2019

Vagal Mediated Heart Rate Variability And Cognitive Impairments In Hiv-Seropositive Women

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VAGAL MEDIATED HEART RATE VARIABILITY AND COGNITIVE IMPAIRMENTS IN HIV-SEROPOSITIVE WOMEN

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2019

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ABSTRACT

Regardless of sufficient viral suppression, HIV exerts an ongoing inflammatory process that promotes chronic autonomic nervous system (ANS) dysfunction, accelerates physiological aging, and increases the risk of developing a spectrum of cognitive disorders (known as HIV-associated neurocognitive disorders [HAND]). Given this, identifying pathological mediators of this inflammatory response could provide insight into the mechanisms driving HAND. The vagus nerve (indexed by vagal-mediated heart rate variability [vmHRV]) could provide such a mediator as it regulates ANS activity via reciprocal cardio-neural pathways, which regulate inflammation and homeostasis. Vagal dysfunction is associated with persistent inflammatory signaling (e.g., stress or inflammatory-based disorders [such as HIV]), emotional dysregulation, and cognitive impairments. Chronically reduced vmHRV indices are observed in HIV-seropositive (SP) persons; however, cognitive studies examining vagal-HIV associations are lacking.

In this dissertation, three articles were presented which focused on the vagal-HIV relationship to cognitive impairments. Article 1, a review of literature published in the journal of *Neuropsychiatric Disease and Treatment*, focused on vagal-mediated inflammatory processes relative to shared cognitive-behavioral symptomology (i.e., "sickness behavior") in HIV infection and depression alike. This article identified vagal-HIV associations by utilizing a firmly established inflammatory-based disorder that primarily affects cognitive function (i.e., depression). It concluded with an appeal to

conduct cognitive research in HIV utilizing vagal-mediated measures, which leads to Article 2. Article 2, submitted to the *Journal of Affective Disorders*, examined the concept of self-regulation in HAND. This article operationalizes self-regulation (emotional and cognitive domains) as an interrelated, adaptive, vagal-mediated process (i.e., cardio-neural continuum between cortical and sub-cortical systems) influenced by inflammatory activity. While unexplored in HIV literature, self-regulatory function (indexed by vmHRV) provides an indicator of cognitive impairment that is sensitive to emotional stressors (e.g., early mal-adaptive experiences) that are known to predispose HIV-SP persons (particularly women) to worse outcomes. Therefore, using vmHRV as a measure of ANS activity, Article 3 examined HIV's effect on cognitive function in HIV-SP women. Article 3 was the primary research study for this dissertation, which integrates assumed inflammatory effects of HIV and compounding stressors on vagal-mediated measures relative to cognitive function. From this, earlier detection and interventions for cognitive impairments could result.

Keywords: HIV, RSA, women, cognitive functioning, inflammation

DEDICATION

I would like to dedicate this dissertation to my loving wife, Kristin, who is my constant. She has demonstrated unfettered support and patience throughout this process. I can't thank her enough for suspending her career goals, so that I might be able to achieve one of mine. Additionally, if not for the support of my father (Mel), sister (Kristin), brother (Chase), and brother-in-law (Michael), I would have never had the opportunity to pursue my goal of obtaining a PhD.

ACKNOWLEDGMENTS

First and foremost, I want to thank my mentor and committee chair, Dr. David Vance. Without his guidance, intellect, expertise, commitment, and endurance throughout this process, I certainly would not be in this position. His undeterred trust and willingness to immerse with me in this process, despite many challenges in developing my program of research and my general disposition, inoculated my confidence and augmented the passion I have for research. I truly cherish both the tangible and intangible effects he has had on helping shape the type of person I aspire to be. I also want to thank Drs. Shacka, Fazeli-Wheeler, Kempf, Moneyham, and Clay for serving on my dissertation committee. Each willingly stepped up to provide their expertise, support, advice, and time without any hesitation. Their contributions helped both diversify and humble how I approach research and science. I truly am undeserving of such a remarkable committee and only hope I can somehow return this gesture in some way. A special thanks to the Women's Interagency HIV Study Chicago cohort and, in particular, Kathleen Weber for helping me gain access to this amazing cohort and dissertation data. Also, I thank my colleagues at the University of Alabama at Birmingham School of Nursing. The school of nursing gave me a home and set a standard for what every university should aspire to be. I can't imagine being here without it or the people representing it. In particular, Drs. Doreen Harper, Karen Heaton, Rita Jablonski, Karmie Johnson, Yasmin Turkman, Bryan Combs, and Norman Keltner along with Ms Simone Durand. Each of them, even without their knowledge, have been instrumental in shaping this journey and I appreciate their support in me.

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ABBREVIATIONS

α7	alpha-7 nicotinic receptor
AIC	Akaike Information Criterion
ANS	Autonomic Nervous System
β	standardized beta coefficient
BDNF	brain derived neurotropic factor
BMI	body-mass index
cART	combination antiretroviral therapy
CAP	cholinergic anti-inflammatory pathway
CD4+	cluster of differentiation 4
CD8+	cluster of differentiation 4
CDC	Center for Disease and Control
CES-D	Center for Epidemiologic Studies-Depression Questionnaire
CNS	central nervous system
CRP	C-reactive protein
CVD	Cardiovascular Disease
EF	executive function
ELISA	enzyme-linked immunosorbent assay
HAND	HIV-associated neurocognitive disorder
HCV	Hepatitis C Virus
HF	high-frequency
HIV	Human Immunodeficiency Syndrome
HIV-SN	HIV-seronegative

HIV-SP	HIV-seropositive
HVLT	Hopkins Verbal Learning Test
HPA	hypothalamus-pituitary-adrenal
vmHRV	vagal-mediated heart rate variability
IL	interleukin
iVNS	implantable vagus nerve stimulation
M	mean
MCI	mild cognitive impairment
MDN	median
RSA	respiratory sinus arrhythmia
PCL-C	PTSD Checklist-Civilian
p	statistical significance
PTSD	Posttraumatic Stress Disorder
PSS	Perceived Stress Scale
SD	standard deviation
SDMT	Symbol Digit Modalities Test
T cell	type of lymphocyte
TNF-α	tumor necrotic factor-alpha
WAIS IV	Wechsler Adult Intelligence Scale IV
WIHS	Women's Interagency HIV Study
WRAT	Wide Range of Abilities Test-Recognition Subtest
VN	vagus nerve
tVNS	(transauricular) vagus nerve stimulation

INTRODUCTION

BACKGROUND AND SIGNIFICANCE

As of 2016, it is estimated that 17.8 million women worldwide are living with HIV and represent 51% of all HIV-seropositive (SP) adults. In the United States (U.S.) alone, HIV-SP women constitute 23% of all persons living with HIV (Center for Disease Control, 2016). Advancements in antiretroviral therapy have increased life expectancy in HIV, thereby increasing the number of people aging with the disease. In fact, by the year 2020, approximately 75% of those living with HIV in the U.S. will be 50 years and older (United States Senate Special Committee on Aging, 2013). Unfortunately, aging with HIV has also resulted in a disproportionate number of persons developing cognitive disorders compared to HIV-seronegative (SN). Alarmingly, 30-60% of adults in this population experience a spectrum of cognitive disorders known as HIV-associated neurocognitive disorders (HAND) (Grant, 2008). Deficits in executive function, memory (working and learning), verbal fluency, speed of processing, and psychomotor speed characterize the cognitive impairments observed in HAND (Heaton et al., 2011).

Despite women representing the majority of adults living with HIV worldwide and the increasing number of women aging with HIV, most studies examining cognitive disorders in this population have focused on men. The lack of research focused on women is particularly germane as they could be more vulnerable to HIV-associated cognitive impairments in comparison to HIV-SP men (particularly as they age) (Maki & Martin-Thormeyer, 2009). HIV-cognitive impairments can interfere with occupational performance, social function, ability to multi-task, self-management of medications/treatment as well as increases in depressive symptoms and poor emotional

processing (Blackstone et al., 2012; Ettenhofer et al., 2010; Slater et al., 2013; Vance, Humphrey, Nicholson, & Jablonski-Jaudon, 2014). As such, early identification of cognitive impairments is critical to improve the quality of life burdens often imposed on this population.

The increased risk for cognitive impairments in HIV-SP women is poorly understood. However, increasing evidence suggests distinct autonomic nervous system (ANS) reactivity to HIV's infectious process and other inflammatory-based stressors (e.g., substance use, medical/psychiatric comorbidities, psychosocial, mal-adaptive early life experiences) is a potential mechanism underlying cognitive risks in women (Hong & Banks, 2015). While HIV studies are lacking in women, one potential mediator of this ANS reactivity is the vagus nerve due to its central role in regulating immune responses and possessing sex-specific differences in physiological activity throughout the lifespan.

Respiratory sinus arrhythmia (RSA) is an index of vagal function. RSA represents reciprocal neural connections to the sinoatrial node of the heart and provides a valid index of vagal-parasympathetic activity (Berntson, Cacioppo, & Grossman, 2007; Porges, 2009). Greater vagal-parasympathetic activity reflects homeostatic ANS activity along with adaptive cognitive and immune function. Greater baseline RSA or vagal-mediated heart rate variability (vmHRV) is suggested to provide a protective mechanism against inflammatory or stress-based disorders (e.g., cardiovascular, metabolic, cognitive), which confers to increased resiliency against stressors and better cognitive performance (Guiliano, Gatzke-Kopp, Roos, & Skowron, 2017; Park, Vasey, Van Bavel, & Thayer, 2013; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). Contrarily, chronically reduced vmHRV is associated with unregulated inflammatory states and ongoing infectious

processes (Huston & Tracy, 2011). Reduced vmHRV is predictive of all-cause mortality and poorer disease outcomes in adults. Interestingly, as women age, they demonstrate a more pronounced loss of vagal tone (as reflected by decreased vmHRV) when compared to their male counterparts (Heilman et al., 2013; Koenig & Thayer, 2016); therefore, reduced vagal-function could help explain their increased risk for cognitive impairments over time. Given the lack of cognitive research in this area, this dissertation will focus on examining vagal-HIV associations relative to cognitive impairment in women.

Vagus Nerve and Autonomic Nervous System Function

ANS regulation is under putative control of the parasympathetic nervous system (more specifically, the vagus nerve). Regulation occurs via an intrinsic vagal cardio-neural network that communicates physiological demands (e.g., slower breathing, heart-rate slowing, release of anti-inflammatory cytokines) from the sinoatrial node of the heart to cortical and subcortical brain regions in response to a stimulus (e.g., pro-inflammatory signals). This cardio-neural regulation is critical for healthy physiological adaptations and reversing inflammatory states. The vagus nerve's primary function is to maintain ANS homeostasis by engaging or withdrawing its function when an acute stress stimulus is presented, thereby allowing the sympathetic nervous system to mobilize when triggered by a stressor. After adaptation to or neutralization of a stress-stimulus, vagal activity increases (functioning as a braking mechanism for sympathetic arousal) and physiologically assists a return to metabolically conservative states (Thayer et al., 2012).

Greater tonic vagal-activity, indexed by increased vmHRV, is associated with increased functional and regulatory capacity in both emotional and cognitive domains

(sometimes referred to as self-regulation). Optimal vagal-activity is associated with better physical health, medical outcomes, and resilience, which contributes to the preservation of cognitive reserve over the lifespan (Beuchaine & Thayer, 2015; Thayer & Lane, 2012). Contrarily, chronic reductions in vagal-activity are associated with dysautonomia via unregulated stress signaling and sympathetic dominance. Dysautonomia is strongly associated with a person or populations inflammatory status. In fact, the degree of inflammation inversely relates to vagal activity and is suggested to explain the greatest amount of variance in the context of reduced vmHRV indices across populations. In support of this, increased inflammatory markers (e.g., monocytes, Tumor Necrotic Factor (TNF)-α, C-reactive protein [CRP], interleukin [IL]-6) have been directly associated with reduced vmHRV, emotional dysregulation, and cognitive impairments (Sajadieh et al., 2004; Schram et al., 2007; Trollor et al., 2012).

A recent vmHRV meta-analysis of studies conducted in the combination antiretroviral (cART) era, provides strong support for ongoing dysautonomia in HIV (McIntosh, 2016). From the eight studies identified, 292 HIV-SP adults (M_{age} = 38.7) and 201 HIV-SN adults (M_{age} = 35.1) were included in the analysis. The study found reduced resting vmHRV revealed a chronic pattern of sympathetic dominance in HIV-SP participants. These findings support previous studies (which were not included in the meta-analysis), which demonstrated similar reduced vagal profiles in persons with HIV (Askgaard et al., 2011; Becker et al., 1997; Lebech et al., 2007). Despite growing evidence recognizing differences in ANS reactivity between sexes (Kershaw et al., 2016; Thayer & Fisher, 2009), the majority of HIV-vmHRV studies have been conducted in men; furthermore, of the few conducted in mixed samples, researchers did not

specifically look at sex differences in vmHRV activity. As such, more HIV research is needed to elucidate distinct ANS differences between men and women to better understand cardio-neural pathology and its contributions to cognitive function.

Vagus Nerve, Cognitive Function, and HIV-SP Women

Consistent with the notion of chronic dysautonomia, viral neuroinflammatory properties accelerate the aging process such that those with HIV may exhibit age-related neurocognitive changes earlier than their non-clinical counterparts (Ding et al., 2017; Tierney et al., 2017). Importantly, HIV-SP women experience age-associated increases in monocyte production at a much higher rate compared to HIV-SP men despite expressing higher CD4+ counts and decreased viremic levels. Martin and colleagues (2013) demonstrated increases in monocyte production in both HIV-SP and HIV-SN women; however, after adjusting for age, HIV-SP women exhibited increased monocyte profiles equivalent to HIV-SN women that were aged 10-14 years older. This robust immune response in the context of HIV worsens as women age and increases the risk for cognitive disorders (Mathad et al., 2016). A recent study by Rubin and colleagues (2018) found IL-6 markers and CRP variability predicted performance in executive function, attention/working memory, and psychomotor speed domains. These findings support previous HIV-SP women studies demonstrating associations between elevated pro-inflammatory profiles (e.g., monocytes and cytokines) and impaired performance in multiple cognitive domains (e.g., verbal and learning memory, working memory) (Imp et al., 2017; Rubin et al., 2017).

In the only RSA study specific to HIV-SP women, Heilman and colleagues (2013) found reduced RSA profiles in those with HIV when compared to HIV-SN women. There were no significant associations found between RSA and the HIV-stratum (e.g., viral load, CD4+, and chronicity of HIV). Though limited, these findings suggest that RSA reductions could be caused by inflammatory profiles (e.g., TNF-α, CRP, IL-6) driven by the effects of HIV and compounded by other genetic, environmental, and physical conditions (rather than mere viral presence as reflected by the HIV-stratum) known to acutely or chronically increase inflammatory profiles. In other words, HIV likely augments vagal dysfunction via an unregulated inflammatory process (even in the presence of cART) that results in dysautonomia. However, instead of HIV being an independent mediator of dysautonomia, HIV's strong and synergistic associations (particularly in Black minorities) to lower socioeconomic status, increased medical comorbidities, psychiatric disorders, psychosocial issues, and genetic/environmental predispositions to systemic disease likely explains the RSA reductions observed by Heilman and colleagues (Green et al., 2016; Keary, Hughes, & Palmieri, 2009; Meyer et al., 2016). These factors undoubtedly compound the vagal-inflammatory burden observed in persons with HIV and, ultimately, contribute to impaired cognition over time.

In support of compounding vagal dysfunction, chronic emotional disorders are well established as predictors of earlier onset cognitive impairments (and later dementia) and reduced cognitive reserve (Ismail, Gatchel, Batement, & Barcelos-Ferreira, 2018). Moreover, emotional dysregulation is among the strongest predictors of vmHRV (Beauchaine & Thayer, 2015). Likewise, emotional dysregulation (prolonged vagal recovery) is consistently associated with increased basal IL-6 and CRP. Notably, women

demonstrate a heightened pattern of emotional reactivity and CRP variability relative to both acute and chronic stress exposures (Sin, Graham-Engeland, Ong, & Almeida, 2015). In two similar studies involving the Women's Interagency HIV Study (WIHS) cohort, Rubin and colleagues (2015) found significant interactions between HIV and increased stress that corresponded to deficits in verbal memory; likewise, in a separate study, increased stress was associated with worse performance in psychomotor speed along with verbal memory and learning domains. The researchers concluded increased vulnerability to cognitive impairments in HIV-SP women was likely the result of chronic stress exposure and/or early life trauma (Rubin et al., 2016).

Slopen and colleagues (2010) suggest early life adversity, traumatic stressors, and chronic emotional dysregulation are predictive of increased inflammatory profiles and reduced vmHRV at midlife for Blacks, but not Caucasians. These researchers suggested that early and prolonged stress exposures could accelerate the aging profile faster in Blacks. Given that a majority of Black women are represented in HIV and WIHS studies, consideration of co-inflammatory burden is critical for predicting the expected contributions of vagal dysregulation to differences in cognitive performance between HIV and HIV-SN groups.

Theoretical Framework

The Polyvagal Perspective (Porges, 1995, 2007) and Neurovisceral Integration Model (Thayer & Lane, 2000, 2009) provide an organized framework for understanding the reciprocal cardio-neural pathways that underlie cognitive and emotional systems via adaptive ANS function. Conceptually, RSA indexes the vagus nerve's broad adaptive

ability to respond flexibly to dynamic emotional, behavioral, social, and cognitive demands in response to environmental stimuli (Bernston et al., 2008; Miyake & Friedman, 2012). Adaptive vagal activity results from an interaction between neural, physiological, and genetic systems (known collectively as the central autonomic network) that originates within multiple prefrontal cortices (e.g., medial prefrontal, orbitofrontal, dorsolateral, anterior cingulate) and bi-directionally coordinates with multiple subcortical systems (e.g., striatum, amygdala, insula, hippocampus, among others). The cortical/subcortical coordination influences oscillatory output of cardiorespiratory centers via brainstem networks (e.g., nucleus tractus solitarius, dorsal motor nucleus of the vagus nerve, medulla, among others). The central autonomic network is an integrated system (operating on variable time-scales) and provides the substrate for coordinating vagal ANS activity, which produces the phenomenon of RSA and/or vmHRV.

Overall Purpose

The primary purpose of this dissertation was to examine HIV's effect on vagal function in the context of cognitive impairments. Specifically, the dissertation features three articles: one focusing on the contributions of vagal-mediated inflammatory processes to the cognitive-behavioral and physical symptomology shared by HIV and depression alike; a second focusing on combining emotional and executive function into a vagal-mediated concept (i.e., self-regulation as measured by RSA) to account for the influence of early, inflammatory-based stressors on risk for HIV-cognitive impairments; and a third focusing on integrating the inflammatory effects of HIV and emotional

stressors on vagal-mediated measures and cognitive function in HIV-SP women. The next section includes a detailed description of each article.

Synthesis of Articles

Three articles surrounding the theme of vagal function in the context of HIV-associated cognitive impairments were presented to examine this relationship. The articles focused on the manifestation of cognitive impairments as being a function of compounding inflammatory stressors (e.g., comorbidities, emotional disorders) that exert a pathological influence on the ANS of adults (in particular women) with HIV. The three articles will be synthesized in the following section.

Article 1: The Potential Role of Vagus Nerve Stimulation in the Treatment of on HIV-related Depression: A Review of Literature

The first article was a comprehensive review of literature focusing on the contributions of vagal-mediated inflammatory processes to the cognitive-behavioral and physical symptomology shared by HIV and depression disorders alike. In both disorders, dysautonomia results from dysregulatory neuroendocrine and neuroimmunological systems producing a chronic cascade of pro-inflammatory events resulting in attenuation of parasympathetic tone (reduced RSA), psychomotor slowing, depression, alterations in mood, anhedonia, fatigue, apathy, cognitive disorders, poor sleep, and social withdrawal. This cluster of symptoms is referred to as “sickness behavior” and is mediated by reciprocal cardio-neural pathways of the vagus nerve. Chronic vagal disruption results from increases in pro-inflammatory cytokines (e.g., IL-6, CRP, TNF-α) in response to

compounding and unregulated stressors, which leads to alterations in homeostasis via constant activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathomedullary system. Aside from increasing medical comorbidities and mortality in both HIV and depression, disrupted vagal-mediation of cytokine production interferes with neurogenesis, neuroplasticity, and maintenance of normal cognitive function. In this context, HIV and depression are pathologically related via their effect on the vagus nerve and resulting cognitive impairments. Unfortunately, HIV and vagus nerve studies are lacking in the context of cognitive function. As such, the article closed by suggesting novel interventions targeting the vagus nerve and an identified need to conduct cognitive research in HIV utilizing vagal-mediated measures (such as RSA). Article 1 was accepted for publication in the journal of *Neuropsychiatric Disease and Treatment*.

Article 2: HIV, Aging, and Cognitive Impairment: Can Heart Rate Variability Be Used as a Pre-Symptomatic Marker for Neurocognitive Disorders?

The second article examined vagal-mediated RSA as a potential clinical marker for prodromal HAND. Utilizing the concept of self-regulation, emotional and executive function are operationalized as an adaptive interaction of vagal-mediated processes. Self-regulation represents the functional capacity of both executive (i.e., cognitive flexibility, working memory, inhibition; extending to decision-making, verbal learning, psychomotor and processing speed) and emotional domains to effectively interpret, predict, and respond to incoming information to facilitate goal-directed behavior. RSA provides a measure of adaptive self-regulation in dynamic environments (e.g., social settings) by corresponding to frontostriatal modulations of ANS, limbic, and brainstem activity that

occur via reciprocal cardio-neural pathways (collectively referred to as the central autonomic network) of the vagus nerve. Chronically reduced RSA is associated with self-dysregulation (impaired executive and emotional function) and occurs in response to inflammatory processes. Interestingly, in the post-cART era, HIV-cognitive impairments have shifted predominately towards executive and memory domains, thereby potentiating alterations in self-regulation and positioning RSA as a possible measure for HAND.

While unexplored in the HIV literature, self-regulation provides a more comprehensive indicator of cognitive impairment due to its inclusion and sensitivity to emotional stressors (e.g., early mal-adaptive experiences, trauma-based disorders, psychosocial issues) that are known to predispose persons with HIV (particularly women) to poorer medical and cognitive outcomes. Article 2 was submitted for publication to the *Journal of Affective Disorders* and pending review.

Article 3: Exploratory Examination of Respiratory Sinus Arrhythmia and Cognitive Function in Women Living with HIV

Article 3 featured the primary research project for this dissertation and consisted of a secondary data analysis from the WIHS Chicago cohort. In a predominately Black sample, this article focused on exploring whether or not RSA was associated with cognitive function differences in a sample of HIV-seropositive and HIV-seronegative women. There are currently no HIV studies that have examined RSA in the cognitive context, which suggests research is needed in this area.

Many studies acknowledge sex and ethnic physiological differences exist, which contribute to variation in disease (e.g., cardiovascular) and disorder (e.g., cognitive)

outcomes. Disparities in cardiovascular disease (CVD) prevalence, morbidity, and mortality account for a substantial portion of observed differences in life expectancy between Black and Caucasians (Kochanek, Arias, & Anderson, 2013). Furthermore, one of the most consistent findings in cardiovascular research is the alarming prevalence of hypertension in Blacks relative to other racial groups (Ogedegbe et al., 2012). Reduced vmHRV is strongly associated to both CVD and related risk factors, including substance use, obesity, depression, anxiety, metabolic disorders (particularly increased lipids and insulin resistance), and age, among others (Thayer, Yamamoto, & Brosschot, 2010). Reduced vmHRV is suggested to predict the onset of hypertension, as well as increased CVD risk and all-cause mortality (Thayer & Lane, 2007). Importantly, these CVD risk factors are also strongly associated with cognitive impairments via independent and comorbid contributions to dysautonomia. Given the disproportionate cardiovascular and inflammatory burden inherent in both Black persons and women alike, it seems plausible that Black women would demonstrate reduced resting vmHRV profiles relative to their racial and sex-specific counterparts. Interestingly, Black women generally demonstrate greater resting vmHRV profiles until approximately midlife.

Hill and colleagues (2015) conducted a meta-analysis of 17 studies reporting gender differences in resting vmHRV between Caucasian and Black persons. Greater resting vmHRV was observed in Black women relative to Caucasian women. This effect remained robust in both clinical and non-clinical samples after adjusting for moderating factors. Likewise, Fuller-Rowell, Williams, and Ryff (2013) analyzed a national dataset with 204 Black and 833 Caucasian persons before and after controlling for socioeconomic status. No differences were found in resting vmHRV profiles between

groups. However, after exposing both groups to a cognitive stressor, Black persons showed marked vagal reactivity by demonstrating pronounced and prolonged reductions of vmHRV with age as compared to Caucasians. While reduced vmHRV occurs normally with aging, the observed reductions were considerably steeper among Black persons and suggestive of faster rates of ANS decline in this group. These results suggest, in the absence of stressors, Black persons generally demonstrate greater or equal resting vmHRV profiles relative to Caucasians; however, in the presence of stress, they demonstrate an exaggerated reduction in vmHRV profiles. Interestingly, these findings are consistent with previous studies demonstrating disproportionate vmHRV reductions in Black persons in the context of acute and chronic stress exposures/conditions (particularly those traumatic in nature such as discrimination, stigma, environment, abuse, etc.) (Neblett & Roberts, 2013; Wagner, Lampert, Tenen, & Feinn, 2015).

Pathological vmHRV reductions in response to stressors may be particularly germane to Black persons, as they constitute approximately 65-70% of women with HIV (CDC, 2016). They are at a greater risk for poverty, less educated, more likely to abuse substances, have poorer psychiatric (e.g., depression, emotional disorders) and psychosocial health, increased exposure to trauma and early life stressors, and greater genetic/environmental predispositions to systemic inflammatory conditions (e.g., HCV, cardiovascular disease, and metabolic disorders). Studies suggest these variables independently and collectively compound, promote, and reinforce systemic stress (as evidenced by reduced RSA and increased inflammatory profiles), which predisposes Black women with HIV to vagal dysfunction. For example, lower socioeconomic status is strongly associated with increased exposure to traumatic events thereby increasing rates

of developing psychiatric and medical comorbidities. In fact, comorbid post-traumatic stress disorder (PTSD) occurs in approximately 30% of HIV-SP women (which is five times higher than non-HIV populations). By prematurely and chronically disrupting ANS tone, early life adversity or traumatic stressors are suggested to be predictive of increased inflammatory profiles and reduced RSA at midlife for Blacks, but not Caucasians. Importantly, this effect remains after controlling for health behaviors, BMI, and depressive symptomology, which supports early and prolonged stress exposures significantly accelerates the aging profile in Blacks relative to Caucasians (Green et al., 2016; Keary, Hughes, & Palmieri, 2009; Meyer et al., 2016; Slopen et al., 2010).

