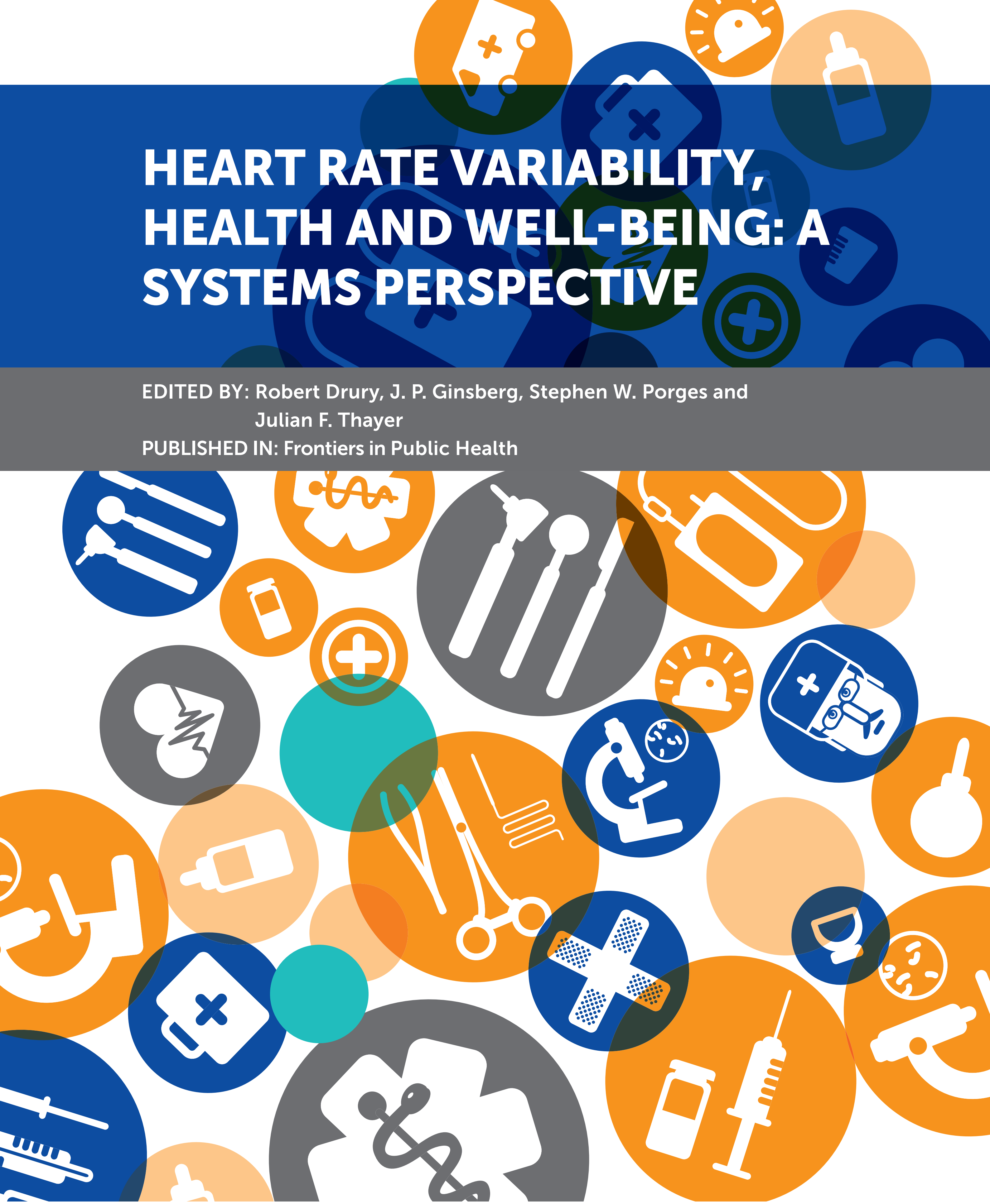

HEART RATE VARIABILITY, HEALTH AND WELL-BEING: A SYSTEMS PERSPECTIVE

EDITED BY: Robert Drury, J. P. Ginsberg, Stephen W. Porges and Julian F. Thayer

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frontiers Research Topics

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HEART RATE VARIABILITY, HEALTH AND WELL-BEING: A SYSTEMS PERSPECTIVE

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The development of a new tool, analytic device, or approach frequently facilitates rapid growth in scientific understanding, although the process is seldom linear. The study of heart rate variability (HRV) defined as the extent to which beat-to-beat variation in heart rate varies, is a rapidly maturing paradigm that integrates health and wellness observations across a wide variety of biomedical and psychosocial phenomena and illustrates this nonlinear path of development. The utility of HRV as an analytic and interventive technique goes far beyond its original application as a robust predictor of sudden cardiac death. This Research Topic aims to provide a conceptual framework to use in exploring the utility of HRV as a robust parameter of health status, using a broad and inclusive definition of 'health' and 'well-being'.

From the broadest perspective, current biomedical science emerged from shamanistic and religious healing practices and empirically observed interventions made as humans emerged from other hominins. The exponential growth of physics, chemistry and biology provided scientific support for the model emphasizing pathology and disorders. Even before the momentous discovery of germ theory, sanitation and other preventive strategies brought about great declines in mortality and morbidity. The revolution that is currently expanding the biomedical model is an integrative approach that includes the wide variety of non-physio/chemical factors that contribute to health. In the integrative approach, health is understood to be more than the absence of disease and emphasis is placed on optimal overall functioning, within the ecological niche occupied by the organism. This approach also includes not just interventive techniques and procedures, but also those social and cultural structures that provide access to safe and effective caring for sufferers. Beyond the typical drug and surgical interventions - which many identify with the Western biomedical model that currently enjoys an unstable hegemony - such factors also include cognitive-behavioral, social and cultural practices such as have been shown to be major contributors to the prevention and treatment of disease and the promotion of health and optimal functioning.

This Integrative Model of Health and Well-being also derives additional conceptual power by recognizing the role played by evolutionary processes in which conserved, adaptive human traits and response tendencies are not congruent with current industrial and postindustrial global environmental demands and characteristics. This mismatch contributes to an increasing incidence of chronic conditions related to lifestyle and health behavior. Such a comprehensive model will make possible a truly personalized approach to health and well-being, including and going far beyond the current emphasis on genomic analysis, which has promised more that it has currently delivered.

HRV offers an inexpensive and easily obtained measure of neurovisceral functioning which has been found to relate to the occurrence and severity of numerous physical disease states, as well as many cognitive-behavioral health disorders. This use of the term neurovisceral refers to the relationships between the nervous system and the viscera, providing a more focused and specific conceptual alternative to the now nearly archaic "mind-body" distinction. This awareness has led to the recent and growing use of HRV as a health biomarker or health status measure of neurovisceral functioning. It facilitates studying the complex two way interaction between the central nervous system and other key systems such as the cardiac, gastroenterological, pulmonary and immune systems. The utility of HRV as a broad spectrum health indicator with possible application both clinically and to population health has only begun to be explored. Interventions based on HRV have been demonstrated to be effective evidence-based interventions, with HRV biofeedback treatment for PTSD representing an empirically supported modality for this complex and highly visible affliction. As an integral measure of stress, HRV can be used to objectively assess the functioning of the central, enteric and cardiac nervous systems, all of which are largely mediated by the vagal nervous complex. HRV has also been found to be a measure of central neurobiological concepts such as executive functioning and cognitive load. The relatively simple and inexpensive acquisition of HRV data and its ease of network transmission and analysis make possible a promising digital epidemiology which can facilitate objective population health studies, as well as web based clinical applications. An intriguing example is the use of HRV data obtained at motor vehicle crash sites in decision support regarding life flight evacuations to improve triage to critical care facilities.

This Research Topic critically addresses the issues of appropriate scientific and analytic methods to capture the concept of the Integrative Health and Well-being Model. The true nature of this approach can be appreciated only by using both traditional linear quantitative statistics and nonlinear systems dynamics metrics, which tend to be qualitative. The Research Topic also provides support for further development of new and robust methods for evaluating the safety and effectiveness of interventions and practices, going beyond the sometimes tepid and misleading "gold standard" randomized controlled clinical trial.

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Table of Contents

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EDITORIAL
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Editorial: Heart Rate Variability, Health and Well-Being: A Systems Perspective

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Keywords: heart rate variability (HRV), integrative health, autonomic nerve activity, cardiac control, coherence

Editorial on the Research Topic

Heart Rate Variability, Health and Well-Being: A Systems Perspective

The Guest Editors of this Frontiers Research Topic are excited at the interest that our collection of articles has generated so far and the evident contribution to the field that this publication has had and will have. The topic co-editors have all been involved in its successful production, each with respect to his particular strength. We gratefully acknowledge the patient and thoughtful effort 70 contributors who are responsible for doing the hard work necessary to make this achievement possible.

The impact from 130,000 views of our Research Topic as of May 2019 is a testament to the power that the Frontiers platform offers scientists, researchers, clinicians, and authors to get their work out in front of readers. This special issue is put into large-scale perspective by the opinion piece by Grippo who gives us an overview of the commonality of comparative mammalian behaviors that HRV can be used to characterize. This point of view illuminates the richness of insight that understanding HRV can yield, and Grippo uses a correspondingly vast bibliography to support her exposition.

Readers may find the following organizational framework a helpful guide through the remaining variety of papers about the centrality of HRV in a systems perspective on health and well-being. The articles can usefully be grouped into three sections related inquiry: (1) What are we measuring when we measure HRV and how do we measure it? (2) What do HRV measurements tell us? (3) HRV interventions to promote behavioral health and treat behavioral disorders.

Section (1) includes the two articles by Ernst, the overview of HRV quantitative measures by Shaffer and Ginsberg, and the article by Davila et al. describing the validation of the PhysioCam by an exciting and potentially game-changing new method of heart beat detection and analysis. In the first of his two articles ("More than Heart Beats"), Ernst returns us to the origins of modern scientific appreciation of HRV with citations from classic work of the 1980's and 1990's (e.g., Axelrod, deBoer, Karemaker, and Armor) and even back to the 1970's, In the second of the two joined-at-the-hip articles ("Hidden Signals"), we go even farther back in time, to antiquity and traditional eastern medicine then jumping forward to nineteenth century medical studies of blood pressure, heart rate, and respiration before electronic apparatus existed. The bibliographies of Ernst's two articles along with the articles themselves might be thought of as an essential collection of readings for the scientist, researcher, and clinician interested in understanding HRV. The article by Shaffer and Ginsberg on the nature and collection of quantitative aspects of HRV has proven to be hugely popular, with over 8,600 views as of this writing, a quantitative indicator of the interest that studies of HRV are generating.

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The development of the PhysioCam, documented in the article by Davila et al., is intended to overcome the limitations of contact sensors for ambulatory recording of heart rate. The PhysioCam is capable of measuring arterial pulse from a distance with sufficient precision to derive HRV during different challenges, using an off-the-shelf passive digital color video camera sensor to extract arterial pulse from the slight variations of light reflected from an individual's face. Still in development, the PhysioCam is a technology that allows for unobtrusive monitoring of heart rate, which will have many applications for furthering understanding of the role that HRV and autonomics plays in everyday life and which we will surely be hearing much more about.

Section (2) is comprised of five articles placing HRV in the context of human physiology system function and dysfunction. The experience of threat-related autonomic responses, and their adverse effects on health, is placed in a bio-evolutionary framework in the paper by Kolacz and Porges. Their analysis is grounded in the neural architecture integrating cardiac autonomic control, pain, and the gastrointestinal tract, so in this way the functional gastrointestinal disorders (FGID's) can be seen as part of bio-psycho-social adaptation. Hage et al. considered the evidence for autonomic nervous system dysregulation in bipolar depressed patients, using HRV. Their question is an extension of the previously established observations that lower HRV accompanies unipolar depression. The experimental design called for random assignment to one of two medication groups (escitalopram + celecoxib or escitalopram + placebo), and included a healthy control group. They found evidence that patients had lower HRV power and higher heart rate pre-treatment, with not discernable effects of medication treatment on the cardiac measures. Their work is part of a larger movement to explore the potential diagnostic and prognostic value of HRV and other psychophysiological variables as biomarkers for psychotropic treatment outcome of mental disorder in adults. Borelli et al. contributed a study of "Reflective Functioning" in children. Reflective functioning is based on introspective processing of emotional experience. They used a protocol designed to evoke reactions regarding the experience and expression of attachment-related needs which they correlated with attachment coded from semi-structured interview. Their important, if not unsurprising, finding was that RF was associated with lower cardiovascular reactivity and better recovery, mediated by level of attachment (more attachment, better cardiovascular function). This work appears to be a significant contribution to developmental theory of physiological emotion regulation in children. Psychophysiological reactivity on a body-system scale in active duty military personnel was reported by Haufler et al. to be a significant predictor of performance-related adaptive behavior in a standardized, simulated operational environment. The implications of this type of thorough clinical research for fitness and readiness (and not limited to soldiers) is enormous. The commentary article on HRV and Dentistry by Drury and Simonetti is novel in showing that "gentle dentistry" as it is commonly called today, is based on an understanding of the cardiovascular and neuroendocrine elements of response to stressful dental treatments. The piece has, and has a surprisingly deep bibliography to support it and is of interest in pointing the direction for future development of HRV indicators of situational health status.

