Cognitive Reserve Over the Lifespan: Neurocognitive Implications for Aging With HIV

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Abstract

Approximately 59% of adults living with HIV experience HIV-associated neurocognitive disorder, a collection of symptoms and cognitive deficits in various cognitive domains. As the HIV population ages, the prevalence and severity of such cognitive deficits are expected to grow. Understanding how these cognitive deficits manifest is important for nurses and health care providers. This article provides an overview of cognitive reserve and evidence of how it is compromised by HIV, aging, and individual characteristics. Within this context of cognitive reserve, the role of neuroinflammation, neurotoxicity, substance use, comorbidities, depression and anxiety, social isolation, and sedentary lifestyle is reviewed. From this, strategies used to address cognitive deficits are provided, including topics such as psychostimulants, cognitive training, multimodal lifestyle interventions, and compensation strategies. Scenarios of successful and unsuccessful cognitive aging are presented to provide a lifespan perspective of cognitive reserve. Implications for clinical practice and research are provided, as it relates to aging.

Key words: cognitive reserve, cognitive training, cognitive deficits, HIV-associated neurocognitive disorder, neuroplasticity

People living with HIV (PLWH) are more likely to develop cognitive problems that interfere with everyday functioning and quality of life (Cody & Vance, 2016) in comparison to those who are uninfected. HIV-associated neurocognitive disorder (HAND) represents a collection of cognitive symptoms indicative of cognitive performance that is more than one *SD* below one's age and education normed performance scores on two or more cognitive domains, such as verbal memory, psychomotor ability, and executive functioning (Vance, Cody, & Moneyham, 2017). Based on a large cohort of 1,555 adults living with HIV across six sites in the United States, Heaton et al. (2010) found that the prevalence of HAND was 59%. The severity of HAND can vary as well, ranging from 33% with asymptomatic neurocognitive impairment to 12% with mild neurocognitive impairment to 2% with HIV-associated dementia.

Normal, nonpathological cognitive aging may contribute to the severity and prevalence of these cognitive deficits (Kinai et al., 2017). In a sample of 728 adults living with HIV, Kinai et al. (2017) identified increasing age and incomplete virological suppression as contributing factors for developing mild neurocognitive disorder and HIV-associated dementia. In fact, older adults (50 years and older) living with HIV are more likely to develop such cognitive deficits and are three times more likely to develop HIV-associated dementia than younger adults (20–39 years old) living with HIV (Valcour et al., 2004). In a sample of 3,313 adults living with HIV, a related study found that the odds of experiencing such a neurocognitive impairment increased by approximately 20% for each decade of life after age 40 years (Coban et al., 2017). Considering that by 2020, nearly 70% of those living with HIV in the United States will be 50 years and older, age and the management of HAND within this older population is becoming a major concern (United States Senate Special Committee on Aging, 2013).

These cognitive problems exert real-world consequences for this population. In numerous studies, HAND has been shown to negatively impact medication adherence (Kamal et al., 2017), instrumental activities of daily living such as shopping and financial management (Woods et al., 2017), and even automobile driving ability (Vance, Fazeli, Ball, Slater, & Ross, 2014). Furthermore, HAND is associated with poor planning, which is needed for everyday functioning (Cattie, Doyle, Weber, Grant, Woods, & HIV

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Neurobehavioral Research Program, 2012), risky decision making (Iudicello, Woods, Cattie, Doyle, Grant, & HIV Neurobehavioral Research Program Group, 2013), and a greater likelihood for being unemployed (Cattie et al., 2012; Fazeli et al., 2014).

As nurses and clinicians care for increasing numbers of older adults living with HIV, they require a working understanding of how these cognitive deficits manifest and impact everyday life, as well as how to prevent, treat, or compensate for such emerging cognitive deficits. From this understanding, nurses and clinicians can guide and educate their patients about HAND. The purpose of this article is to provide the neurological and psychosocial context in which older adults develop cognitive deficits leading to HAND. In order to do so, first a model of cognitive reserve over the lifespan is presented to provide the foundational concepts in which cognition is preserved or compromised. Second, major areas in which HIV and related comorbid and psychosocial factors that deplete cognitive reserve are examined (Figure 1). Third, to embody this information, hypothetical case scenarios of unsuccessful and successful cognitive aging are examined (Figures 2 and 3). Fourth, a brief description of recent strategies for preventing, remediating, or compensating for such cognitive deficits is reviewed. Finally, implications for clinical practice and research are provided.

Lifespan Perspective of Cognitive Reserve

Cognitive reserve refers to the processes in which the brain and neurons compensate for damage and continue to function. Robust cognitive reserve is characterized by one having numerous and healthy synaptodendritic connections between neurons within certain brain structures, connected by healthy white matter tracts that allow them to engage and interact with each other. From this interaction, cognition emerges; as one interacts with the environment, cognitive reserve can be augmented, through a process commonly described as neuroplasticity (Biessels, Deary, & Ryan, 2008; Vance, Eagerton, Harnish, McKie-Bell, & Fazeli, 2011).

