The Role of Medical Imaging in Defining CNS Abnormalities Associated with HIV-Infection and Opportunistic Infections

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Summary: In this review of the current literature, we examine the role of medical imaging in providing new and relevant information on central nervous system (CNS) injury associated with human immunodeficiency virus (HIV) infection and various clinical manifestations of this injury. Common imaging modalities used to examine CNS injury in HIV infection include structural magnetic resonance imaging, magnetic resonance spectroscopy, diffusion tensor imaging,

functional MRI, and positron emissions tomography. Clinical implications for the findings are discussed for each of these modalities individually and collectively. In addition, the direction for future studies is suggested in an attempt to provide possible methods that might answer the many questions that remain to be answered on the evolution and progression of CNS injury in the context of HIV infection. **Key Words:** HIV, MRI, DTI, PET, MRS, cognition.

INTRODUCTION

Magnetic resonance imaging (MRI) has been used to examine the impact of human immunodeficiency virus (HIV) on the central nervous system (CNS) since the beginning of the pandemic. Consequently, our understanding of the evolution and progression of CNS injury in the context of HIV has grown tremendously. However, the specific role of imaging over the years has yet to be realized in the current era of treatment where many questions remain regarding the evolution and progression of HIV-associated CNS injury.

Recent imaging studies highlight the potential of imaging to provide proxy markers of common pathological processes in HIV infection. These findings are particularly relevant because HIV activity and its translation to CNS involvement can differ greatly among individuals. Clinical markers of disease evolution and progression are therefore essential for examining host and viral variables that might affect disease progression and or treatment efficacy. These questions are particularly important in the current era of combination

antiretroviral therapies where there has been a reduction in the number of patients who experience significant cognitive symptoms (*i.e.*, HIV-associated dementia) but an increase in the incidence of mild and moderate cognitive symptoms [1–3]. These studies clearly demonstrate the continued involvement of the CNS even in the context of stable disease. In future studies, the emphasis will be on identifying specific imaging phenotypes that can be used to evaluate the effects of these generic and CNS-specific treatments among HIV-infected patients.

In this review, we highlight recent publications on neuroimaging and identify future directions that we believe will provide valuable insights into HIV-associated injury. The research reported here is organized along general lines into sections on the most common imaging modalities used to examine HIV-associated CNS injury, including structural magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), positron emission tomography (PET), and functional MRI (fMRI).

Structural magnetic resonance imaging

Structural imaging techniques have primarily been used to measure volumetric alterations in brain tissue associated with HIV infection. This line of investigation was initiated early in the HIV pandemic and quickly established a variety of pathological effects observable *in vivo*. The most common findings included regional gray matter atrophy, particularly in the basal ganglia [4–6],

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white matter lesions [7, 8], ventricular expansion [9], and global cerebral atrophy [7, 10–12]. More recent studies have further elucidated these effects using more advanced image acquisition and volumetric measurement techniques.

Atrophy of subcortical gray matter structures is one of the most common findings in volumetric HIV neuroimaging. In particular, volumes of the basal ganglia are commonly decreased in HIV-infected patients [4–6, 13, 14] and have been shown to be associated with cognitive function [4, 15] and biomarkers of HIV progression [16, 17]. Specifically, atrophy of the caudate has been widely reported [6, 15, 18, 19] and found to be associated with cognitive [5, 20] and motor [21] dysfunction as well as lower CD4 T-cell counts [17].

Postmortem studies have confirmed increased viral load [22, 23] and vasculopathy [24] in basal ganglia structures, which further suggest direct damage to these structures during HIV infection. Avison et al. [25] confirmed the presence of vasculopathy *in vivo* by examining intravenous contrast-enhanced MRI scans of HIV-infected patients. These authors found significantly increased contrast leakage into basal ganglia structures associated with the severity of cognitive dysfunction, implicating decreased blood–brain barrier (BBB) integrity as a pathological mechanism of basal ganglia damage and neurocognitive injury in HIV. These findings built on those of a previous study by this group showing diminished BBB integrity in the caudate [26].

Other cerebral structures have also been shown to be vulnerable in HIV infection. Reductions in cerebral cortex volume have been reported [13, 15] and linked with total white matter hyperintensity (WMH) volume [27]. Analyzing cortical thickness, Thompson et al. [28] found up to a 15% decrease in the cortical thickness of primary motor and sensory as well as premotor cortices in patients with acquired immune deficiency syndrome (AIDS) relative to controls. Though thinning was present in a lesser degree in high-level association cortices, a number of associations were found between atrophy and biomarkers of HIV progression. Interestingly, the authors also observed increased cortical surface complexity in AIDS patients, which is supported by findings of increased sulcal volume in a previous imaging study confirmed by postmortem analysis by Archibald et al. [13]. These findings are likely secondary to cortical atrophy and provide another possible imaging marker of underlying pathology.

