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Mini-review: Elucidating the Psychological, Physical, and Sex-Based Interactions Between HIV Infection and Stress

Hannah Stadtler[a], **Gladys Shaw**[b], **Gretchen N. Neigh**[b,#]

[a]Department of Medicine, Virginia Commonwealth University, Richmond, VA, USA

[b]Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA, USA

Abstract

Stress is generally classified as any mental or emotional strain resulting from difficult circumstances, and can manifest in the form of depression, anxiety, post-traumatic stress disorder (PTSD), or other neurocognitive disorders. Neurocognitive disorders such as depression, anxiety, and PTSD are large contributors to disability worldwide, and continue to affect individuals and communities. Although these disorders affect men and women, women are disproportionately represented among those diagnosed with affective disorders, a result of both societal gender roles and physical differences. Furthermore, the incidence of these neurocognitive disorders is augmented among People Living with HIV (PLWH); the physical ramifications of stress increase the likelihood of HIV acquisition, pathogenesis, and treatment, as both stress and HIV infection are characterized by chronic inflammation, which creates a more opportunistic environment for HIV. Although the stress response is facilitated by the autonomic nervous system (ANS) and the hypothalamic pituitary adrenal (HPA) axis, when the response involves a psychological component, additional brain regions are engaged. The impact of chronic stress exposure and the origin of individual variation in stress responses and resilience are at least in part attributable to regions outside the primary stress circuity, including the amygdala, prefrontal cortex, and hippocampus. This review aims to elucidate the relationship between stress and HIV, how these interact with sex, and to understand the physical ramifications of these interactions.

Keywords

HIV-1; Stress; Cognition; Neuropsychiatric disorders; HAND; Aging; HIV Comorbidities

1. Introduction

Stress is broadly classified as any mental or emotional strain resulting from difficult circumstances. Stress can manifest in the form of depression, anxiety, post-traumatic stress

[#]**Address correspondence to:** Dr. Gretchen Neigh, PhD, 1101 East Marshall Street Box 980709, Richmond, VA, 23298, gretchen.mccandless@vcuhealth.org.

disorder (PTSD), or other neurocognitive disorders. Depression is the leading cause of disability, impacting more than 322 million people worldwide. Anxiety disorders are not far behind with 264 million people impacted globally. Although these disorders impact both men and women, women are disproportionately represented among those diagnosed with affective disorders[2]. Despite the undoubtable differences in stress burden experienced by men and women due to gender roles[3], the over-representation of the behavioral manifestation of stress in female laboratory rodents indicates that biological sex differences are an important driver of sex differences in the response to stress and thereby stress-related neural health effects such as depression and anxiety disorders[3].

Additionally, the incidence of depression is further augmented among People Living with HIV (PLWH) and this sex difference is maintained for depression and other stress-related disorders including PTSD[4–6]. The over-representation of depression and other stress-related disorders among PLWH can be particularly detrimental because it increases risks of non-adherence to essential anti-retroviral therapies and risks of HIV-associated cognitive dysfunction. Understanding the complex and multidimensional relationships among sex, stress, and HIV will lead to better treatment interventions that can increase quality and quantity of life for PLWH. In order to build a foundation of current understanding, this review begins with an examination of the complex influence of stress burden on HIV acquisition, pathogenesis, and treatment response. Following this essential background, the review considers biological relationships that fuel the complex interactions among sex, stress, and HIV and considers essential areas of future focused research efforts.

2. Stress Burden on PLWH

2.1. Stress Susceptibility

Susceptibility to the experience of chronic stress plays a significant role in HIV acquisition, as demographically, individuals with increased exposure to stress are more likely to also be infected with HIV. Individuals especially vulnerable to experiencing chronic stress include those who have experienced childhood trauma, are of lower socioeconomic status, or have experienced oppression, racism, or other traumatic instances throughout their life[7]. Not everyone exposed to a traumatic event develops PTSD, just as not everyone who experiences stress will develop a neurocognitive disorder[8–10]. PTSD susceptibility is correlated with impaired cognition, a general negative cognitive bias while coping with difficult circumstances, pre-trauma anxiety, greater environmental stressors (ex: work, home), and greater systemic stressors (ex: poverty)[8,11]. Similarly, elevations in depression and anxiety symptoms are associated with quarrelsome behavior suggestive of helplessness[12], and individuals with early childhood trauma are more likely to develop depressive disorders later in life[1,13]. Chronic stress and its subsequent neurocognitive manifestations have further physical and behavioral ramifications. As PTSD symptoms increase, so do an individual's emotional responses associated with particular memories, indicating the ability for memory alteration after a traumatic or stressful experience[14,15]. Furthermore, as chronic stress increases, so does the likelihood of developing substance abuse and addictive behaviors, especially in socially disadvantaged groups[16].