McIntosh, Tartar, Wimayer, and Rosselli (2015) found HIV-SP women showed an attentional bias to negative stimuli and patterns of emotional dysregulation. Importantly, these effects remained after adjusting for apathy, anxiety, and depression. Heilman and colleagues (2013) examined the effect of HIV on both visceromotor (RSA) and somatomotor (affect recognition). The sample compared 61 HIV-SP women (51 of which were Black; M_{age} = 42) to 22 HIV-SN women. Reduced RSA and poorer performance on somatomotor tasks were found in the HIV group versus control. Moreover, CD4+ counts negatively correlated with their ability to accurately detect certain emotions (inability to distinguish threatening from neutral threats). Several studies in women support the reduction of neurocognitive resources during higher ordered cognitive and emotional tasks in the context of chronic stressors and HIV chronicity (Neigh, Michopoulos, Ofotokun, & Jovanovic, 2017; Tartar et al., 2014). The lack of discriminatory or adequate cognitive-emotional responses suggests a chronic sympathetic

disposition in HIV-SP adults and positions the vagus nerve as being a primary target for HIV and co-inflammatory pathology alike.

RSA or vmHRV is purportedly a stable, trait-like measure that reflects individual physiological differences in their capacity to navigate contextual challenges and demands in the environment. Optimal RSA profiles correspond to better regulatory capacities (e.g., emotion and cognitive) that confer ANS resilience to inflammatory processes (Beauchaine & Thayer, 2015; Williams et al., 2015). However, given HIV disproportionately affects Black women that possess an increased predisposition to co-inflammatory vagal burdens, this HIV-cohort likely exhibits chronically reduced RSA profiles and are at an increased risk for earlier-onset cognitive impairments compared to HIV-SN women. Thus, Article 3 featured the first study to examine vagus function (indexed by RSA) in the context of cognitive function in HIV-SP women. The study was conducted to answer the following research aims:

- AIM 1: Examine the relationship between RSA and global cognitive function and specific cognitive domains (i.e., executive function, attention, speed of processing, fine motor, verbal fluency, verbal recall, and memory) in HIV-SP compared with HIV-SN women.
    - Research Question 1a: Do HIV-SP women with reduced RSA indexes perform worse on global measures of cognitive function?
    - Hypothesis 1a: Adult women with HIV will not exhibit reduced RSA indexes and lower global cognitive scores compared to HIV-SN women

- Research Question 1b: Do HIV-SP women with reduced RSA indexes perform worse on measures of executive function, attention, psychomotor speed, fine motor, verbal fluency, verbal recall, and memory?
- Hypothesis 1b: Adult women with HIV will exhibit reduced RSA indexes and demonstrate poorer performance in select executive, psychomotor, and fine motor domains compared to HIV-SN women.

- AIM 2: Explore the interaction between HIV status and RSA indexes on significant global and specific cognitive domains in HIV-SP women.
  - Research Question 2: Does HIV serostatus account for suppressed RSA indexes and significant specific and/or global cognitive impairments?
  - Hypothesis 2: RSA will interact with HIV serostatus in adult women to influence performance in specific cognitive domains.

In summary, Article 3 presented a cross-sectional, descriptive study utilizing 18 months of secondary data from the Chicago WIHS site (collected between October 2014 and July 2017). A sample of 144 women (100 HIV-SP, 44 HIV-SN) aged 32-72 years consented to participate in the parent study. WIHS core study visits occur every six months and include medical examinations, lab work (e.g., HIV status, hepatitis C [HCV]), surveys (e.g., demographics, substance use history), and psychiatric assessments. Core study visits provided the covariates for the current study. WIHS's standardized neurocognitive battery is performed every two years to monitor and screen cognitive function status. Each participant's neurocognitive testing was conducted on the

same day or within three months following their WIHS core study visit. Seven cognitive domains were measured by two neurocognitive tests (Cronbach's $\alpha > .70$; $r = > .70$): 1) verbal learning ("Hopkins Verbal Learning Test"; Brandt & Benedict, 2001), 2) verbal memory ("Hopkins Verbal Learning Test"), 3) verbal fluency ("Letter and Semantic Fluency Tasks"; Benton, 1968), 4) attention/concentration ("Wechsler Adult Intelligence Scale-IV: Letter Number Sequence"; Wechsler, 2009), 5) executive function ("Stroop Test: Trial Three"; Stroop, 1935; "The Trail Making Test: Part B"; Reitan, 1978), 6) psychomotor speed ("Stroop Test: Trial Two"; Comalli et al., 1962; "Symbol Digit Modalities"; Smith, 1973), and 7) fine motor ("The Grooved Pegboard"; Reitan & Wolfson, 1985).

The RSA collection occurred within 18 months of their most recent neurocognitive testing visit. CardioBatch software (Brain-Body Center, the University of Illinois at Chicago) provided the RSA values for this study. The software quantifies RSA amplitude based on age-specific parameters that are sensitive to maturational shifts in the spontaneous breathing frequency, which allows for comparisons between participants and groups regardless of age (Porges, 1985).

Statistical Analysis

All analyses were performed using R statistical software R 3.5.0 (with R Studio version 0.99.491) (R Core Team, 2014). Statistical significance was set at an alpha level of 0.05. Benjamini–Hochberg procedure utilized for false discovery rate (set at 0.10). For missing data, pairwise deletion was given priority. Descriptive statistics ($N = 144$) for HIV-SP and SN women were conducted using chi-square and *t*-tests. General and interaction regression modeling was used to examine associations between RSA and

cognitive domains (and within-group analysis [HIV-stratum]). Spearmen correlations examined associations between continuous predictors and cognitive variables. Independent *t*-tests were utilized for mean group differences (Cohen's *d* for effect) (Cohen, 1992). Given the small sample size, regression models only included variables if 1) significant correlations (covariates and cognitive outcomes) or differences were found between groups and 2) strong evidence from previous WIHS studies found covariates were associated with cognitive domains.

Final regression models were built using backward selection (variable removal effect checked by unadjusted R^2 and partial permutation) and inspected with q-q plots. Goodness of Fit with adjusted *R*-squared, overall *F*-test, residuals, *p*-values, residual standard errors, and Akaike Information Criterion (AIC) were reported (coefficient estimates cross-validated with iterative permutation tests). For global cognitive function, ordinal regression (cumulative link) models were estimated by iterative maximum likelihood (adjusted fits) (Agresti, 2002; Kosmidis, 2013). Log-likelihood differences evaluated proportional odds assumptions (estimates were exponentiated to extract odds ratio and confidence intervals).

Conclusion

In conclusion, this dissertation supported the theme of a dysfunctional vagus nerve in HIV via inflammatory mechanisms; furthermore, it outlined how multiple vagal-mediated inflammatory disorders precipitate dysautonomia and compound HIV's effect on cognitive function. Black women might be particularly susceptible to ANS dysfunction given their increased co-inflammatory burdens, which increases their risk for earlier cognitive impairment. By recognizing the vagus nerve's potential role in this

phenomena, it is possible to develop novel assessments and treatments that can restore ANS function and improve cognitive outcomes. The findings from this dissertation support the need for future HIV cognitive studies that target the vagus nerve and central autonomic network as a potential substrate for pathological activity.

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THE POTENTIAL ROLE OF VAGUS NERVE STIMULATION IN THE TREATMENT OF HIV-RELATED DEPRESSION: A REVIEW OF LITERATURE

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Journal of Neuropsychiatric Disease and Treatment, 13, 1677-1689.
doi: 10.2147/NDT.S136065

ABSTRACT

Depression is the most common comorbidity and neuropsychiatric complication in HIV. Estimates suggest that the prevalence rate for depression among HIV-SP individuals is three times that of the general population. The association between HIV and clinical depression is complex; however, chronic activation of inflammatory mechanisms which disrupt central nervous system (CNS) function may contribute to this association. Disruptions in CNS function can result in cognitive disorders, social withdrawal, and sleep disturbances which are common manifestations in depression and HIV alike. The parasympathetic-associated vagus nerve has homeostatic properties which restore CNS function following a stress response; moreover, reduced vagus nerve function is correlated to symptom severity in both depression and HIV. Unfortunately, about 30% of adults in HIV are resistant to standard psychotherapeutic and psychopharmacological treatments for depression. Vagus nerve stimulation (VNS) and its benefits as a treatment for depression have been well documented, but remain unexplored in the HIV population. Historically, VNS was delivered using a surgically implanted device; however, transcutanous VNS with non-surgical auricular technology is now available. Although it currently lacks FDA approval in the U.S., evidence suggests several advantages of tVNS including a reduced side-effect profile when compared to standard treatments and comparable results to implantable VNS in treating depression. Thus, tVNS could offer an alternative for managing depression in HIV via regulating CNS function; moreover, tVNS may be useful for treatment of other symptoms common in HIV. From this, implications for nursing research and practice are provided.

Key Words: tVNS, depression, HIV, vagus nerve

THE POTENTIAL ROLE OF VAGUS NERVE STIMULATION IN THE TREATMENT OF HIV-ASSOCIATED DEPRESSION: A REVIEW OF LITERATURE

Depression is the most common comorbidity and neuropsychiatric complication in HIV-positive adults with an occurrence rate of approximately 40-60% over a life-time; moreover, estimates suggest that the prevalence rate for depression among HIV-SP individuals is three to four times that of the general population (Arseniou, Arvaniti, & Samakouri, 2014; Everall et al., 2009; Nanni, Caruso, Mitchell, Meggiolaro, & Grassi, 2015). Approximately 55-65% of adults with HIV treated for depression experience a reduction in depressive symptoms (Sherr et al., 2011). Yet, as many as 30% of adults with HIV-associated depression are resistant to standard treatments (e.g., psychopharmacology and psychotherapy), thus requiring alternative treatment approaches.

The association between HIV and clinical depression is complex. Chronic activation of stress mechanisms which disrupt central nervous system function likely drives this association as both conditions present with pathological pro-inflammatory states. According to Thase (2016), a significant relationship exists between depression and increases in pro-inflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α]), and C-reactive protein, etc.); moreover, severity of depression is correlated to reductions in brain-derived neurotrophic factor (BDNF). Likewise, pro-inflammatory cytokines and reduced BDNF have been associated with the progression of HIV and its associated neurocognitive disorders (Fields et al., 2014; Lotrich, Albusaysi, & Ferrell, 2013). Comorbid depression in HIV reduces antiretroviral medication adherence, which independently leads to poor disease outcomes related to inflammation; however, depression is also independently and adversely associated with HIV progression via

decreased CD4+ and CD8+ T lymphocytes along with increased viral loads (Arseniou, Arvaniti, & Samakouri, 2014; Sin & Dimatteo, 2014).

In both disorders, the dysregulation of neuroendocrine and neuroimmunological systems produce a cascade of events resulting in attenuation of parasympathetic tone, pain, psychomotor slowing, depression, alterations in mood and cognition, anhedonia, fatigue, apathy, cognitive disorders, dysregulated sleep, appetite disruptions, and social withdrawal. These symptoms are collectively referred to as "sickness behavior" and are mediated by the vagus nerve (Andreasson, Arborelius, Erlanson-Albertsson, & Lekander, 2007; Dantzer et al., 2008; Imeri & Opp, 2009). Chronic disruption of the vagus nerve in response to stress leads to alterations in homeostasis via constant activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathomedullary system (Thrivikraman, Zejnelovic, Bonsall, & Owens, 2012). This activation increases cytokine production and, in turn, induces a chronic "sickness state." In this context, HIV and depression could be pathologically-related via their effect on the vagus nerve and interventions targeting it could provide clinical benefit.

Implantable vagus nerve stimulation (iVNS) and its benefits in treatment-resistant depression have been well documented (Albert et al., 2015; Bajbouj et al., 2010; George et al., 2005; & Sackheim et al., 2001). iVNS is achieved via a surgically-implanted device; however, transcutaneous vagus nerve stimulation (tVNS) with non-surgical auricular technology is now available and offers potential advantages due to its comparable benefits to VNS, ease of use, higher accessibility, and reduced side effect profile (Ben-Manachem, Revesz, Simon, & Silberstein, 2015). Yet, the effectiveness of these technologies remains unexplored in HIV.

The main purpose of this article is to explore tVNS's potential use for depression in the HIV-SP population. First, it will provide an overview of the vagus nerve's association to HIV and depression. Second, it will briefly describe tVNS. Third, the clinical efficacy of iVNS in depression will be discussed. Fourth, studies evaluating tVNS's effectiveness in the treatment of depression since its introduction in 2010 will be reviewed. Finally, implications for nursing research and practice are provided.

Vagus Nerve's Inflammatory Association to HIV and Depression

A comprehensive description of the inflammatory response is beyond the scope of this article. Though, in order to understand the association between depression and HIV, a brief and basic overview of their relationship to inflammation in the context of the vagus nerve is described. Psychological stress (e.g., stigmatism related to HIV diagnosis, discrimination, etc.), recurrent stressors, resilience, and the inflammatory properties of HIV are likely synergistic to the chronic activation of immune cells and resultant depression. As such, HIV and depression will be referred to as HIV-associated depression for simplicity and to indicate their relationship via immune disruption. This section focuses on HIV as being the primary stressor which contributes to depression. Specifically, discussion is focused around sickness behavior in the context of HIV-associated depression followed by associations with the vagus nerve.

Sickness Behavior in HIV-associated Depression

HIV activates T-cells and monocytes (e.g., CD4+, etc.) which enter into the central nervous system (CNS). Upon entry, these activated cells infect microglia and astrocytes while also inducing the production of pro-inflammatory cytokines. This cell activation (together with perivascular macrophages) causes the release of neuroexcitatory amino acids (e.g., glutamate, etc.), thereby disrupting calcium channels and propagating an inflammatory state. Additionally, cell activation promotes the formation and release of non-structural proteins such as HIV-Tat and gp120. As a result, the blood-brain barrier is weakened and becomes vulnerable to peripheral cytokines which further perpetuates the inflammatory cycle and disrupts neuronal integrity (Hong & Banks, 2015; Saylor et al., 2016; Sweeney, Ayyadurai, & Zlokovic, 2016).

During inflammatory states of HIV-associated depression, locus coeruleus-norepinephrine projections to the hypothalamus and brainstem are activated. In response, the amygdala and HPA-axis stimulates the release of glucocorticoids (cortisol) and activates the sympathomedullary system which releases catecholamine's (noradrenaline and adrenaline) into the peripheral blood. This activation coordinates glucocorticoid and catecholamine's interaction with immune cells, thereby regulating cytokines and their transcription factors to suppress and maintain the immune system during the stress response (Rivera-Rivera et al., 2016).

Consequently, cytokine release activates an adaptive state to inflammation which manifests as "sickness or depressive behavior" (detailed below). Under normal conditions, this behavior is protective and regresses as cytokines normalize along with the inflammatory response. The re-balancing of cytokines allows them to resume their

trophic responsibilities in promoting neurogenesis, neuroplasticity, and maintenance of cognitive function (Calabrese et al., 2014; Raedler, 2011). Importantly, the vagus nerve is grossly responsible for initiating "sickness behavior" via its interaction with cytokines and is a critical response to immune activation.

Vagus Nerve and Sickness Behavior

Herz and Kipnis (2016) suggest the vagus nerve mediates "sickness behavior." The vagus nerve is a major component of the autonomic nervous system that influences neuronal, endocrine, and immune functions (neuro-endocrine-immune axis) via its efferent (motor) and afferent (sensory) pathways. The vagal cholinergic anti-inflammatory pathway (CAP) interacts with the CNS and is primarily responsible for "sickness behavior."

CAP is activated in the presence of a stressor and is responsive to pro-inflammatory signals which initiate an immune response. Vagal afferents detect central or peripheral pathogens (via toll-like receptors, etc.) and carry pro-inflammatory cytokine signals to the brainstem nuclei. These signals are converted to the nucleus tractus solitarus and project to autonomic output centers (e.g., limbic system, hippocampus, frontal cortex, etc.). The medulla coordinates this response and stimulates vagal efferent fibers which project to the celiac ganglion. Vagal fibers develop synapses on cell bodies within the celiac ganglion, thus activating innate immune responses in the spleen. Splenic nerves then release norepinephrine which communicates with beta-2-adrenergic receptor-expressing T cells. Consequently, T-cells release acetylcholine to interact with α7 nicotinic receptors which are present on the cell surfaces of macrophages and other

inflammatory cells (e.g., monocytes, etc.). Complex, vagal-associated brain activity and signaling inhibits inflammation due to suppression of cytokines, thereby regulating their release and stabilizing the stress response (Cuoco, Fennie, & Cheriyan, 2016; McCusker & Kelley, 2013).

Contrarily, chronic inflammation (such is the case with HIV-associated depression) interferes with the vagus nerves ability to regulate the immune response successfully by disrupting signaling in the CAP. As a result, glutamate and gamma-aminobutyric acid along with central cytokine systems are chronically disrupted (creating a persistent pro-inflammatory state) which interfere with their trophic and homeostatic function. CD4+ and CD8+ T-lymphocytes are dysregulated at the splenic level which disrupt catecholamine function, thereby perpetuating stress signaling to the CNS (Arsenious et al., 2014; McCusker & Kelley, 2013; Rivera-Rivera et al., 2016).

Increased cytokine and stress signaling via a disrupted CAP compromises the prefrontal cortex and its functional capacity to maintain executive function, attention, memory, and adaptive social behaviors. Moreover, increased cytokine signaling to the basal ganglia results in psychomotor disturbances (agitation or slowing). Persistent activation of the amygdala, HPA-axis, and sympathomedullary system occurs which interferes with appetite and sleep; moreover, this allows excessive cortisol to bind to glucocorticoids and increasing insulin resistance. The resulting hypercortisolism and the actions of HIV's gp120 protein interferes with BDNF's energy metabolism which supports brain health by lowering blood glucose, reducing insulin resistance, and regulating food intake. Consequently, BDNF is reduced and metabolic disruptions occur which interfere with neuroplasticity and neurogenesis. Additionally, during this

dysfunctional immune response, nucleus accumbens' activity is significantly down-regulated which interferes with the reward pathway (motivation, pleasure, and reinforcement learning), thus promoting anhedonia and apathy. Ultimately, this disruption perpetuates pathological social withdrawal, anhedonia, lethargy, psychomotor disturbances, and alterations to both mood and cognition or "sickness behavior" (Crane et al., 2013; Gold, 2015; Kamat et al., 2014; Thase, 2016).

The chronic stress mechanisms in HIV-associated depression are complex and have not yet been fully elucidated; however, the overlapping symptomology in HIV-associated depression symptoms and their relationship to vagus nerve function should be considered as a potential target for treatment interventions.

Vagus Nerve Stimulation

The U.S. Food and Drug administration (FDA) approved iVNS for use in treatment-resistant depression in 2005 while tVNS was approved in Europe for depression in 2010 (Howland, 2014). One such tVNS device called NEMOS® (developed by Cerbomed in Erlangen, Germany) has received authorization for use in epilepsy, depression, and pain conditions. Likewise, another tVNS device called gammaCore (developed by electroCore LLD in Basking Ridge, New Jersey, USA) has European approval for use in prophylactic and acute treatment of migraines and headaches; however, it is not approved for depression. Currently, tVNS is not approved in the U.S., but is being used for research trials across multiple populations (e.g., eating disorders, rheumatoid arthritis, IBS, etc.) (Howland, 2014).

Transauricular Vagus Nerve Stimulation (tVNS)

The tVNS unit attaches to a battery powered control unit that connects to a headset with bilateral electrodes which are placed on the outer ear (See Figure 1). Alternatively, adhesive anodes and cathodes can be placed over the mastoid process juxtaposed to the outer ears. Electrodes can be applied either unilaterally or bilaterally depending on the device specifications (Trevizol et al., 2016).

Three sensory nerves supply the outer ear (i.e., auriculotemporal and great auricular), but the tVNS unit specifically targets the auricular branch of the vagus nerve (ABVN) and, to a lesser degree, the greater auricular nerve. The ABVN predominantly innervates the external auditory meatus and concha (cymba and cavum) which provides the cutaneous access field of the ABVN targeted by tVNS (Ellrich, 2011; Howland, 2014). Concha's nerve fibers provide the electrical stimulation point which allows changes in intensity, pulse duration, and frequency from the tVNS unit to induce signals via the myelinated Aβ fibers of the ABVN (Ellrich, 2011). These ABVN fibers terminate in the nucleus of the solitary tract of the brainstem. Neuronal projections from this nucleus relay excitatory and inhibitory signals. These vagal-projections are stated to be responsible for its neuroplastic, neurogenic, neuroprotective, and anti-depressant properties (Grimonprez, Raedt, Baeken, Boon & Vonck, 2015).

Stimulation can be self-administered. Yet, stimulation parameters have not been established; therefore, clinical models for this device do not include a standardized duration, frequency, or administration paradigm. The manufacturers recommend daily use (1-4 times) for at least one hour (maximum of 4 hours); however, research regarding the efficacy of these specific parameters is limited. Various approaches have been

researched, but are contingent on which specific tVNS unit is being utilized (Hein et al., 2013; Rong et al., 2012). In all studies, intensity is adjusted based on perceptual tolerance and is kept below each individual's pain threshold. Pain thresholds are defined as the minimal amount of stimulation that evokes a tingling or unpleasant sensation.

The side effect profile for tVNS is appealing due to it being the least innocuous of standard biological treatments for depression. Adverse effects tend to be stimulation related and tend to occur during those time intervals. The most common symptoms reported are itching, outer ear discomfort, local pain on stimulation side, and neck pain which corresponds anatomically to the location of the electrodes. Additionally, VNS can be safely used in pregnancy along with concomitant psychotropic medications (e.g., antidepressants) and electroconvulsive therapy (Ben-Menachem, Revesz, Simon, & Silberstein, 2015).

Depression and iVNS

Approximately 21 research studies have been conducted to examine the relationship between iVNS and treatment-resistant depression. Numerous meta-analytic and systematic reviews (Berry et al., 2013; Cimpianu et al., 2016; Martin & Martin-Sanchez, 2012) have found a beneficial effect for iVNS in this population. These beneficial results support the inclusion of iVNS as a treatment option in national guidelines for depression (e.g., The Canadian Network for Mood and Anxiety Treatments, The British Association for Psychopharmacology, The National Institute for Health and Care Excellence, etc.) (Cimpianu et al., 2016; Cleare et al., 2016; NICE, 2012; Milev et al., 2016).

Yet, due to methodological limitations of iVNS (cost, surgical requirements, and the higher risk posed to participants by implanting a sham device), a majority of the iVNS studies did not utilize a control group. Thus, this limits the inferences that can be made about the findings. Instead, most utilized a before-after design which increases the potential for a placebo-effect and could explain a portion of beneficial results, thereby minimizing the overall effect (Martin & Martin-Sanchez, 2012).

Of note, in the studies where randomized control trials were utilized, results were mixed. Rush and colleagues (2005a) did not demonstrate any significant benefits for VNS in a 10-week (n = 235), acute, blind, randomized controlled trial. Contrarily, in a 12-month naturalistic follow-up to this study, Rush and colleagues (2005b) found a significant reduction in depressive scores and global improvement. Likewise, Sackheim and colleagues (2007) conducted both a pilot and randomized control study. In the latter study, participants were randomized into active or sham groups (n = 205) with 15% of the early responders showing a 50% reduction in depressive symptoms at 30 months and 77% maintaining this response at 24 months. Of the late responders, 20% showed a reduction at 12 months and 65% maintained this response at 24 months.

Due to the lack of adequate control trials and mixed results of the randomized studies available, more research is needed to determine the utility of iVNS as an effective intervention for treatment-resistant depression. Fortunately, the novel tVNS devices allow researchers to bypass the limitations of the traditional iVNS and enable more rigorous clinical trials. As such, it is important to review the available tVNS research to determine its efficacy for depressive symptomology and whether the advantageous non-surgical, transauricular design improves on the previous methodological limitations of

traditional iVNS. If effective, these devices could offer those experiencing HIV and comorbid depression an alternative for treatment.

Methods

A systematic Pub Med search of the literature was conducted on December 1st, 2016 from 2010-2016. The Prism approach (see Figure 2) was used as the method for conducting the literature review (Moher, Liberati, Tetzlaff, Altman, 2009). The year 2010 was chosen due to the tVNS unit being made available to the general research market at that time. Two studies were conducted in 2007 and 2008 utilizing these devices which did not directly measure the effects of tVNS on depression, and thus were not included. The search was restricted to peer-reviewed research articles published in English. Keywords operated in the search were "tVNS and depression" yielding 35 articles and "tVNS and HIV" yielding 0 articles. The tVNS and depression results were narrowed by removing the words, "epilepsy", "tinnitus", and "implantable" which resulted in 10 articles. Inclusion criteria further limited the review to quantitative clinical trials and human studies which netted 5 articles. Due to a small number of results, case-studies were added back resulting in a total of 6 articles. A more detailed review of these studies can be found in Table 1.

Results

Hein and colleagues (2013) conducted the first pilot study to explore the effects of tVNS in major depression ($N = 37$). Two randomized sham controlled (add-on) studies were conducted with participants being stimulated for 5 days each week for 14 days. The

first study (n = 22) used an active-control group (N = 11) and a sham control group. The sham control received stimulation to the center of the left ear lobe, which is without vagal innervation. The stimulation intensity ranged from 0-600 mA (milliampere) with a frequency of 1.5 Hz (Hertz) for 15 minutes daily. Ranges were adjusted just below the participant's perception threshold. In the second study (n = 15), seven participants were given active-stimulation while the remaining received sham stimulation. However, the stimulation occurred 15 minutes twice daily (morning and evening) with fixed parameters of 130 mA and 1.5 Hz. The Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory (BDI) were administered at baseline (day 0) and at the conclusion of the study (day 14). Using pooled analysis, both studies showed a significant mean difference between the active group and sham group on the BDI. Contrarily, neither showed significant differences on the HAM-D. No significant side effects were noted due to tVNS use.