The five articles of section (3) focus on ways the autonomic cardiac control system can be managed to achieve desired health outcomes. The first article is a laboratory investigation into the inter-relations between HRV, blood pressure, and mood performed by Steffen et al.. The researchers use quantitative indicators in a carefully controlled experiment. The responsivity of this nexus of adaptive functioning to simple but controlled perturbation by slow ("resonant frequency") breathing tells us a lot about the tools people can use to successfully manage themselves in their ecological niche. Kirby et al. write an article that delves into the modulation of social engagement by the ventral vagal nerve control of HRV. This work describes a procedure to train people to better experience compassion and thereby improve social engagement and its psychophysiological correlate. The same idea is pursued in greater anatomical depth in relation to the use a "a non-invasive, computer-guided, acoustic stimulation neurotechnology" called closed-loop allostasis, reported by Shaltout et al. This technique led to notable improvements in HRV and most impressively, baro-reflex sensitivity (BRS) and several measures of arerial blood pressure, a major effector of systemic blood pressure homeostasis that is closely related to heart rate. Significant decreases in self-reported insomnia and depression were also recorded. By measuring regional brain electrical activity, a trend for improved balance of temporal lobe high frequency amplitudes was noted. Non-invasive vagal nerve stimulation is a rising alternate treatment technique to produce increases in vagal tone and parasympathetic function to address the behavioral and emotional symptoms of sympathetic hyper-arousal. In their article, Lamb et al. publish their data in 22 combat Veterans. These clinical researchers collected autonomic physiological reactivity data at baseline and after transcutaneous vagal nerve stimulation (tVNS). Veterans were classified as either mTBI-PTSD or healthy and randomized to stimulation or sham control conditions. The tVNS intervention was well-tolerated and results suggested that effects did occur on systems that modulate emotional regulation. In closing, McCraty is a well-known person throughout the HRV community, having been a proponent of HRV Biofeedback for decades. His experience in the field can be traced to the very roots of awareness of the power and plain excitement of HRV engagement. Among his many areas of study and advocacy can be found the concept of "social coherence." These ideas springboard off simple group HRV Biofeedback infused with the basic scientific notions of social nervous system and its role in social engagement a la Porges' polyvagal theory, past the newly emerging field of scientific study of interoception, and lands in the field of electromagnetic potentials in the evolutionary dynamics of ecosystems. Sound thinking prevails in the article's central thesis that feedback of individual and group HRV will increase group cohesion, thereby promoting pro-social behaviors, such as kindness and cooperation among individuals, improved communication, and decreases in social discord and adversarial interactions. "Biomagnetic fields produced by the heart may be a primary mechanism in mediating HRV synchronization among group members" he writes. Peripheral, implicit, and embedded in this message is the "Global Coherence Initiative" (GCI). GCI takes social coherence to its farthest limits and into the frequency zone that is shared by solar-geomagnetic field synchronization and Schuman Resonances, where it has been noted that these resonant frequencies directly overlap with those of the human brain and cardiovascular system.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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PERSPECTIVE
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The Current and Future Role of Heart Rate Variability for Assessing and Training Compassion

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The evolution of mammalian caregiving involving hormones, such as oxytocin, vasopressin, and the myelinated vagal nerve as part of the ventral parasympathetic system, enables humans to connect, co-regulate each other's emotions and create prosociality. Compassion-based interventions draw upon a number of specific exercises and strategies to stimulate these physiological processes and create conditions of "interpersonal safeness," thereby helping people engage with, alleviate, and prevent suffering. Hence, compassion-based approaches are connected with our evolved caring motivation and attachment and our general affiliative systems that help regulate distress. Physiologically, they are connected to activity of the vagus nerve and corresponding adaptive heart rate variability (HRV). HRV is an important physiological marker for overall health, and the body–mind connection. Therefore, there is significant value of training compassion to increase HRV and training HRV to facilitate compassion. Despite the significance of compassion in alleviating and preventing suffering, there remain difficulties in its precise assessment. HRV offers a useful form of measurement to assess and train compassion. Specific examples of what exercises can facilitate HRV and how to measure HRV will be described. This paper argues that the field of compassion science needs to move toward including HRV as a primary outcome measure in its future assessment and training, due to its connection to vagal regulatory activity, and its link to overall health and well-being.

Keywords: compassion, compassion interventions, heart rate variability, vagal break, evolution, compassion-focused therapy

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INTRODUCTION

Many species, such as fish, turtles, and other egg-laying reptiles produce large numbers of young ones, who need to disperse rapidly afterbirth to avoid predation, including, at times, from their own parents (1). Thus, fish and reptilian young are born to be mobile, be able to seek their own protection, and be self-sustaining. This is sometimes referred to as *r* selection. The evolution of warm-bloodedness, live birth, small numbers of young, and post birth parental/caring investment, sometimes referred to as *k* selection, required substantial changes to the physiology of threat avoidance and approach behavior, allowing for close interpersonal contact and connection. As a result, mammalian young infants did not have to be self-protective or self-sustaining, indeed there was a very different pattern of parental investment. First, parent and offspring needed to be attracted to stay close to each other rather than disperse. Second, resources and stimuli provided by the parent would have major impacts on the growth and physiological regulation of the infant (2). Third, in species where parents did provide food for offspring, in particular primates, infants are required to be quiescent for much of the time as they grow and develop (e.g., infants require lots of sleep). Fourth, because infants cannot move or provide food for themselves, the parent is responsible for providing such needs and regulating them, that is provide a *safe haven*. Fifth, as infants become more mobile, parents act as a *secure base*, facilitating gradual exploration of their environment (3).

To facilitate these interactional sequences, *k* selected regulation processors operated through a sequence of adaptations. One of these major adaptations was the evolution of part of the myelinated parasympathetic system—the dorsolateral vagal nerve that links a range of internal organs to central control systems. Indeed, the vagus nerve is connected to a range of organs including the heart and gut, and with the brain through its link to inhibitory prefrontal–subcortical circuits. One of the key functions of parental investment is sensitivity to distress and preparedness to act appropriately to relieve that distress. This is also the basic sentiment and core of compassion (4, 5), and as we will discuss, compassion utilizes the same evolved physiological pathways as basic caring behavior.

COMPASSION

Compassion has been defined in various ways, with many focusing on describing certain qualities and attributes that comprise compassion (6). Other definitions stress the motivational nature of compassion, exploring its goal and focus and the various competencies necessary for that motive to operate successfully. Compassion as a motivation is central to many of the contemplative traditions (7–9). This is captured in such definitions as having *a sensitivity to suffering in self and others, with a commitment to alleviate and prevent it* (5). One way to better focus future research in compassion science is *via* evolutionary insights into its origins and functioning situated within its neurophysiological architecture (4, 5, 10, 11).

Along with compassion there are many human motives including self-protection (harm-avoidance), sexual (finding a mate and reproducing), and caring-based motives (5, 12, 13). All motives have two basic processes, which when applied to compassion include (1) having a motive-appropriate signal detection (input) to suffering (i.e., sensitivity and awareness of distress) and (2) having a behavior–output repertoire that allows appropriate responsiveness to suffering (i.e., taking action to alleviate and prevent suffering).

COMPASSION AND PHYSIOLOGY

It is now well recognized that a key process that assists with affect regulation is through caring affiliative and affectionate behaviors. Polyvagal theory, outlined by Porges (14), details how the activation of the myelinated parasympathetic nervous system helps in the regulation of the fight/flight response (autonomic sympathetic nervous system), thus enabling calmness and soothing to be achieved through having close proximity to others, giving/receiving affiliative, caring, and prosocial behavior (5, 15, 16). This is reflected in the dynamic balancing of the sympathetic and parasympathetic nervous systems that give rise to variability in heart rate [Heart Rate Variability (HRV); (14)]. In fact, the autonomic nervous system enables emotion-related action tendencies, which, in the case of compassion, are approach and caregiving. The inhibition of heart rate through the activity of the parasympathetic nervous system has shown to be linked to the orienting response and sustained outward attention, which constitute a core action tendency of compassion (17). Consistently, compassion-evoking stimuli (videos of other's suffering) have shown to generate vagally mediated heart rate deceleration in children (18) and in adults, whose self-reports of sympathy and compassion were positively related to heart rate deceleration (19). Moreover, children with higher heart rate deceleration during evocative films showed increased subsequent compassionate behavior (20). Interestingly, children with higher baseline HRV were rated by teachers and parents as more helpful and more able to regulate their emotions than those with lower HRV (21) and showed increased self-reports of sympathy, both dispositionally and in response to distress-inducing films (22). This suggests that tonic HRV might represent the physiological signature of a trait-like compassionate responding. Increased HRV in adults has been found to be specifically connected to the emotional state of compassion and not to positive affect in general (23), supporting the correlation between vagal activity and state-like episodes of compassion. Moreover, recent findings (24) have shown that increases in vagally mediated HRV induced by Transcranial Direct Current Stimulation over the left temporal lobe, topographically close to the left insular cortex, was associated with increases in soothing positive affect: a feeling of perceived safeness and warmth which has been considered the emotional underpinning of a compassionate motivation. Feeling safe is linked to HRV, and higher HRV is linked to a greater ability to self-soothe when stressed (14), thus facilitating engagement with the suffering (in one selves and others), while inhibiting the distress-related tendencies to fight with or withdraw from suffering.

Specific strategies, such as breathing practices, friendly voice tones, and facial and body expressions, can activate the parasympathetic system, aiming to calm and soothe the individual, which improves HRV (25). Moreover, when the sympathetic nervous system is activated under threat, this decreases the ability for higher order cognitive capacities, such as mentalizing to occur (e.g., theory of mind, empathizing, perspective taking), whereas activating the parasympathetic system helps provide a feeling of safeness, which increases the ability to activate the prefrontal cortex and enable mentalization (26–28). Thus, the focus on activating affiliative processing systems (e.g., parasympathetic system) assists in the regulation of affect, and helps calm individuals when distressed. HRV, as a marker of increased emotion regulation which facilitates, and is facilitated by, an approach motivation to suffering, might be considered one of the primary measures when assessing and training compassion. Measuring HRV in compassion science is uncommon, yet there are many important nuances that need to be teased out and examined between HRV and compassion, thus more data are required to help improve understanding the interaction and precision of links between compassion and HRV.

THE BENEFITS OF COMPASSION

There is now considerable evidence that being the giver and recipient of caring behaviors, particularly compassion, has a range of health benefits (29, 30) and can affect genetic expression (31, 32). Compassion training improves general well-being and social relationships (33, 34), with increasing evidence of its effectiveness as a psychotherapy (11, 35, 36). A recent review of several compassion-based interventions (e.g., compassion-focused therapy, compassion cultivation training) found moderate effect sizes for reducing symptoms of depression, anxiety, and stress, as well as increasing individuals' levels of compassion, mindfulness, and well-being (11). Practicing compassion also has an impact on neurophysiology due to neuroplasticity (27), with a recent study showing that it has significant impacts on HRV (Matos et al., under review). What is required now is a more coordinated and integrated research program on the physiological changes that are brought about through compassion training.

CURRENT STATE OF COMPASSION TRAINING AND PROBLEMS OF ASSESSMENT

There are various approaches to compassion training, with different approaches having different definitions and consequently different forms of assessment (11). The assessment methods used in compassion training relies predominantly on self-report measures, such as the Self-Compassion Scale (37), and a recent review that critically examined the assessment measures for compassion concluded that self-report questionnaires assessing compassion have serious psychometric weaknesses (6). Thus, other assessment options need to be considered. One such approach is through physiological assessment; however, for this to be an appropriate assessment, it needs to align with the model of compassion used by the intervention. All the available compassion interventions are secular in design, however, theoretically these interventions have been typically influenced by Tibetan Buddhist traditions (11), and as such the definitions of compassion in the majority of compassion interventions do not include links to evolutionary models or physiology (11). Compassion-focused therapy is notably different to the other interventions, as the theoretical underpinning is based on an evolutionary model that links to physiology (11). Thus, assessing HRV as an assessment would be appropriate for that model, as one could interpret the assessment outcomes to its model of intervention.

PRELIMINARY RESEARCH INVESTIGATING HRV AND COMPASSION

Moving beyond the use of the limited reliability of self-reports or more complex fMRI, HRV is a relatively easy measure to acquire and offers windows on a number of important physiological systems including the frontal cortex (38) and people's relative state of psychological flexibility. The value of using HRV both as a process/state and outcome measure is linked to three major domains. First, that psychopathology (depression, anxiety, paranoia) and underlying processes, such as self-criticism, negative rumination, shame, and worry, are linked to lower levels of HRV. Second, that compassion is correlated to HRV. Third, compassion-based practices can directly increase HRV and potentially other biological, physiological, and neurophysiological measures, such as cortisol, and diminish the expression of proteins associated with inflammation. We will look at these in turn.

To date, there have been several cross-sectional studies demonstrating lower levels of HRV in conditions, such as depression (39), anxiety (40), rumination (41), and self-criticism (42). Second, there have been some correlational studies demonstrating the links between compassion and HRV. For example, trait self-compassion, measured by the Self-Compassion Scale (37) was found to be correlated to resting HRV and an increase in parasympathetic nervous system tone (43).

