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BIOBEHAVIORAL PREDICTORS OF EXECUTIVE FUNCTION DECLINE IN MID- AND LATE LIFE ADULTS

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BIOBEHAVIORAL PREDICTORS OF EXECUTIVE FUNCTION DECLINE

IN MID- AND LATE LIFE ADULTS

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Abstract

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Biobehavioral Predictors of Executive Function Decline in Mid- and Late Life Adults

Chairperson: Stuart Hall, Ph.D.

Using data from the Midlife in the United States (MIDUS) Longitudinal Study of Health and Well-Being, this study examined high frequency heart rate variability as a longitudinal predictor of cognitive change in key executive function domains: inhibition, shifting, and updating. This study further explored the interactions between HF HRV and important health factors (inflammation, stress, sleep, and mood and anxiety) in predicting executive function decline.

The results of this investigation demonstrated that while high frequency heart rate variability and inhibition decline were correlated, HF HRV was not a significant predictor of decline in any executive function. However, results did show an interaction effect between HF HRV and depression in predicting inhibition and shifting declines in mid-life adults. Further, main effects of sleep quality and anxiety on inhibition and shifting declines were identified. Implications of these findings as well as limitations and future research directions are discussed.

Keywords: cognitive performance, executive function, heart rate variability, Midlife in the United States, aging

Dedication

This work is dedicated to the many research participants who generously shared their time in support of science. It is further dedicated to the extensive number of researchers integral in conducting the Mid-life in the Unites States Study on Health and Well-being. It took a national community to make this study feasible, and I thank each person who worked to collect and compile study data.

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Background

The Brain-Body Connection

The question of the relationship between brain and body has a long and varied history; yet, what is clearly demonstrated across scientific disciplines is that the brain and the body are intimately connected. Oxygen and glucose are exchanged between our cardiovascular system and our cerebral vasculature, our gut communicates through neurotransmitters to our brains, and certain central nervous system nerves innervate our bodily organs (Roy & Sherrington, 1890; Breit, Kuperberg, Rogler, & Hasler, 2018). What's more, when we exercise the body we stimulate the mind, and when we engage our minds we can alter our physiology (Webb & Acevedo, 2018). Even in an act as simple as breathing, an intricate dance between mind and body is occurring.

Given that the brain and body coordinate actions within a changing environment, an important aspect of their interrelated function is adaptability. Indeed, in order to survive, humans must actively change and adapt as we navigate diverse environments. Importantly, we need to be able to think, feel, and act flexibly. Whether solving complex cognitive problems or adjusting our emotional style to different contexts, flexibility in both brain and body functions has been key in evolutionary human success (Riganello, Garbarino, & Sannita, 2012).

Nervous System Flexibility

Indeed, flexibility in both the central and autonomic nervous system increases humans' ability to adapt and regulate cognitive, affective, physiological, and behavioral responses to environmental cues. Further, research supports that flexibility in these systems is related to wellbeing, cognition, and affective health (Mulcahy, Larsson, Garfinkel, & Critchley, 2019). In

contrast, when cognitive and/or visceral systems become rigid, we often see decreased cognitive, physical, and emotional functional ability and an increase in mental and physical disorder and disease. Of course, this is a balance—too much flexibility or too little rigidity can be non-beneficial as well.

We know this from research as well as from practical knowledge—when our muscles are too rigid our movement is limited; when we are too restricted in emotion we fail to engage adaptively across situations; and when our thinking is not flexible enough we get cognitively stuck. While this may seem like common sense, research is limited in understanding how physical, emotional, and cognitive systems interact. However, it is suspected that positive and negative feedback cycles between these systems may contribute to health versus disease (Seeman & Gruneswald, 2006). Parsing apart the interactions between these dynamic systems and their relationship to health outcomes is a vast and imperative field of study.

Theoretical Underpinnings

Systems Theory

The notion of such dynamical interaction is integral to systems theory, which posits that effective adaptation to changing environments requires a flexible relationship among the dynamic parts of a living system (Nesselroade, 1990; Weiss, 1969). In this view, the more variable the parts of a system are, the more effective the system works overall. This is also in line with the concept of allostasis, wherein organisms maintain homeostasis through physiological and behavioral change. Extensive research supports this and shows low variability in system functions is related to disorder and disease while higher variability is related to health and adaptability (Seeman & Grunewald, 2006). Indeed, pathological states are commonly related to

extreme predictability and low variability in physiologic markers such as heart rate (Goldberger, 1992; Goldberger, 1996).

Researchers suggest these associations are related to homeodynamics. In this view, system functions are dependent on multiple inputs at any given moment (Apple et. al., 1989). Thus, disruptions of feedback loops within lower-order system parts can contribute to increasingly higher-order system disruptions, at times resulting in pathology. As examples, increases in physiological rigidity are shown to be related to shifts towards rigidity in perception, behavior, and cognition resulting in the psychopathology of both Generalized Anxiety Disorder and Panic Disorder (Friedman et al., 1993, Friedman et al., 2000, Friedman and Thayer, 1998a, Thayer et al., 1996, Thayer et al., 2000).

Polyvagal Theory

In contrast to the systemic rigidity found in pathology, when mammals are functioning healthily, there is a flexible tradeoff between system levels. This is important given that we are social creatures living in a constantly variable environment. We need to be able to assess when we are faced with environments of threat versus safety and adapt effectively at physiological, affective, and cognitive levels.

Polyvagal theory supports that these flexible changes are carried out by the vagus nerve, which signals between visceral and neural systems as part of the parasympathetic branch of the autonomic nervous system (Porges, 1995). The autonomic nervous system is broadly made up of the parasympathetic and sympathetic nervous systems. In sympathetic nervous system (SNS) activation, epinephrine and norepinephrine act on beta-adrenergic receptors leading to the release of hormones throughout the bloodstream. These hormones are then able to act on multiple organ

systems to ready an organism to fight, flee, or freeze in order to mitigate threat (e.g., heart rate increases, vasculature constricts, sweating increases, etc.). In contrast, during parasympathetic nervous system (PNS) activation, the vagus nerve releases acetylcholine which acts on muscarinic and nicotinic receptors, causing specific intracellular effects which result in a multisystem response preparing an organism to "rest and digest" in times of safety (e.g., blood vessel dilation, decreased heart rate, etc.). Interestingly, the cholinergic effects of the PNS also function to degrade norepinephrine and attenuate the response of adrenergic receptors to sympathetically activated neurotransmitters (McCorry, 2007). In this way, sympathetic activation is dependent on disinhibition of the parasympathetic response. In normally functioning organisms, the parasympathetic response is the greatest determinant of autonomic function and many research studies therefore focus on PNS activity as a marker of the autonomic stress response.

Across numerous disciplines, specific assessment of PNS function has relied on the measurement of vagal modulation, which has been supported as an important indicator of the physiological adaptation to stress. This is unsurprising given the impact of the vagus nerve in the PNS response (Porges, 2011). Yet, how do we measure this significant organismal response in humans? Years of research have shown that a valid marker of vagal modulation is high frequency heart rate variability (HF HRV), a measure of variability in beat-to-beat heart rate intervals (Billman, Huikuri, Sacha, & Trimmel, 2015).

Heart Rate Variability

Overall, heart rate variability is a broad term, encompassing numerous measures. Heart rate variability began its journey towards becoming a well-established quantitative marker of

autonomic activity as early as 1965, when Hon and Lee discovered that changes in physiological rhythms in beat-to-beat heart rate intervals preceded changes in heart rate in cases of fetal distress. Later researchers found that HRV was a strong, independent predictor of mortality following myocardial infarction, and in the Framingham Heart study, reductions in HRV were able to predict mortality beyond traditional key risk factors (Tsuji et al., 1994). With the development of measurement technology such as power spectral analysis and ECG recordings, HRV is now used in numerous fields to assess autonomic function and its relation to diverse human health factors (Akselrod et. al, 1981; McCraty & Shaffer, 2015).

HRV analyses include the quantification of time domain and frequency domain measures. Time domain measures revolve around R to R (RR) intervals, a measure of the time between QRS complexes evidenced on electrocardiogram (ECG) recordings. The QRS complex refers to Q, R, and S which are specific points in the wave form which represent a heartbeat. RR intervals measure the time between R wave forms and are also called normal-to-normal (NN) signifying "normal" heartbeats (Figure 1). Common time domain measures include the square root of variance of NN (SDNN) and the root mean square of the standard deviation (RMSDD). On the other hand, frequency domain measures assess how the variance in power distributes as a function of frequency. Heart rate rhythm is made up of multiple frequency bands which can be separated out through power spectral analysis. Common frequency domain measures include low frequency (LF) and high frequency (HF) HRV (Figure 2). LF heart rate variability is measured between 0.04 and 0.15 hertz and HF heart rate variability is measured between 0.15 and 0.40 hertz (Society of Cardiology Task Force Report, 1996).

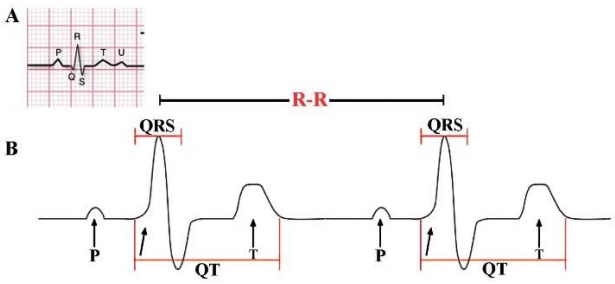


Figure 1. ECG waveform analysis is used for HRV measurement. RR intervals are the intervals between R waves within recorded QRS complexes. Figure adapted from Dong (2016).

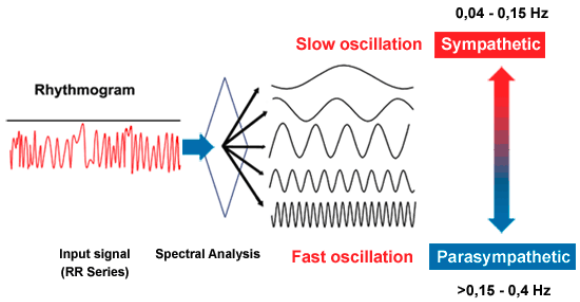


Figure 2. Frequency domain measures are used for measuring autonomic cardiac control. Power spectral analysis identifies high and low frequency waveform activity which can then be used to determine HF or LF HRV. Figure retrieved from ans-analysis.com.

While heart rate variability can be measured in many ways, it is important to understand that the high frequency aspect of HRV has the most biological relevance when investigating the relationship between neural and visceral systems. Particularly, this is because it is directly tied to parasympathetic nervous system activity and vagal modulation. Indeed, efferent vagal activity is a main contributor to HF HRV. This is evidenced in studies of electrical vagal stimulation, muscarinic receptor blockade, and vagotomy (Task Force Report, 1996). HF HRV is an exciting measure of autonomic function as it taps into vagal nerve function and has been shown to be a

promising indicator of both psychological and behavioral function, as well as health and disease (Labord, Mosley, & Thayer, 2017).

Indeed, replicated studies have found that lower HF HRV is associated with affective disorders such as depression and anxiety (Gorman and Sloan, 2000, Kemp and Quintana, 2013, Kemp et al., 2012, Kemp et al., 2010) and that higher HF HRV is associated with better emotion regulation ability (Appelhans and Luecken, 2006, Butler et al., 2006, Ingjaldsson et al., 2003, Lane, 2008, Melzig et al., 2009, Ruiz-Padial et al., 2003, Thayer and Brosschot, 2005). HF HRV has also been related to cognitive function, with greater HF HRV correlated to better performance on cognitive tasks involving memory, attention, and executive function (Hansen et al., 2009, Hansen et al., 2004, Hansen et al., 2003, Johnsen et al., 2003, Saus et al., 2006, Thayer et al., 2005). Additionally, HF HRV has been associated with numerous health outcomes including all-cause mortality, cardiovascular disease, reduced risk for stroke, better glucose regulation, reduced inflammation, and better function of the hypothalamic-adrenal-pituitary axis (Brosschot et al., 2007, Liao et al., 2002, Thayer and Fischer, 2009, Thayer and Lane, 2007, Thayer and Sternberg, 2006).

Neurovisceral Integration (NVI) Theory

So how is it that vagal modulation can exert such widespread effects? A predominant scientific theory developed by Thayer et. al, (2000) suggests the answer lies in neurovisceral integration. The neurovisceral integration model was first conceptualized in order to provide a theoretical basis for the mechanisms by which vagal control relates to cognition, affect, and physical health.

At its core, NVI proposes that vagal modulation is enacted through reciprocally connected areas of the central autonomic network (CAN) which work to dynamically modulate self-regulation and organismal adaptation (Thayer & Lane, 2000).

Briefly, the CAN is comprised of the ventromedial prefrontal cortices, the insula, the anterior cingulate, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaquaductual gray matter, the parabrachial nucleus, the nucleus of the solitary tract (NTS), the nucleus ambiguous, the ventrolateral medulla, the ventromedial medulla, and the medullary tegmental field, among others (Thayer et al., 2009; Ellis and Thayer, 2010). Its primary output is to the sino-atrial (SA) node of the heart via preganglionic sympathetic and parasympathetic neurons which innervate the stellate ganglia and vagus nerve.

The SA node, also known as the pacemaker of the heart, is supported to control context-specific cardiac regulation taking into account information from both the body and the external environment. It is thus a juncture of heart and brain integration. Interestingly, HF HRV is proximally determined at the SA node, and therefore it is suggested that HF HRV can be understood as an index of the level of integration between the central and autonomic nervous system (Shaffer & Venner, 2013).

Research studies have supported the NVI model at these structural and functional levels, showing that HF heart rate variability is associated with described neural networks and with the regulation of physiology, affect, and cognition. Indeed, the CAN has been supported to contribute to flexible, adaptive responses to environmental demands at visceromotor, neuroendocrine, and behavioral levels (Thayer and Lane, 2000; Thayer et al., 2009; Park et al., 2013a).

In 2017, the NVI model was expanded to incorporate developments in functional neuroanatomy and computational neuroscience. At a basic level, Smith, Thayer, Khalsa, and Lane (2017), proposed that a series of hierarchical feedback loops interact to regulate heart and brain function. This system of feedback loops spans from output in the sinoatrial node of the heart to prefrontal cortical activity. The series of loops reflects a multi-level neural architecture in which all levels are influenced by, generate, and/or express vagal control. Each level and their associated functions are depicted in Figure 3. The purpose of these integrated interactions is suggested to aid in minimizing prediction errors as we continually adjust and flexibly adapt to our environment.