Trevizol and colleagues (2015) reported the first case-study utilizing tVNS in a 38-year old man with major depression. This patient received stimulation for 5 days each week for 14 days at 120 Hz with a pulse duration of 250 μs (microsecond) for 30 minutes daily. The HAM-D was administered at baseline along with the Montreal Cognitive Assessment (MOCA). After 14 days, this patient's symptoms went into complete remission and remained stable after a two month follow-up. No significant side effects were noted due to tVNS use.

Trevizol and colleagues (2016) conducted a proof-of-concept trial (N = 12) exploring the effects of tVNS in major depressive disorder. HAM-D was the primary instrument used to evaluate depression with endpoint response being defined as a 50%

reduction in baseline scores. Patients received stimulation for 5 days each week for 14 days at 120 Hz with pulse duration of 250 μs, intensity was set at 12 mA for 30 minutes daily. After 14 days, all participants demonstrated a clinical response with a 50% reduction in depressive symptoms. Five patients exhibited remission of depressive symptoms (score of < 8 on HAM-D). Response was maintained at a 1-month follow-up. Cognition remained stable as measured by the MOCA. No adverse effects were reported. Ten participants reported diurnal sleepiness after stimulation with 6 patients experiencing nausea, but no medication or treatment was required. There were no drop outs reported.

Fang and colleagues (2016) conducted a single-blinded clinical trial ($N = 49$) exploring the effects of tVNS in mild to moderate major depression. A total of 34 patients were included in the study analysis (after 14 dropped out and 1 excluded for excessive head movement) and were divided into an active ($n = 18$) and sham group ($n = 16$). The active group received stimulation at 20 Hz with a wave width less than 1 ms with intensity adjusted based on tolerance or perception threshold (range from 4-6 mA). Stimulation occurred twice a day for 30 minutes at least 5 days a week for 1-month. Using functional magnetic resonance (fMRI) and HAM-D to evaluate depression symptoms, the results supported the efficacy of tVNS as significant decreases in depressive symptoms (≤ 50% reduction) were found. In support, the fMRI results corresponded to increased functional connectivity in the default mode network of the brain (known to be decreased in depression). No significant side effects were noted due to tVNS use.

Rong and colleagues (2016) conducted a non-randomized study ($N = 160$). The study was divided into an active group ($n = 91$) that received tVNS for 12 weeks and a

control group (n = 69) that received sham stimulation for 8 weeks followed by 4 weeks of tVNS. A total of 148 participants completed the trial at 1 month and 138 participants at 2 months. Stimulation parameters were set at 20 Hz (width of 0.2 ms) with intensity increased gradually from 0 until tolerance threshold was achieved (range from 4-6 mA). As per the other studies' protocols, stimulation was administered twice daily at 30 minutes per session. Depression was assessed using the HAM-D. After 1 month of treatment, there was a significant difference between the active group and the sham group with a decrease in scores (≤ 50% reduction). Additionally, this improvement was maintained at 12 weeks. Interestingly, this study explored sub-groups within the tVNS participants to determine if there was a difference in response when comparing mild (HAM-D score of < 20) to moderate depression. Although the effect size was smaller, this study demonstrated a significant reduction in mild symptoms as well. No adverse side effects were noted due to tVNS use.

Research from the same research group (Fang et al., 2016) and utilizing the same experimental and stimulation procedures as Rong and colleagues (2016), Lui and colleagues (2016) conducted a single-blind clinical trial (N = 49) exploring the neurological effects of tVNS in depression. Stimulation occurred over a 1-month period. Resting fMRI scans were conducted pre and post tVNS intervention while depressive symptomology was assessed utilizing the HAM-D as the primary endpoint. After 1 month of treatment, HAM-D scores significantly reduced in the tVNS group when compared to the sham. Moreover, the functional connectivity between the amygdala-lateral prefrontal networks showed a significant increase. Increases in this resting-state

connectivity corresponded to the HAM-D reduction in depressive symptomology. No significant side effects were noted due to tVNS use.

Discussion

The purpose of this article was to examine tVNS's potential use in HIV-associated depression via a review of its use in the depression population. Overall, the results of the review were promising and supported the findings of previous studies which utilized the traditional iVNS devices. Each found a significant reduction in depressive symptoms. Furthermore, as expected, no significant side-effects occurred from utilizing the tVNS units. In an effort to standardize stimulation parameters, each study relied on a similar protocol developed by Hein and colleagues (2013) for experimental reference and utilized similar procedures. This effort and replication of positive results provides the first step in developing a standardized clinical paradigm for its use in a clinical setting for depression. Contrarily, the limited stimulation parameters (see parameters Table 1) restrict interpretability or feasibility of use outside of those parameters. In reference to HIV-associated depression, its utilization could require a different stimulation protocol that has not yet been researched.

Interpretations of positive results should be approached with caution as there are only a small number of research studies available which restricts any conclusive statements about tVNS's efficacy. While some were adequately powered (Rong at al., 2016), other trials were restricted to a case-study design (Trevizol et al., 2015) or used participants from the same cohort (Lui et al, 2016; Fang et al., 2015). Additionally, due to

one instrument being utilized as the outcome measure (HAM-D) in each of these studies, it cannot be ruled out that this instrument is not capturing a heterogeneous population.

Simply, contention surrounds the accuracy of the HAM-D cutoff scores for remission versus active depression. In addition, it does not include specific diagnostic information which is included in other depression screening scales, thereby providing a more general assessment of depression. Thus, the construct validity of the HAM-D is of concern due to it lacking the conceptual clarity of other available measures. This limitation could restrict the HAM-D's identification of depressive symptom sub-types (Möller, 2009). For example, Hein and colleagues (2013) found depressive symptoms remitted utilizing the HAM-D in both the sham and control groups. A similar effect was found in Fang et al., (2016). This finding could suggest that the improvements in depression, as it relates to tVNS, are not as specific in the HAM-D versus other scales; therefore, this could affect interpretability in the context of various types of depression (such as HIV-associated depression). Despite these methodological limitations, the results of this review suggest tVNS should be considered as a treatment option for HIV-associated depression.

Limitations to this review were the restriction of review articles to those in English. It is possible that other research trials have been published in the non-English literature which could have added valuable results to this review. Considering the lack of research examining tVNS and depression in humans, animal studies (which have to be considered with caution) could have provided a deeper understanding of tVNS's potential use in HIV-associated depression.

Future Implications for HIV Research

Based on this review, the most compelling evidence for tVNS's use in HIV-associated depression is found in studies conducted by both Fang and colleagues (2016) and Lui and colleagues (2016). Each of these studies explored the neurological effects of tVNS on depression via brain imaging and rating scales. The results identified improved functional connectivity in the default mode network (e.g., hippocampus, amygdala, medial prefrontal cortex, and anterior cingulate, etc.) which is involved in affect, cognition (particularly prospective memory), and emotional regulation. This confirms previous studies in depression which have implicated altered default mode network connectivity as playing a primary role in its expression. Moreover, studies have shown cytokines have a profound effect on this network and its sensitivity to inflammation has been linked to depression and cognitive impairment (Marsland., 2017).

Evidence from the HIV CHARTER cohort study suggests depressive episodes (over a life-time) were present in approximately 50% of cases with neurocognitive impairment (Heaton et al., 2010). Interestingly, in a cross-sectional study (N = 111; 58 HIV-SP/53 HIV-), Thomas and colleagues (2013) demonstrated diminished functional connectivity in the default mode network as playing a critical role in the neurodegenerative process of HIV or, more specifically, HIV-Associated Neurocognitive Disorder (also known as HAND). Furthermore, they demonstrated HIV's disruption of connectivity in the salience and executive control networks which are responsible for working memory and emotional-conflict processing.

In a recent short-term study with 30 healthy adults (15 women), Jacobs and colleagues (2015) found tVNS improved associative memory performance in this sample

when compared to a control group. These researchers' hypothesized tVNS mediated stress-related effects (e.g., inflammation) on memory function via its interaction with beta-adrenergic receptors located on afferent vagal fibers that project into the nucleus tractus solitarus. This vagal activation stimulates the locus coeruleus to release norepinephrine, thereby modulating cortical and sub-cortical network activity. The results suggest tVNS changes the functional pathways for learning and consolidation which favors neuroplasticity. Interestingly, functional decline in learning efficiency and memory retrieval has increased in HIV during the antiretroviral era (Cohen et al., 2015).

Bachis and colleagues (2003) demonstrated BDNF's ability to inhibit HIV's gp120 protein showing an inverse relationship in their expressions. This suggests BDNF helps reduce microglial and astrocyte infection in the CNS via independent and anti-inflammatory properties. Therefore, they posited that increased BDNF could counteract gp120's interaction with monocytes. Interestingly, Biggio and colleagues (2009) demonstrated long-term iVNS's ability to increase BDNF expression in the hippocampus and induce neuroplasticity. This effect diminished after 3 weeks without iVNS. They concluded long-term BDNF promoted the survival and trophism of new granule cells in the hippocampus which persisted in the presence of iVNS.

In support of this, Furmaga, Carreno, and Frazer (2012) demonstrated iVNS promoted increased BDNF activity via phosphorylation of its primary receptor (TrkB). These researchers noted that this activity provided an anti-depressant effect that was independent of those accomplished with anti-depressant medications. This mechanism suggests tVNS could augment current anti-depressant medications (e.g., paroxetine, sertraline, etc.), thus providing an enhanced effect or offering an alternative neurological

pathway for treatment. Importantly, tVNS has been shown to modify pro-inflammatory cytokines in murine models (Huston et al., 2007). More recently, in a healthy sample of 20 men and women, Lerman and colleagues (2015) demonstrated tVNS's ability to downregulate inflammatory cytokines in the context of lipopolysaccharides (induce an inflammatory response). While tVNS has not been explored in the context of BDNF, research supports its comparability to iVNS. This suggests that tVNS could help provide both anti-inflammatory and anti-depressant effects for HIV-associated depression via increased BDNF activity and cytokine regulation. Additionally, tVNS could possibly provide a treatment option for HIV-Associated Neurocognitive Disorders.

Not only are the results promising in these pilot studies as it relates to depression, but other tVNS studies have implications in conditions that comorbidly present in HIV and depression alike. For example, Ay, Nasser, Simon, and Ay (2016) demonstrated in rat models that cutaneous VNS inhibited cerebral ischemia-induced immune activation. Furthermore, it reduced the degree of tissue injury and functional deficiencies that resulted from the cerebral event. The effectiveness in ischemia has implications for HIV and related cerebrovascular pathology. HIV patients are admitted to hospitals 60% more often for stroke despite a reduction in overall hospitalizations in the general population. Research suggests cerebrovascular inflammation via chronic immune activation could play a critical role in HIV-Associated Neurocognitive Disorders (Hong & Banks, 2015). Likewise, Ayerbe and colleagues (2013) report a 29% prevalence of depression up to 10 years post-stroke with a 40-52% cumulative incidence within 5 years. Importantly, predictors of this depression were pre-stroke depression and cognitive impairment.

Currently, no studies exist that explore tVNS as a treatment option for HIV; furthermore, no infectious models exist in non-humans that can actually duplicate the physiological effects HIV has on humans which suggests the need to test it directly in adults with HIV (Hatziooannou & Evans, 2012). The safety, effectiveness, and tolerability of tVNS have been reviewed for sepsis, atrial fibrillation, depression, epilepsy, migraines, and tinnitus which provide a strong foundation for its use in HIV. In consideration of current knowledge and available technology, research in HIV-associated depression is warranted with tVNS. The potential benefits of this research are not restricted to depression or cognitive disorders, but could also be utilized as a buffer to comorbidities associated with HIV (e.g., stroke, metabolic disruptions, etc.) or that result as a consequence of HIV treatment.

Future Implications for Nursing

The safety, efficacy, and self-administration capabilities of the tVNS units have clinical utility for nurses and practitioners alike. If research determines their efficacy in the HIV population, these devices could provide a cost-effective and safe alternative for HIV-associated depression treatment. In an outpatient setting, these devices can be calibrated, prescribed for use at home, and utilized as augmenting agents to standard anti-depressant treatments or individual therapies for comorbid depression and HIV symptomology (e.g., cognitive disorders, etc.). If effective, these devices could help reduce the polypharmacy often faced in HIV by replacing select psychotropic medications and select cardiovascular medications (Tseng et al., 2013); moreover, they could potentially alleviate or help control common side-effects that result from the use of

these medications (e.g., QRS elongation, tinnitus, metabolic disturbances, motor dysfunction, etc.) (Bet et al., 2013; Casaretti et al., 2015; Jernigan et al., 2013).

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Figure 1. Transcutaneous Vagus Nerve Stimulation Device

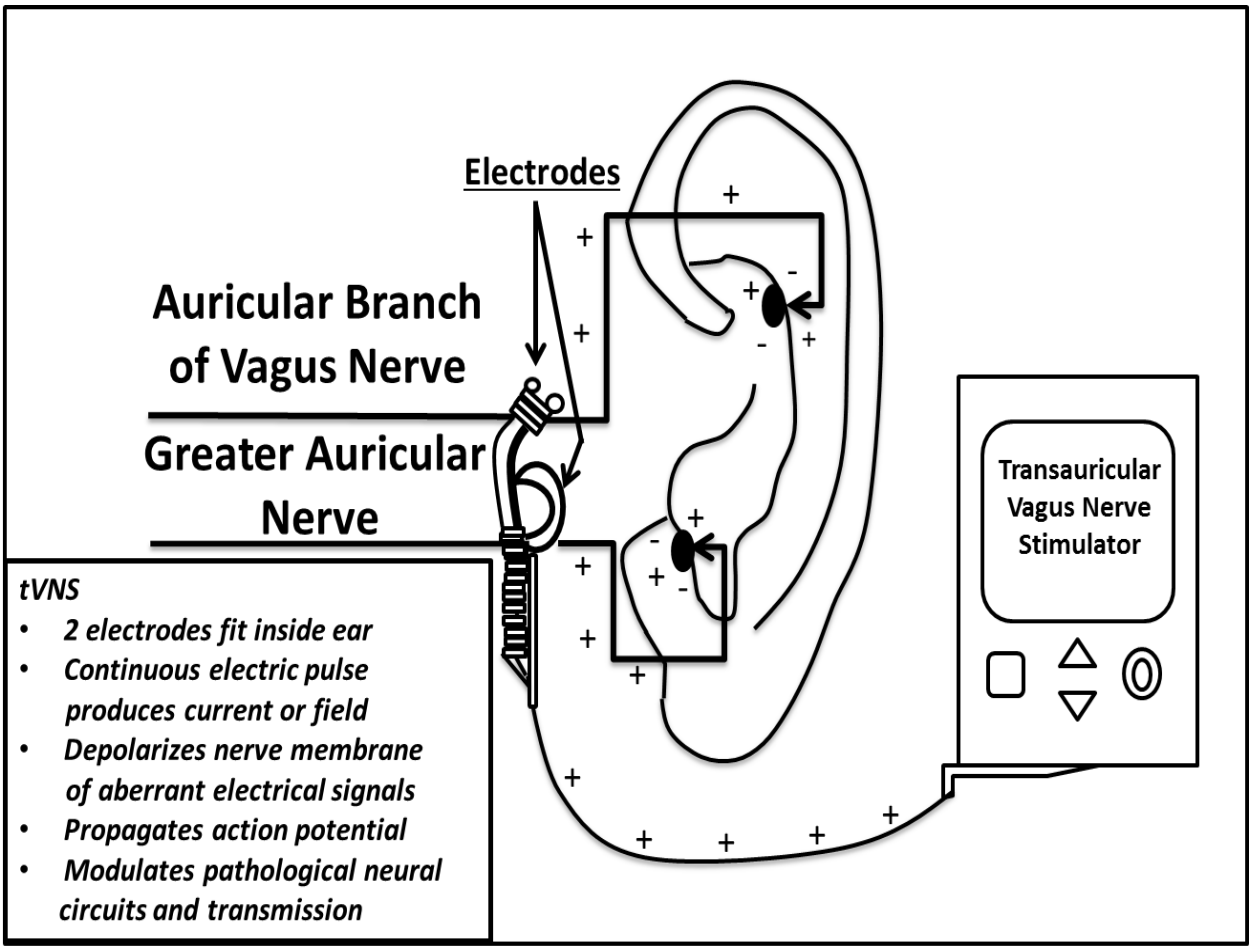

Figure 2. Systematic Review of Literature Methodology and Results

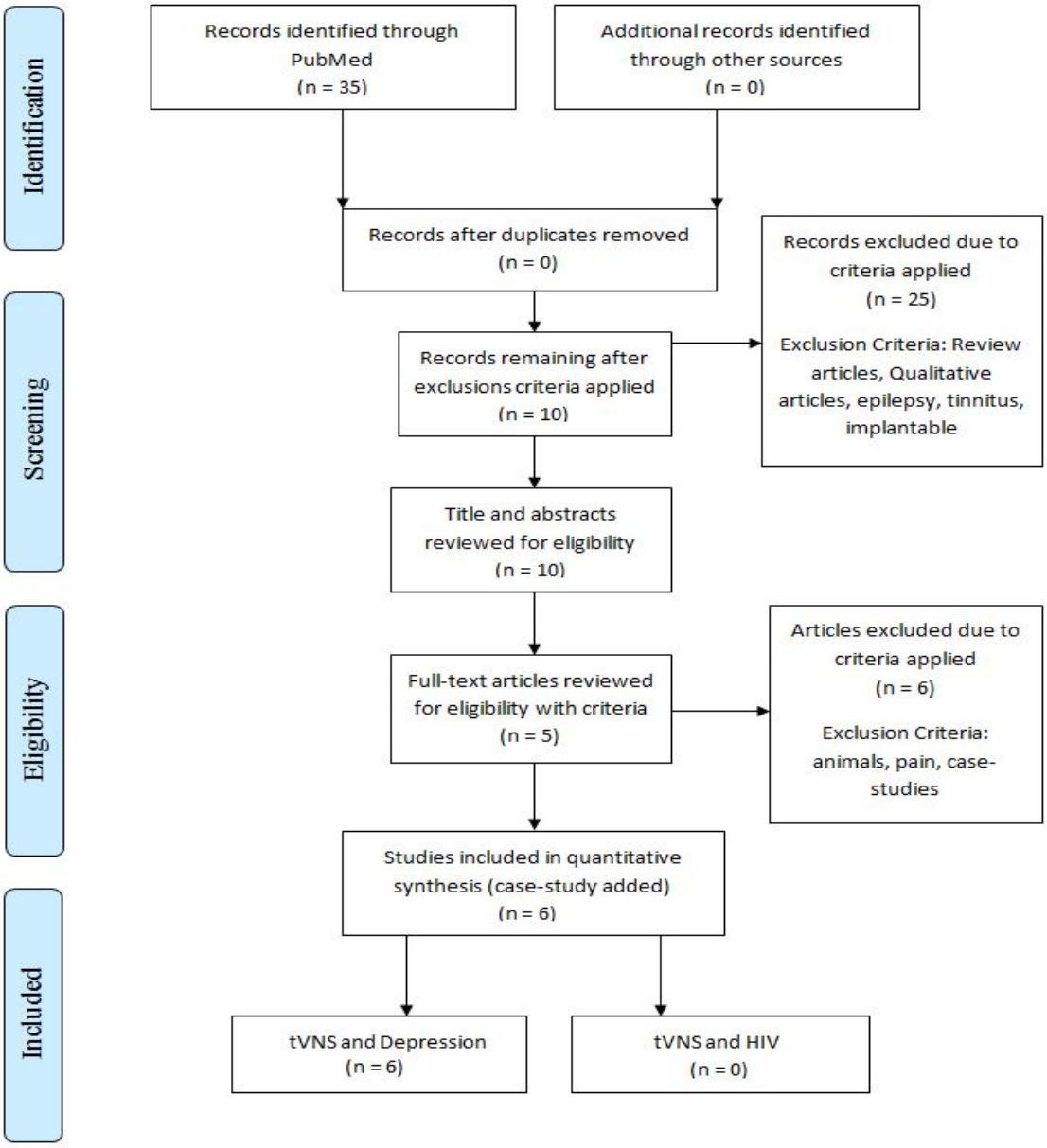

Figure 2 PRISMA flow diagram demonstrates screening method for articles.

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Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

HIV, AGING, AND COGNITIVE FUNCTION: CAN HEART RATE VARIABILITY BE USED AS A PRE-CLINICAL MARKER FOR NEUROCOGNITIVE DISORDERS

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ABSTRACT

Antiretrovirals have shifted HIV-cognitive impairments to frontostriatal pathways in the brain with deficiencies in executive function being observed. Executive dysfunction likely results from ongoing inflammatory processes and partly characterize a spectrum of HIV-associated neurocognitive disorders (HAND) affecting 25-59% of adults aging in this population. Neurocognitive performance tests remain the gold standard for diagnosing HAND; however, they lack clinical feasibility, may underreport cognitive impairments, and exhibit reduced sensitivity in detecting discrete neurocognitive changes that precede HAND diagnoses. As such, clinical markers are need to better identify prodromal HAND. Vagal-mediated heart rate variability (vmHRV) could provide such a marker due to its capacity for measuring adaptive self-regulation (i.e., executive and emotional functioning) and autonomic flexibility. vmHRV reflects frontostriatal activity and is sensitive to inflammatory processes, which could position it as a predictor of future cognitive impairments. Unfortunately, HRV and self-regulation studies are lacking in HIV. Current research in healthy aging adults without HIV suggests HRV could be a valuable clinical tool as it demonstrates sensitivity in detecting self-regulation; furthermore, it bypasses the limitations imposed by self-report measures via adding an objective physiological component. These features could be of clinical interest in HAND given the limitations of neurocognitive tests.

Key Words: HIV-associated neurocognitive disorders, HRV, vagus nerve, self-regulation

HIV, AGING, AND COGNITIVE IMPAIRMENT: CAN HEART RATE VARIABILITY BE USED AS A PRE-SYMPTOMATIC MARKER FOR NEUROCOGNITIVE DISORDERS?

Advancements in combination antiretroviral therapy (cART) have increased life expectancy in HIV, thereby increasing the number of people aging with the disease. In fact, by the year 2020, approximately 70% of those living with HIV in the U.S. will be 50 years and older (United States Senate Special Committee on Aging, 2013). Unfortunately, aging with HIV has resulted in a disproportionate number of persons developing cognitive disorders compared to those without HIV. Despite adequate viral suppression, 25-59% of adults experience a spectrum of cognitive disorders known as HIV-associated neurocognitive disorders (HAND) (Kinai et al., 2017). Deficits in executive function (EF), memory (working and learning), verbal fluency, speed of processing, and psychomotor speed characterize the cognitive impairments observed in HAND (Heaton et al., 2011). Compared to younger adults, the risk for developing HAND increases two-fold in those 50 years of age and older; however, discrete changes in cognitive domains could occur up to ten years prior to diagnosis (Ernst et al., 2010; Harezlak et al., 2011).

Presently, clinical markers that can assist with diagnosis or detection of HAND are lacking. Neurocognitive performance tests remain the gold standard for diagnosing HAND; however, such a performance battery is time-consuming and lacks feasibility in routine clinic settings. Concerns also exist regarding their sensitivity to detect discrete, prodromal neurocognitive changes that underlie asymptomatic or milder forms of HAND thereby delaying access to timely interventions (Ances & Hammond, 2014). Self-reports of one's functional cognitive capacity are also less reliable in providing added data for

detecting HAND at pre-symptomatic stages (Tedaldi, Minniti, & Fisher, 2015). For example, HAND impairs meta-cognitive function (e.g., complex concepts); however, self-reported meta-cognitive impairments are highly influenced by emotional disturbances instead of objective cognitive performance. Likewise, cognitively impaired persons self-report their cognitive abilities with less accuracy and underreport the level of impairment (Blackstone et al., 2012; Juengst, Skidmore, Pramuka, McCue, & Becker, 2012). Given these limitations, clinical markers are needed to increase the sensitivity of detecting discrete cognitive impairments earlier in HIV.

Beauchaine and Thayer (2015) suggest heart rate variability (HRV) could provide a transdiagnostic biomarker for conditions involving psychopathology due to it measuring general self-regulation. On a cognitive level, self-regulation represents the functional capacity of both EF (i.e., cognitive flexibility, working memory, and inhibition) and emotional domains to effectively interpret, predict, and respond to incoming information to facilitate goal-directed behavior. Neurologically, the frontostriatal pathways of the brain help coordinate adaptive self-regulatory behaviors in the context of dynamic environments (e.g., social). Physiologically, HRV reflects adaptive self-regulation by corresponding to frontostriatal modulations of autonomic nervous system (ANS) activity via reciprocal (i.e., bi-directional), intrinsic cardio-neural pathways. HRV represents an adaptive balance between parasympathetic and sympathetic function during resting or reactive EF and emotional challenges (Thayer et al., 2009).

Select HRV indices utilize vagus nerve activity (i.e., parasympathetic nervous system) as the primary measure for ANS function. Greater resting vagal-mediated HRV is associated with increased efficiency and effectiveness of self-regulation, which

represents a more adaptive functional capacity of select frontostriatal and hippocampal networks. Contrarily, chronically reduced HRV (vagal-withdrawal) is associated with persistent inflammatory signaling (e.g., chronic stress or inflammatory-based disorders), EF impairment, and emotional dysregulation (McCraty & Shaffer, 2015). Interestingly, in the post-cART era, HIV-cognitive impairments have shifted predominately towards EF and memory domains (Heaton et al., 2011), thereby potentiating alterations in self-regulation and positioning HRV as a possible measure for HAND.

Consistent with HRV as a clinical marker, chronic reductions in HRV are observed in adults with HIV. Reduced HRV via ANS dysregulation likely occurs from chronic inflammatory processes precipitated by viral activity, medical comorbidities, psychosocial, and demographic risk factors, among others (McIntosh, 2016). Hippocampal and frontostriatal pathways could be particularly sensitive to chronic inflammatory signaling and, in the context of HRV, may provide a substrate for measuring physiological disruption and cognitive impairment in those aging with HIV (Ellis, Langford, & Masliah, 2007).

Given these associations, HRV could increase detection sensitivity of pre-symptomatic HAND due to it adding an objective physiological component to neurocognitive performance-based measures. Unfortunately, HIV studies frequently lack HRV measures in the context of cognitive function. The need for clinical markers cannot be understated as impaired EF and memory are associated with reduced occupational performance, ability to multi-task, ability to self-manage medications and treatment, and quality of life as well as increases in risky/impulsive behavior and poor emotional processing in persons aging with HAND (Vance, Humphrey, Nicholson, & Jablonski-

Jaudon, 2014).