In another study, Thompson et al. [29] demonstrated significant thinning of the corpus callosum (CC) in HIV-infected patients who had progressed to AIDS, finding an association between anterior callosal atrophy and lower CD4 counts. This observation supports previous findings of global callosal atrophy in the context of HIV infection [30], and both findings have recently been confirmed

using postmortem morphometric analysis [31]. Local areas of abnormal signal intensity have also been observed in the CC [20] and have been linked to AIDS dementia complex severity [7]. In a recent study of a large ($n=216$) HIV-infected multisite cohort, CC atrophy was demonstrated in both asymptomatic and symptomatic patients on combination antiretroviral therapies [32]. In addition, the reduction in the size of the CC was related to nadir CD4 cell counts, such that patients with the worst history of immunologic suppression (lower nadir CD4 cell counts) had the most atrophy, suggesting the need to closely monitor and manage the clinical severity of HIV progression (see FIG. 1). Among this same cohort, prospective findings demonstrated substantial (up to 4–6%) progressive atrophy that can be observed in the CC over the course of 1 year, suggesting that the atrophy is not only progressive but possibly also irreversible [32]. Thus, quantification of the CC may provide a biomarker of disease progression that could be used to monitor the effects of treatment.

General white matter atrophy has also been reported by some [13, 15, 17] and correlated with cognitive dysfunction [14]. Others have described localized white matter damage observed as signal intensities (i.e. WMHs) on T2-weighted or fluid attenuated inversion recovery (FLAIR) scans [13, 27, 33], although these findings have been contradicted [16] and shown to be unrelated to HIV biomarkers [27]. The mechanism underlying WMHs in HIV is not yet well understood as the pathological specificity of WMHs in structural imaging is not known in HIV; it has, however, been speculated that white matter injury may be secondary to gray matter damage [15]. This hypothesis is supported by evidence that WMH volume in the frontal lobe is linked to frontal cortical atrophy [27]. One common theme expressed in these studies is the limitation of structural imaging in studying white matter injury, and many researchers have concluded that a more sensitive modality, such as DTI, may be more effective.

Ventricular expansion or increased cerebrospinal fluid volume is another common finding in HIV-infected patients [13, 33], with increases reported as high as 218%. Early research suggested a relationship between ventricular enlargement and neurocognitive injury, even in non-demented patients [9]. However, recent studies suggest this may only occur in severely immunocompromised patients [17, 34]. Significant ventricular surface profiles have been observed using tensor-based morphometry in CDC stage C AIDS patients [35], further implicating long-standing immunocompromise as a prerequisite for ventricular enlargement. Unlike the direct HIV-mediated regional tissue atrophy described above, ventricular/cerebrospinal fluid volume enlargement is likely an *ex vacuo* process, i.e., secondary to the atrophy of cerebral structures that compose the

FIG. 1. Illustration of the cross-sectional corpus callosum method and results. (a) The five segments examined in this study. (b) Comparison of asymptomatic and symptomatic human immunodeficiency virus (HIV)-infected patients demonstrates differences for 3 of the 5 sections. (c) Nadir CD4 cell counts are shown to be related to 3 of the 5 sections. Current CD4 cell count (d) and PVL (e) were not significantly associated with any section. PVL = plasma viral load. (High resolution version of this image is available in the [electronic supplementary material](#).)

ventricular walls. This mechanism is supported by the finding that regional ventricular enlargement has been observed in the absence of total enlargement in an HIV-positive cohort, which is thought to reflect specific areas of ventricular wall atrophy [36].

Interestingly, studies of global cerebral tissue atrophy are often equivocal, despite the widely published reports of localized structural atrophy. Some authors report significantly decreased parenchymal volumes [4, 15, 37]. Others have found no differences in HIV-infected patients relative to controls [14, 16, 28, 38]. A number of factors likely contribute to this puzzling lack of consensus. For example, varying patient demographics, image acquisition, and volumetric protocols across studies reduce the comparability of data. Additionally, only some studies have reported correcting total parenchymal volume for intracranial volume in their methods. Finally, it is possible that some studies do not have sufficient power to detect small differences in global volumes compared to those of more localized gray matter structures.

There is still much to be elucidated by structural imaging. One important area of investigation will be the

effect of anti-retroviral therapy on the pathologies described above. Studies to date on this issue regularly yield conflicting results [16, 25, 28, 39], and many findings published prior to the HAART (highly active antiretroviral therapy) era have yet to be re-examined in the context of HAART. Additionally, MRI image acquisition and volumetric processing are continually improving, and the use of more sensitive and accurate protocols may confirm or call into question findings of previous studies. For example, a study by Castelo et al. [38] found no significant differences between HIV-infected patients and controls in terms of hypertrophy of the putamen bilaterally, although the difference was significant in the right putamen. Furthermore, hypertrophy in the right and left putamen was associated with lower motor speed and, paradoxically, higher CD4 counts, respectively. Rather than cast surprising results such as these aside as outliers, we should take them as an indication of the need to continue structural imaging studies as technology improves in order to re-validate (or invalidate) previous findings.

In summary, structural imaging findings appear to be more sensitive to changes at later stages of HIV infection,

with the most common findings being global white matter atrophy and caudate volume atrophy. These MRI findings are often (although not always) associated with performance on cognitive tests and, as such, are thought to be useful in examining the brain/behavior relationships among HIV infected patients. Associations with immunological function (CD4) or disease severity (viral load) are not always found, although longitudinal prospective imaging studies may improve our understanding of progressive CNS involvement among HIV-infected cohorts.

