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Imaging of Brain Structural and Functional Effects in People With Human Immunodeficiency Virus

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Before the introduction of antiretroviral therapy, human immunodeficiency virus (HIV) infection was often accompanied by central nervous system (CNS) opportunistic infections and HIV encephalopathy marked by profound structural and functional alterations detectable with neuroimaging. Treatment with antiretroviral therapy nearly eliminated CNS opportunistic infections, while neuropsychiatric impairment and peripheral nerve and organ damage have persisted among virally suppressed people with HIV (PWH), suggesting ongoing brain injury. Neuroimaging research must use methods sensitive for detecting subtle HIV-associated brain structural and functional abnormalities, while allowing for adjustments for potential confounders, such as age, sex, substance use, hepatitis C coinfection, cardiovascular risk, and others. Here, we review existing and emerging neuroimaging tools that demonstrated promise in detecting markers of HIV-associated brain pathology and explore strategies to study the impact of potential confounding factors on these brain measures. We emphasize neuroimaging approaches that may be used in parallel to gather complementary information, allowing efficient detection and interpretation of altered brain structure and function associated with suboptimal clinical outcomes among virally suppressed PWH. We examine the advantages of each imaging modality and systematic approaches in study design and analysis. We also consider advantages of combining experimental and statistical control techniques to improve sensitivity and specificity of biotype identification and explore the costs and benefits of aggregating data from multiple studies to achieve larger sample sizes, enabling use of emerging methods for combining and analyzing large, multifaceted data sets. Many of the topics addressed in this article were discussed at the National Institute of Mental Health meeting "Biotypes of CNS Complications in People Living with HIV," held in October 2021, and are part of ongoing research initiatives to define the role of neuroimaging in emerging alternative approaches to identifying biotypes of CNS complications in PWH. An outcome of these considerations may be the development of a common neuroimaging protocol available for researchers to use in future studies examining neurological changes in the brains of PWH.

Keywords. MEG; MRI; PET; harmonization; neuroimaging; structure.

HIV invasion of the central nervous system (CNS) occurs within days after exposure [1]. The ensuing inflammatory cascade results in a transient aseptic meningitis or encephalitis that can lead to neuronal death in acute infection prior to the initiation of antiretroviral therapy (ART) [2]. This neuronal damage may be responsible for neuropsychological dysfunction in virally suppressed people with HIV (PWH), also known as the "legacy effect." In virally suppressed PWH, persistent inflammation in the CNS and CNS viral reservoirs may also contribute to neuropsychological dysfunction in the chronic phase of infection. While it remains difficult to assess these changes in the brain, neuroimaging provides a reliable and reproducible noninvasive in vivo method to measure and track changes in brain structure and function in PWH.

STRUCTURAL BRAIN IMAGING

Macrostructural Magnetic Resonance Imaging Techniques

Structural magnetic resonance (MR) imaging has been used to measure macrostructural differences in PWH since the early days of the HIV epidemic. Macrostructural neuroimaging using conventional T1-weighted MR imaging provides measures of whole-brain or regional gray matter (GM), white matter

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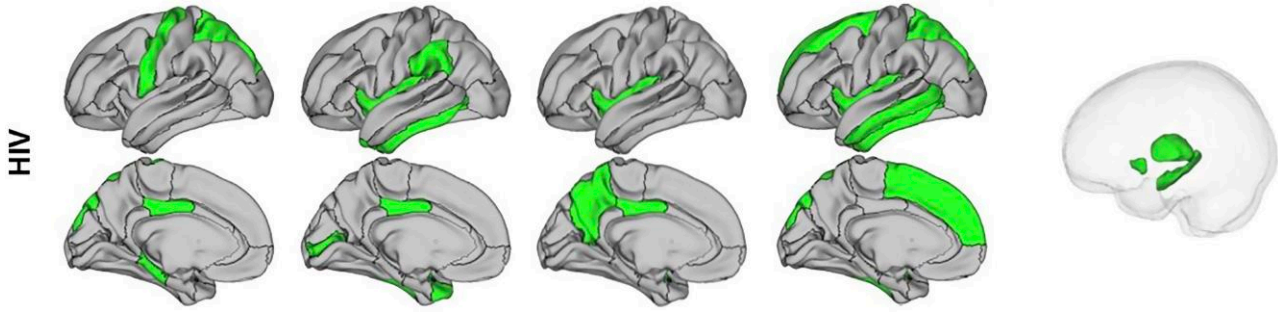