Third, experimental studies have also documented the impacts of compassion on physiology. For example, Rockliff and colleagues (42) examined the impact of compassionate imagery (i.e., imagine compassion coming from an external source, human or non-human) on HRV. In this study, HRV was derived by inter-beat interval time series of electrocardiography and CMetx software (44). Results were mixed with some participants having a reduction in HRV, while others showed increased HRV in response to compassion imagery. Individuals who experienced decreases in HRV in response to compassionate imagery were those that had lower levels of social safeness, and had higher scores on self-criticism, self-coldness, anxious attachment, and psychopathologies. Results indicate that compassion is linked to HRV; however, depending on an individual's levels of self-criticalness and insecure attachment style compassionate imagery may be perceived as a threat, which decreases HRV. A second study (45) including 105 undergraduate college women (Mean age = 19.53) found that participants who had received self-compassion training (following audio guided recordings of loving-kindness and self-compassion phrases) had smaller reductions in HRV before and after exposure to a psychosocial stressor as compared to two control groups (an attention control—reading a psychology textbook or no intervention). Another study (46) found compassion meditation increased positive emotions and HRV, and that effect moderated by baseline vagal tone. Finally, a recent study by Petrocchi et al. (47) found that compassionate self-talk increased HRV and soothing positive affect, and that the effects on both physiological and self-report measures were amplified when participants were asked to repeat the phrases in front of a mirror. A time domain measure of HRV (root mean square successive differences) were obtained using HRV Analysis Software (48). These results provide further evidence for the impact of compassionate-based exercises in activating the soothing affect system connected with parasympathetic nervous system activity, and influencing HRV.

HOW HRV IS USED PRESENTLY IN COMPASSION TRAINING

There are now a number of compassion-based interventions that are aimed to improve well-being and social relationships, such as compassion cultivation training, cognitively based compassion training, mindful self-compassion, cultivating emotional balance, compassionate mind training, and others (28). Each of these approaches have been examined in randomized controlled trials, with early findings indicating compassion-based interventions are a promising intervention to help increase well-being and reduce suffering (28). Importantly, the only compassion training intervention model that has used HRV to date is compassion-focused therapy (CFT). As mentioned CFT (5), has its theoretical underpinnings based upon evolutionary psychology and attachment theory, which is linked to physiological systems, which makes assessing HRV in its model suitable (5).

To date, CFT is the only psychotherapy to actively target physiological processes in therapy; with a recent randomized controlled trial including 117 participants showed that it was able to increase HRV for participants (Matos et al., under review). Participants in the CFT intervention received online recordings covering: (a) body grounding and soothing rhythm breathing (five breaths per minute), mindfulness, compassion postures, facial expressions, and voice tones; (b) practising oneself as a compassionate person; (c) practising receiving compassion and care from another sentient caring mind; (d) working compassionately with self-criticism; and (e) bringing one's compassionate self into everyday life and its difficulties. The intervention components described were included as they specifically focused on increasing compassion related competences and affiliative emotions which are specifically indexed by increased vagal tone and HRV [Matos et al., under review; (14)]. Compared to the control group the CFT condition experienced significant increases in: positive emotions associated with feeling relaxed and also safe and content; self-compassion, compassion for others and compassion from others. There were also significant reductions in shame, self-criticism, depression, and stress. Importantly, only the CFT condition reported significant improvement in HRV.

THE FUTURE OF COMPASSION INTERVENTIONS AND HRV

The findings from the recent RCT on CFT for HRV outcomes are encouraging (Matos et al., under review); however, experimental studies are also required to determine which specific practices and for what duration influences HRV. Exercises that can help activate HRV include focusing and practicing breathing, facial expressions, posture, and visualization strategies (4, 49). Another key practice to examine is the inner vocal tone of the client, if one's self-talk is hostile and aggressive this can impact threat-based physiology, whereas if one's inner self-talk is encouraging this has the potential to activate the affiliative/soothing emotional system (14). Thus, each of these specific practices require experimental testing to determine if each contributes to increasing HRV. However, insecure attachment and social safeness need to be explored as potential moderators of these effect.

If other compassion training models wish to use HRV as an assessment outcome, theoretical considerations need to be made to evolutionary models and physiological systems. For example, if other compassion interventions begin to use HRV as an outcome there will be potential difficulties in understanding and interpreting the data if it does not link to a model of compassion which links to physiological systems. Although other compassion interventions do incorporate a number of different body grounding exercises this is often with the direct aim to reduce suffering, without specific theoretical links made to physiological shifts and dynamic balancing of the sympathetic/parasympathetic systems and vagal tone (28). Thus, with the increasing use of HRV as a physiological proxy for measuring compassion, other models might begin to become more inclusive of evolutionary and physiological models to understanding compassion.

An alternative approach to cultivating compassion to increase HRV, is to target HRV directly. Recent technologies aimed at providing biofeedback in order to increase HRV are also showing promise (50), although researchers are suggesting that technologies used to increase HRV are potentially more effective when combined with mindfulness or compassion-based techniques (50). Importantly, what would be interesting in future research is to examine whether targeting increases in HRV alone can lead to increases in compassion motivation toward self and others, particularly behaviorally.

Finally, researchers examining HRV in compassion science need to consider the complexity of HRV and its dynamic relationship with vagal tone and emotion regulation. There can be a tendency as more researchers in the field of compassion science begin to assess HRV to refer to it as being a singular outcome, with higher HRV only related to positive outcomes. Indeed, there are times when high sympathetic tone is desired, for example, when helping to target states of helplessness (14). Therefore, greater precision is needed when reporting on HRV, for example if using five-minute protocols of HRV it is important to report the time of day it was assessed and for how long, which would be different when compared to reporting on 24 hour HRV protocols. Furthermore, in CFT a focus of intervention is to help improve safeness for the client, and although this is hypothesized to generally be associated with higher HRV, it may also help a client feel empowered and give them confidence to challenge themselves, which could be linked to a higher resting sympathetic tone. These nuances between HRV, vagal tone, and compassion need to reported and examined with precision to better understand the relationship.

CONCLUSION

The fact that HRV is an output from the cardiovascular system is due to the evolution of the mammalian prosocial and caring behavior which has become highly tuned in humans. A range of physical and mental health conditions are linked to the degree to which people feel a sense of safeness and connected in the social environments, and HRV is increasingly considered a marker of those physical and mental states. New therapies are developing to directly influence and increase feeling of safeness, interconnection, and compassionate motivation, and HRV should be considered a primary outcome for research exploring the efficacy of those novel psychotherapy approaches.

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Non-invasive Vagal Nerve Stimulation Effects on Hyperarousal and Autonomic State in Patients with Posttraumatic Stress Disorder and History of Mild Traumatic Brain Injury: Preliminary Evidence

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Posttraumatic stress disorder (PTSD) is a reaction to trauma that results in a chronic perception of threat, precipitating mobilization of the autonomic nervous system, and may be reflected by chronic disinhibition of limbic structures. A common injury preceding PTSD in veterans is mild traumatic brain injury (mTBI). This may be due to the vulnerability of white matter in these networks and such damage may affect treatment response. We evaluated transcutaneous vagal nerve stimulation (tVNS), a non-invasive, low-risk approach that may alter the functions of the limbo-cortical and peripheral networks underlying the hyperarousal component of PTSD and thus improve patient health and well-being. In this single visit pilot study evaluating the impact of tVNS in 22 combat veterans, we used a between-subjects design in people with either PTSD with preceding mTBI or healthy controls. Participants were randomized into stimulation or sham groups and completed a posturally modulated autonomic assessment and emotionally modulated startle paradigm. The primary measures used were respiratory sinus arrhythmia (high-frequency heart rate variability) during a tilt-table procedure derived from an electrocardiogram, and skin conductance changes in response to acoustic startle while viewing emotional images (International Affective Picture System). The stimulation was well tolerated and resulted in improvements in vagal tone and moderation of autonomic response to startle, consistent with modulation of autonomic state and response to stress in this population. Our results suggest that tVNS affects systems underlying emotional dysregulation in this population and, therefore, should be further evaluated and developed as a potential treatment tool for these patients.

Keywords: posttraumatic stress disorder, traumatic brain injury, hyperarousal, autonomic, transcutaneous vagal nerve stimulation, vagal, transcutaneous, sympathetic

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a common mental illness affecting military veterans (1). Even in transient cases, recurrence can occur in older age. In Vietnam veterans, 10% experienced recurrence of PTSD symptoms nearly three decades after their worst trauma (2). Chronic emotional dysregulation is associated with impairment in quality of life as well as early onset of cognitive decline and serious health consequences (3–6). A common preceding comorbidity is mild traumatic brain injury (mTBI). The etiological contribution of mTBI to manifestation of symptoms of PTSD is not known. However, disruption of limbic white matter may play a role (3), as has been reported in neuroepidemiological studies of the phenomenology of white matter injury in mTBI (7, 8). These systems are directly germane to shifts in emotional and autonomic state to a vigilant and mobilized disposition.

A core deficit in PTSD is a bias toward a defensive strategy to environmental features along with an inability to shift away from a defensive state (3). This defensive strategy manifests in part as hyperarousal features including decreased respiratory sinus arrhythmia [RSA, high frequency heart rate variability (HRV)] and increased sympathetic nervous system response to stressors. In order to shift from defensive dispositions to socially engaging dispositions (e.g., interacting positively with other people), the individual needs to determine safety and inhibit limbic structures that control flight, flight, or freeze behaviors. PTSD is associated with chronic disinhibition of limbic structures such as the amygdala, which may explain symptoms such as exaggerated startle and autonomic nervous system (ANS) mobilization. Because mTBI may effect white matter and, in particular, limbic white matter inputs (7), there may be increased neurological vulnerability to development of symptoms of PTSD and of emotional dysregulation. Though PTSD is a transient condition in many patients, factors such as preceding mTBI may increase the likelihood of a chronic presentation.

The chronic stress associated with PTSD is a critical health issue as the physiological reaction to threat detection is clinically costly. Patients with PTSD have reduced HRV in response to trauma cues, require a longer recovery time (9), and have higher blood pressure (10) than their non-PTSD peers. Several features in resting autonomic behavior are correlated with mortality (11, 12). Reduced resting low frequency HRV is linked to coronary artery disease (13), and lower nighttime RSA is linked to increased stroke risk (14). Further, HRV in patients who recover from PTSD is indistinguishable from healthy controls (15). This suggests that negative health consequences of PTSD may be reversible if treatment success is achieved prior to cumulative damage from chronic stress.

Comorbidities are frequent in patients with PTSD, possibly due to issues with diagnostic clarity [see the recently revised DSM-V (16)], but also because trauma-induced responses are unpredictable and may represent a continuum of defensive state modulation. This produces behaviors consistent with fight, flight, or immobilization that fluctuate depending on internal state and interactions with perceived threat (17–19). Variations in these defensive response styles may, for example, present as depression (immobilization), intermittent explosive disorder (fight), or anxiety (flight).

Many currently available treatments target these states or associated disrupted emotional systems; however, the degree of effectiveness is variable. For example, a common first line pharmacotherapy approach is to use selective serotonin reuptake inhibitors. Unfortunately, clinical response rates, defined as a >30% reduction in symptoms, are rarely over 60%, and fewer than 20–30% of patients with PTSD taking these medications achieve full remission (20–23). Further, although a double-blinded placebo-controlled trial of venlafaxine, a serotonin–norepinephrine reuptake inhibitor, achieved a 78% clinical response rate, only 40% achieved remission (24). Several psychotherapies have been demonstrated to be helpful; however, the effect size varies significantly between reports, and combinations of therapy approaches were more effective in many, but not all, studies (23, 25–28), thus novel approaches are needed to treat those who do not achieve remission with current treatments.

Transcutaneous vagal nerve stimulation (tVNS) is a non-invasive nerve stimulation technique in which the auricular branch of the vagus is targeted. tVNS has been shown to have an impact on the neuronal systems that are involved in emotional regulation (29, 30), including the amygdala, and should be effective in the treatment and rehabilitation of PTSD. In addition, tVNS has been demonstrated to have a low risk profile, which is a significant departure from implanted vagal nerve stimulation (31, 32).

The putative mechanism of action of tVNS is through activation of the nucleus tractus solitarius, which has widespread projections throughout key brain networks involved in emotional regulation and PTSD, and the locus coeruleus. Published pilot fMRI studies have reported BOLD signal alterations in both the nucleus tractus solitarius and the locus coeruleus in the brain stem as well in amygdala activity in response to tVNS as contrasted to a sham stimulation (30). These fMRI changes were observed in healthy individuals who were given tVNS or active sham stimulation. The specific sham or contrasted stimulation varies between studies depending on the specific hypotheses tested; however, findings have generally been consistent. These data support the proposed mechanistic hypothesis, as a reduction in the BOLD signal in emotional (limbic) brain networks should correspond to diminished emotional reactivity and increased socially adaptive emotional regulation (inhibition of fight or flight behaviors), and these same regions and networks are abnormally active in response to emotional stimuli in individuals with PTSD.