There is evidence that social stratification influences vulnerability to stress-induced activities that may further lead to additional risky behaviors and this can be replicated in the laboratory. For instance, in a 2018 preclinical study, two groups of mice were established: submissive and dominant. Both groups were then exposed to chronic mild stress; the submissive mice were 400% more likely to demonstrate an increase in cocaine attraction, while the dominant mice did not differ in cocaine attraction from their non-stressed state[17]. Furthermore, the stigma associated with HIV infection also negatively impacts psychological stress of PLWH, indicated by the negative health outcomes in PLWH who live in communities with increased amounts of HIV-associated stigma; experiencing increased stigma from other individuals has more of a negative impact on psychological health for PLWH or children of parents living with HIV than their own attitudes towards HIV infection[18]. Higher levels of stigma are also associated with less frequent HIV-specific doctor's visits and an increase in negative physical health outcomes, although these effects can be mitigated with the addition of increased social support and thus increased personal resilience[19]. Beyond socially disadvantaged groups specifically, there is a link between traumatic experiences and substance abuse[20]. A preclinical study found that male, but not female, mice with a history of chronic repeated stress compulsively and voluntarily consumed alcohol despite being paired to a negative stimulus[20]. Focusing on humans, it has been shown that 24% of adolescent girls and almost 30% of adolescent boys with PTSD also exhibited substance abuse[21]. A review of methamphetamine use disorder found that individuals may administer methamphetamine as a form of self-medication to relieve uncomfortable mood and body-relevant sensations, and that this relationship may be stronger in female individuals rather than their male counterparts, indicating that females may be more likely to utilize substance abuse as a coping mechanism for adverse events[22]. The same review also noted that females are more likely to experience emotional or sexual childhood trauma, further exacerbating this phenomenon[22]. Furthermore, in an expansive survey of more than 8000 adults, individuals who reported five or more stressful childhood experiences were seven to ten times more likely to suffer from substance abuse[23,24].

2.2. HIV Acquisition

Stress history is an important consideration when examining HIV acquisition, as evidenced by the substantial overlap in risk factors for stress and increased likelihood of HIV infection. Even with antiretroviral therapy (ART) and other treatments to decrease the transmission of HIV, HIV infections remain rampant, with 1.7 million new infections in 2018, and 37.9 million PLWH globally. Similar to the impact of chronic stress, HIV disproportionately impacts populations that have traditionally suffered from health disparities, including minority populations and those of lower socioeconomic status[25,26,27]. Women account for a large number of new HIV infections annually, as a variety of social, economic, and political factors and associated stigma contribute to women's vulnerability to HIV infection[28]. Substance abuse is another compounding factor to susceptibility of HIV acquisition, that not only impacts infection rates but also impacts adherence to treatment and care [27].

A 2016 study found that substance abuse and other risk factors associated with HIV infection are intertwined[25]. In Black men who have sex with men (MSM), the group identified as the most vulnerable to HIV infection, this study found that Black MSM were

the most likely demographic group to be socioeconomically disconnected (defined as neither in school nor working), HIV positive, and likely to binge drink and exhibit other substance abuse behaviors[29]. Additionally, individuals who suffer from stress or engage in substance abuse are also more likely to engage in risky sexual behavior, increasing the likelihood of HIV acquisition and transmission[30,31]. A United States study that examined the effect of syndemic stress in partnered gay men found that there was a negative correlation between levels of syndemic stress, condom use, and HIV disclosure[32]. The study concluded that participants who reported higher levels of stress were more likely to engage in condomless anal intercourse earlier than individuals who did not report significant levels of stress, further supporting the increased risk of sexual transmission for PLWH also suffering from stress[32]. Similarly, studies have found that Black MSM who have additional stress as a result of racism or associated stigma were also more likely to engage in condomless anal intercourse[33,34]. Although a 2019 study has indicated the positive effect educational programs can have on risky sexual behaviors, especially for these particularly vulnerable groups, more research needs to be completed to come to a concrete conclusion on the efficacy of such programs[35].