Figure 1. A novel machine learning approach identified a human immunodeficiency virus (HIV) diagnostically specific pattern of cortical and subcortical volume, surface area, mean curvature, or thickness deficits in the regions, noted in green. The top 4 sagittal images mark the precentral motor strip, superior parietal cortex, pars triangularis, insula, inferior and middle temporal gyri, and superior frontal cortex. The bottom 4 sagittal images mark the caudal anterior cingulum, parahippocampal gyrus, occipital cortex, pericalcarine, fusiform, temporal pole, precunneus, and medial frontal cortex. The leftward-facing sagittal image marks the thalamus, hippocampus, and accumbens. The pattern of cortical and subcortical regions specific to HIV emerged from a novel machine learning approach that differentiated HIV from other diagnoses (alcohol use disorder, HIV plus alcohol use disorder, and controls. (This image is a portion of figure published elsewhere [3, p 4], reprinted with permission from Elsevier.)

(WM), and cerebrospinal fluid. GM measures include volume, thickness, and surface morphometry [3, 4]. Automated segmentation of brain structures can be performed using brain atlases in standardized anatomical spaces [5].

The effects of HIV have diminished with time in all CNS tissue compartments, likely related to widespread use of ART [6, 7]. Nevertheless, brain structural differences can still be detected in chronically infected, virally suppressed PWH with voxel-wise volumetric approaches [8–10], cortical surface shape analysis [11–14], and cortical thickness estimation approaches [8, 15]. Yet to be determined is whether aging interacts with treated HIV infection to diminish improvement in pretreatment structural changes conferred by ART.

GM volume deficits in virally suppressed PWH relative to uninfected controls have been reported in frontal and parietal cortices [16], the transitional cortex of the insula and cingulum [16], and subcortical structures comprising basal ganglia, thalamus, and hippocampus [3, 16–18] (Figure 1). The smaller hippocampus, thalamus, and putamen and enlarged ventricles were associated with current $CD4^+$ cell counts, viral load, and ART status [19]. Cortical and subcortical GM volume deficits were more pronounced in those with AIDS-defining illness history [20].

WM structures exhibiting volume deficits in PWH included centrum semiovale and corpus callosum [21, 22]. Stratification by clinical symptoms and cognitive performance as unimpaired, asymptomatic neurocognitive impairment, mild neurocognitive disorder, or HIV-associated dementia revealed the following: (1) smaller medial orbitofrontal WM volume in asymptomatic neurocognitive impairment; (2) enlarged lateral ventricles and small volumes of frontal, cingulate, and parietal WM occurring in mild neurocognitive disorder; and (3) smaller volumes correlated with $CD4^+/CD8^+$ cell count ratios [23, 24]. Lower $CD4^+$ cell count nadir and detectable HIV RNA were associated with smaller total WM volumes [25].

The greater presence of WM hyperintensities, often quantified with fluid-attenuated inversion recovery (FLAIR) imaging, occurs with older age, longer HIV infection duration, and $CD4^+$ cell counts <500/mL [26, 27]. There is also evidence that cerebrovascular risk factors contribute more than HIV-seropositive status to the development of WM lesions in PWH [28, 29].

The noninvasive nature of MR imaging enables safe, longitudinal studies in PWH [7, 30]. Some longitudinal studies of virally suppressed PWH provide confirmation of similar cross-sectional findings across the aging spectrum [13], including accelerated volume loss associated with older age, higher plasma viral loads, lower $CD4^+$ cell counts, and cognitive deficits [21, 31–33]. Such longitudinal work also showed HIV-by-age interactions in frontal and posterior parietal volumes in PWH [16]. Controversy remains, however, regarding how chronic HIV shapes brain aging [34], with some studies finding no differences in rates of change of structural (or other neuroimaging) measures over approximately 2 years [8, 35].

Structural MR imaging findings in PWH can help identify CNS correlates of clinical symptoms. For example, objective signs of neuropathy in virally suppressed PWH are correlated with smaller cerebellar vermis volumes, while subjective symptoms of neuropathy were associated with smaller precuneus volumes [36]. Furthermore, lower pontocerebellar volumes in PWH were correlated with impaired postural stability and psychomotor speed [37].

