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Advancing the Preclinical Study of Comorbid NeuroHIV and Substance Use Disorders: Current Perspectives and Future Directions

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Abstract

Human immunodeficiency virus (HIV) remains a persistent public health concern throughout the world. Substance use disorders (SUDs) are a common comorbidity that can worsen treatment outcomes for people living with HIV. The relationship between HIV infection and SUD outcomes is likely bidirectional, making clear interrogation of neurobehavioral outcomes challenging in clinical populations. Importantly, the mechanisms through which HIV and addictive drugs disrupt homeostatic immune and CNS function appear to be highly overlapping and synergistic within HIV-susceptible reward and motivation circuitry in the central nervous system. Decades of animal research have revealed invaluable insights into mechanisms underlying the pathophysiology SUDs and HIV, although translational studies examining comorbid SUDs and HIV are very limited due to the technical challenges of modeling HIV infection preclinically. In this review, we discuss preclinical animal models of HIV and highlight key pathophysiological characteristics of each model, with a particular emphasis on rodent models of HIV. We then review the implementation of these models in preclinical SUD research and identify key gaps in knowledge in the field. Finally, we discuss how cutting-edge behavioral neuroscience tools, which have revealed key insights into the neurobehavioral mechanisms of SUDs, can be applied to preclinical animal models of HIV to reveal potential, novel treatment avenues for comorbid HIV and SUDs. Here, we argue that future preclinical SUD research would benefit from incorporating comorbidities such as HIV into animal models and would facilitate the discovery of more refined, subpopulation-specific mechanisms and effective SUD prevention and treatment targets.

Keywords

HIV; Addiction; Preclinical models; Comorbidity; Techniques

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1. Introduction

Substance use disorders (SUDs) are chronic conditions characterized by enduring impairments in the control of motivated behavior that are often comorbid with other physical or neuropsychiatric disorders and diseases. Rates of human immunodeficiency virus (HIV) infection are much higher among individuals with SUDs compared to the general population, and SUDs are known to complicate HIV treatment efforts (Hartzler et al., 2017). For example, substance misuse is associated with reduced healthcare utilization and antiretroviral therapy (ART) adherence and with poor viral load management among people living with HIV (PLWH; Durvasula & Miller, 2014). Importantly, addictive substances may also impair ART efficacy through direct drug-drug interactions, which can contribute to less successful HIV treatment outcomes (Rasbach et al., 2013; Kumar et al., 2015). While PLWH can live long, relatively healthy lives with ART, many individuals who achieve viral suppression still develop HIV-associated neurocognitive disorder (HAND). Affecting nearly half of all PLWH (Heaton et al., 2010; Simioni et al., 2010), HAND is characterized by a spectrum of cognitive dysfunction, ranging from asymptomatic neurocognitive impairment to HIV-associated dementia (Clifford and Ances, 2013), although the vast majority of HAND cases in the current ART era are asymptomatic and only identified via cognitive testing (Vastag et al., 2022). HIV may also exacerbate drug-induced cognitive dysfunction and age-related cognitive decline (Becker et al., 2004; Valcour et al., 2004a; Norman et al., 2009; Alford and Vera, 2018), which complicates long-term health outcomes for individuals living with SUDs. These concerning realities highlight the need for targeted therapeutics to treat SUDs in PLWH. The preclinical application of translational animal models is vital towards this goal.

Since the late 1980s, research has indicated that use of addictive drugs is inextricably linked to increased HIV risk (Weiss, 1989), which is most commonly due to increased risk-taking behaviors such as needle sharing and unprotected sex. Preclinical animal models have been instrumental towards improving our understanding of the neurobiological and behavioral sequelae of comorbid HIV and SUDs. We discuss several prominent animal models of HIV and describe key findings that characterize the pathophysiological milieu of these models. We then highlight key preclinical findings across numerous animal models of comorbid HIV and SUDs and identify lingering gaps in the literature that require further research. Finally, we provide selected examples of modern, cutting-edge behavioral neuroscience tools within these preclinical models of HIV and SUDs that we expect to advance our knowledge of the neurobiological and behavioral intersections of comorbid HIV and SUDs. As highlighted in Table 1, HIV animal models come with unique caveats that ultimately constrain the interpretations and extrapolations one can generate from these models. Nevertheless, we broadly argue that future medications development efforts to address SUDs must consider comorbidities such as HIV to improve treatment outcomes and that next-generation neuroscience tools will aid in revealing novel therapeutic targets.

2. Animal Models of NeuroHIV

A broad spectrum of rodent and non-human primate (NHP) animal models has been developed to understand the pathophysiology of HIV and its impact on central nervous

system (CNS) function. Models ranging from exogenous HIV-1 protein exposure to HIV-1 transgenic rodents and HIV-like viral infections in NHPs have provided crucial insights into the neurocognitive and behavioral outcomes of HIV, many of which parallel clinical observations of cognitive and behavioral impairments among PLWH (Jaeger and Nath, 2012; Clifford and Ances, 2013; Moran et al., 2014; Mallard and Williams, 2018). Importantly, research from animal models of neuroHIV indicates that mesocorticolimbic reward circuits are particularly vulnerable to HIV and its protein products. Further, convergent research indicates that HIV interacts additively or synergistically with addictive drugs to promote reward system and neuroimmune dysfunction and neurocognitive impairment.

HIV enters the CNS predominantly via infected monocytes and T cells, where it establishes a productive infection within microglia (Figure 1). Within the periphery and the brain parenchyma, HIV-induced dysregulation of immune signaling, such as through upregulation or suppression of various cytokines and chemokines, can disrupt homeostatic neuronal function, leading to impaired cognition and behavior. PLWH exhibit a persistent viral reservoir within the CNS that contributes to neuroHIV and HAND. This persistence of chronic, low-levels of HIV protein within the CNS may contribute to HIV-associated neuroimmune, cognitive, and behavioral dysfunction. Preclinical animal models each capture a unique set of key pathophysiological features of neuroHIV and HAND and vary in key immunological characteristics captured in the model, each with distinct advantages and disadvantages (Table 1).

2.1. Exogenous HIV Protein Exposure

One *in vivo* methodology to study the neurobiological and behavioral sequelae of neuroHIV is the administration of HIV proteins, such as envelope glycoprotein 120 (gp120) and trans-activator of transcription (Tat), directly into the CNS. Both systemic and neuroanatomically discrete administration of HIV proteins have been examined across numerous studies. Early *in vitro* studies provided clear evidence of HIV protein-induced neurotoxicity (Lipton, 1991; Sabatier et al., 1991; Müller et al., 1992; Bennett et al., 1995; Weeks et al., 1995; Yeung et al., 1995; Nath et al., 1996), which served as the foundation for *in vivo* experiments in rodents probing the neurotoxic effects of HIV protein exposure within mesocorticolimbic reward circuitry. One of the first studies to examine HIV protein neurotoxicity *in vivo* found that microinfusions of the basic domain of the Tat peptide into the brain – including administration to the lateral ventricles, hippocampus, or thalamus - of mice produced neuroinflammation and reactive astrogliosis. These deficits were attenuated by pharmacological inhibition of the proinflammatory cytokine tumor necrosis factor alpha (TNFα) (Philippon et al., 1994), implicating proinflammatory signaling as critical mediator of Tat-induced CNS dysfunction (Rappaport et al., 1999).

Intracerebroventricular (i.c.v.) administration of HIV-1 Tat in rats is also associated with increased astrocytosis and peripheral immune cell infiltration into the parenchyma (Jones et al., 1998), suggesting impaired blood brain barrier (BBB) permeability induced by HIV protein exposure. In addition to Tat effects on the BBB, HIV-1 gp120 administration into the dorsal striatum of rats enhances the activation of extracellular matrix metalloproteinase 2

(MMP-2) and MMP-9 and downregulates essential proteins for regulation of BBB integrity – laminin and claudin-5 –, which is consistent with impaired BBB integrity (Louboutin et al., 2010). Interestingly, striatal MMP-2 and MMP-9 activity have been implicated in drug-seeking behavior (Smith et al., 2014; Namba et al., 2022), while changes in claudin-5 expression and reduced BBB integrity are associated with depression-like behaviors (Menard et al., 2017). Other studies show that mice exposed to Tat exhibit increased neuroinflammation within the CNS and depression-like behavior (Pu et al., 2003; Lawson et al., 2011). Viral vector-mediated overexpression of antioxidants such as glutathione peroxidase and Cu/Zn superoxide dismutase can attenuate HIV protein-induced oxidative stress (Louboutin et al., 2010; Agrawal et al., 2012). Taken together, these studies provide clear evidence of neuroinflammatory and neurotoxic consequences of direct administration of HIV proteins into the CNS, and further studies have demonstrated mesocorticolimbic circuit dysfunction following HIV protein exposure.

Exogenous HIV protein administration into the CNS elicits neurodegenerative and neurotoxic effects on dopamine neurons (Nath et al., 2016; Gaskill et al., 2017). For example, direct administration of HIV-1 Tat into the rat striatum – a primary target of midbrain dopamine projections – reduced tyrosine hydroxylase (TH) staining within dopamine cell bodies in the substantia nigra (SN) and caused Parkinson's-like locomotor deficits, thus implicating dopamine projection neurons as vulnerable to HIV protein exposure (Zauli et al., 2000). Microinfusions of Tat or gp120 within the rat striatum increased cell death, induced reactive astrogliosis, and enhanced oxidative stress (Bansal et al., 2000; Aksenov et al., 2001, 2003). Further investigation into the mechanism by which HIV proteins induce these neurotoxic effects revealed supporting evidence of retrograde neurodegeneration of dopamine neurons induced by intra-striatal gp120 administration (Nosheny et al., 2006), an effect that is attenuated by viral vector-mediated overexpression of brain-derived neurotrophic factor (BDNF; Mocchetti et al., 2007). In support of the hypothesis that dopamine neurons are particularly vulnerable to the neurotoxic effects of HIV, dopamine neurons of rats exposed to intra-striatal gp120 exhibit more rapid degeneration, and at lower gp120 doses, than non-dopamine neurons. These effects were prevented by viral-vector mediated overexpression of antioxidant enzymes (Agrawal et al., 2010). Altogether, these studies highlight the complex neuroinflammatory and neurotoxic effects of HIV protein exposure within the CNS and implicate mesocorticolimbic reward circuitry as particularly vulnerable to HIV infection.

One primary advantage of the protein exposure models is their spatiotemporal precision. Specifically, these models allow investigators to expose discrete brain regions to HIV proteins, at specific doses and experimental timepoints of interest, which can be particularly useful when assessing the interactions between HIV and addictive substances on cognition and behavior. However, there is a paucity of studies that directly compare the impact of systemic (e.g., i.c.v.) versus neuroanatomically specific administration of HIV proteins on neurotoxicity, neuroinflammation, and impairments in neuronal physiology and behavior, which is particularly important given the potential for local exposure to HIV proteins to have broad neuroinflammatory effects. Another distinct advantage of these models, which complements their spatiotemporal precision, is that they allow isolation of HIV-associated pathophysiological processes to one or more specific HIV proteins. One key limitation of

these protein exposure approaches is that they are generally limited to acute or subchronic exposure periods and to only one or two viral proteins, which does not necessarily reflect the chronic, persistent exposure to multiple HIV proteins that occurs in PLWH. The doses used in many studies are also often much higher than the expected concentration of HIV protein within the CNS of PLWH, and the distribution of viral protein throughout the CNS may not reflect what is observed in humans. Further, there is no progressive viral infection and replication, which limits the translational extrapolations one can draw from these protein exposure studies. As described below, other animal models have been developed to address these caveats.

2.2. SIV-infected Non-Human Primates (NHPs)

Immunodeficiency in captive macaque monkeys that resembled human acquired immunodeficiency syndrome (AIDS) was first reported in 1983 by Letvin and colleagues (Letvin et al., 1983), and the cause of this condition was eventually identified as Simian Immunodeficiency Virus (SIV; Bailes et al., 2003; Gao et al., 1999; Peeters et al., 1989). HIV-1 is closely related to SIVcpz, which infects chimpanzees of West-Central Africa and is believed to be the origin of the HIV-1 group ‘M’ that comprises the majority of HIV-1 infections in humans (Simon et al., 1998; Nerrienet et al., 2005). Similarly, HIV-2 is closely related to SIVsmm, which infects sooty mangabeys (Lemey et al., 2003). Infecting macaques with HIV-1 is difficult due to cellular proteins found in macaques that restrict HIV-1 replication (Stremlau et al., 2004; Misra et al., 2013). Today, many NHP models of HIV infection utilize rhesus macaques infected with various strains of SIVmac, which recapitulates many immunological and serological features of HIV-1 infection in humans (Garcia-Tellez et al., 2016). Considered the ‘gold-standard’ animal model of HIV infection in humans (Mallard and Williams, 2018), SIV-infected NHPs have been crucial to our understanding of the pathophysiology of neuroHIV.

Akin to HIV protein administration into the CNS of rodents, SIV infection in NHPs produces profound neuroimmune dysfunction. Early work investigating neuroinvasion of SIV in rhesus monkeys found that SIV facilitates macrophage infiltration into the brain parenchyma as early as 7 days post-inoculation, which coincides with enhanced microglial activation and neurovascular injury (Chakrabarti et al., 1991). More recently, studies have utilized CD4 or CD8 T lymphocyte depletion to enhance viral replication in macrophages, neuroinvasion of infected monocytes/macrophages into the brain parenchyma, and tropism for microglia. For example, depletion of CD8 lymphocytes and infection with the viral swarm SIVmac251 results in rapid onset of AIDS and a higher rate of SIV encephalitis (Williams et al., 2005). Similarly, CD4 lymphocyte depletion prior to SIV infection also results in enhanced viral replication and progression to AIDS as well as increased microglial infection (Micci et al., 2014). Circulating cytokine and chemokine levels within the CNS and the periphery of SIV-infected macaques are also dysregulated (Keating et al., 2012). Acute infection with SIVmac251 results in a transient upregulation of IL-1β, IL-6, IL-10, and TNFα mRNA expression in peripheral blood mononuclear cells (PBMCs), which may produce early disruptions to BBB integrity and contribute to early CNS infection (Benveniste et al., 1996). A recent study demonstrated that SIVmac251 infection upregulates CCL2, IL-6, CXCL10, and IFNγ levels within the cerebrospinal fluid, and ART treatment

only significantly attenuates the increase in CXCL10 (Solis-Leal et al., 2022). Consistent with these findings, ART treatment does not completely resolve HIV-induced dysregulations to peripheral cytokine expression in PLWH (Keating et al., 2011), which may be a mechanism underlying the persistence of HIV within the CNS as well as HAND in the ART era. These studies collectively highlight the importance of peripheral immune cell activity and CNS neuroimmune signaling as key mechanisms that mediate HIV-induced neuropathogenesis.

SIV-infected rhesus macaques also exhibit both motor and cognitive deficits that are not specifically related to the extent and anatomical location of virus-induced lesions within the brain (Murray et al., 1992). Moreover, reactive astrogliosis in SIV-infected macaques is associated with the onset and progression of neuropsychological impairments regardless of immunodeficiency syndrome (Rausch et al., 1994). A time-dependent increase in reactive astrogliosis and synaptic impairments was observed within the frontal cortex of SIV-infected macaques, which is a likely mechanism mediating the cognitive deficits observed in the previous studies (González et al., 2000). Another early study demonstrated that SIVmac251-infected macaques exhibit dendritic spine loss as early as 2.5–3 months post-infection (Montgomery et al., 1999), suggesting that early CNS infection may impair cortical synapses and promote cognitive dysfunction. These studies provided early evidence for the hypothesis that SIV and HIV can rapidly invade the CNS and elicit significant neurological, cognitive, and behavioral deficits through more global CNS dysregulation irrespective of virus-induced neurotoxicity or disease severity. These findings also suggest that high concentrations of HIV protein within a discrete brain region may not be necessary to produce impairments within that region, which helps inform lingering gaps in the literature regarding the differences between local versus systemic exposure to exogenous HIV protein. As SIV-infected macaques treated with ART still have detectable SIV *env* DNA within the basal ganglia and brain stem, CNS viral reservoirs may persist within the mesocorticolimbic system even with ART treatment (Perez et al., 2018). The chronic, low-level HIV proteins secreted by these viral reservoirs may contribute to global CNS dysregulation. This has significant implications for the present-day clinical landscape of neuroHIV in humans, where chronic neuroinflammation and CNS reservoirs of HIV can persist despite undetectable viral loads in the periphery (Heaton et al., 2010; Sari et al., 2022).

Beyond the direct contribution to our understanding of the preclinical landscape of neuroHIV and SUDs, many studies using the SIV model to study HAND have revealed important insights into HIV-induced neurocognitive dysfunction that could have important implications for the study of comorbid HIV and SUDs. Early studies in NHPs demonstrated that SIV infection in rhesus macaques can produce psychomotor impairments (e.g., slower choice reaction times and forelimb movement) as well as cognitive and behavioral dysfunction that includes impaired discrimination learning, memory retention, attention, and motivation (Murray et al., 1992; Gold et al., 1998; Marcario et al., 1999; Weed et al., 2003). These SIV-induced behavioral impairments do not appear to be dependent on discrete virus-induced lesions within the brain (Murray et al., 1992). Indeed, neuroimmune activation and subsequent neuronal dysfunction may underlie these psychomotor and cognitive impairments. For example, one study demonstrated a significant correlation

between psychomotor impairments in SIV-infected macaques and associated axonal damage, microglial activation, and peripheral macrophage infiltration (Weed et al., 2003). Exposure to addictive substances may exacerbate these neurobehavioral effects. For example, SIV-infected NHPs injected with methamphetamine exhibit increased CCR5 expression in the brain, which is correlated with viral load, and methamphetamine exposure also increases the proportion of microglia infected by SIV within the CNS (Najera et al., 2016; Niu et al., 2020). Opioids such as morphine may also augment the pathophysiology of SIV infection and enhance virus-induced neurocognitive deficits (Reddy et al., 2012; Marcario et al., 2016; Acharya et al., 2021). However, these effects likely depend on drug type, duration of drug exposure, and withdrawal (Molina et al., 2011; Weed et al., 2012; Wang et al., 2019b). Nevertheless, most studies probing the interactions between SIV infection and addictive substances utilize experimenter-delivered methods of drug exposure, which does not model how humans consume drugs. Drug self-administration models (Section 3) will advance study of the impact of drug use on HAND-like cognitive impairment in the SIV model, although there are additional limitations to consider here (Table 1).

Like rodents exposed to exogenous administration of HIV proteins within the CNS, SIV-infected NHPs display impairments in mesocorticolimbic monoamine transmission. SIV-infected macaques exhibit elevated levels of the dopamine metabolite 3,4-dihydroxy-phenylacetic acid (DOPAC) within the cerebrospinal fluid (CSF), which is also accompanied by a progressive, time-dependent increase in serotonin metabolites within 8 months from initial infection (Koutsilieri et al., 1997). While administration of selegiline (a monoamine oxidase inhibitor that increases CNS dopamine availability) or levodopa (L-DOPA) to SIV-infected macaques restored SIV-induced dopamine deficiency, it also worsened CNS viral replication and SIV-induced neuropathology (Czub et al., 2001). Both selegiline and L-DOPA also potentiate proinflammatory TNFα mRNA expression across the mesocorticolimbic reward system in SIV-infected macaques (Czub et al., 2004, although see Emanuel et al., 2022). Reduced dopamine levels within the striatum of SIV-infected macaques correlate with increased microglial activation (Scheller et al., 2005), and treatment with minocycline – which blocks microglial activation - can ameliorate this striatal dopamine decline (Meulendyke et al., 2012). This perhaps suggests that aberrant microglial activation promotes mesolimbic dopamine deficiency and the potential for bidirectional interaction between neuroimmune and monoamine outcomes. However, one study observed dopamine deficiency within the nucleus accumbens (NAc) of asymptomatic, SIV-infected macaques prior to any HIV-induced neuropathology, indicating that impaired monoamine signaling may precede HIV-induced neuropathogenesis (Jenuwein et al., 2004). These studies collectively suggest that HIV-induced monoamine impairments could contribute to HIV-associated neuroinflammation and neurocognitive dysfunction and that dopamine-modulating drugs, such as addictive drugs, may exacerbate these processes. Akin to findings from exogenous HIV protein models described above, these systems represent common mechanisms of HIV-induced pathology within the CNS that could be effective treatment targets. Despite the tremendous advancements produced by SIV-infected NHP models of HIV, work with NHPs comes with certain limitations that include low sample sizes as well as ethical and regulatory concerns (J. D. Estes et al., 2018; Table 1). Moreover, another limitation of NHP models is that there are generally fewer validated tools, compared

to rodent models, that can precisely elucidate molecular, cellular, and circuit-specific mechanisms that mediate neurobehavioral impairments produced by combined HIV and drug use. The advent of sophisticated transgenic rodent models and chimeric HIV viruses that infect murine cells have greatly facilitated the investigation of the neural underpinnings of comorbid HIV and SUDs.

2.3. Transgenic Mice

Several transgenic (Tg) mouse models that express HIV-1 proteins, either constitutively or conditionally, have been utilized to model some aspects of the pathophysiology produced by HIV-1 infection within the CNS. One such model is the HIV-1 gp120 Tg mouse, which constitutively expresses gp120 in astrocytes under the control of the glial fibrillary acidic protein (GFAP) promoter. First described by Toggas et al., these mice exhibit cortical neurodegeneration, dendritic vacuolization and synapse loss, astrogliosis, and microglial activation across the brain (Toggas et al., 1994; Kang et al., 2010; Maung et al., 2014; Thaney et al., 2017, 2018). These mice also exhibit impaired long-term potentiation (LTP) within the CA1 region of the hippocampus, which likely contributes to spatial working memory deficits seen in these mice (Krucker et al., 1998; Hoefer et al., 2015). As in SIV-infected NHP and exogenous protein models, HIV-1 gp120 Tg mice also exhibit enhanced BBB permeability (Toneatto et al., 1999; Cioni and Annunziata, 2002; Strazza et al., 2011), suggesting that chronic gp120 exposure may facilitate HIV-1 neuroinvasion. A recent *in vivo* PET imaging study revealed an increase in translocator protein (TSPO) binding, which is indicative of microglial activation in mice, in multiple neural substrates (the striatum, hypothalamus, ventral tegmental area (VTA), and hippocampus) of Tg mice in response to lipopolysaccharide (LPS) exposure, suggesting a hypersensitive response to inflammatory stimuli within the mesocorticolimbic reward system of these mice (Young et al., 2022). Indeed, this has significant implications for SUDs, where PLWH may experience greater neuroinflammation and subsequent neurocognitive impairment due to the proinflammatory effects of many addictive drugs (Cui et al., 2014; Namba et al., 2021).

One disadvantage of the constitutive HIV-1 gp120 Tg mouse model is the lack of temporal control over CNS exposure to HIV proteins. To overcome this barrier, a conditional Tg mouse line that expresses HIV-1 Tat in GFAP+ cells upon doxycycline (i.e., a tetracycline antibiotic) exposure was developed. This mouse model produces Tat protein in astrocytes in a doxycycline-dependent manner that can be released to directly interact with neurons (for review, see Langford et al., 2018). This results in cortical atrophy, astrocytosis, dendritic degeneration, neuronal apoptosis, and infiltration of peripheral monocytes and T lymphocytes into the brain parenchyma (Kim et al., 2003a). These mice also exhibit corticostriatal neuroinflammation, increased BBB permeability, and increased striatal and hippocampal microglial activity (Kim et al., 2003a; Fitting et al., 2010; Leibrand et al., 2017). In addition to immune dysregulation, HIV-1 Tat Tg mice have altered dopamine transmission within the PFC and striatum. For example, Tat induction in these mice increases phasic dopamine release within the dorsal striatum through dopamine transporter (DAT) inhibition and stimulation of synaptic release of dopamine (Davis et al., 2023). Another study demonstrated that within the PFC, Tat induction reduces DAT-mediated dopamine reuptake and concomitantly inhibits action potential firing among layer V

prelimbic cortex pyramidal neurons (Strauss et al., 2020). In contrast, another study showed increased action potential firing in layers II/III of the mPFC and decreased firing within the CA1 region of the hippocampus (Cirino et al., 2020). Given the significant immunomodulatory role of dopamine (Gaskill et al., 2017; Nolan and Gaskill, 2019; Xia et al., 2019), this dysregulation of dopamine homeostasis within the reward system could further impair neuroimmune signaling, thus contributing to Tat-induced neuropathology. However, as these studies highlight, it is possible that Tat-mediated dopamine impairments and subsequent dysfunction of neuronal activity could be brain region-specific.

While this model provides experimenters with greater temporal specificity over HIV protein expression, the expression of Tat in astrocytes represents a limitation of this model given that HIV primarily infects microglia in the CNS. Moreover, these tetracycline-inducible transgene expression systems are “leaky” and can produce chronic, low-level protein HIV-1 protein expression even in the absence of doxycycline (Fitting et al., 2010). Depending on perspective and experimental question, this could be viewed as either an advantage or disadvantage. On the one hand, uncontrolled expression of Tat detracts from the temporal control feature of this model. However, this may better model the chronic, low-level HIV protein exposure that occurs with neuroHIV among virally-suppressed individuals. In support of this, a recent study demonstrated that mice chronically exposed to low-level Tat (in the absence of doxycycline treatment) exhibit decreased cortical expression of the synaptic markers synaptophysin and PSD95 as well as increased hippocampal astrocytosis and neuroinflammation (Dickens et al., 2017). Constitutive, systemic expression of Tat in Tg mice is associated with an increase in evoked cortical glutamate release and a concomitant decrease in GABA release (Zucchini et al., 2013), suggesting that mice chronically exposed to HIV-1 Tat may exhibit impairments in cortical excitatory neurotransmission, which has important implications for the pathophysiology of SUDs (Kalivas, 2009; Koob and Volkow, 2016). It is important to note that doxycycline treatment is typically administered for shorter time periods (e.g., about one week) via i.p. injections or for longer periods (e.g., several weeks) orally via doxycycline-containing chow, and these different methods of administration can produce differential effects on neuropathology and behavior. Specifically, anxiety-like behavior, motor function, as well as spatial memory and reversal learning exhibit differential profiles of impairment between these two exposure paradigms (Joshi et al., 2020). Moreover, the neuropathology produced in the brain, such as gliosis, dysregulation of neuroimmune signaling, and impaired neurotransmission, differs between i.p. doxycycline-treated mice compared to doxycycline chow-fed mice (Kim et al., 2003b; Bruce-Keller et al., 2008; Fitting et al., 2010; Carey et al., 2012, 2013; Miller et al., 2018), emphasizing the need to consider the duration and route of doxycycline administration in inducible Tg models.

