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Methamphetamine and Cannabis: A Tale of Two Drugs and their Effects on HIV, Brain, and Behavior

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Abstract

HIV infection and drug use intersect epidemiologically, and their combination can result in complex effects on brain and behavior. The extent to which drugs affect the health of persons with HIV (PWH) depends on many factors including drug characteristics, use patterns, stage of HIV disease and its treatment, comorbid factors, and age. To consider the range of drug effects, we have selected two that are in common use by PWH: methamphetamine and cannabis. We compare the effects of methamphetamine with those of cannabis, to illustrate how substances may potentiate, worsen, or even buffer the effects of HIV on the CNS. Data from human, animal, and ex vivo studies provide insights into how these drugs have differing effects on the persistent inflammatory state that characterizes HIV infection, including effects on viral replication, immune activation, mitochondrial function, gut permeability, blood brain barrier integrity, glia and neuronal signaling. Moving forward, we consider how these mechanistic insights may inform interventions to improve brain outcomes in PWH.

Graphical Abstract

This review summarizes literature from clinical and preclinical studies demonstrating the adverse effects of METH, as well as the potentially beneficial effects of cannabis, on the interacting systemic (e.g., gut barrier leakage/microbial translocation, immune activation, inflammation) and
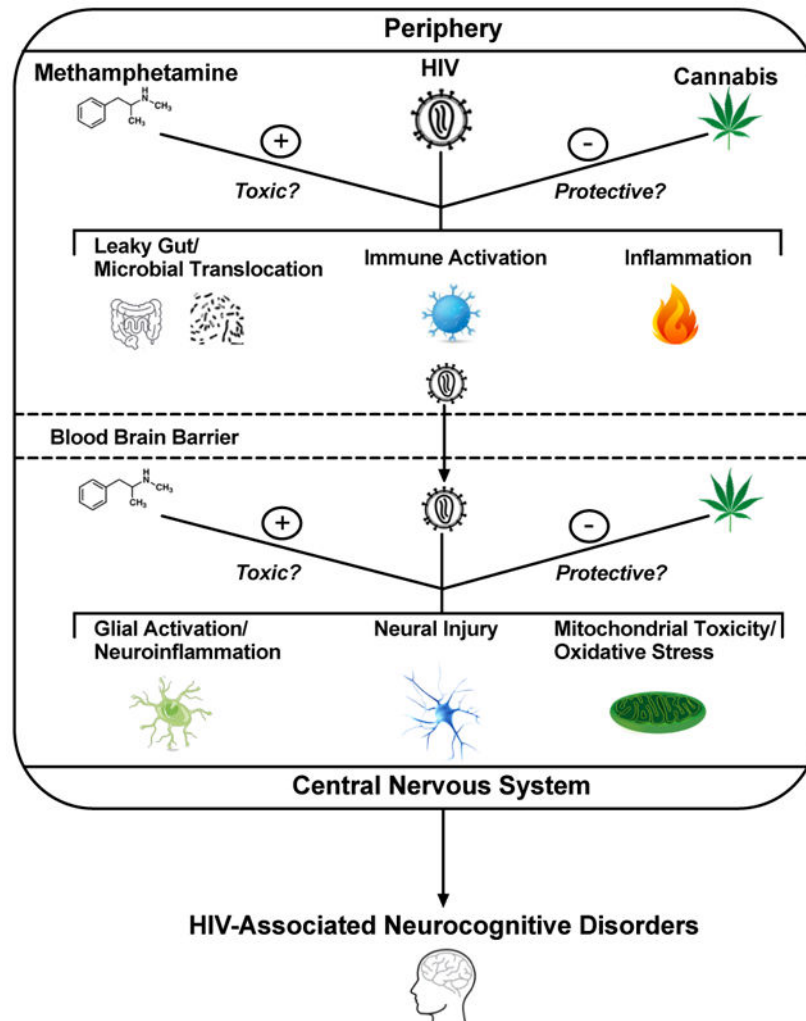

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CNS-specific (e.g., glial activation/neuroinflammation, neural injury, mitochondrial toxicity/ oxidative stress) mechanisms underlying HIV-associated neurocognitive disorders.

Introduction

Despite the success of combined antiretroviral therapy (cART) in prolonging the lifespan of persons with HIV (PWH), HIV-associated neurocognitive disorders (HAND) remain prevalent. HIV-associated dementia, a more severe complication from the persistence of HIV in the brain, has become relatively rare since the introduction of cART. However, milder forms of HAND, specifically asymptomatic neurocognitive impairment and mild neurocognitive disorder, have been reported in 30-50% of PWH, even despite suppressive ART, and can affect quality of life as well as everyday function (Heaton et al., 2010; Heaton

et al., 2011; Saloner and Cysique, 2017). The profile of HAND is heterogeneous; fronto-striatal dysfunction, manifested by disruptions in planning and reasoning (executive function) is most commonly observed, but problems in learning and memory, reduction in speed and efficiency of information processing, and attentional difficulties can also occur. The domain-specific pattern of deficits and the trajectory of these deficits over time varies between and within individuals (Woods et al., 2009; Morgan et al., 2011; Heaton et al., 2015; Dastgheyb et al., 2019; Arce Rentería et al., 2020). Importantly, HIV-associated neurocognitive deficits confer risk for impairments in real-world functioning, including unemployment, poor medication adherence, and impaired driving (Heaton et al., 2004; Marcotte et al., 2004; Moore et al., 2018a).

The heterogeneous presentation of HAND is not fully explained by inter-individual differences in disease management, but is also attributable to interactions of HIV disease with comorbidities that alter CNS function. Substance use disorders (SUDs) have long been considered a risk factor for the acquisition and transmission of HIV as well as a barrier to optimal HIV disease management (Moore et al., 2012; Elkbuli et al., 2019). Methamphetamine (METH) use has resurged nationally as indicated by the exponential increase in overdose deaths involving METH over the past decade (National Institute on Drug Abuse, 2020). METH users are at high risk of being exposed to HIV through unsafe sex practices and needle sharing (Hoenigl et al., 2016) and PWH are more likely to report METH use than persons without HIV. National rates of cannabis use have also increased due to the growing legalization of cannabis for medical and recreational use (Substance Abuse and Mental Health Services Administration, 2019). PWH frequently use cannabis recreationally and to treat HIV-related medical symptoms including neuropathic pain; compared to persons without HIV, PWH report significantly higher rates of cannabis use in their lifetime (77% vs. 45%) and within the past year (34% vs. 11%) and month (25% vs. 7%; (Montgomery et al., 2019).

The aim of this review is to provide an overview of the preclinical and clinical studies examining the pathological mechanisms, neuroimmune response, and general CNS consequences of METH and cannabis in HIV. We will not exhaustively review the literature regarding all possible pathological mechanisms. Rather, we will focus on select mechanisms involved in the neuroimmune response to METH and their neurobehavioral implications in the context of HIV infection. We will also contrast how cannabis use may exert an opposing influence on the CNS in HIV disease. Toward this end, we will in part draw upon our own experience conducting translational research studies on the CNS effects of METH and cannabis at the Translational Methamphetamine AIDS Research Center (TMARC; (Soontornniyomkij et al., 2016a).

Early studies on neuropsychological implications of HIV have highlighted the need to consider comorbid SUDs in the evaluation of HAND (Antinori et al., 2007). One influential study from Rippeth et al. (2004) reported that neurocognitive impairment was most prevalent among PWH who had METH dependence (HIV+/METH+: 58%) compared to single-risk groups (HIV+/METH−: 38%; HIV−/METH+: 40%) and HIV−/METH− controls (18%; (Rippeth et al., 2004). Carey et al. (2006) further demonstrated additive effects of immunosuppression and METH-dependence on neurocognitive impairment within PWH

(Carey et al., 2006). METH+ individuals with CD4$^+$ counts lower than 200 exhibited a 77% rate of global impairment compared to 55% among METH+ individuals with CD4$^+$ 200, 44% among METH− individuals with CD4$^+ <$ 200, and 33% among METH− individuals with CD4$^+$ 200. In the absence of HIV, Gonzalez et al. (2004) also observed higher rates of impairment in METH+ individuals (50%) compared to METH− individuals (22%; (Gonzalez et al., 2004). Interestingly, it was also observed that impairment rates were attenuated in METH+ individuals with a comorbid history of cannabis use disorder (33%). Collectively, these findings have stimulated work aimed at elucidating possible neuroimmunological mechanisms underpinning the increased risk of HAND in some persons with SUDs.

HIV-mediated activation of cells of the immune system triggers inflammatory processes, as well as the production of neurotoxic viral proteins, which contribute to neuronal injury. In addition to the release of pro-inflammatory cytokines, the presence and persistence of HIV in the brain causes alterations in glutamatergic and dopaminergic systems, mitochondrial damage and oxidative stress, with important degradation of blood-brain-barrier (BBB) integrity. *In vivo* neuroimaging studies have shown compromised integrity of gray and white matter, as well as neurometabolic alterations during early infection, and many of these neuroimaging abnormalities are still observed in chronically-infected PWH on cART (Ances et al., 2009; Valcour et al., 2012; Masters and Ances, 2014; Ragin et al., 2015). Neuropathological data has demonstrated reduced concentrations of dopamine in frontostriatal regions, cerebral atrophy, synaptodendritic and myelin loss, astrocytosis, and microglial activation (Everall et al., 2009; Kumar et al., 2009; Desplats et al., 2013). Thus, HIV infection of the CNS affects neuronal and BBB integrity, through the development of an inflammatory environment, which is largely influenced by substantial changes in neurotransmitter systems in the context of drug use (Nolan and Gaskill, 2019). Neurotransmitters such as dopamine, in turn, further enhance infection and inflammation (Gaskill et al., 2014; Basova et al., 2018).

Addiction is also recognized as a condition with a neurobiological disease state characterized by the "hi-jacking" of endogenous neurotransmitter systems (Volkow et al., 2016). For example, similar to HIV, chronic stimulant use is associated with reduced dopaminergic tone, gray and white matter abnormalities, microglial activation, and frontostriatal hypometabolism (London et al., 2015; Moszczynska and Callan, 2017). From a neuroimmunological perspective, the intersection between neuroHIV and drug use results in dynamic CNS alterations that are commensurate with the complexity of the clinical manifestations of HAND. NeuroHIV as a CNS condition can be affected by drug use at different molecular and cellular levels, due to the numerous modes of action of different drugs and the diversity of molecular pathways activated during signaling, not only leading to addictive behaviors, but also interfering with cells that are targets of HIV infection in the brain, such as macrophages and microglia (Bortell et al., 2015).