Microstructural MR Imaging Techniques

MR imaging diffusion tensor imaging (DTI) of WM microstructure yields measures of fiber organization (fractional anisotropy [FA]) and unrestricted water motility (mean diffusivity [MD]). Many studies have found alterations in FA and in MD in PWH, particularly in subcortical brain regions, such as the basal ganglia and corpus callosum [30, 38–40]

Abnormalities in DTI parameters suggest compromised tissue and HIV-associated neuroinflammation. Diffusion basis spectrum imaging, using a tensor model sensitive to the effects of cellularity, found higher cellularity in aviremic PWH, which also suggests persistent inflammation [41]. Diffusion alterations in PWH correlated with elevated levels of inflammatory biomarkers, such as cytokines (eg, tumor necrosis factor α and interleukin 6), chemokines (eg, monocyte chemoattractant protein 1) and metalloproteinases, even in virally suppressed PWH [30, 41–44]. Markers of inflammation also were identified as discriminating features in machine learning models of HIV-induced brain injury, as quantified with diffusion and brain volume measures [30].

Cross-sectional studies found associations between clinical indices and diffusion measures. Higher FA and lower MD were associated with high CNS penetrance of HIV treatment, higher $CD4^+$ cell counts, and greater recovery from the $CD4^+$ cell count nadir [45, 46]. Furthermore, a greater number of years with $CD4^+$ cell counts <500/μL was associated with lower FA and higher MD in the projection, association, and callosal fiber systems [47]. A controlled study using DTI fiber tracking found higher MD in posterior corpus callosum, internal and external capsules, and superior cingulate bundles in PWH than in controls. Among the PWH, diffusivity differences from the control group in the posterior corpus callosum, fornix, and superior cingulate bundle were greatest in those with an AIDS-defining event [48].

FUNCTIONAL MR IMAGING

Functional imaging studies, including blood oxygen level–dependent (BOLD)–contrast functional MR imaging and perfusion MR imaging, are used to assess neuronal functioning that complements structural neuroimaging techniques. BOLD-contrast functional MR imaging can evaluate brain function at rest or during a task by measuring the MR imaging signal changes associated with varying levels of oxygenated versus deoxygenated hemoglobin. Images obtained with resting-state functional MR (rsfMR) imaging are readily acquired and amenable to myriad analysis approaches. The brain at rest has low-frequency spontaneous fluctuations that exhibit coherent activity across spatially distinct networks. These correlations are used to estimate interregional functional connectivity.

PWH show subtly altered functional connectivity in some networks regardless of age [49]. rsfMR imaging that evaluated PWH in various stages of HIV-associated neurocognitive disorder (HAND) found altered connectivity in canonical brain networks, including the salience, default mode, and executive networks [50]. Network disruptions were detected even in those with acute HIV infection [51]. By contrast, task-related functional MR imaging requires participants to perform specific tasks or view images that can elicit regional brain activity change. PWH typically showed lower task-induced activation within the normal networks but greater activation in reserve brain regions with the more demanding tasks and greater attentional load [52–59] or risk-taking behaviors [60–62]. These studies detected neural abnormalities with increasing cognitive demand in PWH. While task functional MR imaging is more challenging to implement in routine clinical care, it is generally associated with large changes in BOLD-contrast, and therefore may be more sensitive than rsfMR imaging for monitoring treatment or intervention effects [63].

Other functional imaging techniques, such as dynamic susceptibility contrast and arterial spin labeling (ASL), have been used more rarely to study brain perfusion in PWH. Dynamic susceptibility contrast showed relative changes in regional perfusion in PWH but requires a gadolinium contrast agent [64]. ASL is easier to acquire since it does not require gadolinium or radioactive tracers; instead, it assesses regional cerebral blood flow with radiofrequency pulses to label water molecules in the cerebral vasculature. Lower perfusion is seen in the lentiform nuclei in both acute and chronic phases of HIV infection [65], whereas cortical perfusion findings vary [65, 66]. Age, viral load, and treatment status can influence perfusion [66, 67].

PROTON MR SPECTROSCOPY

Proton MR spectroscopy noninvasively probes neuropathology by measuring levels of metabolites that reflect neuronal health and integrity or neuroinflammation. By reliably detecting chronic HIV infection effects, proton MR spectroscopy may be useful for assessing the pathophysiology associated with cognitive and sensorimotor decline following HIV infection. For localized proton MR spectroscopy, typical voxel placement used to evaluate PWH includes the basal ganglia, WM, and cortical GM [68]. Meta-analysis of HIV neurometabolite studies showed consistently lower total *N*-acetyl-aspartate (NAA)/total creatine (tCr), higher total choline (tCh)/tCr, and higher myoinositol (mI)/tCr ratios associated with chronic HIV infection [49]. Although many studies used tCr as a reference and reported metabolite ratios [68], HIV infection may influence tCr concentrations [69]. Hence, absolute quantification of metabolite concentrations removes the ratio confounding factor in assessment of neurochemical abnormalities. Levels of neuronal metabolites, including NAA, are lower in later stages of HAND, whereas glutamate levels are already lower in earlier stages of HAND and correlated well with cognitive deficits [70]. Levels of glial metabolites, especially mI, along with tCr and tCh, are also elevated in early stages of HAND, suggesting ongoing neuroinflammation and glial activation.

