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Improving Cognitive Predictors and Everyday Outcomes in Adults with HIV

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IMPROVING COGNITIVE PREDICTORS AND EVERYDAY OUTCOMES IN ADULTS WITH HIV

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ABSTRACT

As adults age with HIV, they may encounter challenges with cognitive impairments. Perhaps, the neurobiological effects of HIV, subtle lifestyle changes, and the aging process may negatively influence cognitive functioning. Some cognitive impairments may interfere with everyday functioning and even compromise quality of life. In this dissertation, three articles were presented which focused on the overall theme of HIV and cognition. Article 1, a review of literature published in the *Neurobiology of Disease*, focused on how HIV affects the brain independently and the synergistic effects of HIV and aging on cognitive health. Also, the article closed with a section on cognitive interventions and future directions for novel cognitive interventions (e.g., transcranial direct current stimulation). Article 1 provided extensive literature that supports the relationship between HIV and cognition, which leads to Article 2 that examined the impact of HIV-related cognitive functioning on everyday outcomes such as proactive coping. Article 2, which was published in the *Journal of Neuroscience for Nursing*, examined the role of cognitive functioning in predicting proactive coping in middle-aged and older adults with HIV. Given some adults with HIV may incur cognitive damage to prefrontal areas, such damage may negatively influence their executive functioning ability which is necessary to engage in proactive coping behaviors such as planning and problem solving. In this study of 98 adults with HIV, spirituality/religiosity rather than

cognitive functioning was found to be a significant predictor of proactive coping. Implications for research and nursing practice are provided.

In addition, other everyday outcomes such as sleep quality has shown to be affected in older adults with HIV. Using data from two pilot studies, Article 3 examined the effects of a low current brain stimulation known as transcranial direct current stimulation (tDCS) and speed of processing (SOP) training on sleep quality in older adults (50+) with HIV (n = 33) and without HIV (n = 33). Participants were randomized to receive either tDCS with SOP training or sham tDCS with SOP training. At baseline, adults with HIV had significantly poorer sleep quality and worse performance on the Letter Comparison Test compared to adults without HIV. tDCS or sham tDCS with SOP training did not improve sleep quality in any of the groups; therefore, this finding must be considered when using tDCS in combination with cognitive training to ameliorate sleep quality. Performance on Useful Field of View, a measure of visual SOP and divided attention, improved across all training groups. Perhaps, novel cognitive interventions to improve cognitive functioning may in turn improve everyday outcomes for the growing HIV population, especially as more of them age with the disease.

Keywords: sleep, HIV and aging, tDCS, cognitive functioning, speed of processing

DEDICATION

I would like to dedicate this dissertation to my loving children, Antwon and Arriana, who were there to brighten my darkest days during this journey. I could not have made it to the finish line without the unconditional love and support of my father (Randy Staples), my sister (Dr. Tamara Payne), and my dear friend (Mrs. Alice Fleeton). Most of all, I dedicate this dissertation in memory of my mother, Mary Staples, who would have been proud to witness me persevere through hardships and achieve my academic goals.

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COGNITION IN ADULTS AGING WITH HIV

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AIDS	Acquired Immune Deficiency Syndrome
ANI	asymptomatic neurocognitive disorder
ANOVA	analysis of variance
ApoE4	apolipoprotein E4
ARB	angiotensin II receptor blockers
BBB	blood brain barrier
BDNF	brain derived neurotropic factor
cART	combination antiretroviral therapy
CCB	calcium channel blockers
CNS	central nervous system
CSF	cerebral spinal fluid
DCA	didehydro-cortistatin A
fMRI	functional magnetic resonance imaging
HAART	highly active antiretroviral therapy
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HIV	Human Immunodeficiency Syndrome
HPA	hypothalamus-pituitary-adrenal

IADL	instrumental activities of daily living
JCV	John Cunningham Virus
LSNS	Lubben Social Network Scale
MAO	monomine oxidase inhibitor
MCI	mild cognitive impairment
METH	methamphetamines
MND	mild neurocognitive disorder
NNRTI	nonnucleoside reverse transcriptase inhibitors
PCS	Proactive Coping Scale
PI	protease inhibitors
PML	progressive multifocal leukoencephalopathy
POMS	Profile of Mood States
PSQI	Pittsburgh Sleep Quality Index
REM	rapid eye movement
SD	standard deviation
SOP	speed of processing
SPSS	Statistical Package for the Social Sciences
SRI	serotonin reuptake inhibitors
tDCS	transcranial direct current stimulation
UFOV	Useful Field of View

BACKGROUND AND SIGNIFICANCE

While combination antiretroviral therapy (cART) is sustaining life for many adults with HIV, many still experience cognitive impairments. The introduction of cART in the late 1990's led to a decrease in viral replication, lower incidence of opportunistic infections, and a decrease in the number of AIDS cases. Despite these benefits of cART, higher prevalence of milder forms of HAND remain; hence, Heaton and colleagues (2010) found that 52% of adults with HIV experienced HAND, of which, 33% had asymptomatic neurocognitive disorder (ANI) which involves cognitive impairment with no functional impairment, and 12% had mild neurocognitive disorder (MND) which involves cognitive impairment with some functional impairment, and only 2% experienced HIV-associated dementia (HAD) which is a severe form of HIV-associated neurocognitive disorder (HAND). Studies have shown that some cognitive impairments can interfere with performance of everyday tasks such as taking medication (Ettenhofer et al., 2010), managing finances (Thames et al., 2011), and may even affect one's ability to engage in adaptive, proactive coping behaviors (Cody et al., 2016). In fact, even subtle changes in cognitive functioning can have physical and psychosocial influences which can negatively affect quality of life in those aging with HIV.

Cognition, HIV, and Aging

Given the rapid increase in the number of adults living longer with HIV, concerns mount that HIV and the aging process may synergistically have adverse effects on cognitive functioning. According to the United States Committee on Aging (2013),

approximately 70% of adults with HIV will be 50 and older by 2020. Age has consistently shown to play a key role in the manifestation of cognitive impairments in normal adults as well as those with HIV. In a longitudinal study of 74 adults with (n = 54) and without HIV (n = 30) ages 40 and older, Seider and colleagues (2014) found that older adults with HIV had declines in verbal memory after 1 year compared to younger adults with HIV and younger and older adults without HIV; hence, data findings suggest that HIV may accelerate cognitive aging such that people with HIV in their early 50's may have similar cognitive function as normal adults in their 70's and 80's. Likewise, Ciccarelli and colleagues (2012) examined 154 older and younger adults with HIV and 39 matched (i.e., age, education) HIV-negative controls and found that, compared to younger adults with HIV and the HIV-negative control group, older adults with HIV performed worse on memory tasks. The study findings also suggest that HIV and aging may have some synergistic effects on cognitive functioning.

In addition, some studies suggest that HIV may accelerate or accentuate aging in the brain. Given HIV affects the cerebral cortex and subcortical areas of the brain (e.g., basal ganglia), some adults with HIV may develop cognitive impairments during mid-life similar to those seen in neurodegenerative diseases such as Alzheimer's disease (Cohen, Seider, & Navia, 2015). Perhaps, cognitive damage from HIV may induce neurodegenerative diseases at an early age (acceleration) or even affect how cognitive impairments are expressed in older adults. Accentuation of cognitive impairments may also be an issue as adults age with comorbidities such as hypertension, which can also adversely affect cognitive functioning (Pathai, Bajillan, Landay, & High, 2014). In fact, HIV and aging have been shown to independently contribute to reductions in brain

volume (Ances et al., 2012) and white matter integrity, which has been associated with metabolic risk factors (e.g., abnormal glucose levels) and impaired cognitive function (Archibald et al., 2014; Nir et al., 2014). Possibly, manifestation of structural changes in white matter may be more pronounced in older adults with HIV which may also increase their brain's vulnerability to cognitive impairments and/or HAND. In a study of 51 older adults with HIV on cART and 31 healthy matched controls (i.e., sex and age), Nir and colleagues (2014) found that those with HIV had more diffuse white matter abnormalities throughout the brain which correlated with poor cognitive performance. In a more recent study, Seider and colleagues (2016) found that older adults with HIV had more diffuse white matter abnormalities compared to younger adults with HIV and younger and older HIV-negative controls, suggesting a possible HIV by age interaction which may exacerbate cognitive impairments in some adults as they live longer with the disease. In the normal aging population, metabolic risk factors have been associated with reduced brain volume and cognitive impairments (Akhlaghi et al., 2016); however, the use of cART in adults with HIV has also been associated with several metabolic risk factors which may possibly contribute to premature cognitive impairments (Cohen et al., 2015). In a cross-sectional study of 222 adults with HIV on cART, Archibald and colleagues (2014) found several metabolic variables including hyperlipidemia and high blood glucose levels to be associated with abnormal white matter, suggesting that the effects of HIV and metabolic risk factors may be associated with greater cognitive damage which may contribute to persistent cognitive impairments among adults aging with HIV in the cART era.

Although it is uncertain whether HIV accelerates cognitive aging or accentuates cognitive impairments, increasing challenges with cognitive functioning in those aging with HIV are likely given evidence shows that, in general, risk factors for vascular and neurodegenerative disease are highly prevalent among older adults (Cohen et al.). Yet, not all adults with HIV develop cognitive impairments, and differential exposure to other risk factors (e.g., substance use) may account for some variability in cognitive functioning (Byrd et al., 2013). Several predictors of cognition have been identified and may be potential targets for improving HIV-related outcomes in adults aging with chronic disease.

Cognitive Predictors

Among adults with HIV, several cognitive predictors may explain why some people develop cognitive impairments and others do not. Although cognitive functioning in some adults with HIV may worsen with age, there are also factors such as depression (Fialho, Pereira, Mendonca, & Ouakinin, 2013), sedentary lifestyle (Fazeli et al., 2014), poor sleep hygiene (Gamaldo et al., 2013), psychoactive drug use (Meyer et al., 2014), and many others that may accelerate or accentuate cognitive decline over the lifespan. In a study of 139 community-dwelling adults with HIV, Fazeli and colleagues (2014) found that those who those with more active lifestyle factors such as physical exercise had better cognitive functioning; hence, their findings were consistent with previous studies in that physical exercise, when considered with other factors (e.g., employment and social activity), has been shown to influence cognitive performance across several domains including memory, attention, reasoning, executive functioning, and speed of processing. Given age has consistently been a predictor of cognitive performance among adults with

HIV, active lifestyle factors may be neuroprotective against cognitive impairments especially when facing concurrent cognitive injury. Too, those who engage in active lifestyle factors may be at a lower risk for comorbidities such as heart disease which may also affect cognition. Cognitive predictors must be considered given cognitive performance has shown to be a significant predictor of one's ability to independently perform everyday real-world tasks (Scott et al., 2011). For example, in a study of 26 adults with HIV age 40 and older, Vance and colleagues (2014) found poor performance on the Useful Field of View (UFOV®) test, a measure of visual speed of processing and attention, to be predictive of poor driving simulator performance (e.g., greater number of pedestrians hit and slower reaction time). As adults age with HIV, many will experience cognitive impairments that may adversely affect their driving performance and increase their risk for at-fault crashes. In addition, the interrelationship of cognitive domains may contribute to executive functioning impairments in older drivers which may explain their inability to make good decisions on the road. Fortunately, some cognitive impairments can be improved (e.g., attention) which may transfer to safer driving behaviors among older adults with HIV.

HIV and Everyday Functioning

Although life expectancy for adults with and without HIV is almost equivalent (Nakagawa et al., 2012; Samji et al., 2013), some adults with HIV experience cognitive impairments that interfere with their ability to perform their routine day-to-day tasks. As the number adults with HIV over age 50 increases, aging and HIV-related risk factors for cognitive impairments may coexist, thus leading to poor cognitive functioning which may negatively impact everyday functioning. For example, Thames and colleagues (2011)

examined 51 adults with HIV and found that, compared to younger adults with HIV, older adults performed significantly worse on measures of medication and financial management. Moreover, older adults with cognitive impairments performed significantly worse on measures of everyday functioning compared to those without cognitive impairments (Thames et al.). In a similar study of 80 adults with HIV, Andrade and colleagues (2013) found that deficits in working memory were associated with lower medication adherence, and better medication adherence predicted greater decreases in cerebrospinal fluid HIV RNA. Study findings confirm that cognitive impairments may contribute to poor medication adherence which can result in suboptimal viral suppression and viral resistance. Consequently, suboptimal viral suppression which may be related to poor penetration of cART across the blood brain barrier and potential drug neurotoxicity, can exacerbate cognitive impairments and possibly impair everyday functioning.

Similarly, cognitive impairments may adversely affect performance of job-related tasks (Weber et al., 2012). Several studies have shown that, compared to the general population, adults with HIV have a higher rate of unemployment (Dray-Spira et al., 2007; Rabkin et al., 2007). Although there are several reasons (e.g., illness) many adults with HIV are unemployed, few studies suggest that cognitive impairment may be a predictor of unemployment. For example, Blackstone and colleagues (2012) examined 1,574 adults with HIV and found that, compared to those who were deemed impaired by clinical rating or global deficit scores only, those who were deemed cognitively impaired by both clinical ratings and global deficit scores were more likely to have AIDS, have more severe comorbidities, have more severe depressive symptoms, be unemployed, and report impairments in everyday functioning. In another study, Woods and colleagues (2011)

examined fifty-nine unemployed and 49 employed adults with HIV and found that those who were unemployed demonstrated significantly lower cognitive performance (e.g., omission errors) on prospective memory task compared to those who were employed. Such findings suggest that some adults with HIV experience cognitive impairments that interfere with job-related tasks which may deem them unable to perform their job safely. While some studies suggest that cognitive impairments may lead to unemployment, others suggest employment has numerous cognitive benefits and unemployment may worsen cognitive impairments (Fazeli et al., 2014; Vance et al., 2015). In fact, Vance and colleagues (2015) proposed that employment encourages socialization, stimulates learning, provides a routine which may regulate sleep, provides a sense of purpose which may counteract depression, and gives adults with HIV more income to pursue cognitively stimulating activities. On the other hand, lack of employment can produce financial burden and stress which over time may stimulate excess cortisol release from the adrenal glands, thus leading to neuroinflammation and worsening cognitive functioning (Patterson et al., 2013). Also, adults with HIV who retire prematurely are unable to obtain cognitive benefits from employment; thus, they may isolate themselves and their minds may become consumed with negative thoughts about their disease and/or finances. According to Ellwardt and colleagues (2013), individuals who are isolated tend to experience a more rapid cognitive decline compared to those who are socially engaged. Thus, adults with HIV are at an increased risk for social isolation due to various factors including stigma and depression, all of which can negatively affect cognitive functioning and quality of life (Slater et al., 2013). Researchers suggest that social engagement can promote positive psychological influences in adults with HIV (Asante 2012; Vance,

2013); perhaps, such positive influences may result in better adaptation (e.g., proactive coping) for older adults with HIV may in turn improve cognitive health (Cody et al., 2016), a vital component to successful aging (Depp et al., 2012; Malaspina et al., 2011).

In summary, this literature review outlines the interplay between HIV, cognition, and aging and their effects on everyday functioning. Given the increased prevalence of HAND and neurodegenerative diseases expected to accompany growth of the HIV aging population, further investigation of cognitive predictors and their direct and indirect mechanisms on the aging brain is warranted. Although several factors have been identified that can influence an individual's susceptibility to cognitive impairments, there is no clear explanation for the varying degrees of cognitive impairment among adults with HIV. However, researchers suggest that the delay or absence in manifestation of cognitive impairments and daily functional impairments in some adults with HIV may be linked to their level of cognitive reserve (Foley et al., 2012; Vance, Fazeli, Grant, Slater, & Raper, 2013). According to Stern (2012), cognitive reserve refers to the brain's ability to counteract injury from disease, trauma, and/or aging and maintain normal cognitive functioning. In the context of adults with HIV, those experiencing cognitive-related impairments in everyday functioning may have lower cognitive reserve compared to others with cognitive impairments that do not interfere with everyday functioning. Furthermore, over the lifespan, cognitive reserve can be strengthened by exposure to cognitive stimuli (e.g., learning a new skill) and weakened in the absence of such stimuli (Vance et al., 2012).

T*heoretical Framework*

Cognitive reserve is a concept that derives from the cognitive reserve hypothesis which suggests that some experiences over the lifespan (e.g., higher education, employment, increased physical activity, social gatherings, and intellectual activities) may increase cognitive reserve which can be neuroprotective against the effects of neural injuries (Vance et al., 2010). Also, building cognitive reserve involves strengthening connections between neurons and more efficient use of cognitive networks (Barulli & Stern, 2013); stronger, more dense connections between neurons is associated with greater cognitive reserve which may delay negative effects of cognitive injury or neurodegenerative diseases (Vance et al.). In addition, the cognitive reserve hypothesis suggests that cognitive reserve is depleted over the lifespan; however, the rate of depletion may be slower in adults who engage in cognitively-stimulating activities. In the same manner, the rate of depletion may be faster in adults who do not engage in cognitively-stimulating activities which increases their risk for premature development of cognitive impairments. In the context of HIV and aging, cognitive interventions designed to strengthen cognitive reserve may reduce the effects of HIV and trauma in the aging brain which may also decrease the rate of HAND.

Overall Purpose

The purpose of the dissertation was to examine cognitive predictors such as aging and their potential impact on everyday outcomes in adults with HIV. Specifically, the dissertation features three articles: one focusing on the neurobiological effects of HIV when acting alone and synergistically with other cognitive predictors; a second focusing on how HIV affects everyday outcomes such as proactive coping; and a third focusing on

the use of cognitive interventions (i.e., speed of processing training and transcranial direct current stimulation) to improve everyday outcomes (i.e., sleep quality) and speed of processing. The next section includes a detailed description of each article.

Synthesis of Articles

In this dissertation, there were three articles surrounding the theme of HIV and cognition were presented. These three articles suggested key predictors of cognitive functioning, both modifiable and non-modifiable, and discussed the predictive value of HIV, cognition, and aging on everyday outcomes. These articles focused on the manifestation of cognitive impairments in adults as they age with HIV, an ongoing challenge with the steady growth in baby boomers.

Article 1: The Neurobiology of HIV and its Impact on Cognitive Reserve: A Review of Cognitive Interventions for an Aging Population

The first article was a comprehensive review of literature focusing on the neurobiological effects of HIV viral entry into the central nervous system and disruption of the blood brain barrier. As HIV enters the brain, the virus produces neuroinflammation and weakens the blood brain barrier thus making it easy for neurotoxic substances and HIV-infected leukocytes to enter the brain. The accumulation of neurotoxic substances in the brain can result in poor cognitive functioning and deplete cognitive reserve thus increasing the brain's susceptibility to other cognitive impairments. Also, the article examined how HIV affects cognition alone through several mechanisms including dysregulation of neurotransmitters, which may contribute to the development of mood disorders and disruptions in the sleep cycle; hence, such factors may deplete cognitive reserve and lead to poor cognitive functioning. The article also focused on the synergistic

effects of HIV on cognition when coexisting with substance use, comorbidities and aging, physical activity, sleep hygiene, and mood dysregulation; hence, the potential effects of those factors on cognitive reserve may be harsh in adults with HIV given their increased susceptibility to cognitive impairments and neuroinflammatory-induced brain atrophy and structural changes (reductions in gray and white matter). The article examined cognitive reserve and neuroprotective benefits of cognitive exercise or mental stimulation such as learning a new skill. Last, the article includes a section on current cognitive interventions and future directions for novel interventions. Article 1 was accepted for publication in the *Neurobiology of Disease* which has an impact factor of 5.2.

Article 2: The Influence of Neurocognitive Functioning on Proactive Coping Behaviors in Adults with HIV

Article 2 featured a cross-sectional study that examined potential neurocognitive influences on proactive coping behaviors in adults with HIV. Given some adults with HIV may be susceptible to early deterioration of the fronto-striatal regions, such as observed in HAND, they may also have impairments in executive function. Such impairments can inhibit their ability to engage in proactive coping behaviors (e.g., planning and problem-solving) and instead promote negative coping behaviors (e.g., ignoring their problems). Impairments in cognitive functioning observed among adults with HIV may impact how some deal with everyday stressors; therefore, proactive coping is an important outcome for this vulnerable population that may encounter challenges with their disease process, stigma, and now HIV and aging. Generally, proactive coping has been linked to better outcomes and a better quality of life which is critical for those aging with HIV; hence, this study hypothesized that cognitive functioning was a predictor

of proactive coping behaviors in that those with better cognitive functioning may be more likely to take a more direct approach to handling their stressors compared to those with poor cognitive functioning. In this study, neurocognitive and psychosocial measures were used to determine if cognitive functioning and other factors such as spirituality/religiosity predicted proactive coping behaviors. Several variables were included in the hierarchical multiple regression analysis including: demographics (gender, minority status, sexual orientation, education level, number of prescribed medications, and age), psychosocial measures (spirituality/religiosity, social network, mood state), and cognitive measures (Trail Making Test A, Trail Making Test B, Wechsler Memory Scale-III Digit Span, and Useful Field of View). These variables were used in the analysis to determine the best model to predict the dependent variable proactive coping, measured by scores on the Proactive Coping Scale (PCS). Although cognitive functioning did not predict proactive coping as hypothesized, spirituality/religiosity was found to be a significant predictor of proactive coping behaviors suggesting that those who seek a meaningful purpose and believe in a higher power are more likely to engage in proactive coping. A discussion section followed the results, and the article closed with implications for practice and research. This article was accepted for publication in the *Journal of Neuroscience in Nursing*.

Article 3: The Effects of Speed of Processing Training and Transcranial Direct Current Stimulation on Global Sleep and Speed of Processing in Older Adults with and without HIV

Article 3 featured the primary research project for this dissertation which consisted of a secondary data analysis from two research studies: one examining the

impact of tDCS and SOP training on cognitive functioning in adults with HIV age 50 and older, and another examining the impact of tDCS and SOP training on cognitive functioning in adults without HIV age 50 and older. This article focused on a secondary aim examining differences in global sleep quality and SOP among older (50+) adults with and without HIV who received tDCS and SOP training. In general, some adults experience poor sleep quality especially as they age with chronic disease. Many studies conducted in the pre-HAART era found higher rates of sleeping problems among adults with HIV compared to the general population; however, there were no studies that focused on older adults (50+) with HIV, and many lacked a reference group of adults without HIV. The pathophysiology of sleeping problems among adults with HIV may be related to several factors including the ability of HIV to infect the central nervous system (Gamaldo et al., 2013) or the effects of antiretroviral medications (Jean-Louis et al., 2012). However, poor sleep quality among older adults with and without HIV has been identified as a risk factor for cognitive impairments and poor quality of life (Byun, Gay, & Lee 2016); hence, challenges with sleep and cognitive functioning may become more prevalent with the age-shift in the HIV population.