Diffusion tensor imaging

Diffusion tensor imaging is a technique that can be used to investigate white matter in the brain in a manner not possible with conventional structural MRI techniques. The recent advent of DTI has made it possible to evaluate the structural tissue organization and coherence of white matter fiber tracts in a way not possible with typical imaging resolution. Because white matter pathology is common in HIV-infection, there has been a great deal of interest in using DTI to examine HIV-associated CNS injury.

DTI findings demonstrate consistent reductions in fractional anisotropy (FA) measures and intermittent increases in mean diffusivity (MD) as primary measures of white matter damage. In 2001, using DTI metrics, Pomara et al. [40] found a statistically significant decrease in FA for the frontal lobes in a cohort of six HIV-infected patients compared to nine healthy controls. The analysis revealed the absence of significant group differences in the parietal lobes, temporal lobes, and the two CC region-of-interest (ROI)s. In a similar study, Ragin et al. [41] examined the whole-brain FA differences between an HIV cohort of six patients and nine healthy controls. The results suggested that whole-brain FA measures were significantly reduced in the patient group, even though the whole-brain apparent diffusion coefficient (ADC), a variant of MD, values indicated no significant difference between the groups. In 2008, Smith et al. [42] evaluated gender effects on HIV-associated white matter alteration using a voxel analytic approach. Their results suggested that HIV contributes to sex-specific microstructural alterations in white matter that appear normal on conventional MRI.

While a great deal of progress has been made in delineating white matter abnormalities, researchers have also sought to elucidate the relationship of clinical measures (*i.e.*, viral load and CD4) with DTI measures. In 2002, Filippi et al. [43], conducted a study relating diffusion tensor metrics to viral load in the white matter of ten HIV-positive patients. The results showed significantly lower FA values in the splenium and genu of the CC in patients together with higher viral loads. In 2005, Thurnher et al. [44] studied 60 HIV patients and 30 healthy controls and found a significant difference in DTI measures (FA and MD), similar to that of the Filippi et al.

study [43]. However, no correlation was found between plasma viral load or CD4 counts and FA/MD values [44].

In addition to examining clinical measures in the context of HIV, several groups have also begun to use DTI to assess cognitive function. In several studies, Ragin et al. showed that DTI metrics were significantly related with the loss of function in cognitive domains [41, 45, 46] as well as the severity of dementia [47]. In addition, the Wu et al. study [47] demonstrated correlations between increases in MD measures and deficits in motor speed, as well as significant correlations between genu FA values and visual memory performance. Recently, our group [48] sought to examine the association between quantitative DTI tractography metrics with cognitive performance among HIV-infected patients (FIG. 2). DTI tractography is a method of examining inter-voxel diffusion coherence capable of producing images of gross white matter. The application of this method enabled us to examine multiple different tractography metrics obtained from global tractography maps. The results demonstrated a significant difference between HIV-positive and -negative patient groups for global tractography FA ($t=2.13$, $p=0.04$). Cognitively, associations were noted between tractography metrics, speed of processing, fine motor speed/control, and executive function for the HIV-infected patients. These findings highlight the importance of subtle white matter changes in examining cognitive performance and the clinical value of tractography methods/metrics.

In 2007, Pfefferbaum and colleagues [49] conducted a study that highlighted the importance of controlling for neurologic risk factors when studying HIV-infected cohorts by assessing four subject groups: alcoholism alone ($n=87$), HIV infection alone ($n=42$), alcoholism and HIV infection comorbidity ($n=52$), and non-affected controls ($n=88$). The results of their study demonstrated that the two alcoholism groups had significantly lower FA and higher MD in the genu and splenium, as well as an alcoholism-HIV-related effect based on disease severity (an AIDS-defining event or CD4+ counts <200). The HIV/alcoholism comorbid group exhibited an increased significance in FA and MD abnormalities compared to the more immunologically intact patients. The authors' findings in the context of HIV-alcoholism comorbidity highlight the role of white matter abnormalities as HIV progresses to AIDS and that the sensitivity of DTI to white matter disruption may provide for earlier diagnosis of HIV-related dementia.

In a more recent study, Pfefferbaum and colleagues [50] expounded on their previous fiber tracking study to quantify the integrity of 11 projection and association fiber bundles and the full extent of the CC in 42 nondemented HIV-positive patients. The results demonstrated damage to association and commissural tracts, as seen in posterior callosal sectors, fornix, and superior longitudinal fascicu-

FIG. 2. Global tractography maps illustrating significant qualitative differences noted between HIV-infected patients and demographically matched controls. HIV-infected patients show tractography drop-out in the frontal, subcortical, and cerebellum regions compared to controls. (High resolution version of this image is available in the [electronic supplementary material](#).)

lous, suggesting that subcortical white matter damage is occurring even in non-demented patients.