Neural Mechanisms and Neuroinflammation

Although cART limits viral replication and improves CD4$^+$ T-cell counts, chronic inflammation due to sustained immune activation and possibly cART itself are implicated as

a driving force behind the progression of HIV disease in the CNS in the cART era, including the persistence of HAND (Heaton et al., 2010; Heaton et al., 2011; Xu et al., 2017; Zulu et al., 2018; Fields et al., 2019). Microglia and perivascular macrophages (both cell types of myeloid lineage) initiate and regulate immune responses in the brain, signaling to astrocytes and other brain cells (Minagar et al., 2002; Liddelow et al., 2017). Microglia and perivascular macrophages also regulate clearance of extracellular aggregates, such as beta amyloid, from the brain, a process that may be impaired in reactive brain macrophages in PWH (Green et al., 2005; Achim et al., 2009; Fields et al., 2018; Mackiewicz et al., 2019; Fields et al., 2020). Astrocytes react rapidly and robustly with gene expression, metabolic, and morphological changes, that when unchecked, perpetuate chronic inflammatory signaling (Khakh and Sofroniew, 2015; Bortell et al., 2017a; Liu et al., 2018). The expression of chemokine receptors CCR5 and CXCR4 are thought to mediate the viral infection of perivascular macrophages and microglia (Kaul et al., 2007), whereas astrocytes may be capable of harboring the virus within CD81-lined vesicles (Gray et al., 2014). Even with systemic viral suppression, these CNS viral reservoirs may generate low-level HIV replication that triggers the release of viral proteins and proinflammatory cytokines and chemokines (Hellmuth et al., 2015; Marban et al., 2016). Though the extent to which astrocytes may harbor virus remains a matter of debate (Li et al., 2016; Ko et al., 2019), there is little question that they contribute to increased chemotaxis and monocyte activation following activation via HIV-infected macrophages (Muratori et al., 2010; Bortell et al., 2017a).

The notion of a chronic neuroinflammatory state in the context of suppressive cART is supported by elevated CSF and MRS markers of monocyte activation and neuroinflammation among well-treated PWH, particularly those with HAND (Harezlak et al., 2011; Masters and Ances, 2014; Anderson et al., 2015b; Schrier et al., 2015). Neuropathological studies have revealed increased presence of reactive microglia and astrocytes concomitant with increased expression of inflammatory cytokines in brain tissues from PWH and HAND (Fields et al., 2018; Swinton et al., 2019). Recently, positron emission tomography (PET) imaging studies have focused on the expression of the translocator protein (TSPO) 18kDa, a marker for microglial activation and thus neuroinflammation. These studies confirm increased microglial activation in PWH on suppressive cART and report associations between higher TSPO binding in the medial temporal lobe and thalamus with worse memory (Coughlin et al., 2014; Garvey et al., 2014; Vera et al., 2016).

Methamphetamine (METH)

Non-neuronal cells, especially innate immune HIV targets in the brain, microglia and infiltrating macrophages, are phenotypically affected by drugs of abuse, such as METH (Marcondes et al., 2010; Bortell et al., 2015; Mediouni et al., 2015; Najera et al., 2016; Basova et al., 2018). These cells may directly experience interactions with drug chemical structures, but also express receptors for the neurotransmitters that are enhanced locally by neuronal responses to drugs, including dopamine (Gaskill et al., 2012). Innate immune HIV target cells express all the DA receptors, making them responsive to the hyperdopaminergic environment of the brain in METH users (Gaskill et al., 2012; Gaskill et al., 2014; Basova et

al., 2018). One of the innate immune phenotypic characteristics that are relevant in HIV infection is the expression of the chemokine receptor and co-receptor for viral entry CCR5, which is upregulated in the brain upon METH chronic administration in macaques and in human cells (Marcondes et al., 2010; Bortell et al., 2015; Najera et al., 2016). Our group has shown that DA signaling that is increased in the context of METH can increase the expression of CCR5 and influence viral entry and spread (Basova et al., 2018). Others have shown that DC-SIGN, a molecule that also facilitates HIV dissemination, is upregulated via DA receptors (Nair et al., 2006).

Microglia and astrocytes also exhibit inflammatory responses in the presence of drugs of abuse, which in part contribute to the maladaptive alterations to neural circuitry that underlie addictive behaviors (Hauser and Knapp, 2014; Bortell et al., 2017b; Kohno et al., 2019). Our group recently reported that compared to non-transgenic control mice, Tat-transgenic mice display increased recruitment of midbrain dopamine neurons and locomotor sensitization in response to METH (Kesby et al., 2017). These reward-system adaptations in Tat mice following METH exposure were also accompanied by the elevated expression of ionized calcium binding adaptor molecule (IBA-1), a marker for microglial activation (Fig. 1). Importantly, this finding corroborated our group's prior observation that IBA-1 levels are higher in post-mortem temporo-parietal tissue of PWH with a lifetime history of METH dependence relative to those without a history of METH dependence, suggesting that METH use contributes to focal cerebral microgliosis among PWH (Soontornniyomkij et al., 2016b). An early MRS study from Chang et al. (2005) similarly found elevated glial activation and neuroinflammation, indicated by higher *myo*-inositol and choline levels, in the frontal white matter of PWH with METH use (Chang et al., 2005). Taylor et al. (2007) did not detect main effects of METH-dependence on MRS metabolites in PWH; however, higher plasma HIV RNA levels correlated with higher *myo*-inositol levels in frontal white and gray matter only among the METH-dependent group (Taylor et al., 2007).

Astrocytes regulate many aspects of brain homeostasis including BBB permeability, glucose transport, neurotransmission, synapse formation, and other processes that are disturbed during chronic inflammation (Sofroniew, 2000; Hamby and Sofroniew, 2010; Sofroniew and Vinters, 2010; Khakh and Sofroniew, 2015). These critical astrocytic functions are compromised in preclinical models of HIV-induced neuroinflammation, and the addition of drugs of abuse, including opiates and stimulants, exacerbates astrocytic dysfunction (Buch et al., 2012; Hauser and Knapp, 2014; Borgmann and Ghorpade, 2015). Astrocytic gliosis and decreased expression of excitatory amino acid transporter-2 (EAAT-2), suggestive of glutamatergic excitotoxicity, is evident in cortical tissue from PWH (Xing et al., 2009). METH has also been shown to downregulate astrocytic EAAT-2 expression via the trace amine associated receptor-1 (TAAR-1; (Borgmann and Ghorpade, 2015). Recent clinical data from our center also implicates disruption of the Wnt/β-catenin signaling pathway, which promotes astrocytic-mediated reuptake of glutamate via EAAT-2, in the pathogenesis of HAND (Yu et al., 2017a). Nevertheless, the influence of METH on biomarkers of astrocyte homeostasis in PWH remains poorly understood.

Cannabis

There is emerging evidence that cannabis use may buffer the deleterious neuroimmune effects of high inflammation (O'Sullivan and Kendall, 2010; Bilkei-Gorzo et al., 2017; Rizzo et al., 2019; Ellis et al., 2020; Henriquez et al., 2020; Watson et al., 2020). This may occur through cannabinoid $(CB)_1$ receptor-mediated dampening of glutamatergic excitotoxicity and CB_2 receptor-mediated initiation of anti-inflammatory cascades (Rom and Persidsky, 2013). Some recent human studies suggest that active cannabis use may limit HIV viral replication and attenuate HIV-related immunosuppression and inflammation (Thames et al., 2016; Rizzo et al., 2018; Chaillon et al., 2019). Recent data from our group suggest that a lifetime history of cannabis use disorders lowers the odds of neurocognitive impairment in PWH (Fig. 2; (Watson et al., 2020) and may even promote "youthful" and resilient neurocognitive abilities among adults aging with HIV (Saloner et al., 2019b). Despite these promising findings, reports are inconsistent on the effects of cannabis on the brain in PWH. In a study of the combined and independent effects of chronic cannabis use and HIV on brain metabolites, Chang et al. (2006) found that cannabis use was associated with a decrease in neuronal and glial metabolites, yet a normalization of glutamate levels in PWH (Chang et al., 2006). Chronic cannabis use has also been associated with reduced gray matter volumes and memory deficits in cohorts comprising both PWH and seronegative controls (Cristiani et al., 2004; Chang et al., 2006; Battistella et al., 2014; Thames et al., 2017).

The effects of cannabis use on neuroimmune function and neurocognition are highly complex and may be dependent upon patterns of consumption, among other cannabis use characteristics. Moderate use may mitigate HIV-induced neuroinflammation and microglial activation, while heavy exposure may promote toxicity that eclipses any anti-inflammatory benefits (Childs et al., 2017; Calabrese and Rubio-Casillas, 2018). 9-tetrahydroconnabinol (THC) effects on neurogenesis and memory are not linear, with low to moderate concentrations stimulating neurogenesis and high doses inhibiting neurogenesis and memory in multiple model systems. For example, THC provides protection from neurodegenerative processes by reducing inflammation in aged mouse models for neurodegenerative diseases but induces memory impairment in healthy mice, young or aged mice (Fishbein-Kaminietsky et al., 2014; Bilkei-Gorzo et al., 2017). Similarly, endocannabinoids exert neuroprotective effects through CB_1 in models for HIV Tat-induced neurotoxicity (Xu et al., 2017).

THC may be neuroprotective by disrupting macrophage and T-cell to astrocyte inflammatory signaling, resulting in reduced inflammatory gene expression (Rizzo et al., 2019; Henriquez et al., 2020). It has been suggested that cannabinoids (e.g., THC), and possibly other agonists particularly of the CB2 receptor, promote the transformation of microglia from their proinflammatory, cytotoxic (M1) state to neuroprotective, healing (M2) state (Tang and Le, 2016). The modulatory effects of THC on microglial/macrophage and astrocyte activation may be mediated by activation of peroxisome proliferator-activated receptors (PPARs), which has been shown to block glial inflammatory responses (Janabi, 2002; Drew et al., 2006; Xu et al., 2006; Pautz et al., 2010; Kozela et al., 2017). This may happen through direct effects of THC on PPAR transcriptional activity (O'Sullivan et al., 2005; O'Sullivan et

al., 2009; O'Sullivan and Kendall, 2010; Takeda et al., 2014), as well as indirectly through a protein kinase-dependent mechanism of PPARα and γ phosphorylation (Rueda et al., 2000). Activation of PPARα/γ and CB_1 and CB_2 in microglia and astrocytes by inhaled cannabis may explain the neuroprotective properties in PWH, but these interactions *in vivo* in the context of HIV and cART have not been studied.