Alteration of nucleus tractus solitarius activity should increase high frequency HRV, which has been demonstrated with tVNS in healthy controls (33). Increased high frequency (0.15–0.4 Hz) HRV (RSA) is associated with improved social function, better health outcomes, and better cognitive function. Conversely, lower RSA is associated with many psychiatric and psychological disorders including major depressive disorder, generalized anxiety disorder, high levels of aggression, and trauma history (34–36). tVNS has been shown in healthy people to induce an increase in high frequency HRV for at least 15 min after tVNS use without appreciably altering mean heart rate and other cardiovascular safety measures (32). The latter is important, as it further speaks to the relative safety of tVNS when compared with its implanted counterpart (31). It is unknown whether tVNS has these same positive effects in patients with PTSD or those with disruptions in fronto-limbic function and further, whether tVNS changes emotionally modulated autonomic response.

Because of the high rates of PTSD, particularly subsequent to mTBI, combined with the large proportion of patients who do not achieve clinical response, let alone remission, there is a need for novel treatment approaches. Given the reported impact of tVNS on many brain regions implicated in the development and expression of PTSD, as well as autonomic state, it is a logical tool to develop to potentially treat PTSD. As an initial step toward that end, we have designed the current study to evaluate the impact of tVNS on indices of hyperarousal including vagal tone, as measured by high frequency HRV, and sympathetic nervous system activity in response to emotionally modulated startle as measured by electrodermal activity. We hypothesized that vagal tone would increase and that emotionally modulated sympathetic nervous system activity would attenuate in response to tVNS.

MATERIALS AND METHODS

Subjects

We recruited and received informed consent from 22 combat Veterans to participate in a U.S. Department of veterans affairs (VA) funded, University of Florida IRB approved pilot study designed to assess the effects of tVNS on autonomic symptoms of PTSD. Participants were recruited from a study designed to evaluate the impact of white matter damage in mTBI on the manifestation of PTSD cluster symptoms. Participants were contacted randomly, and three people declined participation due to logistical issues. Participants either had been diagnosed with both PTSD and closed-head mTBI injury ($n = 12$) or were healthy combat controls with no diagnosis of either ($n = 10$). At time of participation, average age was 29.7 years (SD 7) for the healthy combat control group and 30.4 years (SD 5.4) for the PTSD and mTBI group; minimum age was 22, maximum 43. Diagnosis status of mTBI and PTSD were verified *via* a clinical consensus conference using established criteria for each category using VA and DOD diagnostics guidelines. mTBI was defined as an injury to the head as a result of blunt or blast injury with any period of observed or self-reported transient confusion, disorientation or impaired consciousness, dysfunction of memory immediately before or after the time of injury, loss of consciousness less than 30 min, and signs of neurological or neuropsychological dysfunction identified soon after the injury. PTSD status was determined *via* a structured interview and electronic medical record review (VA PTSD clinical evaluations) and self report scales including the PCLD checklist—military (PCL-M), and Symptom Checklist 90—Revised (see **Table 1**). We also calculated symptom domains by aggregating PCL-M items, with re-experiencing (items 1–5), avoidance (6–7), dysphoria (8–15), and hyperarousal (16–17) as suggested by Pietrzak et al. (37). Mean PCL-M total scores were 24.6 ± 4.83 and 28.0 ± 2.94 ($p = 0.23$) for the healthy combat controls in the tVNS and sham groups, respectively, and 48.5 ± 4.43 and 42.0 ± 12.3 ($p = 0.31$) in the PTSD and mTBI group for the tVNS and sham groups, respectively. The average time since diagnosis of PTSD was 3.55 years, with a range of 1 month to 9 years, although symptom history typically began several years prior to diagnosis after the experienced trauma. One apparently healthy control was excluded upon *post hoc* review of their medical record for sickle cell anemia and one mTBI/PTSD subject was excluded for not having a DOD or VA reported history of mTBI.

TABLE 1 | SCL-90-R, BDI-II, and PCLD checklist—military (PCL-M) symptoms per group, mean ± SD, and two sample *t*-test *p*-value.

	Healthy control	Posttraumatic stress disorder/ mild traumatic brain injury	p
SCL-90-R scale			
Somatization	0.43 ± 0.43	0.89 ± 0.74	0.101
Obsessive–compulsive	0.91 ± 0.58	1.71 ± 0.76	0.016
Interpersonal sensitivity	0.54 ± 0.45	1.07 ± 0.48	0.022
Depression	0.54 ± 0.32	1.22 ± 0.75	0.016
Anxiety	0.41 ± 0.29	1.05 ± 0.69	0.016
Hostility	0.61 ± 0.56	1.38 ± 0.8	0.021
Phobic anxiety	0.14 ± 0.23	0.82 ± 0.64	0.006
Paranoid ideation	0.67 ± 0.43	1.14 ± 0.48	0.032
Psychoticism	0.23 ± 0.24	0.7 ± 0.5	0.160
Global severity index	0.51 ± 0.28	1.12 ± 0.56	0.007
Positive symptom distress index	1.45 ± 0.31	1.72 ± 0.37	0.092
Positive symptom total	30.89 ± 15.59	55.91 ± 20.64	0.006
BDI_II	8.22 ± 4.44	18.18 ± 10.85	0.015
PCL-M			
Disturbing memories	1.33 ± 0.5	2.8 ± 0.79	<0.001
Disturbing dreams	1.11 ± 0.33	2.8 ± 1.03	<0.001
Re-experiencing	1.11 ± 0.33	1.7 ± 0.67	0.029
Upset when reminded of experience(s)	1.67 ± 0.71	2.4 ± 0.7	0.037
Physical reactions when reminded of experience(s)	1.22 ± 0.44	2.4 ± 0.97	0.004
Avoid thinking or talking about experience(s)	1.33 ± 0.71	3 ± 1.25	0.003
Avoid activities or talking about experience(s)	1.56 ± 0.73	2.8 ± 1.23	0.016
Trouble remembering experience(s)	1.33 ± 0.5	2.1 ± 1.1	0.069
Loss of interest	1.56 ± 0.73	2.8 ± 1.4	0.027
Feeling distant or cut off	1.56 ± 0.73	3 ± 1.49	0.017
Feeling emotionally numb	1.22 ± 0.67	2.7 ± 1.25	0.006
Feeling future will be cut short	1.11 ± 0.33	1.9 ± 1.2	0.072
Difficulty sleeping	1.89 ± 0.93	3.3 ± 0.82	0.003
Irritability or angry outbursts	1.89 ± 0.93	2.5 ± 1.27	0.245
Difficulty concentrating	2.11 ± 0.78	2.8 ± 1.23	0.161
Hyperarousal (alert or on guard)	2.11 ± 1.05	2.9 ± 0.88	0.097
Feeling jumpy or easily startled	2.11 ± 1.17	2.8 ± 1.14	0.210
PCL-M total	26.11 ± 4.26	44.6 ± 10.83	<0.001
PCL-M aggregate symptom domains			
Re-experiencing	1.29 ± 0.20	2.42 ± 0.53	<0.001
Avoidance	1.44 ± 0.68	2.90 ± 1.22	0.006
Dysphoria	1.58 ± 0.27	2.63 ± 0.80	0.002
Hyperarousal	2.11 ± 1.08	2.85 ± 0.91	0.13

Exclusion criteria were: premorbid severe psychiatric disorders, other neurological disorder, traumatic brain injury of greater severity than mild (e.g., open-head TBI; loss of consciousness greater than 30 min), medications, which affect ANS responses (e.g., β blockers such as propranolol), and current substance abuse. Assessment of medical exclusion/inclusion criteria was achieved *via* both consensus conference review of VA and DoD medical records and self-report during a structured interview as part of this study. In the healthy combat control group, some participants had recently (within 2 weeks) taken ibuprofen, omeprazole, hormonal birth control, clindamycin, and adalimumab (for colitis/Crohn's). In the participants with mTBI and PTSD, most (7) were not currently medicated; one was taking simvastatin, trazodone and gabapentin at night, and omeprazole; one venlafaxine, gemfibrozil, ibuprofen, docusate, and trazodone and prazosin at night; one each were taking mirtazapine and paroxitine. Trazadone and prazosin have α-adrenergic pharmacological impacts, but minimal/no β-adrenergic activity, and testing was conducted several half-life durations after most recent dose. Mirtazapine antagonizes α_{2A} and α_{2A} receptors, and to a much lesser extent α_1, but not β, so an impact on norepinephrine (NE)-mediated effects of tVNS is not expected. Paroxetine has NE transport inhibition and weak α1 receptor activity, but again not β, so an impact on NE-mediated effects of tVNS is not expected.

Study Design

Participants were randomized into either tVNS or sham (stimulus calibration only) subgroups and were then given a series of assessments of ANS function including emotionally modulated startle and postural HRV assessments. All participants were fitted with custom tVNS electrodes and had comfort threshold calibration, but stimulus amplitude was set to 0 (sham) or 80% of threshold (tVNS) for the remainder of each participant's session as pre-assigned by randomization.

Blinding

A researcher blinded to the stimulus condition conducted the self-report questionnaires, structured interview, and data processing. Stimulus grouping (stim versus sham) was un-blinded for interpretation of statistical analysis. Participants were not informed of their stimulus condition but were informed that, after calibration, the stimulus intensity would be set below the calibration level. The investigator who conducted the calibration and set the stimulus level according group (stim/sham) was a different researcher than those who interviewed participants and conducted data processing.

Vagal Nerve Stimulation

The tVNS stimulus was a 20 Hz, current controlled, 100 µS, alternating polarity pulse delivered *via* an earpiece custom molded for each participant's left ear with an Ag/AgCl disk electrode held at the interface of the poster wall of the left external auditory meatus and the posterior face of the left tragus, a convenient location to access the auricular branch of the vagus nerve (38). A return electrode was affixed just anterior to the tragus, minimizing stray currents and constraining stimulation. Prior to calibration, participants were informed that the stimulus would be slowly increased until they reported any discomfort, and that the stimulus intensity would then be reduced to a comfortable level for the remainder of the experiment. Individual sensitivity to tVNS stimulation was evaluated with a structured stepped-ramp protocol, with a brief pause at each step during which the participant was asked what the stimulus felt like to them and if they experienced any discomfort. The stimulation intensity was then set to 80% of threshold or 0%, for stimulus and sham groups, respectively; the mean threshold for comfort was 5.6 mA (range 3–11.3 mA). Discomfort was typically described as a mild buzzing or scratching sensation.

Postural HRV

Participants stood with their backs against a motorized tilting table/bed that can be slowly tilted (~2°/s) from 90° (standing) to prescribed angled supine positions (60° and 30°) with the soles of their feet supported at all times by a steel platform (see **Figure 1**). Continuous blood pressure and electrocardiograms were recorded in 3-min intervals at 90° (standing), 60°, and 30° static table angles. R waves were extracted with a data collection software package (AcqKnowledge 4.1, Biopac systems Inc.) and processed with custom Matlab scripts to correct for missed R-wave detections and apply appropriate filters to extract RSA high frequency HRV. RSA was then analyzed with a mixed effects model with fixed factors for angle and stimulus condition and a random effect of subject in R v3.2.3. One healthy control was dropped from RSA analysis due to having an abnormally low RSA (mean of 2.97, next lowest subject mean RSA was 4.06, overall mean across subjects was 4.99).

Startle-Blink Paradigm

Participants were given an emotionally modulated startle test while receiving tVNS (or sham stimulation). Participants viewed images from the international affective picture system (39, 40) and were asked to provide an evaluation of the valence (positive—negative) and arousal (neutral/none—high) of each image. During the viewing of these images, an acoustic startle probe (a 50 ms, 95 dB white noise pulse) was delivered during viewing for a predetermined subset of the images. Startle responses, particularly the electrodermal responses (EDA) were recorded and time-synched to the startle probe. Participant's perceptions of the valence and intensity of affective content were recorded. The resulting electrodermal response (EDA) data were processed with Ledalab V3.4.8, decomposing the signal into tonic

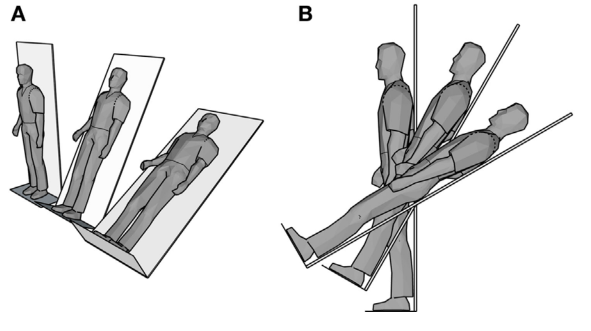

FIGURE 1 | Schematic of postural heart rate variability tilt table test. **(A)** Isometric perspective and **(B)** side view of the three positions (90°, 60°, 30°).

and phasic components (41), with analysis epochs triggered on the startle probe onset. Non-responding participants, one sham PTSD/TBI, one tVNS PTSD/TBI, and one tVNS control, identified by no or minimal changes in EDA signal throughout the task, were dropped from analysis; approximately 10% of participants are generally expected to be non-responders (42). We applied a mixed model in R v3.2.3 with fixed effects of group (PTSD/TBI or healthy control) and stimulus (tVNS or sham) and a random effect of subject, with dependent variables measured within each response window of maximum total deflection (phasic and tonic) continuous decomposition (CDA) measure of maximum phasic activity (Phasic Max) and amplitude sum as calculated by Ledalab (41).