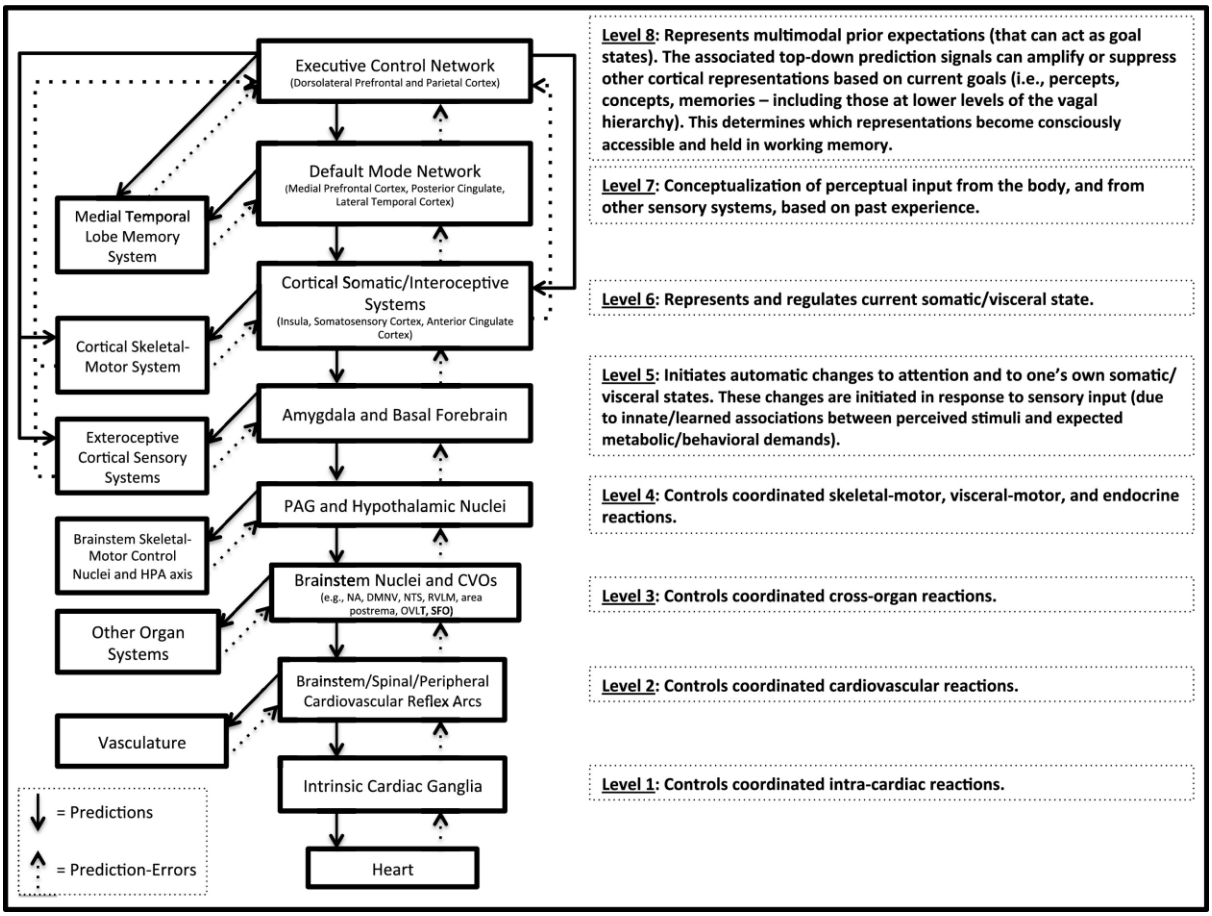


Figure 3. Hierarchical levels of neurovisceral integration and their functional and structural relationships. Figure retrieved from Smith et. al (2017).

Heart Rate Variability and Executive Function

This theory is appealing to philosophers and mathematicians as it has properties of a complex nonlinear dynamic system. But without diving headlong into the joys of chaos theory, we can use neurovisceral integration theory to examine relationships between system levels and to predict what factors might modulate these relationships. For instance, we expect the function of the heart to affect the function of the brain. We also expect that the more flexible autonomic function is, the more flexibility we will observe in cognitive functions. Using HF HRV and executive function as measures of these domains, prior research supports these expectations.

Indeed, the majority of published studies investigating the relationship between HF HRV and executive function have found that heart rate variability and executive function are positively correlated. Specifically, increased HF HRV is shown to relate to higher executive function in undergraduates (Bailey, Potter, Lang, & Pisoni, 2015; Alderman, & Olson, 2014; Williams, Thayer, & Koenig, 2016; Williams, et al., 2019; Colzato, et al., 2018), working age adults (Stenfors, Hanson, Theorell, & Osika, 2016; Zeki Al Hazzouri, Elfassy, Carnethon, Lloyd-Jones, & Yaffe, K, 2017), seniors (Albinet, Abou-Dest, André, & Audiffren, 2016; de Oliveira Matos, Vido, Garcia, Lopes, & Pereira, 2020), panic disorder patients (Hovald et al., 2012), and young male sailors of the Royal Norwegian Navy (Hansen, Johnsen, & Thayer, 2003; Hansen Johnsen, Sollers, Stenvik, Thayer, 2004).

That said, other studies have not found a clear relationship between autonomic and cognitive function. For instance, Britton et al. 2008 did not find any consistent associations between HF HRV and EF and while Jennings et al, 2015 did find a small number of correlations between specific executive functions and HF HRV, it did not find those same associations in the

African American participants. It is possible this reflects the inconsistent use of measures and covariates between studies.

We would also expect that factors affecting neurovisceral integration would moderate the relationship between HF HRV and executive function. Indeed, if the effects of HF HRV are communicated through a series of hierarchical feedback loops embedded in certain organ systems and neurological networks, we would expect that factors affecting these systems and networks would affect the relationship between HF HRV and executive function, given that executive function is the final common pathway in neurovisceral integration.

In particular, inflammation, cortisol, sleep, and mood and anxiety are all shown to affect components of neurovisceral integration. The vagus nerve controls the inflammatory reflex, a central component of immune homeostasis (Tracey, 2002). Cortisol is released as part of the hypothalamic pituitary adrenal axis response during the physiologic stress response (Thayer & Sternberg, 2006). Further, HF HRV and executive function have been found to be reduced in those with Major Depressive Disorder and Generalized Anxiety Disorder (Kemp, et. al, 2012), and insomnia symptoms have been related to decreased cognitive performance on executive function tasks (Hovland et al., 2013). Yet, while many neuroendocrine, autonomic, and neural mechanisms contribute to neurovisceral integration components, very little is known regarding what may moderate the observed relationship between HF HRV and cognitive performance.

Overall, it is clear more research is needed to better understand the relationship between HF HRV and EF. Moreover, it is important to understand not only if this relationship exists in additional research samples but also how it is moderated and how it develops over time. This is especially crucial given the role executive function plays in the lives of aging adults. Increasing our awareness of the contributing factors to executive function decline, and researching

potentially modifiable factors for its maintenance, may underscore our society's ability to live well into old age.

Executive Function and Aging

Indeed, in the next 15 years, and for the first time in history, the United States population is projected to have more older adults than children under the age of 18 (Census, 2020). While living longer underscores significant advancement in health and medicine, research regarding how to live better in older age is a nascent field of study which requires significant attention.

What we do know is that one important predictor of quality of life in older adults is cognitive function. More specifically, executive function has emerged as the best cognitive predictor of the ability to perform instrumental activities of daily living (Mograbi, 2014). This is highly relevant to the quality of life of American older adults, as the ability to perform these instrumental activities is what allows individuals to live autonomously and independently (Chaves, 2015). The fact that executive function is vital for independence is unsurprising when examining the cognitive abilities it represents.

Executive Functions

Executive function is a broad term which comprises a multitude of skills such as planning, problem-solving, reasoning, inhibition, task switching, memory updating, performance monitoring, and cognitive flexibility. Each function involves multiple cognitive processes and a complex network of brain areas (Phillips & Henry, 2008).

A predominant theory of executive function indicates that executive functions are both unitary and distinct. Through latent variable analysis, Miyake et al. (2000) indicate measurable distinct aspects of executive function are inhibition, shifting, and updating in working memory.

Inhibition is one's capacity to supersede responses that are prepotent in a given situation (i.e., the ability to stop and reflect before acting on impulse/strong emotion). Shifting is one's cognitive flexibility to switch between different tasks or mental states (i.e., the ability to adapt thoughts and behaviors to new, changing, or unexpected events), and updating is the continuous monitoring and quick addition or deletion of contents within one's working memory (i.e., the ability to hold in the mind actions and behaviors as they are carried out to ensure everything is going to plan). Each specific function has a differential influence on cognitive aging, and thus, it is recommended that executive functions be considered independently in research (Miyake & Friedman, 2012).

In terms of neuroanatomical correlates, executive functions have often been associated with the frontal lobes (Stuss, 2011). More particularly, specific executive functions have been associated with prefrontal regions including the dorsolateral, ventromedial, anterior cingulate, and orbitofrontal subcortical circuits (Alvarez & Emory, 2006). However, it is suggested that the frontal lobes, and particularly the prefrontal cortical areas, are necessary though not sufficient for executive functions. This is because these cortical areas do not operate in isolation as they receive input from a multitude of other cortical, subcortical, and brainstem sites (Bressler & Menon, 2010).

High Frequency Heart Rate Variability and Executive Functions

Interestingly, the notion that cognition is the result of dynamic interactions of distributed brain areas rather than an outcome of isolated neural networks isn’t all that old. In some ways, the idea that cognition is actually a result of even broader inputs is a natural progression of our understanding of neuroscience. In recent years, researchers have suggested that we must look

beyond the brain and to the larger organism-environment system to understand cognition (Kiverstein & Miller, 2015).

In the case of the prefrontal cortex, the predominant site of executive function, if we zoom out, we find a number of neural networks. If we zoom out further, we find that many of these neural networks are regulated by vagal control. Neuroimaging and pharmacological studies allow us to see this both structurally and functionally. From the prefrontal cortex, to the cingulate cortex, to the insula, to the amygdala, to the midbrain, to the brainstem, to cardiac ganglia, to the heart—systems are dynamically related (Mulcahy, Larsson, Garfinkel, & Critchley, 2019). What's more, healthy connectivity in these regions has been related to better, more flexible control of physiological resources. In contrast, atypical connectivity has been related to a decreased ability to recruit and utilize appropriate physiological support to meet changing environmental demands (Friedman, Thayer, 1998a, 1998b; Thayer, Friedman, 1997; Thayer, Friedman, 2004).

Direction of Research

Underscored in all of this is that a flexible environment requires flexibility in the body, the brain, and the integration of the two. So, how can we better understand how to keep our brains and our bodies flexible as we age? To answer this question is the work of a vast interdisciplinary field of research. Key in this work is the theory that multiple variables at diverse system levels act to induce positive feedback loops with negative consequences for human health. Thus, parsing apart the interactions between these variables and their relationship to health outcomes is an imperative field of study. In order to begin to tackle these complex questions, we must continue to investigate: a) what the relationships are between multilevel system factors, b) how these factors interact and relate, c) which factors in this system are

modifiable, d) how this varies across different population characteristics, and e) the effects of all of this on diverse, longitudinal health outcomes.

Neurovisceral integration suggests that heart rate variability and executive function are related. However, what moderates this interaction, how this relationship changes depending on distinct executive functions, and the predictive power of heart rate variability on executive function decline have all received limited scientific attention. Strikingly, nearly all published studies examining cognitive function in relation to heart rate variability are cross-sectional by design. If, in theory, increased rigidity in autonomic systems marks the beginning of hierarchical system dysregulation resulting in cognitive decline, it is necessary for research to look at the longitudinal effects of autonomic function on cognition. Moreover, it is imperative that research investigate executive function components rather than executive function as only a unitary construct, given the distinguishable contributions of different executive functions to the executive system overall. Further, exploring how this relationship is modified is an open area for research which holds promise for cognitive intervention and increased quality of life in an aging population.

Dissertation Study

The present study aims to better understand the relationship between autonomic nervous system functions and longitudinal cognitive decline in aging adults. The study particularly investigates whether HF HRV can be used to predict declines in measures of distinct executive functions (i.e., shifting, inhibition, and updating). It further examines biological and psychological moderators of the relationship between HF HRV and executive functions; including inflammation (Interleukin-6), stress (salivary cortisol), sleep (PSQI), and mood and anxiety (MASQ-D and MASQ-A).

This study is important in that it investigates possible predictors of decline in a cognitive domain essential for daily functioning and quality of life. It is both innovative and novel in that it utilizes a longitudinal design and examines distinct executive function outcomes. Results from this study add to the growing literature on the neurovisceral integration theory, deepen our knowledge regarding how interrelated nervous system processes relate over time, and provide insight into potential areas for intervention and further research in the field of healthy aging.

Hypotheses

Our hypotheses were as follows:

Based on neurovisceral integration theory, which posits that HF HRV measures a dynamic regulatory system with direct effects on prefrontal brain networks, we hypothesize that HF HRV will predict declines in specific executive functions. Specifically, we expect that:

1). Adults with higher HF-HRV at baseline will have a lesser decline in inhibitory executive function (as measured by latency scores on the SGST) relative to those with lower baseline HF-HRV.

2). Adults with higher HF-HRV at baseline will have a lesser decline in shifting executive function (as measured by latency scores on the Mixed SGST) relative to those with lower baseline HF-HRV.

3). Adults with higher HF-HRV at baseline will have a lesser decline in updating executive function (as measured by total trial score on backwards Digit Span) relative to those with lower baseline HF-HRV.

Given that known biological, mental, and behavioral health factors are related to both HF HRV and executive function, we also hypothesize that such factors will modify the predictive relationship between HF HRV and executive function declines. Specifically, we expect that:

4). There will be an interaction effect between HRV and anxiety such that the predictive power of lower HRV on decline in each executive function domain will be lower for adults with lower levels anxiety as assessed by the total score on the Mood and Anxiety Symptom Questionnaire-Anxiety Symptoms.

5). There will be an interaction effect between HRV and depression such that the predictive power of lower HRV on decline in each executive function domain will be lower for adults with lower levels depression as assessed by the total score on the Mood and Anxiety Symptom Questionnaire-Depressive Symptoms.

6). There will be an interaction effect between HRV and sleep such that the predictive power of lower HRV on decline in each executive function domain will be higher for those with lower global sleep scores on the Pittsburgh Sleep Quality Index.

7). There will be an interaction effect between HRV and inflammation such that the predictive power of lower HRV on decline in each executive function domain will be higher for those with higher inflammation as measured by blood levels of Interleukin-6.

8). There will be an interaction effect between HRV and stress such that the predictive power of lower HRV on decline in each executive function domain will be higher for those with higher salivary cortisol.