The main purpose of this systematic review article is to explore HRV's potential as a clinical biomarker for neurocognitive impairments in those aging with HIV. First, a brief overview of vagal-mediated HRV is presented. Second, a conceptual overview of HRV and self-regulation is introduced; then, a brief discussion of their relationship to HIV and aging follows. Third, HRV studies in healthy, adults 40 years and older will be systematically reviewed. From this, implications for HAND are provided.

Cardio-Vagal Heart Rate Variability Measures

A basic overview of the vagus nerve and HRV measures specific to vagal-function is germane to the self-regulation concept. The vagus nerve is a major parasympathetic component of the ANS, which has the ability to adjust inflammatory, cardiovascular, respiratory, neuronal, and hormonal activity both locally and centrally via reciprocal signaling from the body and brain. Coordination of systemic physiological responses occur due to its approximate 90% afferent (sensory) and 10% efferent (motor) capacity (Browning, Verheijden, & Boeckxstaens, 2017). The vagus nerve's primary function is to maintain ANS homeostasis by engaging or withdrawing its function when an acute stress stimulus is presented, thereby allowing the sympathetic nervous system to mobilize when triggered by a stressor. After adaptation to a stress-stimulus, vagus nerve activity increases (functioning as a braking mechanism for sympathetic arousal) and physiologically assists the persons return to a metabolically conservative state or homeostasis (Thayer et al., 2012).

The parasympathetic arm demonstrates more tonic control over heart frequencies and contractility, which allows for faster reactions to both external and internal stressors relative to the sympathetic arm. The sinoatrial node of the heart mediates this interaction due to a putative sensitivity to vagal impulses via acetylcholine and associated receptors. The faster reaction time of the parasympathetic nervous system positions it as a primary measure of ANS function as it accounts for acute dynamic changes to stressors reflected by beat-to-beat variations in the heart. These dynamic changes are produced by an integration of neural networks, blood pressure, heart rate, and respiratory systems thereby providing phasic variations in ANS rhythms or, simply, vagal-mediated HRV (Shaffer & Venner, 2013).

The HRV spectrum is divided into different frequency ranges based on variance and amplitude of ANS rhythms (Shaffer, McCraty, & Zerr, 2014). Select frequency and time domains of HRV purportedly index vagal function. The most researched frequency domain in the HRV literature is high frequency (HF) and is considered a primary measure for vagal activity. A proxy for HR-HRV is respiratory sinus arrhythmia (RSA) as its amplitude is highly correlated with variations in vagal modulation of the heart with the degree of modulation being a function of respiration conditions (Laborde, Mosley, & Thayer, 2017; Lewis et al., 2012). The most common time measure is root mean square of the successive differences (RMSSD), which provides a measure of complex interactions in the ANS and reflects response robustness and fragility. Like RSA, RMSSD is highly correlated to HF-HRV; however, unlike its frequency-domain counterpart, it is relatively free of respiratory influences (Ernst, 2017).

Overview of HRV and Self-Regulation

The Polyvagal Perspective (Porges, 1995, 2007) and Neurovisceral Integration Model (Thayer & Lane, 2000, 2009) provide an organized framework for understanding the reciprocal cardio-neural pathways that underlie dynamic adaptive self-regulation. Conceptually, self-regulation is a broad adaptive ability to coordinate emotional, behavioral, social, and cognitive processes in response to environmental stimuli (Bernston et al., 2008; Miyake & Friedman, 2012). Self-regulation results from an interaction between neural, physiological, and genetic systems (known collectively as the central autonomic network) that originates within multiple prefrontal cortices (e.g., medial prefrontal, orbitofrontal, dorsolateral, anterior cingulate, among others) and bi-directionally coordinates with multiple subcortical systems (e.g., striatum, amygdala, insula, hippocampus, among others). The cortical/subcortical coordination influences oscillatory output of cardiorespiratory centers via brainstem networks (e.g., nucleus tractus solitarius, dorsal motor nucleus of the vagus nerve, medulla, among others) (Bridgett, Burt, & Edwards, 2015). Simply, self-regulation is an emergent phenomenon produced by this integrative cardio-neural system, which promotes prefrontal cortex activation to inhibit subcortical structures and sympathetic activity via vagal inputs to the sinoatrial node of the heart and projecting signals to the brain.

Wei, Chen, and Wu (2018a) provide strong support for the central autonomic network, HRV, and self-regulation associations. These researchers found structural covariance between aforementioned cortical/subcortical networks and resting HRV; furthermore, they demonstrated HRV modulation occurs via neural pathways in the amygdala. Extending from this study, the same research group demonstrated inverse

associations between HF-HRV and grey matter volumes in limbic and striatal networks. Importantly, this association remained after controlling for age and gender (Wei, Chen, & Wu, 2018b). These findings support recent neuroimaging studies, which identified the prefrontal, amygdala, and hippocampal networks as being associated with resting HRV during task-evocation (Allen et al., 2015; Chang et al., 2013; Sakaki et al., 2016). A recent HRV meta-analysis (Allen, Jennings, Gianaros, & Manuck, 2015) demonstrates select brain areas represented in the central autonomic network are under putative vagal control in both resting and reactivity states. This analysis demonstrated greater resting and/or more efficient HRV responses reflect better parasympathetic control over cardiac function and optimal prefrontal cortex activation.

Several mild-cognitive impairment studies have demonstrated significant associations between neurocognitive test performance and HRV across different age groups and conditions (de Vilena Toleda & Junqueira, 2010; Frewen et al., 2013). A recent study conducted by Lin and colleagues (2016) evaluated physiological stress regulation in mild cognitive impairment during a 60-minute stress protocol. Utilizing measures of cognitive fatigability as a predictor of HF-HRV activity and examining the frontostriatial networks as a neural substrate for this interaction, the researchers found lower cognitive fatigability was associated with more efficient HF-HRV reactivity (shorter suppression intervals) to environmental challenges. This finding supports growing research associating adaptive HF-HRV to increased resiliency against stressors and better cognitive task performance (Guiliano, Gatzke-Kopp, Roos, & Skowron, 2017; Park, Vasey, Van Bavel, & Thayer, 2013; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). Contrarily, Lin and colleagues found those with increased cognitive fatigability

and worse performance on cognitive-stress protocols demonstrated a chronic pattern of HF-HRV suppression. Similarly, this finding supports previous research demonstrating cognitive inflexibility (indexed by reduced HRV) could be predictive of future cognitive impairments and even incident Alzheimer's disease (Zulli et al., 2005).

Functional Executive and Emotional Capacity as Self-Regulation Indices

EF, as a neuropsychological construct, is a subcomponent of self-regulation that reflects functional cognitive capacity. EF capacity is instrumental to problem solving, planning, goal selection, reasoning, and other regulatory processes in the service of information-driven, goal-directed behaviors (Collins & Koechlin, 2012). While the specific areas that define EF are debated amongst researchers, most studies adhere to three distinct (though interrelated) domains (i.e., cognitive flexibility [also known as set shifting], inhibition [self/behavioral control and selective attention/cognitive], and working memory [updating/maintenance]) (Miyake et al., 2000). In general, these three domains organize cognitive processes that initiate, monitor, redirect, and regulate adaptive responses (e.g., actions) to environmental demands. It is important to note that broader domains are associated with EF (e.g., decision-making, verbal learning, psychomotor speed, and processing speed) and, by extension, self-regulation (Thayer, Hansen, Saus-Rose, & Johnson, 2009).

Emotional capacity constitutes the other subcomponent of self-regulation and interacts both independently and symbiotically with EF in the service of cognitive control (e.g., reappraisal, suppression, inhibition). It reflects adaptive (as opposed to reflexive) neurophysiological coordination of affective responses (reactive vs inhibition, control)

that optimize desired outcomes relative to contextual dynamics. Successful inhibitory control of maladaptive emotional responses to contextual stressors is reflected by increased resting HRV (Holzman & Bridgette, 2017).

Adaptive self-regulation has been associated with increased social engagement, better quality of life (e.g., increased well-being, less psychopathology), and better performance in educational and occupational settings (Blair & Diamond, 2008; Geisler, Kubiak, Siewert, & Weber, 2013; Hofmann, Luhmann, Fisher, Vohs, & Baumeister, 2014; Porath & Bateman, 2006). Importantly, while psychosocial stressors can influence disease status both acutely and chronically, increased self-regulation can buffer against the negative outcomes of this influence (Evans & Fuller-Rowell, 2013). Maladaptive or restricted self-regulation in response to a stress-stimulus is reflected by reduced HRV profiles and has been shown to independently predict disease and mortality outcomes (Williams et al., 2015).

Heart-Rate Variability as a Biomarker for Self-Regulation

Beauchaine and Thayer (2015) suggested HRV could function as a transdiagnostic biomarker of self-regulation. Addressing inconsistent results in studies trying to specify either emotion or EF as independent biomarkers, these researchers along with others (Bridgett et al., 2015; Zhou et al., 2012) acknowledge the considerable overlap in neuronal substrates and present self-regulation as a combined and dimensional function. This conception is based on observations from multiple studies demonstrating reduced resting HRV and pronounced HRV withdrawal to both cognitive and emotional stressors across a sundry of psychopathological conditions (e.g., depression, anxiety,

attentional problems, apathy, and cognitive impairment). Contrarily, increased resting HRV, more efficient reactivity, and/or no change in overt HRV modulation is often observed when healthy or at-risk groups are exposed to similar cognitive tasks (Graziano & Derefinko, 2013).

Beauchaine and Thayer (2015) suggest poor prefrontal control over cognitive-behavioral responses to stressors represents general rather than specific vulnerability to psychopathology; moreover, this vulnerability can be attributed to poor EF as measured by HRV. Additionally, they suggest specific vulnerabilities to emotional dysregulation occur at the subcortical levels. Providing considerable support for HRV as a general biomarker for self-regulation, a recent comprehensive meta-analysis of 123 studies (N = 14,347) ranging across the lifespan found significant (albeit with a small effect [$r = 0.09$]) associations between resting HRV and self-regulation (Holzman & Bridgett, 2017). Stronger HRV associations were found in older adults when compared to younger samples with a linear decline in HRV being observed as age increased. Importantly, age moderated the associations between self-regulation and HRV. Moreover, Holzman & Bridgett (2017) found HRV was equally sensitive to both self-report and performance-based measures of self-regulation thereby supporting its validity across neurocognitive testing approaches. Given these findings, self-regulatory dysfunction (as measured by HRV) could provide an early indicator of both ANS and cognitive impairments; therefore, self-regulation in HAND is considered.

HIV, Heart Rate Variability, Aging, and Self-Regulation

The relationship between ANS dysfunction, inflammation, and cognitive

dysfunction was recognized quickly in the HIV epidemic with numerous early studies demonstrating reduced HRV profiles in this population (Freeman, Roberts, Friedman, & Broadbridge, 1990; Rogstadt et al., 1999). The overt and unregulated inflammatory processes intrinsic to untreated HIV grossly contributes to AIDS-associated dementia. However, the advancement of cART has drastically reduced the prevalence of AIDS-associated dementia by suppressing HIV's viral expression and helping regulate overt pro-inflammatory cytokine release (e.g., interleukin [IL]-1β, IL-6, IL-8, tumor necrotic factor-α [TNF-α], C-reactive protein [CRP]). Without overt cytokine expression, immune function remains grossly intact and HIV-SP persons are able to age with the virus. Despite extensive viral suppression and immune regulation by cART, mild inflammatory processes persist and promote chronic ANS dysfunction (Cohen, Seider, & Bradford, 2015; Gongvatana et al., 2013).

HIV's chronic, mild inflammatory processes are suggested to disrupt frontostriatal and hippocampal pathways, which have shown heightened sensitivity to increased cytokine signaling. Functional deficiencies in these pathways have been identified in those aging with HIV and reflect the presence of neuroinflammatory and neurodegenerative processes (for a review, see Fields, Dumaop, Langford, Rockenstein, & Masliah, 2014). This inflammatory process is suggested to contribute to both the behavior and cognitive impairments observed in the HAND population (Hong & Banks, 2015). Furthermore, this aligns with ongoing research in non-HIV persons suggesting increased inflammatory profiles are associated with impaired self-regulation and predict worse EF over time (Jefferson et al., 2011; Marsland et al., 2015).

Strong support for ongoing ANS dysfunction was recently demonstrated in a

meta-analysis of HIV and HRV studies in the cART era (McIntosh, 2016). From the eight studies identified, 292 HIV-SP adults (M_{age} = 38.7) and 201 HIV-SN adults (M_{age} = 35.1) were included in the analysis. The study found reduced resting HRV in both the time (RMSSD) and frequency (HF-HRV) domains, which suggests a chronic pattern of sympathetic dominance in HIV-SP participants. These findings support previous studies (which were not included in the meta-analysis) that identified similar reduced HRV profiles in persons with HIV (Askgaard et al., 2011; Becker et al., 1997; Lebech et al., 2007).

Consistent with the notion of chronic ANS dysfunction, data suggests that viral neuroinflammatory properties accelerate the aging process such that those with HIV may exhibit age-related neurocognitive changes earlier than their non-clinical counterparts (Ding et al., 2017; Tierney et al., 2017). As such, those aging with HIV are more susceptible to age-related cognitive effects (Becker et al., 2012; Thomas et al., 2013). Under normal conditions, as persons age beyond mid-adulthood, there is a gradual decline in frontostriatal mechanisms such that reduced connectivity in the prefrontal cortex and normal reduction in regulatory capacity over select EF cognitive functions over time is observed (Opitz et al., 2012; Sowell et al., 2004; Sakaki et al., 2016). HIV appears to accelerate this effect as altered neurophysiological activity and anatomical changes occur in the frontostriatal network, which corresponds to increasing self-regulatory impairments as persons age with the infection (Caldwell et al., 2014; Isper et al., 2015; Plessis et al., 2014). Specifically, neurocognitive studies in HAND suggest simple attention typically remains intact in favor of impairments in complex information processing (EF), selective attention, and emotional capacity. HIV appears to exert a

preferential pathological effect on self-regulatory domains in an accelerated manner. Despite overlapping brain areas in both self-regulation and HIV, there are a lack of studies addressing this concept.

Dispersion studies have suggested those with HAND demonstrate a reduced ability to maintain cognitive processes that help coordinate behavior relative to dynamic environments (Badre, 2008). Similar to self-regulation, dispersion represents functional performance or response variability in cognitive domains across multiple tasks and greater dispersion represents dysfunction in EF via reduced top-down regulation or reduced integrity of frontal systems (Strauss, Bielak, Hunter, & Hultsh, 2007). Importantly, a recent HIV study found dispersion resulted from a synergistic effect of HIV status and age. After controlling for demographic and medical variables, older HIV-SP adults demonstrated increased levels of dispersion relative to younger HIV-SP individuals regardless of the mean level of performance (Morgan, Woods, Delano-Wood, Bondi, and Grant, 2011). In the case of HAND, successful activation of adjacent brain networks typically occurs during simpler cognitive-behavioral outcomes; however, a pathological and inefficient activation (greater dispersion) often occurs during tasks of increasing complexity. Additionally, inefficient activation of adjacent brain networks has also been observed during resting-states (or non-task engaged) in persons with HAND. Importantly, these pathological activation patterns were observed in those with asymptomatic HAND and were apparent prior to any cognitive impairments detected by neurocognitive performance tests (Hakkers et al., 2017).

Given that HIV-associated pathological changes in frontostriatal (and associated pathways) activity appear to precede cognitive changes captured by neurocognitive

performance tests and HRV has been shown to correspond to self-regulatory changes in these areas, HRV measures could provide a more sensitive assessment of detecting HAND in its pre-clinical stages. Unfortunately, few studies have examined persons aging with HIV in the context of HRV and self-regulation (particularly, the cognitive function sub-component).

Notably, questions exist in HAND research regarding the weighted contribution of age versus HIV infection to neurocognitive changes observed in this population. As such, prior to HRV's consideration as a clinical marker for HAND, a better understanding of aging and HRV in the context of cognitive function is needed. However, few large-scale HRV studies have examined self-regulation in the context of healthy aging populations to determine its ability to detect cognitive impairments. To help elucidate HRV's potential usefulness as a cognitive biomarker in the context of aging, HRV and self-regulation studies in healthy, adults 40 years and older are reviewed. Importantly, due to HAND criteria and neurocognitive batteries largely focusing on cognitive function as opposed to emotional capacity (though these can be added and can certainly influence cognitive results), the reviewed articles will focus primarily on the cognitive sub-component (EF).

HRV and Considerations for Systematic Review

The current systematic review was conducted based on the standards established by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Malik, 1996) and the Society for Psychophysiological Research (Berntson et al., 2017) for HRV and vagal function. In

addition, as recommended by Laborde, Mosley, and Thayer (2017), more recent summative articles reporting on methodological approaches and controversies in HRV research were utilized to help refine the systematic review (Billman, Huikuri, Sacha, & Trimmel, 2015; Quintana, 2017; Quintana, Alvares, & Heathers, 2016; Shaffer, McCraty, & Zerr, 2014). Importantly, articles referenced above focus on methodological reporting specific to vagal-mediated HRV. In referencing these articles, it should be noted that some controversy exists in physiological research as it relates to HRV analysis (linear vs non-linear) and the contributions of parasympathetic vs sympathetic (e.g., baroreflex) to activity within select HRV indices. Nonetheless, this article presents the current operationalization of vagal-mediated HRV.

Search Strategy for HRV and Cognitive Function in Healthy Populations

A systematic review of HRV and cognitive function in healthy (non-HIV) older adults was conducted from a PubMed search on January 1st, 2018. PubMed was selected as it provides a comprehensive database that incorporates a range of multidisciplinary scientific publications relative to neurocognition and physiology. The PRISMA approach (Moher, Liberati, Tetzlaff, Altman, 2009) (see Figure 1) provided the method for conducting the literature review. The search was restricted to peer-reviewed research articles published in English. The initial search included combinations of heart-rate variability, cognitive function, self-regulation, and HIV yielding zero results. Keywords operated in the second search were “heart rate variability and cognitive function” yielding 215 articles and “heart rate variability and cognition” yielding 169 articles. To ensure all relevant articles were identified, both cognitive and HRV terms were specified and paired

individually. Key HRV terms were “RMSSD”, “high-frequency heart rate variability”, and “respiratory sinus arrhythmia” were each individually paired with cognitive domains “speed of processing”, “verbal fluency”, “executive function”, “verbal learning and memory”, “attention and concentration”, “fine motor”, “psychomotor speed”, and “memory” yielding 143 articles.

Results were narrowed by excluding children, pregnancy, 24-hour or less than two-minute HRV measurements, non-linear measurement, and interventional studies (e.g., biofeedback, physical exercise). Inclusion criteria applied to remaining articles were quantitative studies in healthy adults with a mean age of 40 and older; sample sizes greater than 100; sociodemographics adequately defined in each study; resting HRV at baseline (at least 5 minutes); HRV indices were restricted to cardio-vagal measures: RMSSD, RSA, and HF-HRV; and measurement context must have been adequately reported (e.g., position, recording period, detection, sampling frequency, artifact removal, respiration [paced or not], calculation). After criteria application, a total of six articles were included in the review. A more detailed review of these studies can be found in Table 1.

Results

In a socioeconomically diverse, large-scale cohort (Midlife Development in the United States [MIDUS]), Kimhy and colleagues (2013) examined the association between EF and cardiac vagal control in a sample of 817 participants (M_{age} = 57.11 years; 456 women). The Brief Test of Adult Cognition (BTACT) provided a measure for speed of processing, working memory, verbal ability and speed, and fluid intelligence (Tun &

Lachman, 2006). To measure task switching (attention and inhibitory control), The Stop & Go Switch Task (SGST) was utilized (Tun & Lachman, 2008). These tests provided a combined measure of both accuracy and latency (i.e., reaction time) of responses. A global EF score was used for the primary analysis.

HF-HRV provided the measure for vagal function (rest and recovery) and was analyzed in a seated position over three periods: baseline (11 minutes total), cognitive stress tests (12 minutes total), and recovery (12 minutes total). In order to provoke an acute stress response to evaluate vagal control, either a mental arithmetic task (Turner et al., 1986) or the Stroop color-word conflict were assigned to participants for challenge one. The second challenge consisted of completing the opposite test assigned in the first challenge. Each challenge lasted six minutes with a six-minute recovery period following. Notably, EF was measured at a separate time than HRV (ranging from 1-61 months; $M = 24.18 \pm 14.09$). All analyses were adjusted for time due to the age-related changes that can occur in both EF and HRV over time.

Primary analysis of resting HRV found associations between global EF, speed of processing, and task-switching among those with comorbidities and vagal-influencing medications; however, once demographics (age, sex, and education) was added, these associations were negated. Likewise, there were no significant associations between vagal recovery and global EF. Adjusting for respiration, exploratory post-hoc analyses found associations between resting vagal control and fluid/intelligence, working memory, speed of processing, EF global score, and task switching. However, once covariates were added to the models, these associations were negated. Contrarily, after adjusting for respiration and covariates, a significant association was found between vagal recovery

and task switching (β = .157, p = .010). Although reduced, this association remained after adjusting for the influence of cardiovascular conditions and vagal-influencing medications.

Utilizing the same MIDUS cohort as Kimhy and colleagues (2013), Lin, Heffner, Mapstone, Chen, and Porteisson (2014) examined if older adults with greater cardiovascular reactivity to acute stress would show positive associations to EF. Secondarily, engagement in regular mentally stimulating activities (MSA) was examined as a moderator for this cardiovascular reactivity and EF association. Using a six point ordinal scale with a lower score representing high mental engagement (cutoff median of ≤ 3.50), two groups (N = 487) were created based on participant's level of engagement in six assigned MSA's (reading, word games, card playing, attending lectures, computer activities, and writing).

The high mentally stimulated (HMSA) group (n = 214; 130 women; M_{age} = 65.14) and low mentally stimulated (LMSA) group (n = 266; 117 women; M_{age} = 64.95) completed the BTACT and SGST. A composite EF score was created from an average of z-scores. The frequency domains low-frequency (LF) and HF provided the measures for reactivity. The methodology and acute stress challenges were the same as Kimhy and colleagues (2013). For reference, LF-HRV is suggested to measure the baroreflex in resting states, which couples both sympathetic and parasympathetic activity in response to cardiac stretching. This coupling allows blood pressure adjustments during prolonged stressful states by decreasing peripheral resistance, heart rate suppression, and slowed contractility of the heart. Importantly, during periods of slow breathing (e.g., rates below 7.5 breaths per minute) or deep sighs, vagal influences can generate oscillations in the LF

band (Wang, Kuo, Lai, Chu, Yang, 2013).

The three reactivity periods (baseline, stress, and recovery) were analyzed separately. As expected, both groups' heart rate increased significantly during stressors, while both LF and HF decreased in response to stressors with a greater decrease observed during the Stroop test. When MSA was added to all models, increased mental engagement exhibited a higher baseline LF and greater decrease in LF and HF reactivity. Using a regression approach and controlling for covariates, there were no associations found between baseline HRV and EF. During stress tasks, heart rate and LF were significant predictors of EF. When MSA was added, it predicted EF in all models and explained 9% of the variance in EF. A significant interaction was found between heart rate and MSA (explaining an additional 1% of the variance). Given this interaction, heart rate and MSA were examined in the two groups. After controlling for covariates, this interaction remained significant for the LMSA group only.

In a sample of 440 participants (M_{age} = 43 years) with approximately 53% women, Jennings, Allen, Gianaros, Thayer, and Manuck (2015) examined the neurovisceral integration hypothesis in the context of HF-HRV (0.12 - 0.40 Hz), regional blood flow, and EF. A one-hour neurocognitive battery was administered in a single session to assess working memory and interference control (cognitive flexibility, attention, and speed of processing). Utilizing controlled respiration (11 breaths per minute) paced by two auditory cues to inhale and exhale, HF-HRV was measured in a seated position over a five minute period.

A bivariate correlation was found between HF-HRV and Stroop interference for the entire sample. No other associations were found. Given the influence of both sex and

race (n = 70 were African-American) on both HRV and EF measures, bivariate correlations were conducted for these sociodemographics. Among Caucasians, HF-HRV was associated with better performance in working memory and interference (backwards digit span, Trails B [$p < 0.05$]; and Stroop interference [$p < 0.01$]). Notably, these correlations demonstrate a similar pattern and magnitude found by Kimhy and colleagues (2013) prior to demographic adjustments. No correlations were found for Blacks.

Based on previous studies demonstrating HRV being a functional index of self-regulatory capacity, Mann, Selby, Bates, and Contrada (2015) attempted to test this concept via structural equation modeling. In a sample of 533 (M_{age} = 54.9; 286 women) participants involved in the MIDUS Biomarker cohort, HRV was examined relative to EF and negative affect. HF-HRV (0.15 - 0.50 Hz) and respirations (non-paced) were measured in a seated position over a 10-minute baseline period (divided into two five-minute epochs). Like previous MIDUS studies, the BTACT measured episodic verbal memory, inductive reasoning, working memory, processing speed, verbal fluency, and task switching and was collected separately from HRV. The Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977) and Speilberg State Trait Anxiety Inventory-Trait Version (STAI-T) measured negative affect (Speilberger, 1983). Collection periods occurred separately over two years and varied for HRV, affect, and EF (M = 24.12; SD = 14.11).

Bivariate correlations were found between HRV and attentional set-shifting/inhibition. Structural equation modeling was used (includes both latent and measured variables) to better represent hypothesized interrelationships in the context of multiple variables. After preliminary analyses, three models were created. The

measurement model treated negative affect and EF as latent variables and demonstrated good fit with all indicators having significant factor loadings. As expected, EF and negative affect were inversely associated. The structural model (full model) demonstrated good fit and, as expected, a positive relationship was found between HR-HRV and EF. No association was found between negative affect and HRV or EF. The best model was the covariate-adjusted model and included only confounders that demonstrated bivariate correlations to HRV. Interestingly, the association between HRV and EF disappeared in this model. Whereas, the EF and negative affect relationship re-emerged significantly. Age was found to significantly predict both EF and negative affect. Inverse relationships between covariates and HRV were retained throughout this model testing. Based on these results, a constrained covariate model and a model with HRV as a predictor of both negative affect and EF (covariates non-constrained) were compared. The latter model showed superior fit.

