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EDITORIAL COMMENT

Bioenergetics and neuroimaging research: a neuropathophysiological linkage in the setting of cocaine use amongst persons with HIV

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Despite innovations in antiretroviral therapy (ART) that have transformed HIV infection from an acute illness with high mortality risk into a chronic, largely manageable disease, the viral reservoir that persists in brain continues to pose a risk for neurocognitive impairment and other deleterious clinical outcomes. ART regimens can inhibit viral integration and suppress replication to nondetectable levels in plasma and cerebrospinal fluid (CSF) but do not eliminate viral reservoirs, including that in brain [1]. Moreover, HIV transcripts within CSF cells have been associated with brain injury despite suppressive ART [2]. Comorbid HIV and cocaine use exacerbates brain atrophy and neurocognitive decline despite viral suppression [3–5]. Intersecting factors disrupted by chronic cocaine use among people with HIV (PWH) contribute to HIV-associated neuropathology, including neurotransmitter signaling (particularly dopamine), neuroinflammation, blood–brain–barrier (BBB) integrity, and energy metabolism. Further, the neuropathological severity associated with HIV and cocaine is spatially heterogenous [6–8]. The healthy brain is energetically expensive and complex with region-specific, unique functional roles [9–11]. Further, compartmentalization of HIV infection in brain contributes to this heterogeneity [12]. Mechanistic links between HIV and cocaine require additional characterization to assess region-dependent contributions to develop therapeutic interventions for cocaine use disorder comorbid with HIV.

Mamidi *et al.* [13] focused on associations between chronic cocaine use and HIV on glucose uptake. Using ^{18}F-FDG PET/CT in a 2 × 2 experimental design with HIV (present/absent) and cocaine (present/absent) ($N = 63$), they showed the lowest uptake with both HIV and cocaine. One factor – HIV or cocaine – showed intermediate uptake, and neither factor showed the highest uptake. The pronounced impact of cocaine on HIV-associated neuropathology is, in part, due to disruption of dopaminergic neurotransmission. The dopamine system is linked to inflammation and immunological function. Brain regions with high basal dopamine levels, such as the striatum and substantia nigra, are amongst the most vulnerable to HIV [14]. Dopamine exposure to human macrophages results in elevated production of pro-inflammatory cytokines and chemokines [14]. Acutely, elevated dopamine concentrations due to cocaine use increase oxidative stress, exacerbated by Tat [15,16]. Chronically, cocaine use is associated with dopamine depletion, demonstrated by PET scanning research [17]. In addition, HIV itself is associated with dopamine depletion as well as neurocognitive impairment and depression [18] not investigated here. This constellation suggests a synergistic effect of HIV and cocaine on dopaminergic transmission. To the extent that dopaminergic neurotransmission impacts glucose uptake, only additive effects of HIV and cocaine were reported here. No interaction of HIV and cocaine was observed.

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A major hallmark of chronic HIV is elevated pro-inflammatory cytokine and chemokine production. Suppressed PWH still have elevated neuroinflammation in the parietal and occipital cortex and the globus pallidus. Neuroinflammation is associated with decreased neurocognitive performance and increased white matter damage supported by a PET study with [^{11}C] PBR28 and neuropsychological testing [8]. Viral proteins, Tat and gp120, both facilitate the production of pro-inflammatory cytokine and chemokines that decrease BBB tight junction protein expression and are directly neurotoxic [19]. Loss of BBB integrity allows free virus and HIV-infected monocytes to enter brain, exacerbating neuronal damage [20]. Similarly, cocaine increases neuroinflammatory markers by activating microglial cells and disrupting BBB integrity – decreasing tight junction protein expression in human pericytes [21]. When measuring chronic cocaine-induced microglial activation *in vivo*, rhesus macaques displayed increased TSPO PET expression in dopamine-rich regions via [^{3}H] PK-11195 [6,7]. However, humans with a history of chronic cocaine use assessed with TSPO PET via [^{11}C] PBR28 displayed no significant changes [6,22]. Of note, increased TSPO expression using current tracers does not distinguish between microglial and astrocytic activation. Further, there are other limitations with the utility of both PK-11195 and PBR28 tracers. Hence, PET scanning studies are currently inconclusive, though studies using other methodologies support neuroinflammatory effects associated with cocaine. Cocaine has been linked with increased TNF-α expression and is well known to stimulate HIV replication through induction of NF-κB and activation of transcription through the HIV LTR. The increased expression of TNF-α induced by HIV might exacerbate that by cocaine. Pro-inflammatory cytokine production has been associated with dopamine depletion outside of HIV infection. This suggests an intrinsic link between chronic HIV despite suppression, ongoing neuroinflammation, and persistent dopamine depletion, which is associated with depression and neurocognitive symptoms. This linkage may also reflect the results reported here and suggests the possible clinical utility of TNF-α inhibitors and dopaminergic agonists for the treatment of depressive and neurocognitive symptoms in virally suppressed PWH, supporting normalization of brain glucose uptake.