Nevertheless, cognitive training has shown to be a therapeutic approach to improving sleep quality in older community-dwelling adults. Cognitive training, a form of brain fitness, involves several mental exercises designed to improve and/or preserve cognitive abilities in multiple domains including attention and visuospatial processing. In an eight-week study, Haimov and colleagues (2012) examined the effects of a home-based computerized cognitive training program on sleep in older adults and found that, compared to the control group that engaged in simple tasks that were not cognitively

stimulating, the active group that engaged in a higher level cognitive training program showed improvements in sleep quality and cognitive function. Likewise, improvements in cognitive function have been seen in older adults with HIV who engage in similar types of cognitive training, particularly SOP training. SOP training is another type of cognitive training program consisting of visual and auditory tasks designed to increase the accuracy and speed at which individuals can process information (Ball et al., 2007). Several studies have demonstrated the benefits of learning on sleep architecture, and there are a few mechanisms for how learning may improve sleep quality. In a study of rats, Nader and colleagues (2015) examined neurons in the motor cortex while they learned a new motor skill and during sleep both before and after the training session. They found subsets of neurons were activated while engaging in learning, and these subsets were reactivated during subsequent sleep blocks. After sleeping, the speed and accuracy in which rats performed the task increased; thus, after learning, reactivation of those neurons during sleep may act as a catalyst for brain plasticity which may result in better cognitive performance over time. Perhaps, the relationship between cognitive training and sleep quality may be bi-directional. Mental exertion from cognitive training may increase the duration in rapid eye movement (REM) sleep, thus altering sleep architecture (Haimov & Shatil, 2011). Also, inability to execute sleep-dependent cognitive processes and perform procedural tasks have been associated with lack of restorative sleep. Perhaps, SOP training may lead to cognitive fatigue and increase the demands for restorative sleep; also, such training can enhance plasticity which may reduce the impact of age-related cognitive changes in adults with and without HIV.

Another therapeutic approach to improving sleep, transcranial direct current stimulation (tDCS), involves a direct low current to the brain via electrodes on the scalp. Although the effects of tDCS on sleep in adults with HIV is unknown, it has been shown to improve sleep in adults with chronic insomnia (Saebipour et al., 2015). Too, some studies found improvements in cognitive function in older adults with the use of tDCS alone (Meinzer et al., 2013) and in combination with cognitive training (Park et al., 2014). For example, in a study of adults age 65 and older, Park and colleagues (2014) examined two groups: one that engaged in 10 sessions of cognitive training combined with active tDCS, and another that engaged in 10 sessions of cognitive training combined with sham/fake tDCS. They found significant improvements in accuracy of the verbal working memory task in those who completed the cognitive training combined with active tDCS; hence, findings suggest that tDCS may potentiate the effects of cognitive training, thus improving cognitive performance. Perhaps, cognitive training combined with tDCS may produce similar cognitive gains in older adults with HIV; also, such combination therapy may improve sleep quality given the benefits seen with their independent use. Thus, Article 3 featured the first study to examine the impact of tDCS and SOP training in older adults with HIV. The study was conducted to answer the following research aims:

- Aim 1: Examine global sleep quality and SOP (at baseline) between older adults with and without HIV
- Aim 2. Examine global sleep quality (measured by the Pittsburgh Sleep Quality Index) and SOP (measured by scores on Letter Comparison Test, Pattern Comparison Test, Digit Symbol Test, Digit Copy Test, and Useful Field of View

Test) among older adults with and without HIV who received tDCS or sham tDCS with SOP training (controlling for age, education, and baseline scores)

- Aim 3: Examine change scores for global sleep quality and SOP measures in older adults with and without HIV who received tDCS or sham tDCS with SOP training.

In summary, Article 3 presented data from two pilot studies with identical protocols. These protocols were administered to adults with and without HIV (age 50+) after they were randomized to one of two groups: a training group receiving 2 milliamps of tDCS while engaging in 10 one-hour sessions of computerized speed of processing training, or a fake/sham training group receiving 2 milliamps of tDCS for 30 seconds and finishing 10 one-hour sessions of speed of processing training after the current ramped back down to zero. Each group completed 10 hours of training (1-hour sessions twice a week) over a period of five weeks. The main outcome variables were sleep measured by global scores on the Pittsburgh Sleep Quality Index (PSQI) and speed of processing measures by scores on the Letter Comparison Test, Pattern Comparison Test, Digit Symbol Substitution Test, Digit Copy Test, and the Useful Field of View Test. The PSQI has seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. In this analysis, a global PSQI score was calculated from the sum of the questions in the seven components, with scores greater than 5 indicating poor sleep quality. In a study of 3,059 men (mean age = 76.4 years), internal consistency for the PSQI was good ($\alpha = .69$) (Allavena et al., 2016). Likewise, Beaudreau and colleagues (2012) found internal consistency for the PSQI in a sample of 2,968 women age 70 and older was good ($\alpha =$

.72), even when examined by race/ethnicity (α = .72 for older white women and .74 older black women).

Statistical Analysis

The data were analyzed using SPSS 21 software. Two data points were missing for the PSQI measure, one was in the HIV-positive tDCS + SOP group and the other was in the HIV-negative sham tDCS + SOP group. Linear regression was used to impute the missing values based on the remaining PSQI scores. To examine Aim 1, independent samples t-test (for continuous variables) and chi-square analysis (for categorical variables) were used to examine demographics (i.e., age, gender, race, marital status, income, education, employment, income, and marital status), baseline SOP scores, and baseline global PSQI scores between adults with and without HIV (see Table 1). ANOVAs and chi square analyses were used to examine demographics, baseline SOP scores, and baseline global PSQI scores for the four training groups: adults with HIV receiving tDCS with SOP training (n = 17); adults with HIV receiving sham tDCS with SOP training (n = 16); adults without HIV receiving tDCS with SOP training (n = 19); and adults without HIV receiving sham tDCS with SOP training (n = 20) (see Table 2). To examine aim 2, pre-post mean scores and standard deviations for global PSQI and SOP measures were examined for all four groups. Separate ANCOVAs (controlling for age, education, and baseline global PSQI and SOP scores) were performed to examine differences between groups with alpha set at 0.05. Also, main and interaction effects of independent variables (HIV status and training group) were examined (see Table 3). Post hoc analysis using least significant difference were performed for all significant effects. Finally, Pearson-product-moment correlation analyses were performed to examine

change scores for PSQI and SOP measures (see Table 4A and 4B) for adults that received tDCS or sham tDCS with SOP training.

Conclusion

In conclusion, this dissertation supported the theme of HIV, aging, and cognition. Overall, the articles outlined the effects of HIV on cognitive functioning in older adults and the influence of cognitive functioning on everyday outcomes such as proactive coping and sleep. Inter-individual variation has been observed in cognitive functioning among adults with HIV; thus, some cognitive influences on everyday outcomes may be detrimental and inhibit successful aging. Successful aging includes being "cognitively-fit" which can be accomplished by building cognitive reserve. While cognitive interventions targeting cognitive reserve are likely to improve cognitive functioning, cognitive interventions designed to improve everyday outcomes (e.g., sleep) may indirectly improve cognitive functioning. Perhaps, cognitive influences mentioned in this dissertation may lead to novel ways of strengthening existing neural networks, which may in turn, minimize clinical manifestations of HIV and age-related cognitive changes.

THE NEUROBIOLOGY OF HIV AND ITS IMPACT ON COGNITIVE RESERVE: A REVIEW OF COGNITIVE INTERVENTIONS FOR AN AGING POPULATION

by

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Abstract

The medications used to treat HIV have reduced the severity of cognitive deficits; yet, nearly half of adults with HIV still exhibit some degree of cognitive deficits, referred to as HIV-associated neurocognitive disorder or HAND. These cognitive deficits interfere with everyday functioning such as emotional regulation, medication adherence, instrumental activities of daily living, and even driving a vehicle. As adults are expected to live a normal lifespan, the process of aging in this clinical population may exacerbate such cognitive deficits. Therefore, it is important to understand the neurobiological mechanisms of HIV on cognitive reserve and develop interventions that are either neuroprotective or compensate for such cognitive deficits. Within the context of cognitive reserve, this article delivers a state of the science perspective on the causes of HAND and provides possible interventions for addressing such cognitive deficits. Suggestions for future research are also provided.

Key Words: HAND, HIV/AIDS; cognitive impairment; speed of processing; speed of processing training; cognitive remediation; cognitive compensation

The Neurobiology of HIV and Its Impact on Cognitive Reserve: A Review of Cognitive Interventions for an Aging Population

In the United States, it is estimated that by 2020, 70% of adults with HIV will be 50 and older (U.S. Senate Special Committee on Aging, 2013). Accompanying this rapid growth in the number of adults aging with HIV are concerns about cognitive deficits endemic in this population. Although cART has tremendously lowered the prevalence of HIV-associated dementia, cognitive deficits among adults living with HIV persist; in fact, ~52% of adults with HIV experience HIV-associated neurocognitive disorders (HAND) (Heaton et al., 2010).

Given increasing age is associated with greater cognitive deficits and the development of dementia, adults aging with HIV may be at a higher risk for cognitive deficits (Vance et al., 2014e). In a recent study of 155 older adults with HIV, Greene et al. (2015) examined the prevalence of the following geriatric syndromes: falls, urinary incontinence, functional impairment, frailty, sensory impairment, depression, and cognitive deficits. The study findings show greater frequency of prefrailty, difficulty with instrumental activities of daily living, and cognitive deficits which were associated with an increasing number of comorbidities. Also, Jahanshad et al. (2012) examined how neural pathways (white matter integrity) differed in older adults with and without HIV using magnetic resonance imaging (MRI) and found that, compared to adults without HIV (n = 30), frontal and motor pathways were compromised in the adults with HIV (n = 55) even with the use of antiretrovirals. Jahanshad et al. (2012) also compared neural

pathways of adults with HIV who were carriers and noncarriers of the apolipoprotein E4 (ApoE4) genotype, a genetic factor associated with neurodegeneration. Compared to noncarriers of ApoE4 with HIV, those with HIV who were carriers of the genotype had additional white matter deficits in the temporal and parietal regions which appeared worse with prolonged duration of illness. Findings from these studies suggest that age-related brain changes may also contribute to cognitive deficits in older adults with HIV, and disruption of neural pathways may be exacerbated with genetic susceptibility and in the presence of comorbidities, a key concern as more adults with HIV merge into the geriatric population.

Several studies have shown that cognitive deficits in adults with HIV lead to significant challenges performing job-related tasks, taking medications, and driving (Foley et al., 2013; Patton et al., 2012; Vance et al., 2014a). Andrade et al. (2013) found that memory deficits in adults with HIV are associated with poorer medication adherence, which suggests that antiretroviral non-adherence in adults with such deficits may result in suboptimal viral suppression and poorer health outcomes. In a study of 26 middle-aged and older adults with HIV, Vance et al. (2014a) found that those with poorer visual speed of processing had poorer driving performance, which suggests that those with cognitive deficits may be at a higher risk for automobile accidents. Findings from this study demonstrate the negative influence cognitive deficits can have on everyday functioning.

The purpose of this article is to examine the neurobiology of HIV and its impact on cognitive reserve in lieu of viral-induced neuroinflammation and neurotoxic substances. This article reviews the basic cellular mechanisms involved with the neurobiology of HIV, beginning with viral entry into the central nervous system (CNS),

disruption of the blood brain barrier (BBB), Tat and other neurotoxic molecules, and the role of microglial cells. From this, a discussion of larger structural changes in the brain along with how they impact the dysregulation of neurotransmitters (glutamate, dopamine, and serotonin) is provided. Accompanying this is a dialogue about the synergistic effects of co-exposure to substance use, comorbidities and aging, and mood disorders that subsequently affect brain health and cognition. This leads to a discussion of cognitive reserve and the role of neuroplasticity, as it relates to the Frascati criteria, a guide for classifying different forms of cognitive disorders associated with HIV. Next, this article provides a review of the cognitive interventions used in adults with HIV including (cART) and other medications (i.e., modafinil), lifestyle changes (i.e., physical activity, sleep hygiene), cognitive remediation strategies (i.e., cognitive training), and compensatory strategies (i.e., spaced-retrieval method). In closing, the article presents future directions of novel cognitive interventions (i.e., transcranial direct current stimulation).

Neurobiology of HIV

HIV targets the CNS and weakens the BBB which contributes to the following cascade of events: influx of HIV-infected microglia cells or white blood cells in the CNS; secretion of neurotoxic viral proteins such as Tat; release of proinflammatory cytokines (e.g., IL-Iβ); disruption in neurogenesis; damage to synaptodendritic connections (Vance et al., 2014d; Yadav and Collman, 2009). These events damage some brain structures and neural circuits, which increases the brain's susceptibility to other neurological disorders, psychiatric comorbidities, neurodegenerative disorders, and cognitive decline (Watkins and Treisman, 2012; Wendelken and Valcour, 2012). To understand the neurobiology of

HIV, it is necessary to first explain the purpose of the BBB and what occurs when HIV enters the brain, the neurotoxic effects of viral proteins (Tat and gp120), and the role of microglial cells in neuroinflammation.

Blood Brain Barrier (BBB)

The BBB, which separates blood circulating through the body from the brain, is composed of endothelial cells connected by tight junctions that allow the passage of nutrients, water, and gases necessary for brain function. The BBB also prevents potential neurotoxins from entering the brain. As HIV infection disrupts the tight junctions and weakens the BBB, this allows the infiltration of white blood cells (i.e., HIV-infected monocytes and macrophage) and other neurotoxic substances into the brain. These infected white blood cells in the periphery are then able to cross the BBB, a phenomenon referred to as the "Trojan Horse" method. As HIV enters the brain and disrupts tight junctions within the BBB, permeability increases which further facilitates viral entry into the CNS; as a result, neurotoxic viral proteins (i.e., Tat, gp120) cross the BBB which may intensify the degree of neuroinflammation and result in poor cognitive function (Kovalevich and Langford, 2012). While there may be question whether HIV-related damage to the BBB is reversible, there are no studies suggesting interventions to strengthen the BBB. Delivery systems such as nanocarriers have been examined to allow certain antiretrovirals to enter the CNS. While this may not restore the integrity of the BBB, delivery of some antiretrovirals to specific areas in the brain may help reduce neuroinflammation and replication of the virus (Gomes et al., 2014).

Tat and gp120

Tat is primarily responsible for increasing permeability of the BBB, thus allowing more HIV-infected white blood cells to enter the brain. Tat potentiates neurotoxic effects by activating HIV-infected white blood cells to release neuroinflammatory molecules (e.g., IL-1β, IL-6, TNF-α), which then lead to neuronal apoptosis (Giunta et al., 2011). In addition, Tat-induced neuroinflammation creates a neurotoxic environment which further weakens the BBB; this usually results in further neuronal damage and may eventually lead to the development of HAND (Strazza et al., 2011).

Another potent viral protein, gp120, is formed on the outer surface of HIV and its neurotoxic effects may also be responsible for CNS damage. Similar to Tat, gp120 promotes the release of neuroinflammatory molecules (IL-6 and TNF-α), which facilitate neuronal death, and with such elevated levels, it contributes to deficits in memory, language, and executive function (Vance et al., 2014e). Also, gp120 impairs neurogenesis and synaptodendritic connections in the hippocampus (Lee et al., 2013). Another way in which gp120 affects the brain is by promoting the virus to bind to HIV receptors, CCR5 and CXCR4 which are found on peripheral macrophages and T-cells respectively; thus, fusion of the viral and cellular membranes facilitates HIV's entry into the CNS (Arrildt et al., 2012). Although the mechanisms in which gp120 and Tat impact the brain remain unclear, a cascade of neuroinflammatory events emerge with the secretion of these viral proteins from HIV-infected microglial cells. Recently, the Tat inhibitor didehydro-cortistatin A (dCA), has been examined as an novel approach to reduce residual HIV-1 levels of viral transcription in latently infected cells and block events of viral reactivation (Mousseau et al., 2015). Perhaps, dCA combined with cART can halt viral replication

and reactivation of latent HIV-infected cells, which in turn may reduce neuroinflammation. However, further exploration of such Tat inhibitors is necessary to determine its role in reducing the neurobiological effects of HI **Microglial Cells**

Rather than affecting neurons themselves, HIV infects microglial cells which secrete Tat and gp120, thus initiating neuroinflammatory events. After HIV-infected monocytes cross the BBB, HIV replicates in the CNS and targets microglial cells which are responsible for phagocytosis, a process of engulfing bacteria and neurotoxins in the CNS (Strazza, et al., 2011). Inhibition of phagocytosis contributes to a neurotoxic environment that compromises neuronal health. Also, during activation of HIV-infected microglial cells, neurotransmitters are released (Potter et al., 2013). Some of these neurotransmitters are excitatory, while others are inhibitory, which means they stabilize the brain when there is excessive stimulation or firing of neurons. The homeostatic function of neurotransmitters is often disrupted when HIV infects the brain; imbalances in their concentrations can produce neurotoxic effects in the brain. Such imbalances are observed with glutamate, dopamine, and serotonin (Harris et al., 2014).

Glutamate Excitotoxicity

Glutamate is an excitatory neurotransmitter which is necessary for cognitive functions including memory and learning, and is highly involved in homeostasis of cellular development; however, too much or not enough glutamate can be neurotoxic and induce neuronal death (Ernst, et al., 2010). With HIV, glutamate excitotoxicity occurs when astrocytes, another type of glial cell, fail to remove excess glutamate from the synaptic cleft and return it to homeostatic levels, thus leaving it to accumulate in the extracellular space (Potter et al., 2013). The release of cytokines, Tat, and gp120

contributes to increased extracellular glutamate and decreased glutamate reuptake by the astrocytes. As a result, excess extracellular glutamate can induce intracellular levels of calcium which promotes the release of more glutamate from astrocytes; hence, glutamate excitotoxicity leads to neurotoxicity which is associated with decreased cognition and the development of HAND (Potter et al.). Likewise, reductions in inhibitory neurotransmitters such as dopamine can affect cognition.

Dopamine Depletion

Studies have shown that adults with HIV have decreased levels of cerebral spinal fluid (CSF) dopamine, a neurotransmitter located in a subcortical region of the basal ganglia called the substantia nigra (Obermann et al., 2009). Since HIV has a strong affinity for damaging subcortical regions, these areas may result in depletion of dopamine in the CSF which impair functional connectivity in the fronto-striatal-thalamo circuitry. Kumar et al., (2011) found that, compared to adults without HIV, adults with HIV had a 45% decrease in dopamine in the substantia nigra which was associated with poorer cognitive function across the following domains: speed of processing, memory, learning, and verbal fluency. Depletions in dopamine levels have been observed in adults with HIV despite being on cART; however, this generates concern for adults aging with HIV who are at a higher risk for neurodegenerative diseases such as Parkinson's disease that may further deplete dopamine levels (Saravanan and Turnbull, 2009).

Serotonergic Neurons

Another inhibitory neurotransmitter, serotonin, is important for stabilizing mood. HIV may not directly affect serotonin; however, studies suggest that serotonin deficiency in this population is associated with the pathophysiology of psychiatric disorders such as

depression, anxiety, schizophrenia, and substance dependence just to name a few (Ances et al., 2008; Letendre et al., 2007). In a study of 658 adults with HIV, Letendre et al., (2007) found that of the 71% who used cART, 30% who were taking serotonin reuptake inhibitors (SRIs) were more likely to have undetectable CSF HIV viral load compared to those who were taking cART alone. Perhaps, the reduction in depression or anxiety facilitated better medication adherence. In addition, those who were taking SRIs demonstrated significant improvement on cognitive testing, which suggests that this class of drugs may be used as an adjunct therapy to enhance cognition (Letendre et al., 2007).

Changes in Brain Structures

In adults with HIV, damage to the BBB, the damage caused by Tat and gp120, the neurotoxic effects of infected microglial cells, and neurotransmitter imbalance can produce changes in brain structures and volume reductions in gray and white matter, which over time are associated with cognitive deficits (Kuper et al., 2011; Strazza et al., 2011). The next section discusses the effects of HIV on brain structures, particularly gray and white matter atrophy. Then, information is presented related to the additive effects of substance use, comorbidities and aging, and mood disorders which can contribute to further cognitive deficits.

Gray Matter and White Matter Atrophy

Atrophy in the cortical and subcortical regions (e.g., basal ganglia) with significant reductions in gray and white matter have been documented in adults with HIV (Kuper et al., 2011). In a study of 84 adults with HIV and 71 adults without HIV, Becker et al. (2011a) found significantly more atrophy in the putamen and caudate nucleus and volume reductions in the basal ganglia over time in the adults with HIV, despite being

virologically well-controlled on cART. In a study of 48 adults with HIV, Kuper et al., (2011) found that volume reductions in gray matter (dendrites and synapses) along the prefrontal cortices correlated with lower CD4 count, longer duration of disease, and poorer cognitive function.

HIV is also associated with reductions in white matter, consisting of nerve fibers and myelin, which is essential for effective brain signaling between brain areas (Kuper et al., 2011; Nir et al., 2014). Alterations in gray and white matter may occur soon after HIV diagnosis when neurotoxic viral proteins, particularly Tat, injure synaptodentritic connections between neurons in the basal ganglia and result in damage to the fronto-striatal-thalamo circuitry, a region known to incur damage before the development of HAND (Plessis et al., 2014).

Substance Use

The synergistic effects of HIV and substance use on cognitive function can be detrimental and accelerate neurodegeneration (Hauser and Knapp, 2014). In adults with HIV, substance use causes damage to structures in the fronto-striatal-thalamo circuitry. Concurrent substance use with HIV may potentiate inflammation, impair the BBB, trigger neuronal death, disrupt neural circuitry, and increase oxidative stress (Blackstone et al., 2013). Three commonly used neurotoxic drugs are methamphetamines (METH), opiates, and cocaine.

Methamphetamines (METH)

METH use has been associated with high-risk sexual behaviors and transmission of HIV; hence, the prevalence of METH use is estimated around 43% among men who have sex with men (Freeman et al., 2011). In a recent study, Blackstone et al., (2013)

found that METH users with HIV had poor global cognitive functioning and were more likely to report difficulty performing instrumental activities of daily living (IADL) such as shopping, compared to adults with HIV who did not use METH and METH users without HIV. Studies with similar findings suggest that concurrent use of METH with HIV may exacerbate the neurotoxic effects of gp120 and Tat and weaken the BBB allowing more HIV-infected monocytes to enter the brain (Blackstone et al., 2013; Rippeth et al., 2004). Also, HIV and METH are associated with mitochondrial damage and affect dopaminergic neurons; hence, the additive effects of HIV and METH use on dopaminergic signals increases the risk of cognitive disorders given dopamine depletion is independently associated with HIV (Kovalevich and Langford, 2012). Possibly, the fronto-striatal-thalamo circuitry may incur some damage with concurrent METH use and HIV since the dopaminergic neurons are located in the nigrostriatal pathway, circuits connecting the substantia nigra with the striatum (Blackstone et al., 2013).

Opiates

Opiates can disrupt the function of microglial cells by intensifying the neurotoxic effects of CXCR4 and CCR5, receptors that facilitate the entry of HIV and neuroinflammatory proteins into the CNS, which increases activation of microglial cells by gp120 (Byrd et al., 2012; Hauser and Knapp, 2014). Co-exposure to opiates exacerbates HIV-induced neuroinflammatory reactions by over activating microglial cells which results in Tat release and more extracellular glutamate, cytokines, and reactive oxidative species (Hauser and Knapp, 2014). Opiates further enhance the neurotoxic effects of HIV which ultimately leads to neuronal injury or death, thus heightening the risk of cognitive deficits (Banerjee et al., 2011; Byrd et al., 2012). Some studies suggest

that perhaps such damaging effects of opiates and HIV-Tat co-exposure may be evident in as little as 24 hours of initial use (Fitting et al., 2010). Regardless, chronic opiate use and HIV disrupts neuronal growth, microglial function, and synaptic connections, which over time impairs cognition (Hauser and Knapp, 2014).