Stenfors, Hanson, Theorell, & Osika (2016) examined the effects of cardiovascular regulation and EF in a sample of 119 participants (M_{age} = 47.98; 94 females) from the Swedish Longitudinal Occupational Survey of Health. In addition to LF and HF, the time-domain of HRV (RMSSD) and a QT variability index (QTVI) were utilized to evaluate cardiovascular regulation. The study operationalized QTVI as providing a ratio between sympathetic and parasympathetic tone (with increases representing sympathetic activity) and measuring cardiac repolarization lability. HRV was collected in a supine position over a five-minute period (after a two-minute rest period prior to recording); then, a neuropsychological battery measuring EF (memory, verbal working memory, attention-shifting, psychomotor speed, maintenance/updating,

and inhibition) was administered immediately following HRV collection.

Bivariate correlations found increased RMSSD and reduced QTVI were associated with better inhibition, shifting, updating, and psychomotor speed. No associations were found between EF and HF-HRV. Age, as expected, demonstrated an inverse association with RMSSD, and HF-HRV along with a positive association to QTVI. Interestingly, it appeared as if QTVI was less affected by aging. Notably, sex was associated with RMSSD, HF-HRV, and EF measures; however, educational level and physical activity were not. Similar to previous research, once age and sex were adjusted, the associations for RMSSD disappeared. Interestingly, after adjusting for all covariates (including age and sex), the associations between increased QTVI and poorer performance on multiple executive measures remained.

Building from previous research in the MIDUS cohort, Crowley and colleagues (2016) examined if adults with faster cardiovagal recovery would demonstrate better task switching when compared to adults of similar age with slower cardiovagal recovery. In a sample of 817 participants (M_{age} = 57.11 years; 456 women), three groups were created: 1) young adults (35 - 54 years old; n = 354), 2) middle adults (55 - 64 years old; n = 260), and 3) older adults (65 - 86 years old; n = 203). With the exception of only using the SGST as a measure of task switching, other methodological protocols were the same as described in Kimhy and colleagues (2013).

Using a regression approach, a main effects model for age, vagal recovery, and age/vagal recovery interaction as predictors of EF was tested. A similar model for vagal reactivity was also tested. Confirming previous studies, an inverse relationship was found between cardiovagal control and age both before and after adjusting for respiration. Both

vagal recovery and reactivity were also associated with age. Likewise, an inverse relationship was found for age and EF as reaction time to switch/non-switch trials decreased with age. The primary finding was the moderating effect of vagal recovery on the EF and age associations. All effects remained significant after adding and controlling for demographic, medical, and health covariates. Following from these results, models were tested against the three age groups. Before and after respiration adjustment, vagal recovery was significantly related to EF in the older group only.

Discussion

The lack of available HAND biomarkers that can detect early cognitive impairments limit our understanding of the contributing or causal mechanisms that underlie neuropathological changes. Furthermore, neurocognitive performance tests utilized to diagnose HAND lack clinical feasibility and sensitivity in detecting prodromal or early cognitive impairments. The purpose of this review was to determine if vagal-mediated HRV could provide a clinical marker for detecting earlier impairments in HAND relative to self-regulatory function (specifically EF) in aging adults with an average age of 40 years old. Based on this review of larger-scale studies, HRV could be a useful clinical marker for the aging HIV population in the context of self-regulation.

Mann, Selby, Bates, and Contrada (2015) provide the strongest support for HRV as a clinical marker for self-regulation. The results of this study were consistent with previous research demonstrating the EF lowering effects of salient negative affect (Kaiser et al., 2014; Spangler, Bell, & Deckard, 2015). The addition of age into their covariate model suppressed the relationship between HRV and EF, which is consistent with current

research identifying age as a moderator of self-regulation and HRV (Holzman & Bridgette, 2017).

The findings also support the importance of including emotional capacity as a feature of cognitive research due to chronically dysregulated affective networks impairing EF cognitive performance and contributing to impaired cognitive function over time (Ortner, Zelazo, & Anderson, 2013). Chronic emotional disorders are well established as predictors of earlier onset cognitive impairments (and later dementia) and reduced cognitive reserve (Ismail, Gatchel, Batement, & Barcelos-Ferreira, 2018). Moreover, emotional dysregulation is among the strongest predictors of vagal-mediated HRV (Beauchaine & Thayer, 2015). Likewise, emotional dysregulation (prolonged vagal recovery) is consistently associated with increased basal IL-6 and CRP relative to both acute and chronic stress exposures (Sin, Graham-Engeland, Ong, & Almeida, 2015). Given this, self-regulatory measures (such as HRV) may be particularly relevant to earlier diagnosis of HAND as affective dysregulation earlier in life (e.g., post-traumatic stress, perceived stress, adversity [lower socioeconomic status, discrimination], among others) targets frontostriatal and hippocampal pathways. Furthermore, maladaptive emotional capacity has been associated with poorer social and cognitive outcomes in HIV (Rubin et al., 2016; Thames et al., 2017; Womersley, Seedat, & Hemmings, 2017).

The EF impairments that characterize HAND often remain undetected until persons are older and/or when symptoms become sensitive enough for neurocognitive tests; however, emotional processing deficits are observed in both younger and older persons with HIV thereby indicating earlier affective impairments in this population (Clarke et al., 2015). Grabyan and colleagues (2018) recently demonstrated that persons

with HAND were ten times more likely to have impaired emotional processing accuracy relative to HIV-SP adults without HAND and concluded this feature could have clinical value as an independent predictor of functional cognitive capacity. In one of the few HRV studies in HIV focusing on emotional processing, Heilman, Harden, Weber, Cohen, and Porges (2013) found reduced HRV and poorer performance on affective recognition tasks in a middle-aged cohort of HIV-SP women. Importantly, reduced HRV (specifically delays in vagal recovery) has been associated with impaired emotional processing across the life span (Park & Thayer, 2014). It is possible that dysfunctional self-regulatory patterns could precede the detectable cognitive impairments that characterize HAND; however, emotional domains are not specifically included in the current diagnostic criteria for HAND.

This review also supports vagal activity as an indicator of cognitive function in the aging population as Crowley and colleagues (2016) found faster vagal recovery was associated with better performance in EF and cognitive inhibition domains. Importantly, despite aging adults having a longer cardiovagal recovery time, faster recovery predicted performance on EF measures. Kihmy and colleagues (2013) found faster HRV recovery was correlated to task-switching after controlling for comorbidities, demographics, and health behaviors. However, notably, associations were not found for resting or recovery HRV in EF composite scores. These findings align with previous research suggesting that HRV is not sensitive to all components of EF, but is better conceptualized as a general biomarker for components represented in those associated with self-regulation (e.g., set-shifting) (Bridgette et al., 2013; Zhou et al., 2012). Given those with HAND experience an accelerated-aging decline in cognitive performance, a delayed vagal-recovery profile

(less efficient HRV) earlier in the lifespan of those with HAND could indicate prodromal ANS signs of impending cognitive impairment.

Lin and colleagues (2014) did not find any associations between resting HRV and EF. This was similar to the findings of Stenfors, Hanson, Theorell, and Osika (2016). One potential explanation for the insignificant findings between resting HRV and EF was the absence of emotional measures. For example, Spangler, Bell, and Deckard (2015) found a strong quadratic association in high emotional suppression with resting RSA and EF. These researchers suggested that RSA could better predict poor EF if emotional regulatory activity is diverting resources away from executive domains (e.g., prefrontal cortices). Notably, Lin and colleagues did find associations between increased HR during cognitive stressors (suggesting vagal-withdrawal or reactivity) with those that consistently engage in mentally stimulating activities showing more efficient reactivity to cognitive challenges. Importantly, in the context of covariates, heart rate and EF interactions remained significant for those with low engagement in mentally stimulating activities. This suggests a more adaptive self-regulatory response to cognitive stressors in those that continually engage in cognitive-oriented tasks throughout their life. These findings confirm previous studies that found an association between cardiovagal reactivity and EF (Ginty, Phillips, Der, Deary, & Carroll, 2011).

Findings from cardiovagal reactivity studies could have implications for HAND relative to chronic inflammatory processes. Early studies (Manuck et al., 1991) and more recent meta-analyses (Marsland, Walsh, Lockwood, & John-Henderson, 2017; Steptoe et al., 2007) demonstrate the degree of cardioreactivity directly corresponds to individual inflammatory marker activity (IL-6, TNF-α, CRP, among others) in response to an acute

stressor (e.g., cognitive, psychological). Importantly, both IL-6 and TNF-α are chronically elevated in HAND (Sartori, Vance, Slater, & Crowe, 2013) and are associated with corresponding reduced HRV profiles in both younger and older HIV cohorts (Chow et al., 2011; McIntosh et al., 2016; Mittal et al., 2004). This cardiovagal reactivity could be particularly pronounced in HIV-SP women as they demonstrate age-associated increases in inflammatory marker production at a much higher rate compared to HIV-SP men. This progressive increase in inflammatory markers accelerates physiological aging via dysautonomia such that HIV-SP women demonstrate an "immune age" 10-14 years older than their non-clinical counter parts (Martin et al., 2013; Touloumi et al., 2004). Several large HIV registry studies in women (Nuo, Lo, & Grinspoon, 2016; Triant et al., 2007) support a three to four-fold increase in risk of cardiovascular disease, cardiac events, and metabolic disorders at an earlier age, which is suggested to be directly associated to increased inflammatory profiles. Importantly, healthy women demonstrate greater resting HRV relative to men from infancy until approximately 50 years old. As such, identifying reduced HRV profiles earlier in the life span for HIV-SP women could indicate a higher risk for developing cognitive impairments. Research suggests estrogen and oxytocin (among other variables) could provide ANS protective effects until the post-menopause phase diminishes these vagal-mediated effects (Koenig & Thayer, 2016). Future HIV studies examining HRV and self-regulation should consider gender as a biological variable.

Clinical Implications

Understanding the relationship between age, gender, and medical comorbidities

(e.g., Hepatitis C, substance use) in the context of HRV is still in its infancy; therefore, standardized normative and clinical data are needed before it can hold independent diagnostic value for any disorder. More large-scaled studies such as the ones reviewed in this article are needed to determine these variables contributions to HRV as persons age. As such, approaching HRV as a general clinical marker for self-regulatory dysfunction (as suggested by Beauchaine & Thayer, 2015) could optimize its potential benefit relative to current research. With that, consideration should be given to HRV's routine use in the HIV clinical setting as it could identify cognitive impairments earlier than standardized neurocognitive batteries (Haakers, 2017; Zulli et al., 2005) and is a strong indicator of general health (Thayer, Ahs, Frederikson, Sollers III, & Wager, 2012). Furthermore, given the contributions of both emotional and cognitive domains to the impairments observed in HAND, HRV could provide an objective and reconciliatory measure (due to neurocognitive tests emphasizing emotional capacity less) of this duality via its relationship to self-regulation.

From a practical position, measuring HRV in the clinical setting is far more efficient relative to the administration of neurocognitive batteries (can range anywhere from one to three hours pending the comprehensiveness of the battery). HRV can be measured over about ten minutes and reduces the administration burden on both provider and patients alike. However, manual processing of these data are traditionally needed to extract valid clinical information. This requires considerable training, increases individual variation in editing (making it more difficult to compare across different clinics or populations), and is time-intensive. Fortunately, though more extensive psychometrics are needed, automated algorithms are being developed that can bypass the

manual processing limitations and reduce variation in individual HRV editing. For example, Hegarty-Craver and colleagues (2017) developed an automated algorithm for processing HRV that demonstrated minimal bias and absolute differences in comparison to manual editing (mean differences = -0.02-0.10). Furthermore, across scoring methods, HRV changes from baseline to EF performance were reliably similar with an absolute agreement of 96-100% (k = .83-1.0). Automated HRV algorithms could increase clinical feasibility, earlier detection, and timely interventions in those experiencing or at-risk for developing HAND.

Conveniently, many commercial products (e.g., watches and phones) are also available that possess built in and wearable electrocardiogram sensors that can provide general information to patients about their HRV status. This makes the patient an active participant in their care and provides them daily feedback about changes in their physiological status. Moreover, many of these products collect this information into software programs or applications that provide day-to-day data to the patient. If needed, these data could also be accessible to clinical providers to help evaluate responses to treatment or interventions. While the validity and reliability of these commercial devices are controversial, technology is rapidly advancing in this field with many of these devices (e.g., Polar) being used both in research and commercial settings (Giles, Draper, & Draper, 2016).

Limitations

The review included only six articles based on strict methodological guidelines for inclusion; furthermore, it was conducted in non-clinical populations due to the limited

studies available in HIV. Thirdly, many of the reviewed studies utilized similar participant cohorts (i.e., MIDUS), measurement protocols, and cognitive assessments (e.g., BTACT, SGST), which were largely based on those established by Kimhy and colleagues (2013). Moreover, the MIDUS study also collects HRV and cognitive data at different time intervals (over a two-year period). While HRV has been shown to be reliable and valid for up to three and one-half years in longitudinal studies in cardiovascular burdened participants (Goedhart et al., 2007), more research is needed to determine if HRV is affected by aging in the context of self-regulatory domains. While our ability to generalize the results of these studies seems plausible, it cannot be ruled-out that the cognitive assessments utilized or MIDUS cohort do not select for or show an increased sensitivity to vagal-mediated HRV measures. For example, using Alice-Heim 4-I and Mill Hill Vocabulary Tests, Britton and colleagues (2008) did not find an association between vagal-mediated HRV measures and cognitive function in a large (N = 5,375), middle-aged, UK Whitehall II cohort. Lastly, this review focused primarily on the cognitive sub-component of self-regulation due to the standardized diagnostic criteria of HAND (Antinori et al., 2007) and neurocognitive tests focusing primarily on cognitive performance. Given this, any conclusions drawn should be generalized to the need to research HAND in the context of general self-regulation and HRV.

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Figure 3. Systematic Review Methodology and Results

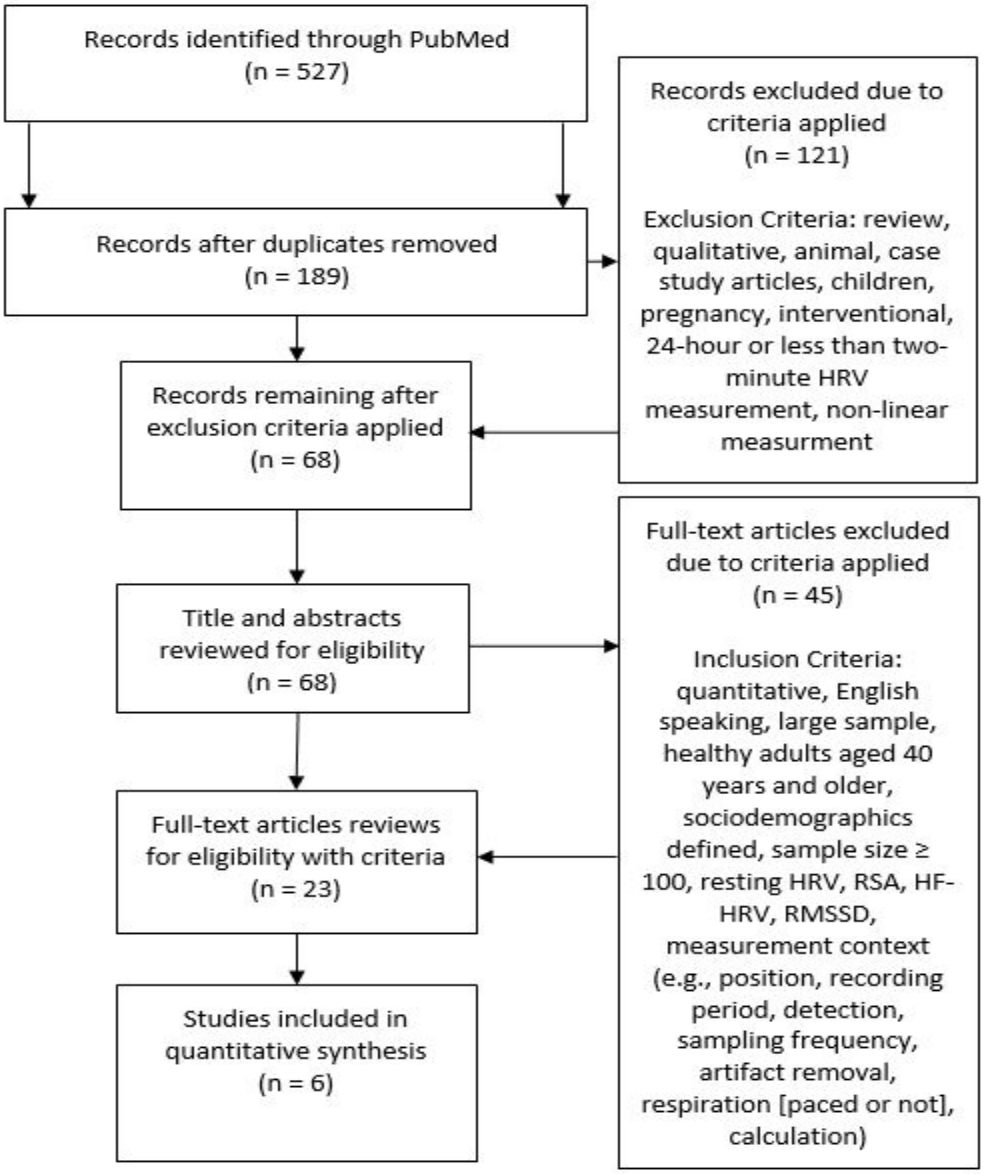

Figure 3 PRISMA flow diagram demonstrates screening method for articles.

Note: Copyright © **2009**. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA statement. PLoS Med. @009;6(7): e10000097. doi: 10.1371/journal.pmed1000097.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

EXPLORATORY EXAMINATION OF RESPIRATORY SINUS ARRYTHMIA AND COGNITIVE FUNCTION IN WOMEN LIVING WITH HIV

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ABSTRACT

Background. HIV-seropositive (HIV-SP) women exhibit proinflammatory profiles that are compounded by chronic stress factors (e.g., socioeconomic, biological, and emotional), which dysregulate vagus nerve-related autonomic nervous system (ANS) activity and drive vulnerability to select cognitive impairments. Vagus nerve function (indexed by reduced baseline respiratory sinus arrhythmia [RSA]) is compromised during chronic inflammatory states, which correspond to impaired stress resiliency and cognitive flexibility over time; therefore, vagal dysfunction could be associated with select cognitive impairments observed in HIV-SP women. **Methods**. Secondary data obtained from a Chicago Women's Interagency (WIHS) HIV Study cohort of 100 HIV-SP and 44 HIV-seronegative women provided baseline RSA averages, seven neurocognitive domain total scores (attention, executive, psychomotor speed, fine motor function, verbal fluency, memory, and learning), and a global function score. Group differences were tested with general regression models. **Results.** A significant interaction model (F (1, 134) = 3.47, p = 0.00) was found between reduced RSA and worse fine motor function for HIV-SP women (β = .37, p = 0.04) (though interaction did not depend on HIV viral markers). Greater income had a positive influence in this interaction (β = 0.19, p = 0.02). Increased RSA values corresponded to better psychomotor speed performance in both groups (β = 0.18, p = 0.03); whereas, emotional burden negatively influenced this association (β = -0.15, p = 0.05). **Conclusions**. Taken together, this study supports that vagal dysfunction could have implications for the psychomotor impairments observed in HIV-SP women.

Key Words: WIHS, RSA, HIV-associated cognitive impairments, vagus nerve

EXPLORATORY EXAMINATION OF RESPIRATORY SINUS ARRYTHMIA AND COGNITIVE FUNCTION IN WOMEN LIVING WITH HIV

Despite adequate viral suppression, approximately 30 to 60% of persons living with HIV will experience cognitive impairments (Grant, 2008). While research is ongoing, cohort studies (i.e., Women's Interagency HIV Study [WIHS]) have identified distinct differences in the cognitive domains affected by HIV in comparison to their male counterparts (Maki et al., 2018). HIV-seropositive (HIV-SP) women demonstrate pronounced impairments in fine motor, verbal learning, memory, psychomotor speed, verbal fluency, and discrete executive domains (e.g., attention and concentration) when compared to HIV-seronegative (HIV-SN) women and mixed HIV samples (Vance et al., 2016; Walker & Brown, 2018).

Many studies acknowledge stress-based autonomic nervous system (ANS) differences exist between men and women in the context of proinflammatory activity (particularly viral diseases), which could contribute to variation in neurocognitive outcomes (Derry, Padin, Kuo, Hughes, & Glaser et al., 2015; Klein & Schwartz, 2018; Lischke et al., 2019; Moeieni et al., 2019). The vagus nerve (indexed by respiratory sinus arrhythmia [RSA] or vagal-mediated heart rate variability [vmHRV]) has been suggested as a potential mediator of these differences due to its putative role in regulating ANS-inflammatory activity, stress responses, and maintaining homeostasis via coordinated parasympathetic activation (Laborde et al., 2017). Increased resting vagal activity (greater baseline vmHRV) is associated with adaptive homeostasis, greater resiliency against neuroinflammatory disorders, improved cognitive flexibility, mortality rates, and medical outcomes (Guiliano, Gatzke-Kopp, Roos, & Skowron, 2017; Park et al., 2013).

Notably, as healthy women experience age-related transitions into postmenopausal stages, a pronounced loss of vagal tone naturally occurs in comparison to men. This vagal decline results in an accelerated reduction of vmHRV that increases women's likelihood of developing select age-specific inflammatory disorders due to elevations in microglia-activated cytokine activity (Klein & Schwartz, 2018; Koenig & Thayer, 2016). Given this, any chronic, pathological acceleration of vagal decline or dysfunction is suggested to put women at a higher risk for microglial driven cognitive impairments (e.g., Alzheimer's disease) (Capuron & Miller, 2011) and, possibly, HIV-associated cognitive impairments (Delgado-Velez et al., 2015).

Differently than men, women's response to acute and chronic stressors grossly result in depressive and emotional dysregulation patterns (e.g., social isolation, physical pain, anxiety, low mood), which reflect hyper-activation of microglial and other cytokines (e.g., interleukin [IL]-1β, IL-6, Tumor-necrosis factor alpha [TNF-α]) (Bourke & Neigh, 2011; Singhal & Baune, 2017). Both depression and emotional dysregulation affect women's ANS disproportionately (reduced vmHRV), increase earlier onset cognitive impairments, reduce cognitive reserve, and are directly mediated by vagus nerve activity (Kuang et al., 2019; Ismail, Gatchel, Batement, & Barcelos-Ferreira, 2018; Williams et al., 2018). HIV-SP women, particularly Black women, report higher levels of persistent depression and emotional dysregulation (e.g., increased stress perception) relative to their SP and SN counterparts (Kessler et al., 2005; McIntosh, Tartar, Wimayer, & Rosselli, 2015; Rubin & Maki, 2019).

This trend is particularly concerning given Black women represent the majority of women living with HIV; and, they are exposed to considerable stressors that impact vagal

function including increased rates of psychological (e.g., PTSD), psychosocial (e.g., income status, education level), medical (e.g., hepatitis C [HCV]), and substance use issues (Sandermann et al., 2018; Valdez, & Jovanovic, 2016; Valdez, Rubin, & Neigh, 2016). Previous WIHS studies have found compounding stress factors either independently or collectively contribute to worse performance in psychomotor, fine motor, select executive, and verbal memory and learning domains (Rubin & Maki, 2019; Rubin et al., 2016; Rubin et al., 2015), which could indicate an increased vagal-burden in this population. Given chronic inflammatory and reduced vmHRV profiles (Addo & Altfield, 2014; Heilman et al., 2013) have been observed, vagal-dysfunction could increase susceptibility to select cognitive impairments observed in HIV-SP women.

While research examining the relationship between vagal-activity and cognitive function is ongoing, a central component of vagal-ANS regulation occurs via an intrinsic vagal cardio-neural network (commonly referred to as the central autonomic network) (see Benarroch, 1993; Vigo, Siri, & Cardinali, 2018). This vagal network communicates physiological demands (e.g., slowed breathing and heart-rate, anti-inflammatory cytokine release) from the sinoatrial node of the heart to subcortical (e.g., brainstem, limbic, basal ganglia) and cortical brain regions (e.g., prefrontal cortex, hippocampus) in response to neuroinflammatory cytokine signaling or stress challenges (e.g., complex cognitive tasks) (Kraynak, Marsland, Wager, & Gianors, 2018). Vagal activity purportedly helps maintain cognitive-emotional reserve over the lifespan via cognitive (or "top-down") regulation over behavioral, emotional, and peripheral responses to stressors (Bridgette et al., 2015; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012).

Importantly, a recent meta-analysis of 123 studies (N = 14,347) ranging across the lifespan found significant (although with a small effect [r = 0.09]) associations between resting vmHRV and cognitive-emotional processes. Their findings support increasing evidence that cognitive-emotional domains functionally intersect and bi-directionally relate to vagal-ANS activity via top-down processes (Holzman & Bridgett, 2017). In part, regulation results from greater vagal activity in select cognitive domains such as discrete executive (e.g., reappraisal), attention (Hansen, Johnsen, & Thayer, 2009), working memory (Hansen et al., 2004), spatial memory (Matthews, Dywan, Snysder, Tays, and Segalowitz (2011), motor function (Casado, Zabala, Morales, Mateo-March, & Sanabria, 2013), and psychomotor speed (Sackheim et al., 2001). These findings could be particularly relevant given increased peripheral cytokine production and stress sensitivity in select vagal-network brain areas play a critical role in many of the cognitive-emotional impairments observed in HIV-SP women (e.g., psychomotor speed, fine motor, and select executive)(Comasco, Frokjaer, & Sundstrom-Poromaa, 2014; Luine, 2014; Newhouse & Albert, 2015).

Notably, not all studies have found associations between baseline vmHRV and select cognitive domain activity (Britton et al., 2008; Capuana, Dywan, Tays, & Segalowitz, 2012; Ohira et al., 2013; Zahn et al., 2016). While studies examining associations between baseline vmHRV and select cognitive domain function are mixed (possibly due to emotional measure exclusion or differences in methodology [see Billman, Huikuri, Sacha, & Trimmel, 2015; Laborde, Mosley, & Thayer, 2017; Holzman & Bridgett, 2017]), evidence generally supports greater resting vmHRV is associated with enhanced performance on select cognitive tasks and indicates adaptive ANS

function. Given the cognitive-emotional impairments observed in HIV-SP women, vagal-ANS activity could warrant investigation.