Blood Brain Barrier Mechanisms

The BBB is a complex structure that divides the CNS from the periphery and is critical in preventing CNS infiltration of peripheral pathogens (Ballabh et al., 2004). The BBB endothelium, composed of brain microvascular endothelial cells (BMVECs) and tight junction proteins (TJPs), communicates with other components of the neurovascular unit (i.e., astrocytes, microglia, perivascular macrophages, pericytes, neurons) to coordinate biomolecular traffic in and out of the CNS (Ballabh et al., 2004). In the setting of HIV infection, proinflammatory cytokines and viral proteins induce the expression of matrix metalloproteinases and adhesion molecules (including E-selectin, vascular cell adhesion molecule 1 [VCAM-1], and intercellular cell adhesion molecule 1 [ICAM-1]) on BMVECs, which in turn facilitates the neuroinvasion of HIV-infected monocytes and $CD4^+$ cells (Eugenin et al., 2006; Atluri et al., 2015). Over time, the neuroimmune response to CNS infection can produce a vicious cycle of neuroinflammation and endothelial damage that accelerates deterioration of the BBB and further promotes transmigration of HIV and peripheral toxins into the CNS (Kaul et al., 2005; Persidsky et al., 2006).

METH

Using *in vitro* cell cultures of primary BMVECs and an *in vitro* BBB model, Mahajan et al. (2008) demonstrated that HIV protein gp120 in combination with METH increased BBB permeability and altered the expression of TJPs, including ZO-1, JAM-2, Occludin, Claudin-3, and Claudin-5 (Mahajan et al., 2008). Furthermore, gp120 and Tat mice treated with METH show reductions in TJPs that can be restored with antioxidant treatment, highlighting a role of oxidative stress in stimulant-induced BBB compromise (Ramirez et al., 2009; Banerjee et al., 2010). Yao et al. demonstrated that cocaine induces the expression of monocyte chemotactic protein-1 (MCP-1) in rodent microglia as well as activated leukocyte cell adhesion molecule in human BMVECs, which results in the accelerated adhesion and transmigration of HIV-infected monocytes across the BBB (Yao et al., 2010; Yao et al., 2011).

These cellular studies are consistent with clinical studies indicating increased neuroinvasion of peripheral viruses, including HIV and hepatitis C virus (HCV), in drug users (Kousik et al., 2012). Increased BBB permeability has also been proposed as an explanation for the unexpected observation that METH use is associated with *increased* cortical area and volume in PWH (Jernigan et al., 2005; MacDuffie et al., 2018). Under this hypothesis, HIV– and METH-related neuroinflammation alters aquaporin 4 function, a water channel protein expressed in astrocytes at cortical BBB junctions, resulting in cerebral edema that is detected as an increased volumetric signal on MRI (St Hillaire et al., 2005; Benga and Huber, 2012; MacDuffie et al., 2018). However, there is a dearth of clinical literature on the interactions

between HIV and drugs on CSF and neuroimaging biomarkers of BBB integrity. Elevated CSF/serum albumin ratio (CSAR), indicative of BBB leakage, is observed even in PWH on effective cART and has been linked to CSF biomarkers of neuronal injury and diffusion tensor imaging (DTI) markers of white matter integrity (Wright et al., 2015; Calcagno et al., 2016; Rahimy et al., 2017; Farhadian et al., 2019). A recent study also reported elevated capillary permeability in the basal ganglia and anterior frontal white matter, estimated using dynamic contrast enhanced perfusion MRI, in virally-suppressed HAND patients compared to controls (Chaganti et al., 2019). These *in vivo* studies excluded participants with drug abuse histories, did not report drug use histories, or included PWH with comorbid SUDs but did not examine SUDs as a predictor of BBB integrity. In preliminary analysis of the TMARC cohort, HIV and METH-dependence additively contributed to higher plasma levels of VCAM-1 (Fig. 3; Iudicello et al., unpublished data), a marker of endothelial cell activation that is linked to inflammation and vascular conditions such as atherosclerosis and small vessel disease (Arba et al., 2018; Kong et al., 2018). Higher levels of VCAM-1 in plasma were in turn associated with worse neurocognitive functioning, providing insight into the potential role of vascular/BBB mechanisms in HIV and METH associated neurocognitive impairment. Nevertheless, more clinical studies are needed to determine whether substance-related compromise of BBB integrity observed *in vitro* translates to fluid-based and neuroimaging biomarkers of the BBB in PWH.

Cannabis

In contrast to stimulants, cannabinoids may stabilize the BBB under conditions of high neuroinflammation. CB_2 receptor expression is increased in post-mortem BMVECs of patients with HIV encephalitis (Persidsky et al., 2011), yet several studies demonstrate that CB_2 receptor agonists reduce lipopolysaccharide (LPS)-induced inflammatory responses at the BBB, thereby increasing TJP expression and trans-endothelial resistance while reducing the surface expression of ICAM-1 and VCAM-1 (Calapai et al., 2020). Cannabinoid agonists inhibit HIV gp120-induced release of Ca^{2+} and significantly decrease the down-regulation of TJPs and permeability of BMVECs *in vitro* (Lu et al., 2008). The same study also reported that cannabinoid agonists inhibited the transmigration of human monocytes across the BBB using an *in vivo* model of mannitol-induced BBB permeability in mice. Very recent work from our group has extended these findings into the clinical realm. Using CSAR and soluble urokinase plasminogen activator receptor values to derive a composite BBB index, Ellis et al. (2020) reported a significant HIV by cannabis interaction on BBB integrity such that more frequent use of cannabis in the past month related to lower BBB index values (less "leakage") in PWH but not HIV− individuals (Ellis et al., 2020). Notably, lower BBB index values associated with less CSF neurofilament light, a marker of axonal injury.

Mitochondrial Function and Oxidative Stress Mechanisms

Since the beginning of the epidemic, PWH have presented with disease markers associated with mitochondrial damage and oxidative stress. HIV proteins and cART induce changes in mitochondria that likely lead to increases in oxidative stress (reviewed by (Fields and Ellis, 2019). In postmortem brain specimens of PWH, evidence has been found for disruptions in mitochondrial biogenesis, mitochondrial dynamics fission and fusion, mitochondrial

transport, and recycling of damaged mitochondrial via mitophagy (Fields et al., 2015a; Fields et al., 2015b; Avdoshina et al., 2016; Swinton et al., 2019). Metabolomic studies have also found that PWH with depression exhibit reduced plasma levels of acylcarnitine, indicative of mitochondrial dysfunction (Cassol et al., 2015). Another study found reduced levels of N-acetylaspartate (NAA), a putative marker of neuronal integrity and mitochondrial injury (Bates et al., 1996), in frontal white matter of PWH taking didanosine or stavudine (Schweinsburg et al., 2005). Moreover, neuroimaging studies from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort indicate negative correlations between frontal cortex levels of NAA and markers of monocyte activation (IP-10 and MCP-1) in PWH (Anderson et al., 2015a), as well as lower basal ganglia and frontal white matter levels of NAA on MRS in PWH with severe comorbidity burden (Saloner et al., 2019a).

HIV proteins, namely gp120, Tat, Nef, and Vpr are all associated with mitochondrial damage and oxidative stress in *in vitro* and *in vivo* models (Fields and Ellis, 2019). Moreover, antiretroviral drugs have also been associated with mitochondrial damage. The original reverse transcriptase inhibitors damaged mitochondrial DNA in the periphery, likely through inhibiting mitochondrial polymerase g, which is responsible for mtDNA replication (Fields and Ellis, 2019). More recently, the new generation of cART drugs has been shown to alter mitochondrial function *in vitro* and *in vivo* (Fields et al., 2019). Despite these findings, surprisingly little is known about how various drugs of abuse affect mitochondrial function and oxidative stress in PWH.

METH

In the aforementioned MRS studies, Chang et al. (2005) observed additive effects of HIV and METH on lower NAA in the basal ganglia and frontal gray and white matter (Chang et al., 2005), while Taylor et. al (2007) observed a correlation between higher plasma HIV RNA and lower NAA in frontal white matter in HIV+/METH+ (Taylor et al., 2007). In a post-mortem analysis of frontal brain tissues from controls without a history of METH use and PWH with and without a history of METH use, Var et al. (2016) quantified mitochondrial injury as the proportion of mitochondrial DNA carrying the "common deletion," a genetic mutation reflective of oxidative stress (Var et al., 2016). HIV+/METH– demonstrated the highest levels of mitochondrial injury, which in turn correlated with worse global cognition within the HIV+/METH– group. An opposite effect was detected in tissues from HIV+/METH+ donors such that this group had the lowest proportion of mtDNA carrying the common deletion, yet this apparent reduction in mitochondrial injury also conferred risk for poorer neurocognition. These findings are consistent with prior observations from our group that increased cortical volumes and higher fractional anisotropy values relate to better neurocognition in PWH but worse neurocognition in METH+ individuals (Jernigan et al., 2005; Soontornniyomkij et al., 2016a), which may reflect a compensatory consequence of METH-related neuropathology as opposed to a neuroprotective effect of METH.

In a rodent model of self-administration of METH under long access conditions, which elicits compulsive METH intake similar to patterns of consumption in METH-dependent

humans, HIV-transgenic rats exhibited greater evidence of impaired aerobic glucose metabolism, neural injury, and inflammation compared to wild-type rats (de Guglielmo et al., 2020). Langford et al. (2003; 2004) demonstrated that the combination of HIV and METH reduces calbindin-immunoreactivity in nonpyramidal neurons and these neurotoxic effects were accompanied by mitochondrial damage and oxidative stress, possibly through a mechanism involving the mitochondrial calcium potential (Langford et al., 2003; Langford et al., 2004). Importantly, a follow-up study of PWH with METH use reported that memory deficits 6-months prior to death correlated with loss of frontal calbindin interneurons at autopsy (Chana et al., 2006). Similarly, a DTI study in mice demonstrated that METH-induced increases in hippocampal mean diffusivity also correlated with a loss of hippocampal calbindin expression (McKenna et al., 2016). *In vitro* studies have shown that METH may induce mitochondrial damage and oxidative stress in astrocytes exposed to HIV (Borgmann and Ghorpade, 2018). Banjeree et al found that a combination of gp120, Tat and METH induced robust increases in markers for oxidative stress, GSH and MDA. Importantly, N-acetylcysteine amide (NACA) protected the BBB from oxidative stress-induced damage, though the mechanisms of this protection were not determined. However, a study by Zeng et al. (2018) using *in vitro* and *in vivo* models showed that Tat– and METH-induced oxidative cellular injury is mitigated by NACA via modulation of mTOR signaling (Zeng et al., 2018).