Cocaine

Although the neurotoxic effects of cocaine alone is clear, the combined neurotoxic effects of cocaine and HIV viral proteins has not been fully expounded. There is an overlap in neurobiological mechanisms in which cocaine and HIV independently influence cognitive function. Cocaine promotes HIV viral replication and expresses adverse effects on various cells including astrocytes, which form gap junctions that compromise the integrity of the BBB causing harmful substances to enter the CNS (Eugenin et al., 2011). As a result, there is an increased migration of HIV-infected microglia cells into the CNS and induction of neuroinflammatory cytokines which triggers neuronal death of neighboring cells. Another mechanism in which cocaine affects cognitive functioning is by increasing oxidative stress, an imbalance in the production of reactive oxygen species and the body's ability to repair the harmful effects of free radicals (Dalvi et al., 2014). In a healthy individual, the body produces antioxidants that promote detoxification of free radicals, thus rendering them harmless to other cells; however, cocaine triggers the production of free radicals which may exceed the body's ability to manage detoxification. Damage from free radicals and the neuroinflammation promotes neurotoxicity which ultimately leads to poor cognitive functioning. HIV-positive participants from the Women's Interagency HIV Study were examined comparing current cocaine users, former users, and non-users. Current users performed

worse on tests of verbal learning and memory. Furthermore, using functional magnetic resonance imaging (fMRI), the left dorsal medial prefrontal cortex and the left anterior cingulate cortex showed poorer activation in current and former users compared to non-users. This lower activation correlated with poorer performance on measures of verbal memory (Meyer et al., 2014). Given the neurobiological effects of HIV and cocaine alone are similar, cocaine use in adults with HIV may increase their vulnerability to cocaine-related cognitive effects and foster increased prevalence and severity of HAND.

Comorbidities and Aging

With increasing age, challenges with cognitive function are likely and there is a higher risk for comorbidities such as diabetes and heart disease which can compromise brain health. In a study of 452 adults 50 and older with HIV, Balderson et al. (2013) found that 94% of their sample reported having a chronic health condition in addition to HIV. Aging with comorbidities and the neuroinflammatory effects of HIV can be taxing on cognitive function. Yet, certain comorbid and metabolic disorders (i.e., hypertension, diabetes), if not managed over time, can damage cerebral blood vessels and lead to reduced oxygenation to the brain which negatively influences cognitive function (Vance et al., 2011b). In a study of 145 adults with HIV, Valcour et al. (2012) found that, despite being on cART, participants with increasing insulin resistance exhibited poorer cognitive performance. Likewise, in a sample of 78 middle-age (40+) and older adults with HIV, Fazeli et al. (2014a) conducted a cluster analysis of cognitive subtypes and two clusters emerged: cluster 1 with poorer cognitive performance across all domains except psychomotor speed, and cluster 2 with better cognitive performance similar to the reference group of 84 adults without HIV. Compared to cluster 2 (n = 46) and the adults

without HIV, adults in cluster 1 (n = 32) had poorer cognitive performance and were older with a higher prevalence of hypertension and prior stroke. Findings from these and other studies suggest that age and associated comorbidities such as diabetes and hypertension account for some of the variability in cognitive function in older adults with HIV (Fabbiani et al., 2013; Vance et al., 2014b); hence, treatment of comorbidities may be just as important as early initiation of cART to preserve cognitive reserve as people age with this disease.

Both hypertension and diabetes have been associated with structural changes in the brain which may explain why some adults living with these comorbidities are more susceptible to cognitive impairments. In a recent study of 84 older adults, Li et al. (2015) examined cognitive functioning and neuronal effects of hypertension and found that, compared to the patients without hypertension (n = 40), those with hypertension (n = 44) showed decreased attention and executive function. Also, results from the fMRIs showed that, compared with the patients without hypertension, those with hypertension exhibited reduced integrity of white matter in the bilateral superior longitudinal fascicles and changes in the patterns of the frontoparietal networks, specifically in the inferior parietal lobe, left inferior frontal lobe, and precuneus (Li et al., 2015). Perhaps, these deficits in the white matter and disrupted functional connectivity in those areas of the brain may contribute to poor cognitive functioning in some adults with hypertension. Likewise, in a study of 1,437 older adults with diabetes and a diagnosis of normal, mild cognitive impairment (MCI), or dementia, subcortical infarctions, reduced hippocampal volume, reduced whole brain volume and prevalent MCI was associated with midlife diabetes (Roberts et al., 2014). Also, hypertension was associated with infarctions, whole brain

volume, and declines in executive function. These infarctions and brain atrophy may contribute to poor cognitive functioning; however, management of glucose levels in adults may reduce or prevent the adverse effects of comorbidities on cognitive health. Although, these are studies of adults without HIV, midlife onset of such comorbidities in adults with HIV may be more detrimental to long-term cognitive functioning if left untreated, thus making it more difficult for the brain to withstand the neurotoxic effects of Tat and other viral proteins (Roberts et al., 2014; Tzourio, et al., 2014).

Hypothalamus-Pituitary-Adrenal Axis and Mood Disturbances

The rate of mood disorders among adults with HIV is higher than the general population (Fellows et al., 2013); therefore, when mood disorders co-exist with HIV, it may further compromise cognition. Normally, the hypothalamus-pituitary-adrenal (HPA) axis stimulates the adrenocorticotropic hormone to release cortisol, a hormone that regulates metabolism and immune response to stress (Satori et al., 2012). Cortisol normally peaks after awaking and gradually declines over the course of the day to its lowest at bedtime. This rhythm becomes altered with repeated stressful events, which is common for many adults with HIV (Mugavero et al., 2009). Moreover, in adults with HIV, neuroinflammation and release of gp120 and Tat can make it difficult for cortisol levels to return back to its normal rhythm. This disruption of cortisol homeostasis and prolonged exposure to excess cortisol can induce hypertension, hyperlipidemia (elevated cholesterol), and insulin resistance which are risk factors for vascular disease, all of which influences brain health and cognition. Excess cortisol is also linked to neurotoxicity and reduced neuronal growth in the limbic system and hippocampus, which is involved in emotion regulation and memory. Also, cortisol-induced neuroinflammation

of the hypothalamus may contribute to mood and psychiatric disorders in adults with HIV. While these disruptions of the HPA axis does not explain why some adults with HIV exhibit cognitive and psychiatric symptoms and others do not, perhaps part of this can be explained by the role of cognitive reserve. Some brains may have more physiological resources than others to weather such neurological disruptions (Barulli & Stern, 2013; Vance et al., 2014d).

Cognitive Reserve and Neuroplasticity

The stronger, more sophisticated the synaptodendritic connections between neurons, the greater one's cognitive reserve, which may be neuroprotective against neurological insults (Vance et al., 2014e). While neuroinflammation is a primary cause for depletion of cognitive reserve and poor cognitive functioning in adults with HIV, other negative influences (e.g., comorbidities) may also contribute to depletion of cognitive reserve. Vance (2013a, 2013b) proposed that cognitive reserve is also dependent on one's exposure to positive and negative neuroplastic events across the lifespan. Positive neuroplasticity is associated with stronger neuronal connections (greater cognitive reserve), which occurs with exposure to an enriched environment and novel stimuli (e.g., learning a new language); contrastingly, negative neuroplasticity is associated with brain atrophy and weak neuronal connections (lower cognitive reserve), which occurs when there is lack of cognitive stimulation or chronic exposure to negative influences such as stress and depression (Vance et al., 2012b).

Low cognitive reserve plays a role in the development of HAND. The Frascati criteria was introduced as a way to diagnose different levels of HAND based on the presence of clinical symptoms, number of cognitive domains affected (e.g., memory,

speed of processing, verbal fluency), and the degree to which cognitive function impacts everyday activities. HAND is diagnosed as one of three types: asymptomatic neurocognitive impairment (ANI), mild neurocognitive impairment (MNI), or HIV-associated dementia (HAD). According to the Frascati criteria, HAND is classified as ANI if cognitive impairment involves at least two cognitive domains and cognitive performance is at least 1 standard deviation (SD) below the normative mean with no interference with everyday functioning. A classification of MNI involves the same criteria for ANI, but cognitive impairment interferes with everyday function. HAD, the most severe level of HAND, involves cognitive impairment in at least two cognitive domains with cognitive performance at least 2 SD below normative means, and cognitive impairment produces marked interference with everyday activities (Antinori et al., 2007). Approximately 20% of adults with HIV, over time, experience bi-directional fluctuations from one level of HAND to another, whereas, others may remain asymptomatic for years (Antinori et al.); this suggests malleable changes in neuroplasticity and cognitive reserve. Fortunately, several strategies may bolster cognitive reserve and improve cognition; these include medication, lifestyle, and cognitive remediation. Likewise, when neurological damage is irreversible, compensatory strategies must be considered.

Preventative Strategies

A simple way to strengthen cognitive reserve is through preventative strategies. Despite the use of some of the preventative strategies, particularly cART, nearly half of adults continue to experience HIV-related cognitive deficits (Heaton et al., 2010). Referred to as the Continuum of Care, of the adults in the United States infected with HIV, 80% are diagnosed, 62% are linked to care, 41% are retained in HIV care, 36% are

on cART, and only 28% achieve optimal (undetectable) viral suppression (Centers of Disease Control and Prevention [CDC], 2011). Solutions to improving cognitive functioning may involve addressing barriers to linkage to care and early initiation of cART to improve retention in care.

Linkage to Care

Persistent development of cognitive deficits may result from lack of access to cART which is commonly associated with poor retention among newly diagnosed adults with HIV. Obviously, early initiation of cART is important but key barriers to linkage to care must be acknowledged. Several predictors of linkage to HIV care have been suggested including female gender (Eberhart et al., 2015), African American race (Whiteside et al., 2014), lack of insurance (Springer et al., 2011), stigma (Govindasamy et al., 2012), substance use (Westergaard et al., 2013), and mental illness (Mayston et al., 2014). In a study of 87 adults newly diagnosed with HIV, homelessness was a significant predictor of linkage to care, and consistent with previous studies, unemployment and substance use were found to be associated with failure to link when testing site was controlled (Aaron et al., 2015). Strategies to improve linkage to care may be one solution to improving cART adherence and viral suppression, both which may in turn improve cognitive functioning in adults with HIV.

Retention in Care

Another possible contributor to the incidence of cognitive deficits is retention in care which is a major challenge and has shown to be poorer among patients who have not initiated cART compared to those on cART (McNairy and El-Sadir, 2014). For example, of 842 adults with a new HIV diagnosis, Clouse et al. (2013) found that retention before

initiation of cART was 69.8%; however, retention increased with initiation and time on cART from 80.2% in 6 months to 95.3% between 6 and 12 months. In addition to previous studies that have shown adequate viral suppression and cognitive improvement following early initiation of cART, this study suggests that initiation of cART immediately after receiving a HIV diagnosis can improve retention in care over time; hence, advoiding delays in cART treatment is likely to lead to adequate viral suppression, reduced transmission rates, decreased opportunistic infections; all of which may positively influence cognitive functioning and quality of life in adults with HIV. Long term effects of cART and potential drug interactions is still a primary concern in older adults with HIV who are prone to the burden of polypharmacy and complex medication regimens.

Combination Antiretroviral Therapy (cART)

By stopping HIV from replicating, cART allows the immune system the opportunity to reconstitute. From this alone, cART has contributed to significant reductions in severe forms of HAND and lower incidence of HIV opportunistic CNS infections such as Progressive Multifocal Leukoencephalopathy (PML), a demyelinating disease of the CNS characterized by subcortical white matter lesions and progressive cognitive decline (Eisfeld et al., 2013). PML is caused by the John Cunningham Virus (JCV) which remains dormant in the CNS and other organs such as the kidneys, and then emerges when the immune system is depleted. The neurobiological effects of HIV on the brain makes the CNS a favorable environment for JCV; thus, release of neuroinflammatory proteins and Tat weakens the BBB and JCV-infected white blood cells (Bellizzi et al., 2013). Once in the brain, JCV-infected B lymphocytes infect

oligodendrocytes, specialized glial cells that create myelin which insulates the axon and increases the speed of neuronal signaling. Commonly affected areas include the parietal and frontal lobes; hence, clinical features of PML often include generalized weakness, headaches, gait disorders, confusion, sensory loss, and visual impairment (Berger, 2014). Fortunately, PML is relatively rare in the cART era. In fact, cART is the only fact associated with lower PML-attributable mortality; hence, cART may cease replication of JCV by reducing replication of HIV and inflammation in the brain (Kahana et al., 2009).

Mirroring these findings, most studies show improved cognitive functioning as a result of cART adherence and improved immune reconstitution (Al-Khindi, et al., 2011). For example, Cysique et al. (2009) also examined benefits of cART in 37 cognitively-impaired adults with HIV and found that those with HAND demonstrated improvements in cognition soon after initiation of cART (13% at week 12) which continued up to 48 weeks, suggesting that cART may be neuroprotective against manifestation of HIV-related cognitive deficits

Long-term Use and Cost

Despite well-documented effects of cART on improving/protecting cognition, low-grade neurotoxic effects associated with long-term use of cART is a topic of concern. Robertson et al. (2010) followed 167 medically stable (taking $\geq$ 2 cARTs; CD4 > 350 cells/mm^3; HIV RNA viral load < 55,000 cp/ml;) adults with HIV who elected to discontinue their cART medication. From baseline over 24, 48, 72, and 96 weeks later, their cognitive performance steadily and significantly improved. Given possible metabolic effects and mitochondrial dysfunction caused by cART, this may explain such

finding. Yet, given the history of HIV/AIDS and cognitive function, these minor side effects outweigh abstaining from their use for survival.

Moreover, caring for adults with HIV produces new challenges especially with the steady growth of "baby boomers" living with HIV. Although previous studies have shown age to be associated with high rates of medication adherence (Hinkin et al., 2004), older adults with cognitive impairment tend to have the lowest adherence rates compared to those without cognitive impairment (Ettenhofer et al., 2009; Thames et al., 2011). Expectedly, the rate of Alzheimer's disease and the HIV-related cognitive disorders will increase as adults live longer with HIV (Heaton et al., 2010). Given this, some adults may encounter cognitive impairments that interfere with their ability to perform everyday activities which may increase the need for formal and informal caregivers among adults with HIV. In adults aging with HIV, cART adherence may be neuroprotective against cognitive impairments which may reduce caregiver and financial burden associated with the management of HIV-related complications (Cahill and Valadez, 2013). Still concerns mount regarding polypharmacy, particularly the risk of interactions between cART and other medications.

Medication Interactions

As an increasing number of adults age with HIV, treatment of comorbidities remains a challenge because studies suggests some medications interfere with cART by competing for the CYP3A, an enzyme found in the liver and intestine used to metabolize medications. Peyriere et al. (2012) conducted a literature review and found that compared to angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) which are metabolized by the kidneys, calcium channel blockers (CCB) and

some β-blockers are likely to interact with protease inhibitors (PI) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Such interactions may result in increased or decreased amounts of antiretroviral medications and, if not fixed, suboptimal viral suppression and/or neurotoxicity may result, which can negatively influence cognitive functioning.

Other medications that may interact with NNRTIs and PIs include anticoagulants (e.g., warfarin) and cholesterol-lowering agents such as statins (Foy et al., 2014). However, clinical studies of warfarin-antiretroviral interactions, have yielded mixed results. In a study of 73 patients with HIV on maintenance warfarin therapy, Anderson et al. (2012) noted that some patients on NNRTIs, particularly Efavirenz, required lower doses of warfarin, whereas 7 patients required higher doses of warfarin to maintain therapeutic levels; hence, some antiretrovirals may have variable effects on the metabolism of warfarin and close monitoring is essential especially during changes in medication regimen. Last, the contribution of statins to cognitive health remains uncertain. In a cohort from the Israel Diabetes and Cognitive Decline Study, Heymann et al. (2015) found that, compared to 61 patients who did not take statins, 45 patients who used statins at least 90% of the time had better overall cognitive functioning, memory, and executive functioning. Although studies have shown that statin use reduces the risk of cerebrovascular disorders; however, some statins are known to interact with PIs and their use, particularly simvastatin and lovastatin, and are contraindicated in combination PIs (Foy et al.). Treatment with PIs have been shown to cause lipid disorders; however, when 88 adults with HIV treated with boosted PIs were randomized to receive either rosuvastatin 10 mg/day or pravastatin 40 mg/day for hyperlipidemia, those in the

rosuvastatin arm had a 37% reduction in their LDL-c levels compared with a 19% reduction in the pravastatin group (Aslangul et al., 2010). Although both rosuvastatin and pravastatin trough levels were within expected ranges and no adverse effects were observed, studies suggest that concurrent treatment with statins start at lower doses. Strategies to avoid potential interactions among antiretrovirals and medications used to treat comorbidities are few, but maintaining effective viral suppression while reducing drug toxicity are still key goals in providing care for adults as they age with HIV and other chronic diseases.

Methylphenidate

Methylphenidate, a psychostimulant dopamine agonist, has been attempted to improve cognition in adults with HIV. In a double-blind, placebo-controlled study of adults with HIV receiving methylphenidate (n = 8), van Dyck et al. (1997) found no significant differences in cognitive improvement compared to controls. These findings differ from those of another study in which Hinkin et al. (2001) administered methylphenidate to 16 adults with HIV and found that those experiencing more depression and cognitive slowing at baseline experienced more improvements on cognitive tasks such as reaction time (Hinkin et al., 2001). Although longitudinal studies examining the cognitive effects of methyphenidate in adults with HIV are lacking, it has been shown to improve cognition in other populations including multiple sclerosis (Harel et al., 2009) and normal healthy adults (Tomasi et al., 2011). Other benefits of methylphenidate include its ability to decrease total cholesterol, low-density lipoprotein cholesterol, and triglycerides (Charach et al., 2009). This additional benefit may be

neuroprotective against comorbidities, particularly hypercholesterolemia and cardiovascular disease, which is more prevalent in adults with HIV (Vance et al., 2011c).

Modafinil

The psychostimulant, modafinil, which is used to treat sleep disorders and fatigue, may also improve cognition. In a pre-post study of 104 adults randomized to receive modafinil or the placebo over a 4-week period, McElhiney et al. (2010) observed that those administered modafinil (n = 59) showed improvements in global cognitive functioning and reported less cognitive symptoms. Findings failed to show improvements related to specific cognitive domains. Although modafinil has a lower affinity for dopamine receptors compared to other psychostimulants such as methylphenidate, it has neurobiological effects on dopaminergic transmission. Rat models repeatedly show that modafinil increases dopamine levels, which aids in synaptic plasticity and memory processes in the prefrontal cortex, suggesting this is a target area for cognitive improvement (Mereu et al., 2013). Although modafinil also plays a role in serotonin neurotransmission which produces anxiolytic effects, it is unclear whether serotonin mediates modafinil's effects on cognitive function through either reducing negative mood or increasing alertness. As mentioned earlier, in one study of adults with HIV, those taking SRIs experienced improved cognition (Letendre et al., 2007).

Transdermal Selegiline

Mixed findings were observed in adults with HIV taking transdermal selegiline, a monomine oxidase inhibitor (MAO), used to treat depression. In a 10-week study of 14 adults with HIV, those receiving transdermal selegiline showed improvements in verbal memory and psychomotor abilities (Sacktor et al., 2000). Yet, in a larger study of 128

cognitively-impaired adults with HIV, these findings were not replicated. Specifically, over 3 and 6 months, Schifitto et al. (2009) found no differences in cognitive function between the groups receiving either the transdermal selegiline or placebo. Thus, it's efficacy in improving cognition in adults with HIV remains uncertain.

Lithium

Some medications used to treat psychiatric disorders, such as lithium, may be neuroprotective against the toxic molecules of HIV replication and neuroinflammation (Ances et al., 2008; Letendre et al., 2007; Letendre et al., 2006). In a study examining mice exposed to lithium and gp120, Everall et al. (2002) found that prophylactic lithium treatment protected the hippocampus of mice from gp120-mediated toxicity; perhaps, prophylactic use may be neuroprotective against HIV-induced neuroinflammation. Also, Letendre et al. (2006) found that adults with HIV who were taking lithium showed improvement in global cognitive functioning. Hence, the long-term effects of lithium on cognition are worth further investigation with careful consideration of its potential toxic effects on the liver and kidneys.

Hormone Therapy

Estrogen therapy may ameliorate cognition in those with HIV. Microglial cells would obviously be the target of estrogen therapy given they drive neuroinflammation and release neurotoxic substances. Microglial cells have estrogen receptors, and if estrogen therapy is administered early after diagnosis of HIV, it acts as an anti-inflammatory agent and increases neuronal resistance, thus helping them survive neuroinflammation caused by viral proteins and reducing apoptosis (Dye et al., 2012; Vegeto et al., 2008; Zemlyak et al., 2005). One study suggests that the anti-inflammatory

effects of estrogen on microglia cells may prevent the cascade of events that result in neuronal death, including microglial damage caused by exposure to gp120 (Mor et al., 1999). No studies of adults with HIV have considered exogenous estrogen therapy to improve cognitive function; therefore, exploration of its potential anti-inflammatory properties is warranted.

Likewise, the cognitive benefits of testosterone are unsubstantiated; although, it does help increase libido in men and weight loss in women with HIV (Choi et al., 2005). Yet, controversy remains regarding its safety given its association with increased risk for prostate cancer, liver disease, worsening sleep apnea, cardiovascular disease, and other life-threatening conditions (Bassil et al., 2009). Since adults aging with HIV have a higher risk for many of these health conditions, administration of testosterone to improve cognition is not advised.

Alzheimer's Medications

Acetylcholinesterase inhibitors such as donepezil are somewhat effective in treating Alzheimer's disease. Some evidence supports the anti-inflammatory role donepezil plays in decreasing the release of neurotoxic substances from activated microglia cells in the blood and CNS, which could ameliorate cognition. Cognitive benefits of donepezil in adults with HIV have not been explored, but in a study of 168 normal community-dwelling older adults, donepezil had the same effects as the placebo (Yesavage et al., 2008).

Another drug used to treat Alzheimer's disease, memantine, has been investigated in adults with severe HAND. The neurobiology of memantine involves its ability to target the glutamatergic system by binding to NMDA receptors to reduce glutamate activity in

the brain. At normal levels, glutamate aids in learning and memory; when levels are too high, neurons become overstimulated which leads to neuronal death. Also, memantine functions as a dopamine agonist and activates dopamine receptors which is beneficial in some conditions associated with dopamine depletion. In a 16-week study of 140 adults with severe HAND, Schifitto et al. (2007) found no significant improvements in cognitive performance between the memantine or the placebo groups. Thus, research at this time shows Alzheimer's medications lack clinical efficacy for improving cognition in adults with HIV.

Lifestyle

Lifestyle factors can enhance cognitive function and possibly be neuroprotective against age-related cognitive deficits. In particular, management of comorbidities and the benefits of physical exercise and proper sleep hygiene may be relevant for adults with HIV for three reasons: (1) some adults with HIV experience comorbidities such as heart disease at an early age which may be detrimental to vascular health and accelerate cognitive aging (Tzourio et al., 2014); (2) physical exercise reduces oxidative stress and inflammatory markers as well as increases neurogenesis, angiogenesis, and synaptogenesis in the brain (Dufour et al., 2013; Lee et al., 2013); and (3) several comorbidities are associated with poor sleep hygiene including depression, Alzheimer's disease, delirium, cardiovascular disease, and chronic obstructive pulmonary disease; all of which can negatively influence cognitive function (Edd and Flores, 2009). While other lifestyle factors are worthy of consideration, for brevity, this section focuses on strategies to address comorbidities in adults with HIV and the neurobiological effects of physical exercise and proper sleep hygiene.