Further evidence that myoinositol and choline compounds reflect chronic neuroinflammation was shown by their correlations with β-amyloid tracer uptake (Pittsburgh compound B),

typically associated with neuroinflammation, in 311 cognitively normal elderly at risk for Alzheimer disease [71]. Myoinositol levels also appeared to be more sensitive than a microglial positron emission tomography (PET) tracer (PK-11195) for detecting inflammation in patients coinfected with HIV and hepatitis C virus [72].

PET IMAGING

Brain PET imaging performed early in the HIV epidemic found subcortical hypermetabolism on ^{18}F-fluorodeoxyglucose (FDG) PET, interpreted as a reflection of neuroinflammation [73, 74], while hypometabolism was observed in the later stages of disease, assumed to be related to neuronal loss [75].

More recently, brain PET imaging has used various targets and ligands (Table 1) to evaluate both the neuropathophysiology of HIV and the effects of treatment and comorbid conditions, particularly cardiovascular disease [84] (Table 2) [85]. Longitudinal FDG PET demonstrated varied regional brain FDG uptake over the course of treated HIV, decreasing in subcortical structures as peripheral viral load and immune markers (interleukin 6R and soluble CD14) declined 6–8 weeks after ART while increasing in the frontal cortex, suggesting normalization of cortical dysfunction with ART initiation [78]. At 2 years after ART initiation, however, subcortical FDG uptake further decreased, suggesting that neuronal loss that may contribute to cognitive deficits [78]. Cross-sectional FDG PET imaging in well-treated chronic infection revealed lower uptake in mesial frontal and anterior cingulate cortex [79, 80], although the studies were not robustly generalizable owing to a focus on predominantly white men with limited comorbidity. A more recent FDG study in chronically infected, virally suppressed PWH found that HIV status best predicted thalamic hypometabolism, whereas cardiovascular disease was a better

Table 1. Positron Emission Tomography Target and Ligands Used in Human Immunodeficiency Virus Neuroimaging

Target	Radioligand	Study Focus	References
Glucose metabolism	^{18}F-FDG	Neuroimmune response, neuronal function	[59–62, 76, 77]
18-kDa TSPO	^{11}C-PK11195, ^{11}C-DPA-713, ^{18}F-DPA714, ^{11}C-PBR128	Brain injury, neuroimmune response	[63–70]
Synaptic vesicle glycoprotein 2	^{11}C-UCB-J	Synaptic integrity	[78]
Amyloid plaque	^{11}C-PiB; ^{18}F-florbetaben, ^{18}F-AV-45 (florbetapir)	Patterns of localized or whole-brain amyloid plaque	[79–82]
Tau	^{18}F-AV-1451 (flortaucipir)	Patterns of localized tau	[83]
Dopaminergic and serotonergic systems	^{11}C-raclopride, ^{18}F-fallypride; ^{11}C-cocaine, ^{18}F-FP-CMT, ^{11}C-DASB	Neurotransmitter system integrity and function	[71–75, 84]

Abbreviations: FDG, fluorodeoxyglucose; TSPO, translocator protein; PiB, Pittsburgh compound B.

Table 2. Factors Affecting Central Nervous System Measures

HIV infection–related variables

- Degree of viral suppression
- Nadir CD4$^+$ cell count
- Current CD4$^+$ cell count
- HIV infection duration
- AIDS-defining illness history

Treatment-related variables

- Time before beginning ART
- ART type
- ART adherence

Systemic inflammation [86]

- Monocyte activation markers
  - sCD14
  - sCD163
  - Lipopolysaccharide levels
- Cytokines
  - IP-10
  - IFN-α
  - IL-6
  - IL-10
  - IL-15

Comorbid conditions

- Hepatitis C
- Substance use
  - Alcohol
  - Marijuana
  - Cocaine
  - Methamphetamines
  - Nicotine
- Psychiatric disorders
  - Anxiety
  - Major depressive disorders
  - Posttraumatic stress disorder
  - Schizophrenia
- Cerebrovascular risk
  - Cigarette smoking
  - Hypertension
  - Diabetes
  - Hyperlipidemia
  - Hypercholesterolemia

Demographic factors

- Age
- Sex
- Socioeconomic status
- Premorbid cognitive function

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IFN, interferon; IL-6, IL-10, and IL-15, interleukin 6, 10, and 15 ; IP-10, IFN-induced protein 10; sCD14, soluble CD14; sCD163, soluble CD163.

predictor of whole-brain metabolism than HIV status, suggesting an integral role of comorbid conditions, namely cardiovascular disease, in controlling brain involvement in HIV [84].

