaging technique, which quantitatively evaluates the metabolic processes in the living organisms. PET provides the ability to estimate the rate at which the brain utilizes nutrients. Measurement of endogenous compounds in specific regions of the brain reflects dysfunction of the regional brain metabolism which can help understand the pathogenesis of NeuroAIDS [8].

PET and SPECT would discriminate the cases as inflammatory versus noninflammatory or neoplastic. Thallium-201 SPECT can be used in cerebral opportunistic infections in NeuroAIDS [28].

Administration of 2-deoxy-2-[18F] fluoro-d-glucose ([18F] FDG) is a safe and effective tool, which is performed widely in hospitals to examine glucose metabolism by the different body organs. Since glucose is metabolized by rapidly growing cells, the application of this procedure for whole-body tomography is suited for people with primary malignancies like lymphomas and opportunistic infections which may develop in advanced cases of HIV.

Studies using Technetium-99 m hexamethyl-propyleneamine oxime-single-photon emission computed tomography were used to evaluate brain perfusion in HIV infection. Studies showed global and focal decrease in blood flow to the brain in the early stages of infection without showing any signs of dementia or neuropsychiatric impairment [68]. Today arterial spin labeling is safe and noninvasive and can provide the same information without exposing the patient to radiotracers or ionizing radiation.

High active antiretroviral therapy (HAART) has lengthened the life expectancy of patients infected with human immunodeficiency virus (HIV); the risk of cognitive impairment in the aging HIV+ subgroup has continued to increase. Premature aging has been hypothesized as a risk factor for HIV-associated neurocognitive disorders (HAND) and is of great interest to researchers [51, 66, 72, 73]. The questions are: Does premature aging occur in HIV dementia? Is aging a risk factor to early development of HIV dementia in HIV+ individuals?

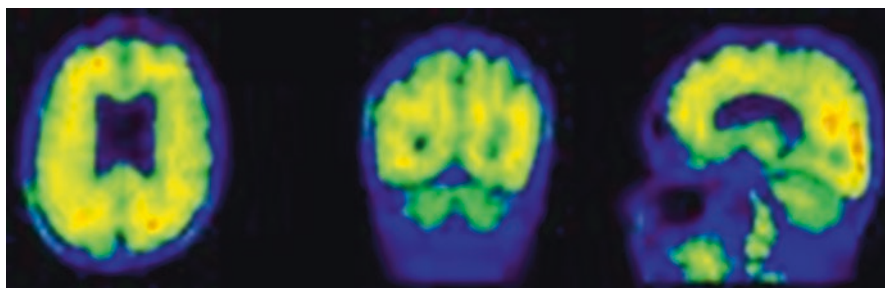


Fig. 6.7 Axial, coronal, and sagittal PET images showing ^{18}F AV45 standardized uptake value ratio (SUVR) image of an HIV+ individual showing high AV45 uptake in the *Precuneus* and the occipital region

PET imaging using ^{18}F AV45 (a specific tracer targeting amyloid plaques) is a new tool to investigate the association of increased amyloid deposition (as measured by standardized uptake value ratio (SUVR) reflecting AV 45 uptake) and aging in HIV. Example of ^{18}F AV45 PET scan in HIV brain is shown in Fig. 6.7.

6.4 Conclusions

Novel neuroimaging techniques are rapidly advancing allowing us to better understand the pathophysiology of the HIV-associated brain changes down to the molecular level. Multiparametric imaging is on the rise where fusion of multiple techniques and modalities would increase the sensitivity of MRI to detect subtle brain changes.

To date, pathological analysis, after a brain biopsy of the human living brain, remains the gold standard to establish the diagnosis of vast brain pathologies; however, nonspecific inflammatory pathology noted in probable cases has been often attributed to sampling of brain tissue [14]. With advanced imaging modalities allowing us to noninvasively diagnose brain pathologies at the molecular level, without resorting to stereotactic brain biopsy, we expect that in the future, neuroimaging will become the “gold standard” for definitive diagnosis of brain pathology.

Conflict of interest The authors report no conflicts of interest.