In adults, the brain's immense energetic demands require roughly 20% of all glucose and constitute approximately the same proportion of total oxygen consumption during resting conditions [23,24]. Maintenance of brain metabolic homeostasis is particularly sensitive to metabolic coupling between types of brain cells that contribute to clinical disorders when disrupted [25–27]. Viral–host interactions after an infection like HIV shift bioenergetics for incompletely understood reasons. Changes in energetic metabolism have been reported to occur *in vitro* using cultured astrocytes, neurons, and microglia due to Tat and gp120 [28–30], cytokines and chemokines [31], oxidative stress [32], and ART [33]. *In vivo*, virally suppressed PWH display decreased glucose uptake in the frontal cortex and the anterior cingulate cortex via FDG-PET [34,35]. Altogether, these changes suggest a shift from metabolism of primarily glucose to other oxidative substrates. Moreover, *in vitro*, cocaine is associated with a similar metabolic shift [29].

As suggested above, energetic demands vary across brain regions. Recent studies suggest that the brain also uses other substrates, such as fatty acids, lactate, pyruvate, glutamate, glutamine, and ketone bodies, more frequently than previously considered [10,11,36]. The composition of substrates used may shift under various factors such as age, diet, brain activity or injury, cognitive reserve, and the presence of viral infections like HIV [26,37]. Hence, future studies should expand from the general study of glucose uptake as the primary substrate to other substrates and associated changes in oxidative stress and mitochondrial function. Clinical research suggests the importance of associated interacting comorbidities, such as cardiovascular disease, with HIV [38] and cocaine [39]. It should be noted that age, ethnicity, and education and concomitant opioid use were not able to be separately analyzed here. Of note, older age is also associated with dopamine depletion, suggesting a more prominent effect amongst older PWH.

In addition to future studies examining other energy substrate outcome measures; improved control of extraneous factors; and integration of clinical outcomes of cocaine use among PWH, neuroimaging studies can be particularly helpful in examining spatial heterogeneity in energetic effects induced by toxic HIV protein and transcript burden as well as pro-inflammatory cytokine secretion associated with cocaine use. Yet, these methods incompletely capture metabolic changes in brain. It can be concluded that there remains much to explore as to how the bioenergetic shifts occurring due to HIV and cocaine may be mechanistically linked to clinical outcomes.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ulfhammer G, Edén A, Mellgren A, Fuchs D, Zetterberg H, Hagberg L, *et al*. **Persistent central nervous system immune activation following more than 10 years of effective HIV antiretroviral treatment.** *AIDS* 2018; **32**:2171–2178.