One limitation of the HIV Tg mouse models discussed above is the lack of chronic, systemic expression of multiple HIV proteins. This is resolved in the HIV-1 Tg26 mouse model, where a replication-incompetent HIV-1 provirus lacking *gag* and *pol* expresses the other seven HIV-1 genes (Dickie et al., 1991). These mice express high levels of HIV-1 transcripts *env*, *tat*, *rev*, *vif*, *vpr*, *vpu*, and *nef* in various tissues, such as skin, skeletal muscle, and brain. The homozygous Tg26 mice exhibit psoriasis-like skin lesions and progressive renal disease, while the heterozygous Tg26 mice have a longer lifespan and develop renal disease

later in life (Dickie et al., 1991; De et al., 1997; Rosenstiel et al., 2009). In particular, Tg26 mice backcrossed with the C57BL/6 strain exhibit longer lifespans with fewer health complications (e.g., minimal renal disease; Gharavi et al., 2004; Mallipattu et al., 2013; Zhong et al., 2005), making these mice a more reliable model for studying HAND. These Tg26 mice also exhibit lower levels of viral transcripts within the brain, perhaps resembling PLWH on ART, which contributes to the translational potential of this model (Putatunda et al., 2018). Furthermore, studies on Tg26 mice have revealed deficits in hippocampal dendritic morphology and sex-specific spatial learning impairments (Putatunda et al., 2018, 2019; Barbe et al., 2020). A recent study demonstrated increased neuroinflammation and astrogliosis within the hippocampus of Tg26 mice (Li et al., 2020), which could potentially contribute to these behavioral and synaptic impairments. These findings point to the potential value of future studies examining addiction-related behaviors within this model.

2.4. HIV-1 Transgenic Rat

Akin to HIV-1 Tg26 mice, the HIV-1 Tg rat constitutively and systemically expresses 7 of the 9 HIV proteins and exhibits many pathological features of HIV infection in humans (Reid et al., 2001; Vigorito et al., 2015). These rats were first reported to exhibit many clinical aspects of AIDS by 5–9 months of age, including cataracts, wasting, respiratory difficulty, neurological abnormalities, and skin lesions (Reid et al., 2001). However, later studies using Tg rats obtained from a commercial vendor observed these symptoms at 18 months or older (Moran et al., 2013; Vigorito et al., 2013). Akin to observations in humans, CD4+ and CD8+ cells from HIV-1 Tg rats exhibit increased susceptibility to activation-induced apoptosis and diminished capacity to generate IFNγ following activation (Reid et al., 2004). Upon exposure to an inflammatory stimulus such as LPS, HIV-1 Tg rats also exhibit an exaggerated cytokine and chemokine response within the spleen and brain compared to controls, suggesting that non-replicative HIV-1 provirus expression in these rats may prime the immune system to produce dysregulated responses to future insults (Homji et al., 2012a). These rats also exhibit a decline in T cells beginning by around 6 months, which is exacerbated with advanced age alongside increased expression of proinflammatory factors such as IL-6 and TNFα (Abbondanzo and Chang, 2014). Overall, the immune system changes that occur over the lifespan of these rats mirrors, to an extent, what is observed in humans. However, the marked health decline of these animals with advanced age should be noted when designing studies with this model, particularly in the case of longitudinal studies and those pertaining to aging and HIV. Moreover, the constitutive expression of viral proteins in cell types not normally infected by HIV-1, which occurs in this model, represents a limitation that should be considered when interpreting findings from this model.

Neuropathology in the HIV-1 Tg rat consists of cortical neuroinflammation, reactive gliosis, neuronal cell loss, and increased BBB permeability and lymphocyte infiltration into the brain parenchyma (Reid et al., 2001; Royal et al., 2012). Within the striatum, HIV-1 Tg rats exhibit loss of TH expression that worsens with age, suggesting a time-dependent dysregulation of striatal dopamine neurotransmission (Reid et al., 2016). Importantly, these animals exhibit significant impairments in synaptic connectivity within the striatum, which includes profound alterations in the distribution of dendritic spine types on medium spiny neurons (MSNs; McLaurin et al., 2018). Specifically, HIV-1 Tg rats exhibit an

increase in thin and mushroom spines proximal to MSN somas and an increase in stubby spines on more distal dendritic branches, as well as sex-dependent morphological alterations in dendritic complexity and organization (McLaurin et al., 2018). Transcriptome sequencing of the prefrontal cortex (PFC), hippocampus, and striatum from HIV-1 Tg rats revealed significant alterations in immune response and neuronal survival pathways across all three brain regions (Li et al., 2013), which may contribute to enduring changes in mesocorticolimbic synaptic connectivity and dendritic spine morphology. Significant alterations in cytokine and chemokine expression are observed in the PFC, NAc, and VTA of HIV-1 Tg rats compared to controls as well as differential immune responses to nicotine treatment (Yang et al., 2016). Within the PFC specifically, these rats exhibit reduced dendritic spine density that is likely driven by gp120-induced upregulation of the proinflammatory cytokine IL-1β (Festa et al., 2015). More recently, it was demonstrated that HIV-1 Tg rats exhibit a decrease in thin spine density within the prelimbic cortex (PrL), which negatively correlated with trials to criterion in an attentional set-shifting task, and that CXCL12 signaling rescues these deficits (Festa et al., 2020). Notably, this reduction in PrL thin spine density contrasts with the increase in striatal thin spine density observed in McLaurin et al., 2018, suggesting important brain region-specific effects of HIV-1 protein exposure on dendritic spine morphology. Collectively, these findings critically underscore the impact of chronic HIV protein exposure on mesocorticolimbic circuit function, which has important implications for drug-seeking behavior.

2.5. EcoHIV Rodent Model of HIV-1 Infection

Achieving a productive HIV infection is difficult in rodents, as they are poorly susceptible to HIV (Sawada et al., 1998; Hinkula et al., 2004). While transgenic rodent models can produce aspects of later stages of infection, such as persistent HIV protein expression, a major goal of HIV animal model development has been achieving primary viral infection in rodents that mirrors the immunological and serological milieu observed in humans. HIV infection begins with cellular endocytosis of HIV through interactions between HIV Env (i.e., gp120 and gp40) and a host cell receptor complex composed of CD4 and co-receptors CXCR4 or CCR5 (Wilen et al., 2012). While rodent cells are capable of persistent production of infectious HIV-1 (Mizrachi et al., 1992; Keppler et al., 2001), the virus does not efficiently bind to rodent cells. This is the principal challenge in producing a rodent model of sustained HIV-1 infection. Previous attempts to resolve this issue by producing transgenic rodents that express human CD4, as well as CCR5 or CXCR4, showed limited capacity to produce persistent infection *in vivo* (Browning et al., 1997; Sawada et al., 1998). To overcome this difficulty, a chimeric HIV-1 viral construct, EcoHIV, was created by replacing the coding region of gp120 with the envelope-coding region of gp80 from ecotropic murine leukemia virus (MLV), permitting infection and viral replication in rodents (Potash et al., 2005). Potash and colleagues demonstrated that EcoHIV produces systemic infection in mice after a single inoculation and that viral mRNA is detected in CD4+ T cells, macrophages, and microglia, which are all major target cell types of HIV-1. EcoHIV mRNA and expression of the viral proteins Tat and p24 were also detected within the brain (Potash et al., 2005). EcoHIV infection in mice also increases BBB permeability through downregulation of claudin-5, which is also observed in the gp120 Tg mouse (Jones et al., 2016). Recent evidence suggests that microinfusion of EcoHIV into the rat brain produces a

detectable infection predominantly in Iba1+ cells, implicating microglia as the predominant cell type that harbors EcoHIV (Li et al., 2021b). As microglia are widely believed to be the primary HIV-1 reservoir within the CNS in humans (Wallet et al., 2019; López et al., 2021), this represents a critical translational advantage of the EcoHIV rodent model.

EcoHIV infection in the CNS induces neuroinflammation and parallel changes in neuronal morphology and synaptic function. Intracerebral infection of EcoHIV in the mouse brain induces synaptodendritic loss in the hippocampus, which is correlated with working memory impairment. This neuronal dysfunction is not associated with apoptosis (Kelschenbach et al., 2019) which mirrors findings in virally-suppressed PLWH who experience cognitive impairment with subtle neurodegeneration rather than cell loss or death (Heaton et al., 2010; Gelman, 2015). Neuronal morphology and synaptic function are also altered in EcoHIV-infected rats. For example, administration of EcoHIV into the rat cortex induces dendritic spine morphology dysfunction in NAc MSNs and medial PFC (mPFC) pyramidal neurons. Specifically, EcoHIV-infected rats show increased relative frequency of shorter dendritic spines, increased head diameter, and increased neck diameter (Li et al., 2021a, 2021b). These synaptic alterations are associated with upregulation of the expression of proinflammatory factors such as NF-κB, TNF-α, and IL-1β within the cortex (Potash et al., 2005; Li et al., 2021a). These neuronal dysfunctions in EcoHIV-rats are associated with deficits in temporal processing as well as long-term memory, which are considered aspects of HAND pathology.

One limitation of the EcoHIV model is that the virus lacks the HIV-1 Env protein gp120. As evidenced by the exogenous protein and transgenic models, HIV gp120 induces neuropathology and alters motivated behavior, including producing synaptodendritic damage. For example, intracerebral microinjection of gp120 in rats reduces spine density and causes dendritic damage in the PFC (Festa et al., 2015), and gp120 Tg mice exhibit dendritic spine deficits within the hippocampus and striatum (Bachis et al., 2016; Speidell et al., 2020). Reduced dendritic spine density within the PrL of HIV-1 Tg rats is correlated with impaired cognitive flexibility (Festa et al., 2020) and it is possible that gp120-induced synaptodendritic deficits contribute to alterations in reward circuit function. Taken together, the contribution of gp120 to HIV-related neurocognitive pathology should not be ignored. In the EcoHIV model, the potential role of gp80 within the mouse CNS has not been fully investigated. One study has reported that MLV (which contains the gp80 envelope protein) does not induce cognitive dysfunction akin to what is observed in EcoHIV-infected mice, indicating that gp80 may not model gp120-driven neuronal impairments within the CNS (Kelschenbach et al., 2019). Unlike gp120, Tat is expressed systemically by EcoHIV and can be detected within the brain (Potash et al., 2005). However, whether EcoHIV-mediated Tat expression contributes to neurocognitive dysfunction akin to other Tat models is still under investigation. These caveats should be noted when interpreting data from EcoHIV studies. Nevertheless, the evidence demonstrating that EcoHIV infects microglia/macrophages and that it induces neuroinflammation and cognitive impairment indicates EcoHIV infection in rodents is a valuable model to study HIV-associated neurocognitive disorders (Kelschenbach et al., 2019; Li et al., 2021a). Importantly, unlike HIV Tg rodent models, EcoHIV produces a sustained infection in wild type mice. However, infected mice do not appear to ever transition to an immunodeficient state after a protracted period of time in the absence of

ART. Indeed, these mice show a precipitous decline in peripheral viral RNA levels by three weeks post-inoculation and exhibit anti-Gag and anti-Tat antibodies for many weeks post-inoculation (Potash et al., 2005; Gu et al., 2018), indicative of an antiviral immune response that limits the extent of EcoHIV infection. Interestingly, this is reminiscent of the asymptomatic phase of HIV infection in humans following primary infection, where individuals maintain immunocompetency. Related to SUDs, this is perhaps a unique and advantageous design feature of this model because it enables researchers to examine how persistent drug use in otherwise-healthy PLWH, under virally-suppressed conditions (which may or may not include ART), alters the course of HIV infection and subsequent changes in reward-associated cognition, behavior, and neurobiology. Nevertheless, it must be noted that once infection is established, ART treatment is ineffective at attenuating viral DNA levels in the spleen and reversing spatial memory impairments induced by EcoHIV infection (Gu et al., 2018). This represents an important caveat of the model and should be considered when designing studies that probe the impact of chronic ART treatment on neurocognitive and behavioral outcomes.

2.6. Alternative HIV-1 rodent models

Beyond these models, multiple additional rodent models of HIV have been developed in which complementary preclinical investigation would inform our understanding of co-occurring HIV-1 infection and SUD. This includes HIV-1 Nef-expressing rodent models. For example, transgenic mice expressing Nef in microglia exhibit striatal neuroimmune dysfunction, reduced levels of dopamine and DAT within the striatum, and behavioral changes such as hyperlocomotion (Acharjee et al., 2014). Another Nef transgenic mouse model, where Nef expression is induced by doxycycline treatment in $CD4^+$ T cells, exhibits T cell activation and depletion as well as AIDS-like disease in nonlymphoid organs such as the lungs and kidneys (Rahim et al., 2009). It is possible that Nef expression alone is sufficient to induce neurobehavioral impairments, as implanting Nef-expressing primary astrocytes into the hippocampus of rats results in neuronal loss and impaired recognition memory, increased CCL2 expression, and peripheral macrophage infiltration (Chompre et al., 2013). Altogether, very few studies have identified a mechanistic role for Nef in HIV-associated neurobehavioral and cognitive impairment, and no studies to date have leveraged HIV-1 Nef models to examine the effect of Nef expression on addiction-related behavior. Future work investigating SUDs and HIV may also benefit from additional work in the severe combined immunodeficient (SCID) mouse model, where mice lack functional T and B cells and can be humanized via the engraftment of human fetal liver, thymus, and lymph node tissue (McCune et al., 1988, 1991; Namikawa et al., 1988). As reviewed in more detail elsewhere (Sil et al., 2021), other humanized mouse models, including the humanized microglia mouse model (Mathews et al., 2019) and the humanized NOD/SCID/γ $chain^{null}$ (NSG) mouse model (Cai et al., 2011), may also be useful for assessing the pathophysiology and neurocognitive burden of HIV-1 infection.

3. Utilization of NeuroHIV Animal Models in Preclinical SUD Research

Co-occurring HIV and SUDs represent a unique clinical challenge. Drug use can impede successful HIV treatment outcomes and, as discussed in detail below, HIV may complicate

SUD treatment efforts through modulation of drug-induced dysregulation of brain reward and motivation processes. For example, we have recently demonstrated that a candidate preclinical medication for treatment of cocaine use disorders – previously shown to successfully suppresses cocaine motivation (Powell et al., 2020) – failed to suppress cocaine relapse-like behavior in rats exposed to gp120 (Namba et al., 2023). This study highlights the need to consider comorbidities such as HIV when designing preclinical SUD models for medications development. Indeed, individuals with multiple diagnoses experience poorer treatment adherence, and integrated treatment approaches have been proven consistently superior to separate treatment of individual diagnoses (for review, see National Institute on Drug Abuse, 2020). Thus, the integration of the aforementioned preclinical HIV models with established animal models of SUDs provides an opportunity for researchers to examine how the pathophysiology of HIV, with or without chronic ART, alters the neurobiology and behavioral sequelae of addiction-related behaviors and, importantly, the efficacy of novel pharmacotherapeutics intended to treat SUDs.

3.1. Behavioral sensitization

Potentiation of behavioral responses to a stimulus after repeated exposure to that stimulus is referred to as sensitization. In the context of addictive substances, behavioral sensitization most often refers to the enhanced frequency of behavioral response to a drug following repeated exposure, which is an effect that can last chronically (Paulson et al., 1991) and occurs across a myriad of drugs (Stripling and Ellinwood, 1977; Joyce and Iversen, 1979; Robinson and Becker, 1986; Benwell and Balfour, 1992; Cunningham and Noble, 1992). Typically, behavioral sensitization within this context is observed when the same dose of a drug produces a potentiated behavioral response and/or when less drug is necessary to produce a particular magnitude of response. This phenomenon is usually measured as sensitization of drug-induced locomotion but can also include behaviors such as psychostimulant-induced stereotypy (e.g., methamphetamine-induced head twitching). Cross-sensitization, where repeated exposure to one drug can produce sensitization to another, is common between addictive drugs and points toward shared neurobiological mechanisms underlying the formation of behavioral sensitization (Vezina et al., 1989; Itzhak and Martin, 1999; Beyer et al., 2001; Cadoni et al., 2001). Importantly, many studies have demonstrated a reduction in drug-induced locomotor sensitization in rodents following treatment with FDA-approved pharmacotherapeutics used to treat SUDs (Chester et al., 2001; Häggkvist et al., 2011; Goutier et al., 2015), highlighting the value of this model towards identifying treatment targets. While the lower face validity of locomotor sensitization relative to other behavioral paradigms discussed here represents a limitation of this model, the neurobiological processes that mediate this behavior overlap with other models of drug use and relapse (Steketee and Kalivas, 2011).

Studies using intracranial microinfusions of HIV protein and transgenic rodents demonstrate that CNS exposure to HIV proteins can alter drug-induced behavioral sensitization and mesocorticolimbic neuroplasticity. One study examining the impact of CNS expression of HIV Tat on methamphetamine (METH) sensitization demonstrated that male HIV-1 Tat Tg mice exhibit enhanced locomotor sensitization and microglial activation within the dorsal striatum relative to control mice (Kesby et al., 2017). This study also demonstrated that

HIV-1 Tat Tg mice have reduced expression of D1, D2, D4, and D5 dopamine receptors within the NAc, implicating altered mesolimbic dopamine transmission as a functional impairment in these mice. Similarly, male HIV-1 Tg rats exhibit enhanced sensitization of METH-induced stereotypic behavior (Liu et al., 2009) and potentiated cocaine-induced locomotor sensitization (Paris et al., 2014a). However, HIV-1 protein effects on drug-induced locomotor sensitization appear to depend on the protein exposure method, sex, and hormonal status of animal subjects. For example, intra-NAc microinfusions of Tat potentiate acute cocaine-induced locomotion but attenuate cocaine-induced locomotor sensitization in ovariectomized female rats (Harrod et al., 2008). In freely-cycling, gonadally-intact female HIV-1 Tat Tg mice, Tat induction attenuates acute cocaine-induced locomotion only during diestrus, whereas Tat induction reduces cocaine-induced locomotor sensitization regardless of cycle phase (Paris et al., 2014b). Similarly, intra-NAc Tat exposure also attenuates cocaine- (Ferris et al., 2010) and nicotine-induced locomotor sensitization in male rats (Zhu et al., 2015). In contrast to these findings, one study found that ovariectomized female HIV-1 Tg rats exhibit sensitization to cocaine-induced locomotion within the periphery of an open field arena (Moran et al., 2013). However, similar to findings from Zhu and colleagues (2015), male HIV-1 Tg rats exhibit attenuated nicotine-induced locomotor sensitization (Midde et al., 2011). While altered behavioral sensitization can implicate disrupted neurobehavioral plasticity, alone it is insufficient to model more complex motivation and reward processes that are fundamental to all SUDs. Indeed, studies examining the incentive motivational effects of the Pavlovian and operant mechanisms that underlie drug use across HIV models have revealed important insights into how HIV may alter the pathophysiology of SUDs.

3.2. Conditioned Place Preference

First developed to assess the reinforcing efficacy of opioids (Rossi and Reid, 1976; Katz and Gormezano, 1979; Mucha and Iversen, 1984), the conditioned place preference (CPP) paradigm is a common behavioral model used to quantify Pavlovian drug-context associations (for review, see McKendrick & Graziane, 2020). In preclinical addiction studies, CPP utilizes a two- or three-chamber apparatus (two primary chambers where conditioning occurs and a middle chamber), each of which consists of distinct visual, tactile, and/or olfactory cues. Testing in the CPP paradigm typically consists of three phases – the pretest, conditioning, and post-test phases. During pretesting, animals are allowed to explore the CPP apparatus to determine their baseline chamber preference. For the conditioning phase, animals receive experimenter-delivered injections of drug and are confined to one of the two primary chambers. In a biased design, drug is paired to the chamber that is opposite to the preferred chamber during pretesting. Conversely, an unbiased design randomly assigns the drug-chamber pairings to each animal. The experimenter-administered drug is repeatedly paired with the designated associated context. On alternating sessions, a neutral stimulus (e.g., saline) is paired with the opposite context, occurring either on the same day or on alternating days. After drug conditioning, animals are tested for expression of CPP, where they are allowed to explore all the entire apparatus and time spent in the drug-paired chamber is measured. Generally, increased time spent in the drug-paired chamber is associated with the rewarding efficacy of the drug. Many CPP studies using the aforementioned rodent models of HIV demonstrate that HIV may potentiate the rewarding

properties of various addictive drugs, providing evidence for a role of HIV in modulating the pathophysiology of SUDs.

The majority of CPP studies in rodent models of HIV have utilized transgenic mice that conditionally or constitutively express HIV proteins. Among male HIV-1 Tat Tg mice, induction of CNS expression of Tat potentiates the expression of cocaine CPP (Zhu et al., 2022). The induction of Tat expression is also sufficient to reinstate extinguished cocaine CPP (Paris et al., 2014a; Mediouni et al., 2015). Tat induction also potentiates ethanol CPP in HIV-1 Tat Tg mice and is sufficient to reinstate this behavior following extinction training (McLaughlin et al., 2014). These findings suggest that Tat expression during reward learning *and* acutely during the expression of place preference is sufficient to impact reward seeking. Importantly, the effect of Tat induction on the reinstatement of drug-seeking behavior, which is a preclinical model of relapse-like behavior, indicates that Pavlovian conditioning processes that drive drug seeking in humans (O'Brien et al., 1992; Perry et al., 2014) may be impacted by HIV infection. Females within this mouse model also express potentiated cocaine CPP due to Tat induction during diestrus (Paris et al., 2014b). Akin to cocaine, male HIV-1 Tat Tg mice also exhibit potentiated morphine CPP (Gonek et al., 2018). This study found that pretreating Tat Tg mice with the CCR5 antagonist maraviroc exacerbates the potentiated morphine CPP response in these mice, which the authors hypothesized is due to complex mu opioid receptor (MOR)-chemokine receptor interactions whereby proinflammatory chemokine stimulation of CCR5 provides inhibitory tone over MOR signaling. Another recent study demonstrated that maraviroc attenuates cocaine CPP and cocaine-induced hyperlocomotion (Nayak et al., 2020). Interrogation of this effect within an HIV rodent model would shed light on whether the mechanisms that mediate HIV-induced potentiation of drug reward (e.g., CCR5 signaling) are drug-specific. Similar to HIV-1 Tat Tg mice, gp120 Tg mice that constitutively express gp120 in GFAP+ cells express greater sensitivity to the incentive motivational effects of METH, exhibiting a leftward shift in the dose response function for METH CPP (Kesby et al., 2014). In contrast to these mouse models, HIV-1 Tg rats do not show potentiation of morphine CPP but may exhibit deficits in extinction learning, although this effect appears to be sensitive to the environmental cues associated with the CPP apparatus (Chang and Connaghan, 2012; Homji et al., 2012b). Surprisingly, there are very few studies that have assessed drug-induced CPP in HIV-1 Tg rats, highlighting a critical gap in the preclinical literature. Another caveat of many of these studies is that animals are often tested for drug-induced CPP in a drug-free state making it unclear whether abstinence-dependent neuroadaptations that are modulated by HIV protein exposure drive the observed findings in the aforementioned studies. Altogether, these findings highlight significant differences in drug-conditioned reward and motivation in animal models of HIV infection. Similar to observations from drug-induced locomotor sensitization studies, factors such as drug type, sex, HIV model, and hormonal status all likely modulate the effects of HIV on drug-induced CPP.

3.3. Drug Self-Administration

Drug self-administration procedures are widely considered the "gold standard" of preclinical animal models for assessing the rewarding and reinforcing properties of psychoactive drugs and studying the neurobiology of SUDs. The key advantage of this model over others is

that animals have volitional control over their drug intake, and this type of contingent drug use involves distinct neurobiological mechanisms relative to non-contingent, experimenter-delivered models of drug exposure (Namba et al., 2018). Drug self-administration employs a complex medley of operant and classical conditioning components as well as positive and/or negative reinforcement whereby animals learn that the rewarding and reinforcing effects of a particular drug are due to distinct response-outcome contingencies. These contingencies, such as the pressing of a lever for the delivery of a drug reinforcer, are associated with contextual and discrete stimuli that, through repeated pairings with the drug, acquire incentive motivational value and facilitate self-administration behavior (Estes, 1948; Davis and Smith, 1976; Arroyo et al., 1998; Carter and Tiffany, 1999; Tiffany, 1999; Caggiula et al., 2001; Perry et al., 2014). The majority of findings on the impact of HIV and its protein products on drug self-administration behavior are derived from HIV-1 Tg rodent models, except for two studies conducted in NHPs. Findings from these studies indicate significant impairments in drug-motivated behavior and associated neuroplasticity and immune dysfunction, which appear to depend on factors such as sex, reinforcer type, drug access conditions, as well as drug withdrawal and abstinence.

One of the first preclinical studies to examine the interactions between HIV infection and drug self-administration utilized the SIV-infected macaque model along with alcohol self-administration (Kumar et al., 2005). In macaques with a chronic history of alcohol consumption, both plasma and CSF viral loads remained persistently elevated beginning at 18- and 10-weeks post-inoculation, respectively, relative to control macaques with no alcohol history. Total alcohol consumption did not appear to escalate substantially post-inoculation, which may suggest that HIV infection does not affect alcohol consumption per se. However, the low sample size of this study necessitates caution when drawing such conclusions. Moreover, these animals did not self-administer alcohol daily, which is an important caveat. Related work found that SIV infection does not alter daily alcohol consumption in macaques but results in reduced levels of circulating CD4+ T cells and elevated levels of monocytes expressing CCR5 relative to control animals (Marcondes et al., 2008). Within the brain, alcohol self-administration reduced the expression of the anti-viral cytokine interferon alpha (IFNα), suggesting a reduced innate immune response to SIV infection. Together, these two studies provided early evidence that a history of drug use may alter the progression and the pathophysiological milieu of HIV. Studies building upon this work address important questions related to the impact of HIV on drug-seeking behavior.

Studies using transgenic rodent models of HIV in combination with self-administration procedures have revealed important insights into how HIV proteins dysregulate drug-seeking or -taking behavior. One study utilizing gp120 Tg mice in a two-bottle choice procedure, where mice have free access to either METH or saccharin and water within their home cage, found that Tg mice exhibit increased preference for both METH and saccharin under restricted access conditions compared to controls, but reduced METH preference under unlimited access conditions. This effect was greater in males compared to females (Kesby et al., 2014). Under certain conditions, saccharin consumption is predictive of future psychostimulant use in rodents (Gosnell et al., 1998; Perry et al., 2007), and restricted or intermittent access procedures may better represent drug use patterns observed in humans

(Kawa et al., 2019). This study highlights sex and drug access conditions as critical variables when assessing the neurobehavioral underpinnings of HIV and addiction-related behaviors.