References

1. Poveda E, Martin-Gayo E (2017) Similar immunological profiles between nonprogressing HIV infection in children and nonpathogenic SIV infection. *AIDS Rev* 19(1):54–55
2. Liu Y et al (2000) Analysis of human immunodeficiency virus type 1 gp160 sequences from a patient with HIV dementia: evidence for monocyte trafficking into brain. *J Neurovirol* 1(6 Suppl):S70–S81

3. Aquaro S et al (2005) Human immunodeficiency virus infection and acquired immunodeficiency syndrome dementia complex: role of cells of monocyte-macrophage lineage. *J Neurovirol* 11(Suppl 3):58–66
4. Price RW, Brew B (1988) Infection of the central nervous system by human immunodeficiency virus. Role of the immune system in pathogenesis. *Ann N Y Acad Sci* 540:162–175
5. Price RW, Brew BJ, Rosenblum M (1990) The AIDS dementia complex and HIV-1 brain infection: a pathogenetic model of virus-immune interaction. *Res Publ Assoc Res Nerv Ment Dis* 68:269–290
6. Price RW, Sidtis J, Rosenblum M (1988) The AIDS dementia complex: some current questions. *Ann Neurol* 23(Suppl):S27–S33
7. Antinori A et al (2007) Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 69(18):1789–1799
8. Vera JH et al (2017) PET brain imaging in HIV-associated neurocognitive disorders (HAND) in the era of combination antiretroviral therapy. *Eur J Nucl Med Mol Imaging* 44(5):895–902
9. Harezlak J et al (2014) Predictors of CNS injury as measured by proton magnetic resonance spectroscopy in the setting of chronic HIV infection and CART. *J Neurovirol* 20(3):294–303
10. Baker LM et al (2017) Topological organization of whole-brain white matter in HIV infection. *Brain Connect* 7(2):115–122
11. Avison MJ et al (2004) Inflammatory changes and breakdown of microvascular integrity in early human immunodeficiency virus dementia. *J Neurovirol* 10(4):223–232
12. Avison MJ et al (2004) Neuroimaging correlates of HIV-associated BBB compromise. *J Neuroimmunol* 157(1–2):140–146
13. Aylward EH et al (1995) Magnetic resonance imaging measurement of gray matter volume reductions in HIV dementia. *Am J Psychiatry* 152(7):987–994
14. Shyam babu C et al (2013) Usefulness of stereotactic biopsy and neuroimaging in management of HIV-1 Clade C associated focal brain lesions with special focus on cerebral toxoplasmosis. *Clin Neurol Neurosurg* 115(7):995–1002
15. Chang L (1995) In vivo magnetic resonance spectroscopy in HIV and HIV-related brain diseases. *Rev Neurosci* 6(4):365–378
16. Cohen RA et al (2010) Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. *J Neurovirol* 16(1):25–32
17. Becker JT et al (2012) Factors affecting brain structure in men with HIV disease in the post-HAART era. *Neuroradiology* 54(2):113–121
18. Becker JT et al (2011) Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging Behav* 5(2):77–85
19. Ma J et al (2015) A fast atlas pre-selection procedure for multi-atlas based brain segmentation. *Conf Proc IEEE Eng Med Biol Soc* 2015:3053–3056
20. Tang X et al (2015) Segmentation of brain magnetic resonance images based on multi-atlas likelihood fusion: testing using data with a broad range of anatomical and photometric profiles. *Front Neurosci* 9:61
21. Wu D et al (2016) Direct estimation of patient attributes from anatomical MRI based on multi-atlas voting. *Neuroimage Clin* 12:570–581
22. Wu D et al (2016) Resource atlases for multi-atlas brain segmentations with multiple ontology levels based on T1-weighted MRI. *NeuroImage* 125:120–130
23. Alessandro L et al (2017) Retrospective study of 48 cases of primary central nervous system lymphoma. *Medicina (B Aires)* 77(1):17–23
24. Fujiki N, Tashiro K (1997) Herpes viruses--herpes simplex virus, varicella-zoster virus, EB virus, cytomegalovirus. *Nihon Rinsho* 55(4):855–860
25. Godi C et al (2017) High b-value diffusion-weighted imaging in progressive multifocal leukoencephalopathy in HIV patients. *Eur Radiol*. PMID: 2816837; doi: [10.1007/s00330-017-4761-8](https://doi.org/10.1007/s00330-017-4761-8) [Epub ahead of print]
26. Arendt G (1995) Imaging methods as a diagnostic tool in neuro-AIDS. A review *Bildgebung* 62(4):310–319