In addition to quantification of glucose metabolism, which reflects a combination of neuroinflammation and neuronal function, animal and human brain PET imaging targeted microglial activation markers [81–83, 87–91], neurotransmitter signaling systems [76, 77, 92–95], synaptic integrity [96] and pathological correlates, such as amyloid and tau deposition [97–102]. Neuroinflammation in HIV is likely due to microglial activation, peripheral monocytes infiltration, astrocytic activation, and possibly lymphocytic infiltration. To date, the most commonly pursued neuroinflammation imaging target in HIV is the 18-kDa translocator protein (TSPO), an outer mitochondrial membrane receptor expressed in resident microglia and monocyte-derived macrophages, astrocytes, endothelial cells, and choroid plexus/ependymal cells. TSPO expression is up-regulated in activated microglia, marking deviation from the normally low levels of parenchymal TSPO expression in healthy brain [103].

Human TSPO-PET imaging in PWH, however, has yielded inconsistent findings, in part likely owing to differences in radiotracer properties across first- and second-generation TSPO-targeting ligands. For example, the first-generation TSPO radiotracer ^{11}C-PK11195 is limited by low target specificity, and while 2 studies found higher TSPO brain uptake in PWH than in controls using ^{11}C-PK11195 [88, 90], another found no group differences [104]. Using a more specific, second-generation radiotracer for TSPO imaging, ^{11}C-DPA713, higher TSPO binding (distribution volume) in the WM, cingulate cortex and supramarginal gyrus relative to GM was detected in PWH relative to controls, suggesting neuroinflammatory changes [105]. Lower global TSPO expression, but higher regional tracer uptake in the parietal and occipital lobes and globus pallidus, were also observed in PWH [87]; however, another second-generation TSPO radiotracer,^{11}C-PBR128 found no group differences [81]. Higher TSPO uptake also correlated with lower cognitive performance in PWH, although the involved regions and cognitive domains varied across studies [81, 82, 87, 88]. These conflicting results may be due to differences in cohort characteristics, ligands used, functions examined, or analysis methods.

HIV protein neurotoxicity, another postulated mechanism of CNS injury, may affect specific neurotransmitter systems, which were assessed using a variety of established PET ligands [76, 77, 92, 94, 95, 106, 107]. Lower synaptic density measured with ^{11}C-UCB-J was found in the frontostriatal-thalamic circuit and other cortical areas of older male PWH on ART compared with uninfected controls, suggesting synaptic loss [96]. Finally, studies investigating amyloid or tau accumulation as underlying causes of HAND found no increased burden of amyloid [97–99, 101] or tau protein [100] in virally suppressed PWH relative to cognitively normal controls.

MAGNETOENCEPHALOGRAPHY

Magnetoencephalography (MEG) is another noninvasive neuroimaging technique with excellent temporal (ie, milliseconds) and spatial precision (ie, 3–5 mm). The method directly measures the minute magnetic fields that naturally emanate from electrophysiological activity in populations of neurons, with the strength of these neuromagnetic fields being proportional to the amplitude of the underlying electrical currents [108]. Almost all the MEG studies in PWH focus on virally suppressed cohorts [109].

One of the most consistent findings in PWH is elevated spontaneous cortical activity in task-related brain regions [110–115]. This activity modulates the oscillatory neural dynamics serving cognitive processing [110–115]. Spontaneous activity reflects the seemingly random neuronal discharges, fluctuations in dendritic currents, and other electrical field phenomena that occur across the cortex in the absence of exogenous and endogenous inputs. In PWH, sharply elevated spontaneous activity was shown in brain regions serving visuospatial attention [110, 114], selective attention [111], somatosensory processing [112, 113, 115], and working memory [116]. Several studies showed increased spontaneous activity that distinguishes cognitively impaired and unimpaired PWH and both HIV groups from controls [110, 111, 113]. Such elevated spontaneous cortical activity is related to both cognitive and motor processing and occurs in healthy aging [117–120], suggesting accelerated aging in PWH [121]. Interestingly, regular cannabis use may normalize elevated spontaneous cortical activity in PWH and thereby improve cortical function and cognitive performance [114].