Beyond a demographic basis of stress increasing the likelihood of HIV acquisition, the physical ramifications of stress also contribute to these disparities. Although acute stress has been found to enhance the body's resistance to infection, chronic stress produces the opposite effect, decreasing the body's ability to fight off infections. Chronic stress, decreases chemotaxis of immune cells and expression of selectin molecules, likely via a sympatho-adrenergic pathway, which ultimately impairs the body's ability to defend the body at sites of infection or inflammation[36]. Chronic stress also impairs β2-adrenergic mediation of T-cell mobilization, further impairing the body's ability to respond to infection[36]. Stress also decreases the body's ability to repair breaks in skin, the first barrier to infection. One study found that the introduction of stress to a group of wounded individuals resulted in delayed repair of the skin barrier by 10% compared to individuals not exposed to stress[37]. This is likely due to a variety of stress-induced physical ramifications, including an increased amount of neuropeptide release from peripheral nerves and increased systemic glucocorticoid levels[36,38]. Additionally, chronic stress has also been found to decrease the efficacy of mucosal immunity, specifically the secretion of the immune factor S-IgA[39]. This is especially important to HIV infection, as HIV can be sexually transmitted and can enter the body through mucosal surfaces[40]. The combination of a demographic overlap for those likely to experience chronic stress and the physical impacts of stress on decreasing the body's immune defenses synergistically contribute to an increase in HIV acquisition within those who experience chronic stress.

2.3. HIV Pathogenesis

Chronic stress not only augments the likelihood of HIV infection, but it also expedites the physical ramifications of HIV infection itself, increasing the likelihood of the development of neuropsychiatric disorders such as depression, anxiety, and PTSD. Stress adds a significant physical burden to PLWH, as it increases the already present levels of inflammation and decreased immune response in the body. HIV infection has effects similar to psychological stress including increased presence of inflammation and cognitive

impartment, affecting various anatomical spaces including the brain[11,41,42]. Akin to the effect of stress on HIV augmentation, similar mechanisms contribute to expedited HIV pathogenesis. Chronic inflammation and a depleted immune system fueled by chronic stress, combine with the inflammation associated with HIV infection, to create a frail systemic condition susceptible to viral propagation throughout the brain[43,44]. This state of inflammation, even for those with viral loads suppressed via antiretroviral therapy (ART), also leaves PLWH more susceptible to further comorbidities and infections[45,46]. Furthermore, HIV infection is associated with negative effects on brain function and the development of depression, anxiety, and/or PTSD[47]. These HIV associated neuropsychiatric disorders can range from mild to severe depending on the stage of the immunodeficiency. The prevalence of PTSD among PLWH ranges from 5–74%, a profoundly greater range than the 7–10% identified in the general population[48,49]. Further exacerbating the relationship between HIV and stress is an identified a link between PTSD diagnosis and reduced ART adherence[48]. Similarly, it has been noted that major depressive disorder may occur in as many as 42% of PLWH[50,51]. Globally, there is a 21– 25% likelihood of a major depressive episode in PLWH, again higher than that within the general population[50,52,53]. Even at those alarming rates, most studies that investigate depression and stress-induced cognitive disorders look at stress disorders in a binary fashion rather than considering cumulative time. Assessing these disorders in a cumulative fashion could result in a better indication of clinical benefits and would give a better indication of the dynamics of depression on PLWH as a whole[54]. PLWH consistently report significantly worse physical and mental health-related qualities of life and an increased likelihood of depression[55]. These neuropsychiatric disorders are a result of many factors PLWH experience, including financial stress, food insecurity, rural geographic location, early life stress in addition to the other risk factors already defined for PLWH, and those likely to experience significant stress[50,56–59]. Understanding and attention to the impact of stress burden and the interaction with the viral impact of HIV will be essential to adequate intervention to prevent and treat neuropsychiatric manifestations in PLWH.