Enriched Environmental Paradigm

Neuroplasticity refers to the numerous biochemical processes in which the connections between neurons are strengthened or weakened in response to environmental stimuli or the lack of environmental stimuli. This process is clearly demonstrated in the classic enriched environmental paradigm (Greenwood & Parasuraman, 2010; Rosenzweig & Bennett, 1972). The enriched environmental paradigm is an experimental design in which researchers observe that when an animal interacts with various degrees of enriching environmental stimuli, cognitive reserve and cognitive function are either increased through engagement (i.e., positive neuroplasticity) or decreased through the lack of engagement or atrophy (i.e., negative neuroplasticity; Cody & Vance, 2016).

Typically, in this experimental paradigm, genetically similar rats are randomized to live in one of three increasingly enriched environments. In the impoverished environment, rats are placed in isolation in cages with no toys to explore. In the standard environment, rats are placed three to a cage but with no toys to explore; in this

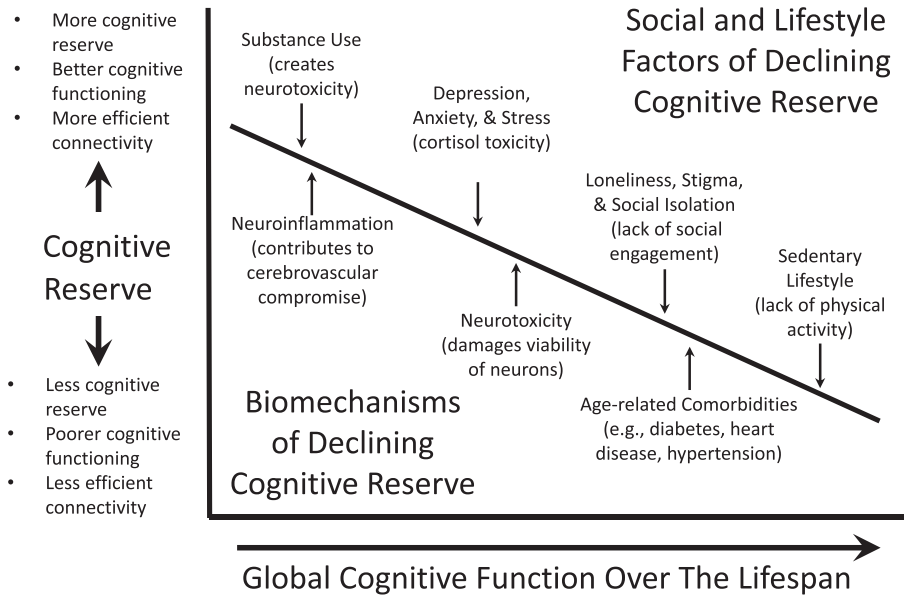

Figure 1. Conceptual model of the causes/contributions and biomechanisms of cognitive reserve over the lifespan.

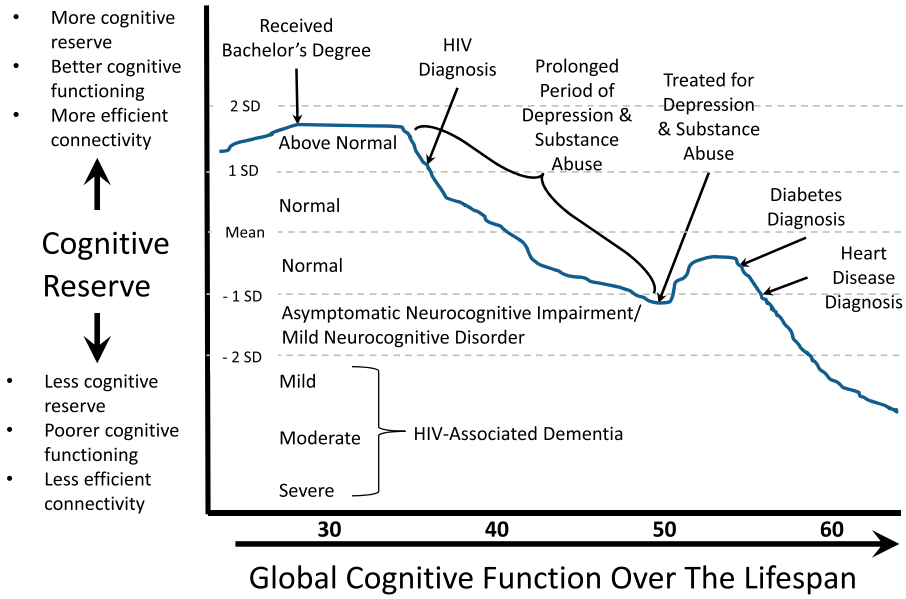

Figure 2. Hypothetical case of unsuccessful cognitive aging with HIV.

condition, rats are socially stimulated by other rats. In the enriched environment, several rats are placed in a cage with several toys to explore which are replaced with new toys periodically; in this condition, rats are cognitively stimulated socially by other rats and by sensory interactions (i.e., touch, sight) with the toys (Greenwood & Parasuraman, 2010; Rosenzweig & Bennett, 1972).