27. Smirniotopoulos JG et al (1997) Neuroimaging--autopsy correlations in AIDS. *Neuroimaging Clin N Am* 7(3):615–637
28. Mitchell WG (1999) Neurocysticercosis and acquired cerebral toxoplasmosis in children. *Semin Pediatr Neurol* 6(4):267–277
29. Chang L et al (1999) Cerebral metabolite abnormalities correlate with clinical severity of HIV-1 cognitive motor complex. *Neurology* 52(1):100–108
30. Chang L et al (2003) Persistent brain abnormalities in antiretroviral-naive HIV patients 3 months after HAART. *Antivir Ther* 8(1):17–26
31. Mohamed MA et al (2010) Brain metabolism and cognitive impairment in HIV infection: a 3-T magnetic resonance spectroscopy study. *Magn Reson Imaging* 28(9):1251–1257
32. Mohamed MA et al (2010) Factor analysis of proton MR spectroscopic imaging data in HIV infection: metabolite-derived factors help identify infection and dementia. *Radiology* 254(2):577–586
33. Sailasuta N, Shriner K, Ross B (2009) Evidence of reduced glutamate in the frontal lobe of HIV-seropositive patients. *NMR Biomed* 22(3):326–331
34. Sailasuta N et al (2012) Change in brain magnetic resonance spectroscopy after treatment during acute HIV infection. *PLoS One* 7(11):e49272
35. Bairwa D et al (2016) Case control study: magnetic resonance spectroscopy of brain in HIV infected patients. *BMC Neurol* 16:99
36. Barker PB (2001) N-acetyl aspartate--a neuronal marker? *Ann Neurol* 49(4):423–424.
37. Ross B, Bluml S (2001) Magnetic resonance spectroscopy of the human brain. *Anat Rec* 265(2):54–84
38. Govindaraju V, Young K, Maudsley AA (2000) Proton NMR chemical shifts and coupling constants for brain metabolites. *NMR Biomed* 13(3):129–153
39. Sailasuta N et al (2016) Neuronal-glia markers by magnetic resonance spectroscopy in HIV before and after combination antiretroviral therapy. *J Acquir Immune Defic Syndr* 71(1):24–30
40. Lopez-Villegas D, Lenkinski RE, Frank I (1997) Biochemical changes in the frontal lobe of HIV-infected individuals detected by magnetic resonance spectroscopy. *Proc Natl Acad Sci U S A* 94(18):9854–9859
41. Wallace DR et al (2006) Delta opioid agonists attenuate TAT(1-72)-induced oxidative stress in SK-N-SH cells. *Neurotoxicology* 27(1):101–107
42. Pannu R, Singh I (2006) Pharmacological strategies for the regulation of inducible nitric oxide synthase: neurodegenerative versus neuroprotective mechanisms. *Neurochem Int* 49(2):170–182
43. Zhao ML et al (2001) Expression of inducible nitric oxide synthase, interleukin-1 and caspase-1 in HIV-1 encephalitis. *J Neuroimmunol* 115(1–2):182–191
44. Rostasy K et al (1999) Human immunodeficiency virus infection, inducible nitric oxide synthase expression, and microglial activation: pathogenetic relationship to the acquired immunodeficiency syndrome dementia complex. *Ann Neurol* 46(2):207–216
45. Kaul M, Lipton SA (2005) Experimental and potential future therapeutic approaches for HIV-1 associated dementia targeting receptors for chemokines, glutamate and erythropoietin. *Neurotox Res* 8(1–2):167–186
46. Nichol KA, Schulz MW, Bennett MR (1995) Nitric oxide-mediated death of cultured neonatal retinal ganglion cells: neuroprotective properties of glutamate and chondroitin sulfate proteoglycan. *Brain Res* 697(1–2):1–16
47. Unterwald EM, Cuntapay M (2000) Dopamine-opioid interactions in the rat striatum: a modulatory role for dopamine D1 receptors in delta opioid receptor-mediated signal transduction. *Neuropharmacology* 39(3):372–381
48. Wang Z et al (2003) Reduced expression of glutamate transporter EAAT2 and impaired glutamate transport in human primary astrocytes exposed to HIV-1 or gp120. *Virology* 312(1):60–73
49. Bhaskar A et al (2015) Measuring glutathione redox potential of HIV-1-infected macrophages. *J Biol Chem* 290(2):1020–1038
50. Turchan J et al (2003) Oxidative stress in HIV demented patients and protection ex vivo with novel antioxidants. *Neurology* 60(2):307–314