2.4. HIV Treatment and Adherence

The development of ART resulted in a drug regimen that inhibited viral replication for PLWH, decreasing systemic viral loads and thus reducing the virus's effect on the body. Consequently, the introduction of ART shifted the virus from an infection with a high mortality rate to a manageable chronic disease, with an estimated 4 million PLWH over the age of 50 in 2018[60,61]. However, ART cannot completely eradicate HIV from PLWH, as a characteristic of the retrovirus is the ability to not only integrate into host DNA, but to then become latent[62–64]. There are multiple anatomical sites that are latent reservoirs for HIV, including the liver, kidney, and brain, but there are also independent reservoirs within the brain itself including microglial cells and astrocytes[65–67]. Additionally, these cells can switch out of latency at any point; thus, in order to avoid an increase in systemic viral load, ART needs to be taken continually to account for the sporadic, and currently unpredictable, switch out of latency[68–71]. Taking a stringent drug regimen daily has its own adverse effects on the body, including an increased body mass index and a greater likelihood of cardiometabolic risk[72–75]. There are also issues with ART adherence for PLWH, which can result in drug resistances or other negative consequences[76–80]. Furthermore, women

have been noted to have worse adverse side effects as a result of ART, decreasing adherence in women specifically[81,82]. Beyond the physical effects of being infected with HIV and taking an intensive drug regimen, these drugs add a financial burden, further increasing psychological stress for PLWH[83–85].

With the increased life span of PLWH, these drug complications and physical results of stressors become even more significant. The median life expectancy of PLWH has surpassed 50 years in the United States, and other countries have experienced similar trends[86]. PLWH are not only experiencing an increase in life expectancy and aging in that regard, they are also experiencing an increase in cellular aging in the form of early cellular senescence, mitochondrial dysfunction, telomere attrition, and epigenetic alteration[87–89]. Older PLWH also experience higher degrees of low muscle mass and loss of bone density when compared to non-HIV infected individuals of a similar age, as well as increased levels of chronic inflammation[46,72,87,90]. Additionally, aging increases the prevalence of non-AIDS associated cancers in PLWH, which are now the leading cause of death for PLWH; most prevalent are hepatocellular, anal, cervical, and lung cancer[91–93]. HIV and stress-associated comorbidities also become more relevant with aging and contribute to impaired neurocognition already affected by HIV infection alone. Other HIV comorbidities have been noted to negatively impact neurocognition, such as substance abuse, impaired renal function, diabetes, increased body mass, and depression[94,95]. These comorbidities are more common in PLWH who have experienced significant stress, making the likelihood of impaired neurocognition even more likely in PLWH who have also experienced stress. Chronic stress in PLWH has also been shown to negatively impact daily functioning, impairing memory, executive functioning, and general activities of daily living, significantly impacting individuals' day to day life[96]. Thus, it is critical to understand the biological relationships between stress and HIV that fuel these complex interactions, in order to understand the future of research needed to mitigate these outcomes.

3. Biological Relationships Among Sex Differences, Stress, and HIV

Considering the overlap in direct effects and ramifications of stress and HIV, it is critical to understand the biological relationships between stress and HIV in order to design efficacious prevention strategies and treatments for HIV-related comorbidities. Recognizing how these biological relationships differ on the basis of sex is important in the understanding of the varying outcomes between men and women living with HIV. In chronic HIV infections, women are more likely to have a lower plasma viral load and a higher CD4+ count suggesting better physical control over HIV infection; however, women are also more likely to develop AIDS when compared to their male counterparts with higher viral loads or lower CD4+ counts, which indicates the presence of sex differences in factors enhancing the progression of disease[28,97]. Furthermore, PLWH who suffered from early life stress have significant volumetric brain differences, the most striking being in the right anterior cingulate cortex, the bilateral hippocampi, the corpus callosum, the left and right caudate, and the left and right putamen[98]. Volumetric changes in these brain regions are associated with poorer neurocognitive performance in terms of processing speed, attention/working memory, abstraction/executive functions, motor skills, learning, and language/fluency[98].