In several studies using this experimental paradigm, researchers have consistently observed macroscopic changes, such as increased cortical weight and thickness, and microscopic changes, such as increased neurogenesis, synaptic size, synaptic number, and dendritic complexity, in rats placed in the enriched environment compared with those placed in the standard environment. Likewise, the same pattern emerged for those rats in the standard environment compared with those in the impoverished environment (Greenwood & Parasuraman, 2010; Rosenzweig & Bennett, 1972). Furthermore, these macroscopic and microscopic changes correspond to cognitive improvement, specifically spatial memory, as measured by time to complete a maze (i.e., Morris water maze). Rats exposed to the enriched environment performed better than those exposed to the standard and impoverished environments; conversely, rats exposed to

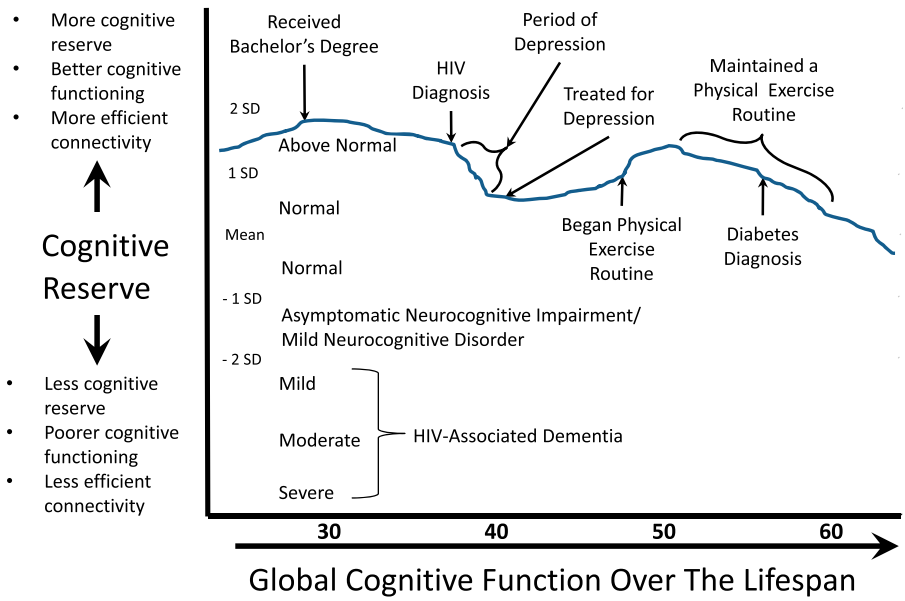

Figure 3. Hypothetical case of successful cognitive aging with HIV.

the impoverished environment performed worse than those in the enriched and standard environments. These studies suggest that increased exposure to novelty, either social or sensory contact, provides the stimuli for learning, which facilitates positive neuroplasticity and supports cognitive reserve. Interestingly, this learning effect is maintained up to 6 months and then fades. This suggests that maintaining novelty is an important component to support such neuroplastic effects.

Lifespan Environmental Enrichment in Humans

Enriched environments in animals parallel the cognitively enriched environments of education, occupation, and leisure activities (i.e., travel, playing a musical instrument) observed in humans to increase and maintain cognitive reserve over the lifespan. Studies demonstrate that individuals with better education experience less cognitive decline with age and are less likely to develop Alzheimer's disease (Greenwood & Parasumara, 2010; Wada et al., 2018). Likewise, studies examining the effects of lifelong employment consistently demonstrate that adults with cognitively complex jobs requiring high levels of learning and novelty experience delayed cognitive decline in older age; this has particular implications for those living with HIV because many do not reap the cognitive benefits of employment (Fisher et al., 2014; Vance, Cody, Yoo-Jeong, Jones, & Nicholson, 2015).

Embedded within the cognitive aging literature are numerous studies exemplifying how environmental and social engagement supports cognitive reserve (Fazeli et al., 2014; Stine-Morrow, Parisi, Morrow, & Park, 2008; Wada et al., 2018). For example, in a sample of 181 community-dwelling uninfected older adults, Stine-Morrow et al. (2008) randomized participants to two groups: (a) an active social group or (b) a no-contact control group. Over a 20-week period, those in the active social group worked as a team to creatively solve problems and compete against other such teams. Compared with the no-contact control group, those in the active social group statistically improved on measures of speed, inductive reasoning, and divergent thinking.

From a lifespan perspective, cognitive engagement and physiological processes that support brain health are fundamental in building and preserving cognitive reserve, even into older age. On the positive neuroplasticity side, factors important for supporting cognitive reserve are (1) education, (2) being engaged with work, particularly cognitively demanding employment, (3) social engagement, (4) physical activity/exercise, (5) maintaining a positive mood, (6) good nutrition, and (7) good sleep hygiene (Cody & Vance, 2016). Likewise, on the negative neuroplasticity side, factors detrimental to cognitive reserve are (1) substance abuse, (2) mood disorders and untreated mental illness, (3) prolonged stress, (4) loneliness, stigma, and social isolation, (5) sedentary lifestyle, and (6) age-related comorbidities (Cody & Vance, 2016).

HIV and Other Insults to Cognitive Reserve

People living with HIV are vulnerable to unique HIV-related biomechanisms of neurological change in addition to normative aging neurocognitive insults that deplete cognitive reserve. Transported through infected monocytes that cross the blood–brain barrier, HIV infects glial cells, which support neuronal health. When these glial cells die, they release neurotoxic molecules that damage the neurons and their capacity to function, thus compromising brain health and cognitive reserve (Cody & Vance, 2016). Furthermore, although combination antiretroviral therapy (cART) is necessary to avoid progression of HIV to AIDS as well as to avoid opportunistic infections that are damaging the brain, several studies suggest that these medications may produce some subtle neurotoxic effects that over time may also diminish cognitive reserve (Cody & Vance, 2016; Funes et al., 2014; Sanchez & Kaul, 2017).