Management of Comorbidities

While challenges with managing comorbidities in adults with HIV persist, several studies show that treatment of comorbidities may be advantageous to cognitive health. For example, in a study of 500 older adults (55+) with and without hypertension, Viamonte et al. (2010) found no group differences in cognitive functioning between older adults who were treated for hypertension and those without hypertension. Recently, Zho et al. (2015) compared cognitive functioning in diabetic and non-diabetic patients with MCI, and examined how medications may impact cognitive function. Overall, in this group of patients with MCI, diabetic patients had the worse cognitive performance in attention, processing speed, and memory compared to non-diabetic patients. Compared to diabetic patients who were treated with insulin or oral diabetes medications only, those who were treated with insulin in addition to oral diabetes medications performed better in verbal memory. Also, patients treated with metformin medication had a better memory outcome compared to patients treated with sulphonylurea medications (e.g., glipizide). Findings from these studies suggest that treatment of comorbidities may be neuroprotective against cognitive impairments, and some medications when given concurrently may enhance cognitive function (Viamonte et al., 2010; Zhou et al., 2015). These results observed in older adults with diabetes are promising for those aging with HIV; however, further research is necessary to determine how to clinically address comorbidities, aging, and HIV which may likely reduce long-term effects of such influences on cognitive function.

Physical Exercise

Physical exercise obviously benefits the body, but it also benefits the brain and cognition. Lee et al. (2013) used a gp120 mouse model, and after allowing mice to run freely and exercise, these researchers found that exercise enhanced neurogenesis and normalized dendritic growth of neurons; hence, these cognitive benefits ceased when there was no exercise. This study suggests that even in the presence of inflammatory proteins (e.g., gp120) associated with HIV, physical activity can stimulate positive neuroplastic changes.

Likewise, physical exercise is associated with better cognitive function in adults with HIV. Fazeli et al. (2014b) found that among 139 adults with HIV, those who actively engaged in physical exercise, social activity, and employment were least likely to demonstrate cognitive deficits. This suggests that physical exercise may be neuroprotective and boost cognitive function, perhaps by protecting cognitive reserve.

Aside from these cognitive benefits, physical exercise has been shown to improve mood. After randomizing 49 adults with HIV to either an experimental group that completed combination aerobic exercise and resistance training at moderate intensity twice a week for 6 weeks or a control group that did not engage in physical exercise, Jaggers et al. (2015) found those in the exercise group exhibited a decrease in depressive symptomatology compared to those in the control group. The positive impact of physical exercise on psychological state is important given depressive symptoms can increase cytokines and other stress hormones (e.g., cortisol) through the HPA axis, which over time can induce neuroinflammation and deplete cognitive reserve. Connected to this idea, in a study of 98 adults with HIV, Fazeli et al. (2011) found that those with higher levels

of mood disturbance had worse cognitive performance on measures of speed of processing, reasoning, visuomotor coordination, and psychomotor speed. Perhaps, if adults with HIV engage in activities that promote positive neuroplasticity such as physical exercise, they may be less likely to develop depressive symptoms which may indirectly facilitate better cognitive functioning.

Sleep Hygiene

Good sleep hygiene is essential for optimal cognitive performance and immune function. In adults with HIV, sleep disruption can increase BBB permeability allowing more inflammatory substances to enter the brain, which is likely to result in manifestation of cognitive deficits (Gamaldo et al., 2013a). Many of the same cytokines released from HIV-infected microglial cells (e.g., TNF-α) control sleep wake patterns; therefore, sleep loss in adults may alter brain structures and disrupt the integrity of the BBB (Gamaldo et al., 2013b). In a study of 36 adults with HIV, Gamaldo et al. (2013a) examined the relationship between sleep patterns and cognitive functioning in 36 adults with HIV and found that, compared to participants with disturbed sleep patterns, better sleep quality was associated with better cognitive functioning on tasks of attention, executive function, and psychomotor speed. These findings suggest that disturbed sleep patterns compromise cognitive functioning in adults with HIV, which produces greater concern for adults as they age, especially since 50% of normal older adults, in general, have difficulty sleeping (Neikrug and Ancoli-Israel, 2010).

Sleep hygiene education may be helpful in improving sleep patterns in adults with HIV which may be neuroprotective against cognitive deficits (Babson et al., 2013). These points are supported by existing literature which suggests that good sleep hygiene in

older adults facilitates synaptic plasticity, procedural learning processes, and working memory (Haimov and Shatil, 2013). Also, studies have shown that some non-nucleoside reverse transcriptase inhibitors (NNRIs), in particular efavirenz, can have prominent effects on sleep and cognition. After randomizing 40 healthy adults to receive placebo or efavirenz 600mg nightly for 7 days after completion of a 3-day placebo run-in period, Simen et al. (2015) found that treatment with efavirenz was associated with reduced time to sleep onset on the Maintenance of Wakefulness Test, an increase in NREM sleep, and reduced performance on an attention switching task. These findings differ from those of other studies that show use of efavirenz is associated with insomnia; hence, efavirenz exhibits serotonin 2A receptor partial-agonists properties which may explain its varying effects on sleep (Simen et al., 2015).

Cognitive Remediation Training

Cognitive remediation training strengthens cognitive functioning through exposure to challenging and repetitive tasks over time, which encourages the brain to undergo neuroplastic changes. In a sample of 66 healthy older adults, Mozolic et al. (2011) randomized them to either a computerized cognitive training group that engaged in exercises designed to help them suppress irrelevant distractors, or a contact control group that simply watched educational health videos; both groups engaged in 1 hour/week of training for 8 weeks. Compared to the contact control group, those in the training group increased their modality specific attention (i.e., being able to ignore background sensory stimuli while performing a cognitive task). Furthermore, using MRIs, those receiving cognitive training experienced significant increases in resting

cerebral blood flow to the prefrontal cortex which was also correlated to the cognitive gains they experienced. Similarly, Lampit et al. (2015) randomized healthy older adults into a computerized cognitive training group that engaged in mental exercises designed to improve multiple cognitive domains, or a control group that simply watched National Geographic videos on the computer. Compared to the control group, those in the cognitive training group experienced improved resting state functional connectivity between the posterior cingulate and the superior frontal gyrus which correlated with cognitive changes 9 hours post-training. As a result, the use of cognitive training has been extended to cognitively-vulnerable populations such as post-stroke patients and adults with HIV.

SmartBrain in Adults with and without HIV

A computerized cognitive remediation program, SmartBrain, was examined for its ability to improve cognition in 30 adults with and 30 adults without HIV (Becker et al., 2012). The adults were partially randomized to a cognitive stimulation group that completed the internet-based cognitive remediation training in their homes or alternative locations over 24 weeks or a usual care control group. SmartBrain featured 14 activities that targeted attention, memory, and executive function domains. The activities were initially easy and the level of difficulty automatically increased when participants completed sessions with few or no errors; in the same manner, the difficulty level decreased when participants made several errors on consecutive sessions. This "double-staircase" method allowed the optimal performance threshold to be achieved. The adherence rate was low; only 54% of those in the cognitive stimulation group used the program more than once. Becker et al. (2012) found that those who made use of the

program the most did, in fact, show significant improvements in cognitive function. This study suggests that, with consistent engagement, this computerized internet-based cognitive remediation training program may be advantageous in adults with HIV.

InSight in Adults with HIV

Vance et al. (2012) examined the effects of a speed of processing training program called Insight in 46 middle-age (40+) and older adults with HIV. Participants were randomized to receive the speed of processing training or to receive no training. Participants assigned to the speed of processing group (n = 22) completed approximately 10 1-hour sessions (twice a week for 5 weeks). This program consists of mental exercises in which participants were presented a target object(s) at various speeds, and then asked to identify the location of the object(s) once it disappeared. Similar to SmartBrain, the difficulty level of the exercises were adjusted based on the individual's performance. Post-intervention evaluation indicated that, compared to the group that did not receive the training, the treatment group had significant improvements on the Useful Field of View (UFOV®) Test and the Timed Instrumental Activities of Daily Living Test, measures of speed of processing and everyday functioning. Since speed of processing training has also been shown to have other neurocognitive effects that extend to improved driving ability, locus of control, health-related quality of life, and depressive symptomatology, this may be an ideal intervention for those with HIV who exhibit difficulties in these areas as well (Vance et al., 2014c).

Compensatory Strategies

When cognitive function cannot be restored, alternative methods can be used to compensate for existing cognitive deficits. Compensatory strategies such as space-

retrieval method and mnemonics may be beneficial for helping cognitively-impaired adults with HIV.

Spaced-retrieval Method

Spaced retrieval method is a type of mnemonic used to help improve memory recall. More specifically, a discrete unit of information (e.g., a phone number, a medication schedule) is recalled over progressively longer periods of time (i.e., 30 seconds, 1 minute, 2 minutes, 4 minutes, 8 minutes, & 16 minutes). Once this information can be freely recalled after approximately 16 minutes, it becomes consolidated into one's long-term memory. Developed and used in adults with Alzheimer's disease, spaced-retrieval method focuses on using existing cognitive processes to counteract the effects of cognitive deficits (Vance et al., 2010). In a pre-post study of 10 older adults with HIV (50+) experiencing memory deficits, Neundorfer et al. (2004) used the spaced-retrieval method to assist participants with memory consolidation in meeting two functional goals (e.g., remembering to take medication). After using spaced-retrieval method for 4 weeks, all participants indicated that the intervention improved their memory and helped them meet their functional goals. These findings suggest that spaced-retrieval method may be a useful compensatory strategy for those adults with HIV who potentially have less cognitive reserve and manifest symptoms of HAND.

Mnemonics

Mnemonics such as chunking, method of loci, and external memory aids are inexpensive and may improve everyday function in adults with cognitive deficits (Vance et al., 2008). For example, sticky notes and checklists are simple external memory aids that can be used to remind people to complete certain tasks such as check their blood

sugar. In adults with HIV, these simple compensatory strategies may be used to help them maintain independence and allow them to safely continue or resume their usual activities (Vance et al., 2015)

Future Directions

Aside from promoting better lifestyle behaviors to strengthen cognitive reserve, there are several novel approaches (i.e., transcranial direct current stimulation (tDCS) & nanocarrier delivery systems) worth exploring. First, tDCS has been shown to augment cognition in adults with and without cognitive deficits (Clark et al., 2012; Falcone et al., 2012; Meinzer et al., 2013; Penolazzi et al., 2014). A second novel approach is the use of nanocarrier delivery systems to transport antiretrovirals and neurotrophics across the BBB (Pilakka-Kanthikeel et al., 2013).

Transcranial Direct Current Stimulation (tDCS)

tDCS has been studied in many populations (e.g., Alzheimer's disease) and has been shown to improve cognition. Nitsche (2011) proposed that the application of a direct current to the cerebral cortex via electrodes to the scalp induces neuronal firing, or excitability, thus leading to changes in neuroplastic processes involved with memory and learning. For example, Clark et al. (2012) randomized 96 healthy adults to receive either 0.1 milliamps or 2.0 milliamps stimulation placed over the right inferior frontal cortex 5 minutes before and 30 minutes after they started playing a virtual game in which they had to locate concealed objects. Compared to the adults who received 0.1 milliamps (considered a sham condition), those who received 2.0 milliamps experienced significant improvements in learning (Clark et al., 2012).

Several studies have examined the use of tDCS as an adjuvant tool for improving cognitive abilities. Martin et al. (2013) observed the synergistic effects of tDCS and computerized cognitive training in a group of adults randomized to either receive the sham, tDCS alone, or tDCS with cognitive training. The group that received the tDCS with cognitive training performed better on the cognitive task over 4 weeks compared to the group that received the sham and the group that received tDCS alone (Martin et al., 2013). To date, there are no studies that have examined the cognitive effects of tDCS with speed of processing training in adults with HIV; however, there is one currently being conducted (NIH/NIA PI: Fazeli – K99AG048762). Yet, Knotkova et al. (2012) found that in 10 adults with HIV who received 2.0 milliamps of tDCS treatment daily for 2 weeks had lower depression scores on their posttest, which is important given depression has been shown to negatively influence cognitive functioning (Fialho et al., 2013; Vance, 2013a, 2013c). These findings are promising for adults with HIV since in one sample of 1,478 adults with HIV, ~40% experienced depression and ~20% experienced anxiety (Vance et al., 2011); such negative mood states can promote negative neuroplasticity and deplete cognitive reserve. Further study of tDCS alone and its use with other cognitive remediation therapies in adults with HIV is warranted.

Nanocarrier Delivery Systems

Some antiretrovirals and neurotrophics are not as effective to reduce neuroinflammation because of their inability to penetrate the BBB. Also, externally-administered brain derived neurotropic factor (BDNF), which has shown to protect against neurotoxicity and synaptodendritic degeneration, has difficulty crossing the BBB (Pilakka-Kanthikeel et al., 2013). In a study of an in vitro BBB model, Pilakka et al.

(2013) examined a magnetic guided nanocarrier to determine if its ability to transport BDNF across the BBB resulted in decreased neuronal death. The BDNF transported via the magnetic guided nanocarrier was just as effective as endogenous BDNF that is typically released in the CNS, and this approach did not disrupt the integrity of the BBB. In adults with HIV, the use of nanocarrier delivery system such as the magnetic guided nanocarrier could be beneficial for delivering antiretrovirals into the CNS while targeting specific areas of neuroinflammation. If the exact sites are targeted in the brain, the neuroprotective effects of some antiretrovirals may even be augmented.

Conclusion

The longer life expectancy of adults with HIV poses many concerns because it is possible that the neurobiological effects of HIV may be exacerbated by the aging process along with other factors such as comorbidities. These negative influences and HIV alone tend to deplete cognitive reserve over time and lead to poor cognitive function; therefore, some adults aging with HIV may be more susceptible to develop neurodegenerative disorders and HAND. The use of cognitive interventions to strengthen cognitive reserve may improve cognitive function in adults with HIV, thus helping them to age successfully with the disease.

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THE INFLUENCE OF NEUROCOGNITIVE FUNCTIONING ON PROACTIVE COPING BEHAVIORS IN ADULTS WITH HIV

by

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Abstract

While many can appreciate the life-sustaining benefits of combination antiretroviral therapy (cART), some adults with HIV continue to have difficulty managing physical, neurocognitive, and everyday stressors. Fortunately, some adults with HIV are able to use accumulated resources (e.g., social networks) to help them engage in proactive coping behaviors such as planning and problem-solving. Others, however, manage their stressors by engaging in avoidant coping, isolating themselves, or ruminating about the negative aspects of their situation. Perhaps, the capacity to engage in proactive coping may be influenced by damage to the fronto-striatal-thalamo circuitry, a region of the brain responsible for executive functioning and often compromised in adults with HIV-associated neurocognitive disorders. This study examined potential neurocognitive influences on proactive coping behaviors in adults with HIV (N = 98). Participants were administered a series of neurocognitive and psychosocial measures to determine if neurocognitive functioning and other factors that have been associated with coping in other populations, such as spirituality/religiosity, influenced proactive coping behaviors. Multiple regression analysis revealed spirituality/religiosity (p = .002), rather than neurocognitive functioning (Useful Field of View, p = .277; Trails A, p = .701, Trails B, p = .365, Wechsler Memory Scale-III Digit Span, p = .864), was a significant predictor of proactive coping. Interventions to address spirituality/religiosity needs of adults with HIV may possibly facilitate proactive coping behaviors and improve mood, both of which are important for healthy neurocognitive functioning.

Key words: HIV; cognition; cognitive remediation therapies; proactive coping

The Influence of Neurocognitive Functioning on Proactive Coping Behaviors in Adults with HIV

Even in the era of combination antiretroviral therapy (cART), physical, psychological, and neurocognitive challenges associated with HIV disease persist. Proactive coping, the ability to utilize internal and external resources to develop strategies for overcoming future potential stressors and planning long-term goals, has been shown to facilitate older adults, in general, with effective management of everyday challenges (Davis & Brekke, 2014). Engagement in proactive coping rather than avoidant coping (e.g., rumination of negative thoughts, suppression of emotions, or ignoring the problem) has generally been associated with more positive outcomes such as improved emotional health, quality of life, and even slower disease progression (Ironson et al., 2005). Thus, engaging in proactive coping behaviors may be advantageous for adults aging with HIV as they face problems such as stigma, depression, unemployment, and disease comorbidities (Hansen et al., 2013; Slater et al., 2013; Vance, Burrage, Couch, & Raper, 2008). In a study of 177 adults with HIV, Ironson and colleagues (2005) found that optimism and proactive coping were associated with slower disease progression; hence, those who were more optimistic had slower declines in $CD4^+$ count and maintained a stable viral load over a period of two years, even after controlling for baseline $CD4^+$ count and viral load, use of antiretrovirals, gender, race, education, and drug use. Likewise, Vance, McGuiness, and colleagues (2011) proposed that those with a sense of hardiness or optimistic view are able to endure stressors, are more likely to

have a robust immune system, and are more likely to use proactive coping strategies. In a study of 60 older gay males with HIV, Slater and colleagues (2013) found that those who engaged in proactive coping had a better quality of life compared to those who engaged in more passive, avoidant coping (e.g., ignoring the problem). In addition to these benefits, proactive coping may help improve decision-making ability and reduce depressive symptoms in adults with HIV.

As adults live longer and age with HIV, they are likely to experience neurocognitive changes that may impact their everyday functioning (e.g., adhering to medications, paying bills); in fact, Heaton and colleagues (2010) found that 52% of adults with HIV experience HIV-associated neurocognitive disorder (HAND). Studies have shown that many adults with HIV undergo premature structural changes in the brain and disruptions in frontal-striatal-thalamo circuitry, a neurocognitive region required for higher level neurocognitive processes such as problem-solving, planning, goal-setting, and emotional regulation (Melrose, Tinaz, Castelo, Courtney, & Stern, 2008; Plessis et al., 2014). It is possible that such changes may be linked to differences in coping behaviors and decision-making abilities among adults with HIV. Melrose and colleagues (2008) used functional magnetic resonance imaging (fMRI) to examine brain activity of 22 adults with and without HIV while they completed a picture sequencing and object discrimination task, two measures of executive function. Compared to adults without HIV, adults with HIV demonstrated reduced activity in the fronto-striatal regions, suggesting that damage to these circuits can occur prior to development of cognitive impairment in people with HIV (Melrose et al.). Similarly, Woods and colleagues (2013) found that adults with HIV performed significantly worse than adults without HIV in

completing a computerized visuospatial temporal order memory task. Given that strategic deficits related to memory encoding and retrieval have been linked to neuronal damage in the fronto-striatal-thalamo circuitry, there may be neuropathological changes influencing strategic planning and problem solving associated with proactive coping.

Early deterioration of the fronto-striatal regions, such as observed in HAND, may possibly contribute to impairments in executive function, which perhaps may be necessary to engage in proactive coping. In a study of 162 adults with HIV and 82 adults without HIV, Cattie and colleagues (2012) found that adults with HAND were slower at completing an executive function task (Tower of London – Drexel Version), had more errors in problem-solving, and inadvertently violated rules of the task compared to those who did not have HAND and adults without HIV. Findings from this study suggest that damage to the frontal lobe may be linked to executive function deficits that commonly occur in adults with HAND. Similarly, adults with HIV, when compared to those without HIV, demonstrated poorer decision-making during a gambling task as they continued to select playing cards from a deck with larger monetary gains despite the risk for infrequent larger penalties (Hardy, Hinkin, Levine, Castellon, & Lam, 2006). This finding of poor strategic planning and decision-making is also compatible with executive function deficits observed in adults with impairments in the fronto-striatal-thalamo circuitry. Perhaps, damage to these areas that regulate executive task performance may also explain variability in proactive coping behaviors among adults with HIV.

Although studies have shown that factors such as spirituality, number of comorbidities, and social networks influence one's ability to cope with HIV (Vance, Brennan, Enah, Smith, & Kaur, 2011), few studies have examined neurocognitive

functioning and its influence on one's inhibitory control over negative thoughts and predictive value in determining how one might respond to potential stressors. Greater understanding of coping differences among people with HIV is a necessary first step in developing interventions that support proactive coping and promote healthy outcomes in this population. Thus, this information is valuable to nursing as it may be used to guide specialized care for adults with HIV and help them learn unique ways to prepare for potential adverse events related to everyday stressors. This study was conducted with the following aims: 1) to determine if neurocognitive functioning, particularly executive function, is associated with proactive coping behaviors in adults with HIV; and, 2) to determine if other variables (e.g., age, minority status, education, spirituality) predict proactive coping behaviors in adults with HIV.

Methods

Participants

Ninety-eight adults with HIV were recruited from Birmingham, Alabama using a variety of methods, including word-of-mouth, university newspaper ads, flyers, and brochures placed at the university's outpatient HIV clinic. Potential participants contacted the research office and received a telephone-screen to determine their eligibility. All participants were at least 21 years old, proficient in English, and diagnosed with HIV for at least one year to control for influence of reactive depression in response to an HIV diagnosis. Participants were excluded if homeless (no address provided to mail appointment letter and compensation), mentally disabled (i.e., Alzheimer's disease, dementia, mental retardation), deaf or blind, currently undergoing chemotherapy or radiation, a history of brain trauma with loss of consciousness greater than 30 minutes, or presence of other significant neuromedical and psychiatric

comorbidities (i.e., schizophrenia). These exclusion criteria were included to ensure that participants were able to effectively engage in neurocognitive measures (e.g., ability to see and hear). In addition, the presence of neuropsychiatric comorbidities such as schizophrenia and bipolar disorder could influence mood and coping assessments as well as produce executive functioning deficits (Vance, Larsen et al., 2011).

Procedures

In this cross-sectional study, participants visited a university research center where they were provided information about the study and asked to sign an approved Institutional Review Board consent form. This 2-hour visit included a neurocognitive battery administered by skilled testers in addition to numerous psychosocial measures of spirituality and religiousness (Ironson- Woods Spirituality/Religiousness Index), social network (Lubben Social Network Scale), mood states (Profile of Mood States), and proactive coping behaviors (Proactive Coping Scale). Participants were compensated $50 for their time.

Instruments

Demographic Questionnaire. This instrument was used to gather background information such as gender (0 = *women*; 1 = *men*), minority status (0 = *non-minority*; 1 = *minority*), sexual orientation (0 = *homosexual/bisexual*; 1 = *heterosexual*), education level (years), number of prescribed medications, and age (date of interview – date of birth). Self-reported age could not be trusted from this potentially cognitively vulnerable population; therefore, age was calculated by subtracting the participants' date of birth from the date they were interviewed.

Psychosocial Measures. The Ironson-Woods Spirituality/Religiousness Index, Lubben Social Network Scale, and Profile of Mood States were psychosocial measures used to examine spirituality/religiosity, social network, and mood states, respectively.

Ironson-Woods Spirituality/Religiousness Index. The Ironson-Woods Spirituality/Religiousness Index consists of 25 items that measures level of spirituality/religiosity related to a sense of meaning in life, a relationship with a higher power, and a sense of wonder and awe of life. Participants responded to statements in four subscales (Sense of Peace, Faith in God, Religious Behavior, and Compassionate View of Others) using a Likert-type scale ranging from 1 *(strongly agree)* to 5 *(strongly disagree)*. A composite score was calculated by adding all 25 items; higher scores indicate greater levels of spirituality/religiosity.

Lubben Social Network Scale (LSNS). The LSNS consists of 10 items that measure the size of one's social network. Participants were asked questions about their family network, friends, confidant relationships, helping others, and living arrangements. Participants were asked questions such as, "How often is one of your relatives available to talk to you when you have an important decision to make?" They responded using a 5-point Likert-type scale ranging from 0 *(never)* to 5 *(always)*. A composite score was calculated by adding all 10 items with scores ranging from 0-50; higher scores indicate larger social networks (Lubben, 1988; Rubinstein, Lubben, & Mintzer, 1994).

Profile of Mood States (POMS). The POMS was used to determine the participants' mood state. Participants were presented with 65 items describing how one might feel (e.g., bitter, blue), and they were asked to rate how much they felt like the items presented based on the past week using responses ranging from 0 (*not at all*) to 4

(*extremely*). The items were summed to create a composite score; higher scores indicate more negative affect/mood (McNair, Loor, & Droppelman, 1992). In this study, internal consistency for the POMS total score was high (Cronbach's alpha = .93).