Cannabis

Cannabinoids, namely THC and cannabidiol (CBD), and some synthetic cannabinoid receptor agonists affect mitochondrial function in different types of brain cells. The effects of cannabis on HIV-induced mitochondrial function and oxidative stress have been investigated using *in vitro* models for brain cells. Some studies have investigated the effects of cannabinoids on HIV-induced neurotoxicity using *in vivo* models, but data on mitochondrial alterations are largely lacking. We recently found that a cannabinoid receptor agonist blocks mitochondrial dysfunction in astrocytes after exposure to pro-inflammatory cytokines that are relevant to HAND (Swinton et al., 2019). Moreover, conditioned media from the reactive astrocytes in culture reduced mitochondrial biogenesis markers in neurons and this was blocked by treating the astrocytes with the CB receptor agonist WIN55,212-2 (Fig. 4). Another study found that THC blocks monocyte mediated activation of astrocytes and subsequent expression of MCP-1, possibly explaining how cannabis users may be protected from HIV and cART-induced neurotoxicity (Rizzo et al., 2019).

Gut Microbiome Mechanisms

Alterations to the gut microbiome (i.e., changes in enteric bacterial diversity) coupled with increased gut permeability can lead to greater microbial translocation, which can in turn disrupt neuroendocrine and neuroimmune homeostasis (Pellegrini et al., 2018). For example, regulatory T-cells survey gut-associated lymphoid tissue (GALT) and changes in gut microbiome composition can promote T-cell brain infiltration. Circulating bacterial factors, such as bacterial LPS which acts on endothelial toll-like receptors, can alter BBB integrity and promote neuroinflammation. Taken together, gut dysbiosis is now implicated in a host of neurological and psychiatric disorders (Kim and Shin, 2018; Ma et al., 2019). An emerging

topic in HIV and substance use research is how these conditions alter the composition of the gut microbiome and how gut changes influence systemic organ and brain functioning. HIV replication in GALT results in immune-mediated damage to intestinal epithelial cells, thereby degrading the integrity of the gut-blood barrier and facilitating the leakage of intestinal bacteria into systemic circulation (Dillon et al., 2016). Similarly, gut dysbiosis has been observed in response to alcohol, stimulants, and opiates, although no specific dysbiotic signature has emerged across or within drug classes (Meckel and Kiraly, 2019). In addition to substance-induced alterations to gut integrity, lifestyle and dietary factors are likely to influence the composition of the gut microbiome in individuals with SUDs (Volpe et al., 2014; Singh et al., 2017).

METH

Recent studies have investigated the impact of METH use on the gut microbiome in HIV-seropositive men who have sex with men. In these studies, METH use moderated the effects of HIV on microbial composition and was also independently associated with microbial alterations favoring the expression of pro-inflammatory bacteria (Fulcher et al., 2018b; Cook et al., 2019). Furthermore, recent METH use related to increased levels of IL-6 and TNF-alpha in rectal sponge samples, regardless of HIV serostatus (Fulcher et al., 2018a). Despite the putative relevance of microbial translocation in the neuropathogenesis of HIV and METH, the combined effects of HIV and METH on gut-brain relationships remain vastly understudied. Some studies suggest that treatments that alter the gut microbiome and reduce microbial translocation may mitigate the effects of HIV disease and drug use on HAND (Gori et al., 2011; Ceccarelli et al., 2017), however future studies must clarify the role of confounds such as poor diet and HCV, integrate comprehensive gut microbiome, CNS biomarker, and neurobehavioral phenotypes, and examine the impact of gut health interventions (e.g., prebiotic supplementation) on neurocognition to allow for such a conclusion.

Cannabis

In addition to the brain, CB_1 and CB_2 receptors are expressed on enteroendocrine L cells that are innervated by enteric glial cells and afferent neurons (Yoo and Mazmanian, 2017). CB receptors in the large intestine are activated by the bioactive lipids anandamide and 2-arachidonoylglycerol and the synthesis and degradation of these cannabinoids is modulated by structurally similar bioactive lipids (Cani et al., 2016a; Acharya et al., 2017; Chiurchiù et al., 2018). Some endocannabinoids and related bioactive lipids function as epithelial barrier "gate-keepers" by reinforcing TJP integrity and reducing inflammation while others function as "gate-openers" by decreasing the thermogenesis of brown adipose tissue and increasing inflammation (Cani et al., 2016b). In addition to CB receptor-dependent mechanisms, the endocannabinoid system may facilitate gut barrier homeostasis via PPAR-dependent pathways (Muccioli et al., 2010). In a recent simian immunodeficiency virus (SIV) model, gut epithelial disruption was accompanied by reduced PPARα signaling and mitochondrial dysfunction, yet restoration of the intestinal barrier was accomplished via probiotic-induced enhancement of PPARα signaling and restoration of mitochondrial function and fatty acid β-oxidation (Crakes et al., 2019). In another SIV study, chronic THC administration inhibited activation of immune and pro-inflammatory pathways in lamina propria leukocytes and gut

epithelium (Kumar et al., 2016). Macrophage shift to the proinflammatory M1 state also contributes to gut cytotoxic cascades. Interestingly CB$_2$ agonists reverse some of the inflammatory processes in models of inflammatory bowel disease, possibly by facilitating a shift to the M2 phenotype. Further, in LPS models of neural injury, CB$_2$ agonists may protect against neurotoxicity, possibly via a similar M1 to M2 phenotype shift (Reiner et al., 2014; Presley et al., 2015). While these preclinical findings suggest that cannabis may ameliorate HIV-induced immune activation, inflammation, and oxidative stress in the gut, either independently or in synergy with probiotics, these mechanisms have not been investigated in humans. Translational paradigms that examine the interface between the endocannabinoid system and the gut-brain axis in both PWH and HIV transgenic animals would importantly bridge this critical gap in knowledge (Fig. 5).

Animal Models of NeuroHIV

Overview

Animal models have been critical for research on HIV-associated brain injury as well as for exploring the mechanistic underpinnings of SUDs. These models span a range of species, including chimpanzees and other non-human primates, cats, rats and mice (Gardner and Luciw, 1989; Klotman and Notkins, 1996; Toggas and Mucke, 1996; Nath et al., 2000; Reid et al., 2001; Keppler et al., 2002; Ambrose et al., 2007; Van Duyne et al., 2009). Of those, non-human primates infected with SIV and rodents (rats and mice) have been the primary models used for neuroHIV and SUD research, including METH and cannabinoids (Olmsted et al., 1989; Clements et al., 1994; Madden et al., 2005; Ambrose et al., 2007; Clements et al., 2008; Williams et al., 2008; Liu et al., 2009; Winsauer et al., 2011; Molina et al., 2015; Najera et al., 2016; Simon et al., 2016; Thaney et al., 2018). One study treated SIV-infected rhesus macaques with THC for several months and found that the animals became tolerant to the behavioral effects of THC while lacking any increase of viral titers in plasma, CSF and brain tissue and displaying reduced CNS pathology in comparison vehicle controls (Winsauer et al., 2011). In contrast, METH exposure increased SIV levels and immune activation in the brain of SIV-infected rhesus macaques (Marcondes et al., 2010).

Rodents are not permissive to productive infection with wild-type HIV-1. However, certain immuno-compromised mouse strains can be 'humanized' by reconstitution with human immune or hematopoietic stem cells. The resulting human peripheral blood cell populations are permissive to HIV infection and thus provide small animal models for HIV/AIDS and neuroAIDS research (Van Duyne et al., 2009; Dash et al., 2011; Thaney et al., 2018). Another important advantage of rodents, both mice and rats, is that they can be genetically modified (Klotman and Notkins, 1996; Toggas and Mucke, 1996; Reid et al., 2001; Van Duyne et al., 2009). Several transgenic mouse lines and a rat have been generated that express an entire HIV genome or a truncated version with certain viral components, such as gp120, Tat or Vpr (Leonard et al., 1988; Iwakura et al., 1992; Hanna et al., 1998b; Hanna et al., 1998a; Reid et al., 2001). A number of studies investigating the intersection of HIV and stimulants have been performed in the HIV gp120-transgenic mouse model, which expresses a soluble viral envelope gp120 of HIV-1 in the brain (Toggas et al., 1994; Roberts et al., 2010; Bandaru et al., 2011; Soontornniyomkij et al., 2016a). This gp120 model shares

hallmarks of neuropathology with human neuroHIV patients, including loss of neuronal dendrites and synapses, activated microglia, astrocytosis, and compromised neurogenesis (Toggas et al., 1994; Okamoto et al., 2007; Crews et al., 2011; Lee et al., 2011; Lee et al., 2013; Avraham et al., 2014; Fields et al., 2014; Maung et al., 2014; Avraham et al., 2015; Steiner et al., 2015; Thaney et al., 2017). In comparison to non-transgenic littermate controls, gp120 mice also display memory impairments, perturbations in electrophysiological function, and share patterns of differential gene expression with human HIV brains (Krucker et al., 1998; D'hooge et al., 1999; Maung et al., 2014; Hoefer et al., 2015; Thaney et al., 2017).

In comparison to non-transgenic controls, the gp120 mice display an altered acute response to METH that is discernable in stereotypic behavior (Roberts et al., 2010). Another study detected in gp120 mice an increased preference for both METH and a highly palatable non-drug reinforcer (saccharin) as well as increased sensitivity to METH-induced conditioned reward, providing a potentially explanation for a frequent abuse by HIV-infected individuals (Kesby et al., 2014). The HIV-transgenic rat has also been employed to assess alterations of behavior and the dopaminergic system associated with HIV infection and the effects of METH on sensorimotor gating and locomotor activity (Liu et al., 2009; Moran et al., 2012; Moran et al., 2013). HIV-expressing rats displayed greater behavioral sensitization due to METH than non-transgenic controls.