These regions were most significantly altered in HIV infected women, indicating that sex plays a role in both physical stress and HIV manifestation[98,99].

Similarly, activation of the hypothalamic-pituitary-adrenal (HPA) axis results in hormonal, neurochemical, metabolic, and physiological alterations in response to stress[100,101,102,103,104]. In response to a stressor, glucocorticoids are released from the adrenal cortex as a result of HPA activation and bind to receptors in the brain responsible for behavioral responses to stress[105]. Although the release of glucocorticoids and HPA axis activation as a whole is a normal biological response, long-term HPA axis activation can lead to chronic inflammatory diseases or other physical ramifications[106107,108]. To this end, PLWH have been found to have abnormal glucocorticoid-mediated immune responses, especially evident in women infected with HIV[109].

Recent studies have begun to uncover a complex interaction between the activity of the HPA axis and the neuromodulator oxytocin (OT)[110]. Basic and clinical research suggests OT levels act to dampen the HPA-axis activity[111,112]. Notably, a study looking at low-income women living with HIV showed a negative correlation between circulating OT and CD4+, but only when oxytocin levels were low[113]. Alternatively, when oxytocin levels were high, this group provided data suggesting a positive correlation with CD4+ levels in this patient sample. Subsequent studies have yet to untangle the complex interaction between stress, HIV, and oxytocin, yet it appears to be a promising avenue in the advancement of sex differences and stress in HIV.

Corticotropin-releasing factor (CRF), norepinephrine, and dynorphin are other neuromodulators similar to glucocorticoids released upon the experience of stress, that are also abnormally affected in PLWH, especially women[114]. The genesis of sex differences in stress-related disorders stems from both chromosomal differences and the organizational and activational effects of sex steroids[115]. The combined influence of chromosomal and hormonal effects generates differences in neural circuitry, neural activation, and subsequent genomic responses to stress exposures and depression[116–118]. These sex differences include relative variances in the function of brain regions, including the amygdala, prefrontal cortex, and hippocampus[119–122]. Although the stress response is facilitated by the autonomic nervous system (ANS) and the HPA axis, when the response involves a psychological component, additional brain regions are engaged. The impact of chronic stress exposure and the origin of individual variation in stress responses and resilience are at least in part attributable to regions outside the primary stress circuity[123], including the amygdala, prefrontal cortex, and hippocampus, and additional insight into the interactions among HIV, sex, and stress require consideration of these brain regions.

3.1. Amygdala

The amygdala modulates the stress-mediated response of fear. Chronic and developmental stress-induced differences in the structure and function of the amygdala have been implicated in stress-related neural and behavioral alterations[124,125]. Although the human amygdala does not appear to be sexually dimorphic[126], developmental patterns of amygdalar expansion differ markedly by sex. The female amygdala develops faster than the male amygdala, with females showing an inflection towards deceleration of expansion at 13 years

of age, whereas males do not demonstrate this inflection towards deceleration until 20 years of age[127]. Such a drastic difference in maturation of an area critical to the neural circuitry of stress is a strong candidate for sex differences in stress responses, especially in relation to the disproportionate influence of trauma during adolescence on females as opposed to males[128,129]. Although there are no gross volumetric differences in the amygdala between sexes[130], the potential for functional differences has been demonstrated in the measurement of blood oxygen level dependent (BOLD) signaling in humans[131] and in the assessment of neurotransmitter and neuropeptide responses in preclinical studies[132].

Corticotrophin releasing factor (CRF) interacts with estrogen within the amygdala to differentially modulate fear and stress responses in a sex dependent manner. CRF activation in the amygdala engages different neural networks dependent upon the organizational effects of sex hormones within the development of the amygdala[133]. Furthermore, sex differences in neurotransmitter availability in the basolateral nucleus of the amygdala are evident both under baseline and stress conditions such that males have a higher endogenous tone of dopamine and serotonin but females have a more robust response to stress exposure[134]. Importantly, positive behavioral therapy has been shown to produce favorable volumetric changes in the amygdala in patients with chronic anxiety[135], suggesting that the changes induced by stress are not static. Sex steroids and their metabolites can be influential in both males and females. Of particular note within the amygdala is the influence of allopregnanolone, a metabolite of progesterone and a GABA-A allosteric modulator of amygdala functional connectivity[136]. The interactions of allopregnanolone are the potential implications for the manifestation of premenstrual dysphoric disorder and postpartum psychosis[137]. Collectively, differences in developmental trajectory and functional activation of the amygdala between males and females are in a key position to drive sex differences in stress responses and subsequently manifestation of stress-related disorders.