Akin to METH self-administration in gp120 Tg mice, studies suggest that HIV-1 Tg rats also exhibit enhanced sensitivity to psychostimulant reinforcement. For example, one study found that intravenous (i.v.) self-administration of cocaine in HIV-1 Tg rats produced a leftward shift in the cocaine dose response function relative to control rats under a short-access, fixed-ratio (FR) 1 schedule of reinforcement paradigm (McIntosh et al., 2015). This was accompanied by greater DAT affinity in striatal preparations from cocaine-experienced HIV-1 Tg rats versus control rats, consistent with their leftward shift in the dose response function. HIV-1 Tg rats also exhibit mPFC hyperexcitability that is augmented by abstinence from i.v. cocaine self-administration (Wayman et al., 2016). Specifically, cocaine abstinence-induced increases in mPFC pyramidal neuron excitability are further augmented in HIV-1 Tg rats, which is attenuated by inhibition of L-type Ca^{2+} channels. Combined with striatal dopamine dysfunction, this type of mPFC pathology could facilitate drug-seeking behavior beyond normal increases across abstinence (Tran-Nguyen et al., 1998; Grimm et al., 2001; Pickens et al., 2011). Indeed, a recent study found that following a month of abstinence from i.v. METH self-administration, HIV-1 Tg rats exhibit greater escalation of METH intake on a long-access, fixed schedule of reinforcement. Compared to wild-type rats, HIV-1 Tg rats also exhibited potentiated breakpoints in a progressive ratio (PR) task that requires animals to exert a progressively increasing effort across a test session to receive a reinforcer delivery, which is thought to test the incentive motivational value of drugs and associated cues (Richardson and Roberts, 1996; de Guglielmo et al., 2020). Interestingly, these behavioral changes were accompanied by enhanced mPFC neuroinflammation in METH self-administering HIV-1 Tg rats relative to wild-type controls with METH experience. In contrast, this group also showed no differences in long-access, i.v. oxycodone self-administration between HIV-1 Tg rats and controls after a period of forced abstinence despite cognitive deficits and transcriptomic evidence of mPFC neuroinflammation (Fu et al., 2022). Within the hippocampus, HIV-1 Tg rats, with or without a history of METH self-administration, show impairment of BBB protein expression and upregulation of MMP-9 and NF-κB expression (Ohene-Nyako et al., 2021), which is associated with enhanced drug-seeking behavior (Bozdagi et al., 2007; Russo et al., 2009; Namba et al., 2020, 2022). METH self-administering HIV-1 Tg rats also exhibit enhanced expression of ΔFosB and downstream dopamine D1 receptor expression within the NAc (Ohene-Nyako et al., 2018). Importantly, ΔFosB is a critical transcription factor that regulates many addiction-related genes, accumulates with repeated drug exposure, and promotes drug-seeking behavior (Nestler, 2008). Altogether, these studies suggest that HIV-1 Tg rats may be more sensitive to psychostimulant reinforcement and exhibit neuropathology that may promote motivation to seek drug in an abstinence-mediated manner.

It is important to note that the preponderance of this work was conducted using only male HIV-1 Tg rats, and recent drug self-administration studies in females have revealed important sex differences in HIV-induced neurobehavioral adaptations. For example, Bertrand et al (2018) demonstrated that both the reinforcing efficacy of cocaine across a range of cocaine doses and the motivation to self-administer cocaine on a PR schedule are diminished in female HIV-1 Tg rats. Furthermore, this study also showed that female HIV-1

Tg rats exhibit diminished choice for cocaine over sucrose compared to controls across a week of repeated testing. Interestingly, DAT abundance (i.e., B_{max}) observed in this study was lower in Tg rats compared to controls and increased by cocaine, which parallels the cocaine-induced increase B_{max} of low-affinity DAT binding sites from male HIV-1 Tg rats used in Mcintosh et al (2015). However, important procedural differences exist between these self-administration studies, such as an extensive history of reinforced lever pressing prior to cocaine self-administration in the female HIV-1 Tg rats used in Bertrand et al (2018) compared to male Tg rats naïve to such training in Mcintosh et al (2015) and Wayman et al (2016). In contrast to the latter two studies, a recent study examining cocaine self-administration behavior in male HIV-1 Tg rats using the same initial training dose as Wayman et al (2016) found that these animals are highly resistant to acquiring cocaine self-administration (Huynh et al., 2020), similar to female Tg rats in Bertrand et al (2018). This is further complicated by a recent study that demonstrated enhanced response vigor for cocaine in female HIV-1 Tg rats (McLaurin et al., 2021). Altogether, these studies highlight the need to consider sex in combination with behavioral history and task parameters when examining the neurobehavioral impact of HIV on addiction-related behaviors.

One limitation of these HIV-1 Tg rat model studies, as well as several of the aforementioned mouse model studies, is that animals are exposed to HIV proteins *prior* to chronic drug use, which is in distinct contrast to the SIV-infected macaque studies that demonstrated an alcohol-induced facilitation of SIV pathophysiology without SIV-induced changes in alcohol consumption (Kumar et al., 2005; Marcondes et al., 2008). One recent study showed that EcoHIV infection via retro-orbital administration in rats with a chronic history of cocaine self-administration disrupted choice behavior for cocaine versus sucrose and also impairs extinction learning (McLaurin et al., 2022). This study also showed synaptic impairments on mPFC pyramidal neurons, including a shift towards increased dendritic spine head and neck diameter and increased spine density on distal branches. This important work addresses the neurobehavioral impairments produced by HIV *following* a chronic history of drug use/exposure, which is a key gap in the extant literature. Considering drug use and associated risky behaviors (e.g., sexual risk taking) are associated with increased risk of HIV infection (Durvasula and Miller, 2014), it is important for preclinical models to elucidate the neurobehavioral consequences of drug history on the pathophysiology of HIV and future addiction-related behaviors following HIV infection. In a longitudinal study assessing predictors of cessation of drug use and relapse among PLWH, HIV seropositivity was associated with a shorter time to relapse following cessation (Shah et al., 2006), suggesting that abstinence-dependent neurobehavioral processes that contribute to drug relapse may be modulated by HIV. Overall, the inconsistent findings across the self-administration literature and the overall paucity of HIV-related operant self-administration studies in the extant literature highlight the need for future investigations that attempt to parse out the individual contributions of these variables to drug-motivated behavior.

4. Leveraging Advanced Behavioral Neuroscience Tools within Animal Models of Comorbid HIV and SUDs

Despite tremendous progress in our understanding of how HIV may alter addiction-related behaviors and how addictive drugs impact the pathophysiology of HIV within the CNS, there remains a need for a mechanistic circuit, cellular, and molecular understanding of the interaction between HIV and addictive drugs to gain insight into novel prevention and treatment strategies. Well-validated techniques used widely across behavioral neuroscience represent a novel future direction for preclinical HIV and SUD research. Here, we will discuss such techniques and how they have advanced our understanding of the neurobiology of SUDs. Specifically, we will briefly discuss key findings from the preclinical SUDs literature that highlight a myriad of techniques that demonstrate the cellular-, molecular-, and circuit-level contributions to addiction-related behaviors. We identify lingering questions related to the neurobehavioral sequelae of comorbid HIV and SUDs and how these techniques could help to close these research gaps. This is by no means an exhaustive review of the preclinical SUD literature employing such techniques. Nevertheless, we discuss key examples from the field of how these studies have substantially advanced our understanding of the neurobiology of SUDs and highlight how these findings may uniquely intersect with preclinical animal models of HIV.

4.1. Dissection of the Circuit-Level Contributions to HIV-Induced Dysfunction of Drug Motivation and Reward

The brain reward system function is especially vulnerable to HIV. However, many questions remain regarding neural circuit contributions to comorbid HIV and SUDs. Corticostriatal neural circuitry is particularly vulnerable to HIV infection (Illenberger et al., 2020; Nickoloff-Bybel et al., 2020), although it is not entirely clear how such circuit dysfunction modulates drug-seeking behavior. Circuit manipulation techniques such as optogenetics and chemogenetics have helped clarify the cell type- and projection-specific mechanisms underlying drug-induced dysfunction of mesocorticolimbic circuits, thus representing a novel approach towards understanding how these circuits might be differentially involved in addiction-related behaviors within an animal model of HIV.

Optogenetics refers to the manipulation of cellular activity on a millisecond timescale via optical stimulation of genetically encoded, light-sensitive proteins (Deisseroth et al., 2006; Miesenböck, 2009; Boyden, 2011). Like optogenetics, chemogenetics involves the use of genetically encoded protein receptors; however, these receptors are stimulated by small molecule ligands and are insensitive to endogenous ligands. Designer receptors exclusively activated by designer drugs (DREADDs) are the most common type of chemogenetic strategy used in preclinical addiction neuroscience studies, which are mutant muscarinic receptors that are G_q-, G_s, or G_i-coupled G-protein coupled receptors (GPCRs) that are activated by clozapine-n-oxide (CNO) (Armbruster et al., 2007; Guettier et al., 2009; Roth, 2016). More recently, a G_i-coupled kappa opioid receptor DREADD (KORD) was developed, which responds to the pharmacologically-inert compound salvinorin B (SALB), thus permitting a multiplexed DREADD approach when combined with muscarinic DREADD receptors (Vardy et al., 2015). Optogenetics and chemogenetics have been

utilized across a wide range of preclinical addiction studies and are powerful tools to help reveal the underlying circuit mechanisms of addiction-related behaviors (Bernstein and Boyden, 2011; Cao et al., 2011; Ferguson and Neumaier, 2015; Vickstrom et al., 2021).

Optogenetics and chemogenetics have revealed key insights into cell type- and circuit-specific mediators of addiction-related behaviors, exemplifying an approach that will advance our understanding of how HIV dysregulates motivated behavior. Of particular relevance to the dopamine system and striatal dysregulation observed in models of HIV, optogenetic dissection of the direct and indirect striatal pathways has challenged the classic understanding of segregated D1 and D2 receptor-expressing MSN projection pathways. Canonically, it was believed that D1 MSNs project directly to output nuclei of the basal ganglia, while D2 MSNs do so through indirect innervation of pallidal neurons, with little overlap between the two pathways (Gerfen and Surmeier, 2011). However, a crucial study by Kupchik et al. (2015) demonstrated that expression of ChR2 within NAc D1 MSNs and light stimulation within the ventral pallidum (VP) results in enhanced excitatory activity in 50% of recorded VP neurons, which was also confirmed via retrograde fluorescent labeling. This study also showed that D2 MSNs can form a direct pathway that disinhibits the thalamus through inhibition of VP → thalamus inhibitory projections. Such findings provide convincing evidence that striatal MSN plasticity may have more complex and nuanced effects over mesocorticolimbic circuit function than what one might predict with the traditional direct/indirect pathway model. Other studies have revealed through optogenetics critical contributions of excitatory projections from the mPFC and basolateral amygdala (BLA) to the NAc in cue-induced motivated behavior (Stuber et al., 2011; Stefanik and Kalivas, 2013; Stefanik et al., 2016), the role of dopamine-independent glutamate transmission from the VTA to the NAc in promoting reward seeking (Zell et al., 2020), as well as the role of calcium-permeable AMPA receptors within mPFC → NAc subcircuits in cue-induced drug seeking (Lee et al., 2013; Ma et al., 2014). These studies provide a crucial foundation upon which similar studies could be conducted in HIV animal models to parse out the unique circuit contributions to drug seeking behavior within the context of comorbid HIV.

Pathway-specific chemogenetic strategies have also been used to dissect the function of specific neuronal circuits in regulating drug-seeking behavior. For example, a recent study by Yager et al (2019) utilized a Cre-lox recombinase strategy to express inhibitory DREADDs specifically within direct pathway-projecting striatal neurons to examine the role of this pathway in regulating cue-induced reinstatement of cocaine seeking. This study revealed that chemogenetic inhibition of these specific neurons suppresses cue-induced cocaine seeking only in rats screened for a “high-risk” addiction-like phenotype (characterized by higher responding for cocaine on a PR schedule and despite foot shock punishment). This group also demonstrated using a similar approach to chemogenetically tag both direct and indirect pathway-projecting MSNs that direct pathway MSNs drive, while indirect pathway MSNs inhibit, cue-induced heroin seeking only in “high-risk” rats (O’Neal et al., 2019). These studies further highlight how the underlying neural circuitry of drug seeking is contingent upon individual differences, which raises important questions regarding the neural circuit contributions to drug seeking in the context of HIV. Another recent study demonstrated that optogenetic stimulation of VTA→NAc core dopamine

neurons induces reinstatement of cocaine seeking and that chemogenetic inhibition of this pathway prevents this behavior (Jing et al., 2022). As discussed previously, several studies suggest that HIV-1 Tg rats exhibit dysregulation of DAT function within the striatum, suggesting that HIV may impair dopamine transmission. Thus, understanding the role of VTA→NAc dopamine signaling within the context of HIV could reveal novel insights into the neural circuitry underlying comorbid HIV and SUDs. In addition to dopamine transmission, many studies implicate altered corticostriatal glutamate transmission as a consequence of HIV and comorbid SUDs (Potter et al., 2013; Vázquez-Santiago et al., 2014; Giacometti and Barker, 2019), and there may be dissociable effects of HIV infection on the plasticity of NAc D1 versus D2 MSNs that receive corticostriatal glutamate input to drive drug-seeking behavior (Schier et al., 2017; Barbour et al., 2021). In combination with the HIV animal models described previously, optogenetics and chemogenetics could be leveraged to isolate cell type-specific neuronal subcircuits (e.g., mPFC glutamatergic projection neurons → NAc D1 MSNs) that are responsible for HIV-induced changes in drug-motivated behavior (Pascoli et al., 2014; Garcia et al., 2018).

It remains unclear whether HIV alters the recruitment and functional influence of these circuits in cue-motivated drug seeking and relapse-like behavior. Optogenetic and/or chemogenetic dissection of circuit contributions to HIV-induced dysregulation of drug-motivated behavior would reveal crucial insight into the development of targeted medications to treat SUDs in the context of comorbid HIV. In particular, combining these approaches with viral vectors capable of transsynaptic labeling would allow for isolation of cell type-specific mesocorticolimbic subcircuits that regulate the interactions between HIV and drug-seeking behavior (Gong et al., 2007; Sjulson et al., 2016). Another outstanding question that remains is whether activity of brain reward circuitry modulates neuroimmune function and, subsequently, the pathophysiology of CNS HIV infection. Presently, it is well accepted that immune signaling crucially modulates neuronal function, particularly within the context of SUDs and associated comorbidities (Namba et al., 2021). However, the concept of neuronal signaling mechanisms (particularly those regulating associative learning processes that critically underly SUDs) shaping immune function in a reciprocal manner is a re-emerging concept that could have important implications for understanding the neurobehavioral intersections of HIV and SUDs (Ader and Cohen, 1975; Goshen and Yirmiya, 2007; Sundman and Olofsson, 2014; Dantzer, 2018; Hadamitzky et al., 2020). A recent study leveraged optogenetics to demonstrate that vagus nerve stimulation in mice confers kidney protection against ischemic injury, which is likely mediated at least in part through stimulation of cholinergic anti-inflammatory signaling (Tracey, 2007; Tanaka et al., 2021). Another recent study showed that optogenetic stimulation of phasic dopamine neuron firing within the VTA of mice stimulates serum IL-2, IL-4 and TNF-α expression, and that pharmacological suppression of VTA activity (induced naturally in males by an encounter with females) can inhibit behavior-induced increases in serum IL-2 expression (Kayama et al., 2022). This work showcases the utility of circuit-manipulating tools such as optogenetics and chemogenetics, which could be combined with preclinical HIV models to study how the activity of specific reward circuits modulate immune function and, subsequently, the pathophysiology of HIV (for reviews of this approach, see Ben-Shaanan et al., 2017; Korin & Rolls, 2018).

4.2. Cell type-specific Identification of Vulnerable Neuronal Subpopulations in Comorbid HIV and SUDs

One limitation of the classic application of optogenetics and chemogenetics is the inability to distinguish and directly manipulate distinct subpopulations of neurons that are specifically activated during discrete addiction-related behaviors. The proportion of cells that are activated by drug exposure or drug-associated experience (e.g., cue exposure) is surprisingly small – about 5% or less (Mattson et al., 2008; Koya et al., 2009; Cameron and Carelli, 2012). These cells comprise a neuronal ensemble that is specific to discrete addiction-related behaviors and is largely non-overlapping with non-drug reward ensembles (Carelli et al., 2000; Cameron and Carelli, 2012; Bobadilla et al., 2017). A variety of techniques have been used to identify and manipulate neuronal ensembles. For example, the Daun02 inactivation method allows for selective, pharmacological reduction of neuronal excitability in *c-fos-lacZ* transgenic rodents that produce the enzyme beta-galactosidase (β-gal) in cells that express the immediate early gene (IEG), c-Fos. In the presence of β-gal, the Daun02 prodrug is converted to daunorubicin and reduces neuronal excitability (Cruz et al., 2013, 2015). This technique was used to demonstrate that only 2–3% of NAc neurons are activated by cocaine within a cocaine-associated environment and mediate context-dependent psychomotor sensitization to cocaine (Koya et al., 2009). This cocaine context-dependent increase in Fos activity was later shown to be associated with silent synapse generation in Fos-expressing neurons of Fos-GFP transgenic mice (Whitaker et al., 2016). Another similar approach, known as Targeted Recombination in Active Populations (TRAP), utilizes transgenic mice that express a tamoxifen-dependent recombinase under the control of an IEG promotor such as c-Fos (Fos^{TRAP} mice; Guenthner et al., 2013). This permits activity-dependent expression of an effector gene, such as a fluorescent reporter, DREADDs, etc., in a cell type-specific manner. A recent study using Fos^{TRAP} mice found that peripheral immune activation activates neurons in the insular cortex, and activation of DREADDs expressed by these activated neurons is sufficient to recapitulate peripheral inflammation (Koren et al., 2021). This bidirectional relationship between CNS function and peripheral immunity, as highlighted above, represents an important area of future research into the mechanisms of comorbid HIV and SUDs. Leveraging this type of approach within an animal model of HIV would facilitate understanding of what cell types (e.g., D1 vs. D2 MSNs) contribute to drug-associated neuronal ensembles within the context of HIV infection or viral protein exposure, and whether activation of these specific ensembles alters peripheral immunity and the pathophysiology of HIV.

One limitation of these studies is that transient Fos expression is not restricted to neurons (Cruz-Mendoza et al., 2022), which can make it difficult to parse out drug-induced transcriptomic and proteomic alterations within neuronal ensembles. One study using fluorescence-activated cell sorting (FACS) to isolate neurons found that cocaine sensitization in c-Fos-lacZ transgenic rats produces a unique gene expression profile within activated neurons compared to nonactivated neurons (Guez-Barber et al., 2011). This could be potentially extended to examining Fos-activated glial cells as well and whether they participate with neurons in drug-specific ensembles. Indeed, a recent study showed chemogenetic activation of astrocytes induces robust cFos expression within hippocampal astrocytes 90 mins after CNO exposure (Adamsky et al., 2018). Recent evidence also

suggests that microglial calcium events coincide with spikes in neuronal activity (Umpierre et al., 2020). Such studies highlight the potential role of glial cell activation in the formation and expression of drug memories. These experimental techniques could provide crucial insights into whether cocaine-associated neuron-glia ensembles are functionally distinct in a rodent model of HIV. Specifically, one important question that emerges from these studies is whether the transcriptomic and proteomic profiles of cocaine-associated neuronal ensembles (or neuron-glia ensembles) are altered by HIV, which could reveal novel treatment targets that are specific to comorbid HIV and SUDs.

Increases in cytosolic calcium are associated with enhanced neuronal activity (Ghosh and Greenberg, 1995; Kawamoto et al., 2012; Brini et al., 2014). Thus, genetically-encoded calcium indicators (GECIs) are an important tool for studying cell type-specific neuronal activity that could yield crucial insights into the pathophysiology of comorbid HIV and SUDs (for a thorough review of GECIs, see Lin & Schnitzer, 2016; Wang et al., 2019). Recently, a technique for observing calcium signaling *and* manipulating neuronal activity, known as Fast Light- and Activity-Regulated Expression (FLARE), was developed. This approach utilizes a unique transcription factor that, when activated by coincidental increases in intracellular calcium and blue light exposure, drives the expression of a transgene (e.g., a fluorescent reporter, light-sensitive opsin, etc.) that can be observed or manipulated at a later timepoint (Wang et al., 2017). This approach would be useful for tagging cellular ensembles that are activated during the acquisition, maintenance, and expression of various addiction-related behaviors and manipulating these ensembles at a later timepoint (e.g., via optogenetics). One interesting question that arises from this type of approach is whether the architecture of corticostriatal ensembles associated with drug self-administration are uniquely altered by HIV infection. The EcoHIV model would be particularly useful here, where cellular ensembles associated with drug self-administration could be tagged with a light-sensitive opsin prior to inoculation with EcoHIV. Ultimately, integration of these approaches into preclinical models of comorbid HIV and SUDs would be useful in dissecting the cell type-specific neuronal ensemble contributions to the many motivational deficits observed in rodent models of HIV.

4.3. Glial Cell Contributions to HIV-Induced Modulation in Neuronal Plasticity and Addiction-Related Behaviors

As highlighted throughout this review, glial cells are highly susceptible to HIV infection. While recent evidence suggests microglia are the primary CNS reservoir HIV that may support productive infection (Joseph et al., 2015; Wallet et al., 2019), many studies implicate astrocytes as mediators of HIV-induced neurocognitive dysfunction (Valcour et al., 2004b; Ton and Xiong, 2013). HIV and addictive drugs produce similar impairments in glial cell function within mesocorticolimbic reward circuitry (Hauser et al., 2007; Hauser and Knapp, 2014; Namba et al., 2021), thus representing a key area of interest for studying the pathophysiology of comorbid HIV and SUDs. For example, both addictive drugs and HIV proteins downregulate expression of the glial glutamate transporter EAAT-2 (i.e., GLT-1), and rescuing this deficit inhibits drug-seeking behavior (Wang et al., 2003; Knackstedt et al., 2010; LaCrosse et al., 2016; Melendez et al., 2016). Similarly, restoration of drug-induced impairments in the catalytic subunit of the cystine-glutamate antiporter (Sxc^{-}), xCT,

reduces drug-seeking behavior (Reissner et al., 2015; Namba et al., 2020). Interestingly, xCT function promotes cellular anti-HIV-1 activity in human macrophages (Rabinowitz et al., 2021). These shared glial mechanisms mediating HIV- and drug-induced plasticity may underlie the unique pathophysiological milieu of comorbid HIV and SUDs. Recent technical innovations such as optogenetic and chemogenetic control of glial cell activity, calcium imaging, and other genetic techniques to manipulate glial cell function have advanced the study of glial cell morphology and physiology within the context of substance use, thus representing a unique opportunity for future investigations to dissect glial cell contributions to comorbid HIV and SUDs.

Glial cell physiology is a key area of interest for preclinical SUD research, and recent studies utilizing optogenetics and chemogenetics to target glia have revealed important insights into non-neuronal mechanisms underlying drug-seeking behavior. One recent study utilizing optogenetics found that activation of VTA astrocytes induces real-time avoidance behavior and that genetic ablation of GLT-1 expression prevents this effect (Gomez et al., 2019). Moreover, this study also showed that concurrent optogenetic inhibition of VTA GABA neurons along with stimulation of VTA astrocytes inhibits dopamine neurons and prevents this avoidance behavior. These findings highlight how astrocytes can play a causal role in the formation of conditioned behavioral responses through modulation of neuronal microcircuit interactions. In another study utilizing a chemogenetic approach to modulate astrocyte function, Scofield et al (2015) demonstrated using a Gq-coupled DREADD driven by a GFAP promoter within the NAc core that chemogenetic activation of astrocytes promotes glutamate release and attenuates cue-induced cocaine (but not sucrose) seeking. Importantly, this effect was blocked by pharmacological inhibition of presynaptic mGlu2/3 autoreceptors, suggesting that astrocytic glutamate transmission within the NAc core contributes to presynaptic glutamate release properties and subsequent drug-seeking behavior. Morphological deficits in astrocytes (e.g., smaller cell volume and surface area) and reduced astrocyte-synapse colocalization were also observed within the NAc following cocaine self-administration and extinction. These effects were reversed by treatment with ceftriaxone, which is an antibiotic that reduces cue-induced cocaine seeking (Knackstedt et al., 2010; LaCrosse et al., 2016). One lingering question that remains from this work is whether astrocytes express spatial and/or functional plasticity around specific neuronal subtypes, such as between D1 and D2 MSNs. A recent study identified two functionally distinct forms of transient astrocyte plasticity (i.e., enhanced D2 MSN colocalization or increased extrasynaptic GLT-1 expression) that suppress cue-induced heroin seeking (Kruyer et al., 2022), suggesting that astrocytes can coordinate synaptic plasticity in a cell type-specific manner, underscoring the nuances of drug-induced astrocyte plasticity that may be relevant to HIV-induced dysregulation of astrocyte physiology.

Calcium signaling is a crucial mechanism through which astrocytes regulate neurotransmission and synaptic plasticity (Kang et al., 1998; Vesce et al., 1999; Bazargani and Attwell, 2016; Covelo and Araque, 2016). Utilizing fiber photometry and expression of the GECI GCaMP6f under control of an astrocyte-specific promoter, Corkrum and colleagues demonstrated that NAc astrocytes exhibit increases in intracellular calcium signaling in response to synaptically-released dopamine, which triggers the release of adenosine and subsequent stimulation of presynaptic autoreceptors to dampen excitatory

transmission (Corkrum et al., 2020). This study reveals the critical role astrocytes play in mediating dopamine-glutamate synaptic interactions, which could have significant implications for HIV. Indeed, HIV protein exposure can impact MSN morphology and physiology and D1- versus D2-MSNs may exhibit differential vulnerabilities to HIV infection (Brailoiu et al., 2017; Schier et al., 2017; McLaurin et al., 2018).

Plasma membrane calcium ATPase (PMCA) pumps that deplete astrocytes of intracellular calcium have been used to study astrocyte calcium signaling regulation of neuronal physiology and behavior (Strehler, 2015). A recent study virally expressed a splice variant of human PMCA2 (hPMCA2w/b) and GCaMP6f in striatal astrocytes, resulting in significant reductions in both spontaneous and evoked calcium signaling (Yu et al., 2018). Reducing striatal astrocyte calcium signaling promoted repetitive self-grooming behavior and led to enhanced GABA-mediated tonic inhibition of striatal MSNs. Another study utilizing hPMCA2w/b in astrocytes found that abolishing astrocytic calcium signaling fully impairs LTP following burst firing of DA neurons and that this form of plasticity is also dependent on astrocytic expression of the D2 dopamine receptor and CB1 cannabinoid receptor (Requie et al., 2022). These findings suggest that astrocytic calcium signaling plays a critical role in modulating the enduring plasticity of VTA dopamine neurons as well as striatal MSN plasticity, which are both vulnerable to HIV-induced impairment.

Microglia are the primary cellular reservoir of HIV within the CNS and are also involved in the pathophysiology of SUDs. Thus, understanding the functional contributions of microglia to the neurobehavioral sequelae of combined HIV and SUDs is crucial. Several studies have utilized optogenetics and chemogenetics as a tool to study microglia, particularly within the context of chronic pain (Parusel et al., 2022), which represents a novel future direction for the preclinical study of HIV and SUDs. In the first study to demonstrate chemogenetic manipulation of microglia, Grace et al., 2016 demonstrated that stimulation of a G_i-DREADD within the spinal cord, the expression of which was driven by a CD68 promotor, attenuates morphine-induced pain sensitization. Chemogenetic manipulation of microglia has been leveraged to advance the study of neuropathic pain and the spinal cord across several other studies (Grace et al., 2018; Saika et al., 2020, 2021), although its use within the brain has been limited. In particular, studies manipulating brain-resident microglia within the context of learning and memory are scarce. However, one recent study using Cx3cr1-Cre transgenic mice and Cre-dependent G_q- or G_i-coupled DREADDs within the dorsal striatum found that G_q-DREADD stimulation of microglia induces conditioned place aversion and proinflammatory cytokine signaling, while G_i-coupled DREADD stimulation blocks the formation of conditioned place aversion to an inflammatory stimulus (Klawonn et al., 2021). This study also showed *ex vivo* chemogenetic stimulation of striatal microglia inhibits MSN excitability and that this is dependent on prostaglandin signaling from activated microglia. One gap in our understanding of the pathophysiology of comorbid HIV and SUDs is whether persistent dysregulation of microglial physiology and activation states by HIV infection directly contributes to altered functional plasticity of neurons within the reward system. The use of microglial DREADDs represents a unique approach towards closing this knowledge gap. However, one must carefully consider the HIV model used in combination with microglial DREADDs, as varying HIV models may differentially alter host immune

responses and susceptibility to viral infection in ways that may impact the effectiveness of this experimental approach.