Many of the studies to date have only focused on comparing HIV-infected patients with healthy controls, and it is unclear whether DTI can discern HIV-associated dementia (HAD) from nondemented HIV-infected patients (HND). In 2009, Chen et al. [51] compared these two groups to normal controls using both ROI-based and voxel-based analysis methods and found significant differences between patients with HND and HAD when compared to healthy controls in terms of mean DTI parameter values in multiple white matter regions (frontal white matter, parietal white matter, temporal white matter, occipital white matter, corona radiata, corpus callosum, optic radiation, and external capsule). More specifically, their results provided evidence that white matter alteration is more severe in HAD than HND, suggesting the potential of DTI to distinguish HAD from HND. Further analysis of different diffusivities suggested that demyelination might be the prominent disease progression in white matter.

In conclusion, as the literature suggests, there is a significant amount of evidence indicating that DTI is sensitive in revealing subtle white matter abnormalities in the HIV-positive cohort. General reductions in FA and increases in MD are apparent in multiple white matter regions, especially in the frontal white matter and the CC, as compared to healthy controls. Research in this field must be continued to further elucidate the role of HIV in disrupting white matter integrity. Particularly, it will be imperative for researchers to control for the confounding influence of alcoholism and to increase the number of patients in future DTI-HIV studies. One additional current limitation in the literature on HIV-positive cohorts is the lack of specific pathological correlates with diffusion metrics. This limitation is being

examined in several other disease modalities postmortem although no specific studies have been conducted in HIV-infected patients. Until such studies have been conducted and until we can fully clarify the specific etiological pathologies that are associated with each of the specific diffusion metrics, results should be interpreted cautiously. Nonetheless, it is important to push forward with these DTI methods, as both clinical and cognitive utility have been established in the CNS of HIV-infected patients. As such, DTI is proving to be an optimal noninvasive white matter imaging modality due to its unique ability to reveal subtle changes in macrostructural changes in tissue organization. With a growing number of more specific and sensitive analysis methods being developed, the clinical utility of DTI for discerning abnormalities due to HIV infection will become even more apparent.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy is an especially useful neuroimaging modality, as it non-invasively provides essential information for understanding the underlying causes of CNS injury in the HIV-infected patient. By quantifying *N*-acetylaspartate (NAA), creatine (Cr), choline (Cho), lactate and myo-inositol (mI), MRS offers insight into the neuronal integrity, cell membrane synthesis and turnover, macrophage infiltration, inflammation status, and levels of microglial activation and astrogliosis within the sampled CNS tissue. Marked differences between metabolite concentrations and their ratios in the CNS of both HIV-infected and simian immunodeficiency virus (SIV)-infected subjects and controls are very well documented [12, 52–62]. By studying these metabolite differences at different stages of the infection, it is possible to chronicle when and how regions of interest are impacted.

Early MRS studies focused on CNS metabolite abnormalities present in symptomatic HIV-infected patients suffering from HAD or AIDS dementia complex, as ascertained by single voxel MRS. These studies consistently revealed a severe reduction of NAA in the cortex and frontal white matter in those with more severe cognitive impairment [54–57, 63–68]. Furthermore, increasing levels of Cho and mI in the basal ganglia and the frontal white matter were also associated with an increasing severity of cognitive impairment and a greater decline in CD4 count [12, 54]. While these findings are fundamental to our understanding of the underlying metabolic mechanisms behind the progression of cognitive decay in patients with HIV dementia, more research is needed to determine how HIV affects those in the early disease stage as well as asymptomatic subjects.

As antiretroviral therapies were emerging, a number of early studies utilized single voxel MRS to monitor metabolic changes in the CNS in response to antiretroviral treatment [69–71]; where improvements in metabolite indicators of inflammation and neuronal integrity posttreatment were observed, these were associated with improvement in CD4 count and cognition status. Paradoxically, subsequent MRS studies conversely found no correlation between treatment and improvement in CNS metabolite markers [72–74]. These disparate findings emphasize the weakness of a single voxel MRS approach in studies aimed at understanding the complex interplay of HIV, treatment, and the CNS, which is known to diversely affect differing regions of the brain at various stages of infection.

One recent approach that holds promise for elucidating this complex interplay is factor analysis of immunological variables, which are indicators of cognitive function and regional metabolic variations obtained from spectroscopy of many different regions of the brain, rather than analysis of a few select voxels, as the former paints a more comprehensive picture of the progression, global and regional impact of infection, and the effectiveness of HIV treatment regimens. For example, Lentz et al. [75] recently used factor analysis to analyze the metabolic variance in seven different regions of the brain as well as immunologic measures and cognitive dysfunction. As a result, several statistically significant surrogate markers emerged for prognosis and for therapeutic monitoring of patients with HIV infection.