Method

Sample

This study used data from the Midlife Development in the United States (MIDUS) research project. The MIDUS project is a complex longitudinal study involving wide-ranging data collection across diverse disciplines which began in 1995 and continues to this day. The project was conceived by a multitude of scholars who were interested in understanding the bio-psycho-social processes of aging. The original MIDUS sample (Wave 1) consisted of 7108 participants. Data collected from Wave 1 of the MIDUS study included phone interview and self-administered questionnaire data. (Brim, Ryff & Kessler, 2004). In Wave 2, 4,963 participants were successfully recruited from the original sample and were administered follow-up surveys as well as cognitive and biomarker measures. Wave 3 successfully retained 3,294 participants and included follow-up measures of previously administered questionnaires and cognitive tests. All waves involved extensive data collection occurring over a number of years. Wave 2 occurred from 2004 to 2006 and Wave 3 occurred from 2013 to 2015. (Radler & Ryff, 2010). ("History & Overview of MIDUS,"). As cognitive data was not available at Wave 1, the current study only used data from Wave 2 and Wave 3 of MIDUS in assessing change in cognition. Further, only participants who had valid biomarker data from Wave 2 were included in the analysis. Thus, a total of 881 participants were included in the current study.

Measures

Cognitive Measures

Executive function was measured using several indices which were administered as part of a larger neuropsychological assessment battery at both Wave 2 and Wave 3 of the MIDUS study (Lachman, Agrigoroaei, Tun, &Weaver, 2014). The larger neuropsychological battery administered was the Brief Test of Adult Cognition developed by Margie Lachman (Lachman,

2012). Specific executive function subtests measured inhibition, set-shifting, and updating components of executive function (described in Miyake et al., 2000).

In the current study, dependent measures of executive function decline were calculated as the difference between Wave 2 and Wave 3 performance scores. Thus, inhibition decline was measured as each participant's inhibition score at Wave 2 minus their score at Wave 3 on the same measure. Shifting decline was measured as each participant's shifting score at Wave 2 minus their score at Wave 3 on the same measure. Likewise, updating decline was measured as the difference in performance scores on Wave 2 and Wave 3. However, in the case of updating, decline was calculated as performance score on Wave 3 minus performance score on Wave 2. In this way, each dependent measure was expressed as a negative score if decline occurred, with more negative scores demonstrating higher levels of decline.

Inhibition

Inhibition was measured using the Stop-and-Go Switch Task (SGST; Tun & Lachman, 2006)-Reverse condition. This condition requires participants to respond "STOP" for 'GREEN' and 'GO' for 'RED' for 20 block trials after being tasked with responding the opposite under the SGST-Normal condition administered prior for 20 blocks. The SGST measures both accuracy (performance scores) and latency (response time in milliseconds). Change in mean latency scores were used in the analyses. Range of possible latency scores was 0 to 150 and higher scores were suggestive of lower inhibitory functioning. Negative difference scores, calculated as mean inhibition latency scores from Wave 3 subtracted from those at Wave 2, represent a decline in inhibition performance over time.

Shifting

Set-shifting was measured by the SGST Mixed-Task Switch block trials (Tun & Lachman, 2006) which requires participants to switch response styles between normal and reverse conditions at random times across 32 trials depending on given cues relating the style to use ('NORMAL' or 'REVERSE'). Data from this measure results in accuracy and latency indices for analysis of set-shifting. Change in mean latency scores were used in the analyses. Range of possible latency scores was 0 to 150 and higher scores were suggestive of lower shifting ability. Negative difference scores, calculated as mean shifting latency scores from Wave 3 subtracted from those at Wave 2, represent a decline in shifting performance over time.

Updating

Updating was measured using digit span-backward which requires working memory capacity to hold information in mind while simultaneously manipulating it. Specifically, participants are required to remember a series of numbers and then asked to repeat them in backwards order. Change in number of correct trials were used in the analyses. Range of possible scores was from 0 to 16. Higher scores were suggestive of higher updating function. Negative difference scores, calculated as updating scores from Wave 2 subtracted from those at Wave 3, represent a decline in performance over time.

Autonomic Measure

High Frequency Heart Rate Variability

Autonomic function was measured using vagally mediated heart rate variability (vm-HRV), also known as high frequency heart rate variability (HF-HRV). HF HRV was measured using beat-to-beat electrocardiogram waveform analysis over an 11-minute resting baseline period. Scores for analysis were derived by averaging HF HRV over two 300 second epochs on the ECG recording. HF HRV was operationalized as the variability in the series of intervals

between consecutive R waves on electrocardiogram (ECG) recordings (specifically in the high frequency band). High frequency was defined as between the 0.15-0.40 hertz range. Procedures for the noise reduction, filtering, and recommended adjustments that were made during the acquisition and processing of ECG signals can be found in the Lachman (2017) physiology protocol. Data was analyzed with HF HRV as a natural log-transformed continuous predictor variable given its known skew. A more detailed overview of the collection of this measure can be found in Appendix A.

Exploratory Measures

Mood and Anxiety Symptoms Questionnaire

The Mood and Anxiety Symptoms Questionnaire (MASQ) is a self-report questionnaire made up of 77-items which measure depressive, anxious and mixed symptomatology (Watson et al., 1995). Within the questionnaire, there are three scales which assess General Distress: depressive symptoms (12 items), anxious symptoms (11 items) and mixed symptoms (15 items). Additionally, there is a depression scale (Anhedonic Depression, 22 items) and an anxiety scale (Anxious Arousal, 17 items). Higher scores reflect higher levels of symptomatology. General Distress-Depressive scores were used to assess mood as a moderator while General Distress-Anxious scores were used to assess anxiety as a moderator. The internal consistency for each scale is reported as excellent with coefficient alphas that range from 0.78 to 0.92.

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a self-report measure that assesses the subjective pattern and quality of sleep in adults (Buysse et al., 1989). It measures 7 specific domains of sleep over a one-month period: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.

Each domain is scored from 0 to 3 with higher scores reflecting more negative sleep outcomes. There is also a global score which combines the scores from each of domain which ranges from 0 to 21. The PSQI global score was used in the analyses to assess sleep quality as a moderator. Higher global scores reflect lower sleep quality. The reliability coefficient (Cronbach's alpha) of the PSQI is 0.83 and it has reported internal consistency.

Interleukin-6

Interleukin-6 (IL-6) is a proinflammatory cytokine which is key for proper immune function. The efferent vagus nerve has been shown to indirectly regulate cytokine production and this neuro-immune communication is deemed the 'cholinergic anti-inflammatory pathway' (Johnston & Webster, 2009). Serum IL-6 was measured using high sensitivity enzyme-linked immunosorbent assay (ELISA). The laboratory intra- and inter- assay coefficients of variance were in acceptable ranges (<10%). The median IL-6 level was 2.15 pg/ml and the interquartile range (IQR) was 1.36–3.47 pg/ml. All values were natural log-transformed to account for the typical positive skew.

Salivary Cortisol

Salivary cortisol measures the short-term accumulation of cortisol in the human body. Salivary cortisol assays were performed using enzymatic colorimetric assay at the Mayo Medical Laboratory in Rochester, MN. The reported inter-assay coefficients of variation for salivary cortisol was 6.1%.

Procedure and Participants

The MIDUS project was reviewed and approved by the Education and Social/Behavioral Sciences and Health Sciences Institutional Review Board at the University of Wisconsin-

Madison. The MIDUS sample was collected through random digit dialing of a nationally representative population. City specific over-sampling was conducted in order for increased racial and geographic representativeness. Eligibility criteria for the sample included being between the ages of 25-74, English speaking, non-institutionalized and living within the coterminous United States.

In Wave 1, participants responded to phone interview questions and a mail-in self-administered questionnaire. Within these questions, information pertaining to sociodemographic statistics and detailed health were collected. In Wave 2, participants responded to these surveys and were additionally administered the cognitive measures over the phone. Additionally, a subset of Wave 2 participants met with researchers in-person for two days at one of three research sites across the U.S. and had biomarker assays conducted. In Wave 3, select participants again responded to survey measures and cognitive measures by phone. The current study analyses included only those participants who had Wave 2 and Wave 3 cognitive data and Wave 2 biomarker and psychological data available. Analyses performed were hierarchical and moderated multiple regressions.

Regression Analyses

Our independent variable in our set of regression analyses was heart rate variability at baseline measured by high frequency heart rate variability. This measure was normalized by taking the natural logarithm and analyzed as a continuous variable. Using this independent variable, we conducted separate hierarchical regression analyses on each of the following continuous dependent measures: inhibitory, shifting, and updating decline as measured by difference scores on SGST-reverse, SGST-switch, and DS-backwards, respectively. Difference

scores were calculated as the decline in performance scores on each executive function task from Wave 2 to Wave 3 of the MIDUS study. In all analyses we controlled for age.

In exploratory analyses, we further tested the hypotheses that global sleep quality (PSQI global score) and depression (MASQ-D score) modify the predicted relationship between heart rate variability and inhibition decline. We also tested whether sleep quality, depression, or anxiety modified the relationship between heart rate variability and shifting decline. We completed these analyses by running moderated hierarchical regressions for each variable listed.

Results

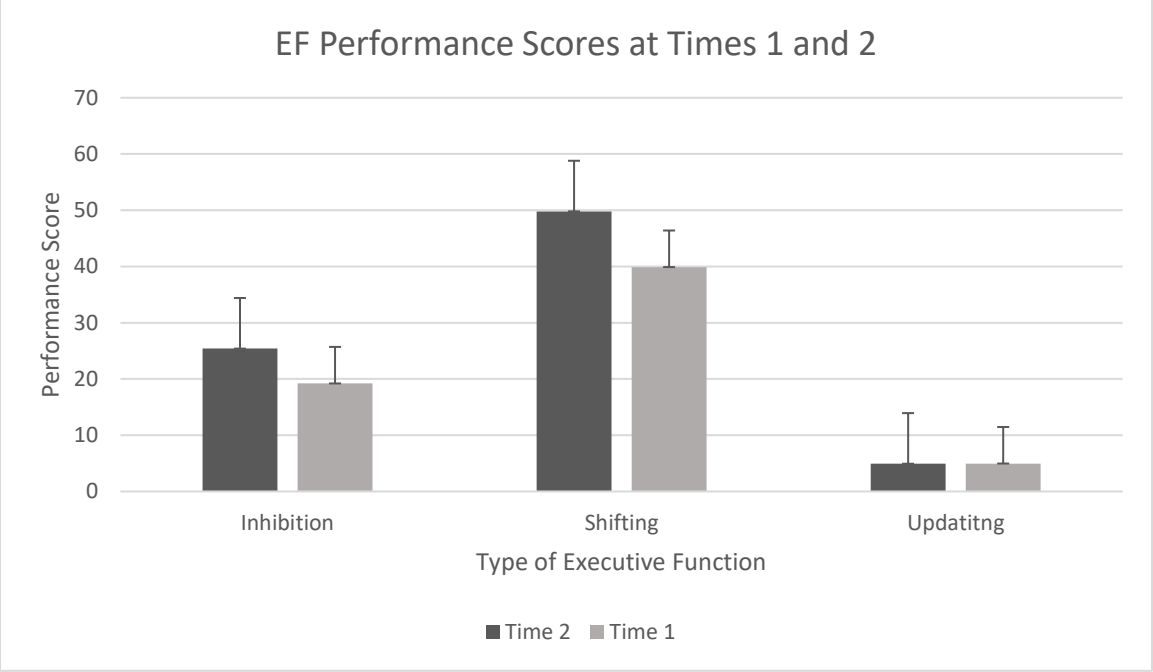
Of the 7,109 MIDUS participants, 881 had valid biomarker and cognitive data and were therefore included in the final analyses. Demographics of these participants are included in Table 1. The included participants differed significantly from drop-out participants with regard to age, education, ethnicity, and baseline cognitive function (i.e., drop-outs were older, less educated, less white, and scored lower on baseline cognitive measures; See Hughes et al., 2018 for further details). Scores on all measures decreased from Wave 1 to Wave 2 in the study sample; however, updating decreased significantly less than inhibition and shifting overall (Figure 1).

Table 1. *Sample Characteristics*

Characteristic	Overall Sample (n=881)	Mid-life (n=485)	Late Life (n=396)
Age: m (SD) range	64(11) 42-94	55.8 (6) 42-65	74.4 (6.4) 66-94
Gender: n (%)			
Female	55.1	55.8	58
Male	44.9	44.2	42
Ethnicity: n (%)			
White	94.9	92.8	96.3
Non-white	5.1	7.2	3.7
Education: n (%)			
Grade school	<1	<1	<1

Middle school	1.1	<1	1.1
Some high school	4.2	2.9	5.9
GED	23.9	20.3	27.2
Some college	29.0	29.4	29.1
College graduate	21.9	25.7	17
Some graduate school	2.3	1.8	3.2
Master's degree	12.5	14.2	10.8
Professional degree	5.2	5.7	5.3
Heart Rate Variability: m (SD)	4.9 (1.3)	5.1 (1.3)	5.0 (1.2)
Inhibition Decline: m (SD)	-.31 (.29)	-.32 (.29)	-.30 (.29)
Shifting Decline: m (SD)	-.36(.59)	-.36 (.51)	-.36 (.56)
Updating Decline: m (SD)	-.09(1.57)	.00 (1.5)	-.14 (1.52)
Salivary cortisol: m (SD)	12.4 (54.8)	12.9 (77)	12.1 (61)
Interleukin-6: m (SD)	2.22 (0.95)	2.1 (0.94)	2.29 (0.94)
Sleep Quality: m (SD)	6.2 (3.8)	6.3 (3.7)	6.1 (3.9)
Depression (MASQ-D): m (SD)	18.6 (6.7)	19.5 (7.1)	17.9 (7.0)
Anxiety (MASQ-A): m (SD)	16.7 (7.9)	17.2 (7.1)	16.2 (8.1)

Figure 1. *Declines in Executive Function Measures from Time 1 to Time 2*



Using a hierarchical framework, we conducted linear regression to examine the effects of heart rate variability on executive function decline over 9 years in mid- and late life adults. Mid-life adults were defined as adults ranging in age from 42 to 65 and late life adults were defined as adults ranging in age from 66 to 94. This cutoff was used based on standard research cutoffs for mid- and late life adults. Of the 881 total participants, 485 were mid-life and 396 were late life adults.

Prior to running analyses, scatterplots of each variable relationship were inspected. Assumptions of normality, linearity, and homoscedasticity were reasonably met. Minimal outliers were observed and none were excluded from analyses. Heart rate variability was naturally log transformed to correct for its positively skewed distribution. Variables within moderated multiple regression analyses were mean centered to minimize multicollinearity.

Bivariate Correlations

We first analyzed bivariate correlations between dependent variables of interest and demographic variables in order to explore these relationships (Table 2). Age was significantly negatively correlated with inhibition and updating decline. Education and gender were not significantly correlated with any of the outcome variables and were not included in any of the models. Age was entered into block one of the hierarchical regression models predicting inhibition, shifting, and updating decline.