Likewise, within the social context in which HIV occurs, there are many social and lifestyle factors that contribute to declining cognitive reserve. For example, in a sample of 137 adults living with HIV, Fazeli et al. (2014) examined the relationship between lifestyle factors and the prevalence of HAND. They observed that if participants engaged in physical activity (i.e., engaged in any strenuous exercise in the past 72 hours), social engagement (i.e., "frequently engage in or initiate activity"), and mental stimulation (i.e., working full or part time), the prevalence of HAND was greatly reduced. In fact, the prevalence of HAND was 20% for those who engaged in all three lifestyle factors, compared to 63% for those who engaged in none and experienced a sedentary lifestyle. This observation parallels that in the cognitive aging literature, avoidance of a sedentary lifestyle and active engagement, physically and mentally, supports brain health and cognitive reserve.

As Figure 1 conceptually demonstrates, these biomechanisms and social and lifestyle factors are intricately intertwined to contribute to declining cognitive reserve across the lifespan. Provided below are a few of the major biomechanisms and lifestyle factors known to compromise cognitive reserve as they relate to aging or HIV. As a caveat of this model, it is important to be cognizant that these biomechanisms and lifestyle factors

occur within the larger social context of poverty and race in which the effects of some of these factors may be exaggerated (Vance, 2017). As such, this model is not meant to be used as an established consensus treatment protocol to treat cognitive problems in adults living with HIV but as a guide for understanding some of the basic overall causes/contributions and biomechanisms of cognitive reserve over the lifespan.

Neuroinflammation and HIV

Neuroinflammation is an acute, normal immune response and important for regulating central nervous system (CNS) immunity against potential harm and protecting the brain from pathogens; however, prolonged neuroinflammation contributes to vascular compromise, oxidative stress, and ultimately brain damage (Cody & Vance, 2016). Research demonstrates that neural injury attributable to neuroinflammation persists despite effective viremia suppression. Thus, it appears that latent viral reservoirs are established in the CNS that allow viral replication, promote chronic low-grade neuroinflammation that overtime compromises the physiological integrity of the brain, and reduce cognitive reserve regardless of viral suppression (Cody & Vance, 2016).

Neurotoxicity

Viral replication in the CNS is a key mediator to progressive cognitive decline and the development of HAND and other neurologic manifestations. Recent data suggest that HIV proteins circulating in the brain, including gp120, gp41, Tat, Nef, and Vpr, are directly toxic to neurons while having limited effects on microglia, resident macrophages, and astrocytes (Rozzi et al., 2017). Thus, HIV contributes directly to neurotoxicity by increasing microglial activation and increasing infiltration of blood-derived macrophages, leading to the expression of proteins that lead to neuronal apoptotic death through autophagy. In addition to this direct pathway, the activation of microglia and macrophages release toxins that also lead to neuronal cell death. Finally, some of these neurotoxins also promote neuronal Ca2+ overload, which results in excess oxidative stress, mitochondrial dysfunction, and eventual neuronal cell death.

Complicating HIV-induced neurotoxicity, concomitant substance use, cART neurotoxicity, and genetic predisposition contribute to neurotoxic burden that reduces cognitive reserve resulting in the ongoing recognition of HAND (Sanchez & Kaul, 2017). Although the evidence clearly shows that the use of cART reduces HIV viral replication and protects brain and cognitive reserve (Cody & Vance, 2016), certain nucleoside reverse transcription inhibitors (NRTIs) induce oxidative stress and mitochondrial toxicity and facilitate neuronal cell death in a similar manner as outlined above. Albeit, the NRTI drugs in current use appear to be less neurotoxic than the D-drugs (dideoxynucleoside reverse transcriptase inhibitors) and thymidine analogs used in the late 1990s and early 2000s (Hung, Chen, Hsieh, & Calkins, 2017).

Efavirenz, a non-NRTI , has well-characterized neuropsychiatric side effects that tend to resolve with time in most patients (Apostolova et al., 2015). Yet, recent data indicate that efavirenz induces endoplasmic reticulum stress and mitochondrial toxicity, thus altering normal autophagy in neurons. Furthermore, certain individuals lack enzymes critical for efavirenz metabolism leading to excess efavirenz metabolites, which exert neurotoxic effects.

In addition, numerous protease inhibitors (e.g., amprenavir) have been implicated in neurotoxicity mediated through oxidative stress and mitochondrial cell damage, leading to excess build-up of amyloid protein and neuronal cell damage (Gannon et al., 2017). There is currently limited data regarding integrase inhibitors, but clinical reports of psychiatric side effects of this class of drugs suggest that they are not free of neurotoxicity (Elzi et al., 2017). Thus, although the benefits of cART with regards to preservation of cognition cannot be minimized, cART clearly has the potential to cause long-term neurotoxicity in patients who are exposed for many years.