To our knowledge, no current HIV studies in women have examined cognitive function in the context of vmHRV. Thus, the primary purpose of this cross-sectional study was twofold: 1) to examine the relationship between RSA and global cognitive function and specific cognitive domains (i.e., executive function, attention, speed of processing, psychomotor speed, verbal fluency, verbal recall, and memory) and, 2) to examine the interaction between HIV status and RSA indexes on significant global and specific cognitive domains in HIV-SP women. We hypothesized RSA would be associated with fine motor, executive, and psychomotor speed domains.

Methods

Participants

Recruitment, protocols, and cohort demographics of WIHS have been previously described (Adimora et al., 2018). IRB approval from the University of Alabama at Birmingham human subject's committee (#300000572) was obtained, which included a data-use agreement from the principal investigator of the original study and WIHS research committee. A concept sheet (W17051) was submitted and approved by the WIHS research group.

This cross-sectional study utilized secondary data collected from a Chicago WIHS RSA Psychoneuroimmunology sub-study (between October 2014 and July 2017). The parent study included a sample of 161 demographically similar, English proficient

women (102 HIV-SP, 59 HIV-SN) that consented in accordance with the US Department of Health and Human Services guidelines to participate. HIV serostatus was determined by ELISA and confirmed by Western blot. All HIV-SP women were ART-experienced, and CD4+ nadir was collected prior to ART initiation. All women were included regardless of concomitant medications, HIV disease severity, or stable comorbidities (except past or current psychotic disorder, stroke, brain injury, and human papillomavirus). Women who were pregnant or up to 12 weeks post-partum, recently hospitalized, had surgery, or recent/current cold were enrolled after those conditions ceased.

Women who were unable to abstain from active substance use for at least 48 hours and/or caffeine use two hours prior to RSA assessment were excluded as well as visual or hearing loss that could affect cognitive performance. While associations between body-mass-index and RSA have been observed, it was excluded due to previous Chicago WIHS studies not finding any group differences (Heilman et al., 2013). Any participant missing RSA values (n = 7) and/or more than two of the cognitive domains were also excluded (n = 10).

Procedure

WIHS core study visits occur every six months and include medical examinations, lab work (e.g., HIV status, hepatitis C [HCV]), surveys (e.g., demographics, substance use history), and psychiatric assessments. WIHS's standardized neurocognitive battery is performed every two years to monitor and screen cognitive function status. For the current study, neurocognitive testing occurred on the same day or within three months

following the most recent WIHS core study visit. Neurocognitive battery protocols have been detailed in previous WIHS studies (Maki et al., 2009; Maki et al., 2015).

RSA collection occurred within 18 months of their most recent neurocognitive testing visit. Approximately 30 minutes was provided to participants for verbal briefing of study and RSA collection device placement prior to collecting physiological data. Three Ag/AgCl self-adhering electrodes were placed on the upper chest and abdomen (lateral surface) of participants, which connected to a LifeShirt® (Vivometrics) device. After electrodes were placed, a three-minute vagal-adjustment period was provided prior to collecting any physiological data. Data were collected with participants in a seated position with free-breathing and minimal motor activity encouraged (e.g., no talking, gross movements). Baseline cardiac data (i.e., RSA, heart rate, and median respiration) were analyzed during sequential 30-second epochs within three-minute blocks to provide five baseline measurements (see Heilman et al., 2013 for more details).

Primary Study Variables

CardioBatch software (Brain-Body Center, the University of Illinois at Chicago) provided the RSA values for this study. The software quantifies RSA amplitude based on age-specific parameters that are sensitive to maturational shifts in the spontaneous breathing frequency, which allows for comparisons between participants and groups regardless of age (Porges, 1985). Briefly, it extracted RSA variance (from original time series) by continually re-sampling over sequential time epochs developed from 500-millisecond intervals (inter-beat). The resulting time series was detrended and filtered to provide residual estimates associated with vagal-specific high-frequency band's (0.12 to

0.4 Hz). Estimate distributions were logarithmically normalized using transformation techniques (i.e., natural log), which produced the mean RSA value for each participant (Lewis et al., 2012; Porges & Bohrer, 1990).

The standardized WIHS neurocognitive battery utilized for this study has been used in previous WIHS studies (Antinori et al., 2007; Maki et al., 2009). The individual cognitive tests included in the battery each demonstrate good reliability (Cronbach's $\alpha >$ .70; $r =>$ .70) in both internal consistency and test-retest properties in adult samples (Maki et al., 2015; Moore et al., 2012; Woods, Moore, Weber, & Grant, 2009). Seven cognitive domains were measured by two neurocognitive tests: 1) verbal learning ("Hopkins Verbal Learning Test"; Brandt & Benedict, 2001), 2) verbal memory ("Hopkins Verbal Learning Test"), 3) verbal fluency ("Letter and Semantic Fluency Tasks"; Benton, 1968), 4) attention/concentration ("Wechsler Adult Intelligence Scale-IV: Letter Number Sequence"; Wechsler, 2009), 5) executive function ("Stroop Test: Trial Three"; Stroop, 1935; "The Trail Making Test: Part B"; Reitan, 1978), 6) psychomotor speed ("Stroop Test: Trial Two"; Comalli et al., 1962; "Symbol Digit Modalities"; Smith, 1973), and 7) fine motor ("The Grooved Pegboard"; Reitan & Wolfson, 1985).

Prior to analysis, due to an absence of cognitive norms for low-income minority women, normative T scores for premorbid levels of cognitive function were created by regressing each outcome on age, Wide Range Abilities Test Reading Recognition score (WRAT-3; a proxy for education level), and race/ethnicity. Consistent with previous WIHS and large HIV cohorts, demographically adjusted, composite T-scores for each domain were created by averaging both cognitive test scores (if only one domain test was

completed, a single T-score was used). A global neurocognitive score was derived for women who had T-scores for at least four of the cognitive domains. Global scores were categorized into no impairment (T-score ≥ 40), borderline impairment, or cognitive impairment (T-score < 35) (see Rubin et al., 2018 for details). Domain scores were adjusted for the number of prior test exposures (baseline, second, third, and later). This standardizing method has been utilized in prior WIHS research and allows for comparisons between HIV-SP and SN groups across cognitive outcomes (see Maki et al., 2015; Manly et al., 2011).

Covariates

Independent variables for neurocognitive function included: baseline hepatitis C virus (HCV) status; current HCV-RNA (≥ 800,000 International Units [IU] considered active); annual household income (above or below $12,000 yearly); self-reported recent (within six months), former (> 6 months), or never use of cigarettes (years smoked was also included). Recent crack, cocaine, heroin, and marijuana use (0 participants endorsed methadone or stimulant use) were also included; self-reported alcohol use included low-risk use (< 7 per week) and high-risk use behaviors (> 7 drinks per week or > 4 drinks in one sitting) (National Institute on Alcohol Abuse and Alcoholism, 2019). Self-report was corroborated with drug test results, participant's medical records, and current prescriptions. For within group HIV-SP analysis, the HIV stratum included: 1) HIV-RNA viral load (≤ 48 = non-detectable; ≥ 49 = detected), 2) Current CD4+ cell count (< 200, 200 - 500, and > 500 cells/mm3), 3) CD4+ nadir, and 4) helper/suppressor ratio (CD4+/CD8+).

Perceived Stress Scale (PSS; Cohen, Karmach, & Mermelstein, 1983), Post-Traumatic Stress Disorder Checklist-Civilian (PCL-C) Version (Weathers et al., 1991), and Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) were also controlled (Cronbach's $\alpha > .70$; $r = > .70$ for each). However, these were combined into a composite score ("Emotional Burden Scale") to reduce variable burden on regression models. A single score decision was based on increasing control for Type I error rate (given the sample size) and providing more meaningful information about the overlapping RSA burden (e.g., collinearity) imposed by stress-based conditions (Kim et al., 2018; Song, Lin, Ward, & Fine, 2013).

Before creating emotional burden scores, a variable correlation matrix was created and examined using a Pearson's approach. Correlations, strength, and sample adequacy suggested factor analysis was appropriate (Bartlett's test of sphericity [χ^2 (3) = 156.32, $p < 0.001$]; Kaiser-Meyer-Olkin = .71). Then, total scores from each emotional measure were standardized (converted to z-scores) to create a summative composite score. Summative scores were cross-validated utilizing a regressive-based principal component analysis score (equally weighting all three variables at 0.33), which resulted in a 0.99 association. Standardized loadings met requirements (CESD = 0.78, PCL-C = 0.90, and PSS10 = 0.88; $\alpha = .81$) and supported a one factor solution (eigenvalue = 2.17; root mean square of residuals = 0.15; $\chi^2 = 18.69$; $p = < 0.001$; fit = 0.94).

Statistical Analysis

All analyses were performed using R statistical software R 3.5.0 (with R Studio version 0.99.491) (R Core Team, 2014). Statistical significance was set at an alpha level

of 0.05. Benjamini–Hochberg procedure utilized for false discovery rate (set at 0.10). For missing data, pairwise deletion was given priority. Descriptive statistics (N = 144) for HIV-SP and SN women were conducted using chi-square and *t*-tests. General and interaction regression modeling was used to examine associations between RSA and cognitive domains (and within-group analysis [HIV-stratum]). Spearmen correlations examined associations between continuous predictors and cognitive variables. Independent *t*-tests were utilized for mean group differences (Cohen's *d* for effect) (Cohen, 1992). Given the small sample size, regression models only included variables if 1) significant correlations (covariates and cognitive outcomes) or differences were found between groups and 2) strong evidence from previous WIHS studies found covariates were associated with cognitive domains.

Final regression models were built using backward selection (variable removal effect checked by unadjusted R^2 and partial permutation) and inspected with q-q plots. Goodness of Fit with adjusted *R*-squared, overall *F*-test, residuals, *p*-values, residual standard errors, and Akaike Information Criterion (AIC) were reported (coefficient estimates cross-validated with iterative permutation tests). For global cognitive function, ordinal regression (cumulative link) models were estimated by iterative maximum likelihood (adjusted fits) (Agresti, 2002; Kosmidis, 2013). Log-likelihood differences evaluated proportional odds assumptions (estimates were exponentiated to extract odds ratio and confidence intervals).

Results

Sample Description

Table 1 provides a comprehensive description of the demographic, emotional burden symptoms, and clinical characteristics of the study sample. Notably, WRAT-3, race, and age are presented for descriptive purposes and not included in the primary regression models due to cognitive domain scores being adjusted prior to analysis. The majority of HIV-SP women (77%) had a current CD4+ count of ≥ 500 (cell/mm^3). The HIV group had an average nadir CD4+ of 681.4 (*SD* = 400.54), a CD4+/CD8+ of 0.91 (*SD* = 0.59), and 76% had undetectable HIV RNA.

Black women made up the majority of the sample in both HIV-SP (82%) and SN (91%) groups (followed by Caucasians). HIV-SP women were, on average, slightly older (51 years old [*SD* = 8.60, range: 33-72]), had lower income (61% vs. 53%), endorsed more depressive symptoms (34% vs. 25%), perceived stress (mild: 31% vs. 30%; and high: 36% vs. 30%), PTSD symptoms (24% vs. 11%), emotional burden (*M* = 0.07, *SD* = 0.91), and baseline HCV (31% vs 23). Smoking (average 22 years) and alcohol use behaviors (high-risk alcohol use = 15%) were equally distributed in both groups. More SN women endorsed smoking cigarettes (61% vs. 55%) and marijuana (27% vs. 17%) within the past six months, while more HIV-SP women endorsed being former smokers. Both groups reported similar patterns of current crack, cocaine, and heroin use. No statistically significant differences were found between the two groups in any of the demographic, emotional burden measures, or clinical characteristics represented in this study.

Serostatus Group Differences in Cognitive Domains and RSA

Table 2 shows independent samples *t*-test comparisons between the HIV-SP and SN groups. Significant group differences were observed in total scores on measures of attention (t (84.50) = 3.55, p = < .001, d = 0.64) as HIV-SP women performed worse (M = 45.87, SD = 10.18) than HIV-SN women (M = 52.28, SD = 0.98). Likewise, significant differences were also observed on measures of verbal fluency (t (77.78) = 2.90, p = .004, d = 0.54) as HIV-SP women (M = 48.32, SD = 8.50) produced lower total scores in comparison to the SN group (M = 52.98, SD = 9.05). No significant group differences were found in the other cognitive domains. As expected, significant differences were found in RSA (t (84.88) = 2.20, p = .03, d = 0.40) with HIV-SP women exhibiting lower RSA values (M = 4.93, SD = 1.48).

Global Cognitive Function

Global cognitive function by group differences can be found in Table 3. HIV-SP and SN groups were similar across the three cognitive factors (no impairment, borderline impairment, and cognitive impairment). A higher percentage of HIV-SP women endorsed both borderline cognitive impairment and cognitive impairments, but these differences were not significant (χ^2 (2, 143) = 3.06, p = .23). After testing proportional odds assumptions, global cognitive function was examined by ordinal logistic regression (see Table 4). The models included RSA, RSA + HIV group status, and RSA x HIV interaction terms (centered and scaled to reduce collinearity effects). While trends for increased odds of lower RSA in the context of increasing cognitive impairment were observed for HIV-SP women, no significant associations were found in any models.

RSA and Cognitive Domains

Unadjusted regression models were conducted to test if any cognitive domains correlated with RSA (see Table 5). The results suggested increased RSA (F (1,142) = 3.22, p = < .05) was associated with improved scores on fine motor tasks (β = 0.16), although with a small effect (R^2 of 0.03). Likewise, a significant regression equation was found for increased RSA (F (1,142) = 9.65, p = < .01, R^2 = 0.06) and better psychomotor speed performance (β = 0.25). Negative RSA trends emerged for verbal fluency and attention, while positive trends were observed for executive function, learning, and memory; however, these trends were not significant.

Multiple Regression and Psychomotor Speed

Based on findings from previous Chicago WIHS studies (Maki et al., 2009; Vance et al., 2016) and data-driven analysis, income, baseline HCV, and current marijuana use were included along with RSA and the Emotional Burden Scale as predictors in the full multiple regression model (see Table 6). Income and marijuana use were eliminated (p-value closer to one and explaining < 1% of variance). The best HIV group status model (F (1, 137) = 4.41, p = 0.00) included RSA, HCV, and Emotional Burden predictors (explaining 9% of the model variance). Emotional Burden, baseline HCV, and HIV were all negatively associated with RSA. However, only RSA (β = 0.18, p = .03, unadjusted R^2 = 0.05) and Emotional Burden Scale (β = -0.15, p = 0.05, unadjusted R^2 = 0.03) demonstrated significant associations in the model. The results suggested a positive association between increased RSA and better performance on

psychomotor speed tasks, which was negatively impacted by emotional burden. RSA x HIV group status interactions were not significant.

Multiple Regression and Fine Motor

The full model for the fine motor regression analysis included RSA, HIV status, the Emotional Burden Scale, HCV status (no HCV at baseline served as reference), income status (≤ $12,000 a year served as reference), and the interaction term RSA x HIV status (see Table 7). Due to non-parametricity, a robust regression analysis (iterated reweighted least squares with bootstrapped standard error and confidence intervals) (Fox, 2002) was utilized on the interaction models. Baseline HCV status and Emotional Burden Scale were removed from the full interaction model (explaining only 2% of the model variance and *p*-values close to 1). HCV removal had little effect on the performance of the full model.

The best-fit model (F (1, 134) = 3.47, p = 0.00) explained 7% of the variance in fine motor scores. A significant RSA x HIV-SP interaction was found (β = .37, p = .04), which suggested for a given fine motor score that reduced RSA was associated with worse performance in HIV-SP women relative to SN women. Those with income greater than $12,000 were less impacted (β = 0.19, p = .02) by this interaction.

Within-Group Analysis for HIV, RSA, Fine Motor, and Psychomotor Speed

To better understand the relationship between HIV, RSA, and fine motor skills in HIV-SP women, a within-group regression analysis was performed including the HIV-stratum (i.e., HIV-RNA, CD4+ nadir, current CD4+, and helper/suppressor ratio

[CD4+/CD8+]). Due to the expectation of multicollinearity, separate models were performed for current CD4+ and helper/suppressor ratio. RSA remained significant in each stratum model with increased values being associated with better performance on fine motor tasks within the HIV-SP group; however, no significant findings were observed for the stratum models or individual predictors. Notably, there was a negative trend for lower CD4+ values and RSA that supported worse fine motor performance; however, this trend was not significant (p = .09).

Similar to fine motor, RSA remained significant in each model for psychomotor speed while none of the individual stratum predictors reached significance. However, a reduced model of RSA (t (1.98) = 1.23, p = .05), Emotional Burden Scale (t (-2.13) = -2.14, p = .03), CD4+ nadir (t (1.96) = 0.01, p = .057), and current CD4+ (> 500) (t (1.74) = 7.41, p = .08) was significant (F (5, 94) = 3.26, p = .00) and explained 10% of the variance. This model suggested those with more stable CD4+ counts demonstrate a trend for higher RSA values and better psychomotor speed performance, but the degree of emotional burden exerts a significant, negative impact on this relationship.

Discussion

The purpose of this study was to examine the relationship between RSA and cognitive function in a sample of HIV-SP and SN women. The study hypothesized that HIV-SP women would exhibit reduced RSA function when compared to SN women, which would correspond to select cognitive impairments (i.e., executive, fine motor, psychomotor speed). Regression modeling found an interaction between RSA and HIV status that corresponded to worse performance on fine motor tasks (particularly those

with lower income status). A model demonstrating greater RSA and better psychomotor performance associations was also found, while emotional burden negatively influenced this model association (and to a lesser extent baseline HCV and HIV-SP status). Overall, the study supported our hypothesis; however, given small effect sizes, interpretation of results beyond this study require larger samples and diverse covariate representation.

Decreased RSA and HIV Status

Consistent with Heilman and colleagues' (2013) WIHS study, the HIV-SP sample demonstrated reduced RSA values when compared to SN women in the current study. Likewise, RSA was not directly associated with HIV viral load, current CD4+ counts, nadir CD4+, or helper/suppressor ratios (CD4/CD8+). The lack of association between RSA and the HIV stratum supports findings from Askgaard and colleagues (2011), where researchers found reduced HRV in HIV-SP persons (both detectable and virally suppressed) was unrelated to HIV duration or viral markers. Our results align with a recent HIV meta-analysis identifying reduced vmHRV profiles despite duration of HIV infection, participants use of ART, and viral suppression (McIntosh, 2016).

Though limited by unmeasured covariates, the findings from the present study provide general support that RSA reductions could be driven by the systemic effects of HIV and compounded by other stress-based factors known to increase inflammatory markers (e.g., cytokines). Instead of ART-treated HIV being an independent mediator of dysautonomia and vagal dysfunction, the augmenting inflammatory effects of lower socioeconomic status, increased medical comorbidities, emotional burden, and psychosocial stressors likely explains the RSA reductions observed in HIV studies rather

than the mere presence of the virus itself (Green et al., 2016; Keary, Hughes, & Palmieri, 2009; Meyer et al., 2016). Multiple factors undoubtedly compound the vagal burden observed in persons with HIV and, likely, contribute to impairments in select cognitive domain function over time.

Coinfections provide one example of the compounding vagal burden. Similar to other HIV studies finding shared inflammatory markers with HCV (Cohen et al., 2011), French and colleagues (2017) demonstrated that coinfection with HCV accelerated HIV disease progression via increased monocytes and TNF-α levels in a large-scale women's HIV cohort. Likewise, chronic HCV is associated with reduced vmHRV profiles even in the absence of active infection (HCV baseline variable in this study), which is a comparable pattern to that observed in HIV (Floris-Moore et al., 2009; Osztovits et al., 2011). Similarly, while a recent meta-analytic review (Fialho et al., 2016) supports HIV-HCV coinfection increasing cognitive impairments, the results of this review did not support HCV RNA as being directly related to the impairments. HCV appears to exert a chronic, residual inflammatory process that disrupts ANS function in HCV-infected persons regardless of their viral RNA status, which potentially supports similar viral-independent, proinflammatory mechanisms being involved in the dysautonomia observed in ART-treated HIV. Importantly, this could also explain the relationship found between reduced RSA and baseline HCV status (and not the presence of viral HCV [HCV RNA]) in the present study. Notably, only 13 of the HIV-SP women in this study had detectable HCV RNA and limited its inclusion in regression models. Nonetheless, the proposed compounding vagal-burden in HIV has implications for the current study in the context of cognitive impairments as well.

Psychomotor Speed, RSA, and HIV-SP Women

The study's regression model found a positive relationship between increased baseline RSA and better performance on psychomotor speed tasks; however, emotional burden negatively influenced this relationship such that women with greater emotional burden had both reduced RSA and psychomotor speed. Zeki Al Hazzouri and colleagues (2017) found similar positive associations between vmHRV and psychomotor speed; however, after adjusting cardiovascular risk factors (e.g., diabetes, and blood pressure) and depressive symptoms, the positive association was negated. The negative trend (though not individually significant) found for both HIV and baseline HCV on psychomotor speed in our regression model could further support a pattern of increased vagal-burden.

Studies have found those with HIV-HCV coinfection were significantly more likely to report depressive symptoms, experience lifetime major depressive episodes, and emotional distress than those with HIV alone (Fialho et al., 2016; Pereira & Canavarro, 2014). Reduced psychomotor speed, depression, and emotional distress have been directly related to both compounding proinflammatory cytokine expression and vagal-disruption (dysautonomic disposition). Furthermore, this inflammatory phenomena appears to disproportionally affect women (Breit, Kupferberg, Rogler, & Hasler, 2018; Heringa et al., 2014; Kemp et al., 2012). As such, it is possible that while HIV-SP status and HCV were not independently associated with worse psychomotor speed (viral RNA or HIV stratum) in this sample, their co-contributions to emotional burden and decreased RSA via unmeasured proinflammatory mechanisms could account for some of the findings in this study. Similar mechanisms are likely involved with fine motor function as

overlapping motor areas are involved in both domains and are sometimes co-measured as processing speed (Shimizu et al., 2011).

Fine Motor, RSA, and HIV-SP Women

Following from the vagal-burden conceptualization, the interaction found in this study between HIV-SP status (but not the viral stratum) and RSA negatively affecting motor function are consistent with a compounding inflammatory effect. Multiple studies have demonstrated the relationship between impaired vagal activity, reduced motor function, and proinflammatory cytokines (Goldsmith et al., 2016; Maydych, 2019). Specific to HIV, Montoya and colleagues (2019) found inverse associations between proinflammatory cytokine composites (soluble CD14, TNF-α, and monocyte chemoattractant protein-1) and complex motor function in HIV-SP persons (n = 90) compared to HIV-SN (n = 94); moreover, inflammatory profiles were greater in women (as compared to men). Importantly, inflammatory profiles were not related to the HIV stratum, but were associated with indirect effects of HIV on inflammation (i.e., cytokines). In support of previous studies (Hong & Banks, 2015; Huck et al., 2018), they suggested HCV, hypertension, diabetes, increased lipids, and a lifetime history of major depressive disorder likely compounded both the inflammatory and psychomotor findings.

HIV-SP Women, Vagus Nerve, and Future Research Directions

While baseline RSA or vmHRV is a general indicator of ANS function, vagal-reactivity (vmHRV during stress exposure) and recovery (vmHRV after exposure) appear to be sensitive indicators of acute ANS responses to stress. Studies suggest dysfunctional

vagal reactivity directly corresponds to the degree of inflammatory marker activity (e.g., IL-6, TNF-α, CRP); moreover, chronic inflammation is associated with delayed vagal recovery (prolonged sympathetic states) after acute stressors (e.g., cognitive, emotional) (Marsland, Walsh, Lockwood, & John-Henderson, 2017). In view of this, vagal-reactivity and recovery could reveal unique ANS dysfunction in HIV-SP women that is undetected by baseline RSA alone. For example, recent studies have suggested Black women demonstrate similar or even greater baseline RSA values relative to Caucasians. Notably, although research is ongoing and mixed, Black women appear to demonstrate greater dysfunction of RSA reactivity and recovery over time in the context of chronic stress (e.g., stigma, environmental, PTSD, medical comorbidities, etc.) relative to Black men and Caucasians (Fuller-Rowell, Williams, & Ryff, 2013; Hill et al., 2015; Neblett & Roberts, 2013).

Vagal reactivity is associated with select executive functions requiring cognitive flexibility (e.g., set-shifting, sustained attention), while faster vmHRV recovery is correlated with better task-switching (Bridgette et al., 2013; Ginty, Phillips, Der, Deary, & Carroll, 2011; Kihmy, 2013). Germane to HIV-SP women, in addition to psychomotor speed and fine motor impairments, they also demonstrate worse performance on select executive functions when compared to their male counterparts (Maki et al., 2019). The non-use of vagal-reactivity and recovery measures could explain the lack of expected findings between RSA and select executive function in the current study. Given this and HIV's disproportionate representation in black women, future HIV-SP studies should evaluate vmHRV across baseline, reactivity, and recovery stress conditions to provide better insight into vagal-ANS cognitive phenomena. By better understanding the vagal-

HIV axis, novel therapeutic approaches targeting the vagus nerve (e.g., stimulation, cholinergic anti-inflammatory pathway modulation) could be introduced that have implications for improving cognitive function and quality of life in persons living with HIV (Capó-Vélez et al, 2018; Delgado-Vélez et al., 2015; Nicholson, Kempf, Moneyham, & Vance, 2017).

Limitations

There are several limitations to this current study and should caution any direct interpretation of the study's results. The study was restricted to women and, given the likelihood that sex differences exist in cognitive domain activity relative to ANS function, it is possible unmeasured sex-specific factors (e.g., hormones) could better inform associations found in this study. The small sample size and secondary data analysis constrained the number of covariates that were included in the models, and while we controlled for many known confounders, it is possible that unobserved associations could account for some of the findings (e.g., cardiovascular disease). The Emotional Burden composite was created to reduce model burden; however, the composite could reduce or exaggerate associations between RSA and select cognitive domains. Future vmHRV studies should examine the independent associations of depression, perceived stress, and PTSD in the context of HIV-associated cognitive impairment along with relevant comorbidities, hormonal activity, among others.