Neurocognitive Measures. Selected neurocognitive measures were used to examine neurocognitive functioning in the following domains: attention (Trail Making Test A), executive function (Trail Making Test B), verbal working memory (Wechsler Memory Scale-III Digit Span), and speed of processing (Useful Field of View).

Trail Making Test A and B. Trails A is a measure of attention, visuomotor tracking, and psychomotor ability (Reitan 1958; Reitan 1979). This is a timed exercise in which participants connect 25 numbered dots from start to finish in chronological order. Less time (in sec) to complete the task with fewer errors reflect better attention. Trails B is a measure of executive function. Similar to Trails A, Trails B is a timed exercise in which participants connect a total of 25 numbers and letters in alternating sequence from start to finish with less time indicating better neurocognitive functioning. Reliability coefficients for this test are typically good, with several reaching .8 and .9 (Spreen & Strauss, 1998; Reitan, 1979).

Wechsler Memory Scale-III Digit Span (WMS-III Digit Span). The WMS-III Digit Span test measures attention and verbal working memory (Wechsler, 1981). First, the tester reads a string of numbers to the participants that increase in length across trials (e.g., 5 – 7 – 2, 8 – 9 – 1 – 4, 6 – 2 – 5 – 9 – 7). Participants then verbally repeat the string of numbers verbatim. Second, participants are asked to repeat the string of numbers in reverse order. The total number of correctly repeated trials is used to compute scores; higher scores indicate better attention and working memory.

Useful Field of View (UFOV®). The UFOV®, a measure of visual speed of processing and attention, is a computerized test consisting of four subsets that increase in difficulty. Objects are displayed on a touch screen monitor at various speeds (17 to 500 ms) and participants were asked to identify the center object (car/truck), identify the center object while simultaneously locating another object (with and without distractors) in one of eight peripheral fields, and discriminate between two objects while identifying the location of the peripheral object. The score in milliseconds for each subset is combined for an optimal visual processing speed; fewer milliseconds reflect faster speed of processing (Ball, Edwards, & Ross, 2007). Test-retest reliability over five weeks is relatively high from 0.74 to 0.81 (Edwards, Vance, Wadley, Cissell, Roenker, & Ball, 2005).

Proactive Coping Scale (PCS). The PCS is a 14-item tool used to measure proactive coping related to goal setting and how one perceives challenges (Greenglass, 1999). Using a 4-point Likert-type scale (1 = *not true at all*; 4 = *completely true*), participants indicate how much they agree with statements such as, "When I experience a problem, I take the initiative in resolving it." The items are summed to create a composite score ranging from 14-56; higher scores indicate greater engagement in proactive coping. In this study, internal consistency was high for PCS (Cronbach's alpha = .82).

Data Analysis

Data were analyzed using SPSS version 14. The means and standard deviations for the variables were calculated for the sample. Correlation analyses were conducted with a significance level of $p = .05$ or $p = .01$ to determine associations between age,

educational level, number of prescribed medications, psychosocial variables, and proactive coping using Pearson's or Kendall's tau when appropriate. Hierarchical multiple regression using a stepwise approach was conducted to determine which set of independent variables predicted the dependent variable (proactive coping). Independent variables were added in the following order for all four steps: in step 1, demographic variables were entered (gender, minority status, educational level, age); in step 2, psychosocial variables (Ironson-Woods, Lubben, and POMS total scores) were added; in step 3, the number of prescribed medications were added; and in step 4, the neurocognitive measures (Trails A, Trails B, WMS–III Digit Span, UFOV®) were added. The order the variables were entered into the model allowed for examination of possible confounding by demographics, psychosocial, and other variables before examining the predictive power of neurocognitive functioning, the main variable of interest, on proactive coping.

Results

As shown in Table 1, the sample included 28 women and 70 men (M_{age} = 45.25 years, range = 23.67 – 66.92). Seventy-two (73.9%) were of minority status, and the mean educational level was 12.58 years (*SD* = 2.08, range = 8.0 – 20.0).

Association among Model Variables

There were no significant relationships found between demographic variables (gender, age, educational level, and minority status), neurocognitive variables (UFOV®, Trail A, Trails B, and WMS-III Digit Span), and proactive coping; however, there were significant correlations between psychosocial measures and proactive coping (Table 2). First, scores on the spirituality/religiosity measure were positively associated with

proactive coping (r = .516, $p \leq .01$), thus suggesting adults with a higher sense of spirituality/religiosity were more likely to engage in proactive coping. Second, scores on the measure of social network were positively associated with proactive coping (r = .316, $p \leq .01$), thus suggesting adults with HIV with larger social networks were more likely to engage in proactive coping. Finally, scores on the POMS were negatively associated with proactive coping (r = -.359, $p \leq .01$), thus suggesting adults with HIV with more negative affect/mood are less likely to engage in proactive coping.

Hierarchical Regression of Variables

There were significant correlations between the following predictor variables: gender and sexual orientation (r = -.548, p = .01); gender and educational level (r = .244, p = .05); and, sexual orientation and educational level (r = -.274, p = .01). Gender and educational level rather than sexual orientation are better predictors of differences in neurocognitive functioning (Martin et al., 2011; Yaffe et al., 2009); therefore, sexual orientation was excluded from the model. The regression analysis showed there were no significant demographic predictors of proactive coping (step 1); this step accounted for only 2.9% of the variance in proactive coping (Table 3). In step 2, both spirituality/religiosity and social network were significant predictors of proactive coping; hence, this step account for 33.8% of the variance in proactive coping. In step 3, the number of prescribed medications was not a significant predictor of proactive coping. Additionally, spirituality remained a significant predictor, however social network was not. Step 3 accounted for 35.7% of the variance for proactive coping. In step 4, neurocognitive variables were added. None of the neurocognitive variables were significant predictors of proactive coping; however, spirituality/religiosity was the most

robust predictor of proactive coping (t = -3.855, $p \leq .001$); Additionally, the measure of executive function (Trails B) approached significance when added with the other variables in the model (β = -.220, t = -1.707, p = .098), suggesting executive function tasks such as strategic planning may possibly (but weakly) be associated with proactive coping behaviors. A total of 39.2% of the variance in proactive coping was accounted for by the final model.

Discussion

The purpose of this study was to determine if neurocognitive functioning, particularly executive function, predicted proactive coping behaviors in adults with HIV. Although there were no significant relationships found between neurocognitive functioning and proactive coping, findings showed a possible association between Trails B and proactive coping which suggest that impairments in the executive function domain may influence proactive coping behaviors. Perhaps, preserving frontal-lobe neurocognitive functions such as planning may facilitate better decision-making and engagement in proactive coping, and may help adults with HIV navigate through everyday challenges. However, further research is needed to determine if in fact executive function impacts the perception of one's coping ability.

Psychosocial measures were more closely associated with proactive coping, although mood/affect was not a significant predictor and social network did not remain a significant predictor of proactive coping. Spirituality/religiosity, as measured by the Ironson-Woods Spirituality/Religiosity Index, was the best predictor of proactive coping behaviors, suggesting that adults with a higher level of spirituality/religiosity are more likely to engage in proactive coping behaviors. Spirituality may influence proactive

coping in several ways. Spirituality may support a more positive and hopeful appraisal of one's life's situation, which in turn supports one in taking action. As such, spirituality can be considered as a possible "psychological resource" that supports proactive coping, or at least one's perception of his or her coping ability. In situations where one may feel they lack control, such as with HIV disease, spirituality may be the most effective coping resource. Vance and colleagues (2008) suggested that gravitation toward hardiness resources such as social network and spirituality may help strengthen coping abilities. In general, adults who rely on their spiritual beliefs for greater meaning tend to be hardier in that they are able to adapt to stressful situations and more likely to age successfully. Perhaps, this too may explain the dynamics in coping behaviors among adults with HIV, suggesting that those who lack such resources may have difficulty adapting to future HIV-associated challenges such as medication regimens and stigma (Vance et al.).

Although social network did not remain a significant predictor of proactive coping behaviors in the final step of the hierarchical regression model, it is another resource of hardiness that has been shown to improve emotional health in general. In a recent qualitative study of 49 older adults (50+), Solomon and colleagues (2014) found that many participants felt their family support and participation in AIDS service organizations encouraged them to have a positive attitude and use problem-solving strategies to overcome stressors. Many of these participants found ways to steer their attention away from their HIV status which involved staying physically active, volunteering, and as some of them would say, getting back to doing the things they would normally do. Likewise, findings from a study of 292 adults living with HIV suggested that social network may possibly facilitate the relationship between religious coping and

depressive symptoms (Dalmida, Koenig, Holstad, & Wirani, 2013). Specifically, participation in religious activities can increase perceived social network which may positively affect mood.

Hierarchical regression analysis showed that religiosity/spirituality, another source of hardiness, was a significant predictor of proactive coping behaviors in adults with HIV. These findings are aligned with other studies that show significant influences of spirituality on stress management. In a study of 421 adults with HIV, Vance and colleagues (2008) found that those who participated in religious gatherings had more perceived social networks, thus allowing them to cope better with their disease. These findings demonstrate how religiosity/spirituality can promote proactive coping behaviors such as social engagement. In another study of 177 adults with HIV, Kremer and Ironson (2014) found that most participants used spirituality to cope with traumatic events and manage their disease. A greater sense of faith in a higher power or increase in religiosity/spirituality after diagnosis predicted slower disease progression, better medication adherence, better medical decision-making, personal growth, and resilience to manage multiple stressors. Likewise, Trevino and colleagues (2010) found that adults with HIV who experienced spiritual struggle, a sense of abandonment by God, had greater levels of depression in addition to less social networks, detectable viral load, poor self-esteem, and poorer quality of life; whereas, those with positive religious coping had higher levels of self-esteem and better health outcomes. Findings from these studies suggest that variations in resources such as spirituality may influence how adults with HIV cope with their disease. While spirituality has shown to positively influence health outcomes, continuous declines in physical function and emotional dysregulation may

possibly foster poor relationships with God, especially for some adults with HIV who exhaust their coping resources as it becomes more difficult to maintain hope over time (Trevino et al.).

Strengths and Limitations

There were two important strengths of this study. First, the inclusion of sociodemographic variables in the regression model helped to rule out and control for confounding variables. Second, the recruitment of a true range of young, middle-aged, and older adults helped to determine if age is a predictor of proactive coping. Likewise, this study does have a few limitations. First, the sample size was small which limited generalizability and power. Specifically, the effect of executive functioning on proactive coping may have a small effect size, as reflected by a trending *p*-value ($p = .098$). Yet other HIV neurocognitive studies show that poorer executive functioning is related to risky-decision making, maladaptive coping behavior, which is akin to the other end of the spectrum to proactive coping behaviors (Thames et al., 2012). Second, the use of cross-sectional data makes it impossible to determine the predictive value of these variables on proactive coping over time. Last, personality traits of the participants may have influenced their coping style; perhaps, adults who are extraverted may be more likely to seek social networks, whereas those who are introverted may isolate themselves and not seek social networks. Given this, it is recognized that the study lacked a reliable personality scale to assess individual character traits (e.g., NEO-Personality Inventory) that may be more relevant to coping. For example, in a study of 104 adults with HIV, Ironson and colleagues (2008) found that those with personality traits of openness, extraversion, and conscientiousness had a slower disease progression. This suggests

these personality traits may facilitate proactive coping behaviors (e.g., seeking out information about medications, maintaining social networks). Finally, as with most self-reported data, participants may not have accurately reported their coping abilities, perhaps overestimating their ability to cope based on their ideal self rather than their actual self (Remue, De Houwer, Barnes-Holmes, Vanderhasselt, & De Raedt, 2013).

Implications for Research

While there were no significant relationships found between executive function and proactive coping with this small sample size, findings may differ for future studies consisting of a larger sample especially since Trails B trended towards significance in this study. Findings in this study may be due to lack of sensitivity of the Trails B test in detecting neurocognitive predictors of proactive coping. Perhaps, other neurocognitive tests (i.e., Wisconsin Card Sort Test, Tower of London) that measure specific components of executive function (e.g., abstraction, inhibition) may be more sensitive in detecting significant associations with proactive coping. In the same manner, the PCS may not be the best measure of proactive coping behaviors in this population.

Interestingly, recent studies suggest that differences in how adults cope with HIV may be attributed to a gene involved in predicting tolerance (PLOS, 2014). This gene varies considerably between individuals, thus causing some individuals to be hardier and have a higher tolerance for stressors related to their HIV disease. Researchers have compared this gene to those that influence resistance and confirmed that these are two distinct genes. If coping behaviors are related to genetics, manipulation of such genes may possibly increase tolerance of HIV and cause adults to cope better with their health condition. While hereditary influences on proactive coping should also be further

explored along with other biological aspects to better understand differences in coping among adults with HIV, these potential genetic influences suggest that some individuals may need more support in effectively coping with their HIV disease. However, the use of proactive coping strategies to manage various aspects of HIV disease may possibly improve quality of life for adults newly diagnosed with HIV and accommodate the psychosocial needs of aging survivors.

Implications for Nursing Practice

Most importantly, there are a few implications for nursing practice. Nurses caring for adults with HIV can perform thorough cognitive and psychosocial assessments which may be key for identifying negative coping behaviors. Some adults with HIV wish to incorporate spirituality /religiosity in their lives to help them cope with health-related physical, emotional, and psychosocial challenges. Others may lack resources of hardiness such as spirituality/religiosity when they are ostracized from their religious affiliation because of their lifestyle or HIV-related stigma. Nurses are able to provide spiritual support and find unique ways to help many adults with HIV include spirituality /religiosity into their plan of care, which may encourage engagement in proactive coping behaviors. In order to address the spiritual needs of adults with HIV, nurses must inquire about their spiritual beliefs and understand the central role spirituality/religiosity plays in their lives. Following a diagnosis of HIV, some adults may question their spirituality/religiosity and purpose in life; hence, questions may emerge such as "Is God punishing me?" Nurses and other healthcare providers are able to make referrals for spiritual counseling which may help some adults with HIV filter through their emotions and find comfort in their spirituality/religiosity; thus, such benefits may result in better

lifestyle choices which may positively influence health outcomes. Spirituality/religiosity is an important, yet neglected, component of quality of life which may strengthen proactive coping behaviors and help adults with HIV overcome adversity as they age.

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Table 1. Demographics and Overall Sample Test Scores ($N = 98$)

Variable	*N* (%)	M (*SD*)	Range
Gender			
Women	28 (28.60%)		
Men	70 (71.40%)		
Minority Status			
Non-minority	26 (26.50%)		
Minority	72 (73.50%)		
Educational Level		12.58 (2.08)	8.00 – 20.00
Number of prescribed medications		5.27 (3.38)	.00 – 12.00
Age (date of interview - DOB)		45.25 (7.61)	23.67 – 66.92
Ironson-Woods		83.26 (14.63)	15.00 – 100.00
LSNS		29.06 (9.38)	4.00 – 47.00
POMS Total Score		34.87 (41.99)	-28.00 – 163.00
Trails A (sec)		43.01 (22.97)	15.59 – 176.53
Trails B (sec)		157.97 (111.58)	32.31 – 489.81
WMS-III Digit Span (# correct)		9.20 (2.47)	4.00 – 15.00
UFOV		690.45 (329.88)	154.00 – 1840.00
PCS Total		44.53 (6.05)	26.00 – 55.00

Note. DOB = date of birth; LSNS = Lubben Social Network Scale; POMS = Profile of Mood States; WMS = Wechsler Memory Scale; UFOV = Useful Field of View; PCS = Proactive Coping Scale.

Table 2. Correlation Matrix Using Variables (N = 98)

	Sexual Orientation	Gender	Minority Status	Educational Level	Number of Meds	Age	Ironson-Woods	LSNS	POMS	Trails A	Trails B	WMS-III Digit Span	UFOV	PCS
Sexual Orientation	1.00													
Gender	-.548**	1.00												
Minority Status	.147	-.124	1.00											
Educational Level	-.274**	.244*	-.222*	1.00										
Number of Meds	.042	-.064	-.076	.003	1.00									
Age	.111	.092	-.023	.168	.275**	1.00								
Ironson-Woods	.105	-.059	.074	.054	-.066	.050	1.00							
LSNS	-.008	-.163	.061	.147	.059	.013	.311**	1.00						
POMS	.093	-.059	-.043	-.196	.162	-.076	-.490**	-2.57	1.00					
Trails A	.103	.035	.126	-.149	-.066	.285**	-.124	-.164	.228*	1.00				
Trails B	.233*	.095	.229*	-.243*	-.058	.302**	-.103	-.155	.128	.427**	1.00			
WMS-III Digit Span	-.164	.089	-.241*	.224*	.214*	.113	.082	.105	-.135	-.215*	-.243*	1.00		
UFOV	.254*	.063	.219*	-.150	-.051	.245*	-.094	-.096	.219*	.469**	.564**	-.277**	1.00	
PCS	-.070	.118	.045	.114	.078	.117	.516**	.316**	-.359**	-.072	-.109	.118	.025	1.00

Note. LSNS = Lubben Social Network Scale; POMS = Profile of Mood States; UFOV = Useful Field of View; PCS = Proactive Coping Scale.

Table 3. Hierarchical Regression Analysis for Variables Predicting Proactive Coping ($N = 98$)

Variable	β	t	R	R^2	Adjusted R^2
Step 1			.172	0.029	-0.019
Gender	0.107	0.944			
Age (date of interview - DOB)	0.094	0.838			
Educational Level	0.061	0.519			
Minority Status (0 = *non-minority*; 1 = *minority*)	0.036	0.315			
Step 2			.581	0.338	0.278
Gender	0.161	1.640			
Age (date of interview - DOB)	0.070	0.735			
Educational Level	-0.057	-0.544			
Minority Status (0 = *non-minority*; 1 = *minority*)	0.010	0.102			
Ironson-Woods	0.416**	3.717**			
LSNS	0.211*	2.052*			
POMS	-0.088	-0.773			
Step 3			.598	0.357	0.289
Gender	0.175	1.789			
Age (date of interview - DOB)	0.025	0.250			
Educational Level	-0.048	-0.464			
Minority Status (0 = *non-minority*; 1 = *minority*)	0.021	0.219			
Ironson-Woods	-0.418**	-3.767**			
LSNS	0.192	1.868			
POMS	-0.119	-1.043			
Number of prescribed medications	0.149	1.504			
Step 4			.626	0.392	0.290
Gender	0.184	1.858			
Age (date of interview - DOB)	0.042	0.356			
Educational Level	-0.054	-0.492			
Minority Status (0 = *non-minority*; 1 = *minority*)	0.016	0.163			
Ironson-Woods	-0.431**	-3.855**			
LSNS	0.166	1.603			
POMS	-0.139	-1.139			
Number of prescribed medications	0.162	1.540			
UFOV	0.204	1.665			
Trails A - Time in Seconds	0.018	0.163			
Trails B - Time in Seconds	-0.220	-1.707			
WMS-III Digit Span	-0.029	-0.262			

Note. DOB = Date of birth; POMS = Profile of Mood States; UFOV = Useful Field of View; WMS-III = Wechsler Memory Scale. $^{**}p < .01$ $^{*}p < .05$

THE EFFECTS OF SPEED OF PROCESSING TRAINING AND TRANSCRANIAL DIRECT CURRENT STIMULATION ON GLOBAL SLEEP QUALITY AND SPEED OF PROCESSING IN OLDER ADULTS WITH AND WITHOUT HIV

by

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Abstract

Many older adults with and without HIV experience poor sleep quality which may impair cognitive functioning; however, for older adults with HIV, such poor sleep quality may be further exacerbated and contribute to poorer cognitive functioning. Independently, transcranial direct current stimulation (tDCS) and cognitive training have been shown to improve sleep quality in older adults; yet their combined influence has not been examined. This study examined the combined influence of these therapies on older adults with and without HIV. Older (age 50+) adults with HIV (n = 33) and without HIV (n = 33) were randomized to receive either tDCS with speed of processing (SOP) training or sham tDCS with SOP training. Thus, there were four treatment groups derived from the two interventions between adults with and without HIV. At baseline and posttest, global sleep quality was examined using the Pittsburgh Sleep Quality Index, and SOP was examined using five SOP measures. The anodal electrode was placed at F10 and the cathodal anode was placed on the contralateral upper arm. Adults with HIV had significantly poorer sleep quality and worse performance on the Letter Comparison Test compared to adults without HIV at baseline; hence, this may be influenced by underlying biological mechanisms related to inflammation, immune suppression, and age-related brain changes. All the groups improved on the Useful Field of View, a measure of visual SOP and divided attention. Given treatment did not improve sleep quality in any of the groups, this finding must be considered when using tDCS in combination with cognitive training to ameliorate sleep quality. Other similar approaches should consider other cranial placements (dorsolateral prefrontal cortex) of the electrodes that may provide more neural stimulation to improve sleep quality.

Key words: HIV, Aging, Sleep Quality, Cognitive Interventions, Cognitive Functioning

The Effects of Speed of Processing Training and Transcranial Direct Current Stimulation on Global Sleep Quality and Speed of Processing in Older Adults with and without HIV

As the life expectancy of adults with HIV approaches normal (Lewden et al., 2012), challenges with cognitive functioning persist. According to some estimates, 52%-59% of adults with HIV experience HIV-associated neurocognitive disorders (HAND) despite the use of combination antiretroviral therapy (cART) (Bonnet et al., 2013; Heaton et al., 2010). Given adults age 50 and older will comprise 70% of the HIV population by 2020, concerns mount that the effects of HIV-related neuroinflammation and the process of aging may have a synergistic impact on cognitive functioning. While there are multiple contributors to poor cognitive functioning, some age-related changes in sleep quality may influence cognition. Interventions targeting sleep quality should be examined in efforts to facilitate better cognitive functioning.

Compared to the general population, some studies suggest there is a higher prevalence of sleeping problems among adults with HIV (Taibi, 2013; Wibbeler, Reichelt, Husstedt, & Evers, 2012). In a study of adults with HIV (n =180) and without HIV (n =120), Wibbeler and colleagues (2012) found that compared to adults without HIV, daytime sleepiness was higher (46.6% versus 19.4%), and the percentage of those with poor sleep quality was higher (63.9% versus 21.0%) in adults with HIV. Although there are numerous factors that contribute to differences in sleep quality, some adults with HIV may be more sensitive to physiological (e.g., immunological state and effects of antiretroviral medications) (Allavena et al., 2014) and socio-psychological changes

such as stress of an HIV diagnosis and lack of employment (Vance et al., 2015) that may adversely affect their sleep quality.

The purpose of this article is to examine the relationship between sleep quality and cognitive interventions, specifically combined tDCS and SOP training. The next section examines potential mechanisms in which sleep quality may affect cognitive functioning. Potential mechanisms in which cognitive training and tDCS may enhance sleep quality are provided. In addition, this is followed by a theoretical framework with specific details on the role of the synaptic homoeostasis hypothesis in regulating sleep. Last, the article focuses on details of the research study which examined differences in sleep quality and the effects of combined tDCS and SOP training in adults with and without HIV.

Sleep and Cognitive Functioning

In adults with HIV, there are some mechanisms in which poor sleep quality may affect cognitive functioning. Poor sleep quality may be defined as one or more of the following: frequent awakenings during the night, delayed sleep onset, shorter duration of sleep, and day-time sleepiness. One mechanism in which poor sleep quality may affect cognitive functioning is by weakening the blood brain barrier (BBB) (Gamaldo et al., 2013a). Many of the same cytokines released from HIV-infected microglial cells (e.g., TNF-α) control sleep wake patterns; therefore, poor sleep quality may alter brain structures and disrupt the integrity of the BBB (Gamaldo et al., 2013b). As a result, toxic substances can more easily enter the brain and induce neuroinflammation, which over time, may lead to poor cognitive functioning.