MEG studies also showed deficits in the neural oscillatory dynamics serving early visual processing [110, 112, 122], motor function [123], selective attention [111, 124], attentional reorienting [125], visuospatial attention [122, 126], working memory [116, 127], and somatosensory processing [86, 112, 113, 115]. Frequently, these oscillatory aberrations were tightly coupled to worse cognitive performance in PWH. Several of these studies also enrolled relatively large samples and examined the impact of aging on cognitive function and the underlying oscillatory dynamics in PWH [113, 122, 124, 125]. Broadly, these MEG studies also show aberrant aging trajectories in PWH. The most recent data, however, suggest that these effects are driven by the cognitively impaired subgroup (ie, those with HIV-associated neurocognitive disorder) [125].

Neural aberrations in the visual and somatosensory cortices were reported across multiple studies focusing on different cognitive constructs (eg, visual attention). Furthermore, the available data do not support simple dichotomies such as deficits in cortical versus subcortical areas or association versus sensory cortices, as studies have found aberrations across multiple sensory regions and a broad variety of association cortices, including prefrontal and parietal attention networks. All but one MEG study focused on virally suppressed PWH [127], and

almost all MEG studies excluded participants with severe psychiatric diseases (eg, PTSD or schizophrenia), substance use disorders, and other possibly confounding conditions. Such an approach ensures that the findings are specific to HIV infection rather than confounders but limits the generalizability to PWH who have a high prevalence of these characteristics.

Work in recent studies suggests that MEG-derived cortical maps are highly reliable for ≥3 years in individual participants [128, 129], which is critical for establishing the veracity and predictive utility of MEG markers [130]. Fortuitously, most active MEG sites in neuroHIV research recently installed identical instrumentation, which allows the merging of data sets across sites to build even larger samples.

USE OF MULTIMODAL NEUROIMAGING TO INFORM RESULTS

Recognizing that changes in cognition may be on asynchronous trajectories with functional or structural brain imaging changes, combining multiple features from neuroimaging data may improve identification and tracking of functional outcomes of the HIV-associated brain injury. Novel "fusion" approaches that jointly analyze multiple neuroimaging features have the potential to reveal interrelated patterns across modalities and in spatially distinct regions beyond detection with a single modality [131]. A 2021 analysis in PWH combined T1-weighted MR imaging, DTI, and rsfMR imaging and found that lower scores on cognitive functions related to abnormal morphometry (smaller volumes of the thalamus and visual, posterior parietal, and orbitofrontal cortices), compromised WM integrity (lower FA throughout the corpus callosum and association fibers), and abnormal activity in frontoparietal and occipital networks [132]. On this identified joint component, PWH had lower loadings for both GM volume and WM integrity, suggesting that HIV-associated alterations in brain structure may contribute to cognitive impairment.

In another multiparametric study of HIV, lower FA in the corpus callosum body correlated with greater functional connectivity in linked GM regions; cognitive impairment was associated with low FA in the corpus callosum; and higher functional connectivity occurred in linked GM regions [133]. Joint analysis of MR imaging and neuropsychological data classified individuals ranging across unaffected controls, HIV without cognitive impairment, HIV with mild cognitive impairment, and HAND [134]. Machine learning algorithms using resting state networks classified individuals by HIV status and cognitive status [135]. They also showed that polysubstance use, race, educational attainment, and volumes of the precuneus, cingulate, nucleus accumbens, and thalamus differentiated membership in the normal versus impaired clusters. These emerging studies demonstrate the value of multimodal data fusion for identifying neural substrates of complex cognitive decline, even when observations for compromise are not in temporal lockstep.

STRATEGIC DESIGN AND ANALYTIC APPROACHES TO ACHIEVE GREATER CONSISTENCY

Given the observational nature of HIV neuroimaging data, both experimental and statistical control can increase sensitivity to detection of subtle HIV effects on brain structure and function. Potential confounds, such as comorbid conditions and variable clinical features common in PWH, raise the question of whether neuroimaging changes reported as HIV effects are related solely to viral infection [7]. Hence, some neuroimaging changes attributed to HIV might have originated from confounding effects [136–138] (Table 2).