2. Suzuki K, Zaunders J, Gates TM, Levert A, Butterly S, Liu Z, *et al*. **Elevation of cell-associated HIV-1 transcripts in CSF CD4+ T cells, despite effective antiretroviral therapy, is linked to brain injury.** *Proc Natl Acad Sci USA* 2022; **119**:e2210584119.
3. Buch S, Yao H, Guo M, Mori T, Mathias-Costa B, Singh V, *et al*. **Cocaine and HIV-1 interplay in CNS: cellular and molecular mechanisms.** *Curr HIV Res* 2012; **10**:425–428.
4. Goodkin K, Shapshak P, Metsch LR, McCoy CB, Crandall KA, Kumar M, *et al*. **Cocaine abuse and HIV-1 infection: epidemiology and neuropathogenesis.** *J Neuroimmunol* 1998; **83**:88–101.
5. Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, *et al*. **HIV-associated neurocognitive disorder — pathogenesis and prospects for treatment.** *Nat Rev Neurol* 2016; **12**:234–248.
6. Leroy C, Saba W. **Contribution of TSPO imaging in the understanding of the state of gliosis in substance use disorders.** *Eur J Nucl Med Mol Imaging* 2021; **49**:186–200.
7. Smith HR, Beveridge TJR, Nader SH, Nader MA, Porrino LJ. **Regional elevations in microglial activation and cerebral glucose utilization in frontal white matter tracts of rhesus monkeys following prolonged cocaine self-administration.** *Brain Struct Funct* 2019; **224**:1417–1428.
8. Vera JH, Guo Q, Cole JH, Boasso A, Greathead L, Kelleher P, *et al*. **Neuroinflammation in treated HIV-positive individuals.** *Neurology* 2016; **86**:1425–1432.
9. Chen X, Vinokurov AY, Zherebtsov EA, Stelmashchuk OA, Angelova PR, Esteras N, Abramov AY. **Variability of mitochondrial energy balance across brain regions.** *J Neurochem* 2021; **157**:1234–1243.
10. Jernberg JN, Bowman CE, Wolfgang MJ, Scafidi S. **Developmental regulation and localization of carnitine palmitoyltransferases (CPTs) in rat brain.** *J Neurochem* 2017; **142**:407–419.
11. White CJ, Lee J, Choi J, Chu T, Scafidi S, Wolfgang MJ. **Determining the bioenergetic capacity for fatty acid oxidation in the mammalian nervous system.** *Mol Cell Biol* 2020; **40**:e00037-20.
12. Shapshak P, Segal DM, Crandall KA, Fujimura RK, Zhang B-T, Xin K-Q, *et al*. **Independent evolution of HIV type 1 in different brain regions.** *AIDS Res Hum Retroviruses* 1999; **15**:811–820.
13. Mamidi RS, Ayubcha C, Rigney G, Kirschner J, Gerke O, Werner TJ, *et al*. **A prospective ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography study of the neurometabolic effects in cocaine use and HIV infection.** *AIDS* 2023; **37**:905–912.
14. Nickoloff-Bybel EA, Calderon TM, Gaskill PJ, Berman JW. **HIV neuropathogenesis in the presence of a disrupted dopamine system.** *J Neuroimmune Pharmacol* 2020; **15**:729–742.
15. Aksenov MY, Aksenova MV, Nath A, Ray PD, Mactutus CF, Booze RM. **Cocaine-mediated enhancement of Tat toxicity in rat hippocampal cell cultures: The role of oxidative stress and D1 dopamine receptor.** *Neurotoxicology* 2006; **27**:217–228.
16. Miller DR, Shaerzadeh F, Phan L, Sharif N, Gamble-George J, McLaughlin JP, *et al*. **HIV-1 Tat regulation of dopamine transmission and microglial reactivity is brain region specific.** *Glia* 2018; **66**:1915–1928.
17. Martinez D, Greene K, Broft A, Kumar D, Liu F, Narendran R, *et al*. **Lower level of endogenous dopamine in patients with cocaine dependence: findings from PET imaging of D 2 D 3 receptors following acute dopamine depletion.** *Am J Psychiatry* 2009; **166**:1170–1177.
18. McLaurin KA, Harris M, Madormo V, Harrod SB, Mactutus CF, Booze RM. **HIV-associated apathy/depression and neurocognitive impairments reflect persistent dopamine deficits.** *Cells* 2021; **10**:2158.
19. McRae M. **HIV and viral protein effects on the blood brain barrier.** *Tissue Barriers* 2016; **4**:e1143543.