Another mechanism in which poor sleep quality may affect cognitive functioning is through excess cortisol secretion. Cortisol is a stress hormone that remains at high levels when sleep is compromised; hence, excess cortisol can induce neuroinflammation which can damage neurons, thus compromising cognitive function (Satori et al., 2012). Disruption of cortisol homeostasis and prolonged exposure to excess cortisol can induce hypertension, hyperlipidemia, and insulin resistance which are risk factors for vascular disease, all of which influence brain health and cognitive functioning (Diekelmann, 2014).

In addition, poor sleep quality inhibits restoration of cortical regions of the brain, primarily the prefrontal cortex, which is necessary for the brain to perform higher level cognitive processes such as executive functioning (Plessis et al., 2014). Given adults with HIV are susceptible to cortical (e.g., cerebral cortex) and subcortical atrophy (e.g., basal ganglia) (Kuper et al., 2011), the effects of poor sleep quality on such areas may be more severe and negatively impact cognitive function. In some adults with HIV, atrophy of subcortical regions of the brain such as the basal ganglia may alter neurotransmitter levels involved in sleep regulation (e.g., serotonin) which can compromise sleep quality (Yaffe, Falvey, & Hoang, 2014). For some adults with HIV who have preexisting problems (e.g., mood disorders) regulating neurotransmitter levels (Cody & Vance, 2016), they may be more susceptible to poor sleep quality which may further impair cognitive functioning.

Sleep architecture may also be influenced by other factors such as aging, substance use, obesity, stress, depression, medications, comorbidities, and consumption of caffeine (Vance, Heaton et al., 2011). Sleep quality has been linked to domain-specific

cognitive function. In a study of 2,822 community-dwelling older men, Blackwell and colleagues (2014) found that those who performed worse on Trails B, a measure of attention/executive function, were more likely to report poor sleep quality which suggests that prefrontal cortical functioning may be sensitive to sleep deficits. Likewise, Gamaldo and colleagues (2013a) examined the relationship between sleep patterns and cognitive functioning in 36 adults with HIV and found that, compared to participants with disturbed sleep patterns, better quality of sleep (greater sleep time and fewer awakenings after sleep onset) was associated with better cognitive functioning on tasks of attention, executive function, and psychomotor speed. Perhaps, this may be due to electrical signals travelling along the fronto-striato-thalamo circuits which are involved in executive function and sleep-regulatory neurotransmitters such as dopamine and serotonin, both of which decline with age (Pace-Schott & Spencer, 2011).

Also, SOP, which has been shown to be a predictor of everyday functioning in older adults with and without HIV (Rebok et al., 2014; Vance, Fazeli, Ball, Slater, & Ross, 2014), may be affected by poor sleep quality. Poor sleep quality can cause fatigue and reduce attention which can significantly impair the rate and efficiency at which the brain can process information. In a sample of 72 older adults, McCrae and colleagues (2012) found that time spent awake in bed and sleep complaints were associated with worse scores on a measure of SOP (i.e., Symbol Digit test), suggesting again that poor sleep quality may impair the integrity of the prefrontal cortex which is highly involved in SOP. The effects of poor sleep quality on SOP produce safety concerns in adults with and without HIV. For example, Vance and colleagues (2014) examined middle-aged and older adults with HIV and found that those with poor SOP performance exhibited poor

driving simulator performance (e.g., slower gross reaction time, greater number of pedestrians hit).

Aging does account for some variation in SOP and sleep quality; hence, many older adults are light sleepers and do not progress well through the sleep-wake-cycle which may contribute to poor cognitive and SOP abilities (Blackwell et al., 2014; Neikrug & Ancoli-Israel, 2010). Age-related deficits in SOP and sleep quality may worsen in those with HIV, especially if they encounter immune dysfunction due to comorbidities (e.g., malignancies) that may exacerbate HIV symptoms. In addition, cognitive variability in older adults may be best explained by Salthouse's Processing-Speed Theory (Salthouse, 1996) which states that age-related deficits in SOP are associated with cognitive impairments in other domains such as working memory. Thus, SOP impairments may negatively impact one's ability to perform tasks of memory, executive function, and even language. Perhaps, SOP, which has been shown to improve SOP in adults with and without HIV (Lampit, Hallock, Suo, Naismith, & Valenzuela, 2015; Vance, Fazeli, Ross, Wadley, & Ball, 2012; Wolinsky, Vander Weg, Howren, Jones, & Dotson, 2013), may be an effective alternative or adjunct treatment for sleep which may also improve cognitive functioning.

Sleep and Cognition

Emerging research shows that sleep is required for the consolidation of memory and normal brain functioning, and poor sleep quality could interfere with the function of neuronal pathways (Stickgold & Walker, 2013). In fact, according to the synaptic homeostasis hypothesis, sleep plays a functional role in synaptic plasticity or strengthening of neuronal connections and promotes growth of new neurons in the

hippocampus, particularly the dentate gyrus which involves the formation of memories (Gorgoni et al., 2013; Stickgold & Walker, 2013; Tononi & Cirelli, 2014). Joo and colleagues (2013) compared hippocampal volume in adults with and without insomnia using magnetic resonance imaging (MRI) and found atrophy with reduced neurogenesis in the dentate gyrus in those with insomnia. Findings suggest that poor sleep quality may disrupt hippocampal integrity which may in turn interfere with cell proliferation and synaptic plasticity associated with learning. Also, hippocampal atrophy was related to poor performance in verbal memory, verbal information processing, and verbal fluency, which suggests that adults with poor sleep quality may be more vulnerable to cognitive impairment (Joo et al., 2013).

Cognitive Training and Sleep Quality

Some cognitive processes associated with learning require more energy and may even lead to fatigue; therefore, sleep may help restore the brain in preparation for later use of higher level cognitive processes (Tononi & Cirelli, 2014). Likewise, learning increases the demands for restorative sleep which is necessary for optimal cognitive performance. The effects of cognitive training on sleep quality has not been examined in adults with HIV; however, Haimov and Shatil (2013) examined such effects after randomizing, using a 2:1 scheme, 51 older adults with insomnia to a cognitive training group (n = 34) or to a control group (n = 17). The cognitive training group completed a home-based computerized cognitive training program (CogniFit®). This Cognifit training was attempted to improve SOP, attention, and memory. The control group completed a home-based computerized program consisting of tasks that do not require use of higher level cognitive processes. Both groups performed three 20-30 minute sessions per week

with a no-training day in between sessions for a period of 8 weeks. At baseline and posttest, participants were asked to wear an actigraph for one week (prior to and after training) to monitor sleep patterns and examine changes in total sleep time (total number of minutes defined as sleep from bedtime to wake time), sleep onset latency (time to fall asleep from bedtime), sleep efficiency (percentage of total sleep time out of total time in bed), wake time after sleep onset (total number of wake minutes after sleep onset), and number of awakenings (during sleep)**.** Also, the participants were asked to keep sleep diaries during actigraphy monitoring for precise measurement of sleep quality. Compared to the control group who did not engage in the higher-level training, the cognitive training group showed improvements in sleep quality, specifically sleep onset latency and sleep efficiency. Those who engaged in the cognitive training also showed improvements in sleep quality and cognitive performance on their eight-week posttest. In addition, better concentration was associated with an increase in the duration of sleep which suggests that sleep may play a role in attention span.

While cognitive training has shown to influence sleep quality, sleep quality may also influence cognitive training. During periods of wakefulness, cognitive demands are the highest and energy is needed to process information during learning. Learning is a form of cognitive exercise that helps strengthen neuronal connections. Subsequent restorative sleep reduces neuronal strength back to baseline levels and prevents over-activation of such connections (Walker, 2010). In the absence of restorative sleep, functional magnetic resonance imaging (fMRI) have shown decreased activation in the prefrontal cortex which negatively influences frontal lobe cognitive functions (Asplund & Chee, 2013; Chee & Tan, 2010; Mullin et al., 2013). Such findings support the

homeostatic role of restorative sleep which regenerates neurons in the prefrontal cortex for later use during tasks that require higher level cognitive processes (Eugene & Masiak, 2015).

Similarly, SOP training is a computerized cognitive intervention designed to increase the speed and accuracy in which participants visually perceive certain stimuli (Ball, Edwards, & Ross, 2007). A series of tasks involve identifying a target object in the center of the monitor and simultaneously locating another object in the periphery. The tasks become increasingly difficult and are adjusted based on the individual performance level (an easier task is presented when a task is performed incorrectly, and a more difficult task is presented when a task is performed correctly). In concurrent tasks of visual discrimination and attention, objects are presented at faster speeds and embedded among distractors. In addition to cognitive gains, SOP training has been shown to improve internal locus of control (Wolinsky, Vander Weg, et al., 2010), quality of life, self-rated health (Wolinsky, Mahncke, et al., 2010), and depressive symptoms **(**Wolinsky et al., 2009). Perhaps, when used alone or as an adjunct treatment, SOP training may improve sleep quality in adults with HIV.

Transcranial Direct Current Stimulation and Sleep Quality

Additionally, no studies have examined the effects of transcranial direct current stimulation (tDCS) on sleep quality in adults with HIV; however, studies have shown positive effects of tDCS on sleep quality in adults with other comorbidities such as bipolar disorder (Minichino et al., 2014). tDCS is a non-invasive technique that uses static direct electrical currents to stimulate the brain, thereby subtly altering membrane potential of neurons (Brunoni et al., 2012). tDCS involves the application of a low (≤ 2

mA) direct current to the scalp using two electrodes, the anode and cathode. The anodal electrode or positive charge is positioned where the current will enter the brain and excite underlying neurons; whereas, the cathode or negative charge is positioned where the current will exit and reduce excitability of neurons (Brunoni et al., 2012). Several studies support the use of anodal tDCS for cortical excitability and targeting the dorsal lateral prefrontal cortex (DLPFC), which according to the 10/20 International Positioning System is located around F8 or F10 (right temple above the sphenoid bone). In a recent study, McIntire and colleagues (2014) randomized 30 sleep-deprived adults to receive either: 1) active tDCS with placebo gum, 2) caffeine gum with sham tDCS, or 3) sham tDCS with placebo gum during 30 hours of extended wakefulness. Anodal tDCS was applied to the DLPFC at 2 mA for 30 min during 30 hours of wakefulness; findings revealed that, compared to the groups who received sham tDCS, the group that received active tDCS with placebo gum had improvements in attention and reported less fatigue and drowsiness. Also, both the tDCS and caffeine produced similar improvements in short-term memory and psychomotor ability when compared to the placebo group, suggesting that tDCS may boost cognitive functioning and/or alertness as effectively as caffeine.

In another study, Minichino and colleagues (2014) used tDCS to improve sleep quality in euthymic bipolar patients. A cathode was placed on the cerebellar cortex and anode over the DLPFC; the intensity of the stimulation was set to 2 mA and delivered for 20 min/day for 2 consecutive weeks. Following the stimulation, there was significant improvements in sleep quality which is consistent with previous literature suggesting anodal stimulation of the DLPFC to improve sleep, mood, and cognitive functioning (da

Silva et al., 2013; McIntire et al., 2014; Minichino et al., 2014; Penolazzi et al., 2014). Given this finding, perhaps, tDCS may improve sleep quality in adults with HIV; neural responses may vary depending on the area of the brain stimulated, the strength of the current, and the duration of time the area is stimulated.

In addition, cognitive training with tDCS may improve sleep quality more so than cognitive training alone. As previously mentioned, the prefrontal cortex may be vulnerable to the negative effects of poor sleep quality given its association with higher level sleep-dependent cognitive processes. In relation to brain exercise, strengthening of the neurons during cognitive training may, over time, lead to cognitive fatigue which may induce restorative sleep; hence, higher energy demands during wakefulness is likely to require more restorative sleep. Perhaps, tDCS with speed of processing training may induce cognitive activation and thereby increase the demands for restorative sleep. Based on prior studies, SOP training has improved SOP and everyday functioning outcomes in adults with and without HIV (Vance et al., 2012); hence, the use of SOP training with tDCS may augment SOP abilities and improve other outcomes such as sleep in adults with HIV.

Purpose

The current study was designed to examine global sleep quality and SOP in older (50+) adults with and without HIV who received tDCS or sham tDCS with SOP. The study was conducted to answer the following research aims: Aim 1. Examine global sleep quality and SOP (at baseline) between older adults with and without HIV; Aim 2. Examine global sleep quality (measured by the Pittsburgh Sleep Quality Index) and SOP (measured by scores on Letter Comparison Test, Pattern Comparison Test, Digit Symbol

Test, Digit Copy Test, and Useful Field of View Test) among older adults with and without HIV who received tDCS or sham tDCS with SOP training (controlling for age, education, and baseline scores); and, Aim 3. Examine change scores for global sleep quality and SOP measures in older adults with and without HIV who received tDCS or sham tDCS with SOP training. For Aim 1, it was hypothesized that, compared to older adults without HIV, those with HIV have poorer global sleep quality and SOP. For Aim 2, it was hypothesized that older adults with and without HIV who received tDCS with SOP training will have better global sleep quality and SOP compared to those who received sham tDCS with SOP training. For Aim 3, based on the bi-directional relationship between sleep and cognition, it was hypothesized that the change score for PSQI will be positively correlated with change scores for SOP measures.

Methods

Design Overview

In this study of adults with and without HIV, stratified randomization (a balanced protocol using race, gender, and Useful Field of View scores) was used to assign participants to one of two groups: a group that received tDCS with SOP training or another group that received sham tDCS with SOP training. Over a period of 5 weeks, participants in the treatment groups received 10 one-hour sessions of either tDCS or sham tDCS with SOP training. Participants received a baseline and posttest comprehensive neurocognitive battery.

Participants

Permission was obtained from the University of Alabama at Birmingham (UAB) Institutional Review Board to enroll participation from older adults in the community and

the UAB 1917 HIV/AIDS Clinic. This pre-post experimental study targeted two groups: adults age 50 and older with and without HIV. Participants were recruited by word of mouth, flyers, and an online ad. Potential participants were instructed to call the study coordinator who then screened them to determine if they met study criteria. Participants were excluded for the following: younger than 50 years of age; homeless; unable to speak and understand English; mentally impaired; deaf or blind; having experienced brain trauma with loss of consciousness greater than thirty minutes; having other significant neuromedical diagnosis (e.g., schizophrenia, bipolar disorder); currently receiving chemotherapy, radiation, or dialysis; undergoing treatment for depression, anxiety, or other mood disorders; being left-handed; having intracranial metal plate implants; having a pacemaker or other biomedical device; having participated in SOP training; not being a licensed driver; having untreated hypertension; and/or lacking experience using a computer mouse. The sample of adults with HIV did not exclude those without a driver's license; however, they were excluded if they have not been diagnosed with HIV for at least 1 year to minimize other confounders that may affect cognition such as reactive depression (Vance, Struzick, & Burrage, 2009). Eligible participants were scheduled an appointment to come in for their baseline visit.

Intervention

A newer version of the SOP program, BrainHQ, was used in this study. Participants were asked to play two games, Double Decision and Target Tracker, for 1 hour twice a week over a period of 5 weeks (10 training sessions total). In Double Decision, participants were presented an object (car/truck) in the center of the computer monitor and a Route 66 sign in one of several peripheral fields at various speeds, and

then asked to identify which central object (car/truck) was presented and the location of the Route 66 sign. When participants performed the exercise correctly, the speed at which the objects were presented increased and then the objects were embedded among distractors, thus making the task more difficult. When participants performed the exercise incorrectly, the correct answer was displayed on the computer screen and the exercise automatically decreased in speed. This double-staircase technique allowed participants to perform the SOP exercises at their maximum threshold level. Based on their initial performance, if participants improved in subsequent exercises, they could proceed to levels that were more challenging. If participants did not improve, they were given the option to replay the game to increase their score at the current level.

Also, the participants played a game called Target Tracker. In this game, participants were initially presented one or more objects (balls or jellyfish) and asked to watch the objects as they moved across the screen among several other balls or jellyfish. When the objects stopped moving, participants were asked to identify the original objects. If participants correctly identified the original objects, they were presented an additional object the next trial. If participants incorrectly identified the original objects, they were presented less objects the next trial. At the end of each set of exercises, those who improved their score had the opportunity to move up to the next level which required participants to identify a greater number of objects. However, participants who did not improve could replay the previous level to try and increase their score. Anytime during the hour, participants could alternate between playing Double Decision and Target Tracker; hence, these exercises were designed to improve visual SOP and divided attention.

tDCS

In applying tDCS, anodal tDCS at a current of 2.0 mA has shown to be both more safe and effective than others (Clark et al., 2012). The 10/20 International Positioning System**,** a guide for placement of the electrodes on the scalp, was used to target F10 which is located directly over the sphenoid bone. Previously, Clark and colleagues (2012) found that stimulation of F10, the right frontal cortex, increased learning and correlated with improvements in correctly identifying concealed objects. In this single-blind study, participants were randomized to one of two groups: an active tDCS group or sham tDCS condition. A 7 cm^2 sponge electrode was placed over the right inferior frontal cortex near F10 and the cathode electrode was placed on the contralateral upper arm. The participants in the active tDCS group received a 2.0 mA current for 20 minutes while engaging in SOP training. After such time, the current was turned off although the participants continued to engage in the SOP training until the end of the hour. Similarly, those in the sham tDCS condition had an identical protocol except they received the 2.0 mA current for only 30 seconds, and then the strength of the current ramped down to 0 mA. During the training, participants were asked to describe the physical sensation of the tDCS after 5 minutes and 15 minutes using the following descriptors: "0) no sensation, 1) cold, 2) some tingling, 3) warm, 4) lots of tingling/some itching, 5) very warm, 6) lots of itching, 7) burning (like a sunburn), 8) burning (like scalding water), 9) 'hurts a lot'" (Clark et al., 2012, p.120). If participants indicated a 7 or higher, they were given the option to continue or reduce the stimulation. Otherwise, participants completed 10 hours of training at the center using the combined SOP and tDCS training protocols.

Study Measures (Baseline and Posttest)

Prior to beginning the study, informed consent was obtained from participants. The baseline and posttest assessments were 2.5-hour visits. At baseline, several measures were used to gather background information and assess cognitive ability and everyday functioning. Neurocognitive measures administered at baseline were repeated at posttest.

Demographic, Psychosocial, and Health Measures.

Demographic Questionnaire. This experimenter-generated measure was used to gather information on age, gender, race (0 = minority, 1 = nonminority), household income before taxes (1 = $0 – $10K; 2 = $10,001 – $20K; etc), and years of education.

Pittsburgh Sleep Quality Index. The PSQI, a questionnaire consisting of 19 items, was used to measure participants' sleep quality in the past month. The seven subscales of PSQI include sleep efficiency, sleep duration, sleep disturbance, sleep latency onset, sleep medication use, and sleepiness dysfunction due to sleepiness. Using a Likert-type scale (*0 = not at all, 1 = less than once a week, 2 = two or more times a week, and 3 = three or more times a week*), participants were asked to what extent does various factors such as waking up in the middle of the night interfere with their sleep. Scores from the subscales were summed to yield a global score ranging from 0 to 21 with scores greater than 5 indicating poor sleep quality. In a study of 80 patients with primary insomnia, test-retest reliability was 0.87 (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002).

Letter and Pattern Comparison Test. These two written tests measured SOP. In the Letter Comparison Test, participants were presented two sets of letters containing three (e.g., HLV, HLX), six (e.g., NLCVZL, NLCVZL), or nine (e.g., SLNFZHMBQ, SLHFZNMBQ) segments. Given 20 seconds per section (6 sections), participants were

asked to write as quickly as possible a "S" if the segments were the same or "D" if the segments were different. The score was the total number of correct responses ranging from 0 to 192, with higher scores indicating faster SOP (Salthouse, 1991). Similarly, the Pattern Comparison Test consisted of 96 pairs of patterns containing three, six, or nine line segments. Given 20 seconds per section (3 sections), participants were asked to write as quickly as possible a "S" if the patterns were the same or "D" if the patterns were different. The score was the total number of correct responses ranging from 0 to 96, with higher scores indicating faster SOP (Salthouse, 1991).

The Wechsler Adult Intelligence Scale (WAIS) Digit Symbol Substitution and Copy Tests. The WAIS Digit Symbol Substitution Test was used to measure visuomotor coordination and attention, while Digit Symbol Copy test was used to measure psychomotor speed (Lezak, 1995). First, participants were administered the substitution test. Participants were presented 9 digits paired with distinct symbols. Participants were given 90 seconds to write symbols that correspond to the digits in each box. The score consisted of the number of correctly written symbols, with higher scores indicating better visuomotor coordination. Similarly, the symbol copy test consisted of 93 symbols and participants were asked to copy the symbol in the adjacent boxes provided. The time it took for participants to complete the task was recorded with less time to complete the task indicating better psychomotor speed.

Useful Field of View (UFOV®). This computerized test was used to measure visual attention and SOP. Like previous studies, this test consisted of four subtests beginning with easy tasks that became more complex. In subtest 1, a measure of simple SOP, an object (car/truck) was displayed in the center of the computer screen at various

speeds between 17 and 500 milliseconds and participants were asked to identify which object (car/truck) was displayed. In subtest 2, a measure of divided attention, participants were presented an object in the center of the computer screen in addition to a car in one of eight peripheral visual fields. Participants were asked to identify the central object while simultaneously selecting the peripheral location of the car. In subtest 3, a measure of selective attention, participants were asked again to identify the central object and location of the car in one of eight peripheral fields; however, the task was more difficult because there were distractors surrounding the central object and the peripheral car. The computer automatically presented the central object at a slower speed when participants answered test items incorrectly; in the same manner, participants were presented the central object at the faster speed when they answered test tasks correctly. Visual SOP was calculated using the total in milliseconds of all three subtests; fewer milliseconds indicated faster visual SOP. Test-retest reliability is quite high and ranges from 0.74 to 0.81 (Ball et al., 2007).

Statistical Analysis

Data were examined using SPSS 21. Linear regression was used to impute PSQI baseline global scores for two participants, one with and the other without HIV. Two participants had a single missing component of the baseline PSQI (sleep quality and sleep disturbance); therefore, the remaining components were used to estimate the missing component for these two participants. From this, baseline global PSQI scores were both calculated. Out of 80 cases, fourteen were excluded from this analysis: nine with missing posttest data (HIV-positive = 4; HIV-negative = 5), one practice participant, and four

other participants in the HIV-positive sample (one with a stroke, two with schizophrenia, and one with a stroke and schizophrenia).

The demographic differences between adults with and without HIV were examined using independent samples *t*-test and chi-square analyses (see Table 1). Pearson-product-moment correlation analyses were performed to examine the relationship between demographics, global PSQI scores, and scores on SOP measures at baseline for the combined sample of adults with and without HIV (see Table 2). ANOVAs and chi-square analyses were used to examined demographics, mean global PSQI scores at baseline, and mean scores on SOP measures at baseline between the four treatment groups: adults with HIV receiving tDCS with SOP training (n = 17); adults with HIV receiving sham tDCS with SOP training (n = 16); adults without HIV receiving tDCS with SOP training (n = 17); and adults without HIV receiving sham tDCS with SOP training (n = 16) (see Table 3). ANCOVAs were used to examine change in pre-post mean scores for global PSQI and SOP measures (controlling for age, education, and mean baseline scores for PSQI and SOP measures) for all four groups (see Table 4); hence, controlling for baseline covariates minimized bias in treatment effects. Baseline PSQI and SOP scores were adjusted to account for variations in sleep quality and SOP abilities which may affect the outcome. Also, main and interaction effects of independent variables (HIV status and training group) were examined.