Because PWH exhibit a wide range of demographic variations and medical comorbid conditions, larger sample sizes will facilitate the formation of stratified subgroups, which can delineate their influences on neuroimaging findings [85]. This stratification will also allow more representative, ecologically valid assessment of chronic HIV infection and its course. Across-diagnostic profile comparisons are also useful for establishing HIV-specific deficit profiles [1, 32].

In addition to cohort characteristics, variation in image acquisition and analysis techniques may contribute to study outcome heterogeneity. Current harmonization methods have reduced, but not eliminated, inconsistencies related to image acquisition and processing differences across sites [139].

Experimental Control

The goal of increasing sample size in HIV neuroimaging studies by pooling data across multiple sites presents challenges. In addition to the administrative overhead needed to coordinate activities among sites, adoption of standardized data acquisition systems and protocols are essential for multisite studies, because using a common scanner platform, hardware, and software (manufacturer, model, field strength, head coil, software version) across sites will minimize these variables. Maintenance of identical acquisition protocols, however, can be complicated by site hardware and software upgrades or replacement, circumstances often beyond the control of study investigators. Nevertheless, a standardized imaging protocol mitigates the risk that observed cohort differences are an artifact of acquisition differences. The Alzheimer's Diseases Neuroimaging Initiative (ADNI), Adolescent Brain Cognitive Development Study (ABCD), and Human Connectome Project (HCP) have successfully implemented standardized protocols across multiple sites [140–142]. Examples of multisite studies in PWH include CHARTER and ENIGMA-HIV, which provide data access to the public for additional analyses [19, 143].

A first-tier, MR imaging protocol should include (1) high-resolution T1-weighted imaging for structural analysis and coregistration with other MR imaging sequences and neuroimaging modalities (eg, PET and MEG), (2) T2-weighted imaging for cerebrospinal fluid–tissue distinction, (3) FLAIR sequences for detecting WM hyperintensities, (4) a high-resolution, multishell diffusion sequence with adequate signal-to-noise for estimation of microstructural WM measures and more complex modeling of structural connectivity, (5) multiband rsfMR imaging to determine functional connectivity, and (6) ASL to assess brain perfusion. Total imaging time for these suggested first-tier sequences can be <1 hour, especially if multiband approaches are used, thus minimizing participant burden and scanner costs. These sequences also allow comparison with standing multisite studies, such as ADNI, HCP, National Consortium on Alcohol and Neurodevelopment in Adolescence, and ABCD, that have publicly available imaging data on healthy controls from preadolescence to senescence for comparison with those in PWH. Using a tiered approach, other sequences such as task functional MR imaging, quantitative susceptibility mapping, or MR spectroscopy, and other modalities (eg, MEG and PET), can be added to site protocols, depending on the research question.

Regarding MEG protocols, resting-state recordings at 1 kHz or faster are essential for assessing spontaneous activity and whole-brain connectivity, while a targeted battery of task-based paradigms would help delineate altered brain dynamics in the cognitive networks most commonly affected in PWH. Selecting a standard set of cognitive tasks with identical stimulus presentation parameters across sites and recording empty-room MEG data to compute noise covariance matrices would allow the data to be effectively coalesced with experimental rigor.

Standardizing PET studies is more challenging than MR imaging and MEG, considering the major differences in scanner models, resolutions, configurations, and reconstruction algorithms, among other site-specific parameters. In addition, multiple ligands with different characteristics (eg, lipophilicity, brain availability, affinity, specific to nonspecific binding) are often used to image the same targets (eg, TSPO). Different analysis approaches and patient populations add to the variability and discordance of PET studies. Despite the generally insurmountable differences in infrastructure and ligand availabilities across centers, reaching a unified approach to compartmental modeling and analysis methods of various ligands, especially those for neuroinflammation, may diminish protocol discordance. Future work could take advantage of novel PET imaging ligands (eg, new inflammations targets [144, 145]) and validated PET imaging ligands and reduce current limitations. Reaching a unified approach for compartmental modeling and analysis methods of target ligands, especially in neuroinflammation imaging, and a thorough assessment of current and historical comorbid conditions in PWH would address potential confounders [144–146].

Quality Control

Rigorous quality control to assure limited head motion, appropriate anatomical coverage, and adherence to protocol parameters can also improve consistency. Regular scanning with structural and functional phantoms (both standardized and human phantoms) provides objective assessment of scanner drift, potential correction factors, and stability measures for across time and multisite harmonization. Thorough quality assurance is particularly important in rsfMR imaging studies, in which the changes in interregional functional connectivity are vulnerable to physiological noise from many sources, including head motion, cardiac activity and respiration [7]. Image analyses may exploit semiautomated or fully automated preprocessing pipelines that facilitate quality assurance procedures. These pipelines can simplify computational effort before statistical analysis, but different pipelines can also introduce variabilities [147–150]. Hence, a common image preprocessing approach for each modality, supported by a centralized imaging core, would decrease heterogeneity in HIV neuroimaging studies.