More recently, studies have revealed CNS metabolite abnormalities in very early HIV infection. For example, in a 2009 study of SIV in macaques [62], MRS was used to monitor metabolite abnormalities in the basal ganglia, frontal cortex, and white matter in 18 SIV-infected macaques from initial infection until 4 weeks postinfection. At peak viremia 2 weeks postinfection, a significant decrease in NAA and NAA/Cr and a significant increase in Cr were found only in the frontal

cortex, indicating a localized decline in neuronal integrity coupled with increased energy consumption in this region. Conversely, mI and mI/Cr levels increased across all three ROIs of interest, indicating microglial activation and astrogliosis and the resultant mounting of global inflammation regardless of ROI [76, 77]. Additionally, Cho and Cho/Cr levels increased initially in all three ROIs at peak viremia, indicating macrophage infiltration, but then decreased below baseline by the fourth week. Another 2009 study [75] of patients with early HIV infection confirmed some of the findings of the Westmorland study [62], including a sharp decline of NAA in the frontal cortex that was significantly correlated with expansion of CD8+ T cells. Thus, neuronal injury occurs in the frontal cortex as early as 2 weeks following the initial infection with HIV, suggesting that an increase in NAA may serve as a surrogate marker for therapy effectiveness in early stage treatment regimens.

MRS has proven to be a very useful tool in studies aimed at understanding how HIV infection affects the CNS. While many single voxel MRS studies have revealed metabolic abnormalities incident to steep cognitive decline, there remains a need for a more powerful and robust factor analysis of many different regional CNS metabolic variations in early stages of the disease which may predict cognitive decline as well as provide surrogate markers for monitoring disease progression and the effectiveness of differing treatment regimens.

Functional MRI

Functional MRI is a unique imaging modality that captures the underlying physiology of the brain as opposed to simply portraying the anatomical components characteristic of structural MRI technology. By exploiting a phenomenon known as the blood oxygenation level dependent (BOLD) effect, fMRI has been useful in monitoring brain activation and detecting early cerebral injury in HIV patients. This is possible because the MR signal can be sensitized to local fluctuations in blood oxygenation levels, in which diamagnetic oxyhemoglobin concentrations increase in activated areas of the brain. The hemodynamic principle is based on cerebral blood flow increasing to satisfy glycolytic demands more rapidly than the oxygen metabolism rate, thereby creating a local imbalance of substrates and a consequent measurable surplus of oxygen in the activated region. This interplay between neural activity and energy metabolism is the basis of functional neuroimaging.

There have been only a limited number of fMRI studies examining HIV patients, partially because only patients with mild cognitive impairment who can follow directions well can be studied, as fMRI is highly sensitive to motion, which may lead to false activation. Nonetheless, the ability to monitor subtle cognitive changes using fMRI in this subset of patients might offer

the best potential for therapeutic intervention prior to further neural damage.

To date, studies conducted using fMRI in HIV patients have documented increased activation of the frontal lobes as a result of disrupted frontostriatal circuitry in association with HIV [78–80]. Although seemingly counterintuitive, it is thought that early injury to the neural substrate causes increased consumption of brain reserve as a compensatory mechanism to maintain normal cognitive function. In essence, the increased brain activation in neuroasymptomatic or mildly impaired HIV patients precedes clinical signs of neurological impairment.

In support of this notion, Chang et al. [79] reported greater activation in mildly impaired HIV patients conducting a working memory task in the periphery regions or in brain regions adjacent to those already showing activation in control subjects. This outward extension of activation, primarily in the lateral prefrontal and supplementary motor areas, suggests a saturation of the neural capacity and the recruitment of adjacent neural substrate. Furthermore, the change in the BOLD signal in the left prefrontal cortex was associated with performance on the working memory task administered, in which patients with HIV and higher BOLD signal changes were slower and less accurate. This study also documented increased brain activation in mildly impaired HIV patients in association with increased difficulty of the task administered, in which the posterior parietal cortex was more activated than controls during simpler tasks and frontal regions were more activated during more complex tasks.

In contrast, when examining neuroasymptomatic HIV patients, Ernst et al. [81] reported increased activation in the lateral prefrontal cortex independent of task difficulty. Furthermore, this study explored the relationship between MRS and fMRI and found no significant association between neural activation and NAA (as measured by MRS), a marker of neuronal integrity found predominantly in cell bodies. However, other glial metabolites, particularly those in the frontal regions, were correlated with increased activation. This finding suggests that inflammatory mediators reduce the efficiency of the normal cortical network, which in turn requires increased recruitment of neural reserves to maintain performance during working memory tasks.

In a follow-up study examining attention by Chang et al. [73], HIV patients with mild cognitive impairment had 25% less total activated brain volume during attention tasks but 277% larger total volume, thereby showing load-dependent increases. This study extended previous findings involving working memory [79, 81] by reporting a correlation between greater disease severity (*i.e.*, decreased CD4 counts and increased viral loads) and greater activation during attention-related tasks in the

right prefrontal, right parietal, and left cerebellar regions. The findings suggest that the right hemisphere is more specialized for the utilization of a reserve network in order to meet greater attention demands and that the working memory impairment reported previously may in fact be secondary to deficits in attention resulting from the overload of reserve capacity and the breakdown of neuroadaptive processes [73]. Finally, Melrose et al. [80] examined the integrity of executive functioning in HIV patients by administering a semantic event sequencing task known to recruit both prefrontal context and basal ganglia (BG) regions. The results showed hypoactivation of the frontal cortex and the BG, suggesting a compromised functional connectivity between the BG and frontal regions during executive function tasks.