In addition, correlation analyses were also performed to examine change scores for PSQI and SOP measures. The change scores for PSQI and the SOP measures were calculated by subtracting the posttest score from the baseline score. Correlation analyses were conducted for adults with and without HIV and separated by training groups (see

Tables 5 and 6). Follow-up post hoc analyses examined the relationship between change scores for PSQI and SOP measures by HIV status (see Table 7) and by training group (see Table 8).

Results

Aim 1: Comparison of Adults with and without HIV at Baseline

As seen in Table 1, ANOVAs and chi-squares were used to compare a sample size of 33 adults with HIV and 33 adults without HIV on each of the demographic and outcome variables (global PSQI scores and scores on SOP measures). The average age of adults with HIV (M_{age} = 55.82, range = 51-71 years of age) was significantly younger than those without HIV (M_{age} = 62.12, range = 50-87 years of age). Compared to adults without HIV, there were significantly more minorities ($\chi^2[n = 28] = 5.99$), $p = .01$) and men ($\chi^2[n = 22] = 10.28$), $p < .01$) among those with HIV. Adults without HIV had a significantly higher income and were more educated than those with HIV ($p < .01$). For mean global PSQI scores, adults with HIV scored higher ($M = 9.65$; $SD = 5.14$) which indicated significantly poorer sleep quality compared to than those without HIV ($M = 5.23$; $SD = 3.24$, $p < .01$). For SOP measures, adults without HIV scored significantly better ($M_{number\ correct} = 31.91$; $SD = 6.90$, $p = .03$) on the Pattern Comparison Test compared to adults with HIV ($M_{number\ correct} = 28.36$; $SD = 6.25$).

In addition, an independent samples *t*-test was performed to examine differences in comorbidities among adults with and without HIV. Thirty-nine percent of adults without HIV and 24% of adults with HIV had at least 3 comorbidities. Compared to adults without HIV, asthma, skin conditions, and mood problems were more common comorbidities among adults with HIV. Adults without HIV had more cases of

osteoporosis, cataracts, angina, glaucoma, hypertension, hypercholesterolemia, and cancer than those with HIV. For the combined sample of adults with and without HIV, correlation analyses indicated significant relationships between demographics, global PSQI, and scores on SOP measures at baseline (see Table 2). There was a negative correlation between age and global PSQI at baseline (r = -.289, $p < 0.05$); increasing age and was associated with poorer sleep quality. Likewise, there was a negative correlation between education and global PSQI at baseline (r = -.288, $p < 0.05$); increasing years of education and was significantly associated with poorer sleep quality. There was a negative correlation between global PSQI and the following three SOP measures at baseline: Letter Comparison (r = -.272, $p < 0.05$), Pattern Comparison (r = -.283, $p < 0.05$, and Digit Symbol Substitution (r = -.333, $p < 0.01$); better performance on these SOP measures were significantly correlated with poorer sleep quality. In contrast, a positive correlation was found between global PSQI and Digit Copy Test (r = .284, $p < 0.05$) at baseline; therefore, better performance on this SOP measure at baseline was significantly associated with better sleep quality.

Aim 2: Differences Between Four Treatment Groups on Demographics, Global PSQI Scores, and SOP Scores at Baseline and Posttest

As seen in Table 3, there were significant differences ($p < .01$) in age, gender, race, education, household income, global PSQI scores, and Pattern Comparison scores among the four treatment groups at baseline. At baseline, the two groups of adults without HIV that received either tDCS with SOP training or sham tDCS with SOP training were older, had more income, were more educated, had lower global PSQI scores (better sleep quality), and scored better on the Pattern Comparison Test.

The means of adults with HIV and without HIV separately by treatment group at baseline and posttest are presented in Table 4, alongside an ANCOVA analysis of the effects of HIV status, tDCS, and their interaction on the post-measures (controlling for age, education, and baseline measures). For the Digit Copy Test, a main effect for HIV (F[1, 59] = 5.26, p = .03) and a main effect for tDCS (F[1, 59] = 5.16, p = .03) were detected; those who had HIV and/or received sham tDCS with SOP training performed better on the Digit Copy Test. A HIV-by-tDCS interaction on the Letter Comparison Test was significant (F[1, 59] = 5.50, p = .02); follow up pairwise comparisons using least significant differences showed that among adults with HIV, those who received tDCS with SOP training scored significantly better than those who received sham tDCS with SOP training (p = .019), while there was no significant difference by condition among those without HIV (p = .244).

Aim 3: Correlations Between Change Scores for Global PSQI and SOP Measures among Adults with and without HIV by Training Group

As seen in Tables 5 and 6, correlations between change scores for global PSQI and SOP measures were examined for adults with and without HIV by training group. For adults without HIV who received sham tDCS with SOP training, change score for global PSQI was negatively correlated with change score for UFOV (r = -.670; p < .01); from baseline to posttest, improvements on PSQI correlated to declines on UFOV (see Table 5). For adults with HIV who received sham tDCS with SOP training, change score for global PSQI was positively correlated with change score for Digit Symbol Substitution (r = -.619; p < .01); from baseline to posttest, improvements on PSQI correlated to improvements on Digit Symbol Substitution (see Table 6). Follow-up post hoc analyses examined correlations between change scores for global PSQI and SOP

measures by HIV status and the findings were similar (see Table 7); for adults without HIV, change score for global PSQI was negatively correlated with change score for UFOV (r = -.381; p < .05). Likewise, further analyses of change scores for global PSQI and SOP measures by training group revealed a positive correlation between change scores for global PSQI and Digit Symbol Substitution for the sham tDCS with SOP training group (r = -.481; p < .01).

For adults with and without HIV receiving tDCS with SOP training, there were no significant correlations between change scores for global PSQI and SOP measures. However, additional analyses were performed to examine within-group differences in global sleep quality post-training for adults with and without HIV. Three categories of sleep quality were examined: stable (no change in global PSQI from baseline to posttest), improved (increase in global PSQI score of 2 points or higher on posttest), and declined (decrease in global PSQI score of at least 2 points on posttest. Among adults with HIV, 15 had stable sleep quality, 5 had improved sleep quality, and 13 had declined in sleep quality. Among adults without HIV, 24 had stable sleep quality, 2 had improved sleep quality, and 7 had declined in sleep quality. Across all groups, UFOV scores improved from baseline to posttest. This finding is consistent with previous studies of SOP training in adults with and without HIV (Ball, Edwards, & Ross, 2007; Vance, Fazeli et al., 2014).

Discussion

For Aim 1, findings supported the hypothesis that older adults with HIV have poorer sleep quality compared to those without HIV; hence, this may be influenced by underlying biological mechanisms related to inflammation, immune suppression, and age-related cognitive changes (Cody & Vance, 2016). As HIV enters the brain, viral

replication produces an immune response involving neurotoxic proteins which leads to cognitive impairment. Some cortical (e.g., cerebral cortex) and subcortical structures (e.g., hypothalamus) that are prone to the inflammatory effects of HIV also play a role in sleep regulation. For Aim 2, no significant improvements in global sleep quality among adults with and without HIV who received tDCS with SOP training were found compared to those who received sham tDCS with SOP training (controlling for age, education, and baseline scores). These findings rejected the hypothesis underpinning the study which were based on the independent effects of tDCS on cognitive functioning (Clark et al., 2012), and the benefits of cognitive training on sleep (Haimov & Shatil, 2013) observed in prior studies.

For Aim 3, among adults with and without HIV that received sham tDCS and SOP training, the relationship between change score for global PSQI and change scores for SOP measures (i.e., UFOV and Digit Symbol Substitution) were inconsistent. Perhaps, the PSQI may not have been a sensitive enough in this study to detect subtle changes in sleep quality; however, this study is the first to show the independent effects of SOP training on sleep in older adults with and without HIV. This study was initially designed to improve SOP not sleep quality which may also explain why there were no significant correlations found between change scores on global PSQI and SOP measures for older adults with and without HIV who received tDCS or sham tDCS with SOP training. Given this, there are several strengths and limitations related to methodology that were observed.

Strengths and Limitations

In this study, two strengths were observed. First, the data were from two studies with identical protocols that included validated measures of SOP and sleep quality. Second, because stratified randomization was used to assign adults with and without HIV to the treatment groups, there was minimal sampling bias. Hence, when comparing demographics and baseline scores among adults with HIV by treatment group, there were minor differences which indicated the groups were comparable. Likewise, the treatment groups among adults without HIV showed little differences at baseline which indicated they were comparable.

Additionally, there were some limitations in this study. First, imputed data could potentially influence the results and limit generalizability; however, as this was conducted for 2 cases only, the possible bias is minimal (Schafer, 1999). Second, PSQI is a subjective measure of sleep quality, and participants may have under or overreported their sleeping problems based on their knowledge of the intentions of the studies. For example, among a group of older adults (n = 39), Landry and colleagues (2015) found that 51% underestimated their sleep quality suggesting that some older adults may perceive their sleep quality to be worse than objectively measured. Furthermore, PSQI only differentiates "good sleepers" from "bad sleepers." In this study, this measure of sleep quality was used to examine differences between adults with and without HIV; however, specific components of sleep quality can be further explored with objective sleep measures. Including an actigraphy watch may have yielded more precise data on sleep patterns across treatment groups. However, actigraphy watches are costly and have limitations, as participants may not consistently wear the watches. In this study, anodal

stimulation of F10 did not produce any improvement on sleep quality; hence, some studies of tDCS on sleep have suggested that the effects may be site specific. For example, Minichino and colleagues (2014) found that placement of the anode (stimulatory electrode) on the left prefrontal area with the cathode (inhibitory electrode) on the right cerebellar cortex improved PSQI scores in euthymic bipolar patients. Last, statistical power was reduced due to the small sample sizes. Larger sample sizes and longitudinal studies are needed to detect true differences across treatment groups in global sleep quality and SOP.

Implications for Practice

For clinicians caring for adults with HIV, it is important to perform thorough assessments focusing on factors that influence cognitive functioning. Routine sleep assessments in the clinical setting can help provide insight on other health issues that can affect cognitive functioning such as depression (Benitez & Gunstad, 2012) and sleep apnea (Yaffe, Falvey, & Hoang, 2014). Additionally, early diagnosis and treatment of sleep problems can improve cognitive functioning which may also help adults aging with HIV remain independent in their everyday functioning activities (e.g., taking medications).

Implications for Research

With the increasing number of adults aging with HIV, more research is needed to identify ways to address problems such as poor sleep given its negative affect on cognitive functioning (Vance, Heaton, Eaves, & Fazeli, 2011). This study's findings were aligned with those of prior studies suggesting older adults with HIV experience poorer sleep quality compared to those without HIV (Gamaldo et al., 2013a; Taibi, 2013).

Whether combined tDCS and SOP influence sleep and SOP should be further examined using larger sample sizes and other sleep measures. Using cognitive interventions to improve cognitive functioning may in turn improve sleep (Haimov & Shatil, 2013); likewise, using sleep interventions to target sleeping problems may in turn improve cognitive functioning.

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Table 1. Baseline Demographic, Sleep, and SOP Differences Between Groups by HIV Status

Variable	HIV-Positive (n = 33) M (SD)	N (%)	HIV-Negative (n = 33) M (SD)	N (%)	p
Age	55.82 (4.34)		62.12 (10.40)		.00**
Gender					.00**
Women		11 (33%)		24 (73%)	
Men		22 (67%)		9 (27%)	
Race					.01**
Minority		28 (85%)		19 (58%)	
Nonminority		5 (15%)		14 (42%)	
Household Income†	1.67 (.645)		4.95 (2.89)		.00**
Education (years)	12.58 (1.86)		14.88 (1.85)		.00**
Letter Comparison (no. correct)	40.15 (9.70)		43.79 (10.52)		.15
Pattern Comparison (no. correct)	28.36 (6.25)		31.91 (6.90)		.03*
Digit Symbol Substitution (no. correct)	40.55 (12.81)		46.39 (15.11)		.10
Digit Copy Test (seconds)	97.33 (30.21)		86.93 (24.67)		.13
Useful Field of View (milliseconds)	427.54 (248.64)		471.70 (248.42)		.47
Global PSQI	9.65 (5.14)		5.23 (3.24)		.00**
Good Sleepers (score < 5)		4 (12%)		14 (42%)	
Poor Sleepers (score ≥ 5)		29 (88%)		19 (58%)	

Note. M = mean; SD = standard deviation; SOP = speed of processing; no = number; tDCS = transcranial direct current stimulation, † = (1 = $0-$10,000; 8 = more than $70,000)
* $p \leq .05$; ** $p \leq .01$

Table 2. Bivariate Correlations of Demographics, Global PSQI, and SOP Scores at Baseline ($N = 66$)

	Age	Gender	Income	Education	Global PSQI	Letter Comparison	Pattern Comparison	Digit Symbol Substitution	Digit Copy Test	Useful Field of View
Age	-									
Gender	.100	-								
Income	.155	-.305*	-							
Education	.148	-.148	.583**	-						
Global PSQI	-.289*	.276*	.260*	-.288*	-					
Letter Comparison (no. correct)	-.227**	-.393**	.173	.225	-.272*	-				
Pattern Comparison (no. correct)	-.387**	-.299*	.328*	.335**	-.283*	.723**	-			
Digit Symbol Substitution (no. correct)	-.230	-.298*	.382**	.371**	-.333**	.698**	.718**	-		
Digit Copy Test (seconds)	.277*	.427**	-.294*	-.318**	.284*	-.671**	-.796**	-.785**	-	
Useful Field of View (milliseconds)	.336**	.069	-.158	-.039	-1.00	-.490**	-.492**	-.494**	.459**	-

Note. * $p < .05$; ** $p < .01$. Correlations indicate the relationship between demographics, Global Pittsburgh Sleep Quality Index, and speed of processing measures at baseline for older adults with and without HIV

Table 3. Demographic, Sleep, and SOP Differences Between Four Groups at Baseline Using ANOVA and Chi-square Analyses

Variable	HIV-Positive tDCS + SOP (n = 17)	HIV-Positive sham tDCS + SOP (n = 16)	HIV-Negative tDCS + SOP (n = 17)	HIV-Negative sham tDCS + SOP (n = 16)	Statistical Test $p/\chi 2$
	M (SD) N (%)	M (SD) N (%)	M (SD) N (%)	M (SD) N (%)	
Age (years)	56.00 (3.24)	55.63 (5.38)	62.65 (11.03)	61.56 (10.01)	.00 **
Gender					
Women	6 (35.3%)	5 (31.3%)	13 (76.5%)	11 (68.8%)	.00**
Men	11 (64.7%)	11 (68.8%)	4 (23.5%)	5 (31.3%)	
Race/Ethnicity					
Minority	14 (82.4%)	14 (82.4%)	13 (76.5%)	7 (43.8%)	.01**
Nonminority	3 (17.6%)	2 (17.6%)	5 (23.5%)	9 (56.2%)	
Education (years)	12.53 (1.77)	12.63 (2.00)	15.05 (2.09)	14.84 (1.91)	.00 **
Household Income †	1.71 (.69)	1.63 (.62)	4.47 (3.04)	5.31 (2.85)	.00**
Global PSQI	9.88 (6.10)	9.44 (4.37)	5.41 (3.81)	5.13 (2.67)	.00**
Letter Comparison	38.82 (10.79)	41.56 (8.50)	44.47 (11.61)	43.06 (9.56)	.17
Pattern Comparison	28.24 (6.91)	28.50 (5.70)	31.24 (6.43)	32.63 (7.51)	.03*
Digit Symbol	39.00 (11.88)	42.19 (13.93)	45.47 (15.28)	47.38 (15.38)	.07
Digit Copy Test	98.64 (31.17)	95.95 (30.11)	88.40 (21.92)	85.37 (27.96)	.14
Useful Field of View	427.68 (278.58)	427.40 (221.59)	479.53 (272.09)	463.38 (229.21)	.48

Note. M = mean; SD = standard deviation; SOP = speed of processing; tDCS = transcranial direct current stimulation; PSQI = Pittsburgh Sleep Quality Index, † = (1 = $0-$10,000; 8 = more than $70,000)

* $p \leq .05$

** $p < .01$

Table 4. Sleep Quality and SOP Baseline and Posttest Descriptive Statistics and ANCOVA Results of HIV, tDCS, and HIV x tDCS Interaction Controlling for Age, Education, and Baseline Scores

	Baseline Descriptives				Posttest Descriptives											
	HIV-Negative		HIV-Positive		HIV-Negative		HIV-Positive									
	sham tDCS + SOP $n = 17$	tDCS + SOP $n = 17$	sham tDCS + SOP $n = 16$	tDCS + SOP $n = 17$	sham tDCS + SOP $n = 17$	tDCS + SOP $n = 17$	sham tDCS + SOP $n = 16$	tDCS + SOP $n = 17$	ANCOVA on Post-tDCS, Controlling for Age, Education and Baseline Scores							
										HIV Status		tDCS		HIV Status x tDCS		
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	Error *df*	*F* (1, *df*)	*p*	*F* (1, *df*)	*p*	*F* (1, *df*)	*p*	R^2
Global PSQI	5.13 (2.67)	5.41 (3.81)	9.44 (4.37)	9.88 (6.10)	3.69 (2.15)	5.12 (3.57)	8.06 (4.74)	8.88 (4.70)	59	1.28	.263	1.89	.174	.266	.608	.710
Letter Comparison ^{Hxt}	43.06 (9.56)	44.42 (11.03)	41.56 (8.50)	38.82 (10.79)	44.44 (10.48)	44.24 (14.32)	41.38 (8.52)	43.29 (10.62)	59	.022	.882	1.661	.203	5.501	.022	.796
Pattern Comparison	32.63 (7.51)	31.24 (6.43)	28.50 (5.70)	28.24 (6.91)	32.56 (6.81)	31.76 (7.61)	31.31 (5.89)	29.82 (7.27)	59	1.095	.300	.267	.608	.873	.354	.781
Digit Symbol Substitution	47.38 (15.38)	45.47 (15.28)	42.19 (13.93)	39.00 (11.88)	52.13 (14.47)	46.41 (14.16)	46.31 (12.28)	43.06 (13.12)	59	.152	.698	3.484	.067	2.183	.145	.888
Digit Copy ^{Hxt}	85.37 (27.96)	88.40 (21.92)	95.95 (30.11)	98.64 (31.17)	81.60 (30.10)	87.88 (27.55)	80.79 (20.26)	92.32 (29.06)	59	5.257	.025	5.163	.027	.547	.463	.812
Useful Field of View	463.38 (229.21)	479.53 (272.09)	427.40 (221.59)	427.68 (278.58)	279.31 (200.57)	287.77 (208.53)	294.07 (218.76)	295.83 (281.58)	59	1.824	.182	.006	.940	.011	.917	.572

Note. *M* = mean; *SD* = standard deviation; SOP = speed of processing; tDCS = transcranial direct current stimulation; PSQI = Pittsburgh Sleep Quality Index; HIV-by-tDCS interaction = ^{Hxt}; HIV main effect = ^{H}, tDCS main effect = ^{t}; *p* significant at .05

Table 5. Bivariate Correlations of Change Scores for Global PSQI and SOP for HIV-Negative Adults by Training Group

		Global PSQI	Letter Comparison	Pattern Comparison	Digit Symbol Substitution	Digit Copy Test	Useful Field of View
sham tDCS + SOP	Global PSQI	-					
	Letter Comparison (no. correct)	-.157	-				
	Pattern Comparison (no. correct)	-.261	.017	-			
	Digit Symbol Substitution (no. correct)	-.289	.363	-.191	-		
	Digit Copy Test (seconds)	.179	-.151	.299	-.413	-	
	Useful Field of View (milliseconds)	-.670**	-.150	.219	-.092	.200	-
tDCS + SOP	Global PSQI	-					
	Letter Comparison (no. correct)	-.204	-				
	Pattern Comparison (no. correct)	.133	.606**	-			
	Digit Symbol Substitution (no. correct)	.120	.141	.301	-		
	Digit Copy Test (seconds)	.097	-.353	-.667**	-.373	-	
	Useful Field of View (milliseconds)	-.150	.554*	.289	-.210	.045	-

Note. * $p < .05$; ** $p < .01$. Correlations indicate the relationship between the change in Global Pittsburgh Quality Sleep Index score and speed of processing measures by intervention group from baseline to posttest.

Table 6. Bivariate Correlations of Change Scores for Global PSQI and SOP for HIV-Positive Adults by Training Group

		Global PSQI	Letter Comparison	Pattern Comparison	Digit Symbol Substitution	Digit Copy Test	Useful Field of View
sham tDCS + SOP	Global Pittsburgh Quality Sleep Index	-					
	Letter Comparison (no. correct)	-.442	-				
	Pattern Comparison (no. correct)	-.183	.388	-			
	Digit Symbol Substitution (no. correct)	-.619*	.103	.429	-		
	Digit Copy Test (seconds)	.034	-.131	-.501*	-.403	-	
	Useful Field of View (milliseconds)	.087	-.157	-.526*	-.197	.063	-
tDCS + SOP	Global Pittsburgh Quality Sleep Index	-					
	Letter Comparison (no. correct)	-.213	-				
	Pattern Comparison (no. correct)	.004	.539*	-			
	Digit Symbol Substitution (no. correct)	.003	.060	.164	-		
	Digit Copy Test (seconds)	-.222	-.343	-.307	.011	-	
	Useful Field of View (milliseconds)	-.094	.481	.136	.154	-.387	-

Note. * $p < .05$; ** $p < .01$. Correlations indicate the relationship between the change in Global Pittsburgh Quality Sleep Index score and speed of processing measures by intervention group from baseline to posttest.

Table 7. Bivariate Correlations of Change Scores for Global PSQI and SOP by HIV Status

		Global PSQI	Letter Comparison	Pattern Comparison	Digit Symbol Substitution	Digit Copy Test	Useful Field of View
HIV Negative	Global PSQI	-					
	Letter Comparison (no. correct)	-.216	-				
	Pattern Comparison (no. correct)	-.008	-.372*	-			
	Digit Symbol Substitution (no. correct)	-.124	.248	.029	-		
	Digit Copy Test (seconds)	.135	-.328	-.363*	-.370*	-	
	Useful Field of View (milliseconds)	-.381*	.243	.245	-.127	.079	-
HIV Positive	Global PSQI	-					
	Letter Comparison (no. correct)	-.230	-				
	Pattern Comparison (no. correct)	-.087	.352*	-			
	Digit Symbol Substitution (no. correct)	-.332	.063	.275	-		
	Digit Copy Test (seconds)	-.044	-.051	-.417*	-.232	-	
	Useful Field of View (milliseconds)	.007	.181	-.169	-.049	-.096	-

Note. * $p < .05$; ** $p < .01$. Correlations indicate the relationship between the change in Global Pittsburgh Quality Sleep Index score and speed of processing measures by HIV-status from baseline to posttest.

Table 8. Bivariate Correlations of Change Scores for Global PSQI and SOP by Training Group

		Global PSQI	Letter Comparison	Pattern Comparison	Digit Symbol Substitution	Digit Copy Test	Useful Field of View
sham tDCS + SOP	Global PSQI	-					
	Letter Comparison (no. correct)	-.312	-				
	Pattern Comparison (no. correct)	-.189	.072	-			
	Digit Symbol Substitution (no. correct)	-.481**	.240	.061	-		
	Digit Copy Test (seconds)	.061	-.020	-.350*	-.316	-	
	Useful Field of View (milliseconds)	-.225	-.177	-.025	-.146	.030	-
tDCS + SOP	Global PSQI	-					
	Letter Comparison (no. correct)	-.235	-				
	Pattern Comparison (no. correct)	.043	.579**	-			
	Digit Symbol Substitution (no. correct)	.021	.206	.264	-		
	Digit Copy Test (seconds)	-.008	-.388**	-.316**	-.279	-	
	Useful Field of View (milliseconds)	-.142	.550**	.236	.015	-.143	-

Note. * $p < .05$; ** $p < .01$. Correlations indicate the relationship between the change in Global Pittsburgh Quality Sleep Index score and speed of processing measures by training group from baseline to posttest.