While HIV and addictive substances may share common mechanisms of action within glial cells, it is possible that they mediate these effects through distinct forms of plasticity. Examination of corticostriatal astrocyte and microglia activation and morphology within rodent models of HIV would provide critical insights into how HIV uniquely alters drug-induced glial cell plasticity. Modulators of glial cell function, such as the antioxidant *N*-acetylcysteine (NAC), have consistently shown success at the preclinical level at reducing drug-seeking behavior and restoring corticostriatal glutamate homeostasis (Moran et al., 2005; Reissner et al., 2015; Israel et al., 2019; Namba et al., 2020). However, clinical translation of such compounds have shown checkered success (LaRowe et al., 2013; Deepmala et al., 2015). Comorbidities such as HIV may alter the efficacy of medications targeting glutamate neurotransmission and glial cell function. Thus, studying these mechanisms within the context of HIV is paramount towards improving our understanding of the pathophysiology of SUDs.

5. Conclusions

Comorbid disorders and diseases are a norm, not an exception, for individuals living with SUDs. Rates of substance misuse among PLWH are substantially higher than among the general population, and drug use is one of several risk factors for HIV transmission. Translation of findings from preclinical studies to the clinic has faced many challenges, and many medications that have shown preclinical success in suppressing addiction-related behavior demonstrate only modest clinical efficacy. This pipeline of medications development could be improved by utilizing translational animal models that account for common comorbidities experienced by those living with SUDs. Indeed, the animal models of HIV discussed herein clearly demonstrate the unique effects of combined HIV and drugs of abuse on the brain and behavior, which raises important questions regarding the therapeutic efficacy of novel medications to treat SUDs in PLWH.

We have reviewed the utility of multiple animal models of neuroHIV and their potential for integration with preclinical SUD models. While these models have generated convergent findings across the literature with regards to the HIV-associated neuropathology they produce, each model has its own unique set of advantages and disadvantages. Likewise, there are many models of drug-seeking behavior that model different components of SUDs, such as acquisition and escalation of drug taking, tolerance and withdrawal, craving, and relapse. Combining multiple different animal models of neuroHIV with preclinical SUD models can generate complementary data sets that can address different aspects of comorbid HIV and SUD. For example, one major gap in our understanding of the biobehavioral interactions between HIV and SUDs is the characterization of immunological changes across the addiction cycle and across various addictive drugs, how HIV modulates these changes, whether the timing of infection relative to drug exposure differentially impacts these interactions, and whether these interactions depend on important variables such as biological sex, hormone status, age, co-infection status, among many others. Integration of multiple animal models can help address these gaps to reveal novel and

effective treatment avenues. Moreover, complementary preclinical datasets across animal models will also help inform future clinical investigations into the neuropsychological and behavioral impact of HIV within the context of SUDs. Much of the existing clinical literature related to HAND does not directly assess important features of SUDs, such as drug craving and relapse, patterns of drug use, polypharmacy, among many others. Many of the neurocognitive domains involved in the diagnosis of HAND, including attention-information processing, learning and recall memory, and executive functioning (Antinori et al., 2007), are also implicated in SUDs, which highlights the important overlap between HAND and SUDs. However, there remains a paucity of studies examining addiction-specific neuropsychological and behavioral domains within the context of HIV irrespective of HAND. For example, brain imaging studies in humans examining neural reactivity to drug and stress cues, which can predict future drug use patterns, have revealed important insights into the neural correlates of addiction-related domains that parallel preclinical data sets (Jasinska et al., 2014; Everitt et al., 2018; Smith et al., 2023). Moreover, clinical studies have also attempted to parse the types of motivation (e.g., reward, relief, habit, etc.) underlying drug use (Grodin et al., 2019), which can be captured by complementary animal models. However, it is unknown whether HIV status is an important modulator of these neurobehavioral relationships, and preclinical animal models of HIV are a useful tool in helping close these knowledge gaps. PLWH may also experience unique environmental and psychosocial stressors that could detract from the success of standard SUD treatment efforts (Avants et al., 1998; Krishnan et al., 2018). More clinical studies are needed to further investigate this issue, and clarifying this clinical framework would facilitate preclinical studies probing neural mechanisms underlying environmental and psychosocial stress effects on addiction-related behaviors. Altogether, these caveats represent important future directions for translational bridges to be built between preclinical and clinical research that may improve SUD treatment outcomes for PLWH.

Another major limitation of the extant preclinical literature is the lack of studies investigating the impact of chronic ART on mesocorticolimbic circuit function and addiction-related behaviors. While some of the models discussed here produce neurobehavioral impairments that resemble those observed in PLWH on ART, this is not the same as investigating the effects of ART on CNS function in the presence of HIV proteins. Future studies incorporating ART into these existing models would greatly advance our current understanding of the neurobehavioral sequelae of comorbid HIV and SUDs. Furthermore, integration of novel techniques and tools in neuroscience with models of HIV will provide a pathway to (1) characterizing brain and system-wide changes in comorbid HIV and SUDs across key levels of analysis, (2) identifying potential therapeutic targets, and (3) performing preclinical testing of potential therapeutic approaches for reducing drug seeking and taking behaviors that characterize SUDs within the context of HIV. Indeed, overcoming technical limitations associated with these models and techniques while attempting to combine them in a way that is informative and translationally relevant is a challenge. Regardless, we posit that careful consideration of the strengths and limitations of each of these models and techniques prior to their combined implementation will yield unique datasets that will substantially improve our understanding of the neurobehavioral complexities underlying comorbid HIV and SUDs.

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References

Abbondanzo SJ, Chang SL (2014) HIV-1 Transgenic Rats Display Alterations in Immunophenotype and Cellular Responses Associated with Aging. PLoS One 9:e105256 Available at: /pmc/articles/PMC4134284/ [Accessed February 24, 2023]. [PubMed: 25127062]

Acharjee S, Branton WG, Vivithanaporn P, Maingat F, Paul AM, Dickie P, Baker GB, Power C (2014) HIV-1 Nef expression in microglia disrupts dopaminergic and immune functions with associated mania-like behaviors. Brain Behav Immun 40:74–84 Available at: https://pubmed.ncbi.nlm.nih.gov/24607605/ [Accessed May 24, 2023]. [PubMed: 24607605]

Acharya A, Olwenyi OA, Thurman M, Pandey K, Morsey BM, Lamberty B, Ferguson N, Callen S, Fang Q, Buch SJ, Fox HS, Byrareddy SN (2021) Chronic Morphine Administration Differentially Modulates Viral Reservoirs in a Simian Immunodeficiency Virus SIVmac251-Infected Rhesus Macaque Model. J Virol 95:1657–1677 Available at: /pmc/articles/PMC8092838/ [Accessed June 5, 2023].

Adamsky A, Kol A, Kreisel T, Doron A, Ozeri-Engelhard N, Melcer T, Refaeli R, Horn H, Regev L, Groysman M, London M, Goshen I (2018) Astrocytic Activation Generates De Novo Neuronal Potentiation and Memory Enhancement. Cell 174:59–71.e14. [PubMed: 29804835]

Ader R, Cohen N (1975) Behaviorally conditioned immunosuppression. Psychosom Med 37:333–340 Available at: https://pubmed.ncbi.nlm.nih.gov/1162023/ [Accessed February 9, 2023]. [PubMed: 1162023]

Agrawal L, Louboutin JP, Marusich E, Reyes BAS, Van Bockstaele EJ, Strayer DS (2010) Dopaminergic neurotoxicity of HIV-1 gp120: Reactive oxygen species as signaling intermediates. Brain Res 1306:116–130. [PubMed: 19815008]

Agrawal L, Louboutin JP, Reyes BAS, Van Bockstaele EJ, Strayer DS (2012) HIV-1 Tat neurotoxicity: A model of acute and chronic exposure, and neuroprotection by gene delivery of antioxidant enzymes. Neurobiol Dis 45:657–670. [PubMed: 22036626]

Aksenov MY, Hasselrot U, Bansal AK, Wu G, Nath A, Anderson C, Mactutus CF, Booze RM (2001) Oxidative damage induced by the injection of HIV-1 Tat protein in the rat striatum. Neurosci Lett 305:5–8. [PubMed: 11356294]

Aksenov MY, Hasselrot U, Wu G, Nath A, Anderson C, Mactutus CF, Booze RM (2003) Temporal relationships between HIV-1 Tat-induced neuronal degeneration, OX-42 immunoreactivity, reactive astrocytosis, and protein oxidation in the rat striatum. Brain Res 987:1–9. [PubMed: 14499939]

Alford K, Vera JH (2018) Cognitive Impairment in people living with HIV in the ART era: A Review. Br Med Bull 127:55–68 Available at: https://academic.oup.com/bmb/article/127/1/55/5032183 [Accessed June 6, 2022]. [PubMed: 29868901]

Antinori A et al. (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1799 Available at: /pmc/articles/PMC4472366/ [Accessed June 8, 2023].

Armbruster BN, Li X, Pausch MH, Herlitze S, Roth BL (2007) Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. Proc Natl Acad Sci U S A 104:5163–5168 Available at: https://www.pnas.org/doi/abs/10.1073/pnas.0700293104 [Accessed August 4, 2022]. [PubMed: 17360345]

Arroyo M, Markou A, Robbins TW, Everitt BJ (1998) Acquisition, maintenance and reinstatement of intravenous cocaine self-administration under a second-order schedule of reinforcement in rats: effects of conditioned cues and continuous access to cocaine. Psychopharmacology (Berl) 140:331–344 Available at: https://pubmed.ncbi.nlm.nih.gov/9877013/ [Accessed July 26, 2022]. [PubMed: 9877013]

Avants SK, Margolin A, Dephilippis D, Kosten TR (1998) A comprehensive pharmacologic-psychosocial treatment program for HIV- seropositive cocaine- and opioid-dependent

patients: Preliminary findings. J Subst Abuse Treat 15:261–265 Available at: https://pubmed.ncbi.nlm.nih.gov/9633038/ [Accessed June 21, 2023]. [PubMed: 9633038]

Bachis A, Wenzel E, Boelk A, Becker J, Mocchetti I (2016) The neurotrophin receptor p75 mediates gp120-induced loss of synaptic spines in aging mice. Neurobiol Aging 46:160–168. [PubMed: 27498053]

Bailes E, Gao F, Bibollet-Ruche F, Courgnaud V, Peeters M, Marx PA, Hahn BH, Sharp PM (2003) Hybrid origin of SIV in chimpanzees. Science (80-) 300:1713 Available at: https://www.science.org/doi/full/10.1126/science.1080657 [Accessed June 9, 2022].

Bansal AK, Mactutus CF, Nath A, Maragos W, Hauser KF, Booze RM (2000) Neurotoxicity of HIV-1 proteins gp120 and Tat in the rat striatum. Brain Res 879:42–49 Available at: https://www.sciencedirect.com/science/article/pii/S0006899300027256?via%3Dihub#FIG1 [Accessed August 2, 2019]. [PubMed: 11011004]

Barbe MF, Loomis R, Lepkowsky AM, Forman S, Zhao H, Gordon J (2020) A longitudinal characterization of sex-specific somatosensory and spatial memory deficits in HIV Tg26 heterozygous mice. PLoS One 15 Available at: /pmc/articles/PMC7775086/ [Accessed June 6, 2023].

Barbour AJ, Nass SR, Hahn YK, Hauser KF, Knapp PE (2021) Restoration of KCC2 Membrane Localization in Striatal Dopamine D2 Receptor-Expressing Medium Spiny Neurons Rescues Locomotor Deficits in HIV Tat-Transgenic Mice: 10.1177/17590914211022089 13 Available at: https://journals.sagepub.com/doi/full/10.1177/17590914211022089 [Accessed August 5, 2022].

Bazargani N, Attwell D (2016) Astrocyte calcium signaling: the third wave. Nat Neurosci 19:182–189 Available at: https://www.nature.com/articles/nn.4201 [Accessed February 13, 2023]. [PubMed: 26814587]

Becker JT, Lopez OL, Dew MA, Aizenstein HJ (2004) Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS 18:11–18 Available at: https://pubmed.ncbi.nlm.nih.gov/15075493/ [Accessed June 6, 2022].

Ben-Shaanan T, Schiller M, Rolls A (2017) Studying brain-regulation of immunity with optogenetics and chemogenetics; A new experimental platform. Brain Behav Immun 65:1–8 Available at: https://pubmed.ncbi.nlm.nih.gov/27890661/ [Accessed February 9, 2023]. [PubMed: 27890661]

Bennett BA, Rusyniak DE, Hollingsworth CK (1995) HIV-1 gp120-induced neurotoxicity to midbrain dopamine cultures. Brain Res 705:168–176. [PubMed: 8821747]

Benveniste O, Vaslin B, Le Grand R, Fouchet P, Omessa V, Theodoro F, Fretier P, Clayette P, Boussin F, Dormont D (1996) Interleukin 1β, Interleukin 6, Tumor Necrosis Factor α, and Interleukin 10 Responses in Peripheral Blood Mononuclear Cells of Cynomolgus Macaques during Acute Infection with SIVmac251. AIDS Res Hum Retroviruses 12:241–250 Available at: https://www.liebertpub.com/doi/10.1089/aid.1996.12.241 [Accessed February 22, 2023]. [PubMed: 8835203]

Benwell MEM, Balfour DJK (1992) The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 105:856 Available at: /pmc/articles/PMC1908718/?report=abstract [Accessed September 23, 2022].

Bernstein JG, Boyden ES (2011) Optogenetic tools for analyzing the neural circuits of behavior. Trends Cogn Sci 15:600 Available at: /pmc/articles/PMC3225502/ [Accessed July 26, 2022].

Bertrand SJ, Mactutus CF, Harrod SB, Moran LM, Booze RM (2018) HIV-1 proteins dysregulate motivational processes and dopamine circuitry. Sci Rep 8:1–17. [PubMed: 29311619]

Beyer CE, Stafford D, LeSage MG, Glowa JR, Steketee JD (2001) Repeated exposure to inhaled toluene induces behavioral and neurochemical cross-sensitization to cocaine in rats. Psychopharmacology (Berl) 154:198–204 Available at: https://pubmed.ncbi.nlm.nih.gov/11314682/ [Accessed September 23, 2022]. [PubMed: 11314682]

Bobadilla AC, Heinsbroek JA, Gipson CD, Griffin WC, Fowler CD, Kenny PJ, Kalivas PW (2017) Corticostriatal plasticity, neuronal ensembles, and regulation of drug-seeking behavior. In: Progress in Brain Research, 1st ed. (Calvey T, Daniels WMU, eds), pp 93–112. Cambridge: Elsevier.

Boyden ES (2011) A history of optogenetics: the development of tools for controlling brain circuits with light. F1000 Biol Rep 3:11 Available at: /pmc/articles/PMC3155186/ [Accessed July 26, 2022]. [PubMed: 21876722]

Bozdagi O, Nagy V, Kwei KT, Huntley GW (2007) In Vivo Roles for Matrix Metalloproteinase-9 in Mature Hippocampal Synaptic Physiology and Plasticity. J Neurophysiol 98:334–344 Available at: http://www.ncbi.nlm.nih.gov/pubmed/17493927 [Accessed June 27, 2017]. [PubMed: 17493927]

Brailoiu GC, Deliu E, Barr JL, Console-Bram LM, Ciuciu AM, Abood ME, Unterwald EM, Brailoiu E (2017) HIV Tat excites D1 receptor-like expressing neurons from rat nucleus accumbens. Drug Alcohol Depend 178:7–14 Available at: http://www.ncbi.nlm.nih.gov/pubmed/28623807 [Accessed August 12, 2019]. [PubMed: 28623807]

Brini M, Cali T, Ottolini D, Carafoli E (2014) Neuronal calcium signaling: Function and dysfunction. Cell Mol Life Sci 71:2787–2814 Available at: https://link.springer.com/article/10.1007/s00018-013-1550-7 [Accessed August 12, 2022]. [PubMed: 24442513]

Browning J, Horner JW, Pettoello-Mantovani M, Raker C, Yurasov S, Depinho RA, Goldstein H (1997) Mice transgenic for human CD4 and CCR5 are susceptible to HIV infection. Proc Natl Acad Sci 94:14637–14641 Available at: https://www.pnas.org/doi/abs/10.1073/pnas.94.26.14637 [Accessed February 2, 2023]. [PubMed: 9405665]

Bruce-Keller AJ, Turchan-Cholewo J, Smart EJ, Geurin T, Chauhan A, Reid R, Xu R, Nath A, Knapp PE, Hauser KF (2008) Morphine Causes Rapid Increases in Glial Activation and Neuronal Injury in the Striatum of Inducible HIV-1 Tat Transgenic Mice. Glia 56:1414 Available at: http://www.ncbi.nlm.nih.gov/pubmed/18551626 [Accessed July 29, 2019]. [PubMed: 18551626]

Cadoni C, Pisanu A, Solinas M, Acquas E, Di Chiara G (2001) Behavioural sensitization after repeated exposure to Delta 9-tetrahydrocannabinol and cross-sensitization with morphine. Psychopharmacology (Berl) 158:259–266 Available at: https://pubmed.ncbi.nlm.nih.gov/11713615/ [Accessed September 23, 2022]. [PubMed: 11713615]

Caggiula AR, Donny EC, White AR, Chaudhri N, Booth S, Gharib MA, Hoffman A, Perkins KA, Sved AF (2001) Cue dependency of nicotine self-administration and smoking. Pharmacol Biochem Behav 70:515–530 Available at: https://pubmed.ncbi.nlm.nih.gov/11796151/ [Accessed July 26, 2022]. [PubMed: 11796151]

Cai S, Wang H, Bailey B, Hartwell JR, Silver JM, Juliar BE, Sinn AL, Baluyut AR, Pollok KE (2011) Differential Secondary Reconstitution of In Vivo-Selected Human SCID-Repopulating Cells in NOD/SCID versus NOD/SCID/γ chainnull Mice. Bone Marrow Res 2011:252953 Available at: /pmc/articles/PMC3200073/ [Accessed June 8, 2023]. [PubMed: 22046557]

Cameron CM, Carelli RM (2012) Cocaine abstinence alters nucleus accumbens firing dynamics during goal-directed behaviors for cocaine and sucrose. Eur J Neurosci 35:940–951 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1460-9568.2012.08024.x [Accessed August 9, 2022]. [PubMed: 22356698]

Cao ZFH, Burdakov D, Sarnyai Z (2011) Optogenetics: potentials for addiction research. Addict Biol 16:531 Available at: /pmc/articles/PMC5767107/ [Accessed July 26, 2022].

Carelli RM, Ijames SG, Crumling AJ (2000) Evidence That Separate Neural Circuits in the Nucleus Accumbens Encode Cocaine Versus "Natural" (Water and Food) Reward. J Neurosci 20:4255–4266 Available at: https://www.jneurosci.org/content/20/11/4255 [Accessed August 9, 2022]. [PubMed: 10818162]

Carey AN, Liu X, Mintzopoulos D, Paris JJ, Muschamp JW, McLaughlin JP, Kaufman MJ (2013) Conditional Tat protein expression in the GT-tg bigenic mouse brain induces gray matter density reductions. Prog Neuro-Psychopharmacology Biol Psychiatry 43:49–54.

Carey AN, Sypek EI, Singh HD, Kaufman MJ, McLaughlin JP (2012) Expression of HIV-Tat protein is associated with learning and memory deficits in the mouse. Behav Brain Res 229:48–56 Available at: /pmc/articles/PMC3580389/ [Accessed June 16, 2023]. [PubMed: 22197678]

Carter BL, Tiffany ST (1999) Meta-analysis of cue-reactivity in addiction research. Addiction 94:327–340 Available at: https://onlinelibrary.wiley.com/doi/full/10.1046/j.1360-0443.1999.9433273.x [Accessed February 7, 2023]. [PubMed: 10605857]

Chakrabarti L, Hurtrel M, Maire MA, Vazeux R, Dormont D, Montagnier L, Hurtrel B (1991) Early viral replication in the brain of SIV-infected rhesus monkeys. Am J Pathol 139:1280 Available at: /pmc/articles/PMC1886455/?report=abstract [Accessed June 9, 2022].

Chang SL, Connaghan KP (2012) Behavioral and molecular evidence for a feedback interaction between morphine and HIV-1 viral proteins. J Neuroimmune Pharmacol 7:332–340 Available at: https://link.springer.com/article/10.1007/s11481-011-9324-1 [Accessed July 13, 2022]. [PubMed: 22083500]

Chester JA, Grahame NJ, Li T-K, Lumeng L, Froehlich JC (2001) Effects of acamprosate on sensitization to the locomotor-stimulant effects of alcohol in mice selectively bred for high and low alcohol preference. Behav Pharmacol 12:535–543 Available at: https://journals.lww.com/behaviouralpharm/Fulltext/2001/11000/Effects_of_acamprosate_on_sensitization_to_the.15.aspx [Accessed July 1, 2022]. [PubMed: 11742148]

Chompre G, Cruz E, Maldonado L, Rivera-Amill V, Porter JT, Noel RJ (2013) Astrocytic expression of HIV-1 Nef impairs spatial and recognition memory. Neurobiol Dis 0:136 Available at: /pmc/articles/PMC3530662/ [Accessed May 24, 2023].

Cioni C, Annunziata P (2002) Circulating gp120 alters the blood–brain barrier permeability in HIV-1 gp120 transgenic mice. Neurosci Lett 330:299–301. [PubMed: 12270651]

Cirino TJ, Harden SW, McLaughlin JP, Frazier CJ (2020) Region-specific effects of HIV-1 Tat on intrinsic electrophysiological properties of pyramidal neurons in mouse prefrontal cortex and hippocampus. J Neurophysiol 123:1332–1341 Available at: https://journals.physiology.org/doi/10.1152/jn.00029.2020 [Accessed February 23, 2023]. [PubMed: 32101482]

Clifford DB, Ances BM (2013) HIV-Associated Neurocognitive Disorder (HAND). Lancet Infect Dis 13:986 Available at: /pmc/articles/PMC4108270/ [Accessed June 6, 2022].

Corkrum M, Covelo A, Lines J, Bellocchio L, Pisansky M, Loke K, Quintana R, Rothwell PE, Lujan R, Marsicano G, Martin ED, Thomas MJ, Kofuji P, Araque A (2020) Dopamine-Evoked Synaptic Regulation in the Nucleus Accumbens Requires Astrocyte Activity. Neuron 105:1036–1047.e5 Available at: https://pubmed.ncbi.nlm.nih.gov/31954621/ [Accessed February 4, 2022]. [PubMed: 31954621]

Covelo A, Araque A (2016) Lateral regulation of synaptic transmission by astrocytes. Neuroscience 323:62–66. [PubMed: 25732135]

Cruz-Mendoza F, Jauregui-Huerta F, Aguilar-Delgadillo A, García-Estrada J, Luquin S (2022) Immediate Early Gene c-fos in the Brain: Focus on Glial Cells. Brain Sci 12:687 Available at: /pmc/articles/PMC9221432/ [Accessed August 9, 2022]. [PubMed: 35741573]

Cruz FC, Javier Rubio F, Hope BT (2015) Using c-fos to study neuronal ensembles in corticostriatal circuitry of addiction. Brain Res 1628:157–173. [PubMed: 25446457]

Cruz FC, Koya E, Guez-Barber DH, Bossert JM, Lupica CR, Shaham Y, Hope BT (2013) New technologies for examining the role of neuronal ensembles in drug addiction and fear. Nat Rev Neurosci 14:743–754 Available at: https://www.nature.com/articles/nrn3597 [Accessed August 9, 2022]. [PubMed: 24088811]

Cui C, Shurtleff D, Harris RA (2014) Neuroimmune mechanisms of alcohol and drug addiction. Int Rev Neurobiol 118:1–12 Available at: http://www.ncbi.nlm.nih.gov/pubmed/25175859 [Accessed June 19, 2017]. [PubMed: 25175859]

Cunningham CL, Noble DC (1992) Conditioned activation induced by ethanol: role in sensitization and conditioned place preference. Pharmacol Biochem Behav 43:307–313 Available at: https://pubmed.ncbi.nlm.nih.gov/1409816/ [Accessed September 23, 2022]. [PubMed: 1409816]

Czub S, Czub M, Koutsilieri E, Sopper S, Villinger F, Müller JG, Stahl-Hennig C, Riederer P, te Meulen V, Gosztonyi G (2004) Modulation of simian immunodeficiency virus neuropathology by dopaminergic drugs. Acta Neuropathol 107:216–226 Available at: https://link.springer.com/article/10.1007/s00401-003-0801-3 [Accessed June 10, 2022]. [PubMed: 14712399]

Czub S, Koutsilieri E, Sopper S, Czub M, Stahl-Hennig C, Müller JG, Pedersen V, Gsell W, Heeney JL, Gerlach M, Gosztonyi G, Riederer P, ter Meulen V (2001) Enhancement of central nervous system pathology in early simian immunodeficiency virus infection by dopaminergic drugs. Acta Neuropatol 101:85–91 Available at: https://link.springer.com/content/pdf/10.1007/s004010000313.pdf [Accessed June 10, 2022].

Dantzer R (2018) Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. Physiol Rev 98:504 Available at: /pmc/articles/PMC5866360/ [Accessed February 9, 2023].

Davis SE, Ferris MJ, Ananthan S, Augelli-Szafran CE, Zhu J (2023) Novel Allosteric Modulator Southern Research Institute-32743 Reverses HIV-1 Transactivator of Transcription-Induced Increase in Dopamine Release in the Caudate Putamen of Inducible Transactivator of Transcription Transgenic Mice. J Pharmacol Exp Ther 384:306–314 Available at: https://jpet.aspetjournals.org/content/384/2/306 [Accessed February 23, 2023]. [PubMed: 36456195]

Davis WM, Smith SG (1976) Role of conditioned reinforcers in the initiation, maintenance and extinction of drug-seeking behavior. Pavlov J Biol Sci 11:222–236 Available at: https://pubmed.ncbi.nlm.nih.gov/1033507/ [Accessed July 26, 2022]. [PubMed: 1033507]

de Guglielmo G, Fu Y, Chen J, Larrosa E, Hoang I, Kawamura T, Lorrai I, Zorman B, Bryant J, George O, Sumazin P, Lefebvre C, Repunte-Canonigo V, Paolo Sanna P (2020) Increases in compulsivity, inflammation, and neural injury in HIV transgenic rats with escalated methamphetamine self-administration under extended-access conditions. Brain Res 1726:146502. [PubMed: 31605699]

De SK, Wohlenberg CR, Marinos NJ, Doodnauth D, Bryant JL, Notkins AL (1997) Human chorionic gonadotropin hormone prevents wasting syndrome and death in HIV-1 transgenic mice. J Clin Invest 99:1491 Available at: /pmc/articles/PMC507967/?report=abstract [Accessed June 6, 2023].