BOLD fMRI has the potential to be a more sensitive tool than neuropsychological testing for detecting brain injury in HIV patients. However, the interpretation of the findings continues to pose challenges, especially since the effects being measured are subtle and therefore, potential sources of artifacts and errors can inadvertently affect the analyses. Nonetheless, this imaging modality has augmented HIV neuroimaging research, allowing scientists to take on a highly interdisciplinary approach in the effort to contextualize the course of neurological infection.

Positron emission tomography

In addition to fMRI, positron emission tomography and single photon emission computed tomography (SPECT) have been to study HIV patients in order to assess neurological function *in vivo*. Both modalities rely on the intravenous injection of a radioactively labeled substrate to demonstrate various aspects of cerebral function, including perfusion, metabolism, and neurotransmitter activity. They also differ in their complexity of use, the amount of specialized equipment required to acquire images, and the types of brain processes they are capable of capturing. SPECT typically has a lower resolution and measures global processes, such as cerebral blood flow (CBF). PET requires more specialized equipment (cyclotron), but through a set of specific radioactive tracers is capable of capturing more specific brain functions (*e.g.*, CBF and glucose metabolism). Of the two modalities, PET has been more widely utilized, likely due to the fact that findings in SPECT studies have been much less consistent.

Utilization of a variety of PET substrates has yielded a number of significant aspects of HIV neuropathology. The most commonly used substrate is [^{18}F]flourodeoxyglucose, which directly measures glucose uptake by brain regions and is a measure of local metabolism. One of the most common findings is hypometabolism, *i.e.*, decreased [^{18}F]flourodeoxyglucose uptake, in the medial frontal region of the cortex [82–84]. Most recently, Andersen et al. [82]

reported this effect in a cohort of immunologically stable (CD4+ cell count >200, undetectable plasma viral load) patients who had been receiving HAART treatment for at least 3 years. A greater degree of hypometabolism was surprisingly associated with a shorter duration of HIV infection, although this was likely due to a correspondingly shorter duration of HAART treatment.

Paradoxically, hypermetabolism (i.e., increased glucose uptake) has also been reported in HIV patients, although hypermetabolism appears to occur earlier in the disease process and is primarily localized to the basal ganglia [83–85]. For example, in a cross-sectional study of 19 HIV-positive patients, von Giesen et al. [84] reported bilateral hypermetabolism in the basal ganglia of 7 patients in the earliest stages of HIV-infection who were essentially asymptomatic. HIV-infected patients manifesting more significant motor symptoms demonstrated medial frontal hypometabolism (9/19 patients). The authors noted that while hypermetabolism preceded motor dysfunction (an early sign of HIV-associated dementia), hypometabolism was associated with the onset of these symptoms. From these findings, the authors proposed that basal ganglia hypermetabolism precedes hypometabolism in the closely connected frontal medial cortex and that the transition between these metabolic abnormalities marked the onset of dementia. This theory has been echoed in more recent studies [82] and represents the most significant insight PET has lent into the neurological sequelae of HIV infection.

PET has also uncovered additional aspects of HIV neuropathology separate from neuronal metabolism. For example, two studies [86, 87] have used radio-labeled cocaine ($[^{11}\text{C}]$ cocaine) and raclopride ($[^{11}\text{C}]$ raclopride) to examine dopaminergic system integrity. The most significant finding was decreased dopamine re-uptake activity in the putamen and caudate associated with performance on a range of neuropsychological tests. However, the function of the dopamine D2 receptor, prominent in the basal ganglia, is evidently not affected. Increased monocyte activation in the frontal lobes, measured using a labeled benzodiazepene receptor ligand ($[^{11}\text{C}]$ PK11195), has also been implicated in the neuropathology of HIV-associated dementia [88]. As additional substrates for PET imaging are explored, additional neuronal injury caused by HIV infection will no doubt be uncovered.

Relative to PET, SPECT has been less useful in HIV neuroimaging. An early SPECT study by Rosci et al. [89] revealed perfusion abnormalities in the majority of their HIV-infected cohort, but these findings were not correlated to immunological status or predictive of a patient being symptomatic. More recently, Modi et al. [90] used SPECT to implicate decreased temporal lobe perfusion in HIV patients who presented with seizures as their first

neurological complication. However, comparisons of SPECT to MRS [91] and SPECT findings in nondemented *versus* demented patients [92] or HAART-treated *versus* nontreated patients [93] have led to the conclusion that SPECT is less sensitive in HIV-infected cohorts than other imaging modalities and is of little value in identifying the neuropathology underlying HIV-associated neurocognitive dysfunction. The conflicting findings in SPECT suggest that applications of this modality to HIV investigation need to be further explored.

PET imaging may still prove useful in future HIV studies. Many new and novel tracers have been developed over the past several years that have the potential to examine very specific metabolites and/or neurotransmitters. For example, the use of the PET ligand $[^{11}\text{C}]$ -PK11195 might provide a window into active areas of inflammatory processes in HIV infection. Thus, there may be additional opportunities to examine the effects of HIV-associated CNS injury using PET technology that will improve our understanding of the pathological processes involved in the evolution and progression of CNS injury.