Despite these potential long-term negative effects on neuronal functioning, cART remains necessary to maintain life and functioning of patients and is recommended over not taking cART, which can lead to a compromised immune system, opportunistic infections that can damage the brain (e.g., John Cunningham virus causing progressive multifocal leukoencephalopathy), and ultimately death. In fact, studies show that when cART is administered to adults living with HIV who were not previously taking cART, their cognitive functioning actually improved. This demonstrates the efficacy of cART in better protecting cognitive and brain health from the effects of HIV versus not treating PLWH with cART (Mora-Peris et al., 2016; Zhuang et al., 2017). In addition to prescribed cART, the use of illicit substances such as opiates and psychostimulants, such as methamphetamines, as well as alcohol abuse have detrimental synergy on neurologic outcomes, as outlined elsewhere in this article.

Age-Related Comorbidities

As PLWH age, the prevalence and severity of certain comorbidities are expected to increase due in part to

systematic HIV inflammation. Using an individual-based model of 10,000+ PLWH, the Dutch ATHENA study estimated that by 2030, of those 50 years and older living with HIV, 84% will have at least one additional comorbidity and 28% will have at least three, compared to 19% without HIV having at least three comorbidities (Smit et al., 2015). Researchers anticipate that these increased comorbidities will be comprised mostly of malignancies (17%), diabetes (17%), and cardiovascular disease (78%). Accompanying these comorbidities are normative age-related, physiological changes that reduce drug metabolism and excretion that include decreased adipose tissue with age and age-related decreased function in renal and hepatic functioning.

These comorbidities and the accompanying polypharmacy issues can compromise brain function and cognitive reserve. It is well documented in the literature that diabetes, cancer treatments, polypharmacy, hypertension, hypercholesterolemia, cardiovascular disease, and other comorbidities including psychiatric illnesses all contribute to poorer cognitive reserve and poorer cognitive functioning through a variety of biomechanisms (Vance, Larsen, Eagerton, & Wright, 2011). For instance, high blood pressure has been shown to contribute to small vessel ischemic disease resulting in brain lesions of axonal loss and demyelination as well as poorer cognitive functioning (Uiterwijk et al., 2018).

Substance Use

In a sample of 6,351 older patients from the Veterans Aging Cohort Study, adults living with HIV more commonly manifested problematic drug use, including cocaine/stimulant, opiate/heroin, and marijuana use compared to demographically matched uninfected people (Green et al., 2010). Substance use was common, with approximately 20% of the cohort reporting past year cocaine use, 52% reporting current tobacco use, 10% reporting past year opioid use, 30% reporting past year marijuana use (Green et al., 2010), and 31% reporting weekly alcohol use (Ikeda et al., 2016).

Substance use damages cognitive reserve in a variety of ways. First, substance use contributes to physiological detriments, such as cardiovascular, hepatic, and renal dysfunctions, which can impair brain function (Sanchez & Kaul, 2017). Second, the neurotoxicity induced by substance use negatively impacts brain health. Overall, self-administration of substances induces detrimental changes in gene expression, via transcriptional and epigenetic mechanisms, and adverse neurochemical, neurophysiological, and structural changes in brain regions as well (Korpi et al., 2015). For instance, common alterations caused by substance use, and reported by neuroimaging studies, occur in the frontal lobe. The combined influence of substance use, HIV, and aging may produce particular detrimental effects that compromise the frontal lobes, which are key for executive functioning, inhibition, and working memory (Sanchez & Kaul, 2017). These findings are complicated further by several factors such as the growing legalization of marijuana, the clinical use of medical marijuana, patterns of marijuana use (chronic heavy recreational use vs. occasional use vs. prescribed use), and potency and purity of the marijuana (Sagar & Gruber, 2018); the widespread use of legal and illegal opiates (Cheng & DeBeck, 2017) and polysubstance use along with alcohol and tobacco is observed in 20% of those with HIV (Hartzler et al., 2017).

Depression, Anxiety, and Perceived Stress

A systematic review of 66 studies that examined persistent psychological symptoms and perceived stigma among adults living with HIV reported elevated depression prevalence of 33% and an anxiety prevalence of 28% in PLWH (Lowther, Selman, Harding, & Higginson, 2014). In fact, the prevalence ratio of current major depression between adults with and without HIV receiving medical care is 3.1, and it is similar when controlling for age, ethnicity/race, and education (Do et al., 2014). The stress response from prolonged depression and other mood problems activates the hypothalamus–pituitary–adrenal (HPA) axis, which increases cortisol and adrenal disturbances, creates immune dysfunction, and promotes excessive secretion of proinflammatory cytokines that damage the brain, particularly the hippocampus; this compromises brain health and cognitive reserve over time (Cody & Vance, 2016).

Mood symptoms are not only relevant for cognitive reserve but also alter behaviors important for maintaining general health, including health domains (i.e., nutrition, physical activity, medication adherence) that impact cognitive reserve, and such positive health behaviors are also important for supporting cognitive reserve (Vance, 2013). For example, malnutrition, a common consequence of depression, anxiety, and perceived stress, is connected to increased cytokine levels, excess of catabolism, and altered production of peptides and hormones (El Chakhtoura, Bonomo, & Jump, 2017). Thus, mood problems can impact cognitive reserve directly through changes in brain chemistry and indirectly through behavioral changes that can impact physical health.