Similarly, the secondary and cross-sectional design limits examination of changes in cognitive function relative to RSA fluctuations over time. This increases the possibility that unidentified or transitory variables could have affected RSA or cognitive function in

a state or trait dependent manner (e.g., bereavement, hydration status, undiagnosed sleep apnea, insulin resistance). Moreover, it is generally recognized that substance use affects vagal-cognitive associations; and although substance use was controlled for, a few substances (e.g., methamphetamine, opioids) likely lacked sufficient representation to identify associations.

The authors recognize the dual effects medications can exert on both cognitive and ANS function (and the increased likelihood of polypharmacy in the HIV population); however, little research is available on the total or interactive effects of any given polypharmacy regimen on vagal-activity and cognitive function in HIV. Evidence suggests certain combinations are protective, while others are deleterious (Ogunmola, Oladosu, & Olamoyegun, 2015; Radtke et al., 2018; Wongcharoen et al., 2014). To that end, future studies should examine medications known to affect vagal-cognitive parameters (e.g., cardiovascular, psychotropics, anti-cholinergics).

Conclusion

HIV-SP women exhibit chronic patterns of ANS dysfunction as measured by reduced RSA values, which could be due to a compounding vagal burden related to multiple stress factors. Chronic vagal burden could impact select cognitive domains such as psychomotor speed as well as emotional regulation. Future large sample, longitudinal HIV-SP studies should explore cognitive function in the context of baseline, reactive, and recovery vmHRV parameters (in addition to compounding stress factors, inflammatory profiles, and associated comorbidities) to better understand the mechanisms involved in the vagal-HIV axis.

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CONCLUSIONS:
RESEARCH AND CLINICAL PRACTICE IMPLICATIONS

by

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2019

CLINICAL AND RESEARCH IMPLICATIONS

Regardless of sufficient viral suppression with antiretroviral therapy, HIV contributes to a chronic and compounding inflammatory process that promotes vagal-autonomic nervous system (ANS) dysfunction and increases the risk of developing a spectrum of cognitive impairments (also known as HIV-associated neurocognitive disorders [HAND]). In part, vagal-ANS disruption in HIV occurs in response to compounding stress factors that perpetuate proinflammatory activity. Psychological stress (e.g., stigmatism related to HIV diagnosis, increased perceptions of stress, PTSD), medical comorbidities (e.g., insulin sensitivity, diabetes), psychosocial stress (e.g., finances), and their accompanying co-inflammatory properties are likely physiologically synergistic to chronic activation of immune cells, increased depression, emotional dysregulation, and degrees of cognitive impairment observed in HIV-seropositive (SP) persons (Valdez, Rubin, & Neigh, 2016). The three articles in this dissertation were written to provide a general overview of HIV and cognition in the context of vagal-ANS disruption as research in this area is still in early stages of development.

Article 1, *The Potential Role of Vagus Nerve Stimulation in the Treatment of HIV-associated Depression: A Review of Literature,* introduced the vagus nerve as a potential treatment target for HIV-associated depression given its mediating role in shared proinflammatory-driven cognitive pathology (Nicholson, Kempf, Moneyham, & Vance, 2017). Article 2, *HIV, Aging, and Cognitive Impairment: Can Heart Rate Variability Be Used as a Pre-Symptomatic Marker for Neurocognitive Disorders*, examined the transdiagnostic benefit of vagal-mediated heart rate variability (vmHRV) in pre-symptomatic HIV-associated cognitive impairments due to its functional associations

with cognitive-emotional domains, bi-directional relationship to vagal-ANS activity, and sensitivity to inflammatory activity in central autonomic brain areas known to be impacted in persons with HIV (e.g., frontostriatal pathway) (Nicholson et al, 2019). Article 3, *Exploratory Examination of Respiratory Sinus Arrhythmia and Cognitive Function in Women with HIV*, explored if differences in resting vmHRV activity corresponded to select cognitive impairments in HIV-SP women relative to HIV-SN women. In view of inflammatory driven ANS dysfunction and select cognitive-emotional impairments, future exploration of vagus nerve function and the neuroinflammatory processes observed in HIV-SP persons is warranted.

Specific consideration should be given to the vagal cholinergic anti-inflammatory pathway (CAP) given it provides a substrate for viral pathogen activity, regulates ANS function, and projects to select neurocognitive domains affected in the HIV population. Given this, the vagal-CAP and its relationship to HIV-associated cognitive impairments will be briefly examined in this chapter. Specifically, primary elements of the three articles in this dissertation are examined within the context of CAP and will emphasize vagal-mediated inflammatory reflexes as a contributor to cognitive-emotional impairments in HIV-SP persons and a target for future research. This chapter closes with general implications for research and practice.

Dysregulated CAP Activity, Inflammation, Cognitive Impairments in HIV

The vagus nerve responds to pathogenic challenges via its efferent arm or more functionally known as CAP. CAP regulates T-cell function via acetylcholine production, enzymes, and receptors acting on macrophages, microglia, and dendritic cells (sometimes collectively referred to as mononuclear phagocytes) to inhibit proinflammatory

mediators. HIV dysregulates adaptive mononuclear phagocyte functions by inhibiting the activation of CAP- alpha 7 nicotinic acetylcholine receptors (α7 receptors), which are well represented in the central nervous system (CNS) and neurocognitive domains (e.g., frontostriatal, limbic, hippocampal networks). CAP-α7 receptors are probably best known for their role in Alzheimer's disease and being responsible for the cognitive benefits associated with controlled nicotine exposure (e.g., improved memory, learning, and attention) via reduced CNS-inflammation and putative neurotransmitter modulation (such as catecholamines, glutamate, γ amino butyric acid [GABA].

In a well-established HIV-SP women's cohort (Wojna et al., 2007), Delgado-Velez and colleagues (2015) found critical HIV proteins (i.e., gp120) and virotoxins (trans-activator of transcription [Tat]) involved in cognitive impairments disrupted CAP function. They demonstrated an upregulation of CAP-associated α-7 receptors in response to HIV's direct modulation of α-7's highly selective calcium activity to promote transcription, replication, and chronic cytokine pathogenesis (for a comprehensive review see Delgado-Velez & Lasalde-Dominicci, 2018). Overexpression of α7 results in excessive calcium influx that triggers oxidative stress damage (neuronal death and apoptosis), which is a pattern consistent with the neuroinflammatory-related cognitive impairments observed in HIV (Lewis et al., 2017).

Capo-Velez and colleagues (2017) demonstrated gp120 induced neuroinflammation in striatal brain areas via the CAP. The observed learning and motor impairments associated with gp120 were reversed by normalizing CAP function. Similarly, Nesil and colleagues (2015) demonstrated CAP stimulation modulated calcium-signaling pathways, which limited neurotoxicity, induced long-term potentiation,

improved spatial and contextual memory deficits, and increased neuroplasticity in the frontal cortex, hippocampus, and striatum in HIV-1 rat models. In a related HIV study, Valdes-Ferrer and colleagues (2009) found that increasing availability of acetylcholine in CAP-α-7 receptors resulted in reduced T-cell viral proliferation and increased anti-inflammatory cytokine production thus helping stabilize ANS function. These findings extend previous HIV-CAP studies (Ballester et al., 2012; Farr et al., 2002; Gonzalez-Lira et al., 2006) that found similar regulating effects in hippocampal and memory performance when CAP activity was normalized. Likewise, α-7 receptors directly regulate striatal excitability (a primary target for HIV) and physiological activity via vagal projections in the frontostriatal pathway (Thayer et al., 2018). As such, dysfunction in CAP could also promote impairment in select cognitive domains represented in HIV (particularly those in psychomotor domains). In view of these studies, vagal-CAP research is positioned to provide novel insights into the mechanisms involved in HIV-associated cognitive impairments. The following sub-section will briefly examine the three dissertation articles in the context of vagal-CAP.

HIV and Vagal Cholinergic Anti-inflammatory Pathway

In Article 1, Nicholson, Kempf, Moneyham, and Vance (2017) examined co-pathology in HIV and depression being driven by dysregulation of neuroendocrine and neuroimmunological systems via vagus nerve dysfunction. The article emphasized the augmenting effects of HIV-associated depression's chronic proinflammatory activity as a likely contributor to select cognitive impairments observed in the HIV population. The article concluded by suggesting transauricular VNS (tVNS) as a potential intervention to

lessen the inflammatory burden, help normalize ANS activity, which could have implications for HIV-depression and cognitive impairments alike. Importantly, a mainstay target for treating both depression and cognitive impairment is brain-derived neurotrophic factor (BDNF); moreover, low-levels of BDNF have been associated with impairment in vagal-mediated prefrontal cortex modulation of ANS activity (decreased vmHRV) (Chang et al., 2018).

HIV stimulation of CAP-α7 reduces hippocampal synaptic plasticity via BDNF down-regulation in response to chronic macrophage release (Pozniak, White, & Khalili, 2014). In particular, gp120 proteins are suggested to mediate this downregulation by disrupting proBDNF (a precursor to BDNF) (Bachis et al., 2012) and contributes to HIV-associated cognitive impairments (O'Leary et al., 2018; Sakata & Overacre, 2017). Notably, evidence also suggests deficient BDNF in the dorsal vagal complex disrupts major cholinergic centers responsible for regulating cardio-neural vagal activity contributing to hypertension, insulin resistance, and metabolic disorders (among others) (Marosi & Mattson, 2014). Given this, CAP- α7 also has implications for targeting the compounding vagal-burden often experienced in HIV-SP persons.

In Article 2, Nicholson and colleagues (2019) the concept of self-regulation was introduced as a combined phenomenon of cognitive-emotional processes represented by vagal cardio-neural network (central autonomic) activity. Specifically, the emotional arm of self-regulation appears to be a sensitive indicator of cognitive function given emotional dysregulation in these vagal network areas (e.g., amygdala) often precedes observable cognitive impairments in HIV-SP persons. For example, Grabyan and colleagues (2018) recently demonstrated that persons with HAND were ten times more

likely to have impaired emotional regulation relative to HIV-SP adults without HAND and concluded this feature could have clinical value as an independent predictor of functional cognitive capacity.

Activation of CAP-α7 in the amygdala modulates emotional dysregulation and decreases hyperactivity in this area (Pidoplichko et al., 2013), which suggests a potential mechanism for CAP-α7 agonism in select self-regulatory dysfunctions in HIV. Another brain region critical for self-regulation in HIV (Santarelli et al., 2003) is the hippocampus. Increasing cholinergic tone in the hippocampus induces cognitive-emotional dysregulation, but blockade of CAP-α7 can reverse these inductions and normalize activity in this area (Mineur et al., 2013). While recent research suggests tVNS can modulate central vagal projections to the prefrontal cortex, amygdala, and hippocampus thereby improving select cognitive-emotional impairments (e.g., sustained attention, contextual memory, depression, anxiety), directly modulating the CAP is a more selective approach to targeting the vagus nerve. CAP-α7 promotes differing cognitive activity as improvement in psychomotor function (fine and processing speed), specific attention (orienting, alerting), short-term episodic memory, long-term verbal recall, and working memory are directly observed (Hahn, 2019).

While tVNS and CAP share similar neuro-immune input/output pathways, focusing on CAP-α7 receptors could have implications related to the findings in Article 3 and HIV-SP women (i.e., impaired motor function and reduced vmHRV). For example, chronic nicotine use (α7 desensitization) reduces circulating estradiol and its availability (β receptor) in the hippocampus, which mirrors the pattern observed in the aging brain and imposes vagal burden (d'Adesky et al., 2018). Nicotine's chronic interactions with

estrogen is directly related to modulation of vagal-CAP activity at the α7 receptor, among others; however, directly agonizing CAP-α7 can restore estrogen receptivity, modulate stress responses, and reduce inflammation (Ma, Gong, Lv, Ma., 2015). Research suggests estrogen modulation could provide ANS protective effects until the post-menopause phase diminishes these effects (Koenig & Thayer, 2016).

Estradiol's physiological response to stressors in women partially relates to greater vagal-estrogen receptor density and diversity of vagal projections that modulate CAP- α7 nicotinic activity in frontal cortex, hypothalamic, brainstem, and midbrain areas (e.g., hippocampus, locus coeruleus, dorsal raphe) (Centeno, Henderson, Pau, & Bethena, 2006; Ciriello & Caverson, 2016). Additionally, increased peripheral cytokine production and stress sensitivity in these brain areas play a critical role in differentiating HIV-seropositive women's cognitive-emotional impairments from their male counterparts (e.g., emotional dysregulation, depression, verbal fluency, memory, processing speed, psychomotor, and attention) (Comasco, Frokjaer, & Sundstrom-Poromaa, 2014; Luine, 2014; Newhouse & Albert, 2015).

Contrarily, most available tVNS devices do not appear to have direct effects on estrogen. In part, this is due to the limited areas accessible (e.g., right nodose ganglion) to electric VNS in humans. It remains possible, with improved vagal stimulation technology (e.g., optogenetic) a more selective response can be achieved (Han, Tellez, Perkins, & Perez, 2018). Nonetheless, given estrogen deficiency or dysregulation has been implicated in some forms of HIV- associated depression and cognitive impairments in women, selective vagus nerve modulation via α7 receptor modulation could be particularly beneficial to HIV-SP women. Given this, the vagal-CAP holds promise for

future research and developing novel interventions to target select cognitive domain impairments. In the following sections, both research and clinical implications are provided.

Implications for Research

Transauricular VNS devices are readily available for research purposes and with minimal known side effects related to their use (Nicholson, Kempf, Moneyham, & Vance, 2017). Likewise, studies have demonstrated its equivalence or superiority to implantable VNS devices in cognitive and inflammatory studies (Lerman et al., 2016). Stimulation parameters have not been established for use in HIV, which will require parameters being set relative to those used in other studies (Bonaz et al., 2017). Though, tVNS studies typically agree higher stimulations affect efferent vagal fibers, which supposedly induce a greater inflammatory response. Lower stimulations affect afferent vagal fibers, which could have a more acute cognitive-emotional or self-regulatory effect (Kwan et al., 2016). Nonetheless, it is worth noting for experimental, interpretation, and pitfalls since parameters remain unestablished.

Pharmacological approaches should be utilized either in tVNS studies or as an alternative approach to stimulate select vagal activity. Partial CAP-α7 agonist (DMXB-A), and CAP-α7 agonist (galantamine or TC-5619), and CAP-α7 antagonists (buproprion) are available and have been safely researched in clinical trials. Specific biopharmacological interaction with CAP- α7 could help elucidate its effects on vmHRV, inflammation (e.g., cytokines), BDNF, and improvement in HIV-associated cognitively impaired domains (i.e., verbal learning, memory, fluency, executive, fine motor,

psychomotor, and attention). Given the upregulation of α7 in the frontostriatal and hippocampal pathways observed in HIV, CAP modulation of these receptors in neuro-immune networks could recalibrate cholinergic neural networks, reduce inflammation, promote self-regulation, and improve select cognitive function.

Implications for Clinical Practice

Understanding the relationship between age, gender, and medical comorbidities (e.g., Hepatitis C, substance use) in the context of vmHRV is still in its infancy and lacks standardized normative data for use in practice as a diagnostic tool. However, implementing vmHRV as a general clinical marker for self-regulatory dysfunction (as suggested by Beauchaine & Thayer, 2015) could optimize its potential benefit relative to clinical practice. With that, consideration should be given to HRV's routine use in the HIV clinical setting as it could identify cognitive impairments earlier than standardized neurocognitive batteries (Zulli et al., 2005) and is a strong indicator of general health (e.g., medical outcomes, mortality) (Thayer, Ahs, Frederikson, Sollers III, & Wager, 2012). Furthermore, given the contributions of both emotional and cognitive domains to the impairments observed in HIV, vmHRV could provide an objective and reconciliatory measure (due to neurocognitive tests emphasizing emotional capacity less) of this duality via its relationship to self-regulation.

From a practical position, measuring vmHRV in the clinical setting is far more efficient relative to the administration of neurocognitive batteries (can range anywhere from one to three hours pending the comprehensiveness of the battery). Contrarily, vmHRV can be measured over about ten minutes and reduces the administration burden

on both provider and patients alike. Though more extensive psychometrics are needed, automated algorithms are being developed for vmHRV and minimize many of the previous limitations to using it in practice (e.g., manual processing, variation or bias in interpreting values). For example, Hegarty-Craver and colleagues (2017) developed an automated algorithm for processing vmHRV that demonstrated minimal interpretation bias and absolute differences in comparison to manual editing and gold-standard vmHRV devices (e.g., Biopac EKG). Automated vmHRV algorithms could increase clinical feasibility, earlier detection, and timely interventions in those experiencing or at-risk for developing HIV-associated cognitive disorders.

Conveniently, many commercial products (e.g., watches and phones) are also available that possess functional electrocardiogram sensors that provide general information to both patients. This makes the patient an active participant in their care and provides them daily feedback about changes in their physiological status. Likewise, these devices could provide a rough estimate of treatment response (e.g., improved ANS flexibility to stressors) for clinicians. While the validity and reliability of these commercial devices are controversial, technology is rapidly advancing in this field with many of these devices (e.g., Polar) being used both in research and commercial settings (Giles, Draper, & Draper, 2016).

Based on the results of the three-article dissertation, future research into the vagal-HIV axis is warranted. Overall, the three articles supported the theme of a dysfunctional vagus nerve in HIV via neuroinflammatory mechanisms; furthermore, it outlined the co-contribution of multiple inflammatory disorders (including HIV) imposing an increasing vagal burden. Chronic vagal burden likely contributes to reduced

vmHRV, ANS dysfunction, and the cognitive-emotional disorders observed in the HIV population. HIV-SP women might be particularly susceptible to ANS dysfunction given their increased co-inflammatory burdens relative to men, which increases their risk for earlier, microglial driven cognitive impairment and ongoing emotional dysregulation. By recognizing the vagus nerve's potential role in HIV's cognitive-emotional phenomena, different research and clinical approaches (tVNS, select CAP-α7 stimulation, vmHRV as a general self-regulatory marker) can be designed with the ultimate goal of improving the quality of life burdens cognitive-emotional impairments impose on many persons living with HIV.

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Table 1. Summary of Transcutaneous Vagus Nerve Stimulation Treatment Studies of Major Depression

Authors	Participants	VNS Parameters	Procedure and Measures	Data Analysis/Findings	Strengths & Limitations
Hein et al. (2013) Auricular transcutaneous electrical nerve stimulation in depressed patients: A randomized controlled pilot study	Study 1 • $N = 22$ ($M_{age} =$ 44 years) • 2 Randomized Groups: • tVNS ($n = 11$) • Sham ($n = 11$) Study 2 • $N = 15$ ($M_{age} =$ 48 years old) • 2 Randomized Groups: • tVNS ($n = 8$) • Sham ($n = 7$)	Study 1 • Intensity: 0 – 600 mA; not fixed • Frequency (Hz): 0.5 – 100 • 15 minutes daily/14 days Study 2 • Intensity: 130 mA; fixed • Frequency (Hz): 1.5 • 15 minutes/2x's daily/14 days	• Study 1 • Bilateral NET-2000 TENS unit inserted inner ears • Sham: Same procedure; no stimulation • Study 2 • Bilateral NET-1000 tVNS unit inserted inner ears • Sham: Same as above • Outcome measures: • Reduced scores on BDI & HAM-D	Study 1 • BDI scores reduced from 27.0 to 14.0 in active group. • No reduction in sham Study 2 • BDI scores reduced from 31.0 – 25.8 in active group. • No reduction in sham Overall • No changes in HAM-D in either study	Strengths • Naturalistic Limitations • Short duration • Co-treatment with anti-depressants/ psychotherapy • No blinding • Small study
Trevizol et al. (2015) tVNS protocol for the treatment of major depressive disorder: A case study assessing the auricular branch of the vagus nerve	• $N = 1$ (38 years old man), case-study	• Stimulation: 120 Hz with 250 µs • 30 minutes daily/14 days	• Ibramed tVNS external device used • Auto-adhesive rubber electrodes of 20 cm^2 placed over the mastoid process bilaterally Outcome measures: • Reduced scores on HAM-D	• HAM-D scores improved • Remission achieved (< 8)	Strengths • Novel study Limitations • Case-study • No sham or control

Trevizol et al. (2016) Transcutaneous vagus nerve stimulation (tVNS) protocol for the treatment of major depressive disorder: An open label proof-of-concept trial	• N = 12 (M_{age} = 45.9 years) • No Randomized Groups	• Intensity: 12 mA • Stimulation: 120 Hz with 250 μs duration • 30 minutes daily/14 days	• Ibramed Neurodyn II external device used • Auto-adhesive rubber electrodes of 15 cm^2 placed over the mastoid process bilaterally <u>Outcome measures</u>: • 50% or greater reduction of scores on the HAM-D	• HAM-D reduction from 27.9 to 8.2 (mean difference = 19.75, SD = 4.2) • All exhibited ≥ 50% reduction in scores • 5 participants exhibited remission (< 8) • Response maintained at 1 month follow-up	<u>Strengths</u> • Proof-of-concept • Follow-up <u>Limitations</u> • No sham, blinding, or randomization • Convenient sample
Fang et al. (2016) Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder	• N = 34 (M_{age} = not reported) • 2 Randomized Groups: • tVNS (n = 18) • Sham (n = 16)	• Intensity: 4-6 mA • Stimulation: 20 Hz with 1 ms duration • 30 minutes 2x's daily/4 weeks	• 40 minute device training • Seated position or laying on side with electrode clips attached bilaterally • Self-administration at home; complete daily log; log checked every 4 weeks • Sham treatment self-administered; electrodes clipped to superior scapha with no vagal connection; required to complete daily entries in a diary log for 4 weeks <u>Outcome measures</u>: • Primarily reduced scores on the HAM-D (> 50%) • Secondarily reduced scores on HAM-A, SAS, and SDS	• Depression scores reduced on HAM-D in tVNS group • Significant interaction between treatment and sham group and treatment time on all measures (except HAM-A)	<u>Strengths</u> • Randomized • Single blind • Longer duration • Sham stimulation <u>Limitations</u> • Self-administered sham protocol • Self-record logs • Small study

Rong et al. (2016) Transcutaneous vagus nerve stimulation for the treatment of depression: A study protocol for a double blinded randomized clinical trial	• $N = 160$ • 2 Randomized Groups: • tVNS ($n = 91$, $M_{age} = 40.10$ years) • Sham ($n = 69$, $M_{age} = 43.88$ years)	• Intensity: 4 – 6 mA • Stimulation: 20 Hz with 0.2 ms width • 30 minutes • 2x's daily/12 weeks	• Same protocol as Fang et al. (2016) with the exception of an active-control (stated below) • After 4 weeks, sham group received tVNS per above protocol for 8 weeks <u>Outcome measures</u>: • Primarily reduced scores on the HAM-D (> 50%) • Secondarily reduced scores on HAM-A, SAS, and SDS	<u>Week 4 (0 – 4)</u> • HAM-D scores reduced in both groups; significantly greater in tVNS group • Significant changes between treatment and sham group on HAM-D • No significant response between tVNS group (at 4 weeks or 4 – 8 weeks) and sham (at 4 – 8 weeks or 8 – 12 weeks) <u>Week 12</u> • Significant response between tVNS groups at 0 – 4, 4 – 8, and 8 – 12 weeks	<u>Strengths</u> • Randomized • Naturalistic • Active control • Large study • Longer duration • Sham stimulation <u>Limitations</u> • Self-administered sham protocol • Self-record logs
Lui et al. (2016) Transcutaneous vagus nerve stimulation modulates amygdala functional connectivity in patients with depression	• $N = 49$ • 2 Randomized Groups • tVNS ($n = 18$, $M_{age} = 37.83$ years) • Sham ($n = 16$, $M_{age} = 42.56$ years)	• Intensity: 4 – 6 mA • Stimulation: 20 Hz with < 1 ms width • 30 minutes 2x's daily/4 weeks	• Same protocol as Fang et al. (2016) • <u>Outcome measures</u>: • Primarily reduced scores on the HAM-D (> 50%) • Secondarily reduced scores on HAM-A, SAS, and SDS	• HAM-D scores reduced • Significant interaction between treatment and sham group and treatment time on all measures • Significant interaction on HAM-D subscales between tVNS and sham group	<u>Strengths</u> • Randomized • Single blind • Large study • Longer duration • Sham stimulation <u>Limitations</u> • Self-administered sham protocol • Self-record logs

Notes. µs = microsecond; BDI = Beck Depression Inventory; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; Hz = Hertz; mA= milliampere; NET = Neuro-Electric Therapy; SAS = Self-Rating Anxiety Scale; SDS = Self-Rating Depression Scale; TENS = transcutaneous electrical nerve stimulation; tVNS = transcutaneous (auricular) vagus nerve stimulation.