RESULTS

Mean RSA was higher with tVNS than sham across all three postural positions (see **Figure 2**) indicative of increased parasympathetic activity [tVNS effect, $F(1, 17) = 3.33$, estimated Cohen's $d = 0.88$]. Diagnosis groups were pooled for this analysis due to insufficient sample size per cell for the full design and the primacy of the question of tVNS efficacy. This finding is consistent with prior reports of increased HRV with tVNS stimulation (32) in healthy populations.

Transcutaneous vagal nerve stimulation appeared to reduce sympathetic reactivity as measured with EDA and analyzed with continuous decomposition into tonic, or baseline, and phasic activity (41). Our primary concern is with phasic EDA measures maximum deflection within the response window (max deflection) and continuous decomposition analysis phasic (transient response to stimulus) response maximum (phasic max). The estimated effect sizes (Cohen's *d*) were 0.74, 0.56, and 0.43 for phasic max and max deflection and amplitude sum, respectively (see **Table 2** and **Figure 3**). This is consistent with our anticipated short-term impact of tVNS on emotional/behavioral measures and on RSA.

DISCUSSION

The primary findings of this preliminary study are that resting parasympathetic activity is increased and task-dependent emotionally modulated sympathetic nervous system activity is decreased with tVNS. The effect size estimates are promising and the estimated effects are consistent, though it is important to note that the sample sizes are small and full interaction models could not be applied. These were predicted effects based on our model of PTSD with mTBI and the putative mechanisms of action of tVNS (3) and promising reports from animal work using implanted VNS (43, 44). These effects suggest that tVNS may modulate emotional state as reflected by downregulating fight-or-flight and upregulating a physiological state conducive to positive social engagement (45). These results show a direct impact on the hyperarousal symptoms of PTSD by tVNS.

The mechanism of action of tVNS on these systems that are core to the experience of PTSD is not fully elucidated. There are both afferent and efferent components that may be relevant including vagal inputs into the heart and neuroanatomical connections whose activity appear to be modulated by tVNS. Furthermore, VNS can upregulate NE (46). NE is a neuromodulator that plays an important role in the mediation of many behaviors, including emotional learning and attention systems (both critical to the behavior of individuals with PTSD) (47, 48). As with all neuromodulators, NE's influences on neural function from the cellular level through interacting brain systems level are complex. For example, NE has opposing effects on amygdala network activity through α-NE versus β-NE receptors (49). In the

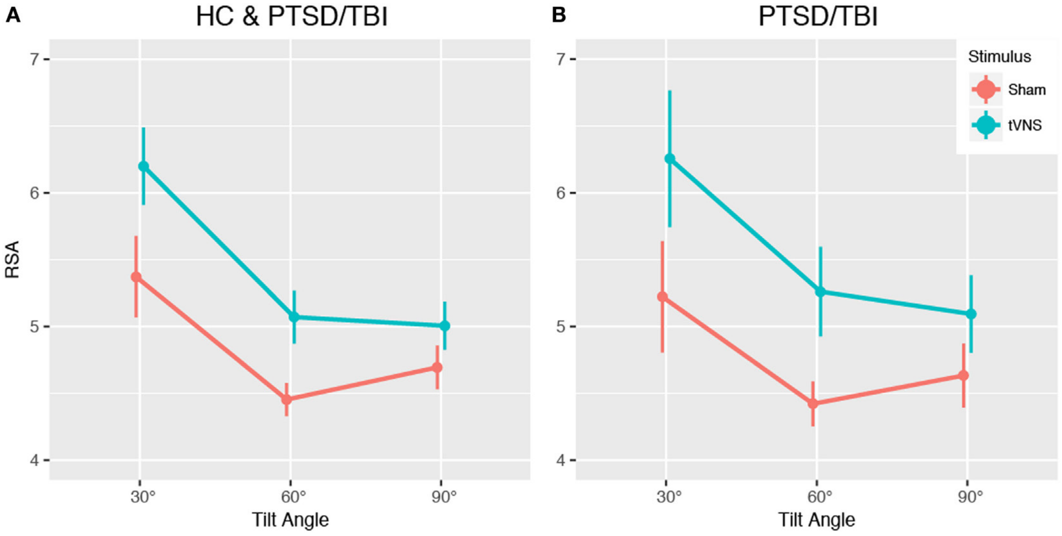

FIGURE 2 | Impact of transcutaneous vagal nerve stimulation (tVNS) on heart rate variability (HRV) during tilt-table experiment. Analysis of pilot data shows a trend toward increased respiratory sinus arrhythmia (RSA) high frequency HRV, indicating increased parasympathetic activity, across all tilt angles in the tilt-table experiment. **(A)** Main effect of tVNS, **(B)** impact of tVNS within PTSD and mTBI group. Data presented are mean ± SEM.

present study, a small subset of participants were prescribed prazosin and/or low-dose trazodone, which have α-adrenergic but not β-adrenergic pharmacology. As these participants took their last dose several half-life durations prior to participation, direct interaction with the NE impacts of tVNS was not expected. One participant was prescribed mirtazapine and another paroxetine, which affect α-adrenergic receptors but not β-adrenergic, so an interaction with the NE impacts of tVNS might have occurred; however, we would expect the most potent attenuation of tVNS to occur with β-adrenergic pharmacology. Instead of avoiding NE pharmacology, as we have done, future studies should consider pharmacologically dissecting the impacts of tVNS with α- and β-adrenergic blocking compounds.

The portions of the frontal lobe that compose networks that interact with the limbic system normally provide inhibition of the autonomic/automatic responses to stimuli previously associated with emotional responses. Consistent with this pattern of inhibition, these portions of the frontal lobes are important in the consolidation of extinction learning (50). In regard to fear learning, there is some evidence that NE-based prophylaxis with β-blockers such as propranolol can prevent the development of PTSD (51). However, this evidence is mixed and complicated by the predominant administration timeline beginning after the traumatic event. β-blocker usage as a treatment adjuvant is also complicated by its impairment of both reconsolidation and extinction learning as well as the attention modulation effects mentioned above.

Prefrontal networks have been strongly implicated in control of the ANS (52, 53). Consistent findings in animals have been found demonstrating a role of the prefrontal cortex in inhibiting sympathetic nervous system mobilization, possibly by modulating parasympathetic action (54, 55) including baroreceptor reflexes (56). Evidence from anatomical, lesion, and electrical stimulation studies suggest that medial prefrontal cortex is preferentially involved in modulating sympathoinhibitory responses, suppressing mobilization of the ANS for fight or flight (57). The full extent of how prefrontal cortex and nuclei involved in autonomic control interact is not known. There are cortical projections to the nucleus of the solitary tract (a major interaction vector for tVNS). These interconnections are involved in blood pressure, vasomotor, and heart rate regulation. In humans, increased heart rate and mean arterial pressure have been associated with decreased regional cerebral blood flow in prefrontal cortex (58).

Transcutaneous vagal nerve stimulation may be considered a parasympathomimetic treatment. It has both direct and indirect potential effects on HRV. Other treatments that manipulate the ANS have shown some promise in alleviating symptoms of PTSD including β-blockers, stellate ganglia blockade, and α channel blockers. Due to the direct impact of tVNS on the underlying brain and autonomic control systems affected by PTSD, tVNS may be a more effective and comprehensive approach to addressing symptoms of PTSD. Core to empirically supported treatments of PTSD are behavioral concepts of extinction and decoupling of a learned threat stimulus from perception of threat and autonomic mobilization. The combination of potential learning system effects (NE), autonomic behavior, and limbic activity may suggest a role of tVNS as a treatment adjuvant.

TABLE 2 | EDA reactivity to emotionally modulated startle shows a trend toward reduced reactivity with transcutaneous vagal nerve stimulation (tVNS) in pilot study.

Measure		Estimate	SE	*F*	*d*
Phasic max	Sham—tVNS	0.678	0.419	2.61	0.74
Max deflection	Sham—tVNS	0.114	0.093	1.49	0.56
Amplitude sum	Sham—tVNS	0.163	0.173	0.88078	0.43

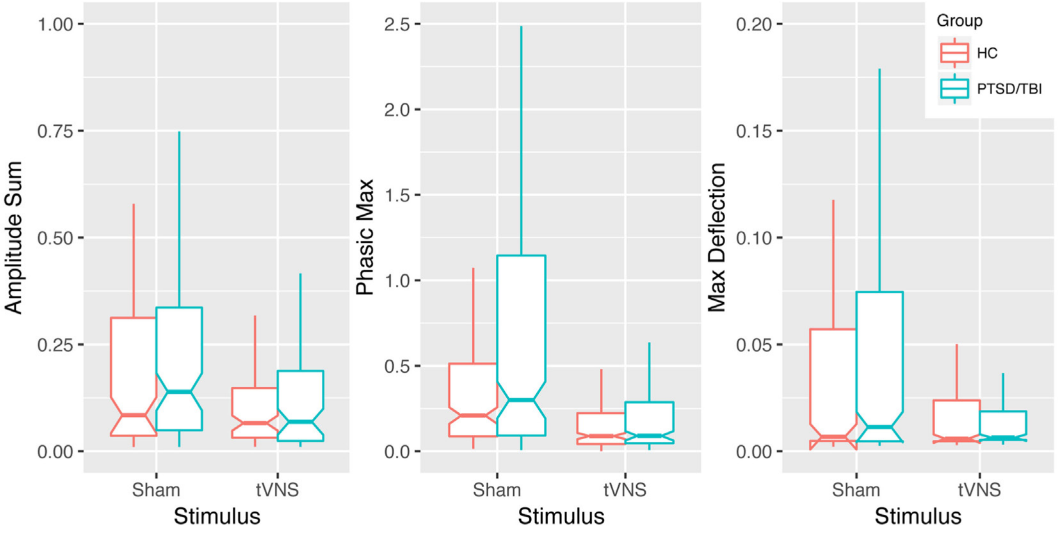

FIGURE 3 | Impact of transcutaneous vagal nerve stimulation (tVNS) on EDA measures. Box plots of phasic max, max deflection, and amplitude sum EDA measures showing a trend of reduced sympathetic activation in response to emotionally modulated startle with tVNS. Notches extend from the median ± 95% confidence interval ($1.58/\sqrt{n} \times$ interquartile range), whiskers extend from lower and upper quartile to 1.5 × interquartile range.

This study has limitations, particularly the sample size is small. Thus, we are limited in the scope of the statistical models we can apply, so, we cannot analyze a full suite of predictors of individual differences in response. Further, the study was a between-subject, single session design. As such, though there was random assignment to condition, the data are between-subjects and, therefore, could reflect sampling. Finally, our subject blinding technique was psychological and not an active sham, i.e., there was no electrical stimulation in the sham condition. A large N crossover or longitudinal design would likely be more statistically powerful and would also allow for intraindividual comparison; however, the current design does avoid spillover effects and habituation as potential confounds.

CONCLUSION

To our knowledge, no studies have been published showing influence of tVNS treatment on alterations of baseline and emotionally modulated autonomic responses in individuals with PTSD. The results of the current preliminary study are promising and should be replicated and extended. What we observed in the current study is a baseline shift in physiological state, i.e., increased markers of parasympathetic nervous system activity. This change in parasympathetic nervous system activity may be interpreted as evidence of a tamping-down of defensive autonomic response and increased amenability to social engagement (45). Further supporting this interpretation, we observed decreased sympathetic nervous system response to emotionally modulated startle. One might conceptualize tVNS as a prosthetic for prefrontal action in inhibiting limbic activity and shifting emotional state to a more socially adaptive form. Autonomic behavior is central to symptoms of PTSD and effective modulation of these systems is associated with better emotional and health outcomes. Thus, further study of tVNS as a potential treatment or adjuvant for patients with emotional dysregulation in the continuum of PTSD is warranted. Follow-up mechanistic work is necessary for delivery impact and optimization and longitudinal effects the symptom clusters of PTSD as well as tolerability and other factors necessary for realization of this tool as a viable treatment approach. In addition to short-term impacts on emotional/autonomic features of PTSD as assessed in the present investigation, tVNS may also have long-term utility with repeated application in reducing symptoms of PTSD.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the University of Florida Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the University of Florida Institutional Review Board.

AUTHOR CONTRIBUTIONS

JW—conception of project, protocol creation, participant screening, data analysis, writing. DL—conception of project, protocol creation, execution of protocol with participants, data analysis, writing. EP—conception of project, protocol creation, data analysis (quantifying EDA), writing. GL—data analysis (ECG), writing.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Impact of Resonance Frequency Breathing on Measures of Heart Rate Variability, Blood Pressure, and Mood

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Heart rate variability biofeedback (HRVB) significantly improves heart rate variability (HRV). Breathing at resonance frequency (RF, approximately 6 breaths/min) constitutes a key part of HRVB training and is hypothesized to be a pathway through which biofeedback improves HRV. No studies to date, however, have experimentally examined whether RF breathing impacts measures of HRV. The present study addressed this question by comparing three groups: the RF group breathed at their determined RF for 15 min; the RF + 1 group breathed at 1 breath/min higher than their determined RF for 15 min; and the third group sat quietly for 15 min. After this 15-min period, all groups participated in the Paced Auditory Serial Addition Task (PASAT) for 8 min, and then sat quietly during a 10-min recovery period. HRV, blood pressure, and mood were measured throughout the experiment. Groups were not significantly different on any of the measures at baseline. After the breathing exercise, the RF group reported higher positive mood than the other two groups and a significantly higher LF/HF HRV ratio relative to the control group, a key goal in HRVB training ($p < 0.05$). Additionally, the RF group showed lower systolic blood pressure during the PASAT and during the recovery period relative to the control group, with the RF + 1 group not being significantly different from either group ($p < 0.05$). Overall, RF breathing appears to play an important role in the positive effect HRVB has on measures of HRV.