Loneliness/Stigma/Social Isolation

Chronic social isolation (i.e., objective measure of social network size; Evans et al., 2018) and loneliness (i.e., perceived lack of social connectedness; Donovan et al., 2017) are psychological stressors associated with diminished cognitive reserve and decreased cognitive function across aging populations. However, older adults living with HIV are particularly vulnerable to perceived loneliness and limited social interaction due in part to HIV stigma (i.e., perceived fear of HIV diagnosis disclosure and/or shame associated with HIV status), greater levels of depression, more frequent health problems, and limited financial resources than similar older populations without HIV (Vance, 2013). The effects of loneliness, stigma, and social isolation on cognitive reserve among those aging with HIV are hypothesized to stem from two mechanisms, prolonged hypercortisolism and diminished neuroplasticity.

First, prolonged hypercortisolism, as observed with HPA axis dysregulation, is associated with neural structure damage and death in key areas of the brain largely responsible for memory and executive functioning (i.e., hippocampus and frontal cortex) as well as decreased dendritic expansion, irregular synapse formation, and increased premature neuronal death (Epel, 2009). In a community sample of 156 older adults without HIV, Adam, Hawkley, Kudielka, and Cacioppo (2006) found that older adults with greater perceived loneliness consistently exhibited higher cortisol values in comparison to those with lower perceptions of loneliness. Thus, it appears that chronic stress, such as from loneliness, stigma, and social isolation, may promote HPA axis dysregulation, which damages neural structures needed for memory and executive functioning (Vance, 2013).

Second, social engagement has been shown to induce neural and synaptic activity, dendrite connectivity, and overall brain density (positive neuroplasticity; Cody & Vance, 2016). In contrast, individuals with limited social engagement demonstrate reduced neural stimulation and less synaptic protein transmission. Reduced frequency of higher cognitive engagement through social engagement is associated with decreased brain structure integrity, diminished brain density, and slower synaptic processing (negative neuroplasticity; Greenwood & Parasuraman, 2010). This means that many older, lonely, and/or socially isolated adults living with HIV experience fewer opportunities for complex and demanding cognitive activities derived from social engagement than comparative aging groups without HIV. In turn, higher social deprivation promotes greater negative neuroplasticity and diminished cognitive reserve in adults aging with HIV.

Sedentary Lifestyle

A sedentary lifestyle is associated with decreased cerebral perfusion, less neural gray and white matter, and decreased cognition across aging populations (Tarumi et al., 2013). For example, self-reported sedentary behavior is associated with greater odds of impaired learning, motor function, and memory in both PLWH and uninfected adults (Monroe et al., 2017). Moreover, when PLWH and uninfected adults were followed over a mean of 2.6 years, participants reporting regular physical activity maintained better neurocognitive function regardless of HIV infection status (Dufour et al., 2018). Furthermore, a physical activity intervention has demonstrated that 24 weeks of aerobic and resistance training can effectively improve cognition in sedentary adults with mild cognitive impairment (Langoni et al., 2018). However, both the length of intervention and degree of existing cognitive impairment should be considered when determining the mechanisms and impact of increased physical activity on cognitive impairment.

Successful and Unsuccessful Cognitive Aging with HIV

The dynamic interaction between these social and lifestyle factors with biomechanisms influence the amount of cognitive reserve one has as one ages. These interactions occur over time and may even counteract each other. For example, one may abuse substances (i.e., weakens cognitive reserve), but the negative cognitive effects of substance abuse may be at least partially mitigated by the cognitive benefits derived from regular physical activity. Figures 2 and 3 conceptualize how these factors may influence cognitive reserve over the lifespan to promote either unsuccessful or successful cognitive aging in adults living with HIV. As an exemplar of unsuccessful cognitive aging, this individual (Dick) in Figure 2, begins life with above average intelligence (1.5 *SD*s above the mean). As Dick gains more education earning a Bachelor's degree, he reaches a peak in his cognitive reserve but returns to his baseline levels after he no longer is actively pursuing higher education. Later in life, he struggles with depression and substance abuse, which contribute to his diagnosis of HIV. This is followed by several years of continued depression and substance abuse that weaken his cognitive reserve, dipping him into the upper range of HAND (1.1 *SD*s below the mean). After receiving treatment for depression and

substance use, Dick recovers some of his cognitive reserve but is later diagnosed with diabetes and heart disease that in conjunction with normal aging, over time, depletes his cognitive reserve resulting in HIV-associated dementia.

As an exemplar of successful cognitive aging, this individual (Jane) in Figure 3 begins her life also with above average intelligence (1.7 *SD*s above the mean). As she gains more education earning a Bachelor's degree, she reaches a peak in her cognitive reserve but returns to baseline levels after she no longer is actively pursuing higher education. Later she also receives a diagnosis of HIV but experiences only a brief time with depression and is treated for it within 2 years; thus, she does not experience a profound loss in cognitive reserve. Years later, she begins a physical exercise routine that not only improves her physical health but also improves her cognitive reserve. Years later, Jane is diagnosed with diabetes, and although this does weaken her cognitive reserve, the effect is minimized due to her maintaining her physical exercise routine. Thus, as an older woman, she has more cognitive reserve than Dick to approach older age and better odds of maintaining her cognitive abilities.