In terms of the relationship between HIV infection and the amygdala, the combination of early life stress and HIV infection has been shown to increase the size of the amygdala compared to HIV-negative individuals, a change that is associated with an increase in neurocognitive dysfunction[98,138]. Increased amygdalar size is also associated with an upregulation of cortisol, the primary glucocorticoid in humans, further exacerbating the physical stress response in PLWH[139]. Additional studies have confirmed that early stress experiences result in reduced levels of amygdalar reactivity relative to those who did not experience early life stress. PLWH who also experienced early life stress had reduced levels of amygdala activity in addition to a higher likelihood of depression, anxiety, and alexithymia[140]. Interestingly, a study focusing on the relationship between HIV, the amygdala, and social adversity later in life found that there was an HIV/social adversity interaction with regard to the size of the amygdala, such that experiencing both resulted in an inward deformation of the structure[141]. Interestingly, impaired memory and learning were present regardless of the timing of stress[98,138,141]. Collectively, these findings demonstrate that PLWH are subject to multiple exposures and biologically sequalae that increase the risk of amygdalar dysfunction.

3.2. Prefrontal Cortex

The prefrontal cortex (PFC) is intimately and bidirectionally linked with the amygdala[142], developmentally differs between males and females[121] and is modified by exposure to stressors[123]. The PFC is instrumental in modulation of the excitability of the amygdala which can augment the influence of PFC effects of stress and sex. The sex difference in the maturation of the amygdala, discussed in previous section, is further complicated by an acceleration of the maturation of the PFC connectivity to the amygdala when early life stress is experienced[143]. It may be this shift in timing of maturation, compounded by early life stress, that synergizes to increase the risk of mental health disorders in females. Additional insight to the influences of sex and stress comes from preclinical studies which demonstrate that the dendrites in the PFC respond to stress in a sex-specific fashion with males demonstrating retraction and females demonstrating expansion of the dendritic arbor; changes which can dramatically impact the excitability of the neurons[144,145]. Further investigation demonstrated the role of sex steroids in these stress-induced changes in dendritic arborization and implicated estrogen as instrumental in driving increased dendritic arborization, even in the absence of stress exposure[145].

HIV infection also has an independent influence on the PFC that may also contribute to dysfunction. HIV transactivator of transcription (Tat) protein has been shown to negatively impact the CNS, potentially contributing to the high levels of HIV-associated neurocognitive disorders (HAND) in PLWH[146,147]. Tat has been found to have an excitatory effect in medial PFC pyramidal neurons, affecting neuronal gain, membrane time constant, resting membrane potential, and membrane excitability[148]. These neuronal changes have been associated with the development of HAND, suggesting the significance of the PFC to the progression of these diseases[148]. Furthermore, increased amplitudes of low-frequency fluctuations in the PFC are associated with increased levels of the inflammatory cytokine IL-6 and depression, supporting the contribution of the PFC to manifestation of depression in PLWH[149]. Aging further exacerbates the effects of HIV on the PFC, as both alter the structure and function of medial PFC pyramidal neurons via altering the activity of voltage-gated and inwardly-rectifying K+ channels[150]. Aging is associated with a decrease in medial PFC neuronal activity, exacerbated by HIV infection which is characterized by initial over-activation followed by loss of firing[150]. Another hallmark of HIV infection is significant epigenetic modification of neural tissue to tissue from individuals not infected with HIV, collectively, the observed modifications are consistent with the interpretation of increased brain age in PLWH suggesting that HIV may accelerate metrics of neural aging[89,151]. Other studies have resulted in identifying neuroimaging markers that demonstrate both caudate-putamen atrophy and cortical atrophy in PLWH, even with undetectable viral loads, as well as changes to neuron functionality and physiology rather than neuronal death[152–154]. These changes in neuroanatomy are heightened as the life expectancy of PLWH increases, as they are infected for longer periods of time, even with viral suppression, and these HIV-related changes will synergize with expected neuroanatomy changes that come with age. Given the key function of the PFC in facilitation and modulation of cognitive processing and performance, the high likelihood of early life stress, impact of HIV itself, and influence of sex on PFC function, create a particular susceptibility for cognitive dysfunction in women LWH and a history of early life trauma.