Deepmala Slattery J, Kumar N, Delhey L, Berk M, Dean O, Spielholz C, Frye R (2015) Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. Neurosci Biobehav Rev 55:294–321 Available at: http://www.ncbi.nlm.nih.gov/pubmed/25957927 [Accessed March 11, 2017]. [PubMed: 25957927]

Deisseroth K, Feng G, Majewska AK, Miesenböck G, Ting A, Schnitzer MJ (2006) Next-Generation Optical Technologies for Illuminating Genetically Targeted Brain Circuits. J Neurosci 26:10386 Available at: /pmc/articles/PMC2820367/ [Accessed July 26, 2022].

Dickens AM, Yoo SW, Chin AC, Xu J, Johnson TP, Trout AL, Hauser KF, Haughey NJ (2017) Chronic low-level expression of HIV-1 Tat promotes a neurodegenerative phenotype with aging. Sci Rep 7:1–11 Available at: https://www.nature.com/articles/s41598-017-07570-5 [Accessed June 21, 2022]. [PubMed: 28127051]

Dickie P, Felser J, Eckhaus M, Bryant J, Silver J, Marinos N, Notkins AL (1991) HIV-associated nephropathy in transgenic mice expressing HIV-1 genes. Virology 185:109–119 Available at: https://pubmed.ncbi.nlm.nih.gov/1926769/ [Accessed May 15, 2023]. [PubMed: 1926769]

Durvasula R, Miller TR (2014) Substance abuse treatment in persons with HIV/AIDS: challenges in managing triple diagnosis. Behav Med 40:43–52 Available at: http://www.ncbi.nlm.nih.gov/pubmed/24274175 [Accessed July 31, 2019]. [PubMed: 24274175]

Emanuel KM, Runner K, Brodnik ZD, Morsey BM, Lamberty BG, Johnson HS, Acharya A, Byrareddy SN, España RA, Fox HS, Gaskill PJ (2022) Deprenyl reduces inflammation during acute SIV infection. iScience 25:104207. [PubMed: 35494221]

Estes JD, Wong SW, Brenchley JM (2018) Nonhuman primate models of human viral infections. Nat Rev Immunol 18:390–404 Available at: https://www.nature.com/articles/s41577-018-0005-7 [Accessed June 10, 2022]. [PubMed: 29556017]

Estes WK (1948) Discriminative conditioning; effects of a Pavlovian conditioned stimulus upon a subsequently established operant response. J Exp Psychol 38:173–177 Available at: https://pubmed.ncbi.nlm.nih.gov/18913666/ [Accessed July 26, 2022]. [PubMed: 18913666]

Everitt BJ, Giuliano C, Belin D (2018) Addictive behaviour in experimental animals: prospects for translation. Philos Trans R Soc B Biol Sci 373:20170027 Available at: /pmc/articles/PMC5790825/ [Accessed June 21, 2023].

Ferguson SM, Neumaier JF (2015) Using DREADDs to investigate addiction behaviors. Curr Opin Behav Sci 2:72 Available at: /pmc/articles/PMC4912135/ [Accessed August 4, 2022].

Ferris MJ, Frederick-Duus D, Fadel J, Mactutus CF, Booze RM (2010) Hyperdopaminergic tone in HIV-1 protein treated rats and cocaine sensitization. J Neurochem 115:885–896 Available at: http://www.ncbi.nlm.nih.gov/pubmed/20796175 [Accessed September 7, 2019]. [PubMed: 20796175]

Festa LK, Gutoskey CJ, Graziano A, Waterhouse BD, Meucci O (2015) Induction of Interleukin-1β by Human Immunodeficiency Virus-1 Viral Proteins Leads to Increased Levels of Neuronal Ferritin Heavy Chain, Synaptic Injury, and Deficits in Flexible Attention. J Neurosci 35:10550 Available at: /pmc/articles/PMC4510293/ [Accessed September 23, 2022]. [PubMed: 26203149]

Festa LK, Irollo E, Platt BJ, Tian Y, Floresco S, Meucci O (2020) CXCL12-induced rescue of cortical dendritic spines and cognitive flexibility. Elife 9.

Fitting S, Xu R, Bull C, Buch SK, El-Hage N, Nath A, Knapp PE, Hauser KF (2010) Interactive Comorbidity between Opioid Drug Abuse and HIV-1 Tat: Chronic Exposure Augments Spine Loss and Sublethal Dendritic Pathology in Striatal Neurons. Am J Pathol 177:1397–1410. [PubMed: 20651230]

Fu Y, Lorrai I, Zorman B, Mercatelli D, Shankula C, Gaytan JM, Lefebvre C, de Guglielmo G, Kim HR, Sumazin P, Giorgi FM, Repunte-Canonigo V, Sanna PP (2022) Escalated (Dependent) Oxycodone Self-Administration Is Associated with Cognitive Impairment and Transcriptional Evidence of Neurodegeneration in Human Immunodeficiency Virus (HIV) Transgenic Rats. Viruses 14:669 Available at: https://www.mdpi.com/1999-4915/14/4/669/htm [Accessed July 25, 2022]. [PubMed: 35458399]

Gao F, Balles E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BH (1999) Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. Nature 397:436–441 Available at: https://www.nature.com/articles/17130 [Accessed June 9, 2022]. [PubMed: 9989410]

Garcia-Tellez T, Huot N, Ploquin MJ, Rascle P, Jacquelin B, Müller-Trutwin M (2016) Non-human primates in HIV research: Achievements, limits and alternatives. Infect Genet Evol 46:324–332. [PubMed: 27469027]

Garcia AF, Nakata KG, Ferguson SM (2018) Viral strategies for targeting cortical circuits that control cocaine-taking and cocaine-seeking in rodents. Pharmacol Biochem Behav 174:41 Available at: /pmc/articles/PMC5702276/ [Accessed August 5, 2022].

Gaskill PJ, Miller DR, Gamble-George J, Yano H, Khoshbouei H (2017) HIV, Tat and dopamine transmission. Neurobiol Dis 105:51–73 Available at: http://www.ncbi.nlm.nih.gov/pubmed/28457951 [Accessed February 29, 2020]. [PubMed: 28457951]

Gelman BB (2015) Neuropathology of HAND With Suppressive Antiretroviral Therapy: Encephalitis and Neurodegeneration Reconsidered. Curr HIV/AIDS Rep 12:279 Available at: /pmc/articles/PMC4427627/ [Accessed July 14, 2022].

Gerfen CR, Surmeier DJ (2011) Modulation of striatal projection systems by dopamine. Annu Rev Neurosci 34:441–466 Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3487690&tool=pmcentrez&rendertype=abstract [Accessed May 16, 2017]. [PubMed: 21469956]

Gharavi AG, Ahmad T, Wong RD, Hooshyar R, Vaughn J, Oller S, Frankel RZ, Bruggeman LA, D'Agati VD, Klotman PE, Lifton RP (2004) Mapping a locus for susceptibility to HIV-1-associated nephropathy to mouse chromosome 3. Proc Natl Acad Sci 101:2493 Available at: /pmc/articles/PMC356977/ [Accessed June 6, 2023].

Ghosh A, Greenberg ME (1995) Calcium Signaling in Neurons: Molecular Mechanisms and Cellular Consequences. Science (80-) 268:239–247 Available at: https://www.science.org/doi/10.1126/science.7716515 [Accessed August 12, 2022].

Giacometti LL, Barker JM (2019) Comorbid HIV infection and alcohol use disorders: converging glutamatergic and dopaminergic mechanisms underlying neurocognitive dysfunction. Brain Res 1723:146390 Available at: /pmc/articles/PMC6766419/ [Accessed August 5, 2022]. [PubMed: 31421128]

Gold LH, Fox HS, Henriksen SJ, Buchmeier MJ, Weed MR, Taffe MA, Huitron-Resendiz S, Horn TFW, Bloom FE (1998) Longitudinal analysis of behavioral, neurophysiological, viral and immunological effects of SIV infection in rhesus monkeys. J Med Primatol 27:104–112 Available at: https://sci-hub.ru/https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0684.1998.tb00234.x?casa_token=WA__qDt_KWYAAAAA:uFDTub85nRQO3bq_3zS8JMry3Imjuf9Ysqkq0wykRaFSTvEXaf4-haolgZ52q60FwN5ShBUHK2aEHek [Accessed June 2, 2023]. [PubMed: 9747951]

Gomez JA, Perkins JM, Beaudoin GM, Cook NB, Quraishi SA, Szoeke EA, Thangamani K, Tschumi CW, Wanat MJ, Maroof AM, Beckstead MJ, Rosenberg PA, Paladini CA (2019) Ventral tegmental area astrocytes orchestrate avoidance and approach behavior. Nat Commun 10:1–13 Available at: https://www.nature.com/articles/s41467-019-09131-y [Accessed February 13, 2023]. [PubMed: 30602773]

Gonek M, McLane VD, Stevens DL, Lippold K, Akbarali HI, Knapp PE, Dewey WL, Hauser KF, Paris JJ (2018) CCR5 mediates HIV-1 Tat-induced neuroinflammation and influences morphine tolerance, dependence, and reward. Brain Behav Immun 69:138 Available at: /pmc/articles/PMC5857418/ [Accessed July 12, 2022].

Gong S, Doughty M, Harbaugh CR, Cummins A, Hatten ME, Heintz N, Gerfen CR (2007) Targeting Cre Recombinase to Specific Neuron Populations with Bacterial Artificial Chromosome Constructs. J Neurosci 27:9823 Available at: /pmc/articles/PMC6672645/ [Accessed August 5, 2022].

González RG, Cheng LL, Westmoreland SV, Sakaie KE, Becerra LR, Lee PL, Masliah E, Lackner AA (2000) Early brain injury in the SIV–macaque model of AIDS. AIDS 14:2841–2849 Available at: https://journals.lww.com/aidsonline/fulltext/2000/12220/early_brain_injury_in_the_siv_macaque_model_of.5.aspx [Accessed June 9, 2022]. [PubMed: 11153665]

Goshen I, Yirmiya R (2007) The Role of Pro-inflammatory Cytokines in Memory Processes and Neural Plasticity. In: Psychoneuroimmunology, 4E ed. (Ader R, ed), pp 337–377. Burlington, MA: Elsevier.

Gosnell BA, Krahn DD, Yracheta JM, Harasha BJ (1998) The relationship between intravenous cocaine self-administration and avidity for saccharin. Pharmacol Biochem Behav 60:229–236 Available at: https://pubmed.ncbi.nlm.nih.gov/9610947/ [Accessed July 22, 2022]. [PubMed: 9610947]

Goutier W, Kloeze MB, McCreary AC (2015) The effect of varenicline on the development and expression of nicotine-induced behavioral sensitization and cross-sensitization in rats. Addict Biol 20:248–258 Available at: https://pubmed.ncbi.nlm.nih.gov/24251901/ [Accessed July 1, 2022]. [PubMed: 24251901]

Grace PM, Strand KA, Galer EL, Urban DJ, Wang X, Baratta MV, Fabisiak TJ, Anderson ND, Cheng K, Greene LI, Berkelhammer D, Zhang Y, Ellis AL, Yin HH, Campeau S, Ricei KC, Roth BL, Maier SF, Watkins LR (2016) Morphine paradoxically prolongs neuropathic pain in rats by amplifying spinal NLRP3 inflammasome activation. Proc Natl Acad Sci 113:E3441–E3450 Available at: https://www.pnas.org/doi/abs/10.1073/pnas.1602070113 [Accessed February 13, 2023]. [PubMed: 27247388]

Grace PM, Wang X, Strand KA, Baratta MV, Zhang Y, Galer EL, Yin H, Maier SF, Watkins LR (2018) DREADDed microglia in pain: implications for spinal inflammatory signaling in male rats. Exp Neurol 304:131 Available at: /pmc/articles/PMC5916033/ [Accessed February 13, 2023].

Grimm JW, Hope BT, Wise RA, Shaham Y (2001) Incubation of cocaine craving after withdrawal. Nature 412:141–142 Available at: http://www.ncbi.nlm.nih.gov/pubmed/11449260 [Accessed August 13, 2019]. [PubMed: 11449260]

Grodin EN, Bujarski S, Venegas A, Baskerville WA, Nieto SJ, Jentsch JD, Ray LA (2019) Reward, Relief and Habit Drinking: Initial Validation of a Brief Assessment Tool. Alcohol Alcohol 54:574–583 Available at: https://pubmed.ncbi.nlm.nih.gov/31557278/ [Accessed June 21, 2023]. [PubMed: 31557278]

Gu CJ, Borjabad A, Hadas E, Kelschenbach J, Kim BH, Chao W, Arancio O, Suh J, Polsky B, McMillan JE, Edagwa B, Gendelman HE, Potash MJ, Volsky DJ (2018) EcoHIV infection of mice establishes latent viral reservoirs in T cells and active viral reservoirs in macrophages that are sufficient for induction of neurocognitive impairment. PLoS Pathog 14:e1007061 Available at: /pmc/articles/PMC5991655/ [Accessed June 8, 2023]. [PubMed: 29879225]

Guenthner CJ, Miyamichi K, Yang HH, Heller HC, Luo L (2013) Permanent Genetic Access to Transiently Active Neurons via TRAP: Targeted Recombination in Active Populations. Neuron 78:784 Available at: /pmc/articles/PMC3782391/ [Accessed February 9, 2023].

Guettier JM, Gautam D, Scarselli M, De Azua IR, Li JH, Rosemond E, Ma X, Gonzalez FJ, Armbruster BN, Lu H, Roth BL, Wess J (2009) A chemical-genetic approach to study G protein regulation of β cell function in vivo. Proc Natl Acad Sci U S A 106:19202 Available at: /pmc/articles/PMC2767362/ [Accessed August 4, 2022].

Guez-Barber D, Fanous S, Golden SA, Schrama R, Koya E, Stern AL, Bossert JM, Harvey BK, Picciotto MR, Hope BT (2011) FACS identifies unique cocaine-induced gene regulation

in selectively activated adult striatal neurons. J Neurosci 31:4251–4259 Available at: https://pubmed.ncbi.nlm.nih.gov/21411666/ [Accessed August 9, 2022]. [PubMed: 21411666]

Hadamitzky M, Lückemann L, Pacheco-López G, Schedlowski M (2020) Pavlovian conditioning of immunological and neuroendocrine functions. Physiol Rev 100:357–405 Available at: https://journals.physiology.org/doi/10.1152/physrev.00033.2018 [Accessed February 9, 2023]. [PubMed: 31437089]

Häggkvist J, Björkholm C, Steensland P, Lindholm S, Franck J, Schilström B (2011) Naltrexone attenuates amphetamine-induced locomotor sensitization in the rat. Addict Biol 16:20–29 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1369-1600.2009.00199.x [Accessed July 1, 2022]. [PubMed: 20192948]

Harrod SB, Mactutus CF, Fitting S, Hasselrot U, Booze RM (2008) Intra-accumbal Tat1–72 alters acute and sensitized responses to cocaine. Pharmacol Biochem Behav 90:723–729 Available at: https://www.sciencedirect.com/science/article/pii/S0091305708002104#bib2 [Accessed August 2, 2019]. [PubMed: 18582493]

Hartzler B, Dombrowski JC, Crane HM, Eron JJ, Geng EH, Christopher Mathews W, Mayer KH, Moore RD, Mugavero MJ, Napravnik S, Rodriguez B, Donovan DM (2017) Prevalence and predictors of substance use disorders among HIV care enrollees in the United States. AIDS Behav 21:1138 Available at: /pmc/articles/PMC6089366/ [Accessed February 18, 2022]. [PubMed: 27738780]

Hauser KF, El-Hage N, Stiene-Martin A, Maragos WF, Nath A, Persidsky Y, Volsky DJ, Knapp PE (2007) HIV-1 neuropathogenesis: glial mechanisms revealed through substance abuse. J Neurochem 100:567–586 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1471-4159.2006.04227.x [Accessed August 12, 2022]. [PubMed: 17173547]

Hauser KF, Knapp PE (2014) Interactions of HIV and drugs of abuse: the importance of glia, neural progenitors, and host genetic factors. Int Rev Neurobiol 118:313 Available at: /pmc/articles/PMC4304845/ [Accessed August 12, 2022].

Heaton RK et al. (2010) HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 75:2087 Available at: /pmc/articles/PMC2995535/ [Accessed January 31, 2022]. [PubMed: 21135382]

Hinkula J, Rollman E, Lundholm P, Benthin R, Okuda K, Wahren B (2004) Genetic immunization with multiple HIV-1 genes provides protection against HIV-1/MuLV pseudovirus challenge in vivo. Cells Tissues Organs 177:169–184 Available at: https://pubmed.ncbi.nlm.nih.gov/15388991/ [Accessed July 12, 2022]. [PubMed: 15388991]

Hoefer MM, Sanchez AB, Maung R, de Rozieres CM, Catalan IC, Dowling CC, Thaney VE, Piña-Crespo J, Zhang D, Roberts AJ, Kaul M (2015) Combination of methamphetamine and HIV-1 gp120 causes distinct long-term alterations of behavior, gene expression, and injury in the central nervous system. Exp Neurol 263:221–234. [PubMed: 25246228]

Homji NF, Mao X, Langsdorf EF, Chang SL (2012a) Endotoxin-induced cytokine and chemokine expression in the HIV-1 transgenic rat. J Neuroinflammation 9:3 Available at: /pmc/articles/PMC3322344/ [Accessed February 24, 2023]. [PubMed: 22216977]

Homji NF, Vigorito M, Chang SL (2012b) Morphine-induced conditioned place preference and associated behavioural plasticity in HIV-1 transgenic rats. Int J Clin Exp Med 5:123 Available at: /pmc/articles/PMC3342709/ [Accessed July 13, 2022].

Huynh YW, Thompson BM, Larsen CE, Buch S, Guo ML, Bevins RA, Murray JE (2020) Male HIV-1 transgenic rats show reduced cocaine-maintained lever-pressing compared to F344 wildtype rats despite similar baseline locomotion. J Exp Anal Behav 113:468–484 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/jeab.586 [Accessed July 25, 2022]. [PubMed: 32077125]

Illenberger JM, Harrod SB, Mactutus CF, McLaurin KA, Kallianpur A, Booze RM (2020) HIV infection and neurocognitive disorders in the context of chronic drug abuse: Evidence for divergent findings dependent upon prior drug history. J neuroimmune Pharmacol 15:728 Available at: /pmc/articles/PMC7719073/ [Accessed July 27, 2022].

Israel Y, Quintanilla ME, Ezquer F, Morales P, Santapau D, Berríos-Cárcamo P, Ezquer M, Olivares B, Herrera-Marschitz M (2019) Aspirin and N-acetylcysteine co-administration markedly inhibit chronic ethanol intake and block relapse binge drinking: Role of neuroinflammation-oxidative

stress self-perpetuation. Addict Biol:e12853 Available at: http://www.ncbi.nlm.nih.gov/pubmed/31733014 [Accessed April 23, 2020].

Itzhak Y, Martin JL (1999) Effects of cocaine, nicotine, dizocipline and alcohol on mice locomotor activity: cocaine-alcohol cross-sensitization involves upregulation of striatal dopamine transporter binding sites. Brain Res 818:204–211 Available at: https://pubmed.ncbi.nlm.nih.gov/10082805/ [Accessed September 23, 2022]. [PubMed: 10082805]

Jaeger LB, Nath A (2012) Modeling HIV-associated neurocognitive disorders in mice: New approaches in the changing face of HIV neuropathogenesis. Dis Model Mech 5:313–322. [PubMed: 22563057]

Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y (2014) Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci Biobehav Rev 38:1–16 Available at: https://pubmed.ncbi.nlm.nih.gov/24211373/ [Accessed June 21, 2023]. [PubMed: 24211373]

Jenuwein M, Scheller C, Neuen-Jacob E, Sopper S, Tatschner T, ter Meulen V, Riederer P, Koutsilieri E (2004) Dopamine deficits and regualtion of the cAMP second messenger system in brains of simian immunodeficiency virus-infected rhesus monkeys. J Neurovirol 10:163–170 Available at: https://link.springer.com/article/10.1080/13550280490448016 [Accessed February 22, 2023]. [PubMed: 15204921]

yi Jing M, yan Ding X, Han X, yun Zhao T, min Luo M, Wu N, Li J, R Song (2022) Activation of mesocorticolimbic dopamine projections initiates cue-induced reinstatement of reward seeking in mice. Acta Pharmacol Sin 43:2276–2288 Available at: https://www.nature.com/articles/s41401-022-00866-x [Accessed September 23, 2022]. [PubMed: 35217811]

Jones LD, Jackson JW, Maggirwar SB (2016) Modeling HIV-1 Induced Neuroinflammation in Mice: Role of Platelets in Mediating Blood-Brain Barrier Dysfunction. PLoS One 11:e0151702 Available at: /pmc/articles/PMC4795798/ [Accessed February 22, 2023]. [PubMed: 26986758]

Jones M, Olafson K, Del Bigio MR, Peeling J, Nath A (1998) Intraventricular Injection of Human Immunodeficiency Virus Type 1 (HIV-1) Tat Protein Causes Inflammation, Gliosis, Apoptosis, and Ventricular Enlargement. J Neuropathol Exp Neurol 57:563–570 Available at: https://academic.oup.com/jnen/article/57/6/563/2609643 [Accessed June 9, 2022]. [PubMed: 9630236]

Joseph SB, Arrildt KT, Sturdevant CB, Swanstrom R (2015) HIV-1 target cells in the CNS. J Neurovirol 21:276–289 Available at: https://link.springer.com/article/10.1007/s13365-014-0287-x [Accessed August 12, 2022]. [PubMed: 25236812]

Joshi CR, Stacy S, Sumien N, Ghorpade A, Borgmann K (2020) Astrocyte HIV-1 Tat Differentially Modulates Behavior and Brain MMP/TIMP Balance During Short and Prolonged Induction in Transgenic Mice. Front Neurol 11:593188. [PubMed: 33384653]

Joyce EM, Iversen SD (1979) The effect of morphine applied locally to mesencephalic dopamine cell bodies on spontaneous motor activity in the rat. Neurosci Lett 14:207–212 Available at: https://pubmed.ncbi.nlm.nih.gov/530497/ [Accessed September 23, 2022]. [PubMed: 530497]

Kalivas PW (2009) The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci 10:561–572 Available at: http://www.ncbi.nlm.nih.gov/pubmed/19571793. [PubMed: 19571793]

Kang J, Jiang L, Goldman SA, Nedergaard M (1998) Astrocyte-mediated potentiation of inhibitory synaptic transmission. Nat Neurosci 1:683–692 Available at: https://www.nature.com/articles/nn1298_683 [Accessed February 13, 2023]. [PubMed: 10196584]

Kang YJ, Digicaylioglu M, Russo R, Kaul M, Achim CL, Fletcher L, Masliah E, Lipton SA (2010) Erythropoietin Plus Insulin-like Growth Factor-I Protects against Neuronal Damage in a Murine Model of Human Immunodeficiency Virus-Associated Neurocognitive Disorders. Ann Neurol 68:352 Available at: /pmc/articles/PMC3733362/ [Accessed February 23, 2023].

Katz RJ, Gormezano G (1979) A rapid and inexpensive technique for assessing the reinforcing effects of opiate drugs. Pharmacol Biochem Behav 11:231–233. [PubMed: 504302]

Kawa AB, Allain F, Robinson TE, Samaha A-N (2019) The transition to cocaine addiction: the importance of pharmacokinetics for preclinical models. Psychopharmacology (Berl) 236:1145–1157 Available at: https://link.springer.com/article/10.1007/s00213-019-5164-0 [Accessed July 22, 2022]. [PubMed: 30820634]

Kawamoto EM, Vivar C, Camandola S (2012) Physiology and pathology of calcium signaling in the brain. Front Pharmacol 3:61. [PubMed: 22518105]

Kayama T, Ikegaya Y, Sasaki T (2022) Phasic firing of dopaminergic neurons in the ventral tegmental area triggers peripheral immune responses. Sci Rep 12:1–9 Available at: https://www.nature.com/articles/s41598-022-05306-8 [Accessed February 9, 2023]. [PubMed: 34992227]

Keating SM, Golub ET, Nowicki M, Young M, Anastos K, Crystal H, Cohen MH, Zhang J, Greenblatt RM, Desai S, Wu S, Landay AL, Gange SJ, Norris PJ (2011) The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of US women. AIDS 25:1832 Available at: /pmc/articles/PMC3314300/ [Accessed February 22, 2023].

Keating SM, Jacobs ES, Norris PJ (2012) Soluble mediators of inflammation in HIV and their implications for therapeutics and vaccine development. Cytokine Growth Factor Rev 23:193–206. [PubMed: 22743035]

Kelschenbach J, He H, Kim BH, Borjabad A, Gu CJ, Chao W, Do M, Sharer LR, Zhang H, Arancio O, Potash MJ, Volsky DJ (2019) Efficient expression of HIV in immunocompetent mouse brain reveals a novel nonneurotoxic viral function in hippocampal synaptodendritic injury and memory impairment. MBio 10.

Keppler OT, Yonemoto W, Welte FJ, Patton KS, Iacovides D, Atchison RE, Ngo T, Hirschberg DL, Speck RF, Goldsmith MA (2001) Susceptibility of Rat-Derived Cells to Replication by Human Immunodeficiency Virus Type 1. J Virol 75:8073 Available at: /pmc/articles/PMC115050/ [Accessed February 2, 2023].

Kesby JP, Hubbard DT, Markou A, Semenova S (2014) Expression of HIV gp120 protein increases sensitivity to the rewarding properties of methamphetamine in mice. Addict Biol 19:593–605 Available at: http://www.ncbi.nlm.nih.gov/pubmed/23252824 [Accessed July 8, 2019]. [PubMed: 23252824]

Kesby JP, Najera JA, Romoli B, Fang Y, Basova L, Birmingham A, Marcondes MCG, Dulcis D, Semenova S (2017) HIV-1 TAT protein enhances sensitization to methamphetamine by affecting dopaminergic function. Brain Behav Immun 65:210–221 Available at: http://www.ncbi.nlm.nih.gov/pubmed/28495611 [Accessed July 29, 2019]. [PubMed: 28495611]

Kim BO, Liu Y, Ruan Y, Xu ZC, Schantz L, He JJ (2003a) Neuropathologies in Transgenic Mice Expressing Human Immunodeficiency Virus Type 1 Tat Protein under the Regulation of the Astrocyte-Specific Glial Fibrillary Acidic Protein Promoter and Doxycycline. Am J Pathol 162:1693–1707. [PubMed: 12707054]

Kim BO, Liu Y, Ruan Y, Xu ZC, Schantz L, He JJ (2003b) Neuropathologies in Transgenic Mice Expressing Human Immunodeficiency Virus Type 1 Tat Protein under the Regulation of the Astrocyte-Specific Glial Fibrillary Acidic Protein Promoter and Doxycycline. Am J Pathol 162:1707 Available at: /pmc/articles/PMC1851199/ [Accessed June 16, 2023].