Other imaging modalities

A limited number of studies utilizing other imaging modalities, including perfusion MRI and magnetization transfer imaging (MTI), have provided additional insight into HIV-associated CNS injury. Perfusion MRI is a method capable of measuring the rate of cerebral blood flow (CBF), cerebral blood volume, and the mean transit time required for blood to flow from one part of the brain to another. Its main advantage over SPECT and PET imaging is that it does not require the use of radioactive tracers. Briefly, these studies have demonstrated decreased CBF in the frontal and subcortical areas of HIV-infected patients that was related to CD4 cell counts [94], motor abnormalities [95], and worsening neurocognitive function [96]. They also demonstrated significant differences in CBF between HIV-infected patients and controls.

As an imaging method, MTI is thought to be sensitive to the bound protons in macromolecules (i.e., cholesterol and galactocerebroside) found in cell membranes of myelin [97]. Despite some obvious technical limitations (i.e., dilutive effect of edema on signal), there have been positive MTI findings which accurately discriminate between HIV-infected patients and controls based on measures of brain atrophy [33]. MTI abnormalities were also related to abnormal DTI metrics (ADC and FA) and reductions in measures of psychomotor speed among a small cohort of HIV-infected patients [45]. These findings suggest that part of the CNS changes observed in HIV-infected patients is related to pathological changes in axonal membranes.

Finally, using contrast agents, such as gadolinium (gd), abnormalities in the permeability of the BBB have been noted in HIV-infected patients [98]. In this study, several areas of increased BBB permeability were noted in the basal ganglia. This finding is of particular interest as there is evidence that HIV infection leads to BBB permeability, and BBB permeability is one of the ways in which HIV gains access to the CNS.

Other infectious diseases

The insidious course of HIV infection leads to immunocompromise and, consequently, a host of opportunistic diseases that eventually lead to the demise of the infected individual. While antiretroviral therapy has reduced the incidence of opportunistic infections (OIs), factors such as limited access to treatment, poor adherence to medication, drug toxicities, and drug-resistant strains of the virus, continue to contribute to the morbidity and mortality associated with HIV infection, especially in resource-limited countries. A brief summary of selected OIs affecting the CNS is provided here.

Toxoplasmic encephalitis (TE) is the most common clinical presentation of *Toxoplasma gondii* infection in HIV patients [99]. MRI continues to be the preferred imaging modality for the diagnosis and management of patients with TE [100–102] (FIG. 3a). Ho et al. [103] examined the clinical and radiologic manifestations of patients with TE at the late stage of HIV infection over the course of 12 years. Based on their findings, these authors suggested that multiple enhanced lesions were most frequently found in the cerebral hemisphere, followed by the basal ganglia, cerebellum, and brainstem. Furthermore, 89.5% of the lesions were multiple on presentation. Distinguishing TE from CNS lymphoma and tuberculosis

can be challenging, as homogenous enhancement may also be present in primary CNS lymphoma [91, 103]. However, the presence of multiple ring-enhancing lesions with surrounding edema is highly suggestive of TE, although imaging findings may vary [103, 104].

Cryptococcal meningitis, caused by the fungus *Cryptococcus neoformans*, is the third most common neurological manifestation in patients with AIDS after HIV and TE [105]. Infected patients undergoing MRI commonly present with dilated perivascular Virchow–Robin (V–R) spaces, typically defined as hyperintense round or oval lesions (FIG. 3b) that are usually smaller than 3 mm on T2-weighted images [106, 107]. Disease progression is associated with increased V–R size and hyperintensities on T2-weighted images in the basal ganglia, cerebellum, and cerebral white matter [107, 108]. The cryptococcal organisms disseminate from the basal cisterns, through the V–R spaces, causing dilation in these spaces, and then spread to the basal ganglia, internal capsule, thalamus, and brain stem [109]. However, enlarged perivascular spaces are not always pathognomonic of cryptococcosis, as dilation can also happen as a consequence of normal aging and, therefore, the appearance of the surrounding tissue on MRI scans must also be taken into account [110].

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the CNS caused by reactivation of the JC virus, a polyomavirus in immunocompromised individuals [111, 112]. By preferentially infecting oligodendrocytes of the white matter, the JC virus leads to progressive demyelination and neurologic deterioration [113]. Imaging studies show extensive, often multifocal, ring-enhancing lesions (FIG. 4) in the hemispheric or cerebellar white matter [114–116]. The lesions are initially round or oval but rapidly progress to

FIG. 3. (a) T2-weighted MR image of a patient with cryptococcal meningitis with bilateral infarctions in the caudate nuclei (white arrows). (b) T1-weighted MR image of a patient with toxoplasmosis. Arrows illustrate the frank lesions as well as edema (dark hypointense area surrounding the bright ringed lesion) resulting from injury. (High resolution version of this image is available in the [electronic supplementary material](#).)