Table 2. *Bivariate Correlations between Outcome Variables and Demographic Variables*

	Shifting	Updating	Age	Education	Gender

Inhibition Decline	.509**	.027	-.069**	-.021	-.014
Shifting Decline		.030	.010	-.020	.008
Updating Decline			-.089**	.018	-.005
Age				-.153**	.008
Education					-.098**

p<.05*, p<.01**, n=881

We also analyzed the bivariate relationships between outcome variables and our other variables of interest (Table 3). Correlational analyses demonstrated that decline in inhibition ability was significantly negatively correlated with HF HRV f ($r = -.072$, $p < .05$, two-tailed), global sleep quality ($r = -.114$, $p < .01$, two-tailed), and depression (r = .-.070, $p < .05$, two-tailed). Decline in shifting ability was significantly negatively correlated with global sleep quality ($r = -.129$, $p < .01$, two-tailed), depression ($r = -.149$, $p < .01$, two-tailed), and anxiety ($r = -.102$, $p < .01$, two-tailed). Updating ability was not correlated with any of the hypothesized moderator variables. Interestingly, inflammation and stress were not correlated with decline in any executive function ability.

However, inflammation was significantly negatively correlated with heart rate variability (r=-.171, p<.01, two-tailed) and global sleep quality (r=0.82, p<.01, two-tailed). Additionally, sleep quality was significantly correlated with depression (r=0.411, p<.01, two-tailed) and anxiety (r-.416, p<.01, two-tailed) scores. Depression and anxiety were also significantly correlated (r=.712, p<.01, two-tailed), as were inhibition and shifting decline (r=.509, p<.01, two-tailed). Stress (as measured by salivary cortisol) was not correlated with any other variable.

Table 3. *Bivariate Correlations between Variables of Interest*

Variable	1	2	3	4	5	6	7	Anxiety
Inhibition	.509**	.027	-.072*	-.114**	-.030	.050	-.070*	-.027
1. Shifting		.030	-.018	-.129**	-.005	.004	-.149**	-.102**
2. Updating			.044	-.032	-.002	.018	.031	-.017
3. HRV				.013	-.019	-.171**	.016	-.002
4. Sleep Quality					-.009	.082**	.411**	.416
5. Stress						.003	.001	.015
6. Inflammation							-.013	-.001
7. Depression								.712**

p<.05*, p<.01**, n=881

Heart Rate Variability as a Predictor of Executive Function Declines

Hierarchical regression was used to identify the significance of heart rate variability in predicting declines in inhibition, shifting, and updating. Age was entered as a covariate in block one of each regression model. In each case, this was followed by entering heart rate variability as a predictor variable. Results of these analyses are shown in Table 4.

In our first hierarchical regression analysis we examine inhibition decline as our outcome variable. At block one, a significant model emerged [F (1, 870) = 15.828, p < .01, R2=.018], with age predicting 1.8% of the variance in inhibition change scores. At block two, upon entering heart rate variability, the model remained significant [F (2, 869) = 8.460, p < .01, R2=.019] and explained 1.9% of the variance in inhibition change scores. However, the change in R square (R2= .001) was not statistically significant [F (2, 869) = 1.090, p = .297]. This suggests that heart

rate variability was not a significant predictor of change in inhibition decline above and beyond age (Table 1, Figure 2).

Another regression was calculated to examine the role of heart rate variability in predicting decline in the cognitive ability of shifting. At block one, a significant model emerged [F (1, 859) = 4.899, p < .05, R2=.006], with age predicting 0.6% of the variance in inhibition change scores. At block two, upon entering heart rate variability, the model no longer remained significant [F (2, 858) = 2.451, p = .087, R2=.006], continuing to explain only 0.6% of the variance in inhibition change scores. This suggests that heart rate variability was not a significant predictor of change in inhibition decline above and beyond age (Table 2, Figure 3).

A final hierarchical regression was calculated to examine the role of heart rate variability in predicting longitudinal change in the cognitive ability of updating. At block one, age was entered, creating a significant model [F (1, 905) = 4.532, p < .05, R2=.005] which explained 0.5% of the variance in updating change scores. At block two, heart rate variability was entered, creating a model [F (2, 904) = 2.549, p= .079, R2=.006] which explained 0.6% of the variance in updating change scores. The change in R square (R2= .001) was not statistically significant [F (2, 904) = 0.568, p = .451, R2=.007]. This suggests heart rate variability was not a significant predictor of updating decline above and beyond age (Table 3, Figure 4).

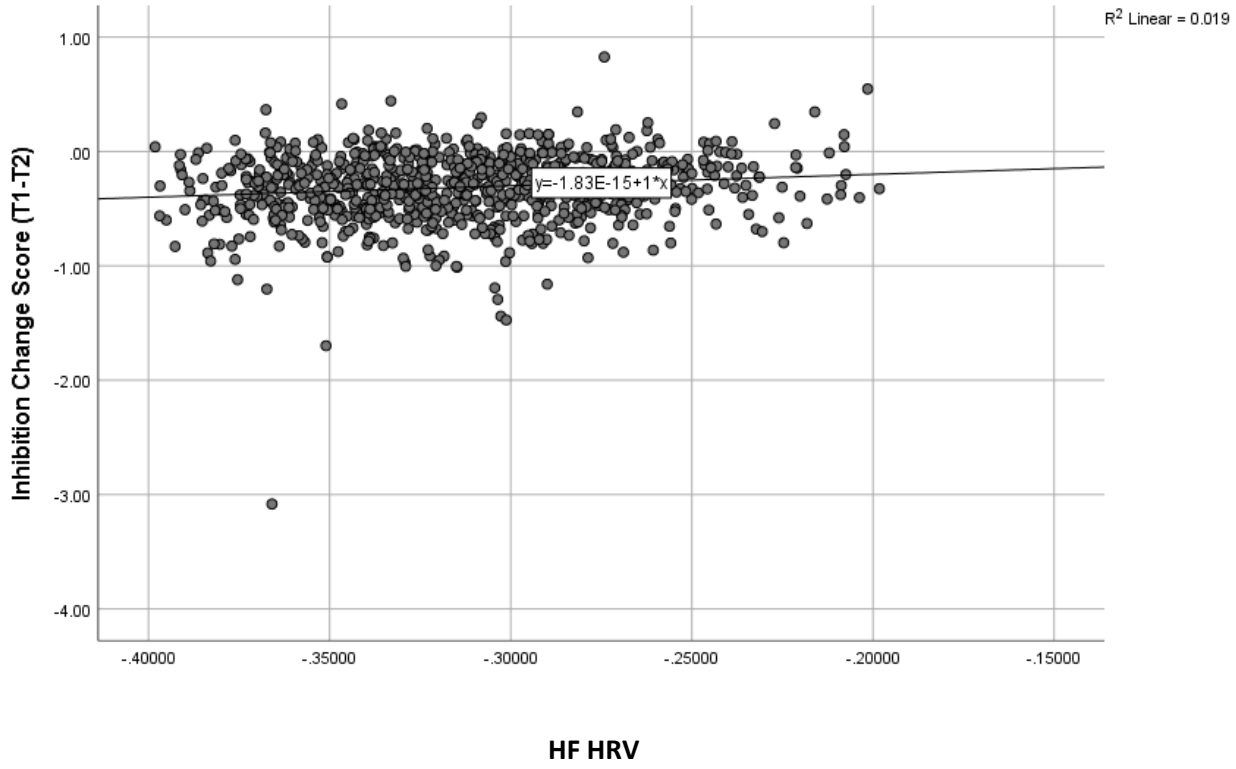
Table 1. *Regression Analyses of HRV as a Predictor of Executive Function Declines*

	Analysis #1: Inhibition Decline		
Predictor	Block 1	Block 2	R (ΔR2)
	b (SE) B	*b* (SE)B	
Age	.004 (.001).134**	.003 (.001) .123**	.134 (.018**)

HRV	-.008 (.008) -.037	.138 (.001)

p<.05*, p<.01**

Figure 2. Regression Scatterplot of HF HRV on Inhibition Decline, Controlling for Age

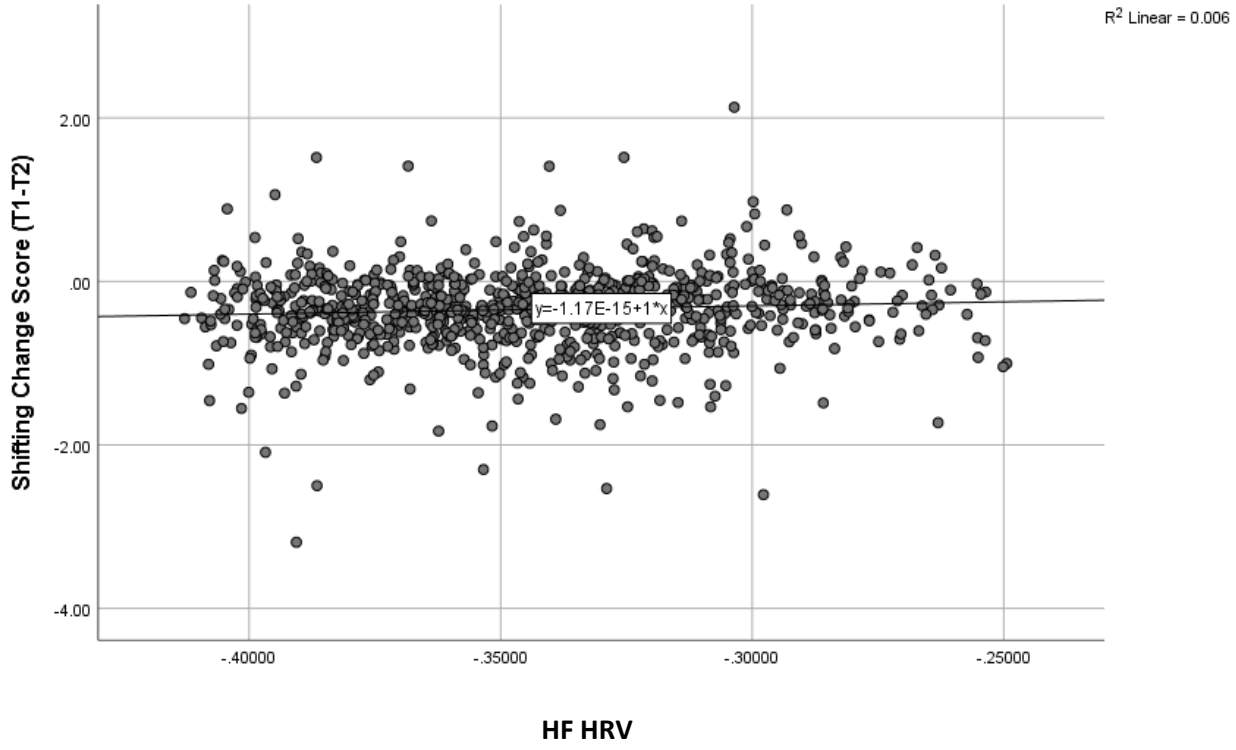


Analysis #2: Shifting Decline

Predictor	Block 1	Block 2	R (ΔR2)
	b (SE) B	*b* (SE) B	
Age	.003 (.002) .075*	.003 (.002) .076*	.075 (.006*)
HRV		.001 (.013) .003	.075 (.000)

p<.05*, p<.01**

Figure 3. Regression Scatterplot of HF HRV on Shifting Decline, Controlling for Age

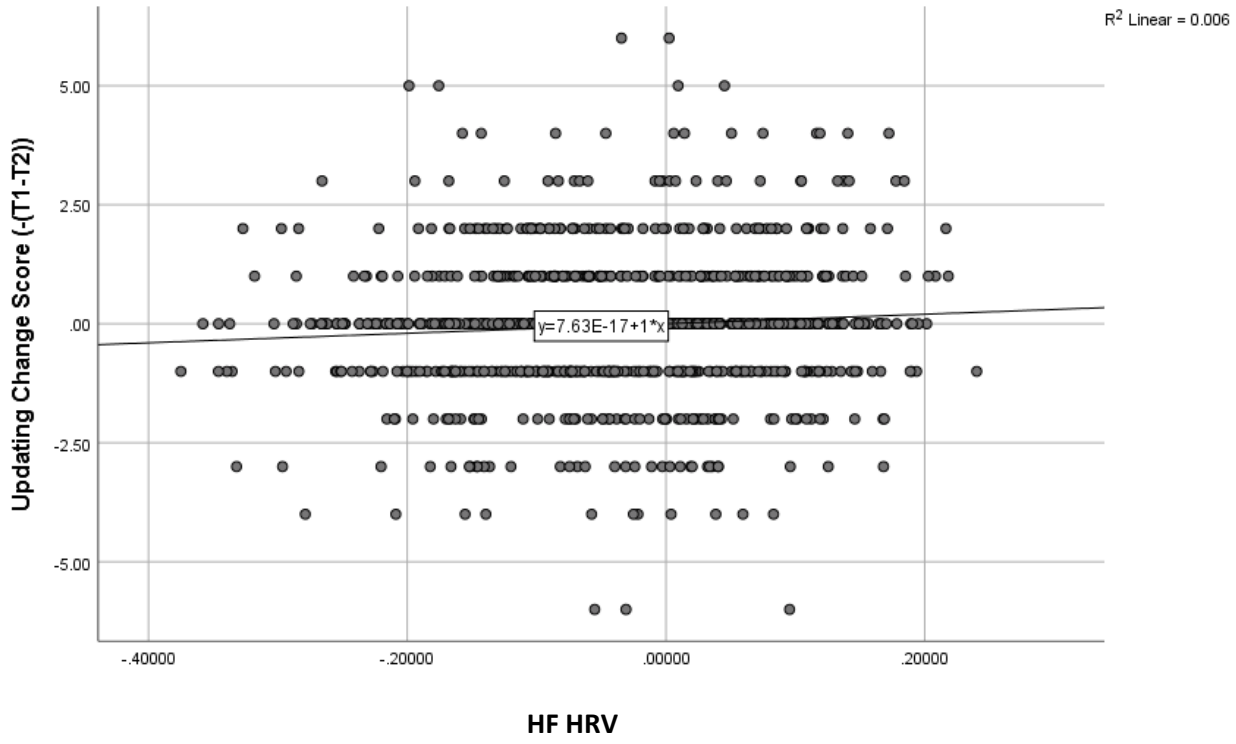


Analysis #3: Updating Decline

Predictor	Block 1	Block 2	R (ΔR2)
	b (SE) B	*b* (SE)B	
Age	-.10 (.005) -.071*	-.009 (.005) -.063 †	.071 (.005*)
HRV		0.31 (.041) .026	.075 (.001)

p<.10 †, p<.05*, p<.01**

Figure 4. Regression Scatterplot of HF HRV on Updating Decline, Controlling for Age



Moderators of Heart Rate Variability and Executive Function Declines

In order to test the impact of hypothesized moderators on the relationship between heart rate variability and executive function declines, specific moderated multiple regressions were analyzed. Sleep quality and depression were examined as moderators of heart rate variability and inhibition decline. Sleep quality, depression, and anxiety were examined as moderators of shifting decline. No moderator analyses were run with updating decline as an outcome variable.