Klawonn AM, Fritz M, Castany S, Pignatelli M, Canal C, Similä F, Tejeda HA, Levinsson J, Jaarola M, Jakobsson J, Hidalgo J, Heilig M, Bonci A, Engblom D (2021) Microglial activation elicits a negative affective state through prostaglandin-mediated modulation of striatal neurons. Immunity 54:225–234.e6 Available at: https://pubmed.ncbi.nlm.nih.gov/33476547/ [Accessed February 13, 2023]. [PubMed: 33476547]

Knackstedt LA, Melendez RI, Kalivas PW (2010) Ceftriaxone Restores Glutamate Homeostasis and Prevents Relapse to Cocaine Seeking. Biol Psychiatry 67:81–84. [PubMed: 19717140]

Koob GF, Volkow ND (2016) Neurobiology of addiction: a neurocircuitry analysis. The Lancet Psychiatry 3:760–773 Available at: http://www.ncbi.nlm.nih.gov/pubmed/27475769 [Accessed June 12, 2019]. [PubMed: 27475769]

Koren T, Yifa R, Amer M, Krot M, Boshnak N, Ben-Shaanan TL, Azulay-Debby H, Zalayat I, Avishai E, Hajjo H, Schiller M, Haykin H, Korin B, Farfara D, Hakim F, Kobiler O, Rosenblum K, Rolls A (2021) Insular cortex neurons encode and retrieve specific immune responses. Cell 184:5902–5915.e17. [PubMed: 34752731]

Korin B, Rolls A (2018) Application of Chemogenetics and Optogenetics to Dissect Brain-Immune Interactions. Methods Mol Biol 1781:195–208 Available at: https://pubmed.ncbi.nlm.nih.gov/29705849/ [Accessed February 9, 2023].

Koutsilieri E, Götz ME, Sopper S, Stahl-Hennig C, Czub M, ter Meulen V, Riederer P (1997) Monoamine metabolite levels in CSF of SIV-infected rhesus monkeys (Macaca

mulatta). Neuroreport 8:3833–3836 Available at: https://journals.lww.com/neuroreport/fulltext/1997/12010/monoamine_metabolite_levels_in_csf_of_siv_infected.34.aspx [Accessed June 10, 2022]. [PubMed: 9427379]

Koya E, Golden SA, Harvey BK, Guez-Barber DH, Berkow A, Simmons DE, Bossert JM, Nair SG, Uejima JL, Marin MT, Mitchell TB, Farquhar D, Ghosh SC, Mattson BJ, Hope BT (2009) Targeted disruption of cocaine-activated nucleus accumbens neurons prevents context-specific sensitization. Nat Neurosci 12:1069–1073 Available at: https://www.nature.com/articles/nn.2364 [Accessed August 9, 2022]. [PubMed: 19620976]

Krishnan N, Gittelsohn J, Ross A, Elf J, Chon S, Niaura R, Martinson N, Golub JE (2018) Qualitative Exploration of a Smoking Cessation Trial for People Living With HIV in South Africa. Nicotine Tob Res 20:1117–1123 Available at: https://pubmed.ncbi.nlm.nih.gov/28637262/ [Accessed June 21, 2023]. [PubMed: 28637262]

Krucker T, Toggas SM, Mucke L, Siggins GR (1998) Transgenic mice with cerebral expression of human immunodeficiency virus type-1 coat protein gp120 show divergent changes in short- and long-term potentiation in CA1 hippocampus. Neuroscience 83:691–700 Available at: https://pubmed.ncbi.nlm.nih.gov/9483553/ [Accessed February 23, 2023]. [PubMed: 9483553]

Kruyer A, Angelis A, Garcia-Keller C, Li H, Kalivas PW (2022) Plasticity in astrocyte subpopulations regulates heroin relapse. Sci Adv 8:eabo7044 Available at: https://pubmed.ncbi.nlm.nih.gov/35947652/ [Accessed September 23, 2022]. [PubMed: 35947652]

Kumar R, Perez-Casanova AE, Tirado G, Noel RJ, Torres C, Rodriguez I, Martinez M, Staprans S, Kraiselburd E, Yamamura Y, Higley JD, Kumar A (2005) Increased viral replication in simian immunodeficiency virus/simian-HIV- infected macaques with self-administering model of chronic alcohol consumption. J Acquir Immune Defic Syndr 39:386–390 Available at: https://journals.lww.com/jaids/Fulltext/2005/08010/Increased_Viral_Replication_in_Simian.2.aspx [Accessed July 21, 2022]. [PubMed: 16010157]

Kumar S, Rao PSS, Earla R, Kumar A (2015) Drug-drug interactions between anti-retroviral therapies and drugs of abuse in HIV systems. Expert Opin Drug Metab Toxicol 11:343–355. [PubMed: 25539046]

Kupchik YM, Brown RM, Heinsbroek J a, Lobo MK, Schwartz DJ, Kalivas PW (2015) Coding the direct/indirect pathways by D1 and D2 receptors is not valid for accumbens projections. Nat Neurosci 18:1230–1232 Available at: http://www.ncbi.nlm.nih.gov/pubmed/26214370. [PubMed: 26214370]

LaCrosse AL, Hill K, Knackstedt LA (2016) Ceftriaxone attenuates cocaine relapse after abstinence through modulation of nucleus accumbens AMPA subunit expression. Eur Neuropsychopharmacol 26:186–194. [PubMed: 26706696]

Langford D, Kim BO, Zou W, Fan Y, Rahimain P, Liu Y, He JJ (2018) Doxycycline-inducible and astrocyte-specific HIV-1 Tat transgenic mice (iTat) as an HIV/neuroAIDS model. J Neurovirol 24:179 Available at: /pmc/articles/PMC6444363/ [Accessed February 2, 2023].

LaRowe SD, Kalivas PW, Nicholas JS, Randall PK, Mardikian PN, Malcolm RJ (2013) A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. Am J Addict 22:443–452 Available at: http://www.ncbi.nlm.nih.gov/pubmed/23952889 [Accessed April 4, 2017]. [PubMed: 23952889]

Lawson MA, Kelley KW, Dantzer R (2011) Intracerebroventricular Administration of HIV-1 Tat Induces Brain Cytokine and Indoleamine 2,3-Dioxygenase Expression: A Possible Mechanism for AIDS Comorbid Depression. Brain Behav Immun 25:1575 Available at: /pmc/articles/PMC3191256/ [Accessed June 9, 2022].

Lee BR, Ma YY, Huang YH, Wang X, Otaka M, Ishikawa M, Neumann PA, Graziane NM, Brown TE, Suska A, Guo C, Lobo MK, Sesack SR, Wolf ME, Nestler EJ, Shaham Y, Schlüter OM, Dong Y (2013) Maturation of silent synapses in amygdala-accumbens projection contributes to incubation of cocaine craving. Nat Neurosci 16:1644–1651 Available at: https://pubmed.ncbi.nlm.nih.gov/24077564/ [Accessed July 28, 2022]. [PubMed: 24077564]

Leibrand CR, Paris JJ, Ghandour MS, Knapp PE, Kim W-K, Hauser KF, McRae M (2017) HIV-1 Tat disrupts blood-brain barrier integrity and increases phagocytic perivascular macrophages and microglia in the dorsal striatum of transgenic mice. Neurosci Lett 640:136–143 Available at: http://www.ncbi.nlm.nih.gov/pubmed/28057474 [Accessed July 29, 2019]. [PubMed: 28057474]

Lemey P, Pybus OG, Bin W, Saksena NK, Salemi M, Vandamme AM (2003) Tracing the origin and history of the HIV-2 epidemic. Proc Natl Acad Sci 100:6588–6592 Available at: https://www.pnas.org/doi/abs/10.1073/pnas.0936469100 [Accessed May 25, 2023]. [PubMed: 12743376]

Letvin NL, Eaton KA, Aldrich WR, Sehgal PK, Blake BJ, Schlossman SF, King NW, Hunt RD (1983) Acquired immunodeficiency syndrome in a colony of macaque monkeys. Proc Natl Acad Sci U S A 80:2718–2722 Available at: https://www.pnas.org [Accessed June 9, 2022]. [PubMed: 6221343]

Li G, Makar T, Gerzanich V, Kalakonda S, Ivanova S, Pereira EFR, Andharvarapu S, Zhang J, Simard JM, Zhao RY (2020) HIV-1 Vpr-Induced Proinflammatory Response and Apoptosis Are Mediated through the Sur1-Trpm4 Channel in Astrocytes. MBio 11:e02939–20 Available at: https://doi.org/10 [Accessed June 6, 2023]. [PubMed: 33293383]

Li H, McLaurin KA, Illenberger JM, Mactutus CF, Booze RM (2021a) Microglial HIV-1 expression: Role in HIV-1 associated neurocognitive disorders. Viruses 13.

Li H, McLaurin KA, Mactutus CF, Booze RM (2021b) A rat model of ecohiv brain infection. J Vis Exp 2021:1–10.

Li MD, Cao J, Wang S, Wang J, Sarkar S, Vigorito M, Ma JZ, Chang SL (2013) Transcriptome Sequencing of Gene Expression in the Brain of the HIV-1 Transgenic Rat. PLoS One 8:e59582 Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0059582 [Accessed June 29, 2022]. [PubMed: 23536882]

Lin MZ, Schnitzer MJ (2016) Genetically encoded indicators of neuronal activity. Nat Neurosci 19:1142–1153 Available at: https://www.nature.com/articles/nn.4359 [Accessed August 12, 2022]. [PubMed: 27571193]

Lipton SA (1991) HIV-Related Neurotoxicity. Brain Pathol 1:193–199 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1750-3639.1991.tb00659.x [Accessed June 8, 2022]. [PubMed: 1669708]

Liu X, Chang L, Vigorito M, Kass M, Li H, Chang SL (2009) Methamphetamine-induced behavioral sensitization is enhanced in the HIV-1 transgenic rat. J Neuroimmune Pharmacol 4:309–316. [PubMed: 19444617]

López AB, Rivera-Baltanas T, Pérez-Rodríguez D, Alonso-Crespo D, Fernández-Pereira C, Olivares JM, Agís-Balboa RC (2021) Microglia: The Real Foe in HIV-1-Associated Neurocognitive Disorders? Biomedicines 9:925 Available at: /pmc/articles/PMC8389599/ [Accessed July 12, 2022]. [PubMed: 34440127]

Louboutin JP, Agrawal L, Reyes BAS, Van Bockstaele EJ, Strayer DS (2010) HIV-1 gp120-Induced Injury to the Blood-Brain Barrier: Role of Metalloproteinases 2 and 9 and Relationship to Oxidative Stress. J Neuropathol Exp Neurol 69:816 Available at: /pmc/articles/PMC4707960/ [Accessed June 9, 2022].

Ma YY, Lee BR, Wang X, Guo C, Liu L, Cui R, Lan Y, Balcita-Pedicino JJ, Wolf ME, Sesack SR, Shaham Y, Schlüter OM, Huang YH, Dong Y (2014) Bidirectional modulation of incubation of cocaine craving by silent synapse-based remodeling of prefrontal cortex to accumbens projections. Neuron 83:1453–1467 Available at: https://pubmed.ncbi.nlm.nih.gov/25199705/ [Accessed July 28, 2022]. [PubMed: 25199705]

Mallard J, Williams KC (2018) Animal models of HIV-associated disease of the central nervous system. In: Handbook of Clinical Neurology, 3rd ed. (Brew BJ, ed), pp 41–53. Amsterdam: Elsevier B.V.

Mallipattu SK, Liu R, Zhong Y, Chen EY, D'Agati V, Kaufman L, Ma'Ayan A, Klotman PE, Chuang PY, He JC (2013) Expression of HIV transgene aggravates kidney injury in diabetic mice. Kidney Int 83:634 Available at: /pmc/articles/PMC3612382/ [Accessed June 6, 2023].

Marcario JK, Pendyala G, Riazi M, Fleming K, Marquis J, Callen S, Lisco SJ, Fowler SC, Cheney PD, Buch SJ (2016) Effects of Morphine on Behavioral Task Performance in SIV-Infected Rhesus Macaques. J Neuroimmune Pharmacol 11:348–357 Available at: https://link.springer.com/article/10.1007/s11481-016-9667-8 [Accessed June 2, 2023]. [PubMed: 27039332]

Marcario JK, Raymond LAM, McKiernan BJ, Foresman LL, Joag SV, Raghavan R, Narayan O, Hershberger S, Cheney (1999) Simple and Choice Reaction Time Performance in SIV-Infected Rhesus Macaques. AIDS Res Hum Retroviruses 15:571–

583 Available at: https://sci-hub.ru/https://www.liebertpub.com/doi/10.1089/088922299311097?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub 0pubmed [Accessed June 2, 2023]. [PubMed: 10221534]

Marcondes MCG, Watry D, Zandonatti M, Flynn C, Taffe MA, Fox H (2008) Chronic Alcohol Consumption Generates a Vulnerable Immune Environment During Early SIV Infection in Rhesus Macaques. Alcohol Clin Exp Res 32:1583–1592 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1530-0277.2008.00730.x [Accessed July 22, 2022]. [PubMed: 18616669]

Mathews S, Branch Woods A, Katano I, Makarov E, Thomas MB, Gendelman HE, Poluektova LY, Ito M, Gorantla S (2019) Human Interleukin-34 facilitates microglia-like cell differentiation and persistent HIV-1 infection in humanized mice. Mol Neurodegener 14:12 Available at: /pmc/articles/PMC6399898/ [Accessed June 8, 2023]. [PubMed: 30832693]

Mattson BJ, Koya E, Simmons DE, Mitchell TB, Berkow A, Crombag HS, Hope BT (2008) Context-specific sensitization of cocaine-induced locomotor activity and associated neuronal ensembles in rat nucleus accumbens. Eur J Neurosci 27:202–212 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1460-9568.2007.05984.x [Accessed August 9, 2022]. [PubMed: 18093170]

Maung R, Hoefer MM, Sanchez AB, Sejbuk NE, Medders KE, Desai MK, Catalan IC, Dowling CC, de Rozieres CM, Garden GA, Russo R, Roberts AJ, Williams R, Kaul M (2014) CCR5 Knockout Prevents Neuronal Injury and Behavioral Impairment Induced in a Transgenic Mouse Model by a CXCR4-using HIV-1 Glycoprotein 120. J Immunol 193:1910 Available at: /pmc/articles/PMC4370188/ [Accessed February 23, 2023].

McCune JM, Kaneshima H, Krowka J, Namikawa R, Outzen H, Peault B, Rabin L, Shih CC, Yee E, Lieberman M, Weissman I, Shultz L (1991) The SCID-hu mouse: a small animal model for HIV infection and pathogenesis. Annu Rev Immunol 9:399–429 Available at: https://pubmed.ncbi.nlm.nih.gov/1910684/ [Accessed June 8, 2023]. [PubMed: 1910684]

McCune JM, Namikawa R, Kaneshima H, Shultz LD, Lieberman M, Weissman IL (1988) The SCID-hu mouse: murine model for the analysis of human hematolymphoid differentiation and function. Science (80-) 241:1632–1639 Available at: https://pubmed.ncbi.nlm.nih.gov/2971269/ [Accessed June 8, 2023].

McIntosh S, Sexton T, Pattison LP, Childers SR, Hemby SE (2015) Increased Sensitivity to Cocaine Self-Administration in HIV-1 Transgenic Rats is Associated with Changes in Striatal Dopamine Transporter Binding. J Neuroimmune Pharmacol 10:493–505 Available at: http://www.ncbi.nlm.nih.gov/pubmed/25749646 [Accessed August 13, 2019]. [PubMed: 25749646]

McKendrick G, Graziane NM (2020) Drug-Induced Conditioned Place Preference and Its Practical Use in Substance Use Disorder Research. Front Behav Neurosci 14:582147. [PubMed: 33132862]

McLaughlin J, Ganno M, Eans S, Mizrachi E, Paris J (2014) HIV-1 Tat protein exposure potentiates ethanol reward and reinstates extinguished ethanol-conditioned place preference. Curr HIV Res 12:415–423 Available at: https://pubmed.ncbi.nlm.nih.gov/25760047/ [Accessed July 12, 2022]. [PubMed: 25760047]

McLaurin KA, Bertrand SJ, Illenberger JM, Harrod SB, Mactutus CF, Booze RM (2021) S-Equol mitigates motivational deficits and dysregulation associated with HIV-1. Sci Rep 11:1–17 Available at: https://www.nature.com/articles/s41598-021-91240-0 [Accessed July 25, 2022]. [PubMed: 33414495]

McLaurin KA, Cook AK, Li H, League AF, Mactutus CF, Booze RM (2018) Synaptic Connectivity in Medium Spiny Neurons of the Nucleus Accumbens: A Sex-Dependent Mechanism Underlying Apathy in the HIV-1 Transgenic Rat. Front Behav Neurosci 12.

McLaurin KA, Li H, Mactutus CF, Harrod SB, Booze RM (2022) Disrupted Decision-Making: EcoHIV Inoculation in Cocaine Dependent Rats. Int J Mol Sci 23 Available at: /pmc/articles/PMC9409394/ [Accessed May 15, 2023].

Mediouni S, Jablonski J, Paris JJ, Clementz MA, Thenin-Houssier S, McLaughlin JP, Valente ST (2015) Didehydro-Cortistatin A inhibits HIV-1 Tat mediated neuroinflammation and prevents potentiation of cocaine reward in Tat transgenic mice. Curr HIV Res 13:69 Available at: /pmc/articles/PMC4416414/ [Accessed July 12, 2022].

Melendez RI, Roman C, Capo-Velez CM, Lasalde-Dominicci JA (2016) Decreased glial and synaptic glutamate uptake in the striatum of HIV-1 gp120 transgenic mice. J Neurovirol 22:358–365 Available at: http://www.ncbi.nlm.nih.gov/pubmed/26567011 [Accessed July 8, 2019]. [PubMed: 26567011]

Menard C et al. (2017) Social stress induces neurovascular pathology promoting depression. Nat Neurosci 20:1752–1760. [PubMed: 29184215]

Meulendyke KA, Pletnikov MV, Engle EL, Tarwater PM, Graham DR, Zink MC (2012) Early minocycline treatment prevents a decrease in striatal dopamine in an SIV model of HIV-associated neurological disease. J Neuroimmune Pharmacol 7:454–464 Available at: https://link.springer.com/article/10.1007/s11481-011-9332-1 [Accessed June 10, 2022]. [PubMed: 22198699]

Micci L, Alvarez X, Iriele RI, Ortiz AM, Ryan ES, McGary CS, Deleage C, McAtee BB, He T, Apetrei C, Easley K, Pahwa S, Collman RG, Derdeyn CA, Davenport MP, Estes JD, Silvestri G, Lackner AA, Paiardini M (2014) CD4 Depletion in SIV-Infected Macaques Results in Macrophage and Microglia Infection with Rapid Turnover of Infected Cells. PLOS Pathog 10:e1004467 Available at: https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004467 [Accessed February 22, 2023]. [PubMed: 25356757]

Midde NM, Gomez AM, Harrod SB, Zhu J (2011) Genetically expressed HIV-1 viral proteins attenuate nicotine-induced behavioral sensitization and alter mesocorticolimbic ERK and CREB signaling in rats. Pharmacol Biochem Behav 98:587–597. [PubMed: 21420997]

Miesenböck G (2009) The optogenetic catechism. Science (80-) 326:395–399 Available at: https://pubmed.ncbi.nlm.nih.gov/19833960/ [Accessed July 26, 2022].

Miller DR, Shaerzadeh F, Phan L, Sharif N, Gamble-George J, McLaughlin JP, Streit WJ, Khoshbouei H (2018) HIV-1 Tat regulation of dopamine transmission and microglial reactivity is brain region specific. Glia 66:1915–1928 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/glia.23447 [Accessed June 16, 2023]. [PubMed: 29733459]

Misra A, Thippeshappa R, Kimata JT (2013) Macaques as model hosts for studies of HIV-1 infection. Front Microbiol 4.

Mizrachi Y, Sternas L, Volsky DI (1992) The establishment of rodent cell lines persistently producing HIV-1. Virology 186:167–174 Available at: https://pubmed.ncbi.nlm.nih.gov/1727596/ [Accessed February 2, 2023]. [PubMed: 1727596]

Mocchetti I, Nosheny RL, Tanda G, Ren K, Meyer EM (2007) Brain-Derived Neurotrophic Factor Prevents Human Immunodeficiency Virus Type 1 Protein gp120 Neurotoxicity in the Rat Nigrostriatal System. Ann N Y Acad Sci 1122:144–154 Available at: https://onlinelibrary.wiley.com/doi/full/10.1196/annals.1403.010 [Accessed June 9, 2022]. [PubMed: 18077570]

Molina PE, Amedee A, Lecapitaine NJ, Zabaleta J, Mohan M, Winsauer P, Vande Stouwe C (2011) Cannabinoid neuroimmune modulation of SIV disease. J neuroimmune Pharmacol 6:527 Available at: /pmc/articles/PMC3208744/ [Accessed June 5, 2023].

Montgomery MM, Dean AF, Taffs F, Stott EJ, Lantos PL, Luthert PJ (1999) Progressive dendritic pathology in cynomolgus macaques infected with simian immunodeficiency virus. Neuropathol Appl Neurobiol 25:11–19 Available at: https://europepmc.org/article/med/10194771 [Accessed February 22, 2023]. [PubMed: 10194771]

Moran LM, Booze RM, Mactutus CF (2014) Modeling deficits in attention, inhibition, and flexibility in HAND. J Neuroimmune Pharmacol 9:508–521. [PubMed: 24764039]

Moran LM, Booze RM, Webb KM, Mactutus CF (2013) Neurobehavioral alterations in HIV-1 transgenic rats: Evidence for dopaminergic dysfunction. Exp Neurol 239:139–147 Available at: https://www.sciencedirect.com/science/article/pii/S0014488612003913 [Accessed September 4, 2019]. [PubMed: 23063600]

Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK (2005) Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. J Neurosci 25:6389–6393 Available at: http://www.ncbi.nlm.nih.gov/pubmed/16000629 [Accessed April 4, 2017]. [PubMed: 16000629]

Mucha RF, Iversen SD (1984) Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. Psychopharmacology (Berl) 82:241–

247 Available at: https://link.springer.com/article/10.1007/BF00427782 [Accessed July 11, 2022]. [PubMed: 6425908]

Müller WEG, Schröder HC, Ushijima H, Dapper J, Bormann J (1992) gp120 of HIV-1 induces apoptosis in rat cortical cell cultures: prevention by memantine. Eur J Pharmacol Mol Pharmacol 226:209–214.

Murray EA, Rausch DM, Lendvay J, Sharer LR, Eiden LE (1992) Cognitive and Motor Impairments Associated with SIV Infection in Rhesus Monkeys. Science (80-) 255:1246–1249 Available at: https://www.science.org/doi/abs/10.1126/science.1546323 [Accessed June 9, 2022].

Najera JA, Bustamante EA, Bortell N, Morsey B, Fox HS, Ravasi T, Marcondes MCG (2016) Methamphetamine abuse affects gene expression in brain-derived microglia of SIV-infected macaques to enhance inflammation and promote virus targets. BMC Immunol 17:1–19 Available at: https://bmcimmunol.biomedcentral.com/articles/10.1186/s12865-016-0145-0 [Accessed June 5, 2023]. [PubMed: 26727976]

Namba MD, Kupchik YM, Spencer SM, Garcia-Keller C, Goenaga JG, Powell GL, Vicino IA, Hogue IB, Gipson CD (2020) Accumbens neuroimmune signaling and dysregulation of astrocytic glutamate transport underlie conditioned nicotine-seeking behavior. Addict Biol 25:e12797. [PubMed: 31330570]

Namba MD, Leyrer-Jackson JM, Nagy EK, Olive MF, Neisewander JL (2021) Neuroimmune Mechanisms as Novel Treatment Targets for Substance Use Disorders and Associated Comorbidities. Front Neurosci 15:650785. [PubMed: 33935636]

Namba MD, Phillips MN, Chen P-J, Blass BE, Olive MF, Neisewander JL (2023) HIV gp120 impairs nucleus accumbens neuroimmune function and dopamine D3 receptor-mediated inhibition of cocaine seeking in male rats. Addict Neurosci 5:100062 Available at: https://linkinghub.elsevier.com/retrieve/pii/S2772392523000020 [Accessed February 7, 2023]. [PubMed: 36909738]

Namba MD, Phillips MN, Neisewander JL, Olive MF (2022) Nuclear factor kappa B signaling within the rat nucleus accumbens core sex-dependently regulates cue-induced cocaine seeking and matrix metalloproteinase-9 expression. Brain Behav Immun 102:252–265 Available at: https://linkinghub.elsevier.com/retrieve/pii/S0889159122000708 [Accessed March 9, 2022]. [PubMed: 35259426]

Namba MD, Tomek SE, Olive MF, Beckmann JS, Gipson CD (2018) The Winding Road to Relapse: Forging a New Understanding of Cue-Induced Reinstatement Models and Their Associated Neural Mechanisms. Front Behav Neurosci 12:1–22 Available at: http://journal.frontiersin.org/article/10.3389/fnbeh.2018.00017/full. [PubMed: 29403366]

Namikawa R, Kaneshima H, Lieberman M, Weissman IL, McCune JM (1988) Infection of the SCID-hu Mouse by HIV-1. Science (80-) 242:1684–1686 Available at: https://www.science.org/doi/10.1126/science.3201256 [Accessed June 8, 2023].

Nath A, Anderson C, Jones M, Maragos W, Booze R, Mactutus C, Bell J, Hauser K, Mattson M (2016) Neurotoxicity and dysfunction of dopaminergic systems associated with AIDS dementia. J Psychopharmacol 14:222–227 Available at: https://journals.sagepub.com/doi/abs/10.1177/026988110001400305?journalCode=jopa [Accessed February 1, 2023].

Nath A, Psooy K, Martin C, Knudsen B, Magnuson DSK, Haughey N, Geiger JD (1996) Identification of a human immunodeficiency virus type 1 Tat epitope that is neuroexcitatory and neurotoxic. J Virol 70:1475–1480 Available at: https://journals.asm.org/doi/abs/10.1128/jvi.70.3.1475-1480.1996 [Accessed June 8, 2022]. [PubMed: 8627665]

National Institute on Drug Abuse (2020) Common Comorbidities with Substance Use Disorders Research Report. Bethesda (MD): National Institutes on Drug Abuse (US). Available at: https://www.ncbi.nlm.nih.gov/books/NBK571451/ [Accessed February 7, 2023].

Nayak SU, Cicalese S, Tallarida C, Oliver CF, Rawls SM (2020) Chemokine CCR5 and cocaine interactions in the brain: Cocaine enhances mesolimbic CCR5 mRNA levels and produces place preference and locomotor activation that are reduced by a CCR5 antagonist. Brain Behav Immun 83:288–292 Available at: http://www.ncbi.nlm.nih.gov/pubmed/31557508 [Accessed March 20, 2020]. [PubMed: 31557508]

Nerrienet E, Santiago ML, Foupouapouognigni Y, Bailes E, Mundy NI, Njinku B, Kfutwah A, Muller-Trutwin MC, Barre-Sinoussi F, Shaw GM, Sharp PM, Hahn BH, Ayouba A (2005)

Simian Immunodeficiency Virus Infection in Wild-Caught Chimpanzees from Cameroon. J Virol 79:1312–1319 Available at: https://journals.asm.org/doi/full/10.1128/JVI.79.2.1312-1319.2005 [Accessed June 9, 2022]. [PubMed: 15613358]

Nestler EJ (2008) Review. Transcriptional mechanisms of addiction: role of DeltaFosB. Philos Trans R Soc Lond B Biol Sci 363:3245–3255 Available at: https://pubmed.ncbi.nlm.nih.gov/18640924/ [Accessed July 22, 2022]. [PubMed: 18640924]

Nickoloff-Bybel EA, Calderon TM, Gaskill PJ, Berman JW (2020) HIV Neuropathogenesis in the Presence of a Disrupted Dopamine System. J neuroimmune Pharmacol 15:742 Available at: /pmc/articles/PMC7905900/ [Accessed July 27, 2022].