COGNITION IN ADULTS AGING WITH HIV

With adults age 50 and older comprising the largest portion of the HIV population, preserving cognitive functioning is becoming an important aspect to promote successful aging. Even in those receiving combination antiretroviral therapy (cART), the development of mild cognitive impairments remains problematic and may interfere with one's everyday functioning (Heaton et al., 2010). Some cognitive predictors are modifiable (e.g., physical activity) while others are not (e.g., age); however, the synergistic effects of such predictors can be more detrimental to cognition in adults with HIV as they age. The three articles in this dissertation were written to provide a general overview of HIV and cognition and their influence on everyday outcomes in adults as they age with this disease.

Article 1, *The Neurobiology of HIV and Its Impact on Cognitive Reserve: A Review of Cognitive Interventions for an Aging Population*, examined neurobiological influences of HIV and several causes of decline in cognition in adults with HIV (Cody & Vance, 2016). Article 2, *The Influence of Neurocognitive Functioning on Proactive Coping Behaviors in Adults with HIV*, examined the negative effects of HIV on frontal areas of the brain associated with executive functioning, which may prevent engagement in proactive coping (Cody, Fazeli, Moneyham, & Vance, 2016). Article 3, *The Effects of Speed of Processing (SOP) Training and Transcranial Direct Current Stimulation on Sleep and SOP in Older Adults with and without HIV*, examined differences in sleep

quality in older adults with and without HIV, which is important given HIV and aging have shown to independently affect circadian rhythms and cognition (Gamaldo et al., 2013; Yaffe et al., 2014). Also, the article examined the effects of tDCS with SOP training on sleep and SOP in older adults with and without HIV. The complexity of HIV in the aging brain warrants future exploration of additional cognitive predictors with consideration of biological and psychosocial influences.

With the increasing longevity among adults with HIV (United States Committee on Aging, 2013), it is important to identify physical, cognitive, and psychosocial risk factors that can prevent successful cognitive aging. The concept of cognitive reserve and how it contributes to the complexity of aging with HIV is examined in the next section. The purpose of this chapter is to examine how the neurobiological effects of HIV, proactive coping, and sleep relate to successful aging. Specifically, the three articles in this dissertation are examined within the context of HIV and aging as they relate to Baltes and Baltes' eight factors of successful aging. This chapter closes with implications for research and practice.

HIV, Aging, and Cognitive Reserve

In several studies, differences in cognitive function have been examined between younger and older adults with HIV. In a study of 162 younger and older adults with and without HIV, older adults with HIV performed the worst on measures of speed of processing, memory, and executive functioning; then older adults without HIV and younger adults with HIV performed at similar cognitive levels; and, younger adults without HIV demonstrated the best cognitive performance (Vance, Fazeli, & Gakumo, 2013). In addition to differences observed between groups, within-group differences were

found among older adults with HIV in that some individuals had better cognitive performance than others (Fazeli et al., 2014; Vance, Fazeli, & Gakumo, 2013). Why some older adults with HIV have better cognitive function than others may be related to early exposure to environmental/lifestyle factors that facilitate positive neuroplasticity which in turn improves cognitive reserve (Cody & Vance 2016; Vance, McDougall, Wilson, Debiasi & Cody, 2014).

Cognitive reserve, or the brain's ability to sustain its function with injury, declines with aging and increases one's susceptibility to cognitive impairments (Foley et al., 2012). Over the lifespan, cognitive reserve changes and some older adults with greater cognitive reserve may exhibit better cognitive functioning despite the presence of disease. Thus, the concept of cognitive reserve suggests that the brain is flexible in its ability to adapt to the negative effects of chronic diseases such as HIV. Based on this concept, higher cognitive reserve in adults aging with HIV may be neuroprotective against premature development of cognitive disorders; whereas, lower cognitive reserve in adults aging with HIV may contribute to early manifestation of neurodegenerative diseases and HIV-associated neurocognitive disorders, both of which can prevent successful aging.

In this dissertation, the three articles examined the relationship between HIV and cognition in addition to some factors that may increase or decrease cognitive reserve in adults with HIV. The first article provided an overview of factors that may facilitate negative neuroplasticity (e.g., HIV-induced neuroinflammation, substance use, depression, poor sleep, comorbidities, and aging). According to Cody and Vance (2016), chronic exposure to such factors facilitates negative neuroplasticity which has been associated with brain atrophy and weaker neuronal connections (lower cognitive reserve).

In addition, several studies suggest other factors (e.g., higher education) that facilitate positive neuroplasticity, thus creating new and improved neuronal connections (higher cognitive reserve). Cognitive reserve is important for successful aging, and in some adults with HIV, there is a concern that lack of cognitive reserve may amplify the negative effects of HIV and aging on cognitive health.

Successful Aging with HIV

Over the years, the definition of successful aging has changed with several studies suggesting that some adults can sustain physical, cognitive, and/or psychological function and "age successfully" (Crowther et al., 2002; Kahana & Kahana, 2001; Rowe & Kahn, 1997). Some definitions and models of successful aging are simple and consist of only a few factors that are applicable to the general population, while others are more precise with multiple interrelated factors of successful aging for vulnerable populations. A more detailed model of successful aging by Baltes and Baltes (1990) encompasses three processes: selection of goals, optimization of internal and external resources to achieve goals, and compensation or maintenance of function with the use of new or unused resources to prevent further loss. Building on this model of successful aging by Baltes and Baltes, Vance and colleagues (2011) proposed eight interrelated factors that are better suited to examine the complexity of successful aging with HIV: 1) length of life, 2) biological health, 3) cognitive efficiency, 4) mental health, 5) social competence, 6) productivity, 7) personal control, and 8) life satisfaction. For some adults with HIV, these eight factors may be compromised with exhaustion of internal and external resources (e.g., cognitive reserve) over the lifespan which can lead to impairments in cognitive function.

In the article by Vance and colleagues (2011), the eight factors are defined in relation to HIV and aging. Length of life or the number of years one is alive is important for successful aging, and in some adults with HIV, may be reduced by the negative effects of HIV and aging on the immune system (biological health). Cognitive efficiency or the optimal neurological function necessary to carry out day-to-day activities has shown to be compromised even for some adults with HIV taking cART. Mental health or emotional stability may be compromised in some adults with HIV and interfere with their social competence (the ability to engage in social networks) and productivity (the ability to attain their personal goals). Personal control or the ability to have control over oneself and their environment may be compromised especially in some adults with HIV who have difficulty performing their usual activities. When one or more of the eight factors are compromised, it can affect how well one is satisfied with their life (life satisfaction) and their perception of how well they are aging (Vance et al., 2011). In the next section, an explanation of how the three articles in this dissertation relate to one or more of the eight factors of successful aging with HIV is provided.

Article 1: The Neurobiology of HIV and Its Impact on Cognitive Reserve: A Review of Cognitive Interventions for an Aging Population

In Article 1, Cody and Vance (2016) examined the neurobiological effects of HIV on cognitive reserve in relation to the six factors of the successful aging model: length of life, biological health, mental health, cognitive efficiency, productivity, and personal control (See Figure 1). According to Vance and colleagues (2011), the stress of an HIV diagnosis alone can negatively affect one's perception of their life expectancy. For some adults who are diagnosed with HIV at a later age, length of life may be compromised

with the synergistic effects of HIV and aging on the immune function. Early initiation of cART is important for biological health and length of life; however, Cody and Vance (2016) mentioned several barriers (e.g., stigma) to healthcare access and consequences of poor retention to care (e.g., higher incidence of cognitive impairments).

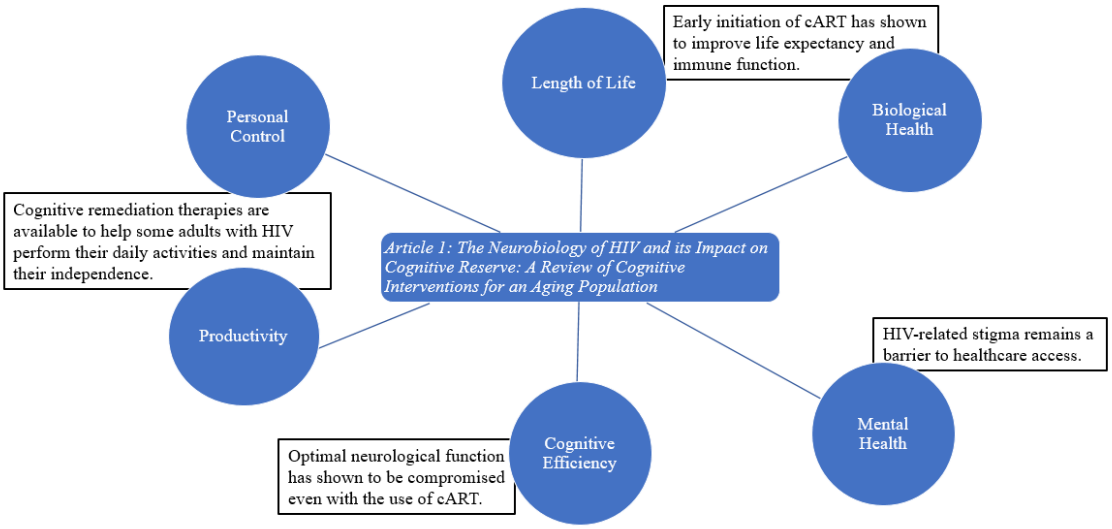

Figure 1. The Relationship Between Article 1 and Successful Aging Model. This figure demonstrates how Article 1 relates to six factors for successful aging with HIV.

In addition, Cody and Vance (2016) identified several threats to cognitive efficiency including substance use and mood disorders; also, we suggested that some lifestyle factors such as good sleep hygiene, regular physical exercise, and management of comorbidities may be neuroprotective against HAND and age-related cognitive impairments. Vance and colleagues (2011) explained that declines in cognitive efficiency in some adults with HIV can interfere with productivity (e.g., working a job) which can be further exacerbated with fear of developing age-related dementia. Fortunately, several cognitive remediation therapies such as speed of processing training and some compensatory strategies (e.g., mnemonics) were recommended by Cody and Vance

(2016) to help some adults with HIV maintain their sense of personal control and independence, both of which are important for successful aging.

Article 2: The Influence of Neurocognitive Functioning on Proactive Coping Behaviors in Adults with HIV

In Article 2, Cody and colleagues (2016) examined proactive coping which is related to six factors of the successful aging model: mental health, cognitive efficiency, social competence, productivity, personal control, and life satisfaction (See Figure 2). Some adults with HIV are vulnerable to damage to the fronto-striatal-thalamo circuitry which can lead to the development of cognitive impairments and even HAND. Frontal areas of the brain are responsible for executive functioning which is important to engage in proactive coping behaviors; therefore, some adults experiencing cognitive impairments may also have difficulty coping with the stress of aging with HIV. In fact, Vance and colleagues (2011) suggested that the extra stress of HIV among older adults can compromise cognitive efficiency which can lead to poor decision-making. As people age with HIV, concerns mount that they will become vulnerable to mental health challenges such as suicidal ideation and loss of personal control which can result in adverse outcomes (e.g., reduced length of life).

Proactive coping, a positive direct approach to challenges (e.g., problem-solving, planning, and goal management) has shown to improve health outcomes for adults in general. In adults aging with HIV, proactive coping is important for biological health as it has shown to slow disease progression (Ironson et al., 2005). In adults aging with HIV, proactive coping may counteract feelings of hopelessness and loneliness commonly associated with retirement, HIV stigma and ageism, and frequent loss of loved ones and

friends (Vance et al., 2011). For some older adults with HIV, social networks may facilitate successful aging by improving mental health and enhancing problem-solving strategies to overcome everyday stressors (Solomon et al., 2014).

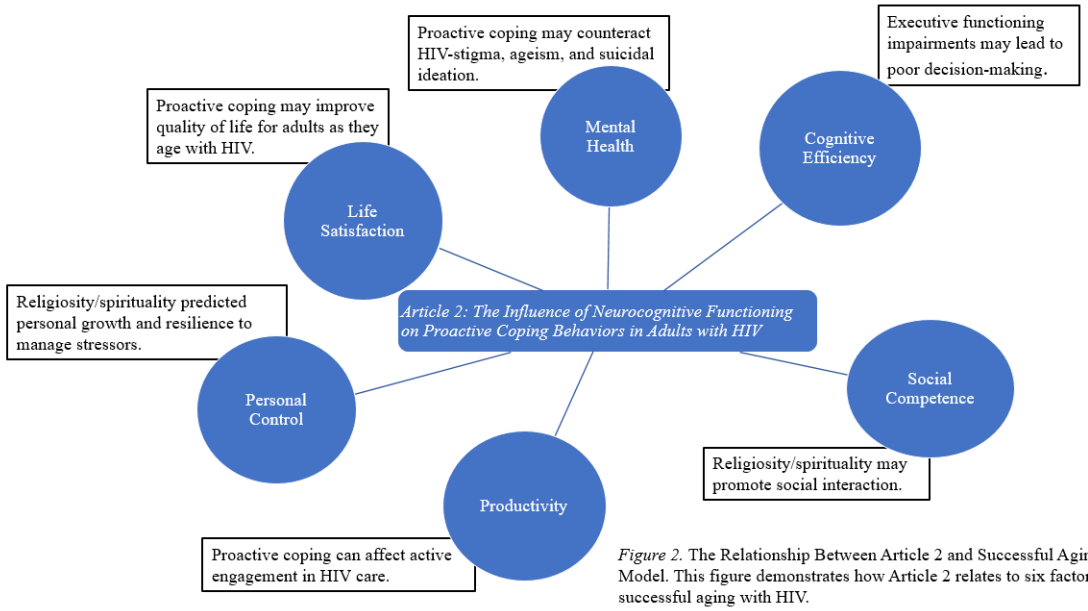

Figure 2. The Relationship Between Article 2 and Successful Aging Model. This figure demonstrates how Article 2 relates to six factors for successful aging with HIV.

As adults age with HIV, hardy characteristics or the ability to endure the detrimental effects of multiple stressors, are important to counteract negative outcomes such as suicidal ideation (Vance, Struzick, & Barrage, 2009). Fortunately, some adults with HIV learn to cope with multiple stressors by adapting a "can do" attitude or hardiness which can help maintain personal control as they age (Vance et al., 2011). Cody and colleagues (2016) examined another source of hardiness, religiosity/spirituality, and found it to be a significant predictor of proactive coping behaviors in adults with HIV. Also, religiosity/spirituality predicted slower disease progression, better medication adherence, better decision-making, personal growth, and resilience to manage multiple stressors (Cody et al., 2016). Given this, loss of social

networks may be a concern for those aging with HIV and negatively affect their personal control, cognitive efficiency, and life satisfaction.

In addition, greater religiosity/spirituality is also associated with fewer depressive symptoms (Lucette et al., 2016). For some adults aging with HIV, church attendance can provide social support and a sense of religious meaning, which can promote positive coping with HIV-related stressors (e.g., stigma); both can maximize physical and cognitive health which are two important components of successful aging (Vance et al., 2011). Some studies suggest that religiosity and spirituality may be related to active engagement in care which is important to length of life and biological health (Pecararo et al., 2015). Certainly, for adults aging with HIV, religiosity/spirituality may promote social interaction and proactive coping behaviors which may positively affect adherence to HIV care; hence, such benefits may improve cognitive reserve in older adults and facilitate successful aging.

Article 3: The Effects of Speed of Processing Training and Transcranial Direct Current Stimulation on Global Sleep Quality and Speed of Processing in Older Adults with and without HIV

In Article 3, sleep quality was found to be worse among older adults with HIV compared to older adults without HIV which relates to five factors of the successful aging model: biological health, mental health, cognitive efficiency, personal control, and life satisfaction (See Figure 3). In relation to biological health, poor sleep quality can weaken the blood brain barrier which allows more toxic substances to enter the brain and produce neuroinflammation thus leading to poor cognitive functioning (Cody & Vance, 2016; Gamaldo et al., 2013b). Some studies suggest that higher levels of depression may been

associated with poor sleep quality which can compromise cognitive efficiency (Gamaldo et al. 2013b; Vance, Heaton, Eaves, & Fazeli, 2011). The high incidence of depression among older adults and those with HIV may further compromise sleep quality in adults as they age with HIV; over time, poor sleep quality can negatively influence quality of life.

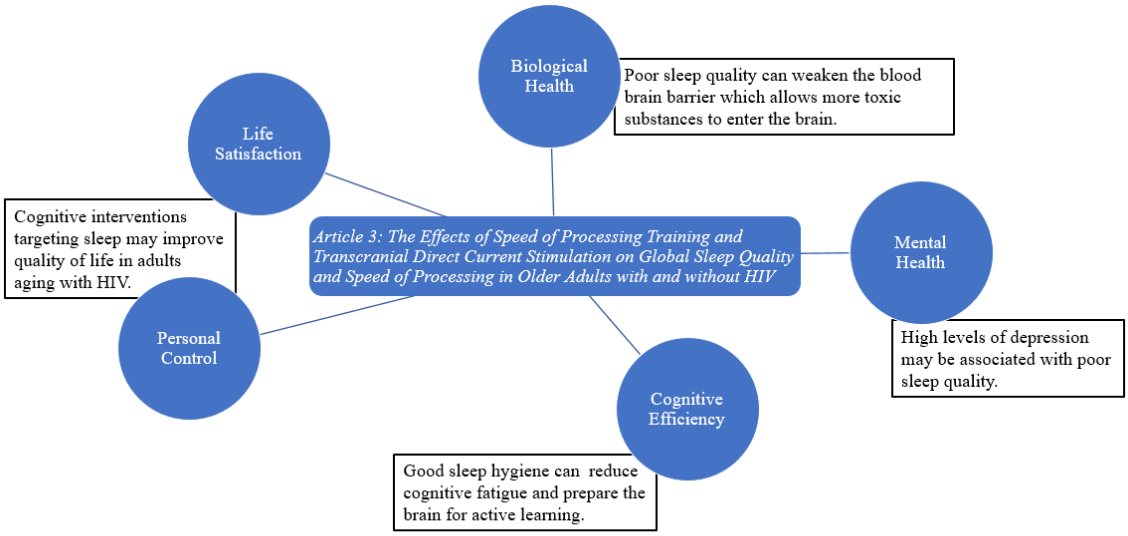

Figure 3. The Relationship Between Article 3 and Successful Aging Model. This figure demonstrates how Article 3 relates to five factors for successful aging with HIV.

Additionally, Article 3 examined the bidirectional relationship between sleep and cognitive function. Possibly, good sleep hygiene can reduce cognitive fatigue and prepare the brain for active learning which can improve cognitive efficiency. Also, cognitive stimulation may increase the body's demand for restorative sleep. In older adults with HIV who may be susceptible to poor sleep quality, it was hypothesized that transcranial direct current stimulation and speed of processing training may improve sleep and global speed of processing. Findings in Article 3 revealed no significant differences in sleep quality between older adults who received tDCS and speed of processing training compared to those who received sham tDCS and speed of processing training. Cognitive

interventions targeting sleep and other predictors of cognitive function may be beneficial in adults aging with HIV, especially with the threat of underlying biological mechanisms such as immune dysfunction, age-related neuroinflammation, and age-related cognitive disease.

Implications for Research

There are some implications for clinical research that are guided by the model of successful aging. There are many definitions of cognitive frailty throughout literature on aging. Frailty, characterized by decreased functional capacity and reduced ability to perform basic activities of daily living, represents a precursor to complications in the aging HIV population (Xue, 2011). With aging, many adults with HIV are vulnerable to adverse outcomes of cognitive frailty phenotypes such as moderate to severe forms of HAND, which can increase physical dependence and prevent successful aging. Wallace and colleagues (2016) examined 103 adults with HIV age 50 and older and found that those classified as being "successful cognitive agers" had fewer HIV-associated conditions, had a lower frailty index, and were less likely to have hypertension. As adults live longer with HIV, their frailty risk may vary depending on several factors including chronic systemic inflammation, lifestyle factors, comorbidities, and long-term use of cART (Willig, Overton, & Saag, 2017). Future research should focus on reducing manifestations of cognitive frailty in adults as they age with HIV which may facilitate successful aging and reduce the incidence of HAND.

In addition, the role of childhood educational quality has shown to influence cognitive function in older adults. In a study of 433 older adults (52% African American), Crowe and colleagues (2013) examined the relationship between educational quality and

cognitive function. These researchers found that higher student-teacher ratio was associated with poorer cognitive function whereas greater school year length was associated with better cognitive function in older Caucasians and African Americans over a period of 4 years. Future research related to cognitive aging in adults with HIV should examine childhood educational quality as a factor rather than years of education alone. Perhaps, differences in childhood school curriculum, college programs of study, and community service activities should also be examined as potential influences on successful aging in adults with HIV.

Implications for Clinical Practice

Implications for clinical practice includes the use of multimodal interventions to target lifestyle factors that affect cognition in adults with HIV. In a recent study of four focus groups of adults with HIV age 50 and older, Vance and colleagues (in press) examined their perceptions of their cognitive health and how it impacts their everyday functioning. In all four focus groups, participants expressed typical cognitive complaints such as misplacing items and/or forgetting appointments. Also, the majority of the participants lacked knowledge regarding how lifestyle factors (i.e., physical activity, mental activity, nutrition, social engagement, sleep hygiene, and substance use) impact cognitive health (Vance et al., in press). Building on this, Vance and colleagues (2017) described and presented a multi-modal intervention called cognitive prescriptions to the same four focus groups and asked what they liked and did not like about it. Overall, participants felt the approach was simple and they liked the idea of working with a healthcare worker to set lifestyle and behavior goals tailored to their specific needs. In the clinic setting, nurses are in a unique position to assess for knowledge deficits related to

cognitive health and implement cognitive prescriptions. Perhaps, educating older adults about cognitive health and how it relates to modifiable lifestyle factors may facilitate behavioral changes that promote successful cognitive aging. Also, in adults with HIV, multimodal cognitive interventions that involve personal goal-setting can provide a sense of personal control and autonomy which are important for successful aging.

CONCLUSION

The longer life expectancy of adults with HIV poses many challenges in that the neurobiological effects of HIV may be exacerbated by the aging process in addition to other lifestyle factors. Given that by 2020 70% of people living with HIV in the United States will be 50 years of age and older (U.S. Senate Special Committee on Aging, 2013), concerns mount that the synergistic effects of HIV and aging may be more taxing on cognitive and everyday function. Some adults with HIV may have greater cognitive reserve to overcome adversities associated with aging, whereas others may have lower cognitive reserve and thus become more susceptible to developing age-related cognitive disorders and HAND. While several mechanisms have been proposed to explain cognitive variation among older adults with HIV, a multimodal approach to address physical, cognitive, and psychosocial factors is essential to promote optimal cognitive health and successful aging.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on November 8, 2021. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator:	CODY, SHAMEKA L
Co-Investigator(s):	
Protocol Number:	**X160509003**
Protocol Title:	*The Effects of Transcranial Direct Current Stimulation and Speed of Processing Training on Sleep and Global Speed of Processing in older Adults with and without HIV*

The IRB reviewed and approved the above named project on_____. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 6/13/17

Date IRB Approval Issued: 6/13/17

IRB Approval No Longer Valid On: 6/13/18

HIPAA Waiver Approved?: Yes

Partial HIPAA Waiver Approved?: No

Marguerite Kinney

Expedited Reviewer
Member - Institutional Review Board
for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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