Keywords: resonance frequency breathing, heart rate variability, blood pressure, mood, biofeedback

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Heart rate variability (HRV) is a key marker of health, mood, and adaptation, and hence improvements in HRV improves health, mood, and adaptation to stress (1, 2). Heart rate variability biofeedback (HRVB) reliably increases HRV, mood, and adaptability (3, 4). A key aspect of HRVB involves identifying each person's unique resonance frequency (RF) breathing rate and then teaching them how to breathe at this rate in the clinic and through home practice. No studies to date, however, have examined if breathing at RF is an important aspect of HRVB training. The purpose of this study was to examine whether different breathing rates would differentially affect measures of HRV, blood pressure, and mood. Specifically, does RF breathing result in more positive outcomes relative to other breathing rates?

Heart rate variability is the variation in time intervals between heart beats (5). Multiple physiological systems influence heart rhythm and greater fluctuations in heart rhythm over time indicate healthy systemic balance and ability to respond to physiological needs (3, 6). Consequently, higher levels of HRV are indicative of a healthy heart and a marker of overall healthy physiological functioning (5). Low HRV, or less responsiveness to physiological needs, predicts mortality and morbidity and also occurs in depression, anxiety, and chronic stress (7). As an example, the central nervous system uses negative feedback loops (such as the baroreflex) to maintain homeostatic balance in heart rate and blood pressure while interacting with the environment (1). However, these feedback loops become less sensitive with chronic stress and sympathetic nervous system arousal found in physical and psychiatric disorders (3). High heart rates are inversely correlated with the levels of HRV, as there is less opportunity for variability between heart beats when they are closer (5). Low HRV predicts negative outcomes in cardiovascular disease and in all-cause mortality (8), with depression playing a significant role in cardiovascular disease as well (1).

Heart rate variability biofeedback reliably improves HRV. Biofeedback is an interactive process where individuals directly learn how to change their physiological activity (9). Sensors placed on their skin measure physiological functions such as heart rate, respiration, muscle tension, etc., and this information is displayed on a computer screen in real time allowing participants to become directly aware of and then change their physiological functioning (5). HRVB is particularly beneficial in learning to regulate the physiological stress response. HRVB is a relatively quick and inexpensive treatment, with protocols typically including ten 30-min sessions, although positive effects on anxiety, depressive symptoms, and cognitive performance have been found after the first session (10–12). HRVB interventions are efficacious for both physical and mental disorders, including treating depression, anxiety, panic disorder, as well as improving outcomes in patients with cardiac problems and asthma (4,14,15).

A key aspect of HRVB is RF breathing. HRV is directly influenced by breathing and respiratory sinus arrhythmia (RSA). RSA is the fluctuation in heart rate corresponding to breathing, with heart rate increasing with inhalation and decreasing with exhalation (15). RSA typically occurs in the high frequency (HF) range of HRV (0.15–0.4 Hz) and is a measure of parasympathetic activity (16). At resting breathing rates (between 9 and 24 breaths/min), heart rate increases with inhalation at about the mid breath point and heart rate decreases with exhalation at about the mid breath point (5). RSA impacts gas exchange such that heart rate tends to be higher when the air in the lungs is richest in oxygen and exhalation occurs when carbon dioxide in the lungs is highest. Hayano et al. (17), however, found that the most efficient gas exchange occurs when heart rate starts increasing at the beginning of inhalation and decreasing as exhalation begins rather than at the mid breath points. Synchrony of heart rate and breathing also increases the amplitude of heart rate oscillations leading to high levels of HRV.

Heart rate and breathing synchronize, or become resonance, at about 6 breaths/min (0.1 Hz). Each person has a unique RF breathing rate, ranging typically between 4.5 and 7.0 breaths/min. In studies of HRV biofeedback, the most common RF breathing rate is 5.5 breaths/min (18). RF breathing rate is identified by having the person breathe at 4.5, 5.0, 5.5, 6.0, 6.5 and 7.0 breaths/min during EKG recording. HRV frequency and time domain measures are then evaluated to find which breathing rate results in the largest changes in HRV. A common approach is to examine the low frequency (LF) range (0.05–0.14) of the HRV spectrum to find the largest frequency spike, which usually occurs at about 0.1 Hz. As people slow their breathing down and approach RF, HRV amplitude increases significantly. When a person breathes at their identified RF breathing rate, heart rate and breathing become synchronized and the highest levels of HRV are typically obtained.

Although breathing at RF is a key part of HRVB training, there are no published studies to date that have examined if RF breathing is essential. We therefore tested the hypotheses that breathing at RF would lead to improved HRV, blood pressure, and mood using a randomized controlled design. Specifically, we examined three hypotheses. First, we hypothesized that the RF group would show higher positive mood and decreased negative mood and anxious arousal following breathing practice relative to the RF + 1 and control groups. Second, we hypothesized that the RF group would score higher on the HRV measures of LF and LF/HF ratio, and lower on HF relative to the RF + 1 and control groups. And third, we hypothesized that the RF group would show decreased blood pressure reactivity during the PASAT stressor relative to the RF + 1 and control groups, and that LF/HF ratio following breathing practice would predict decreased blood pressure reactivity during the PASAT stressor and that this effect would be strongest in the RF group.

METHOD

Participants

A convenience sample of 95 participants (60% female, average age of 20) was recruited from undergraduate psychology classes using an online recruitment site and randomized into three experimental groups: RF breathing, breathing at 1 breath/min above established RF, and a control group that sat quietly. Class credit was given for research participation. Participants were excluded if they reported a history of heart disease or taking medications that affect blood pressure or heart rate. This study was approved by a university institutional review board and all participants read and provided informed consent before starting the study.

Measures

Heart Rate Variability

Heart rate variability was measured using both frequency domain measures (LF, HF, and LF/HF ratio) and time domain measures [standard deviation of normal to normal R-R intervals (SDNN) and Root Mean Square of the Successive Differences (RMSSD)]. HRV was measured using the Nexus 10 and Biotrace software (Mind media software). Data were corrected for artifact and heart variability measures were calculated using the Kubios program (University of Finland). Power spectral analyses (LF and HF) measures examine different frequencies: 0.15–0.4 Hz for HF, and 0.04–0.15 for LF (3, 19). The SDNN measures the standard deviation of the R spike to R spike. Larger SDNN values show more variation in heart rate (3, 19). RMSSD is a time domain measure of HRV, and measures the differences between adjacent heart rates. RMSSD correlated with vagus-mediated components of HRV (3, 19).

Blood Pressure

Data on heart rate, diastolic, and systolic blood pressure were collected using a Dinamp Model 8100 automated blood pressure monitor (Critikon Corporation, Tampa, FL, USA) that uses an oscillometric method. Readings were taken placing a cuff on the upper non-dominant arm of the participant following manufacturer specifications. Two blood pressure readings were averaged for each time period.

Mood and Anxious Arousal

The Scale of Positive and Negative Emotions (SPANE*)* was used to measure current mood. The SPANE consists of 12 items, 6 positive and 6 negative, to assess positive and negative emotions over a specific time frame. These are rated on a Likert scale from 1 ("very rarely or never") to 5 ("very often or always"). The SPANE has demonstrated good internal consistency with Cronbach's alphas between 0.81 and 0.89. It also correlates from 0.57 to 0.70 with other mood scales (20). The anxious arousal subscale was taken from the Mini Mood and Anxiety Questionnaire (21). The anxious arousal subscale contains 10 items and is designed to assess physiological symptoms associated with anxiety such as feeling short of breath, cold hands, or trembling muscles. Items are measured on a 5-point Likert scale, ranging from 0 ("Not at all") to 5 ("Extremely") and the subscale has been shown to have good internal consistency ($\alpha = 0.85$).

Procedure

After obtaining consent, participants were randomly assigned to the RF, RF + 1, or the control conditions. The experimental conditions consisted of breathing at RF, breathing at one breath above the RF (RF + 1), and a control group who are sitting quietly. Participants filled out an initial battery of measures, including the anxious arousal subscale from the Mini Mood and Anxiety Questionnaire, and SPANE. Researchers attached EKG sensors to participants' wrists and forearm. The participant also wore a respiration belt and a blood pressure cuff on their non-dominant arm. RF was determined for all participants, used Rosenthal's HRV determination protocol. The pacer was set at five different frequencies (7, 5, 6.5, 5.5, and 6 breaths/min) for 2 min, resting 1 min between each pace. Because previous studies failed to find students breathing at 4.5 breaths/min, this rate was not included in the present study. Participants then filled out self-report measures of typical stress responses. Participants in the biofeedback conditions then continued to breathe for 15 min, with those in the RF condition breathing at RF, and those in the RF + 1 group at one above their RF. Participants in the control condition sat quietly with their eyes open for 15 min. After this time, participants filled out self-report measures of stress and anxiety symptoms. All participants then took the Paced Auditory Serial Addition Task [PASAT (22)] as a brief laboratory stressor, followed by measures of mood and anxious arousal. Participants then sat quietly for 10 min, followed by measures of mood and anxious arousal, and were then thanked for their time.

Data Analysis

The purpose of this study was to examine the impact of different breathing rates on physiological response using a randomized controlled design. We therefore used repeated measures analysis of variance to test the first two hypotheses, analyzing the impact of group membership on measures of heart variability, blood pressure, and mood during breathing exercises (or sitting quietly), during the PASAT stressor, and during a recovery period. We also used hierarchical linear regression to test the last hypothesis, examining if a measure of HRV (LF/HF) measured during breathing practice predicted blood pressure response to the PASAT stressor. All analyses were conducted using SPSS (IBM SPSS version 23). Three hypotheses were examined.

RESULTS

Mood and Physiological Distress by Experimental Group

The experimental groups did not differ on gender composition or age, and there were no significant differences between groups on reported positive mood, negative mood, or physiological distress at baseline. The 3-Group × 4-Time ANOVAs on positive mood, negative mood, and physiological distress yielded significant main effects of time: $F(3, 276) = 30.38$, $p < 0.001$, $\eta = 0.25$ for positive mood; $F(3, 276) = 30.55$, $p < 0.001$, $\eta = 0.25$ for negative mood; and $F(3, 276) = 16.19$, $p < 0.001$, $\eta = 0.15$ for physiological distress, providing evidence that the experimental manipulations impacted the participants. Compared to baseline, positive mood fell significantly during the PASAT stressor and then recovered somewhat during the recovery period, whereas both negative mood and physiological distress increased from baseline to the PASAT stressor and then decreased during recovery.

The Group × Time interaction was significant for positive mood only, $F(6, 276) = 3.44$, $p < 0.01$, $\eta = 07$. Follow-up contrasts examining the changes from baseline to the end of the breathing practice showed that individuals in the RF group had increased positive mood whereas the other groups did not, $F(2, 92) = 10.73$, $p < 0.001$, $\eta = 0.19$. There were no significant Group × Time interactions for the PASAT and recovery periods.

Measures of HRV by Experimental Group

The main hypothesis of this study was that different rates of breathing would differentially impact measure of HRV, with RF breathing leading to more beneficial results. The 3-Group × 5-Time ANOVAs on frequency domain measures of HRV (LF, HF, and LF/HF) yielded significant main effects of time: $F(4, 372) = 15.78$, $p < 0.001$, $\eta = 0.15$ for LF; $F(4, 372) = 4.13$, $p < 0.01$, $\eta = 0.04$ for HF; and $F(4, 372) = 12.07$, $p < 0.001$, $\eta = 0.12$ for the LF/HF ratio. The control showed little change over time in measures of HRV, whereas the RF and RF + 1 groups increased LF and decreased HF during breathing practice and decreased LF and increased HF during the PASAT stressor. Time domain measures of HRV (SDNN and RMSSD) did not show main effect differences over time nor were there Group × Time interactions.

The Group × Time interactions were significant for LF, HF, and the LF/HF ratio, $F(8, 372) = 3.32$, $p < 0.001$, $\eta = 0.07$ for LF,

$F(8, 372) = 2.18$, $p < 0.05$, $\eta = 0.05$ for HF, and $F(8, 372) = 3.96$, $p < 0.001$, $\eta = 0.08$ for LF/HF. The RF group showed the largest changes during the breathing exercise, particularly for the LF/HF ratio which is a key variable tracked in HRVB. Follow-up contrasts examining changes from baseline to the end of the breathing practice revealed that the RF group increased in LF/HF ratio following breathing practice, whereas the RF + 1 group remained about the same and the control decreased, $F(2, 93) = 4.64$, $p = 0.01$, $\eta = 0.09$. Only the RF group was significantly higher than the control group, with the RF + 1 not being different from either group, indicating that a key therapeutic goal of HRV-B was most clearly achieved in the RF group (**Figure 1**).