These two hypothetical examples are didactics that elaborate the importance of how these factors are important for brain aging and cognitive reserve, especially in those living with HIV. Obviously, the process of cognitive aging is much more complicated. Clearly, most people fluctuate throughout their lives engaging in sporadic periods of physical exercise, substance use, engagement in intellectual pursuits, and other behaviors that may or may not contribute to their cognitive reserve. Thus, Figures 2 and 3 do not reflect reality for everyone, plus only a few cognitive-related factors were considered. Other cognitive-related factors, such as resilience, spirituality, genetics, sleep hygiene, diet, and others, are all important considerations in examining cognitive reserve over the lifespan. For example, Fazeli, Moore, and Vance (2019) observed in a sample of 100 middle-aged and older PLWH, higher levels of resilience was associated with better performance in executive functioning, speed of information processing, working memory, verbal fluency, and global neurocognitive functioning.

Implications for Nursing Practice

Cognitive declines are difficult to treat because the causes are often multifactorial. Even with HAND, it is often assumed that other comorbid conditions contribute to the underlying pathology. For nurses and clinicians caring for their aging HIV patients, suggestions are provided in the following areas: (a) detection and monitoring, (b) prevention and treatment strategies, and (c) compensation strategies.

Detection and Monitoring

One of the primary roles of health care providers is to holistically assess and monitor their patients' health status, including cognition. Clinically, this includes observing if the patient seems confused, disoriented, or forgetful or simply inquiring about the patient's thinking (e.g., "Have you noticed any changes in your thinking?"). If concerns arise, then an accepted screening tool for cognitive impairment such as the Montreal Cognitive Assessment (MOCA; www.mocatest.org/splash/) or the NEU Screen (www.flsida.org/NEU) can be administered quickly during the clinic visit.

The MOCA is particularly well suited for the clinical environment because it takes only a few minutes to administer and has been shown to have good psychometric properties (Fazeli, Casaletto, Paolilo, Moore, & Moore, 2017). Similar to the Mini-Mental Status Exam, scores range from 0 to 30, with higher scores indicative of better cognitive functioning. For adults of 50 years and older living with HIV, a score of 26 and below suggests the presence of cognitive impairment. In fact, in a sample of 100 older (50+ years) adults living with HIV, Fazeli et al. (2017) observed that a score of 26 or less on the MOCA was "the optimal cut-off, balancing sensitivity (84.2%) and specificity (55.8%) compared to the 'gold standard' impairment as measured on a comprehensive neuropsychological battery" (p. 842). Greater total scores on the MOCA were significantly related to each of the cognitive domains of the neuropsychological battery (e.g., memory, reasoning, speed of processing, etc.) except for motor abilities. Greater total scores on the MOCA were significantly related to better self-reported instrumental activities of daily living functioning, fewer self-reported cognitive symptoms, and better functional status as rated by the clinician. Thus, in addition as a screener for cognitive function, the MOCA corresponds to patients' self-reports of cognitive functioning and clinician-rated everyday functioning.

If the results from the MOCA or other cognitive screeners suggest cognitive decline, further steps can be taken including talking with the patient further about such cognitive concerns, referring them to a psychologist or neurologist, and seeking underlying causes of cognitive decline (e.g., depression). Then, the patient is monitored over time for improvement or progression of such cognitive symptoms. For a more detailed algorithm of the steps involved with assessing and monitoring adults

living with HIV, please see Vance, Fazeli, Moneyham, Keltner, and Raper (2013).

Prevention and Treatment Strategies

There are several prevention and treatment strategies that can be used to address cognitive declines. First, treating underlying medical causes of cognitive decline is the primary strategy. Increased HIV viremia, encephalitis, hepatitis, uncontrolled hypertension/diabetes/hypercholesterolemia/heart disease, polypharmacy, substance abuse, sleep disturbances, mood disorders, hormonal imbalances, vitamin deficiencies, or even a combination of these are all possible causes and should be targeted for treatment and prevention.

Second, patient education about brain function is encouraged. In a study of four focus groups of older (50+ years) African American and Caucasian men and women living with HIV, Vance et al. (Vance, Gakumo, Childs, Enah, & Fazeli, 2017a) asked participants what they knew about brain health and what they were doing to promote their own brain health. Although some participants articulated certain behaviors important for maintaining optimal cognition (i.e., eating fish, playing games), overall these older adults had a cursory understanding of what is good for brain health. Many participants expressed that there is very little one can do to offset cognitive aging. Unfortunately, brain health curriculum programs are not widely available (e.g., Vance, Eagerton et al., 2011). Clearly, nurses and clinicians may need to develop and provide brain health education to their patients. The points presented in Figure 1 can help guide the development of such a curriculum so that patients can be encouraged to (1) actively manage their comorbidities, (2) be physically, socially, and mentally active, and (3) avoid substance use and a sedentary lifestyle as has been recommended in prior recommendations for protecting and maintaining cognitive reserve as PLWH age (Vance et al., 2013). As the focus on brain health is a relatively new topic to the literature, this also represents an emerging research topic.