3.3. Hippocampus

The hippocampus is an important modulator of the HPA axis[155] and both sex and stress modify the function of the hippocampus and related circuitry[123]. The hippocampus is well-documented to undergo profound changes in dendritic arborization[156], neurogenesis[157], and gene expression[101], all in response to stressor exposure. In the case of developmental stressors, these changes appear to be long-lasting. Sex differences in the hippocampus are particularly profound, likely due to the substantial concentration of both glucocorticoid and sex steroid receptors within this region[158]. Stress and depression have been linked to reductions in hippocampal volume[159] and changes in hippocampal connectivity[160]. Given the sensitivity of the hippocampus to chronic and traumatic stress-induced changes in structure and function and its connectivity to the PFC and amygdala, sex differences in hippocampal structure and function exert far-reaching effects within the brain. Furthermore, the sensitivity of the hippocampus to sex differences in the sustained effects of developmental stress and the acute effects of adult stress[102,108] create a cascading influence that dictates both current and future stress responses likely through epigenetic mechanisms and the convergent influence of sex steroids. That being said, HIV proteins produced in hippocampal astrocytes can influence the function of the hippocampus and contribute to neurocognitive disorders via the spread of inflammation throughout the body, once again exacerbating the effects of stress on neuroanatomical structures and resulting in worse outcomes for PLWH[161]. Therefore, much like the amygdala and PFC, PLWH are at risk for hippocampal dysfunction due to multifaceted influences and the susceptibility of the hippocampus to stress and inflammation positioning the hippocampus as a key driver of HAND and related disorders.

4. Conclusion

The risk factors for individuals likely to be infected with HIV intertwine with risk factors for experiencing stress, making it likely that individuals could be infected with HIV and also suffer from significant stress. Both HIV infection and stress have negative impacts on cognition, impacts that are synergistic when both present. These impacts on cognition are a result of the physical mechanisms that are altered by HIV infection and experiencing stress, including alterations in the immune system, the nervous system, and the physical effects of inflammation. Collectively, sex differences in the amygdala, prefrontal cortex, and hippocampus initiate a feedforward effect on the sex differences already present in the ANS and HPA axis generating a fundamental divergence in the impact of stress and HIV on the brain and ultimately behavior between males and females.

Although research completed to date has provided tremendous insight into the origins of sex differences in stress responses that likely underlie differences in the manifestation of depression and anxiety disorders, comparatively little work incorporates the important consideration of HIV and related treatments on the function of the brain in the context of stress. A better understanding of the cellular changes that drive and result from sex differences in stress responses will lead to a more mechanistic understanding that will have the potential to build new intervention options. An approach incorporating research domain criteria (RDoC), may clarify the complex interaction between sex, stress, and HIV[162,163,164].

A recent study found there was a high correlation between perceived stress, anxiety, and traumatic experiences in women living with HIV[165], yet a neurobiological approach has not been explicitly explored within the realm of sex, stress, and HIV status limiting the broad applicability of some findings. As RDoC is more consistently integrated into research designs, a greater understanding of complex biological relationships and the influence on neural function and behavior will be facilitated. Particularly promising areas of study include examination of the mitochondrial influences and repercussions of stress on energetic availability at the synaptic level[100,102,166], growth in understanding of the molecular and epigenetic mechanisms that mediate divergent effects of sex steroids[158,167], modulation of function of neural circuits[168,169], and growing recognition of the modifying effects of early life exposures on sex differences in adult responses to stress[170–172].

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Highlights

- HIV, sex, and stress impact neural structures integral in neuropsychiatric disorders and cognition.
- Stress exposure early in life sensitizes neural circuitry further damaged by HIV.
- Sex differences during development increase the risks of adult cognitive dysfunction in the context of HIV.