20. Williams D, Veenstra M, Gaskill P, Morgello S, Calderon T, Berman J. **Monocytes mediate HIV neuropathogenesis: mechanisms that contribute to HIV associated neurocognitive disorders.** *Curr HIV Res* 2014; **12**:85–96.
21. Sil S, Niu F, Tom E, Liao K, Periyasamy P, Buch S. **Cocaine mediated neuroinflammation: role of dysregulated autophagy in pericytes.** *Mol Neurobiol* 2019; **56**:3576–3590.
22. Narendran R, Lopresti BJ, Mason NS, Deuitch L, Paris J, Himes ML, *et al*. **Cocaine abuse in humans is not associated with increased microglial activation: an 18-kDa translocator protein positron emission tomography imaging study with [11C] PBR28.** *J Neurosci* 2014; **34**:9945–9950.
23. Raichle ME, Mintun MA. **Brain work and brain imaging.** *Annu Rev Neurosci* 2006; **29**:449–476.
24. Sokoloff L. **Energetics of functional activation in neural tissues.** *Neurochem Res* 1999; **24**:321–329.
25. Barros L. **How expensive is the astrocyte?** *J Cereb Blood Flow Metab* 2021; **42**:738–745.
26. Cotto B, Natarajaseenivasan K, Langford D. **HIV-1 infection alters energy metabolism in the brain: contributions to HIV-associated neurocognitive disorders.** *Progr Neurobiol* 2019; **181**:101616.
27. Cotto B, Natarajaseenivasan K, Langford D. **Astrocyte activation and altered metabolism in normal aging, age-related CNS diseases, and HAND.** *J Neurovirol* 2019; **25**:722–733.
28. Cotto B, Natarajaseenivasan K, Ferrero K, Wesley L, Sayre M, Langford D. **Cocaine and HIV-1 Tat disrupt cholesterol homeostasis in astrocytes: implications for HIV-associated neurocognitive disorders in cocaine user patients.** *Glia* 2018; **66**:889–902.
29. Natarajaseenivasan K, Cotto B, Shanmughapriya S, Lombardi AA, Datta PK, Madesh M, *et al*. **Astrocytic metabolic switch is a novel etiology for cocaine and HIV-1 Tat-mediated neurotoxicity.** *Cell Death Dis* 2018; **9**:415.
30. Teodorof-Diedrich C, Spector SA. **Human immunodeficiency virus type 1 gp120 and Tat induce mitochondrial fragmentation and incomplete mitophagy in human neurons.** *J Virol* 2018; **92**:e00993-18.
31. González-Scarano F, Martín-García J. **The neuropathogenesis of AIDS.** *Nat Rev Immunol* 2005; **5**:69–81.
32. Sivalingam K, Cirino TJ, McLaughlin JP, Samikkannu T. **HIV-Tat and cocaine impact brain energy metabolism: redox modification and mitochondrial biogenesis influence NRF transcription-mediated neurodegeneration.** *Mol Neurobiol* 2021; **58**:490–504.
33. Robertson K, Liner J, Meeker RB. **Antiretroviral neurotoxicity.** *J Neurovirol* 2012; **18**:388–399.
34. Andersen AB, Law I, Krabbe KS, Bruunsgaard H, Ostrowski SR, Ullum H, *et al*. **Cerebral FDG-PET scanning abnormalities in optimally treated HIV patients.** *J Neuroinflamm* 2010; **7**:13–113.
35. Towgood KJ, Pitkanen M, Kulasegaram R, Fradera A, Soni S, Sibtain N, *et al*. **Regional cerebral blood flow and FDG uptake in asymptomatic HIV-1 men.** *Hum Brain Map* 2012; **34**:2484–2493.
36. Zielke HR, Zielke CL, Baab PJ. **Direct measurement of oxidative metabolism in the living brain by microdialysis: a review.** *J Neurochem* 2009; **109**:24–29.
37. McKenna MC, Scafidi S, Robertson CL. **Metabolic alterations in developing brain after injury: knowns and unknowns.** *Neurochem Res* 2015; **40**:2527–2543.
38. Hammoud DA, Sinharay S, Steinbach S, Wakim PG, Geannopoulos K, Traino K, *et al*. **Global and regional brain hypometabolism on FDG-PET in treated HIV-infected individuals.** *Neurology* 2018; **91**:e1591–e1601.
39. Lai S, Fishman EK, Lai H, Moore R, Cofrancesco J, Pannu H, *et al*. **Long-term cocaine use and antiretroviral therapy are associated with silent coronary artery disease in African Americans with HIV infection who have no cardiovascular symptoms.** *Clin Infect Dis* 2008; **46**:600–610.