FIG. 4. Patient with progressive multifocal leukoencephalopathy (PML). The images illustrate the typical radiological imaging finding typically observed in PML patients, namely, extensive white matter abnormalities (white arrows). (High resolution version of this image is available in the [electronic supplementary material](#).)

become confluent and large, leading to poor prognostic outcomes characteristic of this aggressive disorder [114, 117]. Lesions of PML can be distinguished from those of TE by their nonenhancing character [103]. It has also been demonstrated that cortical atrophy and ventricular dilation are not prominent features of PML, although follow-up studies have suggested some atrophic progression along with increased hypointensity on T1-weighted images [118]. Hyperintensity on FLAIR, an MR technique which can null the signal of fluids and aid in the visualization of brain lesions, is usually due to true progression of PML and is associated with a poor prognosis [117]. In contrast, hypointensity on FLAIR may represent a “burnt-out” process of PML and is associated with longer survival.

Radiological characteristics continue to play diagnostic roles for HIV-infected patients with suspected OIs, in which MR imaging has maintained its role as a sensitive tool for the detection of neurologic changes. However, the challenge in treating HIV-infected patients with the various OIs discussed lies in recognizing the neurologic deficit, identifying the etiologic agent, and initiating the appropriate therapy. Improved prophylaxis and antiretroviral therapies have certainly modified the approach in treating AIDS-related neurologic disease. Giancola et al. [118] showed that HAART does not significantly influence MR characteristics of PML despite the improved prognosis that therapy has offered to patients with this neurological disorder as well as other OIs. Although the HAART era has positively impacted the survival of HIV patients affected by neurological complications as a result of immune suppression, the long-term outcomes continue to pose relevant clinical challenges to the scientific community.

Therapeutic benefits of imaging and future studies

The biological complexity of HIV as a pathogen has proven a true challenge in terms of understanding the impact of the disease on the brain and CNS. At present, the field is just beginning to identify key properties of the virus

(envelope proteins, clade variants, etc) that determine overall impact on the brain, although much more work is needed before a complete neuropathogenic model can be developed. Medical imaging will play a critical role in the development of such a model. It is clear that medical imaging has elucidated many abnormalities associated with HIV-infection and, as such, has the potential to provide sensitive and valid biomarkers of CNS disease evolution and progression among HIV-infected patients.

In many ways, the true therapeutic benefit of medical imaging among HIV-infected patients is yet to be realized. Despite the advances in MRI and the many important findings in HIV-infected patients to date, improvements can be made in several key areas. It should be noted that despite the complexity of the viral factors, additional key host factors also determine the integrity of CNS function in this population. Factors such as alcohol and illicit drug abuse and comorbid infections (e.g., hepatitis C) are common population characteristics embedded within the epidemic, and each of these are known to impact brain function independent of HIV. As already illustrated, Pfefferbaum/Sullivan [36, 119] have demonstrated the significant contribution of alcohol abuse among commonly presenting HIV-infected populations. Much has also been written about other subpopulations within HIV-infected cohorts, such as drug abuse [120, 121], hepatitis C coinfection [122, 123], etc. The use of more controlled research designs will not only broaden our understanding of the neurological effects of these additional factors, but will improve both our understanding of the specific mechanisms of HIV-associated CNS injury and our potential for developing a specific neuropathogenic model.

Further, issues associated with treatment of HIV with antiretroviral compounds, such as efavirenz, and the impact of advanced age on cognitive function have both emerged as areas of research and clinical focus now that treatment of HIV has changed the natural history and demographic climate of the disease. Somewhat frightening is the very real possibility that many of these host factors already work

synergistically to complicate the outcomes associated with the disease and the likelihood that such interactions will increase in frequency in the absence of a cure.

Another significant improvement that will advance the HIV-infection literature will be larger, prospective studies. To date, the vast majority of imaging studies are cross-sectional in design. There are a few notable exceptions, although these studies are often limited to smaller cohorts and limited time points (not more than two time points). One major advantage of prospective studies is their improved statistical power when using participants as their own controls. There has been much work recently reported in the literature on time-series analyses of prospective imaging data among several different patient populations. The interest in this type of imaging data has resulted in a growing set of methods for dealing with longitudinal data, including subtraction imaging. For example, there has been encouraging success in modeling lesion variability in multiple sclerosis patients [124] and global/regional atrophy rates in Alzheimer disease patients [125–127] that might also be applied to HIV-infected patients. These longitudinal studies have revealed significant variability in the rate and progression of neuroimaging abnormalities in the context of disease, and advanced statistical models can link changes in clinical measures with biomarkers of CNS injury to improve our understanding of the temporal relationship between these variables. Elucidating these temporal relationships will improve our ability to develop treatments that can improve CNS outcomes (cognitive and/or imaging outcomes) in HIV-infected patients.

CONCLUSION

In summary, there is a growing interest in understanding the evolution and progression of HIV-associated CNS injury. This is especially true in the context of current treatment where the overall incidence of neurological complications (*i.e.*, dementia) have been dramatically reduced, but where evidence suggests that the CNS continues to sustain injury. In this review, we have demonstrated the potential of medical imaging to provide novel insights into the extent of injury, the progressive nature of injury, as well as provide unique biomarkers that can be used to evaluate treatment regimens.

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