In the regression analyses investigating inhibition decline as the outcome variable, age was entered at block one. In block two, heart rate variability was entered along with either sleep quality or depression. At block three, an interaction term between each either sleep quality or depression and heart rate variability was entered in order to test the significance of each as a moderator. In analyses with shifting as the outcome variable, heart rate variability and either

sleep quality, depression, or anxiety were entered at block one. In block two an interaction term between either sleep quality, depression, or anxiety was entered.

Results demonstrated a significant interaction effect between depression and heart rate variability in regressions on both inhibition (t=2.527 (3, 870), p=.012) and shifting decline (t=2.072 (3, 870), p=.039). Sleep quality did not significantly interact with heart rate variability and either inhibition or shifting decline. However, significant main effects of sleep quality on both inhibition (t=-2.582, (3, 870) p<.01) and shifting (t=-2.775, (3, 870) p=.01) decline were demonstrated. Likewise, while anxiety did not interact with heart rate variability in the regression on shifting decline, there was a significant main effect of anxiety on shifting decline (t=-2.681, (3, 870) p<.01). Results of these analyses are shown in Table 5.

Table 5. *Moderated Multiple Regression Analyses of HRV and Executive Function Declines*

Analysis #1: Depression and Inhibition Decline

	Block 1	Block 2	Block 3	R (ΔR2)
Variable	(SE) B	(SE) B	(SE) B	
Age	(.001) .132**	(.001) .113**	(.001) .108**	.132 (.017**)
HRV (centered)		(.008) -.035	(008) -.038	.145 (.004)
Depression (centered)		(.002) -.050	(.002) -.058 †	
HRV X Depression (centered)			(.001) .085*	.168 (.007*)

p<.10 †, p<.05*, p<.01**

Analysis #2: Depression and Shifting Decline

Variables	Block 1 (SE) B	Block 2 (SE) B	Block 3 (SE) B	R (ΔR2)
Age	(.002) .076*	(.002) .055	(.002) .050	.076 (.006*)
HRV (centered)		(.013) .006	(.013) .005	.151 (.017**)
Depression (centered)		(.003) -.132**	(.003) -.137**	
HRV X depression (centered)			(.002) -.070*	.166 (.005*)

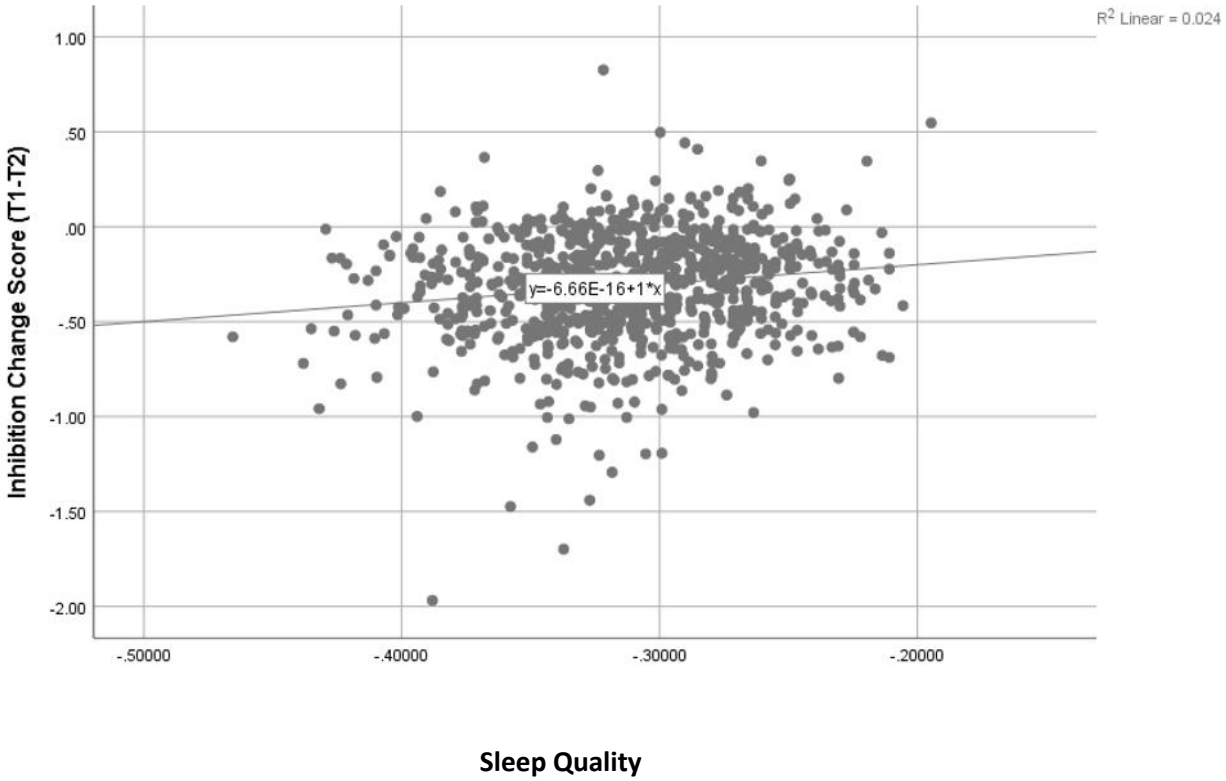
p<.05*, p<.01**

Analysis #3: Sleep Quality and Inhibition Decline

Variable	Block 1 (SE) B	Block 2 (SE)B	Block 3 (SE) B	R (ΔR2)
Age	(.001) .130**	(.001) .113**	(.001) .112**	.130 (.017*)
HRV (centered)		(.008) -.036	(.008) -.036	.162 (.009*)
Sleep Quality (centered)		(.003) -.089**	(.003)-.089**	
HRV X Sleep Quality (centered)			(.002) .021	.163 (.000)

p<.05*, p<.01**

Figure 5. Main Effect of Sleep Quality on Inhibition Decline, Controlling for Age

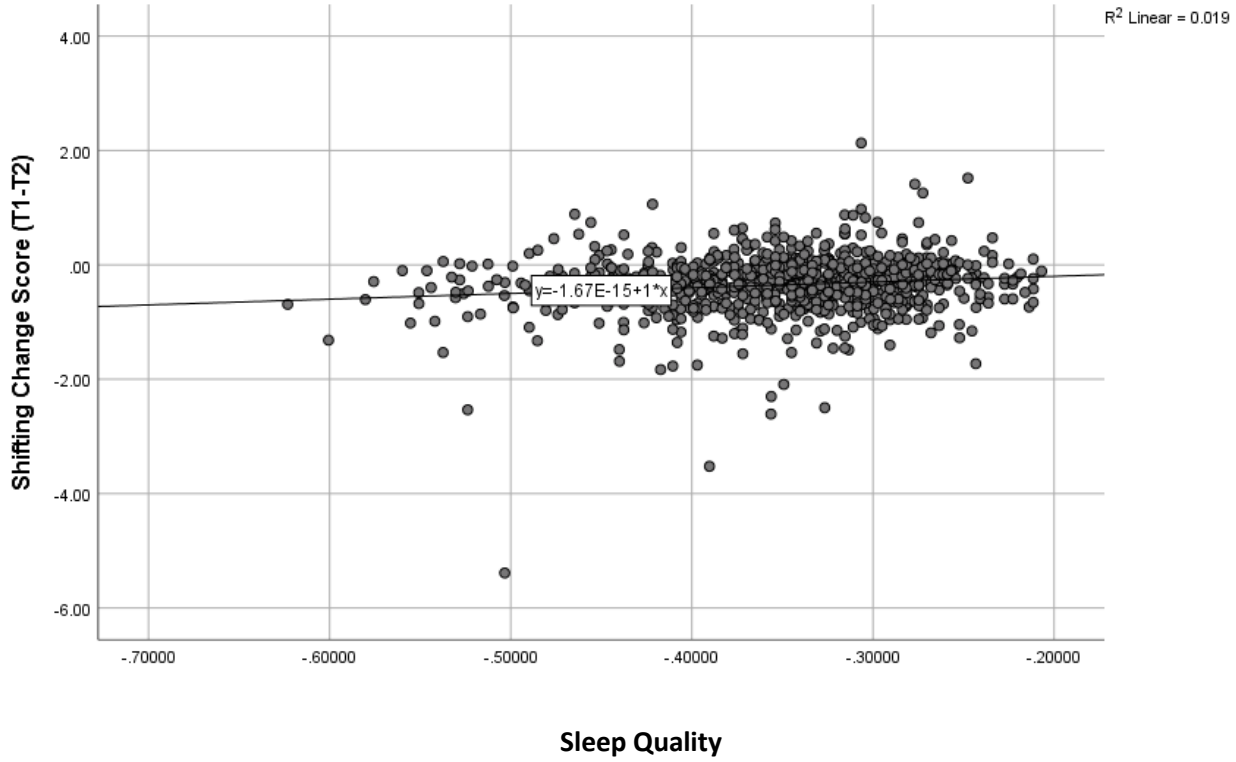


Analysis #4: Sleep Quality and Shifting Decline

Variable	Block 1 (SE) B	Block 2 (SE)B	Block 3 (SE)B	R (ΔR2)
Age	(.001) .069*	(.002) .063 †	(.002) .063 †	.069 (.005*)
HRV (centered)		(.013) .001	(.013) .001	.119 (.009*)
Sleep Quality (centered)		(.005) -.097*	(.005) -.097*	
HRV X Sleep Quality (centered)			(.004) .006	.119 (.000)

p<.10 †, p<.05*, p<.01**

Figure 6. Main Effect of Sleep Quality on Shifting Decline, Controlling for Age



Analysis #5: Anxiety and Shifting Decline

Variables	Block 1 (SE) B	Block 2 (SE) B	Block 3 (SE) B	R (ΔR2)
Age	(.002) .076*	(.002) .065†	(.002) .066†	.076 (.006*)
HRV (centered)		(.013) .002	(.013) .002	.118 (.008*)
Anxiety (centered)		(.003) -.091**	(.004) -.092**	
HRV X Anxiety (centered)			(.002) -.015	.119 (.000)

p<.10 †, p<.05*, p<.01**

Results by Age Group

The sample population included 485 mid-life adults (44-65 years old) and 396 late life adults (66-92 years old). In order to compare the study results between mid- and late life adults, sub-analyses were run to examine how age group affected each regression (Table 6). It was demonstrated that age significantly predicted decline in inhibition and updating in late life adults. In contrast, age was not a predictor of decline in any executive function domain in mid-life adults. Further, depression moderated the relationship between inhibition and HRV and shifting and HRV only in mid-life adults. Sleep quality and anxiety predicted declines in shifting and inhibition only in late-life adults.

Table 6. *Results Compared by Age Group*

Result	Mid-life Adults (42-65)		Late Life Adults (66-94)	
	(SE)	B	(SE)	B
Age as a predictor of inhibition decline	(.002)	-.032	(.002)	-.125*
Age as a predictor of shifting decline	(.003)	.009	(.004)	.060
Age as a predictor of updating decline	(.11)	-.058	(.012)	-.107*
Depression as a moderator of HRV and inhibition decline	(.005)	.139**	(.002)	-.035
Depression as a moderator of HRV and shifting decline	(.002)	.092*	(.004)	-.032
Anxiety as a predictor of shifting decline	(.004)	-.031	(.006)	-.208**
Sleep quality as a predictor of inhibition decline	(.004)	-.075 †	(.004)	-.154**
Sleep quality as a predictor of	(.006)	-.047	(.008)	-.190**

shifting decline

p<.1 †, p<.05*, p<.01**

Discussion

Study results demonstrated that an index of resting high frequency heart rate variability exhibited a correlation with longitudinal decline in executive function. However, it was only significantly correlated with decline in inhibitory executive function. Additionally, it was not predictive of decline in inhibition above and beyond known demographic variables (i.e., age).

These results are counter to our hypotheses in that heart rate variability did not independently predict decline in inhibition, shifting, and updating over time. However, the correlation between HF heart rate variability and inhibition decline does partially align with previous observations which demonstrate a correlational relationship between HF HRV and inhibition ability (Albinet, Abou-Dest, André, & Audiffren, 2016; de Oliveira Matos, Vido, Garcia, Lopes, & Pereira, 2020; Stenfors, Hanson, Theorell, & Osika, 2016; Zeki Al Hazzouri, Elfassy, Carnethon, Lloyd-Jones, & Yaffe, K, 2017). Our results suggest that while HF HRV and executive function are generally correlated, HF HRV may not be a predictor of decline in executive function over time. This is important for considering whether HF HRV is a relevant biomarker of healthy aging and suggests it may serve as a marker of an individual's current cognitive function but not a marker of later cognitive decline.

That said, it will be interesting for future research to examine whether changes in HF HRV are predictive of changes in cognitive decline. It is possible the pattern of change between HF HRV and cognitive variables is more clinically relevant than the relationship between baseline HF HRV and change in cognition. It is also imperative to note that HF HRV is only one

measure of heart rate variability. Inasmuch, future research should examine whether different measures of HF HRV may predict executive function decline. Future research should also investigate whether HF HRV is correlated with raw executive function scores at Wave 1 and Wave 2 within the MIDUS study in order to more clearly understand its correlational versus its predictive relationship to executive function.

Our results also demonstrate the importance of including age as a covariate when analyzing the relationship between heart rate variability and inhibition function in older adults. As Britton et al. (2018) reported earlier, many published studies investigating the relationship between heart rate variability and cognition do not include appropriate covariates (i.e., age) which may vastly skew results presented in the literature. This is a critique of our own study as well—as it will be important to examine our own results with the inclusion of further relevant covariates. Of course, knowing which covariates are most relevant to each cognitive domain and age group requires additional study.

Study results did support a significant interaction effect between depression and HF HRV on inhibition and shifting function declines. These results suggest that depression combined with HF HRV did a better job of predicting both declines than either variable alone. Clinically, this may indicate that depression moderates the long-term impact of HF HRV on executive function. Of note, when the results were investigated on the basis of mid-life (42-65 years of age) versus late life (66-94 years of age) adults, it was found that depression specifically moderated the relationship between heart rate variability and executive function declines in mid- but not late life adults.