Translational Behavioral Findings

A more direct example of a translational, cross-species paradigm is the behavioral pattern monitor (BPM), which constitutes a modification for humans of the traditional open field test for rodents (Perry et al., 2009; Young et al., 2016). The mouse BPM assesses potential inhibition deficits in male and female mice, reflected by increased motor activity, inappropriate perseverative behavior, and elevated exploration of novel stimuli (Henry et al., 2013). The reported observations indicated that both gp120 and chronic METH exposure affected behavioral inhibition in a sex-dependent fashion. While robust gender differences have not been reported in human studies using the BPM, known gender differences in HIV disease warrant further investigation of potential behavioral correlates (Wilson et al., 2006; Addo and Altfeld, 2014).

Prepulse inhibition (PPI) is a measure of sensorimotor gating that is regulated by several neural networks including the dopaminergic circuitry implicated in inhibition and can also be investigated across species. Compromised sensorimotor inhibition, assessed by PPI of the eyeblink startle response, has been reported in PWH with neurocognitive impairment when compared to neurocognitively intact PWH (Minassian et al., 2013). This observation suggested that early inhibition deficits accompany or possibly precede downstream neurocognitive impairment in PWH. In rodent models, PPI is quantified using the whole-body startle response, and PPI in gp120 and METH-exposed mice was investigated (Henry et al., 2014). Prior to METH exposure, female gp120 mice exhibited decreased PPI while male gp120 mice displayed increased acoustic startle response compared to their respective non-transgenic controls. The observations in gp120 and METH treated mice and the results in humans indicating PPI deficits in PWH with neurocognitive impairment (Minassian et al.,

2013) indicate that inhibition deficits are affected by HIV– and METH-induced alterations of dopaminergic neurotransmission, which manifest not as a global phenomenon but rather in association with higher-order cognitive deficits or biological variations, such as sexual dimorphism.

Using an attentional-set-shifting task (Young et al., 2010) to assess discrimination learning in gp120 mice exposed to an escalating-dose, multiple-binge METH regimen, Kesby et al. (2015) demonstrated impaired learning in gp120 mice, regardless of METH exposure, which was concordant with the pattern of learning deficits observed on standard neuropsychological testing in humans stratified by HIV serostatus and METH-dependence (Kesby et al., 2015). In a separate study employing the same METH regimen in gp120 mice, Hoefer et al. (2015) showed that similar to gp120, METH triggered a significant loss of pre-synaptic terminals and neuronal dendrites in the hippocampus and cerebral cortex of non-transgenic animals (Hoefer et al., 2015). Electrophysiology analysis of hippocampal slices demonstrated that METH-treated gp120 mice exhibit significantly reduced post-tetanic potentiation, while both METH and gp120 expression resulted in impaired long-term potentiation. Notably, these pre- and post-synaptic alterations also occurred in conjunction with impaired learning and memory in the METH-exposed gp120 mice. More recently, Kesby et al. (2018) demonstrated additive effects of Tat and METH exposure in mice on perseverative errors during reversal learning, which may reflect Tat– and METH-induced alterations in dopaminergic tone in the orbitofrontal cortex and caudate putamen (Kesby et al., 2018). This executive dysfunction in METH-exposed Tat-transgenic mice is also concordant with perseverative responding observed in METH-using PWH on the Wisconsin Card Sorting Task (Fig. 6), a gold standard neuropsychological measure of executive function. Overall, the similar pattern of outcomes suggests that gp120 and Tat independently and in combination with METH can contribute to behavioral deficits across species, with some indication of a protein-specific dissociation in the constructs involved such that gp120 may preferentially compromise learning and memory whereas Tat may modulate dopaminergic circuitry involved in perseverative responding.

Additional Considerations

Aging

As the proportion of PWH over the age of 50 steadily rises (Centers for Disease Control and Prevention, 2018), attention is shifting toward the interactions of HIV and drug use on neurocognitive and brain aging. In a cross-sectional design, Iudicello et al. (2014) observed a negative impact of a remote history of METH dependence on neurocognition (including memory, attention, and executive function) and everyday functioning (including employment) in older, but not younger PWH (Iudicello et al., 2014), suggesting that older age may enhance vulnerability to the detrimental neurocognitive effects of prior METH use even in currently abstinent PWH. Using longitudinal data from the CHARTER cohort, Heaton et al. (2015) reported that a lifetime history of METH use disorder at baseline resulted in a 70% increase in risk of experiencing clinically-significant neurocognitive decline over an average study period of three-years (Heaton et al., 2015). This indication of an adverse "legacy" effect of historical METH use on age-related neurobehavior in PWH

was supported by a recent study (Paolillo et al., 2019). Frailty, a clinical proxy of biological age indexed by the proportion of accumulated age-related multi-system health deficits, was higher among PWH with a lifetime METH use disorder compared to PWH and HIV− individuals without a history of METH use (Fig. 7). Notably, higher frailty exhibited the strongest association with worse executive function and working memory in the dual-risk METH+ PWH group, suggesting that prefrontal dysfunction linked to past METH use among PWH may in part be explained by the presence of a geriatric phenotype. This is consistent with studies suggesting that HIV-induced immune dysfunction may accelerate cellular aging (Deeks, 2011), which may progress even more rapidly in the setting of METH abuse (Cohen and Torres, 2017; Papageorgiou et al., 2019). HIV and METH can induce astrocyte senescence *in vitro* and across multiple animal models, which contributes to neuronal toxicity via downregulation of β-catenin signaling (Yu et al., 2017b). Other cellular and molecular mechanisms of neuroimmunosenescence that overlap in HIV and METH pathogenesis may involve autophagic dysregulation (Cao et al., 2017), particularly mitophagy (Borgmann and Ghorpade, 2018; Teodorof-Diedrich and Spector, 2018), and brain DNA methylome alterations in genes enriched in neurodegenerative disease (Desplats et al., 2014).

Older adults represent the fastest growing segment of cannabis users nationally, as indicated by a 71.4% increase in the past-year prevalence of cannabis use between 2006 and 2013 among adults aged 50 and older (Han et al., 2017; Lloyd and Striley, 2018). However, findings on the effects of cannabis use on neurocognition and brain integrity in older adults without HIV are scattered and inconsistent (Yoo et al., 2020). A recent systematic review of older adults (ages 50 and older) with and without clinical disorders (e.g., Parkinson's disease) provided some evidence of a modest adverse effect of heavy cannabis exposure on neurocognition, predominantly verbal memory, yet many studies yielded null results and a few studies reported better subjective and global neurocognition in older cannabis users compared to non-users (Scott et al., 2019). The influence of cannabis on neurocognitive and brain aging in HIV is even more limited, and therefore represents a major gap in our current understanding of mechanisms of neurobehavioral resilience and vulnerability in the growing population of older PWH.

Host Genetics

Clinical studies frequently observe heterogeneous patterns of neurocognitive and biomarker profiles in substance-dependent PWH, necessitating an increased focus on moderating co-factors that may help explain inter-individual differences. Self-reported parameters of METH use (e.g., duration of use, frequency of use, length of abstinence) do not strongly correlate with neurocognitive performance (Johanson et al., 2006; Cherner et al., 2010b), suggesting that other factors such as host genetics may better explain susceptibility to METH-related neural injury. To this end, candidate gene studies have examined associations of single-nucleotide polymorphisms (SNPs) involved in putative pathways of HAND and drug use with neurocognitive phenotypes. For example, METH-dependent individuals who carry SNPs that confer sustained dopaminergic signaling through increased dopamine binding affinity or decreased dopamine metabolism do not exhibit the same neurocognitive benefits of high dopaminergic tone as non-users and may be at enhanced risk for

neurocognitive impairment due to dopamine-mediated increases in viral replication (Gaskill et al., 2009; Bousman et al., 2010; Gupta et al., 2011; Cherner et al., 2019). Dopaminergic SNPs similarly moderate the neurocognitive effects of other drugs in PWH and in general are implicated in the heritability of impulsivity and sensation-seeking traits that subserve addictive behaviors (Derringer et al., 2010; Khadka et al., 2014; Holmes et al., 2016). A composite approach that aggregates dopaminergic SNPs into a continuous polygenic risk score has shown promise in identifying individual risk for neurobehavioral impairments in other neuropsychiatric conditions such as schizophrenia and affective disorders (Pearson-Fuhrhop et al., 2014; Wang et al., 2018), but has not been comprehensively explored in the context of HIV and SUDs. Genetic variation in the metabolism of drugs and cART may also alter risk for HAND as they directly influence expression of enzymatic factors (e.g., COMT, cytochrome enzymes) that modulate CNS exposure (levels and duration of exposure) to the exogenous substance and its metabolites, which may also be neurotoxic (Cherner et al., 2010a; Saloner et al., 2020). The crosstalk between drugs in the CNS and neuroimmune factors is likely influenced by genetic variation in other putative pathogenic pathways of HAND, including inflammatory, mitochondrial, immune, iron-regulation, and BBB pathways (Jia et al., 2017; Olivier et al., 2018; Sundermann et al., 2019), yet this is also underexplored.

Summary

It has been long understood that abusive drugs can worsen HIV-related health outcomes and have neurotoxic potential. However, in this review we demonstrate how two commonly used substances in PWH, METH and cannabis, can have opposing actions on the CNS in HIV disease, which in turn contributes to the clinical complexity of HAND. With respect to METH, the extant literature provides converging lines of evidence that HIV and METH conspire to overburden the neuroimmunological system. Pro-inflammatory signaling in the periphery and microbial translocation due to increased gut barrier permeability facilitate the transmigration of activated monocytes across a BBB that is already compromised due to local immunomodulatory effects of HIV and METH. Subsequent enhancement of HIV RNA replication and pro-inflammatory signaling in the CNS contributes to microglial activation and disruption of astrocytic homeostasis. In addition to glial-mediated mechanisms of neuronal injury, such as mitochondrial damage, oxidative stress, and excitotoxicity, viral proteins and METH promote neuroadaptations and neurotoxicity in frontostriatal dopaminergic pathways that impair higher-order neurocognitive functions and perpetuate addictive behaviors. Together, these mechanisms modify HIV infection in the brain, conferring novel characteristics and causing the pathogenesis to become fundamentally different in the context of METH, when compared to neuroHIV in non-using individuals.