51. Cysique LA et al (2013) HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a (1)H MRS study. *PLoS One* 8(4):e61738
52. Edden RA, Pomper MG, Barker PB (2007) In vivo differentiation of N-acetyl aspartyl glutamate from N-acetyl aspartate at 3 Tesla. *Magn Reson Med* 57(6):977–982
53. Grewal M et al (2016) GABA quantitation using MEGA-PRESS: regional and hemispheric differences. *J Magn Reson Imaging* 44(6):1619–1623
54. Harris AD, Saleh MG, Edden RA (2017) Edited 1 H magnetic resonance spectroscopy in vivo: methods and metabolites. *Magn Reson Med* 77(4):1377–1389
55. Landim RC et al (2016) Investigation of NAA and NAAG dynamics underlying visual stimulation using MEGA-PRESS in a functional MRS experiment. *Magn Reson Imaging* 34(3):239–245
56. Porges EC et al (2017) Frontal gamma-aminobutyric acid concentrations are associated with cognitive performance in older adults. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2(1):38–44
57. Saleh MG et al (2016) Simultaneous edited MRS of GABA and glutathione. *NeuroImage* 142:576–582
58. Chan KL et al (2017) Spatial Hadamard encoding of J-edited spectroscopy using slice-selective editing pulses. In: *NMR Biomed*
59. Chan KL et al (2016) HERMES: Hadamard encoding and reconstruction of MEGA-edited spectroscopy. *Magn Reson Med* 76(1):11–19
60. Clark US et al (2010) Facial emotion recognition impairments in individuals with HIV. *J Int Neuropsychol Soc* 16(6):1127–1137
61. Clark US et al (2015) Facial emotion recognition impairments are associated with brain volume abnormalities in individuals with HIV. *Neuropsychologia* 70:263–271
62. Ipers JC et al (2015) HIV infection is associated with attenuated frontostriatal intrinsic connectivity: a preliminary study. *J Int Neuropsychol Soc* 21(3):203–213
63. Melrose RJ et al (2008) Compromised fronto-striatal functioning in HIV: an fMRI investigation of semantic event sequencing. *Behav Brain Res* 188(2):337–347
64. Alger JR (2012) The diffusion tensor imaging toolbox. *J Neurosci* 32(22):7418–7428
65. Chang L et al (2008) Greater than age-related changes in brain diffusion of HIV patients after 1 year. *J Neuroimmune Pharmacol* 3(4):265–274
66. Cysique LA et al (2017) White matter measures are near normal in controlled HIV infection except in those with cognitive impairment and longer HIV duration. *J Neurovirol*. PMID: 28324319; doi [10.1007/s13365-017-0524-1](https://doi.org/10.1007/s13365-017-0524-1) [Epub ahead of print]
67. Ances BM et al (2009) Resting cerebral blood flow: a potential biomarker of the effects of HIV in the brain. *Neurology* 73(9):702–708
68. Schielke E et al (1990) Reduced cerebral blood flow in early stages of human immunodeficiency virus infection. *Arch Neurol* 47(12):1342–1345
69. Bilgic B et al (2016) Rapid multi-orientation quantitative susceptibility mapping. *NeuroImage* 125:1131–1141
70. Schweser F, Deistung A, Reichenbach JR (2016) Foundations of MRI phase imaging and processing for quantitative susceptibility mapping (QSM). *Z Med Phys* 26(1):6–34
71. Carra-Dalliere C et al (2016) Use of quantitative susceptibility mapping (QSM) in progressive multifocal leukoencephalopathy. *J Neuroradiol* 43(1):6–10
72. Chang L et al (2011) Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. *NeuroImage* 58(4):1017–1027
73. Chang L et al (2004) A multicenter in vivo proton-MRS study of HIV-associated dementia and its relationship to age. *NeuroImage* 23(4):1336–1347