Longitudinal Designs

Although most HIV neuroimaging studies are cross-sectional, longitudinal designs are preferred in assessing ART effects on the CNS and disease progression. The repeated measures designs allow each participant to serve as their own control. Because chronic HIV samples are diverse in associated comorbid conditions, a longitudinal design provides within-subject accounting of comorbidity effects. A balanced group of HIV-seronegative controls should be included in studies to account for aging, sex, or other effects. To isolate ART effects on the CNS, investigators may assess PWH both before and after initiating ART. They may also consider statistically adjusting for the CNS penetration-effectiveness score of participants' ART regimens or the Veterans Aging Cohort Study index to estimate risk of 5-year all-cause mortality in PWH [151–153]. While longitudinal studies are preferred to answer many questions, particularly the effects of ART and aging on the CNS, they do require additional resources and comprehensive participant follow-up.

Statistical Control

Even with the most robust efforts to minimize site differences in acquisition protocols and equipment, residual "site" variance is likely to persist. Novel approaches to harmonize data from multiple sites (eg, ComBat [154]) may reduce inconsistencies related to image acquisition and processing differences across sites.

More problematic are the use of poorly matched control groups and the lack of adequate statistical adjustment for the

effects of various confounding factors on imaging measures. To study the effects of "uncomplicated" HIV on brain structure and function, experimental designs often eliminate or minimize confounders, which greatly limits generalizability of the results to the diverse population of PWH. Statistical approaches can adjust for nuisance variables not completely controlled experimentally. However, a large sample size will be required for such adjustments. Successful selection of covariate effects will improve statistical model fit by reducing error variance. Nuisance variables of interest include age, sex, and a range of comorbid conditions (Table 2).

One complexity encountered with this approach is that when nuisance variables exhibit collinearity, their individual contribution to the measure of interest cannot be determined. Examples include strong associations between hepatitis C virus infection and heroin use and the coupling of smoking and other cerebrovascular risk factors. Standard techniques for predictor collinearity can be used to mitigate these effects. Applications of statistical control techniques in large sample sizes afford subgroup stratification that may yield greater generalizability to the PWH population, while still accounting for commonly encountered clinical differences and comorbid conditions.

Another goal for the HIV neuroimaging community is replication of results by facilitating sharing of existing data sets. In addition to harmonized data collection and processing in future prospective studies, replications using existing data collected could be an efficient means to validate current claims that can withstand the process of out-of-sample replication. For instance, from the rapidly growing field of functional MR imaging replication, protocols with the strongest task-related activity have the best replication [155]. The widespread sharing of carefully curated data sets would also facilitate greater use by the machine learning community, and thereby lead to the emergence of new markers of HIV-related cognitive decline and potential targets for future therapeutics. Groups such as ENIGMA have started working toward this goal by pooling data sets. The next steps will include a survey of the HIV neuroimaging community to assess common sequences and numbers of participant among groups.

CONCLUSIONS

HIV neuroimaging studies began nearly 4 decades ago with the predominant use of computed tomography for qualitative characterization of parenchymal atrophy and CNS opportunistic infections associated with AIDS. As knowledge of HIV neuropathology and treatments evolved, we now have multiple advanced imaging modalities to detect the subtle brain injury effects in treated, virally suppressed cohorts. Our next challenge is to undertake the measurement, design, and analysis complexities associated with HIV neuroimaging to achieve greater consistency in the in vivo characterization of HIV infection and to track its dynamic course across the life span. Critical comorbid conditions to address include psychiatric disorders, substance use disorders, and cardiovascular risk factors. Larger samples collected with standardized acquisition protocols that include the suggested first-tier protocol will allow for pooling of data sets across sites. Rigorous experimental and statistical control methods can reduce the variability in estimates of how HIV infection per se affects brain structure and function. These methods include use of well-balanced control groups, adjustment for nuisance variables not completely controlled experimentally, and data harmonization techniques for multisite studies. Critically, these approaches will reveal the neuroimaging data elements best suited for identifying biotypes of CNS complications, HIV-aging interactions, and potential treatment responses in PWH.

Notes

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