In discussing these results, it is important to highlight differences in findings across executive function domains. Ostensibly, while the relationships between HF HRV and inhibition

and shifting declines are modified by depression, the relationship between HF HRV and updating decline is not. An explanation for these results may relate to neurological network structures. Intriguingly, depression is thought to represent dysregulation of frontal cortical networks (Li, Friston, Mody, & Wang, 2018). Similarly, evidence suggests inhibition and shifting abilities are primarily frontally mediated. In contrast, updating relies heavily on working memory and may be regulated by more distributed networks within both the frontal and temporal lobes (Alvarez & Emory, 2006). If such is the case, low HF HRV—which has been shown to correlate with decreased frontal lobe activity—in a depressed individual, may exacerbate dysregulation of frontal networks (Wei, Chen, & Wu, 2018). This could result in a demonstrably compromised ability to engage in cognitively demanding tasks requiring specific frontal network involvement. In contrast, cognitive tasks such as updating, which are more broadly distributed in neurological networks, may be less impacted by both HF HRV and depression.

Altogether, this emphasizes the need to consider cognitive tasks in regards to both the functions they confer as well as the neurological structures integral to their execution. Inasmuch, our results support previous research demonstrating that executive function tasks are distinctive in the functions and structures they measure. Thus, executive functions should be investigated as distinct constructs (Miyake et. al, 2000).

Clinically, the result that depression and HF HRV together predict inhibition and shifting declines makes good sense. In depression, the ability to inhibit negative thoughts and shift thinking and behavior patterns is impaired. Thus, it is not surprising that depression predicts inhibition and shifting function. In addition, HF HRV is analogous to inhibiting and shifting physical energy, enabling us to engage with cognitive tasks at appropriate levels of effort and intensity. The combination of depression and low HF HRV may result in restricted inhibition and

shifting abilities combined with limited energy to engage in such tasks. In contrast, the combination of depression and high HF HRV may result in restricted inhibition and shifting abilities albeit sufficient energy to engage in cognitive performance tasks.

While this interpretation is not perfect, it does highlight how effective integration across mental and physical domains is important for long-term health outcomes. This is not surprising at a commonsense level—physical and mental processes bidirectionally influence one another; for example, when people feel depressed they tend to exercise less and when they exercise less they tend to feel more depressed. What is intriguing is the result that depression and HF HRV combined are not only correlated with cognitive performance but are predictive of declines in cognitive performance over a nine-year period. In accordance with neurovisceral integration theory, these physical and mental markers of dysregulation may be early signs of an underlying process which builds further dysregulation across systems over time.

Overall, moderation results underscore the importance of psychological functioning in mid-life for healthy aging over time. Given that the data suggests depression moderates the relationship between physiological functioning and longitudinal cognitive abilities, clinical interventions for mood in mid-life could have long-term benefits for physical, mental, and cognitive health. Previous research suggests that differences in heart rate variability in depressed individuals may confer greater health risks with regards to physical disease (Van der Kooy et. al, 2006). The current study expands on these findings by supporting that differences in heart rate variability in depressed individuals may confer greater risk of certain neuropsychological declines as well.

Given that there are effective interventions for depression, our results highlight the need to take such intervention seriously. In studies by Hartmann, Schmidt, Sander, & Hegerl (2019)

and Economides et. al (2020), cognitive behavioral therapy, behavioral activation, and antidepressant medication were shown to improve both depression and heart rate variability in mid-life adults. Such research offers hope that similar interventions may lessen specific cognitive declines in addition to improving mental and physical health.

Interestingly, prior research demonstrates that depression is a highly heterogenous disease; and not all depression presents with overt physiological symptoms (Hasler, 2010). However, depression severity is related to changes in physiology, including changes in heart rate variability (Hartmann et. al, 2019). Thus, lower HF HRV may serve as a marker of a more severe depression. In accordance with current study results, it may be that depressed individuals who have marked physiological symptoms of depression may be at greater risk of specific cognitive decline. Previous research has suggested that HRV may serve as a biomarker of depression severity and subtypes (Hartmann et al., 2019). Our results additionally suggest that depression, in combination with HF HRV, may serve as a helpful marker of later cognitive decline.

Due to the relevance of HRV to depression, physiological intervention may be an exciting way to enhance clinical improvement in depressed individuals. Recent intervention trials are promising in this regard. Indeed, research in the elderly showed that an 8-week HRV biofeedback program improved HRV and depression (Zaccaro, 2018). Further, a study by Lin et. al (2019) demonstrated that heart rate variability biofeedback improved HRV indices and depression symptoms in adults aged 20 to 75. Given current results, future research should investigate whether HRV biofeedback can lessen executive function declines as well.

Of note, our result showing that depression and HF HRV moderate executive function decline in mid- but not late-life adults is important to consider. It is possible that dynamic factors, such as depression and HF HRV, are more relevant to health in middle age whereas

static factors carry more weight in older adults. This is further supported by our result that age was only predictive of cognitive decline in late life adults. Alternatively, HF HRV may simply have too restricted a range in older adults to impact the relationship between depression and cognitive decline. However, while HF HRV range has been shown to be more limited in older versus younger adults in previous studies, our study did not demonstrate a range difference in HF HRV between mid- and late life adults (Phyllis et. al, 2009).

Interestingly, results from the current study also demonstrated that sleep quality was a significant predictor of executive function declines in inhibition and shifting above and beyond age. In addition, anxiety was a significant predictor of shifting decline above and beyond age. However, these effects were only significant for late life rather than mid-life adults. These results underscore the importance of additional emotional and behavioral health factors in healthy aging. Importantly, sleep quality is suggested to be a modifiable lifestyle factor (Dalmeses et. al, 2019). Research supports that non-pharmacological interventions such as sleep hygiene, sleep education, phototherapy, stimulus control, relaxation, cognitive behavioral therapy, and exercise can significantly improve sleep quality ratings across age ranges (dos Santos et. al, 2018; Murawaski et al., 2017). Many effective treatments exist for anxiety as well, including diverse psychotherapies and anxiolytic medications (Nutt, 2005).

Of note, investigations into whether stress or inflammation moderated heart rate variability and executive function decline suggested neither were significant moderators. These results were counter to our hypotheses. Such results are intriguing given that biological factors, like cortisol and interleukin-6, are typically considered better biomarkers of disease than mental or behavioral health factors (Thompson & Voss, 2009). However, our results suggest that self-reported depression, anxiety, and sleep quality are all predictors of cognitive health over time

whereas these common biological measures are not. This result highlights the importance of considering mental and behavioral health, in addition to physical health, when researching healthy and diseased aging. It also gives additional credit to the notion of using mental and behavioral factors as biomarkers for health and wellness.

Overall, the results of our study show that specific modifiable factors affect executive function decline. Given the strong relationship between executive function and quality life, it is likely these factors also impact quality of life in both mid- and late life adults. Future research on when and how to change these processes in the course of aging is recommended in order to expand our knowledge of aging well.

Limitations

The current study is noted to have a number of limitations. Particularly, the study used difference scores to determine longitudinal decline. While this demonstrates decline it does so with only two measures rather than with three or more measures over a period of time, conferring less statistical power for observing longitudinal effects. However, measuring cognition with the same measure more than twice during the nine-year study period may have led to practice effects, limiting clinical validity of the observed declines. Thus, the current study utilized a tradeoff between limiting practice effects and limiting the number of test administrations over the course of the study.

In addition, HF HRV was measured at Wave 2 while cognition was measured as a change in performance scores between Waves 2 and 3. While HF HRV is known to change over time, the study did not provide information as to whether or how the Wave 2 HF HRV measure related to HF HRV over the course of the nine-year study period. Given that HF HRV changes moment

to moment, our HF HRV measure—which measured resting HF HRV at only one time point over a ten-minute period—may not have been a sufficiently sensitive measure of participant's average baseline parasympathetic tone. It is possible that future studies investigating longitudinal changes in HF HRV in relation to longitudinal changes in cognition may provide more accurate insight into how HF HRV and cognition relate to one another over time. In addition, future studies may want to utilize long-term HF HRV recordings rather than short-term, if looking to use HF HRV as a predictor of longitudinal declines.

A further limitation is in regards to the measure of updating used in our study. While the lack of predictive capacity of heart rate variability in predicting updating decline may accurately represent the resilience of this function to physiological variation, other conclusions should be considered. Particularly, in descriptive analyses, decline in inhibition and shifting occurred in all age groups. However, significant decline in updating only occurred in participants 70 and older. The limited decline in updating ability may have contributed to the non-significant findings observed in the current study. Further, it is possible that the executive function measures used in the study were different in their levels of sensitivity towards capturing specified executive domains. Future studies may want to examine how heart rate variability relates to updating decline in a sample of old-old adults (75 years and older) or a sample of individuals specifically observed to have significant decline in updating over time. Additionally, investigations into test sensitivity may help clarify how much this contributes to current study results.

Another potential limitation of the study is the large age range of the participants sampled. While we ran sub-analyses to examine how our results differed between mid-life (42-65) and older adults (66-94), it is possible that more fine-grained differences exist. For instance, the relationship between heart rate variability and executive functions for those in their 40s may

be very different from the same relationship in people in their early 60s. Future research should examine these relationships across each decade to provide greater insight into whether and how age modifies these results.

In considering the effects of depression, anxiety and sleep quality on inhibition and shifting decline, it is imperative to mention that these measures were derived from latency scores. Inasmuch, processing speed, in addition to executive function, was likely fundamental to performance. This may skew the interpretation of the results. Future studies should examine how these variables affect measures of processing speed in addition to executive function, as well as examine how these variables affect measures of executive function less reliant on processing speed.

We would also like to note the difference between participants who remained in the study for Wave 3 and those who dropped out after Wave 2. Demographically, drop out participants were less educated, less white, older, and had lower baseline cognitive performance scores than those who remained in the study. Thus, it is cautioned that the study sample is not a true representation of all mid and late life adults in the United States. In fact, these study participants represent a healthier version of aging than is typical of the average American. It is therefore important that future studies examine this study's effects in less healthy aging individuals. Additionally, while over-sampling of demographically under-represented populations was employed in recruiting study participants, the sample used in the current analyses was predominantly white. As previous research has demonstrated differences in the relationship between heart rate variability and executive function in African Americans versus whites, it is important that future research investigate how current results may vary according to race and ethnicity.

A more thorough investigation of confounds in the relationship between heart rate variability, depression, and executive functions may also be warranted. For example, future studies are recommended to examine how cardiovascular disease, diabetes, exercise, and medication use may modify the demonstrated results. While a subjective measure of health was supplementarily examined and found to be unrelated to variables of interest, more specific measures of health are likely to add extensively to the clinical relevance and nuance of the current results.

Finally, while our results demonstrated significant findings, it is essential to note that all of our effect sizes were small. Given our large sample size, such significant statistical findings should be interpreted with caution. Certainly, future research investigating the true clinical relevance of these statistical findings is warranted.

Conclusions

All in all, the current study shows that resting high frequency heart rate variability is not a standalone predictor of decline in specific executive functions. However, HF HRV does significantly moderate the relationship between depression and longitudinal executive function decline in inhibition and shifting. Additionally, findings from this study suggest that anxiety significantly predicts declines in shifting decline and that sleep quality significantly predicts declines in inhibition and shifting above and beyond age.

These results add substantially to the research literature on heart rate variability and cognitive decline. Moreover, the results cast light on prevention and intervention targets for healthy aging. Such targets specifically include depression, anxiety, heart rate variability, and sleep quality in mid- and late life adults. Results show that each of these factors may directly or

indirectly lead to increased decline in executive functions of inhibition and shifting. Imperatively, declines in these functions are related to decreased quality of life in aging adults. Thus, through tackling identified predictors and moderators of cognitive decline, hope exists not only for improving physical, mental, and behavioral symptoms—but for increasing overall quality of life.

References

Ağargün MY, Kara H, Anlar Ö. The validity and reliability of the Pittsburgh Sleep Quality Index. Turk Psikiyatri Derg. 1996;7(2):107–15. https://doi.org/10.1093/bja/aep037

Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science (1981) 213:220–2.10.1126/science.6166045

Alba, G., Vila, J., Rey, B., Montoya, P., & Muñoz, M. Á. (2019). The relationship between heart rate variability and electroencephalography functional connectivity variability is associated with cognitive flexibility. *Frontiers in Human Neuroscience, 13*, 12. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3389/fnhum.2019.00064

Alderman, B. L., & Olson, R. L. (2014). The relation of aerobic fitness to cognitive control and heart rate variability: A neurovisceral integration study. *Biological Psychology, 99*, 26-33. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsycho.2014.02.007

Almeida-Santos MA, Barreto-Filho JA, Oliveira JL, Reis FP, da Cunha Oliveira CC, Sousa AC. Aging, heart rate variability and patterns of autonomic regulation of the heart. Arch Gerontol Geriatr (2016) 63:1–8.10.1016/j.archger.2015.11.011

Alvarez, Julie A.; Emory, Eugene (2006). "Executive function and the frontal lobes: A meta-analytic review". *Neuropsychology Review*. **16** (1): 17–42. doi:10.1007/s11065-006-9002-x. PMID 16794878.

Beer, N. R., Soroker, N., Bornstein, N. M., & Leurer, M. K. (2017). Association between cardiac autonomic control and cognitive performance among patients post stroke and age-

matched healthy controls—An exploratory pilot study. *Neurological Sciences, 38*(11), 2037-2043. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1007/s10072-017-3097-0

Billman GE, Huikuri HV, Sacha J, Trimmel K. An introduction to heart rate variability: methodological considerations and clinical applications. Front Physiol (2015) 6:55.10.3389/fphys.2015.00055

Breit, S., Kupferberg, A., Rogler, G., & Hasler, G. (2018). Vagus nerve as modulator of the brain–gut axis in psychiatric and inflammatory disorders. *Frontiers in Psychiatry, 9*, 15. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3389/fpsyt.2018.00044

Bressler S, Menon V. Large-scale brain networks in cognition: Emerging methods and principles. Trends in Cognitive Sciences. 2010;14(6):277-290

Britton, A., Singh-Manoux, A., Hnatkova, K., Malik, M., Marmot, M. G., & Shipley, M. (2008). The association between heart rate variability and cognitive impairment in middle-aged men and women: The whitehall II cohort study. *Neuroepidemiology, 31*(2), 115-121. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1159/000148257

Boeing, Geoff. "Chaos Theory and the Logistic Map". Retrieved 2020-05-17.

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.

Capuana, L. J., Dywan, J., Tays, W. J., Elmers, J. L., Witherspoon, R., & Segalowitz, S. J. (2014). Factors influencing the role of cardiac autonomic regulation in the service of

cognitive control. *Biological Psychology, 102,* 88-97. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsycho.2014.07.015

Chaves AS, Santos AMD, Alves MTSSB, Salgado Filho N. Association between cognitive decline and the quality of life of hypertensive elderly individuals. Rev Bras Geriatr Gerontol. 2015;18(3):545-56. doi: 10.1590/1809-9823.2015.14043

Chi, G. C., Fitzpatrick, A. L., Sharma, M., Jenny, N. S., Lopez, O. L., & DeKosky, S. T. (2017). Inflammatory biomarkers predict domain-specific cognitive decline in older adults. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences, 72*(6), 796-803. Retrieved from https://search.proquest.com/docview/2220493930?accountid=14593

Colzato, L. S., & Steenbergen, L. (2017). High vagally mediated resting-state heart rate variability is associated with superior action cascading. *Neuropsychologia, 106,* 1-6. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.neuropsychologia.2017.08.