Impact of Experimental Group on Blood Pressure and Impact of LF/HF Ratio on SBP and DBP

We also hypothesized that RF breathing would result in lower blood pressure during breathing practice and reduced physiological responsiveness during a lab stressor. The 3 Group × 5-Time ANOVAs for SBP, DBP, HR revealed significant main effects with physiology decreasing during breathing practice and increasing the PASAT stressor, $F(4, 292) = 36.71$, $p < 0.001$, $\eta = 0.34$, for SBP; $F(4, 292) = 13.86$, $p < 0.001$, $\eta = 0.16$, for DBP; and $F(4, 292) = 10.25$, $p < 0.001$, $\eta = 0.12$, for HR, indicating that the experimental manipulations impacted physiology as expected.

The Group × Time interactions were significant for SBP and DBP but not HR, $F(8, 292) = 3.53$, $p < 0.001$, $\eta = 0.09$, for SBP, and $F(8, 292) = 3.69$, $p < 0.001$, $\eta = 0.09$, for DBP. During breathing practice, both the RF and the RF + 1 groups showed lower SBP and DBP compared to the control group, $F(2, 73) = 3.56$, $p < 0.05$, $\eta = 0.09$ for SBP, and $F(2, 73) = 4.94$, $p < 0.01$, $\eta = 0.12$ for DBP. In response to the PASAT stressor, however, the RF group showed lower SBP compared to both the RF + 1 and control groups, $F(2, 73) = 3.29$, $p < 0.05$, $\eta = 0.04$ for SBP, suggesting that RF breathing buffered the stress response to the PASAT (**Figure 2**).

The final hypothesis was that LF/HF ratio would predict blood pressure response to the PASAT stressor. Using hierarchical linear regression, it was found that higher LF/HF at the end of breathing practice (controlling for baseline levels) predicted lower SBP during the PASAT ($\beta = -0.21$, $p < 0.01$) and during the recovery period ($\beta = -0.28$, $p < 0.01$). When examining effects by group, it was found that the effect was strongest in the RF group, $\beta = -0.43$, $p < 0.02$ for recovery period. Similar results were found for DBP with lower DBP found during recovery only ($r = -0.26$, $p < 0.05$), with the effect strongest for the RF group ($r = -0.64$, $p < 0.05$). These analyses indicate that the higher the LF/HF ratio, the less physiologically reactive people are to stress, with this effect being driven primarily by the RF group.

DISCUSSION

We examined whether breathing at RF would improve HRV, blood pressure, and mood, compared to breathing 1 breath/min above RF and sitting quietly using a randomized controlled design. Following the breathing exercise, the RF group reported the highest positive mood and showed a higher LF/HF ratio. Whereas the RF group increased significantly in LF/HF ratio, the RF + 1 group did not change significantly and the control group decreased. The LF/HF ratio is a key variable in HRVB and only the RF group displayed the increase that is sought for. The RF group also showed larger reductions in BP, particularly in response to the PASAT stressor. We also examined whether LF/HF ratio at the end of breathing practice would predict less BP reactivity during the subsequent PASAT stressor. Higher LF/HF did predict lower BP reactivity and this effect was seen most strongly in the RF group. Overall, results indicate that RF breathing contributes to healthier physiological response and mood, supporting its use in HRVB specifically and stress reduction generally.

Resonance frequency breathing is a key part of HRVB protocols (3). A number of research studies, however, have found positive results only emphasizing slow breathing or breathing at 6 breaths/min (23–25). Lin et al. (23) had healthy college students breathe at 6.0 and 5.5 breaths/min and found that the 5.5 rate resulted in higher HRV. RF breathing rate was not determined,

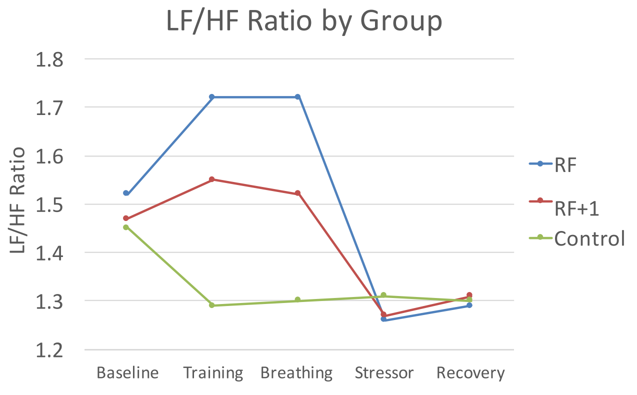

FIGURE 1 | The RF group showed the largest LF/HF response to the breathing practice, with the RF + 1 showing minimal LF/HF changes and the control group decreasing during this time period.

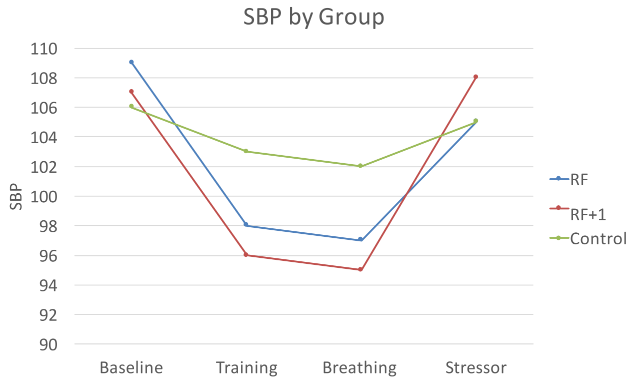

FIGURE 2 | The RF and RF + 1 groups showed decreased blood pressure during breathing training compared to the control group. The RF group showed the smallest increase (least reactivity) in blood pressure in response to the stressor compared to the RF + 1 and control groups.

rather everyone breathed at the same rate. Mason et al. (24) found that breathing at 6 breaths/min as part of yoga exercise improved oxygen saturation and baroreflex sensitivity. Zautra et al. (25) examined fibromyalgia pain patients when they were breathing normally and when breathing at half their normal rate and found slower breathing was related to decreased pain and depressive symptoms. A key finding of this study is that breathing at RF does matter. It is not clear if this would be the case in all situations, but there is evidence that HRVB and RF breathing results in stronger effects (4). Future studies could continue this line of research by examining slow breathing versus RF breathing with different populations and diagnoses to examine these possibilities.

Vaschillo et al. (18, 26, 27) documented that in addition to being an RF for breathing, there is also an RF for vascular tone, and that these resonance frequencies interact. Therefore, vascular tone may be impacted by RF breathing in terms of BP response to stress, with RF breathing decreasing BP and reducing BP response during stress. That is what was found in this study. The RF group increased their LF and HF/LF ratio following breathing practice, and this predicted decreased BP during the PASAT stressor. This confirms earlier research that those with higher HRV are more physically and emotionally resilient (5), but goes one step further to show that this can occur after one 15-min session RF breathing session.

Heart rate variability biofeedback potentially creates favorable outcomes in physical and mental health disorders through several mechanisms of action. Recent research has explored how strengthening and activating the baroreflex and vagal nerve increase physical and emotional resilience (3). Increases in LF and the HF/LF ratio indicate that these systems are being activated and strengthened. Breathing at RF, versus breathing near or slightly above RF, produced the highest LF/HF ratio, which can be interpreted as higher levels of baroreflex and vagal nerve activity. As these are proposed mechanisms of action for the reduction of symptoms in physical and psychological disorders, breathing at RF will produce greater effects in HRV interventions.

A limitation of this study is the cross-sectional design. While positive changes were seen with only one session, it is unknown what would happen over the course of weeks as HRVB is typically administered. Additionally, the sample consisted of college students, so it is unknown if these results would be found in different age groups. We did not assess baroreflex in this study which would have been helpful in understanding the pathways through which HRV changes occurred. A strength of this study was the use of a randomized controlled design with participants not being significantly different on the variables assessed at baseline. Therefore, there is confidence that the changes observed after exposure to the experimental conditions was not due to random effects.

CONCLUSION AND FUTURE DIRECTIONS

Overall, evidence supports RF breathing as a key factor in HRVB. RF breathing, compared to breathing at 1 breath above RF and sitting quietly control group, leads to more positive outcomes, resulted in a more positive mood, a higher LF/HF ratio (a key variable in HRVB), and a decreased BP response to stress. This study contributes to research on HRV showing that breathing at RF, as opposed to breathing near RF, promotes more adaptive physiological and emotional response. Future directions in this line of research include examining these relationships longitudinally over the course of HRVB, to study older age groups, and to explore if these relationships hold in people with clinical diagnoses such as depression or anxiety.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Brigham Young University Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the BYU Institutional Review Board.

AUTHOR NOTES

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AUTHOR CONTRIBUTIONS

PS was involved with study conceptualization, design, statistical analysis, and writing up the manuscript. TA was involved with study design, analysis, data collection, and writing. AD and TB were involved with design, analysis, and data collection.

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Heart-Rate Variability—More than Heart Beats?

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Heart-rate variability (HRV) is frequently introduced as mirroring imbalances within the autonomous nerve system. Many investigations are based on the paradigm that increased sympathetic tone is associated with decreased parasympathetic tone and *vice versa*. But HRV is probably more than an indicator for probable disturbances in the autonomous system. Some perturbations trigger not reciprocal, but parallel changes of vagal and sympathetic nerve activity. HRV has also been considered as a surrogate parameter of the complex interaction between brain and cardiovascular system. Systems biology is an inter-disciplinary field of study focusing on complex interactions within biological systems like the cardiovascular system, with the help of computational models and time series analysis, beyond others. Time series are considered surrogates of the particular system, reflecting robustness or fragility. Increased variability is usually seen as associated with a good health condition, whereas lowered variability might signify pathological changes. This might explain why lower HRV parameters were related to decreased life expectancy in several studies. Newer integrating theories have been proposed. According to them, HRV reflects as much the state of the heart as the state of the brain. The polyvagal theory suggests that the physiological state dictates the range of behavior and psychological experience. Stressful events perpetuate the rhythms of autonomic states, and subsequently, behaviors. Reduced variability will according to this theory not only be a surrogate but represent a fundamental homeostasis mechanism in a pathological state. The neurovisceral integration model proposes that cardiac vagal tone, described in HRV beyond others as HF-index, can mirror the functional balance of the neural networks implicated in emotion–cognition interactions. Both recent models represent a more holistic approach to understanding the significance of HRV.

Keywords: heart-rate variability, autonomous nerve system, sympathetic nerve system, parasympathetic nerve system, systems theory, time series

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INTRODUCTION

The human body consists of many different interacting systems. The brain would not survive without circulation, and circulation is only possible when energy metabolism is working. Eating food is only safe when the liver extracts the toxic substances and the immune system defends against pathological germs, and so on. In reductionist bioscience, the human physiology is investigated by identifying its parts and focusing on one of it. In controlled experiments, one factor is changed and every other possible controlled as much as possible. This approach has been extraordinarily successful in understanding basic principles of human (or animal) physiology. In principle, the reductionist approach assumes that if scientists investigate every part of the human body and its possible interactions with other parts and when they put all together they will understand human physiology.

This approach does not necessarily work out. Even reductionists agree that a brain will die within 3 min when circulation breaks down. However, the reductionist approach does not appreciate the tight interconnection of different parts of the body to function in real time. The basic physiological approach based on research in the nineteenth century is still valid when looking at some general functions. Heart function can be described by a linear equation where cardiac output is multiplied with heart frequency. The view changes, however, when the level of detail is increased. Every heart beat is at least slightly different; cardiac output is influenced by factors as simple as preload, afterload, or systemic resistance, or as complicated as a plethora of humoral factors, a variety of efferent signals and the condition of the heart muscle. Neural inputs are never the same; their patterns are depending on afferent signals from the heart to different brain centers and again humoral signals. These are modified by energy metabolism, immunological signal cascades, the internal state of the brain itself. It is possible to identify hundreds of different factors which probably influence the cardiac output in various ways. However, it is also possible to turn it around. The cardiac cycle has effects on brain function beyond simply providing enough blood flow. Oscillations in the brain are coupled to the heartbeat and oscillations in other systems. The state of the immune system has effects on the brain, which again has effects on the circulation system, apparent in sepsis, but relevant also in less dramatic situations. It turns out that the human body consists of closely interconnected parts which communicate closely in real time on the level of changes in time orders between milliseconds and hours, even days.

Another part of the picture regards the influence of perturbations. In a linear, reductionist world, a change in one condition will have a straightforward effect on the connected system. Increase adrenaline twice, and the heartbeat increases twice. Take away some blood, and the blood pressure decreases, take away twice as much, and the blood pressure decreases twice as much. The reality is different. A change of internal or external factor will often only induce minor changes. Losing a half liter of blood will probably induce small changes in blood pressure and slightly increase heart frequency. Removing more will eventually lead to sudden changes, at the end to a breakdown of circulation.

Meet another paradigm. The human body can be regarded as a system. A system can be defined as a set of interacting or independent components forming a whole. Each system has boundaries defining an inside and an outside. Systems again can consist of a set of systems (subsystems) interacting in the same way. This definition can be applied to physical entities, human bodies, or social constructions in the same way. Systems can be studied by breaking them up into parts as reductionists do, but the notion of the system includes that a system "is more than its parts" (1). Systems, in general, have some properties in common. They can be remarkably stable against perturbations, but they also can be remarkable fragile in case of a specific perturbation, leading to a sudden change. This possible change is frequently termed phase change, and the ability to change is termed emergence. Apparently, sudden system changes due to minor changes in perturbations are not linear, but non-linear. This means simply that a small perturbation might cause a major system change, or a significant perturbation only a minor modification. The advantage using this approach to the human body is that both a sophisticated understanding and sophisticated tools to investigate systems have been elaborated (2, 3).