Niu M, Morsey B, Lamberty BG, Emanuel K, Yu F, León-Rivera R, Berman JW, Gaskill PJ, Matt SM, Ciborowski PS, Fox HS (2020) Methamphetamine Increases the Proportion of SIV-Infected Microglia/Macrophages, Alters Metabolic Pathways, and Elevates Cell Death Pathways: A Single-Cell Analysis. Viruses 12:1297 Available at: /pmc/articles/PMC7697917/ [Accessed June 5, 2023]. [PubMed: 33198269]

Nolan R, Gaskill PJ (2019) The role of catecholamines in HIV neuropathogenesis. Brain Res 1702:54–73. [PubMed: 29705605]

Norman LR, Basso M, Kumar A, Malow R (2009) Neuropsychological Consequences of HIV and Substance Abuse: A Literature Review and Implications for Treatment and Future Research. Curr Drug Abuse Rev 2:156 Available at: /pmc/articles/PMC6167747/ [Accessed June 6, 2022].

Nosheny RL, Bachis A, Aden SA, De Bernardi MA, Mocchetti I (2006) Intrastriatal administration of human immunodeficiency virus-1 glycoprotein 120 reduces glial cell-line derived neurotrophic factor levels and causes apoptosis in the substantia nigra. J Neurobiol 66:1311–1321 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/neu.20288 [Accessed June 9, 2022]. [PubMed: 16967504]

O'Brien CP, Childress AR, McLellan AT, Ehrman R (1992) Classical Conditioning in Drug-Dependent Humansa. Ann N Y Acad Sci 654:400–415 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1749-6632.1992.tb25984.x [Accessed October 7, 2021]. [PubMed: 1632593]

O'Neal TJ, Nooney MN, Thien K, Ferguson SM (2019) Chemogenetic modulation of accumbens direct or indirect pathways bidirectionally alters reinstatement of heroin-seeking in high- but not low-risk rats. Neuropsychopharmacol 2019 458 45:1251–1262 Available at: https://www.nature.com/articles/s41386-019-0571-9 [Accessed September 23, 2022].

Ohene-Nyako M, Persons AL, Napier TC (2018) Region-specific changes in markers of neuroplasticity revealed in HIV-1 transgenic rats by low-dose methamphetamine. Brain Struct Funct 223:3503–3513 Available at: https://link.springer.com/article/10.1007/s00429-018-1701-6 [Accessed July 22, 2022]. [PubMed: 29931627]

Ohene-Nyako M, Persons AL, Napier TC (2021) Hippocampal blood–brain barrier of methamphetamine self-administering HIV-1 transgenic rats. Eur J Neurosci 53:416–429 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/ejn.14925 [Accessed July 25, 2022]. [PubMed: 32725911]

Paris JJ, Carey AN, Shay CF, Gomes SM, He JJ, McLaughlin JP (2014a) Effects of conditional central expression of HIV-1 tat protein to potentiate cocaine-mediated psychostimulation and reward among male mice. Neuropsychopharmacology 39:380–388 Available at: http://www.ncbi.nlm.nih.gov/pubmed/23945478 [Accessed August 13, 2019]. [PubMed: 23945478]

Paris JJ, Fenwick J, McLaughlin JP (2014b) Estrous cycle and HIV-1 Tat protein influence cocaine-conditioned place preference and induced locomotion of female mice. Curr HIV Res 12:388–396 Available at: http://www.ncbi.nlm.nih.gov/pubmed/25613137 [Accessed September 5, 2019]. [PubMed: 25613137]

Parusel S, Yi M-H, Hunt CL, Wu L-J (2022) Chemogenetic and Optogenetic Manipulations of Microglia in Chronic Pain. Neurosci Bull 1:1–11 Available at: https://link.springer.com/article/10.1007/s12264-022-00937-3 [Accessed February 13, 2023].

Pascoli V, Terrier J, Espallergues J, Valjent E, O'connor EC, Lüscher C (2014) Contrasting forms of cocaine-evoked plasticity control components of relapse. Nature 509:459–464 Available at: https://pubmed.ncbi.nlm.nih.gov/24848058/ [Accessed August 5, 2022]. [PubMed: 24848058]

Paulson PE, Camp DM, Robinson TE (1991) Time course of transient behavioral depression and persistent behavioral sensitization in relation to regional brain monoamine concentrations during

amphetamine withdrawal in rats. Psychopharmacology (Berl) 103:480–492 Available at: https://pubmed.ncbi.nlm.nih.gov/2062986/ [Accessed September 23, 2022]. [PubMed: 2062986]

Peeters M, Honore C, Huet T, Bedjabaga L, Ossari S, Bussi P, Cooper R, Delaporte E (1989) Isolation and partial characterization of an HIV-related virus occurring naturally in chimpanzees in Gabon. AIDS 3:625–630 Available at: https://journals.lww.com/aidsonline/Abstract/1989/10000/Isolation_and_partial_characterization_of_an.1.aspx [Accessed June 9, 2022]. [PubMed: 2512955]

Perez S, Johnson AM, hua Xiang S, Li J, Foley BT, Doyle-Meyers L, Panganiban A, Kaur A, Veazey RS, Wu Y, Ling B (2018) Persistence of SIV in the brain of SIV-infected Chinese rhesus macaques with or without antiretroviral therapy. J Neurovirol 24:74 Available at: /pmc/articles/PMC5792315/ [Accessed February 26, 2023].

Perry CJ, Zbukvic I, Kim JH, Lawrence AJ (2014) Role of cues and contexts on drug-seeking behaviour. Br J Pharmacol 171:4672 Available at: /pmc/articles/PMC4209936/ [Accessed July 26, 2022].

Perry JL, Anderson MM, Nelson SE, Carroll ME (2007) Acquisition of i.v. cocaine self-administration in adolescent and adult male rats selectively bred for high and low saccharin intake. Physiol Behav 91:126–133 Available at: https://pubmed.ncbi.nlm.nih.gov/17360010/ [Accessed July 22, 2022]. [PubMed: 17360010]

Philippon V, Vellutini C, Gambarelli D, Harkiss G, Arbuthnott G, Metzger D, Roubin R, Filippi P (1994) The Basic Domain of the Lentiviral Tat Protein Is Responsible for Damages in Mouse Brain: Involvement of Cytokines. Virology 205:519–529. [PubMed: 7526541]

Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y (2011) Neurobiology of the incubation of drug craving. Trends Neurosci 34:411–420 Available at: http://www.ncbi.nlm.nih.gov/pubmed/21764143 [Accessed August 13, 2019]. [PubMed: 21764143]

Potash MJ, Chao W, Bentsman G, Paris N, Saini M, Nitkiewicz J, Belem P, Sharer L, Brooks AI, Volsky DJ (2005) A mouse model for study of systemic HIV-1 infection, antiviral immune responses, and neuroinvasiveness. Proc Natl Acad Sci 102:3765 Available at: /pmc/articles/PMC553332/ [Accessed February 23, 2022].

Potter MC, Figuera-Losada M, Rojas C, Slusher BS (2013) Targeting the Glutamatergic System for the Treatment of HIV-Associated Neurocognitive Disorders. J Neuroimmune Pharmacol 8:607 Available at: /pmc/articles/PMC3661915/ [Accessed August 5, 2022].

Powell GL, Namba MD, Vannan A, Bonadonna JP, Carlson A, Mendoza R, Chen PJ, Luetdke RR, Blass BE, Neisewander JL (2020) The long-acting D3 partial agonist MC-25–41 attenuates motivation for cocaine in sprague-dawley rats. Biomolecules 10:1–16.

Pu H, Tian J, Flora G, Lee YW, Nath A, Hennig B, Toborek M (2003) HIV-1 tat protein upregulates inflammatory mediators and induces monocyte invasion into the brain. Mol Cell Neurosci 24:224–237. [PubMed: 14550782]

Putatunda R, Zhang Y, Li F, Fagan PR, Zhao H, Ramirez SH, Praticò D, Barbe MF, Hu W (2019) Sex-Specific Neurogenic Deficits and Neurocognitive Disorders in Middle-Aged HIV-1 Tg26 Transgenic Mice. Brain Behav Immun 80:499 Available at: /pmc/articles/PMC6660421/ [Accessed June 6, 2023].

Putatunda R, Zhang Y, Li F, Yang XF, Barbe MF, Hu W (2018) Adult neurogenic deficits in HIV-1 Tg26 transgenic mice. J Neuroinflammation 15:287 Available at: /pmc/articles/PMC6182864/ [Accessed June 6, 2023]. [PubMed: 30314515]

Rabinowitz J, Sharifi HJ, Martin H, Marchese A, Robek M, Shi B, Mongin AA, de Noronha CMC (2021) xCT/SLC7A11 antiporter function inhibits HIV-1 infection. Virology 556:149–160 Available at: https://pubmed.ncbi.nlm.nih.gov/33631414/ [Accessed February 10, 2023]. [PubMed: 33631414]

Rahim MMA, Chrobak P, Hu C, Hanna Z, Jolicoeur P (2009) Adult AIDS-Like Disease in a Novel Inducible Human Immunodeficiency Virus Type 1 Nef Transgenic Mouse Model: CD4+ T-Cell Activation Is Nef Dependent and Can Occur in the Absence of Lymphophenia. J Virol 83:11846 Available at: /pmc/articles/PMC2772706/ [Accessed May 24, 2023].

Rappaport J, Joseph J, Croul S, Alexander G, Del Valle L, Amini S, Khalili K (1999) Molecular pathway involved in HIV-1-induced CNS pathology: role of viral regulatory protein, Tat. J

Leukoc Biol 65:458–465 Available at: https://pubmed.ncbi.nlm.nih.gov/10204574/ [Accessed February 21, 2023]. [PubMed: 10204574]

Rasbach DA, Desruisseau AJ, Kipp AM, Stinnette S, Kheshti A, Shepherd BE, Sterling TR, Hulgan T, Mcgowan CC, Qian HZ (2013) Active cocaine use is associated with lack of HIV-1 virologic suppression independent of nonadherence to antiretroviral therapy: Use of a rapid screening tool during routine clinic visits. AIDS Care 25:109–117 Available at: https://www.tandfonline.com/doi/abs/10.1080/09540121.2012.687814 [Accessed February 18, 2022]. [PubMed: 22670566]

Rausch DM, Heyes MP, Murray EA, Lendvay J, Sharer LR, Ward JM, Rehm S, Nohr D, Weihe E, Eiden LE (1994) Cytopathologic and Neurochemical Correlates of Progression to Motor/Cognitive Impairment in SIV-Infected Rhesus Monkeys. J Neuropathol Exp Neurol 53:165–175 Available at: https://academic.oup.com/jnen/article/53/2/165/2610290 [Accessed June 9, 2022]. [PubMed: 8120538]

Reddy PVB, Pilakka-Kanthikeel S, Saxena SK, Saiyed Z, Nair MPN (2012) Interactive Effects of Morphine on HIV Infection: Role in HIV-Associated Neurocognitive Disorder. AIDS Res Treat 2012:953678 Available at: /pmc/articles/PMC3362817/ [Accessed June 5, 2023]. [PubMed: 22666564]

Reid WC et al. (2001) An HIV-1 transgenic rat that develops HIV-related pathology and immunologic dysfunction. Proc Natl Acad Sci U S A 98:9271–9276. [PubMed: 11481487]

Reid WC, Abdelwahab S, Sadowska M, Huso D, Neal A, Ahearn A, Bryant J, Gallo RC, Lewis GK, Reitz M (2004) HIV-1 transgenic rats develop T cell abnormalities. Virology 321:111–119 Available at: https://pubmed.ncbi.nlm.nih.gov/15033570/ [Accessed February 24, 2023]. [PubMed: 15033570]

Reid WC, Ibrahim WG, Kim SJ, Denaro F, Casas R, Lee DE, Maric D, Hammoud DA (2016) Characterization of neuropathology in the HIV-1 transgenic rat at different ages. J Neuroimmunol 292:116–125. [PubMed: 26943969]

Reissner KJ, Gipson CD, Tran PK, Knackstedt LA, Scofield MD, Kalivas PW (2015) Glutamate transporter GLT-1 mediates N-acetylcysteine inhibition of cocaine reinstatement. Addict Biol 20:316–323. [PubMed: 24612076]

Requie LM, Gómez-Gonzalo M, Speggiorin M, Managò F, Melone M, Congiu M, Chiavegato A, Lia A, Zonta M, Losi G, Henriques VJ, Pugliese A, Pacinelli G, Marsicano G, Papaleo F, Muntoni AL, Conti F, Carmignoto G (2022) Astrocytes mediate long-lasting synaptic regulation of ventral tegmental area dopamine neurons. Nat Neurosci 25:1639–1650 Available at: https://www.nature.com/articles/s41593-022-01193-4 [Accessed February 13, 2023]. [PubMed: 36396976]

Richardson NR, Roberts DCS (1996) Progressive ratio schedules in drug self-administration studies in rats: A method to evaluate reinforcing efficacy. J Neurosci Methods 66:1–11 Available at: https://pubmed.ncbi.nlm.nih.gov/8794935/ [Accessed December 7, 2022]. [PubMed: 8794935]

Robinson TE, Becker JB (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res 396:157–198 Available at: https://pubmed.ncbi.nlm.nih.gov/3527341/ [Accessed September 23, 2022]. [PubMed: 3527341]

Rosenstiel P, Gharavi A, D'Agati V, Klotman P (2009) Transgenic and infectious animal models of HIV-associated nephropathy. J Am Soc Nephrol 20:2296–2304 Available at: https://pubmed.ncbi.nlm.nih.gov/19497967/ [Accessed June 6, 2023]. [PubMed: 19497967]

Rossi NA, Reid LD (1976) Affective states associated with morphine injections. Physiol Psychol 4:269–274 Available at: https://link.springer.com/article/10.3758/BF03332869 [Accessed July 11, 2022].

Roth BL (2016) DREADDs for Neuroscientists. Neuron 89:694 Available at: /pmc/articles/PMC4759656/ [Accessed August 4, 2022].

Royal W, Zhang L, Guo M, Jones O, Davis H, Bryant JL (2012) Immune activation, viral gene product expression and neurotoxicity in the HIV-1 transgenic rat. J Neuroimmunol 247:16–24. [PubMed: 22503372]

Russo SJ et al. (2009) Nuclear factor kappa B signaling regulates neuronal morphology and cocaine reward. J Neurosci 29:3529–3537 Available at: http://www.ncbi.nlm.nih.gov/pubmed/19295158 [Accessed June 6, 2017]. [PubMed: 19295158]

Sabatier JM, Vives E, Mabrouk K, Benjouad A, Rochat H, Duval A, Hue B, Bahraoui E (1991) Evidence for neurotoxic activity of tat from human immunodeficiency virus type 1. J Virol 65:961–967 Available at: https://journals.asm.org/doi/abs/10.1128/jvi.65.2.961-967.1991 [Accessed June 8, 2022]. [PubMed: 1898974]

Saika F, Matsuzaki S, Kishioka S, Kiguchi N (2021) Chemogenetic Activation of CX3CR1-Expressing Spinal Microglia Using Gq-DREADD Elicits Mechanical Allodynia in Male Mice. Cells 10 Available at: https://pubmed.ncbi.nlm.nih.gov/33921365/ [Accessed February 13, 2023].

Saika F, Matsuzaki S, Kobayashi D, Ideguchi Y, Nakamura TY, Kishioka S, Kiguchi N (2020) Chemogenetic Regulation of CX3CR1-Expressing Microglia Using Gi-DREADD Exerts Sex-Dependent Anti-Allodynic Effects in Mouse Models of Neuropathic Pain. Front Pharmacol 11:925. [PubMed: 32636748]

Sari H et al. (2022) Multimodal Investigation of Neuroinflammation in Aviremic Patients With HIV on Antiretroviral Therapy and HIV Elite Controllers. Neurol - Neuroimmunol Neuroinflammation 9 Available at: https://nn.neurology.org/content/9/2/e1144 [Accessed March 8, 2022].

Sawada S, Gowrishankar K, Kitamura R, Suzuki M, Suzuki G, Tahara S, Koito A (1998) Disturbed CD4+ T Cell Homeostasis and In Vitro HIV-1 Susceptibility in Transgenic Mice Expressing T Cell Line–tropic HIV-1 Receptors. J Exp Med 187:1449 Available at: /pmc/articles/PMC2212262/ [Accessed July 12, 2022].

Scheller C, Sopper S, Jenuwein M, Neuen-Jacob E, Tatschner T, Grünblatt E, Ter Meulen V, Riederer P, Koutsilieri E (2005) Early impairment in dopaminergic neurotransmission in brains of SIV-infected rhesus monkeys due to microglia activation. J Neurochem 95:377–387 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1471-4159.2005.03373.x [Accessed June 10, 2022]. [PubMed: 16190867]

Schier CJ, Marks WD, Paris JJ, Barbour AJ, Mclane VD, Maragos WF, Mcquiston AR, Knapp PR, Hauser XF (2017) Selective Vulnerability of Striatal D2 versus D1 Dopamine Receptor-Expressing Medium Spiny Neurons in HIV-1 Tat Transgenic Male Mice. Neurobiol Dis 37:5758–5769 Available at: https://www.jneurosci.org/content/jneuro/37/23/5758.full.pdf [Accessed July 29, 2019].

Scofield MD, Boger HA, Smith RJ, Li H, Haydon PG, Kalivas PW (2015) Gq-DREADD Selectively Initiates Glial Glutamate Release and Inhibits Cue-induced Cocaine Seeking. Biol Psychiatry 78:441–451 Available at: http://www.ncbi.nlm.nih.gov/pubmed/25861696 [Accessed March 2, 2019]. [PubMed: 25861696]

Shah NG, Galai N, Celentano DD, Vlahov D, Strathdee SA (2006) Longitudinal predictors of injection cessation and subsequent relapse among a cohort of injection drug users in Baltimore, MD, 1988–2000. Drug Alcohol Depend 83:147–156 Available at: http://www.ncbi.nlm.nih.gov/pubmed/16364568 [Accessed February 29, 2020]. [PubMed: 16364568]

Sil S, Thangaraj A, Chivero ET, Niu F, Kannan M, Liao K, Silverstein PS, Periyasamy P, Buch S (2021) HIV-1 and drug abuse comorbidity: Lessons learned from the animal models of NeuroHIV. Neurosci Lett 754:135863 Available at: /pmc/articles/PMC8108725/ [Accessed June 8, 2023]. [PubMed: 33794296]

Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, Calmy A, Chave JP, Giacobini E, Hirschel B, Du Pasquier RA (2010) Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS 24:1243–1250 Available at: https://pubmed.ncbi.nlm.nih.gov/19996937/ [Accessed June 6, 2022]. [PubMed: 19996937]

Simon F, Mauclère P, Roques P, Loussert-Ajaka I, Müller-Trutwin MC, Saragosti S, Georges-Courbot MC, Barré-Sinoussi F, Brun-Vézinet F (1998) Identification of a new human immunodeficiency virus type 1 distinct from group M and group O. Nat Med 4:1032–1037 Available at: https://www.nature.com/articles/nm0998_1032 [Accessed June 9, 2022]. [PubMed: 9734396]

Sjulson L, Cassataro D, Dasgupta S, Miesenböck G (2016) Cell-Specific Targeting of Genetically Encoded Tools for Neuroscience. Annu Rev Genet 50:594 Available at: /pmc/articles/PMC5630135/ [Accessed August 5, 2022].

Smith ACW, Kupchik YM, Scofield MD, Gipson CD, Wiggins A, Thomas CA, Kalivas PW (2014) Synaptic plasticity mediating cocaine relapse requires matrix metalloproteinases. Nat Neurosci 17:1655–1657 Available at: 10.1038/nn.3846. [PubMed: 25326689]

Smith K, Lacadie CM, Milivojevic V, Fogelman N, Sinha R (2023) Sex differences in neural responses to stress and drug cues predicts future drug use in individuals with substance use disorder. Drug Alcohol Depend 244:109794 Available at: https://pubmed.ncbi.nlm.nih.gov/36758371/ [Accessed June 21, 2023]. [PubMed: 36758371]

Solis-Leal A, Siddiqui S, Wu F, Mohan M, Hu W, Doyle-Meyers LA, Dufour JP, Ling B (2022) Neuroinflammatory Profiling in SIV-Infected Chinese-Origin Rhesus Macaques on Antiretroviral Therapy. Viruses 14:139 Available at: https://www.mdpi.com/1999-4915/14/1/139/htm [Accessed February 22, 2023]. [PubMed: 35062343]

Speidell A, Asuni GP, Wakulski R, Mocchetti I (2020) Up-regulation of the p75 neurotrophin receptor is an essential mechanism for HIV-gp120 mediated synaptic loss in the striatum. Brain Behav Immun 89:371–379. [PubMed: 32717404]

Stefanik MT, Kalivas PW (2013) Optogenetic dissection of basolateral amygdala projections during cue-induced reinstatement of cocaine seeking. Front Behav Neurosci 7:213 Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24399945. [PubMed: 24399945]

Stefanik MT, Kupchik YM, Kalivas PW (2016) Optogenetic inhibition of cortical afferents in the nucleus accumbens simultaneously prevents cue-induced transient synaptic potentiation and cocaine-seeking behavior. Brain Struct Funct 221:1681–1689 Available at: 10.1007/s00429-015-0997-8. [PubMed: 25663648]

Steketee JD, Kalivas PW (2011) Drug Wanting: Behavioral Sensitization and Relapse to Drug-Seeking Behavior. Pharmacol Rev 63:365 Available at: /pmc/articles/PMC3082449/ [Accessed July 1, 2022].

Strauss M, O'Donovan B, Ma Y, Xiao Z, Lin S, Bardo MT, Ortinski PI, McLaughlin JP, Zhu J (2020) [3H] Dopamine uptake through the Dopamine and Norepinephrine transporters is decreased in the prefrontal cortex of transgenic mice expressing HIV-1 transactivator of transcription protein. J Pharmacol Exp Ther 374:241–251 Available at: /pmc/articles/PMC7366287/ [Accessed February 23, 2023]. [PubMed: 32461322]

Strazza M, Pirrone V, Wigdahl B, Nonnemacher MR (2011) Breaking down the barrier: The effects of HIV-1 on the blood–brain barrier. Brain Res 1399:96–115. [PubMed: 21641584]

Strehler EE (2015) Plasma membrane calcium ATPases: From generic Ca(2+) sump pumps to versatile systems for fine-tuning cellular Ca(2.). Biochem Biophys Res Commun 460:26–33 Available at: https://pubmed.ncbi.nlm.nih.gov/25998731/ [Accessed February 13, 2023]. [PubMed: 25998731]

Stremlau M, Owens CM, Perron MJ, Kiessling M, Autissier P, Sodroski J (2004) The cytoplasmic body component TRIM5α restricts HIV-1 infection in Old World monkeys. Nature 427:848–853 Available at: https://www.nature.com/articles/nature02343 [Accessed February 22, 2023]. [PubMed: 14985764]

Stripling JS, Ellinwood EH (1977) Sensitization to Cocaine Following Chronic Administration in the Rat. In: Cocaine and Other Stimulants. Advances in Behavioral Biology, pp 327–351. Springer, Boston, MA. Available at: https://link.springer.com/chapter/10.1007/978-1-4684-3087-5_17 [Accessed September 23, 2022].

Stuber GD, Sparta DR, Stamatakis AM, Van Leeuwen WA, Hardjoprajitno JE, Cho S, Tye KM, Kempadoo KA, Zhang F, Deisseroth K, Bonci A (2011) Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature 475:377–380 Available at: https://www.nature.com/articles/nature10194 [Accessed July 28, 2022]. [PubMed: 21716290]

Sundman E, Olofsson PS (2014) Neural control of the immune system. Adv Physiol Educ 38:139 Available at: /pmc/articles/PMC4056170/ [Accessed February 9, 2023].

Tanaka S, Abe C, Abbott SBG, Zheng S, Yamaoka Y, Lipsey JE, Skrypnyk NI, Yao J, Inoue T, Nash WT, Stornetta DS, Rosin DL, Stornetta RL, Guyenet PG, Okusa MD (2021) Vagus nerve stimulation activates two distinct neuroimmune circuits converging in the spleen to protect mice from kidney injury. Proc Natl Acad Sci 118:e2021758118 Available at: https://www.pnas.org/doi/abs/10.1073/pnas.2021758118 [Accessed February 9, 2023]. [PubMed: 33737395]

Thaney VE, O'Neill AM, Hoefer MM, Maung R, Sanchez AB, Kaul M (2017) IFNβ Protects Neurons from Damage in a Murine Model of HIV-1 Associated Brain Injury. Sci Rep 7:46514 Available at: /pmc/articles/PMC5397848/ [Accessed February 23, 2023]. [PubMed: 28425451]

Thaney VE, Sanchez AB, Fields JA, Minassian A, Young JW, Maung R, Kaul M (2018) Transgenic mice expressing HIV-1 envelope protein gp120 in the brain as an animal model in neuroAIDS research. J Neurovirol 24:156–167 Available at: https://link.springer.com/article/10.1007/s13365-017-0584-2 [Accessed June 14, 2022]. [PubMed: 29075998]

Tiffany ST (1999) Cognitive Concepts of Craving. Alcohol Res Heal 23:224 Available at: /pmc/articles/PMC6760370/ [Accessed February 17, 2023].

Toggas SM, Masliah E, Rockenstein EM, Rail GF, Abraham CR, Mucke L (1994) Central nervous system damage produced by expression of the HIV-1 coat protein gpl20 in transgenic mice. Nature 367:188–193 Available at: http://www.ncbi.nlm.nih.gov/pubmed/8114918 [Accessed June 28, 2019]. [PubMed: 8114918]

Ton H, Xiong H (2013) Astrocyte Dysfunctions and HIV-1 Neurotoxicity. J AIDS Clin Res 4:255 Available at: https://pubmed.ncbi.nlm.nih.gov/24587966/ [Accessed August 12, 2022]. [PubMed: 24587966]

Toneatto S, Finco O, van der Putten H, Abrignani S, Annunziata P (1999) Evidence of blood-brain barrier alteration and activation in HIV-1 gp120 transgenic mice. AIDS 13:2343–2348 Available at: https://journals.lww.com/aidsonline/fulltext/1999/12030/evidence_of_blood_brain_barrier_alteration_and.5.aspx [Accessed June 15, 2022]. [PubMed: 10597775]

Tracey KJ (2007) Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 117:289–296 Available at: http://www.jci.orgvolume [Accessed February 9, 2023]. [PubMed: 17273548]

Tran-Nguyen LTL, Fuchs RA, Coffey GP, Baker DA, O'Dell LE, Neisewander JL (1998) Time-dependent changes in cocaine-seeking behavior and extracellular dopamine levels in the amygdala during cocaine withdrawal. Neuropsychopharmacology 19:48–59. [PubMed: 9608576]

Umpierre AD, Bystrom LL, Ying Y, Liu YU, Worrell G, Wu LJ (2020) Microglial calcium signaling is attuned to neuronal activity in awake mice. Elife 9:1–24.