Behavioral interventions that promote abstinence from METH and adherence to cART in METH-dependent PWH are considered the first-step in mitigating the CNS burden of METH in HIV disease (Moore et al., 2012; Moore et al., 2018b). However, many individuals struggle to maintain abstinence and METH-related neurobehavioral deficits can persist even among PWH with protracted periods of abstinence (Iudicello et al., 2014; Paolillo et al., 2019). Given that there are no established adjuvant therapies for treating HAND (Bougea et al., 2019), identification of molecular targets within these pathogenic pathways is of critical

importance for neurotherapeutic development. HIV and METH may interfere with trophic factor gene expression and signaling cascades, thereby limiting the production of neurotrophic and neuroprotective factors that promote synaptodendritic plasticity and reduce glial activation and neuroinflammation (Ellis et al., 2007). For example, fibroblast growth factor (FGF)-1 inactivates the pro-apoptotic kinase glycogen synthase kinase (GSK) 3β signaling pathway (Crews et al., 2009), which may confer protection against dendritic spine loss due to HIV gp120 and promote the survival of glutamatergic neurons and calbidin-immunoreactive interneurons (Everall et al., 2001; Everall et al., 2002; Ellis et al., 2007). Our group reported that HIV, METH-dependence, and accompanying neurocognitive deficits are associated with lower CSF levels of fibroblast growth factor FGF-1 (Bharti et al., 2016). Pharmacological approaches that upregulate neurotrophic factors like FGF-1, or modulate downstream signaling factors (e.g., GSK 3β), as is the case with oral lithium, may ameliorate neuronal injury due to HIV and METH. The second-generation NMDAR receptor antagonist nitromemantine is a nascent therapeutic that may also protect against glutamatergic toxicity but has yet to be tested in PWH (Takahashi et al., 2015; Nakanishi et al., 2016; Bougea et al., 2019).

Importantly, not all substance use worsens neuroHIV and in the case of cannabis, there may in fact be therapeutic levels that mitigate the aforementioned pro-inflammatory mechanisms of HIV-related neuroimmune injury. Moreover, emerging preclinical data also suggests that CBD may attenuate addictive behaviors across multiple drug classes (Prud'homme et al., 2015; Gonzalez-Cuevas et al., 2018), with recent data showing that CBD administration reduced self-administration of METH and METH-seeking behavior in rats (Hay et al., 2018). Activation of CB_2 receptors may shift the expression of macrophages to an anti-inflammatory phenotype and these anti-inflammatory effects may limit mitochondrial toxicity and help restore gut and BBB integrity. Reduced BBB permeability would importantly limit the entry of HIV and neurotoxins into the CNS, however it would also limit the distribution of cART into the CNS, which may lead to poorer viral suppression but also less potential for cART-induced neurotoxicity. Nevertheless, there is a paucity of research with respect to cannabis exposure in gp120 and Tat mouse models and studies of cannabis effects in PWH are similarly lacking rigorous scientific investigation. Translational paradigms, similar to those that have yielded valuable insights into the effects of METH on neuroHIV, may help inform evidence-based approaches to cannabis in HIV, including the possibility of new neuroprotective strategies. The ecological validity of these paradigms may also be advanced with careful consideration for real-world patterns of drug use, including polysubstance use and differences in route of administration (e.g., METH injection vs. inhalation, cannabis ingestion vs. inhalation). Toward this end, emerging technologies such as ecological momentary assessment offer a promising avenue for real-time measurement of polysubstance use and its neurobehavioral antecedents and consequences in humans (Paolillo et al., 2018), which may in turn inform preclinical experimental manipulations to multiple agents. This may be particularly relevant for METH-dependent PWH who concomitantly use cannabis, as the extent to which cannabis may mitigate the adverse effects of METH is likely dependent upon the relative timing, dosage, and context in which these two drugs are consumed. Given that cannabis may function via a hormetic effect on the brain, with low doses showing beneficial effects while high doses show detrimental effects

(Fig. 8), it is critical to understand both the potential utility and risks of cannabis, and specific cannabinoids, in the treatment and control of chronic HIV disease and its neurologic complications.

Acknowledgments

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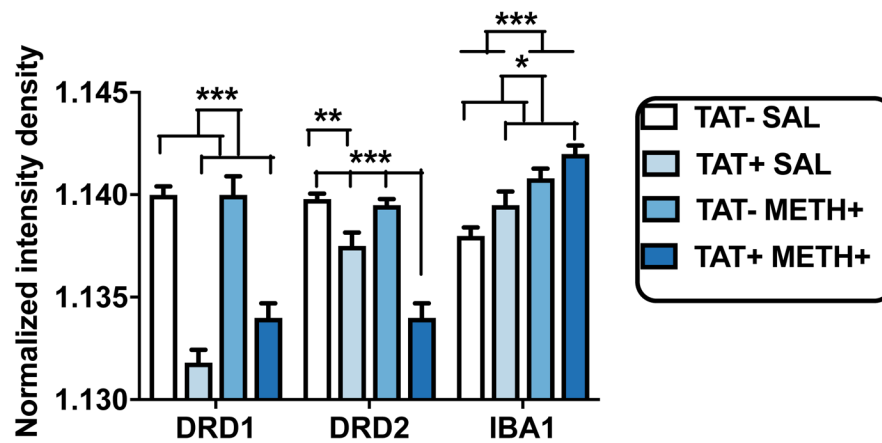
Fig. 1.
Caudate putamen dopamine receptors expression and IBA-1 expression in METH-exposed Tat-transgenic mice. Immunohistochemistry on paraffin embedded sections was utilized to examine the protein distribution and levels of dopamine receptor D1, dopamine receptor D2, as well as of IBA-1 in TAT– and TAT+ mice treated with either saline (SAL) or methamphetamine (METH+). Normalized intensity density data are expressed as mean ± standard error of the mean (n=5). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Adapted with permission from Kesby et al. (2017, *Brain Behavior and Immunity*)
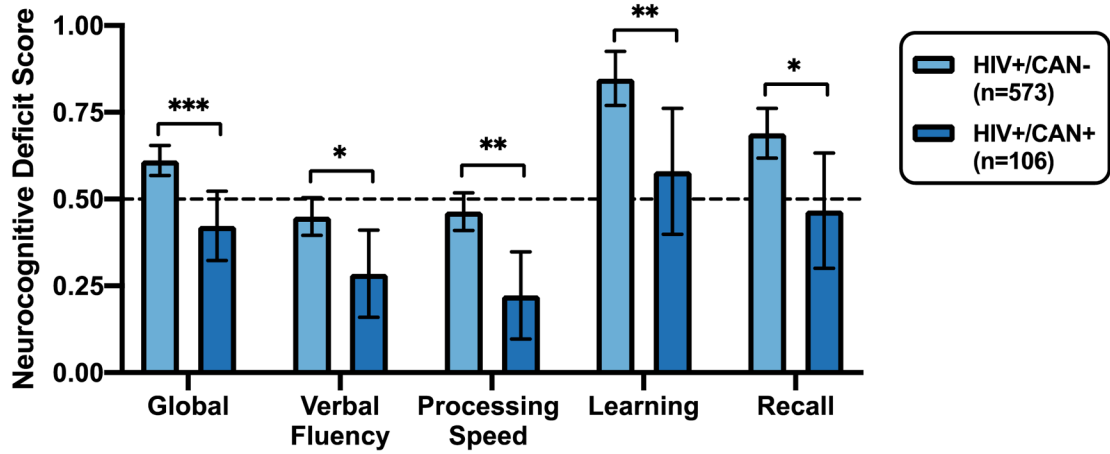
Fig. 2.
Cannabis use is associated with less neurocognitive dysfunction in HIV. Substantial past use with recent exposure cannabis exposure (CAN+) was defined as meeting criteria for a lifetime history of cannabis use disorder with self-reported use in the past year. The CAN− group did not have a history of substantial use (i.e., no lifetime cannabis use disorder and estimated lifetime average grams per day of use<1 gram) nor did they report use in the past year. Deficit scores (higher = worse) for global and domain-specific neurocognition were significantly higher in the HIV+/CAN− group compared to HIV+/CAN+ individuals (p range: .001 to .016). Clinically-relevant impairment is defined at a 0.5 deficit score cut-point. Data are expressed as mean ± standard error of the mean. *p< 0.05, **p< 0.01, ***p< 0.001. Data reanalyzed with permission from Watson et al. (2020)
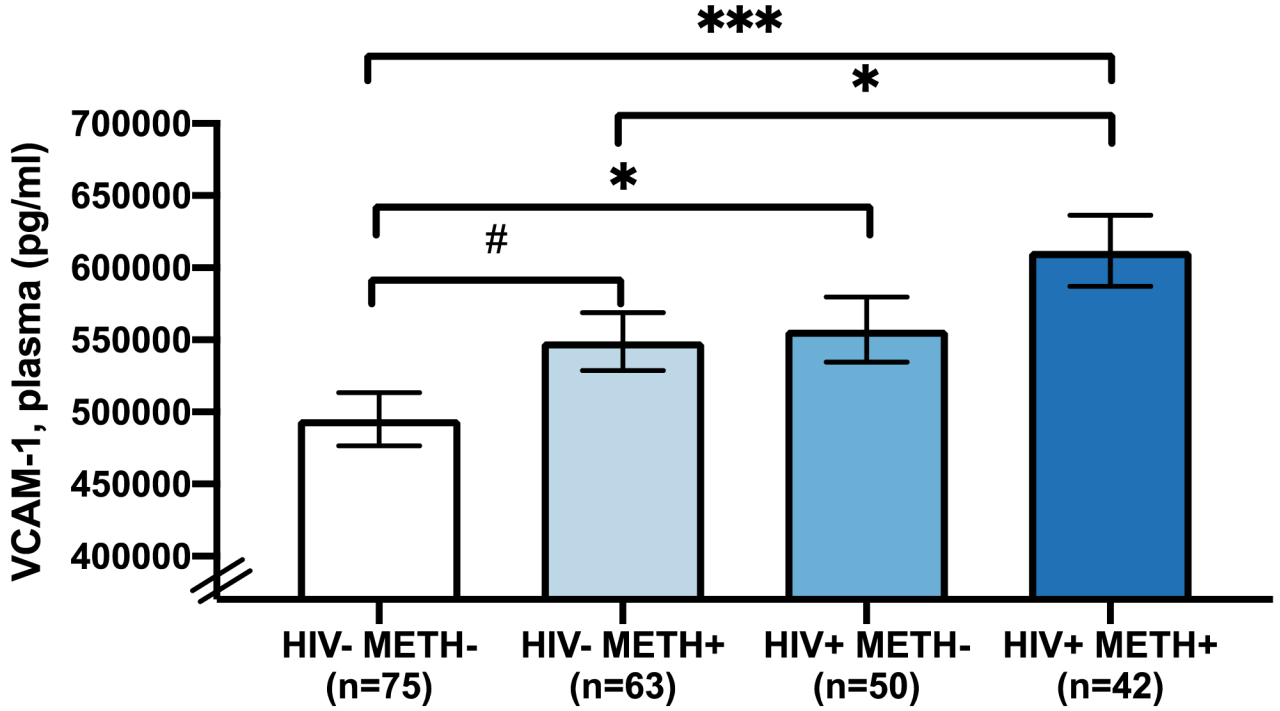
Fig. 3.
Preliminary data from the Translational Methamphetamine AIDS Research Cohort
(Iudicello et al., unpublished data). Regression analyses examining main and interactive
effects of HIV and METH as predictors of plasma vascular cellular adhesion molecule-1
(VCAM-1) levels revealed significant independent main effects of HIV (p=0.006) and
METH (p=0.026). Plasma VCAM-1 levels were highest in the dual-risk group (HIV+
METH+), followed by single-risk groups (HIV− METH+ and HIV+ METH+), and lowest in
the control group (HIV− METH−). Data are expressed as mean ± standard error of the mean.
#p< 0.10 *p< 0.05, ***p< 0.001
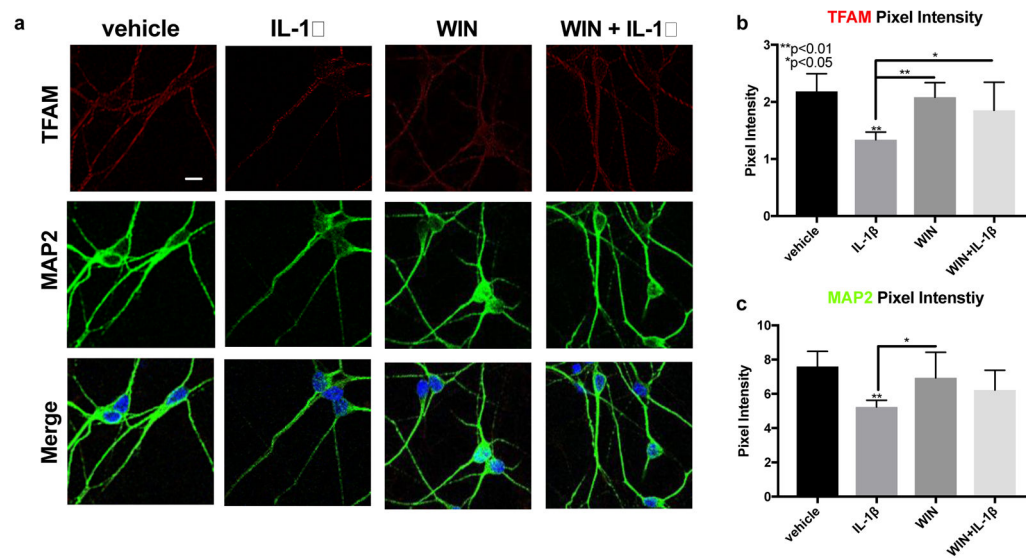
Fig. 4.