Third, computerized cognitive training has been shown to benefit older adults and, in more recent studies, older adults living with HIV (Vance et al., 2017; Vance et al., 2019). Cognitive training protocols have been shown to improve the cognitive ability in which it was targeted, such as attention (i.e., selective concentration), memory (i.e., the ability to recall or recognize information), or reasoning (i.e., the ability to react to information quickly). One of the most effective protocols is speed of processing training; it improves speed of processing as well as locus of control, health-related quality of life and reduces depressive symptomatology. Interestingly, a large cohort study using speed of processing training has shown that compared to a control group, those who completed 10 hours of this cognitive training had a reduced prevalence of dementia by 29% over a 10-year period (Edwards et al., 2017). Although this robust finding is in need of replication, it supports the idea of how such targeted cognitive training can support cognitive reserve over time. Thus, nurses and clinicians can suggest the use of such cognitive training programs.

Compensation Strategies

In the event that cognitive ability is severely compromised, introducing patients to cognitive compensatory strategies is warranted. Such compensatory strategies include mnemonics and organizational devices (e.g., weekly pill boxes). Such compensatory strategies are specific to the type of cognitive decline whether it be poorer episodic memory or lack of attention. For example, low-tech strategies such as making lists and using calendars to keep track of appointments or other information is useful when episodic memory (i.e., memory of events) and prospective memory (i.e., remembering to remember) are compromised. Meanwhile, high-tech strategies, such as banking apps, are helpful when working memory and executive functioning skills needed to manage finances are compromised. Referrals to a social worker, psychologist, or occupational therapist familiar with these rehabilitative techniques are recommended. For a review of such cognitive compensatory strategies specific to HIV, please see Vance, Nicholas, and Cody (2015) where they discuss specific apps and mnemonics to help with financial management, time management, remembering appointments, and other everyday tasks. Additional information about brain health and cognitive apps can be found at American Association of Retired Persons (AARP) (https://www.aarp.org/health/brain-health)."

Implications for Research

Although the neuroAIDS literature has provided an excellent description of the many processes that compromise cognitive reserve, there remain few cognitive interventions described or conducted. Borrowing from the cognitive aging literature, three cognitive interventions are of interest. First, as alluded earlier, cognitive training studies are widely conducted in older adults, but only a few studies have been, or are being, conducted in older adults living with HIV, and most of those focus on speed of processing training (Vance, Cody, & Moneyham 2017; Vance et al.,

in press). Such cognitive programs may actually be used to target particular cognitive domains that contribute to a HAND diagnosis; by improving such cognitive domains, it may be possible to reverse a diagnosis of HAND and restore cognitive functioning as has been shown in one study (Hossain et al., 2017).

Second, multimodal lifestyle interventions seek to improve several lifestyle behaviors, such as physical exercise, intellectual/mental exercise, nutrition, and mood, all of which are known to improve health. Although there are several studies that successfully use such programs (e.g., The AgeWell Program; Clare et al., 2015; Vance, Eagerton, et al., 2011), the neuroAIDS literature does not have such research; however, one study did show that older (50+ years) adults living with HIV are amenable to engaging in such multimodal interventions (Vance, Gakumo, Childs, Enah, & Fazeli, 2017b). Finally, the use of psychostimulants to improve cognition in adults living with HIV has been tried but with questionable long-term effectiveness (McElhiney, Rabkin, Van Gorp, & Rabkin, 2010); unfortunately, the use of other medications (i.e., Aricept) and other neurotropic medications have not been examined (Vance et al., 2013). In fact, with the chronic low-grade neuroinflammation burden observed in HIV, testing of anti-inflammatory medications to protect cognitive reserve and improve cognition is of interest.

Finally, emerging aging literature among other older, cognitively impaired populations (i.e., Alzheimer's and Parkinson's disease, mild age-related neurocognitive impairment) suggests that reductions in dietary sugar intake may reduce systemic and neuroinflammation and thus positively influence cognitive function and/or reserve. To our knowledge, only one recently completed 12-week dietary intervention pilot study has explored these effects on cognition in an HIV population (Morrison, Fazeli, Gower, Willig, & Vance, 2018, November). Preliminary results support that dietary carbohydrate restriction improves cognitive performance, particularly in the domains of executive function and speed of processing. Thus, educating patients regarding primary sources of dietary sugar and recommendations to limit dietary sugar may provide additional cognitive benefit, particularly when combined with other cognitively beneficial health behaviors.

Conclusion

Cognitive reserve does not just develop and then maintain itself; a lifetime of engagement with one's job/career, people, hobbies, and culture as well as one's medical status, medical treatment, and health behaviors all interact to constantly build, repair, or diminish one's cognitive reserve over time. Unfortunately, patients may lack brain health literacy or assume that atrophy of one's brain health is inevitable. As greater cognitive reserve is necessary to successfully weather such age-related, lifestyle-related, and HIV-related neurological insults, people need detailed instruction about how to preserve and maintain their cognitive functioning as they age, as is commonly done with protecting one's cardiovascular health (i.e., exercise, reduce salt intake, reduce stress). This point is particularly germane to adults living with HIV as many possess a cognitive vulnerable phenotype, especially as they age.

Key Considerations

- ❍ Cognitive reserve refers to how much damage the brain can absorb and yet retain mental function.
- ❍ Aging and HIV compromise cognitive reserve over time, making those aging with HIV more vulnerable to cognitive declines.
- ❍ Social and lifestyle factors such as physical exercise, mental activity, including employment and social engagement, and management of morbidities, including HIV, are known to protect and even improve cognitive reserve over the lifespan.

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