Valcour VG, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes O, Holck P, Grove J, Sacktor N (2004a) Higher frequency of dementia in older HIV-1 individuals: The Hawaii Aging with HIV-1 Cohort. Neurology 63:827 Available at: /pmc/articles/PMC1382180/ [Accessed June 6, 2022].

Valcour VG, Shikuma CM, Watters MR, Sacktor NC (2004b) Cognitive impairment in older HIV-1-seropositive individuals: prevalence and potential mechanisms. AIDS 18:S86 Available at: /pmc/articles/PMC1388077/ [Accessed August 12, 2022].

Vardy E et al. (2015) A New DREADD Facilitates the Multiplexed Chemogenetic Interrogation of Behavior. Neuron 86:946 Available at: /pmc/articles/PMC4441592/ [Accessed February 8, 2023].

Vastag Z, Fira-Mladinescu O, Rosca EC (2022) HIV-Associated Neurocognitive Disorder (HAND): Obstacles to Early Neuropsychological Diagnosis. Int J Gen Med 15:4090 Available at: /pmc/articles/PMC9017704/ [Accessed June 16, 2023].

Vázquez-Santiago FJ, Noel RJ, Porter JT, Rivera-Amill V (2014) Glutamate Metabolism and HIV-Associated Neurocognitive Disorders. J Neurovirol 20:331 Available at: /pmc/articles/PMC4098898/ [Accessed August 5, 2022].

Vesce S, Bezzi P, Volterra A (1999) The active role of astrocytes in synaptic transmission. Cell Mol Life Sci 56:991–1000 Available at: https://link.springer.com/article/10.1007/s000180050488 [Accessed February 13, 2023]. [PubMed: 11212330]

Vezina P, Giovino AA, Wise RA, Stewart J (1989) Environment-specific cross-sensitization between the locomotor activating effects of morphine and amphetamine. Pharmacol Biochem Behav 32:581–584 Available at: https://pubmed.ncbi.nlm.nih.gov/2727020/ [Accessed September 23, 2022]. [PubMed: 2727020]

Vickstrom CR, Snarrenberg ST, Friedman V, Liu Q-S (2021) Application of optogenetics and in vivo imaging approaches for elucidating the neurobiology of addiction. Mol Psychiatry 27:640–651 Available at: https://www.nature.com/articles/s41380-021-01181-3 [Accessed July 26, 2022]. [PubMed: 34145393]

Vigorito M, Cao J, Li MD, Chang SL (2013) Acquisition and long-term retention of spatial learning in the human immunodeficiency virus-1 transgenic rat: Effects of repeated nicotine treatment. J Neurovirol 19:157 Available at: /pmc/articles/PMC3643994/ [Accessed January 31, 2022]. [PubMed: 23456952]

Vigorito M, Connaghan KP, Chang SL (2015) The HIV-1 transgenic rat model of neuroHIV. Brain Behav Immun 48:336–349 Available at: http://www.ncbi.nlm.nih.gov/pubmed/25733103 [Accessed September 7, 2019]. [PubMed: 25733103]

Wallet C, De Rovere M, Van Assche J, Daouad F, De Wit S, Gautier V, Mallon PWG, Marcello A, Van Lint C, Rohr O, Schwartz C (2019) Microglial Cells: The Main HIV-1 Reservoir in the Brain. Front Cell Infect Microbiol 9:00362.

Wang W, Kim CK, Ting AY (2019a) Molecular tools for imaging and recording neuronal activity. Nat Chem Biol 15:101–110 Available at: https://www.nature.com/articles/s41589-018-0207-0 [Accessed August 12, 2022]. [PubMed: 30659298]

Wang W, Wildes CP, Pattarabanjird T, Sanchez MI, Glober GF, Matthews GA, Tye KM, Ting AY (2017) A light- and calcium-gated transcription factor for imaging and manipulating activated neurons. Nat Biotechnol 35:864–871 Available at: https://www.nature.com/articles/nbt.3909 [Accessed August 12, 2022]. [PubMed: 28650461]

Wang X, Liu J, Zhou L, Ho WZ (2019b) Morphine Withdrawal Enhances HIV Infection of Macrophages. Front Immunol 10:2601. [PubMed: 31803178]

Wang Z, Pekarskaya O, Bencheikh M, Chao W, Gelbard HA, Ghorpade A, Rothstein JD, Volsky DJ (2003) Reduced expression of glutamate transporter EAAT2 and impaired glutamate transport in human primary astrocytes exposed to HIV-1 or gp120. Virology 312:60–73. [PubMed: 12890621]

Wayman WN, Chen L, Hu X-T, Napier TC (2016) HIV-1 Transgenic Rat Prefrontal Cortex Hyper-Excitability is Enhanced by Cocaine Self-Administration. Neuropsychopharmacology 41:1965–1973 Available at: http://www.ncbi.nlm.nih.gov/pubmed/26677947 [Accessed September 4, 2019]. [PubMed: 26677947]

Weed MR, Adams RJ, Hienz RD, Meulendyke KA, Linde ME, Clements JE, Mankowski JL, Zink MC (2012) SIV/macaque model of HIV infection in cocaine users: minimal effects of cocaine on behavior, virus replication, and CNS inflammation. J neuroimmune Pharmacol 7:401–411 Available at: https://pubmed.ncbi.nlm.nih.gov/21626125/ [Accessed June 5, 2023]. [PubMed: 21626125]

Weed MR, Hienz RD, Brady JV, Adams RJ, Mankowski JL, Clements JE, Zink MC (2003) Central nervous system correlates of behavioral deficits following simian immunodeficiency virus infection. J Neurovirol 9:452–464 Available at: https://link.springer.com/article/10.1080/13550280390218751 [Accessed June 2, 2023]. [PubMed: 12907390]

Weeks BS, Lieberman DM, Johnson B, Roque E, Green M, Loewenstein P, Oldfield EH, Kleinman HK (1995) Neurotoxicity of the human immunodeficiency virus type 1 Tat transactivator to PC12 cells requires the Tat amino acid 49–58 basic domain. J Neurosci Res 42:34–40 Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/jnr.490420105 [Accessed June 8, 2022]. [PubMed: 8531224]

Weiss SH (1989) Links Between Cocaine and Retroviral Infection. JAMA 261:607–609 Available at: https://jamanetwork.com/journals/jama/fullarticle/376103 [Accessed June 6, 2022]. [PubMed: 2535879]

Whitaker LR, Carneiro de Oliveira PE, McPherson KB, Fallon RV, Planeta CS, Bonci A, Hope BT (2016) Associative learning drives the formation of silent synapses in neuronal ensembles of the nucleus accumbens. Biol Psychiatry 80:256 Available at: /pmc/articles/PMC4753139/ [Accessed August 9, 2022].

Wilen CB, Tilton JC, Doms RW (2012) HIV: Cell Binding and Entry. Cold Spring Harb Perspect Med 2:a006866 Available at: /pmc/articles/PMC3405824/ [Accessed July 12, 2022]. [PubMed: 22908191]

Williams K, Westmoreland S, Greco J, Ratai E, Lentz M, Kim WK, Fuller RA, Kim JP, Autissier P, Sehgal PK, Schinazi RF, Bischofberger N, Piatak M, Lifson JD, Masliah E, González RG (2005) Magnetic resonance spectroscopy reveals that activated monocytes contribute to neuronal injury

in SIV neuroAIDS. J Clin Invest 115:2534–2545 Available at: http://www.jci.org [Accessed February 22, 2023]. [PubMed: 16110325]

Xia QP, Cheng ZY, He L (2019) The modulatory role of dopamine receptors in brain neuroinflammation. Int Immunopharmacol 76:105908. [PubMed: 31622861]

Yager LM, Garcia AF, Donckels EA, Ferguson SM (2019) Chemogenetic inhibition of direct pathway striatal neurons normalizes pathological, cue-induced reinstatement of drug-seeking in rats. Addict Biol 24:251 Available at: /pmc/articles/PMC6033698/ [Accessed September 23, 2022]. [PubMed: 29314464]

Yang Z, Nesil T, Connaghan KP, Li MD, Chang SL (2016) Modulation Effect of HIV-1 Viral Proteins and Nicotine on Expression of the Immune-Related Genes in Brain of the HIV-1 Transgenic Rats. J Neuroimmune Pharmacol 11:562–571 Available at: https://link.springer.com/article/10.1007/s11481-016-9679-4 [Accessed February 24, 2023]. [PubMed: 27147085]

Yeung MC, Pulliam L, Lau AS (1995) The HIV envelope protein gp120 is toxic to human brain-cell cultures through the induction of interleukin-6 and tumor necrosis factor-alpha. AIDS 9:137–143 Available at: https://pubmed.ncbi.nlm.nih.gov/7536422/ [Accessed June 8, 2022]. [PubMed: 7536422]

Young JW, Barback CV, Stolz LA, Groman SM, Vera DR, Hoh C, Kotta KK, Minassian A, Powell SB, Brody AL (2022) MicroPET evidence for a hypersensitive neuroinflammatory profile of gp120 mouse model of HIV. Psychiatry Res Neuroimaging 321:111445. [PubMed: 35101828]

Yu X, Taylor AMW, Nagai J, Golshani P, Evans CJ, Coppola G, Khakh BS (2018) Reducing astrocyte calcium signaling in vivo altersstriatal microcircuits and causes repetitive behavior. Neuron 99:1187.e9 Available at: /pmc/articles/PMC6450394/ [Accessed February 13, 2023].

Zauli G, Secchiero P, Rodella L, Gibellini D, Mirandola P, Mazzoni M, Milani D, Dowd DR, Capitani S, Vitale M (2000) HIV-1 Tat-mediated Inhibition of the Tyrosine Hydroxylase Gene Expression in Dopaminergic Neuronal Cells. J Biol Chem 275:4159–4165. [PubMed: 10660577]

Zell V, Steinkellner T, Hollon NG, Warlow SM, Souter E, Faget L, Hunker AC, Jin X, Zweifel LS, Hnasko TS (2020) VTA Glutamate Neuron Activity Drives Positive Reinforcement Absent Dopamine Co-release. Neuron 107:864–873.e4 Available at: https://pubmed.ncbi.nlm.nih.gov/32610039/ [Accessed July 28, 2022]. [PubMed: 32610039]

Zhong J, Zuo Y, Ma J, Fogo AB, Jolicoeur P, Ichikawa I, Matsusaka T (2005) Expression of HIV-1 genes in podocytes alone can lead to the full spectrum of HIV-1-associated nephropathy. Kidney Int 68:1048–1060 Available at: https://pubmed.ncbi.nlm.nih.gov/16105035/ [Accessed June 6, 2023]. [PubMed: 16105035]

Zhu J et al. (2022) SRI-32743, a novel allosteric modulator, attenuates HIV-1 Tat protein-induced inhibition of the dopamine transporter and alleviates the potentiation of cocaine reward in HIV-1 Tat transgenic mice. Neuropharmacology 220:109239. [PubMed: 36126727]

Zhu J, Midde NM, Gomez AM, Sun WL, Harrod SB (2015) Intra-ventral tegmental HIV-1 Tat1–86 attenuates nicotine-mediated locomotor sensitization and alters mesocorticolimbic ERK and CREB signaling in rats. Front Microbiol 6.

Zucchini S, Pittaluga A, Brocca-Cofano E, Summa M, Fabris M, De Michele R, Bonaccorsi A, Busatto G, Barbanti-Brodano G, Altavilla G, Verlengia G, Cifelli P, Corallini A, Caputo A, Simonato M (2013) Increased excitability in tat-transgenic mice: Role of tat in HIV-related neurological disorders. Neurobiol Dis 55:110–119. [PubMed: 23454193]

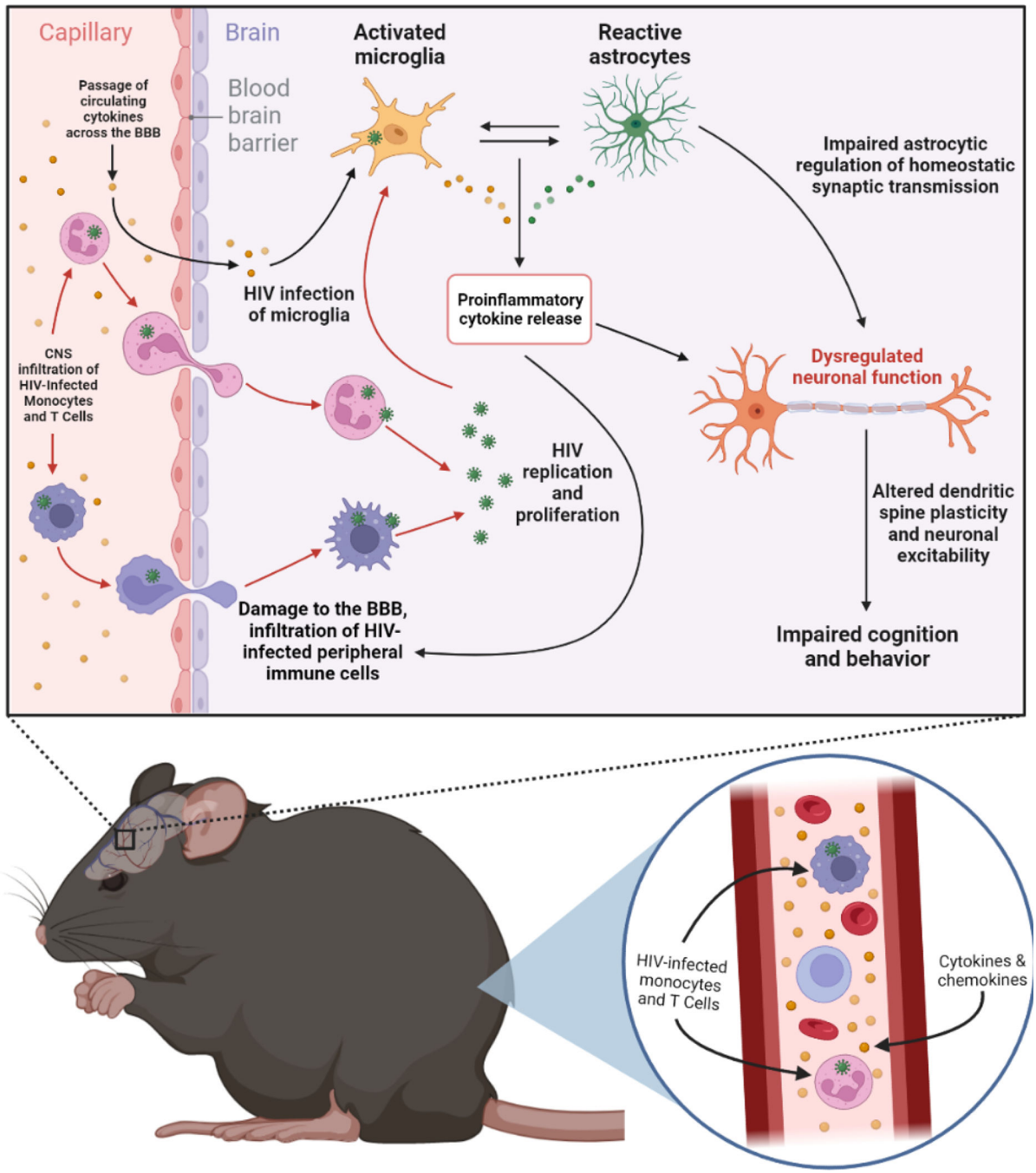

Figure 1. Pathophysiology of HIV-induced dysregulation of CNS function.

Upon primary infection of monocytes and T cells by HIV-1, there is an initial antiviral immune response to rapid viral replication that is accompanied by a burst of proinflammatory immune signaling and flu-like symptoms within the first 2–4 weeks post-infection. After this acute phase of HIV infection, HIV continues to replicate at low levels, where individuals may be asymptomatic during this period of clinical latency. However, without daily ART treatment, HIV remains transmissible. Infected monocytes and T cells can cross the blood brain barrier (BBB) and infiltrate the CNS, especially

during the acute infection phase, where the virus infects brain-resident microglia. Here, proinflammatory cytokine and chemokine signaling by microglia and astrocytes can directly dysregulate neuronal function or do so indirectly through impaired glial cell regulation of homeostatic neuronal activity (e.g., suppression of glial glutamate transport function). Specifically, HIV-induced neuroimmune impairments can alter dendritic spine plasticity and neuronal excitability, leading to downstream alterations in cognition and behavior. Chronic proinflammatory neuroimmune signaling induced by HIV can also further damage the BBB, further contributing to HIV neuroinvasion.

Table 1 –

Key characteristics of neuroHIV animal models

Animal Models	Method of producing viral pathology	Neuroimmunological effects within the CNS	Effects on reward circuitry	Model strengths	Model limitations	References
Exogenous HIV protein exposure	• Proteins infused into discrete brain structures or through ventricles • Acute dose or subchronic administration	• CNS inflammation • Oxidative stress • Astrogliosis • Microgliosis • BBB disruption • Peripheral immune cell infiltration • Extent depends on protein(s), dose(s) duration administered	• DA neurons are particularly vulnerable to neurotoxicity and neurodegeneration • Retrograde neurodegeneration of DA neurons within the VTA and SN can occur after a site-specific injection of protein	• Spatiotemporal precision over protein exposure • Effects can also be precisely isolated to one or more proteins	• HIV protein exposure is acute or subchronic. Does not reflect the chronic exposure to HIV proteins that occurs in PLWH • No progressive viral infection and replication • Distribution of protein exposure across CNS and doses not akin to HIV-1 infection *in vivo* • Limited to only one or two viral proteins	Philippon et al., 1994; Rappaport et al., 1999; Jones et al., 1998; Aksenov et al., 2001; Nosheny et al., 2006; Agrawal et al., 2010
Simian Immunodeficiency Virus (SIV)-infected non-human primates (NHPs)	• SIV administered to primates (e.g., rhesus macaques, pigtail macaques). • Models use different viral clones or swarms, resulting in varying degrees of disease severity and speed of progression	• Monocyte and MΦ activation • MΦ infiltration into brain parenchyma • Astrogliosis • Microglial activation • Acute infection increases expression of peripheral and CNS cytokines • Depletion of lymphocytes → enhanced viral replication, monocyte and MΦ activation, neuroinvasion of peripheral MΦ, and microglial tropism	• Early DA deficiency correlated with enhanced microglial activation. • Viral replication, neuroinflammation, and SIV neuropathology worsened by drugs that enhance mesolimbic DA. • Cognitive deficits likely due to dysregulation of cortical dendritic spines	• Recapitulate many immunological and serological features of HIV-1 infection in humans • Best animal model of human immune and nervous systems • Lymphocyte depletion can hasten AIDS progression. This can be efficient and advantageous depending on experimental conditions.	• Low sample sizes • Ethical and regulatory concerns exist • In some models, very rapid disease progression that may not fully recapitulate human condition • Cellular- and circuit-specific mechanisms more difficult to elucidate • Translational SUD models such as self-administration are costly and difficult to conduct	Letvin et al., 1983; Koutsilieri et al., 1997; Czub et al., 2001, 2004; Scheller et al., 2005; Jenuwein et al., 2004; Keating et al., 2012; Meulendyke et al., 2012; Garcia-Tellez et al., 2016; Mallard & Williams, 2018
HIV-1 gp120 Tg mouse	• Constitutive expression of gp120 in astrocytes under GFAP promoter control	• Enhanced BBB permeability • Cortical neurodegeneration • Dendritic vacuolization • Astrogliosis • Microgliosis (particularly within the cortex and HPC) • Hypersensitive to inflammatory stimuli within the STR, HYPO, VTA, and HPC	• HPC impairments in dendritic structure and function and HPC-dependent behaviors. • STR dendritic spines and Glu transport impaired	• Chronic and constitutive transgene expression allows for more long-term examination of neurobehavioral effects of gp120 exposure.	• Lack of spatiotemporal control of gp120 exposure. • Protein is derived from astrocytes, which are not the primary HIV reservoir in the brain • Only one HIV protein is expressed, and only within the CNS • Lifelong expression does not model HIV-1 acquisition in adulthood	Toggas et al., 1994; Toneatto et al., 1999; Cioni & Annunziata, 2002; Maung et al., 2014; Hoefer et al., 2015; Thaney et al., 2017, 2018; Melendez et al., 2016; Young et al., 2022
Inducible HIV-1 Tat Tg mouse	• Conditional expression of Tat in astrocytes under GFAP promotor control upon doxycycline	• Cortical atrophy • Astrocytosis • Dendritic atrophy • Neuronal apoptosis and infiltration of peripheral monocytes and T lymphocytes into the brain	• Impaired DAT function within the PFC and striatum • Altered neuronal excitability of neurons within the PFC and HPC	• Temporal control of Tat expression within the CNS • Reported brain levels of Tat in this model are claimed to be similar	• Tet-on system can be “leaky”, producing chronic, low-level protein expression even in the absence of doxycycline; Could be advantageous depending on the experiment • Model relies on doxycycline	Kim et al., 2003; Zou et al., 2007; Fitting et al., 2010; Leibrand et al., 2017; Dickens et al., 2017; Langford et al., 2018; Strauss et al., 2020; Cirino

Animal Models	Method of producing viral pathology	Neuroimmunological effects within the CNS	Effects on reward circuitry	Model strengths	Model limitations	References
	exposure through a Tet-on mechanism	• Corticostriatal neuroinflammation • Increased BBB permeability • Increased STR and HPC microglial activity.	- likely region- and cell type-specific	to those reported in PLWH.	treatment; Not pharmacologically inert • One HIV protein is expressed • Tat expressed in astrocytes; Not the primary HIV-1 reservoir in brain	et al., 2020; Davis et al., 2023
HIV-1 Tg26 mouse	• Mice constitutively and systemically express 7 of the 9 HIV proteins (*env, tat, rev, vif, vpr, vpu, and nef*)	• Increased expression of proinflammatory factors (e.g., NF-κB, TNFα, TLR4) in the HPC • HPC astrogliosis • Heterozygous Tg26 lack CD4+ T cell depletion • Elevated renal and serum IL-1β expression	• Sex-specific deficits in HPC neurogenesis • Lower dendritic complexity and length, and reduced thin and stubby spine density within the HPC • Studies examining corticostriatal and other mesocorticolimbic structures involved in addiction-related behaviors are lacking with this model	• Multiple HIV proteins are expressed chronically and systemically • Renal dysfunction that mirrors certain aspects of HIV-associated nephropathy (HIVAN) • Neurocognitive deficits are observed • Heterozygous mice relatively healthy and suitable for most behavioral studies	• Lack of *gag* and *pol* • Lack of spatiotemporal control over protein exposure • HIV-1 protein expression in cells not typically infected by HIV-1 • Does not necessarily model acquisition of HIV-1 in adulthood • Characterization of both peripheral and CNS immune dysfunction within this model is lacking. More studies are needed to address this	Dickie et al., 1991; Kopp et al., 1992; De et al., 1997; Gharavi et al., 2004; Rosenstiel et al., 2009; Mallipattu et al., 2013; Putatunda et al., 2018, 2019; Barbe et al., 2020; Li et al., 2020
HIV-1 transgenic (Tg) rat	• HIV-1 Tg rat constitutively and systemically expresses 7 of the 9 HIV proteins (*env, tat, rev, vif, vpr, vpu, and nef*).	• Cortical neuroinflammation • Reactive gliosis • Neuronal cell loss • Increased BBB permeability • Lymphocyte infiltration into brain parenchyma • CD4+ cell decline • Increased T cell apoptosis, impaired innate and adaptive immune responses to inflammatory insults • Significant decline in T cell counts with advanced age with AIDS-like symptoms. • Transcriptomic alterations in immune response and neuronal survival pathways across the PFC, HPC, and STR	• Dysregulated dopamine neurotransmission in age-dependent manner • Impaired synaptic connectivity among STR MSNs, including altered distribution of dendritic spine types • Reduced spine density within the PrL, which correlates with cognitive deficits • Changes in specific spine types (region-specific)	• Multiple HIV proteins are expressed chronically and systemically • Disease progression among immune cells with age mirrors that in humans • Neurocognitive deficits that mirror HAND • Development of cardiac, respiratory, renal, muscular, and immune abnormalities that may mimic those observed in human HIV/AIDS.	• Lack of *gag* and *pol* • Lack of spatiotemporal control over protein exposure • HIV-1 protein expression in cells not typically infected by HIV-1 • Does not necessarily model acquisition of HIV-1 in adulthood • Due to eventual health decline with age, not well suited for longitudinal preclinical studies of HIV and aging • Health complications, such as muscular wasting and cataracts, can complicate the interpretation of behavioral results	Reid et al., 2001, 2004, 2016; Royal et al., 2012; Homji et al., 2012; Vigorito et al., 2013, 2015; Moran et al., 2013; Li et al., 2013; Abbondanzo & Chang, 2014; Festa et al., 2015, 2020; Yang et al., 2016; McLaurin et al., 2018
EcoHIV-infected rodents	• Chimeric virus where the coding region of HIV-1 gp120 is replaced with gp80 from MLV, which permits viral replication in rodents. • Typically administered i.p. or	• Detectable in spleen and brain tissue, MΦ, and CD4 T cells • Anti-gag and anti-tat produced • Increased brain expression of inflammatory and anti-viral molecules (e.g., complement C3, MCP-1, IL-1β, CD8, TNFα, CCL2, MIP-1α, Iba1, STAT1, etc.) • Seroconversion after ~30–60 days → normalization of	• Direct administration of EcoHIV into the rat cortex induces alterations to dendritic spine morphology within the mPFC and NAc; Impairs temporal processing and long-term memory • Intracerebral EcoHIV infection → synaptodendritic loss in the	• Does not infect human lymphocytes in culture, improving its biosafety • Microglia are the primary CNS reservoir of HIV • Can be combined with conventional or experimental (e.g., transgenic) mouse strains	• No gp120 protein expression and neuropathophysiology. • To date, less well-validated than other models, particularly in its use for the study of SUDs • No progression to an AIDS-like/diseased state. Time course of viremia from initial infection does not mimic that of HIV-1 infection in humans.	Potash et al., 2005; Jones et al., 2016; Kelschenbach et al., 2019; Li et al., 2021a, 2021b; McLaurin et al., 2022

Animal Models	Method of producing viral pathology	Neuroimmunological effects within the CNS	Effects on reward circuitry	Model strengths	Model limitations	References
	directly into the CNS	inflammatory responses • Enhanced BBB permeability	HPC and impairs working memory	• Temporal control over infection • Mice remain healthy despite persistent neurocognitive impairment, which is observed in PLWH on ART		

Table abbreviations: AMY = amygdala; BBB = blood brain barrier; DA = dopamine; DAT = dopamine transporter; HPC = hippocampus; HYPO = hypothalamus; MLV = murine leukemia virus; mPFC = medial prefrontal cortex; MSN = medium spiny neuron; MΦ = macrophage; NAc = nucleus accumbens; PFC = prefrontal cortex; PrL = prelimbic cortex; SN = substantia nigra; STR = striatum; VTA = ventral tegmental area