Cannabinoid (CB) receptor agonism blocks inflammation-induced toxicity in neuronal mitochondria. Similar to the effects of METH, conditioned media from immune-activated (IL-1b) astrocytes is toxic and reduces mitochondria biogenesis in neurons. In the left panels (a), the top row shows in red the mitochondrial transcription factor, TFAM (red). The middle row shows MAP2 (green) and the bottom row combines TFAM and MAP2. The panels on the right show TFAM (b) and MAP2 (c) are both decreased in cells treated with conditioned media from reactive astrocytes. However, a CB agonist blocks toxicity as TFAM and MAP2 levels are normalized in neurons that were exposed to conditioned media from astrocytes that were treated with a CB agonist. Hence, CB agonists may protect neurons from mitochondrial damage caused by HIV and METH induced inflammation in the brain. Adapted with permission from Swinton et al. (2019), *Neurobiology of Disease*
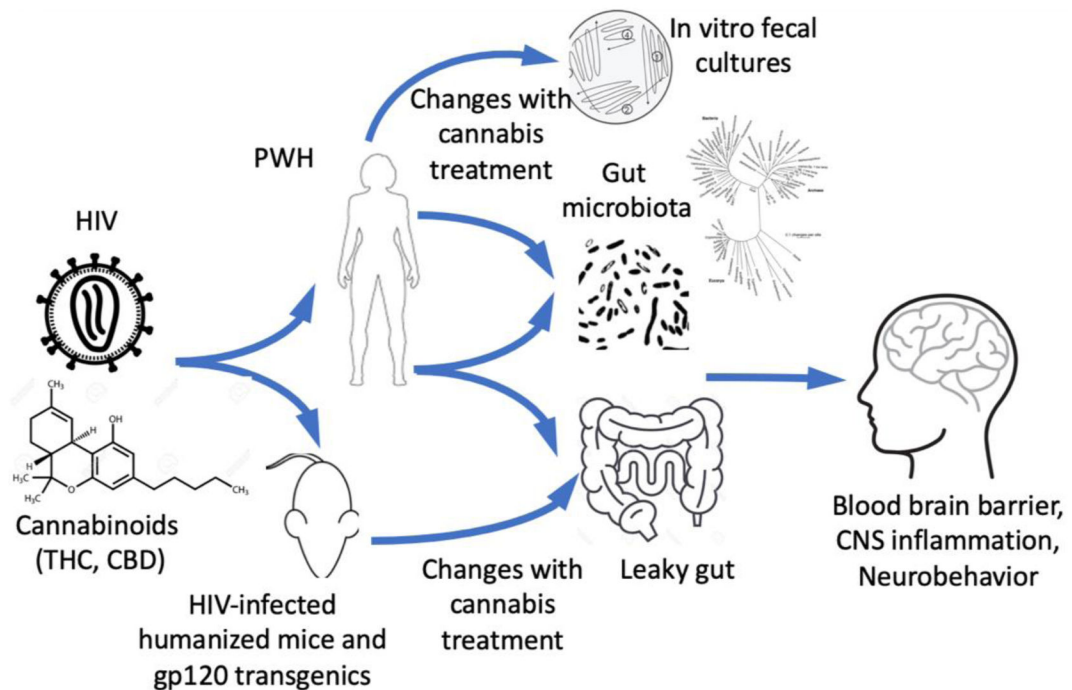
Fig. 5.
This diagram represents a translational approach to evaluating the effects of cannabis and HIV on the gut-brain-axis in five model systems: people with HIV (PWH) and HIV– humans, HIV-infected humanized mice, gp120 transgenic mice and in vitro fecal cultures. Cannabinoid treatment may normalize HIV-related gut dysbiosis and gut barrier permeability, which in turn may reduce systemic and CNS inflammation, restore blood-brain-barrier integrity, and improve neurocognition. Diagram provided courtesy of Ronald J. Ellis, M.D., Ph.D.
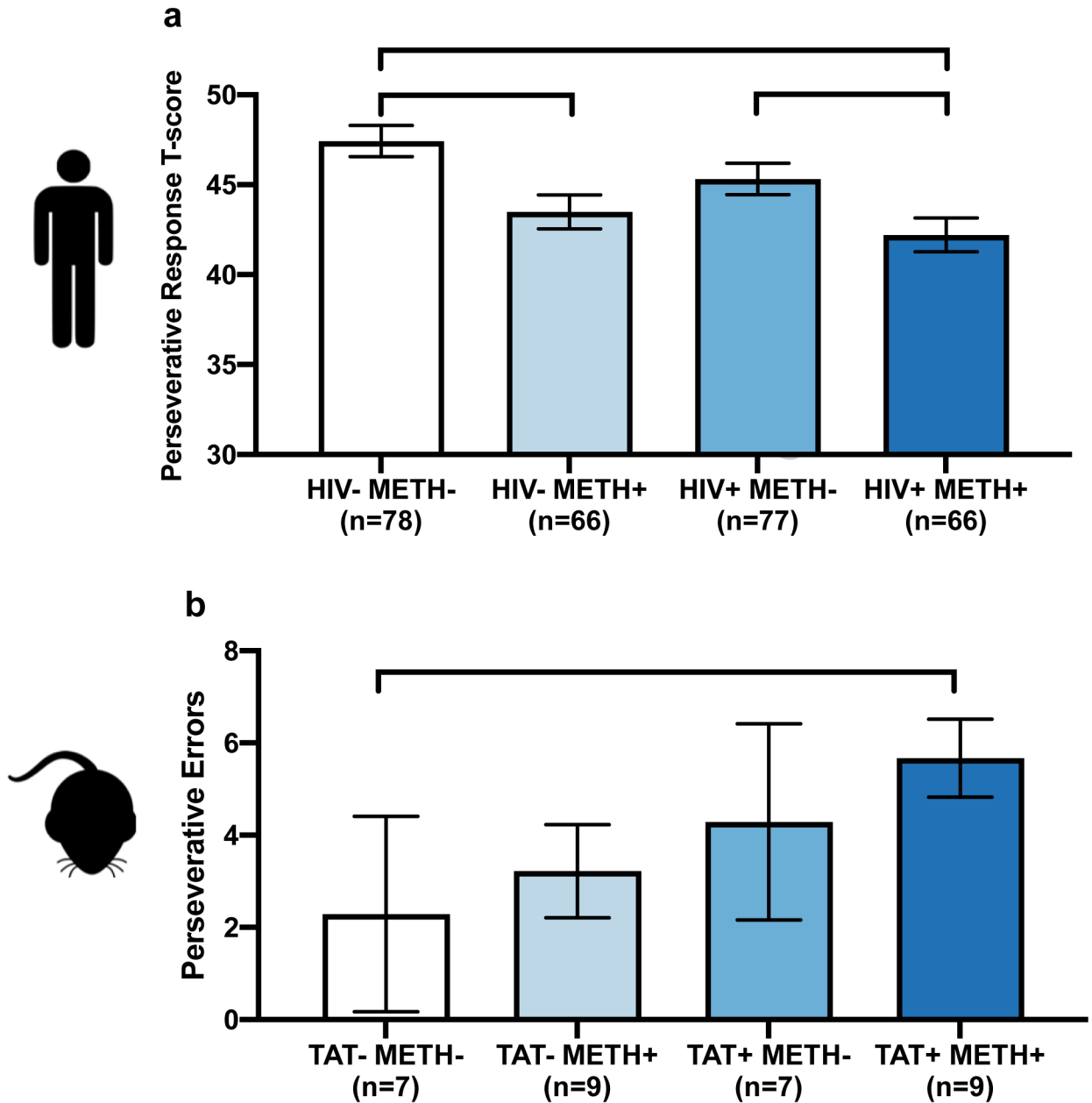
Fig. 6.
Translational evidence of executive dysfunction in HIV and METH. Perseveration was assessed using the Wisconsin Card Sorting Task (WCST) in humans and using a visual discrimination protocol with reversal learning in mice. (a) In the Translational Methamphetamine AIDS Research Center human cohort, demographically adjusted T-scores for perseverative responses on the WCST were significantly lower (signifying more perseveration) in METH-dependent participants within both HIV-serostatus groups. METH+ participants living with HIV (HIV+ METH+) also differed significantly from controls (HIV − METH−). (b) In mice, perseverative errors at the initial reversal of reward contingencies was significantly higher in TAT-transgenic mice exposed to METH (TAT+ METH+)