Colzato, L. S., Jongkees, B. J., de Wit, M., van der Molen, Melle J. W., & Steenbergen, L. (2018). Variable heart rate and a flexible mind: Higher resting-state heart rate variability predicts better task-switching. *Cognitive, Affective & Behavioral Neuroscience, 18*(4), 730-738. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3758/s13415-018-0600-x

Dalmases, M., Benítez, I., & Sapiña-Beltran, E. (2019). Impact of sleep health on self-perceived health status. *Sci Rep* **9,** 7284. https://doi.org/10.1038/s41598-019-43873-5

Darwin C. The Expression of Emotions in Man and Animals. D Appleton; New York, NY: 1872.

Daugherty, A. M., Hoagey, D. A., Kennedy, K. M., & Rodrigue, K. M. (2019). Genetic predisposition for inflammation exacerbates effects of striatal iron content on cognitive switching ability in healthy aging. *NeuroImage, 185*, 471-478. doi:http://dx.doi.org/10.1016/j.neuroimage.2018.10.064

de Oliveira Matos, F., Vido, A., Garcia, W. F., Lopes, W. A., & Pereira, A. (2020). A neurovisceral integrative study on cognition, heart rate variability, and fitness in the elderly. *Frontiers in Aging Neuroscience, 12*, 10. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3389/fnagi.2020.00051

Elliot, A. J., Payen, V., Brisswalter, J., Cury, F., & Thayer, J. F. (2011). A subtle threat cue, heart rate variability, and cognitive performance. *Psychophysiology, 48*(10), 1340-1345. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1111/j.1469-8986.2011.01216.x

Fonzo, G. A., & Etkin, A. (2016). Brain connectivity reflects mental and physical states in generalized anxiety disorder. *Biological Psychiatry, 80*(10), 733-735. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsych.2016.08.026.

Forte, G., Favieri, F., & Casagrande, M. (2019). Heart rate variability and cognitive function: A systematic review. Frontiers in Neuroscience, doi:http://dx.doi.org/10.3389/fnins.2019.00710

Frewen, J., Finucane, C., Savva, G. M., Boyle, G., Coen, R. F., & Kenny, R. A. (2013). Cognitive function is associated with impaired heart rate variability in ageing adults: the Irish longitudinal study on ageing wave one results. *Clinical autonomic research :*

official journal of the Clinical Autonomic Research Society, *23*(6), 313–323. https://doi.org/10.1007/s10286-013-0214-x

Gerritsen, R. J. S., & Band, G. P. H. (2018). Breath of life: The respiratory vagal stimulation model of contemplative activity. *Frontiers in Human Neuroscience,* doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3389/fnhum.2018.00397

Grassmann, M., Vlemincx, E., von Leupoldt, A., Mittelstädt, J. M., & Van, d. B. (2016). Respiratory changes in response to cognitive load: A systematic review. *Neural Plasticity*, *2016*, 16. Retrieved from https://search-proquest-com.weblib.lib.umt.edu:2443/docview/1861353767?accountid=14593

Hansen, A. L., Johnsen, B. H., & Thayer, J. F. (2003). Vagal influence on working memory and attention. *International Journal of Psychophysiology, 48*(3), 263-274. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/S0167-8760(03)00073-4

Hansen AL, Johnsen BH, Sollers JJ 3rd, Stenvik K, Thayer JF. Heart rate variability and its relation to prefrontal cognitive function: the effects of training and detraining. *Eur J Appl Physiol*. 2004;93(3):263-272. doi:10.1007/s00421-004-1208-0

Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. *Clinics in geriatric medicine*, *29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002

Hovland, A., Pallesen, S., Hammar, Å., Hansen, A. L., Thayer, J. F., Tarvainen, M. P., & Nordhus, I. H. (2012). The relationships among heart rate variability, executive functions, and clinical variables in patients with panic disorder. *International Journal of Psychophysiology, 86*(3), 269-275. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.ijpsycho.2012.10.004

Hughes, A. M., Hancock, G. M., Marlow, S. L., Stowers, K., & Salas, E. (2019). Cardiac measures of cognitive workload: A meta-analysis. *Human Factors, 61*(3), 393-414. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1177/0018720819830553

Jennings, J. R., Allen, B., Gianaros, P. J., Thayer, J. F., & Manuck, S. B. (2015). Focusing neurovisceral integration: Cognition, heart rate variability, and cerebral blood flow. *Psychophysiology, 52*(2), 214-224. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1111/psyp.12319

Jester, D. J., Rozek, E. K., & McKelley, R. A. (2019). Heart rate variability biofeedback: Implications for cognitive and psychiatric effects in older adults. *Aging & Mental Health, 23*(5), 574-580. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1080/13607863.2018.1432031

Keary, T. A. (2012). *The role of inflammation in the association between autonomic nervous system dysregulation and cognitive dysfunction in cardiovascular disease* (Order No. AAI3476837). Available from PsycINFO. (1036887177; 2012-99120-428).

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PloS one, 7(2), e30777. https://doi.org/10.1371/journal.pone.0030777

Kimhy, D., Crowley, O. V., McKinley, P. S., Burg, M. M., Lachman, M. E., Tun, P. A., . . . Sloan, R. P. (2013). The association of cardiac vagal control and executive functioning—Findings from the MIDUS study. *Journal of Psychiatric Research, 47*(5), 628-635. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.jpsychires.2013.01.018

Laborde, S., Mosley, E., & Thayer, J. F. (2017). Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Frontiers in psychology*, *8*, 213. https://doi.org/10.3389/fpsyg.2017.00213

Lampert R, Bremner JD, Su S, Miller A, Lee F, Cheema F, et al. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am Heart J (2008) 156:759.e1–7.10.1016/j.ahj.2008.07.009

Lane RD, Reiman EM, Ahem GL, Thayer JF. Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. Brain Cognit (2001) 47:97–100.

Li, B. J., Friston, K., Mody, M., Wang, H. N., Lu, H. B., & Hu, D. W. (2018). A brain network model for depression: From symptom understanding to disease intervention. *CNS neuroscience & therapeutics*, *24*(11), 1004–1019. https://doi.org/10.1111/cns.12998

Lin, F., Ren, P., Wang, X., Anthony, M., Tadin, D., & Heffner, K. L. (2017). Cortical thickness is associated with altered autonomic function in cognitively impaired and non-impaired older adults. *The Journal of Physiology*, *595*(22), 6969-6978. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1113/JP274714

Lin, F., Heffner, K. L., Ren, P., & Tadin, D. (2017). A role of the parasympathetic nervous system in cognitive training. *Current Alzheimer Research*, *14*(7), 784-789. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.2174/1567205014666170203095

Lin, I. (2018). Effects of a cardiorespiratory synchronization training mobile application on heart rate variability and electroencephalography in healthy adults. *International Journal of Psychophysiology, 134*, 168-177. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.ijpsycho.2018.09.005

Lischke, A., Pahnke, R., Mau-Moeller, A., Behrens, M., Grabe, H. J., Freyberger, H. J., . . . Weippert, M. (2018). Inter-individual differences in heart rate variability are associated with inter-individual differences in empathy and alexithymia. *Frontiers in Psychology, 9*, 9. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3389/fpsyg.2018.00229

Luque-Casado, A., Perales, J. C., Cárdenas, D., & Sanabria, D. (2016). Heart rate variability and cognitive processing: The autonomic response to task demands. *Biological Psychology, 113*, 83-90. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsycho.2015.11.013

Mahinrad, S., Jukema, J. W., van Heemst, D., Macfarlane, P. W., Clark, E. N., de Craen, Anton J. M., & Sabayan, B. (2016). 10-second heart rate variability and cognitive function in old age. *Neurology, 86*(12), 1120-1127. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1212/WNL.0000000000002499

Makovac, E., Meeten, F., Watson, D. R., Herman, A., Garfinkel, S. N., Critchley, H. D., & Ottaviani, C. (2016). Alterations in amygdala-prefrontal functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. *Biological Psychiatry, 80*(10), 786-795. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsych.2015.10.013

Mann, S. L., Selby, E. A., Bates, M. E., & Contrada, R. J. (2015). Integrating affective and cognitive correlates of heart rate variability: A structural equation modeling approach. *International Journal of Psychophysiology, 98*(1), 76-86. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.ijpsycho.2015.07.003

McCorry L. K. (2007). Physiology of the autonomic nervous system. *American journal of pharmaceutical education*, *71*(4), 78. https://doi.org/10.5688/aj710478

McCraty R, Shaffer F. Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. Glob Adv Health Med (2015) 4:46–61.10.7453/gahmj.2014.073

Meeten, F., Davey, G. C. L., Makovac, E., Watson, D. R., Garfinkel, S. N., Critchley, H. D., & Ottaviani, C. (2016). Goal directed worry rules are associated with distinct patterns of amygdala functional connectivity and vagal modulation during perseverative cognition. *Frontiers in Human Neuroscience, 10*, 9. Retrieved from https://search-proquest-com.weblib.lib.umt.edu:2443/docview/1847423098?accountid=14593

Miyake, A., & Friedman, N. P. (2012). The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. *Current directions in psychological science*, *21*(1), 8–14. https://doi.org/10.1177/0963721411429458

Mograbi, D. C., Faria, C., Fichman, H. C., Paradela, E. M., & Lourenço, R. A. (2014). Relationship between activities of daily living and cognitive ability in a sample of older adults with heterogeneous educational level. *Annals of Indian Academy of Neurology*, *17*(1), 71–76. https://doi.org/10.4103/0972-2327.128558

Moss D, Shaffer F. The application of heart rate variability biofeedback to medical and mental health disorders. Biofeedback (2017) 45:2–8.10.5298/1081-5937-45.1.03

Nonogaki, Z., Umegaki, H., Makino, T., Suzuki, Y., & Kuzuya, M. (2017). Relationship between cardiac autonomic function and cognitive function in alzheimer's disease. *Geriatrics & Gerontology International, 17*(1), 92-98. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1111/ggi.12679

Nutt, D. (2005). Overview of Diagnosis and Drug Treatments of Anxiety Disorders. CNS Spectrums, 10(1), 49-56. doi:10.1017/S1092852900009901

Ottaviani, C., Watson, D. R., Meeten, F., Makovac, E., Garfinkel, S. N., & Critchley, H. D. (2016). Neurobiological substrates of cognitive rigidity and autonomic inflexibility in generalized anxiety disorder. *Biological Psychology, 119,* 31-41. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsycho.2016.06.009

Ottaviani, C., Zingaretti, P., Petta, A. M., Antonucci, G., Thayer, J. F., & Spitoni, G. F. (2019). Resting heart rate variability predicts inhibitory control above and beyond impulsivity. *Journal of Psychophysiology, 33*(3), 198-206. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1027/0269-8803/a000222

Ouanes, S., & Popp, J. (2019). High cortisol and the risk of dementia and Alzheimer's disease: A review of the literature. *Frontiers in Aging Neuroscience, 11*, 11. doi:http://dx.doi.org/10.3389/fnagi.2019.00043

Petrella, C., Nisticò, G., & Nisticò, R. (2018). In Ismail K., Barthel A., Bornstein S. R. and Licinio J. (Eds.), *Gut-brain axis: Physiology and pathology* Oxford University Press,

New York, NY. Retrieved from https://search-proquest-com.weblib.lib.umt.edu:2443/docview/2431946022?accountid=14593

Phillips, L. H., & Henry, J. D. (2008). *Adult aging and executive functioning.* In V. Anderson, R. Jacobs, & P. J. Anderson (Eds.), *Neuropsychology, neurology, and cognition. Executive functions and the frontal lobes: A lifespan perspective* (p. 57–79). Taylor & Francis.

Phyllis K. Stein, Joshua I. Barzilay, Paulo H. M. Chaves, Peter P. Domitrovich, John S. Gottdiener, Heart rate variability and its changes over 5 years in older adults, *Age and Ageing*, Volume 38, Issue 2, March 2009, Pages 212–218, https://doi.org/10.1093/ageing/afn292

Santos, M., Conceição, A., Ferretti-Rebustini, R., Ciol, M. A., Heithkemper, M. M., & Cruz, D. (2018). Non-pharmacological interventions for sleep and quality of life: a randomized pilot study. *Revista latino-americana de enfermagem*, *26*, e3079. https://doi.org/10.1590/1518-8345.2598.3079

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. Annals of Behavioral Medicine, 37(2), 141-153. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1007/s12160-009-9101-z

Thompson, H. J., & Voss, J. G. (2009). Health-and disease-related biomarkers in aging research. *Research in gerontological nursing*, *2*(2), 137–148. https://doi.org/10.3928/19404921-20090401-09

Ramírez, E., Ortega, A. R., & Reyes, D. P. (2015). Anxiety, attention, and decision making: The moderating role of heart rate variability. *International Journal of Psychophysiology, 98*(3), 490-496. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.ijpsycho.2015.10.007

Riganello, F., Garbarino, S., & Sannita, W. G. (2012). Heart rate variability, homeostasis, and brain function: A tutorial and review of application. *Journal of Psychophysiology, 26*(4), 178-203. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1027/0269-8803/a000080

Roy, C. S., and Sherrington, C. S. (1890). On the regulation of the blood-supply of the brain. *J. Physiol*. 11, 85.17–158.17. doi: 10.1113/jphysiol.1890.sp000321 REVIEW ARTICLE Front. Psychiatry, 13 March 2018 | https://doi.org/10.3389/fpsyt.2018.00044

Sachdev, P. S., Anstey, K. J., Parslow, R. A., Wen, W., Maller, J., Kumar, R., . . . Jorm, A. F. (2006). Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample. *Dementia and Geriatric Cognitive Disorders, 21*(5-6), 300-308. doi:http://dx.doi.org/10.1159/000091438

Samson, R. D., & Barnes, C. A. (2013). Impact of aging brain circuits on cognition. *The European journal of neuroscience*, *37*(12), 1903–1915. https://doi.org/10.1111/ejn.12183

Santiago, C., Herrmann, N., Swardfager, W., Saleem, M., Oh, P. I., Black, S. E., . . . Lanctôt, K. L. (2018). Subcortical hyperintensities in the cholinergic system are associated with improvements in executive function in older adults with coronary artery disease undergoing cardiac rehabilitation. *International Journal of Geriatric Psychiatry, 33*(2), 279-287. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1002/gps.4729