Table 1. Heart Rate Variability and Cognitive Function

Authors	Participants and Design	Measures	Procedure	Data Analysis/Findings
Kimhy et al. (2013) The association of cardiac vagal control and executive functioning-Findings from MIDUS Study	• N = 817 (M_{age} = 57.11 years [SD: 11.15]; f: 456) • MIDUS II Cohort • Cross-sectional • Covariates: Age, sex, education BMI, menopausal status, HTN, diabetes, stroke, asthma, emphysema, COPD, cholesterol, depression, thyroid, menopause, smoking, exercise	• Stress measures: Mental arithmetic and STRP-CWC Task • EF: BTACT, SGST • HF-HRV (0.15 - 0.50 Hz, msec^2) • Continuous 3-lead ECG - Sampling rate 500 Hz • Respiration: Paced; - Position: seated, Stationary	• Participants completed EF 1-61 months before HRV; EF score = average reaction time to switch, non-switch trials of the mixed-task; 75% accuracy needed for inclusion • Participant's randomly assigned to one of the stress measures • A.M. collection, light breakfast, no caffeine • Vagal recovery: difference between recovery period, challenge period Outcome measures: • Association between cardiac vagal control (CVC) and EF • EF performance is differentially associated with cardiac vagal recovery at rest vs. recovery period	• Multiple linear regression with CVC (rest, recovery) as predictor of EF • Adjusted for effects of covariates • Two models: rest-related, vagal recovery • Significant association between resting CVC and EF global score (p = .000); Adding covariates negated association • Medications, disease affecting CVC: association between rest CVC and EF score (p = .002), speed of processing (p = .009), task-switching (p = .046); Adding covariates negated association • Association between vagal recovery, task-switching; remained after adding covariates (p = .010)
Lin et al. (2014) Frequency of mentally stimulating activities	• N = 487 • 2 Groups - HMSA: n = 214 (f: 130); M_{age} = 65.14 years [SD: 7.31] - LMSA: n =	• Stress measures: Mental arithmetic and STRP-CWC task • EF: BTACT, SGST • HRV- Power Spectral (LF [0.04-0.15 Hz], HF [0.15-0.4 Hz]	• Participants randomly assigned to initial stress measure • A.M. collection, light breakfast, no caffeine • HRV measured throughout task:	• EF average of z-scores; higher score equals > function • 3 reactivity indices separately analyzed; repeated measures ANOVA with pair-wise on reactivity to stressors (Bonferroni α = 0.018); multiple linear

modifies the relationship between cardiovascular reactivity and executive function in old age	266 (f: 117); M_{age} = 64.95 years [SD: 7.73] • MIDUS II cohort • Cross-sectional Covariates: age, sex, ethnicity, education, HTN, MI, diabetes, cholesterol, beta-blockers, depression, ETOH, perceived control, smoking, SBP, DBP	• Standard ECG • Respiration: Free • Position: Seated	• 300-second epoch duration; if unscorable, 180-240 sec sections analyzed Outcome measures: • > reactivity to mental stress tasks are associated with > EF • Association between reactivity and EF moderated by mentally stimulating activity (MSA) engagement	regression and ANCOVA for MSA engagement, reactivity, EF and interactions; covariates adjusted • Positive association between EF and HR reactivity • > LF-HRV reactivity associated with EF • Frequency of MSA strongest predictor in HR, LF- or HF-HRV models ($p < 0.001$) • HR reactivity significant interaction with MSA in predicting EF ($p = 0.020$)
Jennings et al. (2015) Focusing neurovisceral integration: Cognition, heart rate variability, and cerebral blood flow	• N = 440 (M_{age} = 43.0 years; [f: approximately 53%]; African-Americans [n = 70]) • Cross-sectional Covariates: age, ethnicity, education, smoking, BMI, depression, SBP, DBP	• EF battery (WMS-II/III; 4WRD-STM; DIGVIG1/2; TMT B; STRP-I) • HF-HRV (0.12 – 0.40 Hz) • Continuous 2-lead ECG; bilateral wrists - Sampling rate 1000 Hz • Respiration: Paced, unpaced; - Position: seated, stationary	• Each participant given 1 hour EF battery • A.M. collection • HRV: 5 min period of paced respiration (11 BrPM = 0.18 Hz); instructed to breath naturally in response to 2 auditory tones signaling inhale/exhale; 5 min unpaced breathing recorded Outcome measures: • > HF-HRV is associated with measures of executive function	• Paced and unpaced natural logs were correlated (r = .84) • Pearson product moment correlations for whole sample; then examined separately by sex and ethnicity utilizing bivariate correlations • Correlations between paced HF-HRV and STRP-INT in entire sample (r = .13, $p < .01$) • Paced HF-HRV associated with better performance in 3 EF tests for Caucasians (WMS-II [r = -0.12, $p < .05$], TMT B [r = -0.12, $p < .05$], STRP-I [r = 0.19, $p < .01$] • No correlations in African-Americans
Mann et al. (2015)	• N = 533; (M_{age} = 54.9 years [SD: 10.7]; f: 286;	• EF: BTACT • Negative Affect: STAI-T; CESD	• HRV and respiration (normal breathing) measured over 10-minutes (divided into two 5-min	• Structural equation modeling for analysis; maximum likelihood analyzed covariance matrices

Integrating affective and cognitive correlates of heart rate variability: A structural equation modeling approach	Caucasian [n = 493]) • MIDUS II Biomarker cohort • Cross-sectional Covariates: smoking, age, sex, education, ethnicity, BMI, smoker, HTN, heart disease, exercise, diabetes, beta-blockers, depression, ETOH, cholesterol, steroid medications, SBP, DBP	• HF-HRV (0.15 - 0.50 Hz, $msec^2$) • Continuous 3-lead ECG; bilateral shoulder and left lower quadrant - Sampling rate 500 Hz • Respiration: Paced; - Position: seated, stationary	epochs) to establish baseline • HR and respiration spectrally analyzed for distribution of power as a function of frequency Outcome measures: • HRV inversely associated with negative affect and positively with EF • Negative affect inversely associated with EF • Controlling for covariates, age inversely associated with HRV, EF, negative affect	• Bivariate correlations found between HRV and attention/inhibition • Measurement model showed good fit; significant factor loadings on all indicators (p = .011-.001); Negative affect, EF inversely associated (p =.04) • Full model showed good fit; Positive association between HRV, EF (p = .02); HRV not associated with negative affect • Covariate adjusted model significant for association between HRV and age (p < .001), BMI (p = .004), diabetes (p = .02) • Covariate adjusted model estimating covariate relationships to primary variables (vs constrained) was superior
Stenfors et al. (2016) Executive cognitive functioning and cardiovascular autonomic regulation in a population-based sample of working adults	• N = 119 (M_{age} = 47.98 years [SD: 10.49]; f: 94) • Swedish Longitudinal Occupational Survey of Health • Cross-sectional Covariates: income, age, physical activity, sex, education, depression, chronic stress, subjective cognitive complaints, SBP, DBP	• EF battery: RST, 2BT, TMT-A/B, STR I/S, LDST • HRV-Time Domain: RMSDD • QT Variability Index (QTVI) • HRV-Power Spectral: LF (0.04-0.15 Hz), HF (0.15-0.4 Hz) • Continuous 3-lead ECG; left, right 5th interspace - Sampling rate 1000 Hz • Respiration: Paced; monitored with ECG bands on chest, abdomen - Position: supine, stationary	• Participant completed EF battery • HRV measurement after 2 min resting period occurred over 5 min • QTVI calculated as time-stretch logarithm of the ratio of normalized QT mean; HR, QT time series sampled at 4 Hz Outcome measures: • > HRV, < QVTI associated with better EF	• Bivariate correlations for QTVI, HRV, and EF • If significant, partial correlations with covariate adjustments • Multiple testing controlled: False discovery rate (α = 0.05) • > RMSSD and < QTVI associated with better EF (except on RST) • HF-HRV not associated with EF • Age inversely associated with RMSSD, HF-HRV, and positively with QTVI (p < 0.001) • > QVTI associated with poorer performance on STRP-I/S (p = 0.009/p = 0.014), 2BT (response: p = 0.005; accuracy: p = 0.024), TMT-A (p = 0.035)

Crowley et al. (2016) Vagal recovery from cognitive challenge moderates age-related deficits in executive functioning	• N = 817 (M_{age} = 57.11 years [SD: 11.15]; f: 456) • Age-group - YA (range 35-54 years: n = 354) - MA (range 55-64 years; n = 260) - OA (range 65 - 86 years; n = 203) • MIDUS II Cohort • Secondary, cross-sectional Covariates: age, BMI, sex, education, HTN, diabetes, stroke, asthma, emphysema, COPD, cholesterol, depression, thyroid, menopause, smoke, physical activity	• Stress measures: Mental arithmetic and STRP-CWC Task • EF: SGST • HF-HRV (0.15-0.50 Hz, $msec^2$) • Continuous 3-lead ECG; bilateral shoulder, left lower quadrant - Sampling rate 500 Hz • Respiration: Paced; - Position: seated, Stationary	• Participants randomly assigned to initial stress measure • A.M. collection, light breakfast, no caffeine • Vagal recovery: difference between recovery periods, challenge periods • Vagal activity: difference between averaged HF during challenges and HF baseline Outcome measures: • Adults would perform worse with increasing age on task-switching • Adults with faster vagal recovery from stressor would perform better than adults of same cohort with slower vagal recovery	• Multiple linear regression for models; stepwise adjustment for effects of covariates • CVC < from baseline to task, > during recovery (before/after respiratory adjustment) • Age with negative correlation to EF (p = .000), vagal reactivity (before/after respiratory adjustment: p = .006/.000), vagal recovery (before/after respiratory adjustment: p = .014/.001) • Vagal recovery moderated effect between age, EF; effects remained significant in all models controlling for covariates • Age-group/vagal recovery interactions associated with EF (p = .016); before/after respiratory adjustment, EF associated with • OA (p = .002/.012); recovery increases in CVC associated with > reaction times in OA to EF (p = .000), but not in other age-groups

Notes. 2-Back Task (2BT); body mass index (BMI); Brief Test of Adult Cognition (BTACT); Center for Epidemiologic Studies Depression Scale (CESD); chronic obstructive pulmonary disease (COPD); cardio-vagal recovery (CVC); diastolic blood-pressure (DBP); Digit Vigilance Time Page 1 and 2 (DIGVIG1/2); executive function (EF); female (f); Four-Word Memory Test (4WRD-STM); heart rate (HR); heart rate variability (HRV); hypertension (HTN); Letter Digit Substitution Task (LDST); middle-aged adult (MA); Midlife Development in the United States (MIDUS); older adult (OA); Reading Span Task (RST); Speilberg State Trait Anxiety Inventory-Trait Version (STAI-T); standard deviation (SD); Stop & Go Switch Task (SGST); Stroop Color and Word Test (STRP-CWC); Stroop Interference and Stroop-Shifting (STRP-I/S); systolic blood-pressure (SBP); Trail Making Test A/B (TMT-A/B); Wechsler Memory Scale II and III (WMS-II/III); young adult (YA)

Table 1

Sample Characteristics Stratified by HIV-Serostatus

Variable	HIV-SP (n = 100)	HIV-SN (n = 44)	p Value
	M ± SD	M ± SD	
Demographics			
Age (years)	51.17 ± 08.60	48.80 ± 10.06	0.15
Race/ethnicity, n (%)			0.37
White/non-Hispanic	10 (10)	1 (2)	
Black/non-Hispanic	82 (82)	40 (91)	
Hispanic	6 (6)	3 (7)	
Other	2 (2)	0 (0)	
Household income: (per year), n (%)			0.50
≤ $12,000	60 (60)	23 (53)	
≥ $12,001	38 (38)	20 (46)	
WRAT-3 (standardized score)	83.93 ± 18.15	88.23 ± 14.98	0.29
Substance use behaviors			
Alcohol status, n (%)			0.99
Low risk alcohol use[a] (0-7 drinks per week)	85 (85)	37 (84)	
High risk alcohol use[a] (> 7 drinks per week)	15 (15)	7 (16)	
Smoking status, n (%)			0.59
Never	14 (14)	7 (16)	
Former (> 6 month ago)	31 (31)	10 (23)	
Recent (within past 6 months)	55 (55)	27 (61)	
Smoking (years)	21.98 ± 14.77	21.65 ± 14.63	0.90
Marijuana use[a]	17 (17)	12 (27)	0.23
Crack use[a]	6 (6)	2 (5)	0.99
Cocaine use[a]	3 (3)	0 (0)	0.60
Heroin use[a]	6 (6)	4 (9)	0.75
Emotional burden symptoms			
Current depressive symptoms (CES-D: score ≥ 16), n (%)			0.38
No depression	66 (66)	33 (75)	
Depression	34 (34)	11 (25)	
Current perceived stress (PSS-10; tertile scores), n (%)			0.62
Low stress	33 (33)	18 (40)	
Mild stress	31 (31)	13 (30)	

High stress	36 (36)	13 (30)	
Current post-traumatic stress symptoms (PCL-C), n (%)			0.12
Minimal trauma	76 (76)	39 (89)	
Moderate-to-high trauma	24 (24)	5 (11)	
Emotional Burden Scale (Composite)	0.07 ± 0.91	0.17 ± 0.66	0.07ǂ
HCV markers			
Baseline HCV status (1st 3 visits), n (%)			0.09ǂ
Yes	31 (31)	7 (16)	
No	68 (68)	36 (82)	
Current HCV RNA positive, n (%)			.99
Yes	13 (13)	5 (11)	
≤ 799,999 (International Units)	5	1	
≥ 800,000 (International Units)	8	4	
No	5 (5)	2 (4)	
HIV stratum			------
CD4+ count, median (IQR)			
CD4+ nadir (cell/mm^3)	681.4 ± 400.54	------	
Current CD4+ T-cell, (cell/mm^3), n (%)			
< 200	5 (5)	------	
≥ 200 - < 500	28 (28)	------	
≥ 500	67 (67)	------	
Helper/suppressor ratio (CD4+/CD8+)	0.91 ± 0.59	------	
HIV RNA Viral Load Detection (copies/mL)			
Detected	24 (24)	-----	
≥ 48 - ≤ 10,000	12	-----	
≥ 10,000	12		
Not Detected (< 48)	76 (76)		

Notes. [a] = within past six months of most recent WIHS visit; ≤ 0.10; WRAT = Wide Range Abilities Test Reading Recognition

Table 2

Sample Characteristics of Primary Study Variables Stratified by HIV-Serostatus Group

Group	Continuous Variable [statistical test]	M ± SD	Mdn	Range	SE	95% CI Intervals Lower	Upper	*p*-value (ES)
	Cognitive Domains							
	Attention							
HIV-SP	[t(84.50)=3.55]	45.88 ± 10.18	45.55	23.42-71.25	1.02	2.82	9.99	0.00***
HIV-SN		52.29 ± 09.88	52.08	30.27-76.77	1.49			(*d*=0.64)
	Fine Motor							
HIV-SP	W = 2517.5	47.18 ± 11.10	49.95	18.57-66.50	1.11	-0.90	5.15	0.17
HIV-SN		50.16 ± 07.57	51.28	32.26-61.57	1.14			
	Verbal Memory							
HIV-SP	[t(87.18)=0.86]	48.42 ± 11.08	48.13	22.13-71.27	1.11	-2.17	5.49	0.39
HIV-SN		50.07 ± 10.44	49.83	19.92-70.34	1.57			
	Verbal Learning							
HIV-SP	[t(96.51)=0.52	49.92 ± 10.75	48.88	21.63-72.42	1.07	-2.50	4.31	0.60
HIV-SN		50.82 ± 08.77	51.77	34.34-74.57	1.34			
	Verbal Fluency							
HIV-SP	[t(77.78)=2.90]	48.32 ± 08.50	46.51	23.70-73.70	0.85	1.46	7.86	0.00**
HIV-SN		52.98 ± 09.05	52.52	26.59-77.59	1.36			(*d*=0.54)
	Executive Function							
HIV-SP	[t(115.33)=1.57]	48.34 ± 12.06	50.44	19.83-82.08	1.26	-0.72	6.20	0.12
HIV-SN		51.07 ± 08.39	50.30	34.05-67.47	1.21			
	Psychomotor Speed							
HIV-SP	W=2508.5	47.91 ± 09.47	49.84	16.59-65.30	0.95	-1.06	5.21	0.18
HIV-SN		50.65 ± 07.13	50.62	36.48-63.39	1.08			
	Vagal Function							
	RSA							
HIV-SP	[t(84.88)=2.20]	04.93 ± 01.48	5.12	0.89-8.30	0.15	0.06	1.10	0.03*
HIV-SN		05.51 ± 01.43	5.44	2.71-9.22	0.22			(*d*=0.40)

Notes: * = ≤ 0.05; ** = ≤ 0.01; *** = ≤ 0.001; CI = Confidence Intervals; ES = effect size; M = mean; Mdn = Median; SD = standard deviation; SN = seronegative; SP = seropositive; W = Non-parametric Wilcoxon

Table 3

Characteristics for Global Cognitive Function and HIV-Serostatus

Global Cognitive Function		No Cognitive Impairment	Borderline Cognitive Impairment	Cognitive Impairment
HIV-SN	Count (%)	26 (59)	8 (18)	10 (23)
HIV-SP	Count (%)	43 (43)	27 (27)	29 (29)
Total		69	36	39

X^2 (2, N = 143) = 3.06, p = .23

Notes. SN = seronegative; SP = seropositive

Table 4

Ordinal Logistic Regression for RSA and Global Cognitive Function

Variable	B	SE	z-value	*p*-value	Odds Ratio	95% Co Intervals Lower	Upper	Log Likelihood	AIC
				RSA					
Mean RSA	-0.09	0.11	-0.85	0.39	0.91	-0.32	0.12	-149.85	305.70
NCI/BCI	-0.56	0.60	-0.94						
BCI/CI	0.48	0.59	0.81						
				RSA and HIV Status					
Mean RSA	-0.07	0.11	-0.67	0.49	0.92	-0.29	0.14	-148.77	305.55
HIV-SP	0.51	0.35	1.45	0.14	1.67	-0.17	1.22		
NCI/BCI	-0.10	0.68	-0.15						
BCI/CI	0.96	0.68	1.40						
				RSA, HIV Status, and Interaction					
Mean RSA	0.02	0.21	0.13	0.89	1.02	-0.39	0.45	-148.61	307.21
HIV-SP	1.29	1.38	0.93	0.35	1.73	-1.42	4.07		
RSA x HIV-SP	-0.14	0.24	-0.58	0.56	0.86	-0.64	0.34		
NCI/BCI	0.47	1.20	0.39						
BCI/CI	1.54	1.21	1.27						

Notes. B = unstandardized coefficient; AIC = Akaike Information Criteria; BCI = Borderline Cognitive Impairment; CI = Cognitive Impairment; Co = Wald Confidence Intervals; NCI = No Cognitive Impairment; SE = Standard Error; SP = seropositive

Table 5

Simple Linear Regression for RSA and Cognitive Variables

Variable	Mdn	B	β	SE	RSE	t value	95% CI Intervals Lower	Upper	*p* value	*F* (df)	R^2
Attention	-0.03	0.88	0.12	0.58	10.35	1.51	-0.26	2.03	0.13	2.29(142)	0.01
Fine Motor Function	0.14	1.14	0.16	0.56	10.04	1.81	0.03	2.26	0.04*	3.22(142)	0.03
Verbal Fluency	-0.09	-0.51	-0.08	0.50	8.84	-1.02	-1.54	0.46	0.30	1.04(142)	0.01
Memory	0.02	-0.09	-0.01	0.61	10.83	-0.15	-1.29	1.11	0.87	0.02(141)	0.00
Verbal Learning	0.00	-0.30	-0.04	0.57	10.12	-0.52	-1.43	0.83	0.60	0.27(141)	0.00
Executive Function	0.11	0.84	0.11	0.62	11.00	1.34	-0.38	2.06	0.17	1.07(142)	0.01
Psychomotor Speed	0.09	1.50	0.25	0.48	8.56	3.10	0.54	2.46	0.00**	9.65(142)	0.06

Notes: RSA: Mean Centered; * = ≤ 0.05; ** = ≤ 0.01; *** = ≤ 0.001; B = unstandardized coefficient; β = standardized coefficients; CI = Confidence Intervals; Mdn = standardized residual median; RSE = residual standard error; SE = standard error; R^2 = variance explained

Table 6

Multiple Regression Analysis for Variables Predicting Psychomotor Speed

Model 1											
Variable	B	*SE*	*t*-value	VIF	*p*-value	R^2*(unad))*	95% CI	Min	Mdn	Max	AIC
RSA	1.03	1.64	2.00	1.12	0.04*	0.04	0.02, 2.04	-29.43	1.14	18.37	1001.80
HIV-SP	-1.22	1.66	-0.73	1.09	0.46	0.01	-1.01, 2.23	RSE	R^2(adj)	*F(df)*	Model *p*-value
EBS	-1.75	0.91	-1.92	1.12	0.05*	0.03	-3.53, 0.03	8.61	0.08	3.05(132)	0.00**
HCV-SP Baseline	-2.54	1.75	-1.45	1.12	0.14	0.02	-0.44, 2.98				
Marijuana Use	2.30	1.84	1.25	1.05	0.21	0.00	-2.95, 0.65				
Income: ≥ $12,001	0.14	1.54	0.09	1.08	0.92	0.00	-1.58, 1.44				
Model 2											
Variable	B	*SE*	*t*-value	VIF	*p*-value	R^2*(unadj)*	95% CI	Min	Mdn	Max	AIC
RSA	1.07	0.50	2.11	1.11	0.03*	0.04	0.08, 2.07	-27.41	1.12	17.87	1018.34
HIV-SP	-1.41	1.60	-0.88	1.05	0.37	0.01	-0.86, 2.27	RSE	R^2(adj)	*F(df)*	Model *p*-value
EBS	-1.65	0.86	-1.92	1.04	0.05*	0.03	-3.34, 0.03	8.52	0.09	4.41(137)	0.00*
HCV-SP Baseline	-2.55	1.68	-1.51	1.09	0.13	0.03	-0.37, 2.93				
Model 3											
Variable	B	*SE*	*t*-value	VIF	*p*-value	R^2(unadj)	95% CI	Min	Mdn	Max	AIC

RSA	1.27	0.49	2.58	1.11	0.03*	0.05	0.30, 2.23	-28.69	1.29	18.08	1031.85
HIV-SP	-1.59	1.57	-1.01	1.05	0.37	0.01	-0.74, 2.34	RSE	R^2(adj)	*F(df)*	Model *p*-value
EBS	-1.68	0.85	-1.97	1.04	0.05*	0.03	-3.35, -0.01	8.52	0.08	5.09(140)	0.02*

Notes: Mean Centered; * = ≤ 0.05; ** = ≤ 0.01; *** = ≤ 0.001; B = unstandardized coefficients; AIC = Akaike Inflation Criteria; EBS: Emotional Burden Scale; CI = confidence interval; Max = maximum; Min = minimum; Mdn = median; RSE = residual standard error; SE = standard error; R^2 = variance explained; SP = seropositive

Table 7

Multiple Regression Analysis for Variables Predicting Fine Motor

Model 1											
Variable	B	*BSE*	*t*-value	VIF	*p*-value	R^2*(unad))*	95% BCI	Min	Mdn	Max	AIC
RSA	-0.96	1.32	-0.70	3.61	0.48	0.02	-4.43, 1.68	-27.41	-0.40	18.05	1042
HIV-SP	-2.22	1.63	-1.32	1.09	0.12	0.01	-4.87, 0.24	RSE	R^2(adj)	*F(df)*	Model *p*-value
Income: ≥ $12,001	3.53	1.44	2.24	1.10	0.04*	0.02	0.46, 5.86	6.61	0.06	2.66(132)	.01*
EBS	-0.67	1.07	-0.74	1.10	0.16	0.01	-2.72, 1.17				
HCV-SP Baseline	-1.66	2.20	-0.93	1.13	0.94	0.01	-5.94, 1.17				
RSA*HIV-SP	2.70	1.09	1.63	3.58	0.06*	0.02	-0.76, 6.22				
Model 2											
Variable	B	*BSE*	*t*-value	VIF	*p*-value	R^2*(unad))*	95% BCI	Min	Mdn	Max	AIC
RSA	-0.85	1.60	-0.61	3.60	0.28	0.02	-4.04, 1.50	-28.29	-0.13	18.24	1041
HIV-SP	-2.36	1.40	-1.41	1.07	0.12	0.02	-5.17, -0.15	RSE	R^2(adj)	*F(df)*	Model *p*-value
Income: ≥ $12,001	3.69	1.47	2.35	1.08	0.02*	0.02	0.71, 6.04	6.92	0.06	2.84(133)	.01*
EBS	-0.61	0.07	-0.67	1.10	0.16	0.01	-2.58, 1.22				
RSA*HIV-SP	2.68	1.07	1.61	3.55	0.06*	0.02	-0.68, 6.17				
Model 3											

Variable	B	*BSE*	*t*-value	VIF	*p*-value	R^2*(unad))*	95% BCI	Min	Mdn	Max	AIC
RSA	-0.90	1.64	-0.65	3.60	0.48	0.03	-3.58, 1.64	-29.01	0.03	18.36	1039
HIV-SP	-2.40	1.44	-1.46	1.06	0.15	0.02	-5.12, 0.02	RSE	R^2(adj)	*F(df)*	Model *p*-value
Income: ≥ $12,001	3.92	1.49	2.60	1.02	0.02*	0.03	0.64, 6.23	6.96	0.07	3.47(134)	.00**
RSA*HIV-SP	2.79	1.04	1.71	3.52	0.04*	0.02	-0.83, 6.10				

Notes: Mean Centered; * = ≤ 0.05; ** = ≤ 0.01; *** = ≤ 0.001; B = unstandardized coefficients; AIC = Akaike Inflation Criteria; BCI = bootstrapped confidence interval; EBS: Emotional Burden Scale; Max = maximum; Min = minimum; Mdn = residual median; RSE = Residual Standard Error; BSE = Bootstrapped Standard Error; R^2 = variance explained; SP = seropositive

APPENDIX A

UAB IRB EXEMPTION LETTER

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 | irb@uab.edu

APPROVAL LETTER

TO: Nicholson, William C.

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 14-Sep-2017

RE: IRB-300000572
Exploratory Examination of Respiratory Sinus Arrhythmia and Cognitive Function in Women with HIV

The IRB reviewed and approved the Initial Application submitted on 11-Sep-2017 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Exempt (Category 4)
Determination: Exempt
Approval Date: 14-Sep-2017
Approval Period: No Continuing Review

Documents Included in Review:

- Exempt.170911
- usepermission(Cook Cty).170911

APPENDIX B

WOMEN'S INTERAGENCY HIV STUDY CONCEPT SHEET APPROVAL LETTER

WIHS Women's Interagency HIV Study

Principal Investigators

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Igho Ofotokun, MD, MSc
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Gina Wingood, ScD, MPH
Columbia University

Birmingham *(2013-present)*
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University of California, San Francisco
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New York University

WDMAC
(Data Management & Analysis Center)
(1997-present)
Stephen Gange, PhD
Elizabeth Golub, PhD
Johns Hopkins University

September 26, 2017

Dear Dr. Nicholson,

Congratulations, your concept sheet **"Exploratory Examination of Respiratory Sinus Arrhythmia and Cognitive Function in Women with HIV"** has been approved by the WIHS Executive Committee. The tracking ("README") number assigned to this project is **W17051.** You should use this number in all correspondence up to and including publication.

The WIHS collaborator assigned to your project is Kathleen Weber, weberkathleen@ameritech.net. Please utilize this person as your point of reference to the WIHS in regards to the development and analysis of your study and eventual manuscript submission.

All analyses tied to this project should pertain to the proposed analyses in the approved concept sheet. If you wish to implement additional analyses, a new concept sheet must be drafted and submitted to the WIHS. Upon approval of the new concept sheet, a new tracking number will be assigned.

The pages following the comments contain information on how to proceed with your project, as well as contact information for key personnel.

We appreciate your involvement in the WIHS! Please don't hesitate to contact me if there is anything that we can do to facilitate your project.

Sincerely,

Phyllis C Tien, MD

Phyllis C. Tien, MD
Chair, WIHS Executive Committee
Professor of Medicine, UCSF