compared to the control group (TAT− METH−). Data are expressed as mean ± standard error of the mean. *p<0.05, **p<.005, ***p<.001. Mice data (b) adapted with permission from Kesby et al. (2018, *Behavioural Brain Research*)
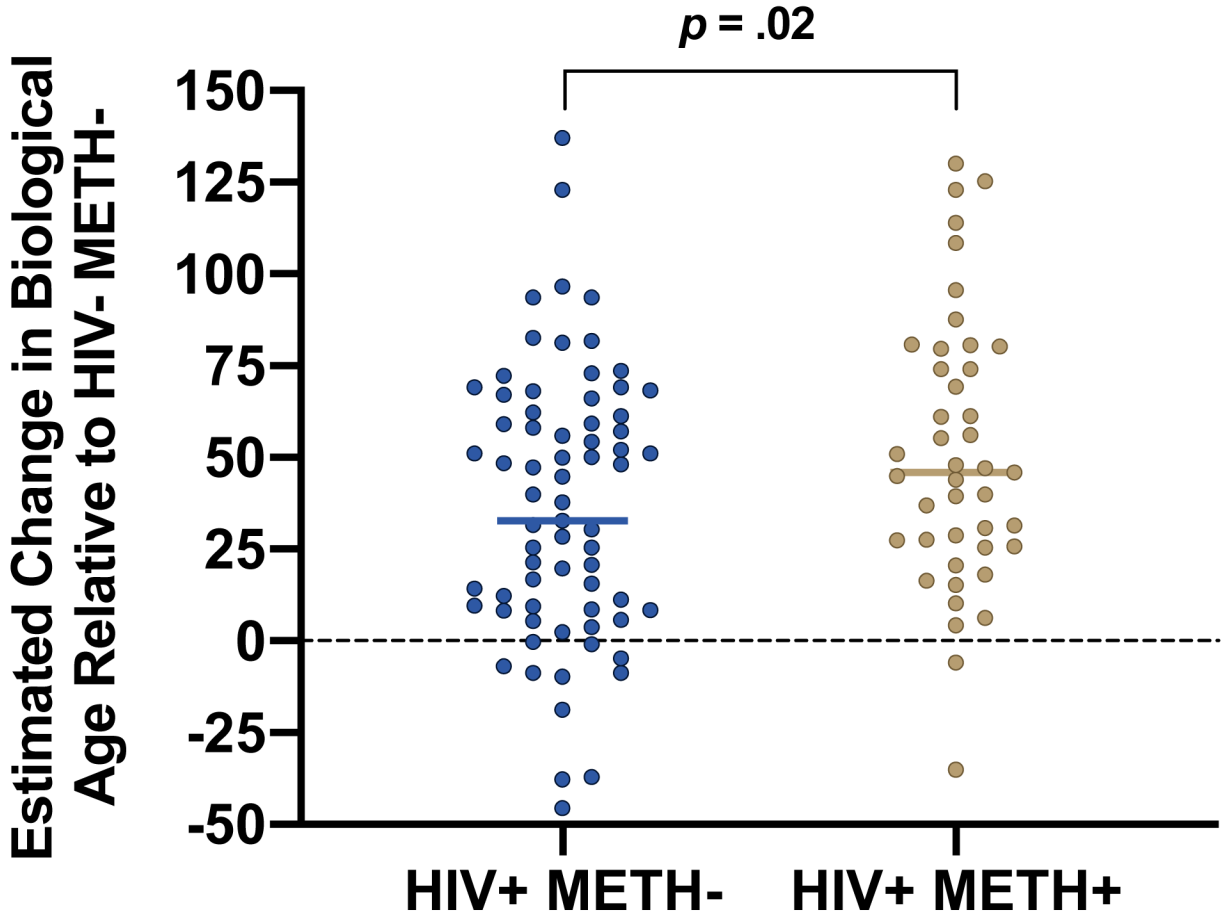
Fig. 7.
HIV and a lifetime history of METH use disorder relate to older biological age. The influence of HIV and lifetime METH use disorder on estimated biological age, based on frailty index scores, was calculated relative to the reference group (HIV−METH−). First, linear regression was employed to estimate the effect of age on frailty index values in the HIV−METH− reference group. Next, biological age was estimated by inserting frailty index scores from the HIV+/METH− and HIV+/METH+ groups into the regression equation for the reference group (HIV−METH−) and solving the equation for age. The resulting estimated biological age was subtracted from chronological age to yield the data in Figure 6. Despite comparable chronological age across groups (mean age: HIV−/METH− = 51.2 years, HIV+/METH− = 50.8 years, HIV+/METH+ = 50.0 years; p = .74), HIV and METH produced incremental increases in estimated biological age, with a median increase in biological age of 45.9 years in the HIV+METH+ group. Data reanalyzed with permission from Paolillo et al. (2019)
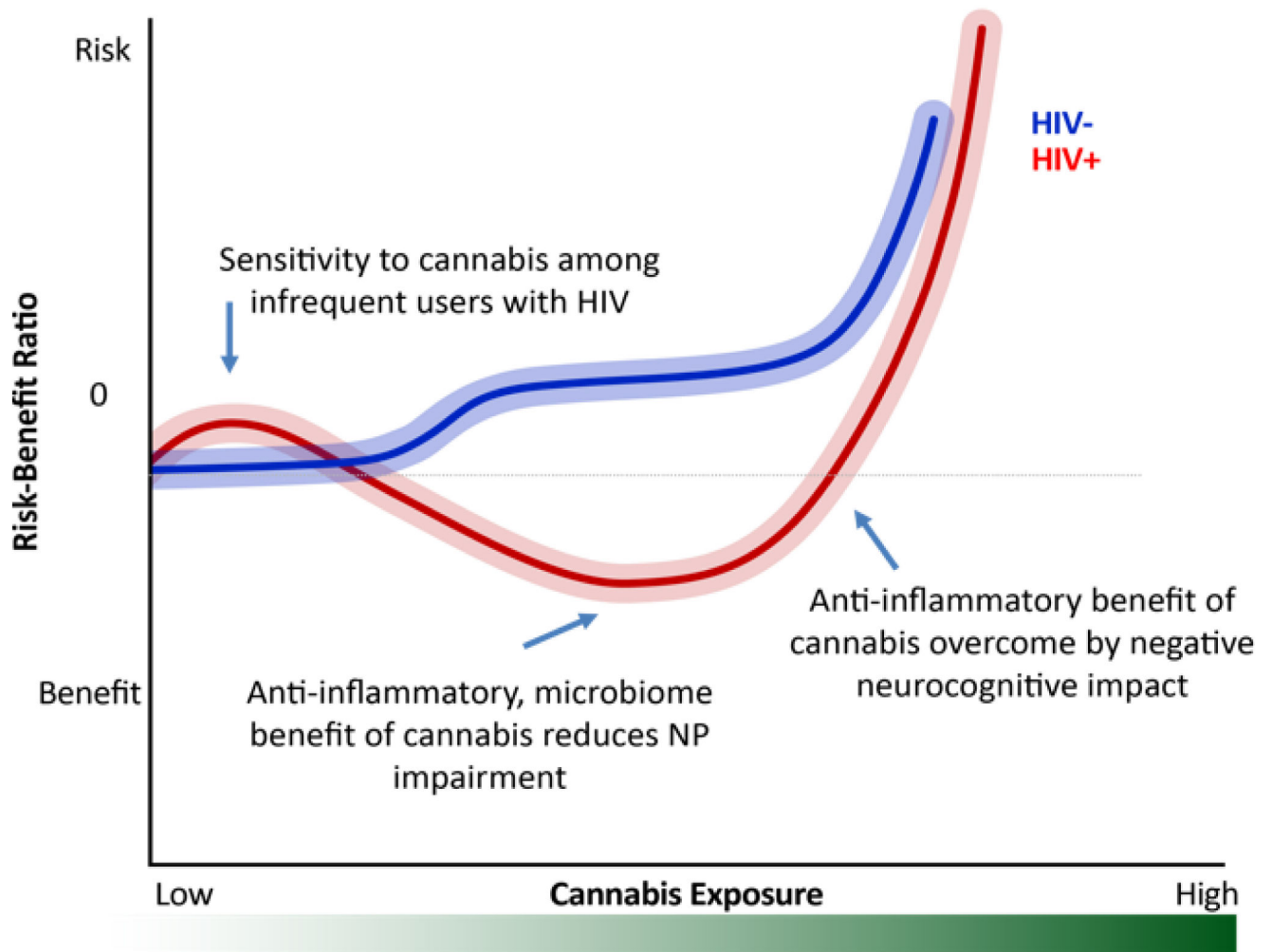
Fig. 8.
Hypothesized HIV group differences in the risk and benefit of cannabis exposure. The risk-benefit ratio of cannabis may differ between PWH (HIV+) and healthy adults (HIV−). In each instance, the risk-benefit ratio is conditioned on cannabis exposure, and in the case of PWH, severity of HIV disease. For HIV− adults, low cannabis exposure may confer little risk and little benefit (since there is no underlying disease process). As use in HIV− increases, risk increases (e.g., neurocognitive impairment [NCI]), which then flattens as tolerance develops. At high exposure, the tolerance is eclipsed by mounting toxicity. For PWH, cannabis's anti-inflammatory effects may dominate with moderate "steady state" exposure [mid-curve] and this may reduce the risk of NCI. This "benefit" would be most pronounced in those who acquire tolerance and maintain moderate use. Infrequent users, in whom the anti-inflammatory effects are intermittent, would experience more risk, because of greater vulnerability to the repeated, acute impairing effects of cannabis. At progressively higher cannabis exposure, mounting toxicity dominates the putative beneficial effects