Santos, C. R., Ruggeri, A., Ceroni, A., & Michelini, L. C. (2018). Exercise training abrogates age-dependent loss of hypothalamic oxytocinergic circuitry and maintains high parasympathetic activity. Journal of Neuroendocrinology, 30(8), 1-13. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1111/jne.12601

Seeman, T. E., & Gruenewald, T. L. (2006). Allostasis and allostatic load over the life course. *Medical and psychiatric comorbidity over the course of life; medical and psychiatric comorbidity over the course of life* (pp. 179-196, Chapter xviii, 301 Pages) American Psychiatric Publishing, Inc., Arlington, VA. Retrieved from https://search-proquest-com.weblib.lib.umt.edu:2443/docview/620949561?accountid=14593

Shaffer F, Venner J. Heart rate variability anatomy and physiology. Biofeedback (2013) 41:13–25.10.5298/1081-5937-41.1.05

Skullin, M. K., & Bliwise, D. L. (2015). Sleep, cognition, and normal aging: Integrating a half century of multidisciplinary research. *Perspectives on Psychological Science, 10*(1), 97-137. doi:http://dx.doi.org/10.1177/1745691614556680

Smith, R., Thayer, J. F., Khalsa, S. S., & Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neuroscience and Biobehavioral Reviews, 75*, 274-296. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.neubiorev.2017.02.003

Spangler, D. P., Gamble, K. R., McGinley, J. J., Thayer, J. F., & Brooks, J. R. (2018). Intra-individual variability in vagal control is associated with response inhibition under stress. *Frontiers in Human Neuroscience, 12*, 9. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3389/fnhum.2018.00475

Stenfors, C. U. D., Hanson, L. M., Theorell, T., & Osika, W. S. (2016). Executive cognitive functioning and cardiovascular autonomic regulation in a population-based sample of working adults. *Frontiers in Psychology, 7*, 13. Retrieved from https://search-proquest-com.weblib.lib.umt.edu:2443/docview/1857840733?accountid=1459

Tan, G., Wang, P., & Ginsberg, J. (2013). Heart rate variability and posttraumatic stress disorder. *Biofeedback, 41*(3), 131-135. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.5298/1081-5937-41.3.05

Task Force Report. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation (1996) 93:1043

Taylor AG, Goehler LE, Galper DI, Innes KE, Bourguignon C. Top-down and bottom-up mechanisms in mind-body medicine: development of an integrative framework for psychophysiological research. Explore (New York, N.Y.). 2010 Jan-Feb;6(1):29-41. https:\\doi: 10.1016/j.explore.2009.10.004.

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine, 37*(2), 141-153. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1007/s12160-009-9101-z

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers,John J., I.,II, & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience and Biobehavioral Reviews,*

36(2), 747-756. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.neubiorev.2011.11.009

Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N. Heart rate variability in normal and pathological sleep. Front Physiol (2013) 4:294.10.3389/fphys.2013.00294

Tsuji H, Venditti FJ, Jr, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation (1994) 90:878–83.10.1161/01.CIR.90.2.878

Vaillancourt DE, Newell KM. Changing complexity in human behavior and physiology through aging and disease. Neurobiol Aging (2002) 23:1–11.10.1016/S0197-4580(01)00247-0

Watson D, Clark LA, Weber K, Assenheimer JS, Strauss ME, McCormick RA. Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. Journal of Abnormal Psychology. 1995;104:15–25. doi: 10.1037/0021-843X.104.1.15. [PubMed] [CrossRef] [Google Scholar]

Watson D, Clark LA, Weber K, Assenheimer JS, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. Journal of Abnormal Psychology. 1995;104:3–14. doi: 10.1037/0021-843X.104.1.3.

Webb, H. E., & Acevedo, E. O. (2018). It's all psychophysiological!—Effects of exercise on your body and psyche. In S. Razon, & M. L. Sachs (Eds.), *Applied exercise psychology: The challenging journey from motivation to adherence; applied exercise psychology: The challenging journey from motivation to adherence* (pp. 20-36, Chapter xii, 457 Pages)

Routledge/Taylor & Francis Group, New York, NY. Retrieved from https://search-proquest-com.weblib.lib.umt.edu:2443/docview/2032686486?accountid=14593

Wei, L., Chen, H., & Wu, G. (2018). Heart rate variability associated with grey matter volumes in striatal and limbic structures of the central autonomic network. *Brain Research, 1681,* 14-20. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.brainres.2017.12.024

Wei, L., Chen, H., & Wu, G. (2018). Structural covariance of the prefrontal-amygdala pathways associated with heart rate variability. *Frontiers in Human Neuroscience, 12,* 11. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.3389/fnhum.2018.00002

Werner, G. G., Ford, B. Q., Mauss, I. B., Schabus, M., Blechert, J., & Wilhelm, F. H. (2015). High cardiac vagal control is related to better subjective and objective sleep quality. *BiologicalPsychology, 106,* 79-85. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsycho.2015.02.00

Williams, D. P., Thayer, J. F., & Koenig, J. (2016). Resting cardiac vagal tone predicts intraindividual reaction time variability during an attention task in a sample of young and healthy adults. *Psychophysiology, 53*(12), 1843-1851. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1111/psyp.12739

Williams, P. G., Cribbet, M. R., Tinajero, R., Rau, H. K., Thayer, J. F., & Suchy, Y. (2019). The association between individual differences in executive functioning and resting high-frequency heart rate variability. Biological Psychology, 148, 9. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsycho.2019.107772

Zaccaro, A., Piarulli, A., Laurino, M., Garbella, E., Menicucci, D., Neri, B., & Gemignani, A. (2018). How breath-control can change your life: A systematic review on psycho-physiological correlates of slow breathing. *Frontiers in Human Neuroscience, 12*, 16.

Zahn, D., Adams, J., Krohn, J., Wenzel, M., Mann, C. G., Gomille, L. K., . . . Kubiak, T. (2016). Heart rate variability and self-control—A meta-analysis. *Biological Psychology, 115*, 9-26. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1016/j.biopsycho.2015.12.007

Zeki Al Hazzouri, A., Haan, M. N., Deng, Y., Neuhaus, J., & Yaffe, K. (2014). Reduced heart rate variability is associated with worse cognitive performance in elderly Mexican Americans. *Hypertension (Dallas, Tex. : 1979), 63*(1), 181–187.

Zulli, R., Nicosia, F., Borroni, B., Agosti, C., Prometti, P., Donati, P., . . . Padovani, A. (2005). QT dispersion and heart rate variability abnormalities in alzheimer's disease and in mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(12), 2135-2139. doi:http://dx.doi.org.weblib.lib.umt.edu:8080/10.1111/j.1532-5415.2005.00508.x

Appendix A: Detailed Psychophysiology Protocol Description

I. Introduction

The MIDUS Biomarker Project (P4) psychophysiology session is a standard, laboratory based stress reactivity protocol. Our study utilized only the resting baseline portion of the protocol to obtain our measure of heart rate variability; however, the entire procedure is described below. The data were collected at UCLA, Georgetown, and the University of Wisconsin and processed at the Columbia University Medical Center (CUMC) in the laboratory of Dr. Richard Sloan.

This section provides additional information about the protocol and variables included in the data file organized as follows: Overview of the protocol; description of the measures; detailed outline of the protocol and data processing; description of variables included in the data file, particularly the primary outcomes of interest (heart rate (HR), heart rate variability (HRV), and salivary cortisol); and naming conventions.

II. Overview of Protocol

A. Purpose.

The psychophysiology protocol in Project 4 is a widely used laboratory based, experimental procedure designed to measure cardiovascular reactivity to and recovery from stress.

B. Procedure.

During the protocol, participants' physiological outcomes are measured during a seated, resting baseline period followed by two cognitive/psychological stressor tasks, also in a seated position. The cognitive tasks are a mental arithmetic task (PASAT or MATH) and a Stroop color–word matching task. After each cognitive stress task, participants undergo another seated, resting period to assess physiological recovery to stress. The last period in the procedure is an orthostatic stressor. Participants move from a seated to standing position and remain standing for several minutes.

C. Physiological outcomes.

Cardiovascular reactivity is assessed via continuous measurement of the electrocardiogram (ECG). The beat-to-beat ECG waveforms are then analyzed to calculate heart rate and several indices of heart rate variability (HRV). Heart rate variability is operationalized as variability in the series of intervals between consecutive R waves (the first upward deflection of the electrocardiogram following the Q-wave, arising from ventricular depolarization).

D. Theory and method.

Throughout this guide, relevant references are cited to provide investigators information about the methodology used in this protocol. We offer the following references, including one *in press* paper using Project 4 data, for an introduction and review of cardiac psychophysiology, and the types of questions that can be investigated with this type of protocol (Carney, Freedland, & Veith, 2005; Gorman & Sloan, 2000; Shcheslavskaya, Burg et al., in press (2009); Sloan, McCreath et al., 2007). A recent special issue of *Biological*

Psychology (Allen & Chambers, 2007) on cardiac vagal control is a good resource. Investigators are encouraged to review the literature in more depth.

III. Measures

A. Physiological Measures

1. Acquisition and Processing of ECG Signals. Beat-to-beat analog ECG signals were collected then digitized at a sampling rate of 500 Hz by a 16-bit National Instruments analog-to-digital (A/D) board installed in a microcomputer. ECG waveforms were submitted to proprietary event detection software to identify R waves. Following established procedures, (Berntson, Quigley, Lang, & Boysen, 1990; Dykes, Ahmann et al., 1986), research staff visually reviewed all ECG waveforms to correct interactively any software errors in identifying normal R waves. The resulting series of normal RR intervals was used to calculate the cardiac variables heart rate (HR) and several standard indices of HRV.

2. Heart rate variability. Time domain indices of RR interval variability include the standard deviation of RR intervals (SDRR) and the root mean squared successive differences (rMSSD). Frequency domain measures include spectral power in the low (0.04-0.15 Hz (LF-HRV)) and high (0.15-0.50 Hz (HF-HRV)) frequency bands. The spectra of RR interval series were calculated using an interval method for computing Fourier transforms similar to that described by DeBoer, et al. (DeBoer, Karemaker, & Strackee, 1984). Prior to computing Fourier transforms, the mean of the RR interval series is subtracted from each value in the series and the series then is filtered using a Hanning window (Harris, 1978) and the power, i.e., variance (in msec2), over the LF and HF bands is summed. Estimates of spectral power are adjusted to account for attenuation produced by this filter (Harris, 1978).

IV. Psychophysiology Protocol Description

The following is a detailed description of the data collection protocol, including equipment setup, protocol order, and data processing.

A. Protocol Flowsheet:

MIDUS staff who conducted this protocol used a data collection form called the psychophysiology flowsheet. A copy of this form is in Section B. The first two pages included questions about handedness, physical characteristics of the participant, and other factors that may influence experimental outcomes (e.g. consumption of caffeine, nicotine etc.), as well as a template of the protocol order. A more detailed version of this template appears in Table 1 below. The remainder of the flowsheet contains a more complete description of the protocol, instructions to research staff, instructions to participants, descriptions of the stress tasks, etc. Throughout the protocol, staff were instructed to record information at designated locations on flowsheet. This information as well as responses to the items at the beginning of the flowsheet were data-entered and included in the MIDUS 2 Project 4 data file.

B. Monitoring Device Setup.

Electrocardiograph (ECG) electrodes were placed on the left and right shoulders, and in the left lower quadrant. Stretch bands were placed around the participant's chest and abdomen to

measure respiration. A Finometer blood pressure cuff was placed on the middle finger of the non-dominant hand, and a Finometer blood pressure arm cuff was placed on the upper arm on the same side as the finger cuff. The participant was then seated and a numeric keypad, for responding to the stress tasks, was secured in a comfortable position relative to the dominant hand. The monitoring devices were then calibrated in the seated position.

C. Protocol Order.
The general protocol order was as follows (*details are in Table 1*): seated baseline (11 minutes); psychological stress task 1 (mental arithmetic or Stroop task – 6 minutes); recovery 1 (6 minutes); psychological stress task 2 (mental arithmetic or Stroop task - 6 minutes); recovery 2 (6 minutes); orthostatic stressor (standing/upright) (6 minutes). No recovery data were collected after exposure to the orthostatic stressor. Participants were instructed to remain silent throughout the procedures. After the second recovery period, participants were assisted in moving to a standing position. The monitoring devices were recalibrated, then the orthostatic stress period began. The seated baseline recordings were used to produce the HF HRV measure used in our study.

V. Data Processing Criteria
The physiological monitoring equipment (ECG, Finometer, Inductotrace respirometer) ran continuously throughout the protocol and produced raw waveform data. These raw data were processed according to standardized algorithms (Task Force, 1996) to create variables (see Key Variables) that can be used in analyses. Analytic data are provided in MIDUS by ***period*** and by ***epoch*** within each period. The MIDUS 2 Biomarker (P4) data includes one set of data from the psychophysiology session, which uses 300 second epochs of data. This section defines these terms and describes the criteria used to select raw physiological waveform data for processing to generate key variables.

B. Data Epochs for Analysis
Within each protocol period, data were analyzed in specified epochs of time, based on different criteria and different types of research questions.

C. Epoch Duration and Number of Epochs per Period
1. 300 sec epoch data set:
a. First, data were analyzed with a specified 300 sec epoch duration.
b. The analysis software was programmed such that, if unscorable data precluded a full 300 sec segment of analyzable data, epoch duration was decreased by 60 sec segments until a continuous data epoch could be analyzed.
c. The minimum epoch length provided in this data set is 180 sec; epochs shorter than that were omitted from this data set. For all variables except the Low Frequency RRV variables, reasonable estimates can be obtained from epochs as short as 180 sec.
d. For the 11 min baseline period, we attempt to provide 2 epochs of 300 sec each. Cases with unscorable intervals of data (due to noisy signal) include 1 or 2 epochs of 300, 240 and/or 180 sec.

VI. Key Variables and Naming Conventions

A. Key Variables.

The key cardiac variables from the psychophysiology session used by CUMC investigators are listed below. These output variables are somewhat standardized based on conventions for measuring heart rate and heart rate variability parameters:

HR: Average heart rate, beats per minute units
SDRR: Standard deviation of RR intervals, msec units
rMSSD: Root mean squared successive differences, msec units
LF_HRV: Low frequency RR interval variability, bandwidth 0.04-0.15 Hz, msec2 units
HF-HRV: High frequency RR interval variability, bandwidth 0.15-0.40 Hz, msec2 units

The data file includes both original and log transformed versions of all HRV variables (the last 4 variables listed above) for each period, and each epoch within a given period, along with variables indicating Epoch Duration (secs) and the Number of R-R intervals analyzed in each epoch.

Note: the CUMC team always uses log-transformed versions of the variables (natural logarithm), a standard practice in HRV research, due to reliable skew in their distributions.