Biomedical research in the last decades has reached an enormous level of detail. Independent of the area of investigation, the knowledge of genetics, translational mechanisms, intracellular pathways, receptor systems and their ligands, or immunological mechanisms have reached a level where it is challenging to understand the system as a whole. It turned out that simple systems are not as simple, physiological systems are best assumed to be more complex than at first apparent until it can be demonstrated otherwise (2). All physiological systems can be understood in a cybernetic way. They consist of control cycles using either positive or negative feedback mechanisms which were identified in the second half of the last century. Systems with more than three positive and negative feedback circles in combinations are often not predictable; they show complex behavior.

At the end of the last century, the increasing level of details provided by biomedical research provoked debates how to understand the whole system. Similar debates also occurred in other scientific disciplines. System theory and cybernetics gradually evolved to something which was termed complexity science although an exact definition was challenging and no unified theory existed. At the same time period, system theory evolved to dynamic system theory beyond other influences also with the help of inputs from chaos theory which in reality investigates the behavior of deterministic non-linear systems (3). Another evolving direction of investigations was based on increasing computational power which it made possible to simulate large artificial systems in real time. Agent base modeling, cellular automata, and genetic algorithms were developed. All these approaches made contributions to understand complex systems; main tools repeatedly used were an analysis of time series of signals and computer simulations (4).

In the beginnings of 2000s systems biology was established. It is a biology-based inter-disciplinary field of study focusing on complex interactions within biological systems on several levels—intracellular, intercellular, hormonal, macroscopic—using a comprehensive approach and as tools data mining, mathematical models, and time series analysis (4, 5). A time series is a sequence of observations made over time, in the case of heart-rate variability (HRV) heartbeats, but also other parameters (like blood sample results, EEG signals, etc.) (6). Time series analysis can help to identify hidden patterns and even causalities in physiological systems (7). Systems biology analyses different parts of the body as a kind of network (8). Most investigations are conducted on the subcellular level, looking on metabolic and genetic regulation networks and then analyzing them with the help of sophisticated network methods, which again are validated with experimental data. Network analysis or models can even be applicated in the case of unknown quantitative relationships or lacking precise data (e.g., By using Boolean networks) (9, 10).

This review is organized as follows. After a short introduction of HRV, some physiological systems with influence on HRV will be reviewed. In the next part, different paradigms of HRV are presented—HRV as time series analysis, as a proxy for the autonomic vegetative systems and as a proxy for a complex regulatory system. Finally, implications will be discussed.

PRINCIPLES AND PARAMETERS OF HRV

The principles of HRV are simple. The heartbeat is measured, usually with the help of an ECG signal which is obtained with an adequate device. A minimum sampling rate between at least 250 and 500 Hz is recommended (11). QRS-distances are measured (called NN-distances) after identification of ventricular and supraventricular extrasystoles which usually are interpolated. Subjects with a high rate of extrasystoles or atrial fibrillation (AF) are usually not feasible for analysis [but see Ref. (12)]. At the end of the measurement period, a time series of milliseconds can be processed in time domain, frequency domain, geometrical measures, and different non-linear measures like fractal parameters or different calculations of entropy (13). The most common used parameters are the SD of NN Intervals (SDNN) and root means successive square difference (rMSSD), calculated by squaring of each NN interval, thus calculating the mean value and drawing the square root (14). Geometric methods are derived from sequences of NN intervals. Different geometrical methods include the 24-h histogram, the HRV triangular index, the triangular interpolation of NN interval histograms, and methods like the Poincaré-plot. Frequency domain (power spectral density) describes the periodic oscillations of the heart-rate signal, transformed into different frequencies areas, and returns numerical values about their relative intensity (14). Most frequently, the frequency-domain parameters are calculated non-parametrically with the fast Fourier transformation. The most used parameters are Total Power, VLF (very low frequency, <0.003–0.04 Hz), LF (low-frequency power, 0.04–0.15 Hz), HF (high-frequency power, 0.15–0.4 Hz), and the ratio LF/HF. HF is often understood as a proxy for the parasympathetic nervous system (PNS). It can be influenced by the frequency of breathing or pathological forms of respiration, but is reliable with normal respiration (15) and is to a certain grade similar to respiratory sinus arrhythmia (RSA) (16). Both the sympathetic nervous system (SNS) and the PNS modulate LF. High LF reflects often increased sympathetic activity. The LF/HF ratio might reflect the global sympathetic/vagal balance. VLF is probably influenced by the renin–angiotensin system and is also associated with the sympathetic activity (15, 17). Non-linear methods often focus on (self)similarities in the time series. Classical algorithms for the analysis of self-similarities are fractal methods. Different forms of entropy measures have been used (18). A standard for measurement and interpretation was published in 1996, and most studies afterward are based on it (11).

HRV IS MORE THAN THE AUTONOMIC NERVE SYSTEM: SOME PHYSIOLOGICAL SYSTEMS WITH INFLUENCE ON HRV

Autonomic Nerve System

The autonomic nervous system (ANS) is an important part in the control of different physiological systems, e.g., the heart, smooth muscles, endocrine, and exocrine glands. It has an afferent (sensory) and efferent parts and is distinct from the somatic nervous system in several ways. The main function of ANS is homeostasis, largely regulated by autonomic reflexes, (almost) not under voluntary control. Sensory information is frequently transmitted through afferent vegetative nerve fibers to homeostatic control centers, processed and specific reactions are sent through efferent vegetative fibers. The ANS has as mentioned specific transmitter substances—mostly acetylcholine (ACh) and norepinephrine (NE)—corresponding receptors and can be divided into preganglionic and postganglionic fibers. The central control of the vegetative nerve system has been identified in several subdivisions of the hypothalamus, but several other brain regions including the association areas of the limbic cortex, the amygdala, and the prefrontal cortex are also connected to these hypothalamus nuclei.

The hypothalamus itself controls two more systems in addition to the ANS, the endocrine system and an ill-defined neural system involved in motivation (19) and social behavior ((20, 21)). The ANS has three major divisions: sympathetic (SNS), parasympathetic (PNS), and enteral (the latter is often underestimated). In a traditional view, the sympathetic and the parasympathetic systems are opposed to each other. In this view, the SNS is responsible for stress reactions and the PNS for relaxing. All visceral reflexes are processed by local circuits in the spinal cord and brainstem (22). The sympathetic system's phasic activity is triggered by (positive and negative) stress and increases cardiac energy demand by increasing heart frequency and contractility through binding of NE to adrenoreceptors on cardiomyocytes (23). The parasympathetic system's more tonic activity maintains homeostatic heart frequencies and contractility without exhausting, triggered by the release of ACh binding directly to muscarinic receptors on cardiomyocytes and also on nicotinic receptors on postsynaptic neurons (24, 25). The PNS reacts faster on external and internal changes, within 1 s, whereas the SNS reacts after >5 s (26). The role of the ANS in the regulation of heart function is important, but much more influences exist, which makes it to a complex system with several likewise complex subsystems. The following interactions with other systems are only examples.

Sinoatrial Node

The sinoatrial node is, of course, the origin for the pace of the heart. It can, however, itself be considered as a system of weakly coupled oscillators with self-organizing properties, synchronized by a mechanism of mutual entrainment or phase locking (27).

Already on the intracellular level, cell organelles behave as weakly coupled oscillators. A combined experimental and simulation study showed with the help of two photon laser scanning microscope an oscillating network behavior of cardiac mitochondria, distinctly different from random behavior in the form of an inverse power law typical for fractal behavior. They might play a role as an intracellular timekeeper and have a long-time memory function of the oscillations, suggested by a calculated fractal dimension close to 1.0 (28). This kind of network behavior is of particular importance when HRV is interpreted within a complexity theory paradigm (8), as discussed below.

Cardiac neurons are localized both in the heart as intrinsic neurons and intrathoracically. They form a local distributive network, controlled by brainstem and spinal cord neurons and processing both central and local information to control the heart (29). Major intrinsic cardiac ganglionated plexus have sensory neurons responding to metabolic changes within particular heart regions (30). Such sensory inputs might be responsible for the generally stochastic behavior displayed by many atrial and ventricular neurons (31). In the same way as intracellular organelles, intrathoracic neurons have long-time memory properties based on cardiovascular events during the last subsequent cardiac cycles and influence efferent neuronal inputs (29). Because of this, perturbations can have effects over the next few cardiac cycles already based on the coupling of intrathoracic neurons. Because of multiple feedback circles complex behavior is already existent on this level. Typical for a complex system, its behavior is robust even when some subpopulations are compromised (32, 33).

Respiratory System

One of the leading causes of sinus arrhythmia is probably central coupling of respiratory drive to cardiac vagal motor neurons (34–36). Medullary respiratory neurons provide efferent signals to medullary sympathetic premotor neurons (36).

The term RSA is used to describe the fluctuation of heart rate during the respiratory cycle. It is highly dependent on the vagal tone in the heart and is observable at a frequency band of 0.15–0.4 Hz. Usually, RSA is interpreted to mirror the vagal activity (37), involving several interaction levels. Beyond others, the fluctuations of blood pressure due to changes in intrathoracic pressure during the respiratory cycle have been discussed as one of the most important mechanisms of RSA (38). The baroreflex—a rapid feedback loop where elevated blood pressure results in decreased heart rate and decreased blood pressure decreases baroreflex activation—has been associated with RSA, but some evidence indicates that the baroreflex is mostly involved in upright, but not in supine position (where HRV frequently is obtained) (37, 39, 40). An alternative explanation is based on the notion that neural networks generating the respiratory drive have also influence on oscillatory patterns in the vagal and sympathetic outflows, as already proposed several decades ago (41–43).

A classical interaction between the respiratory and cardiac system occurs in congestive heart failure, present in more than 50% of the patients (44). The pathophysiology of Cheyne–Stokes respiration is based on the combination of low cardiac output, pulmonary congestion, and high sympathetic activation. Both congested lungs and sympathetic hyperactivity lead to hyperventilation causing a decrease in arterial CO_2 to a level below the apneic threshold. The hyperventilation pattern consecutively becomes periodic because the diminished arterial CO_2 reaches the brainstem delayed due to the low cardiac output. When first the low partial pressure of CO_2 is detected, respiration drive is stopped until CO_2 increases. This again is detected late, which results in hyperventilation until CO_2 is again on a low level and a new cycle begins (45). The increased sympathetic drive is in particular caused by increased CO_2 partial pressure in the blood (46). The significance of Cheyne–Stokes respiration might be a mechanism to improve the efficacy of pulmonary gas exchange by phase-locking heart beats with phasic hyperpnea within the respiration cycle length (47). Cheyne–Stokes respiration again affects both sinus rhythm and AF. The latter does usually not react to normal ventilation, possibly due to changes of the atrioventricular nodal refractory period (48, 49).

Endocrinological System

In difference to other pathological conditions, endocrinological diseases can be associated with increased HRV parameters. Subjects with increased sodium excretion associated with an increased number of CYP11B2-344T alleles showed a higher LF/HF ratio, but not subjects with the AT1R 1166C allele. Increased sodium excretion correlates with expanded plasma volume which might explain the effect on the parasympathetic tone (50). Cortisol concentration is negatively correlated with HRV (51). Estrogen increases the parasympathetic parameters and progesterone sympathetic parameters of HRV (52, 53). Oxytocin application increase (rather moderate) HF and detrended fluctuation scaling exponent (54).

Immunological System

Infection, injury, or trauma causes an inflammatory reaction in the body which aims to restore homeostasis. The inflammatory response of the host is based on a complex combination of different immune mechanisms contributing to the neutralization of the invading pathogens, the restoration of injured tissues and to wound healing (55). The first steps of inflammatory reactions involve the release of pro-inflammatory mediators, especially, interleukin (IL)-1 and tumor necrosis factor (TNF), but also adhesion molecules, vasoactive mediators, and reactive oxygen species. This first release of pro-inflammatory cytokines is initiated by activated macrophages and is considered as crucial to trigger local inflammatory response (56).

Excessive production of cytokines, such as TNF, IL-1, and high mobility group B1, however, is causing more damage than invading pathogenes, like in the case of sepsis where immune reactions cause tissue injury, hypotension, diffuse coagulation, and in a high proportion of patients, death (57). Therefore, the inflammatory response needs to be balanced which is based on the nearly simultaneous release of anti-inflammatory factors like the cytokines IL-10 and IL-4, soluble TNF receptors, and transforming growth factor (TGF-beta). Using the terms pro- and anti-inflammatory is, however, rather simplistic, but widely used in the discussion of the complex cytokine network. If the local inflammation increases, TNF, and IL-1 β starts to circulate in the blood and other body fluids. This has major consequences for the CNS because these molecules are also signal molecules for the activation of brain-derived neuroendocrine immunomodulatory responses. Another superordinate control instance of the immune reaction is based on neuroendocrine pathways, as the well-known hypothalamic–pituitary–adrenal axis, but, usually underestimated, the sympathetic division of the ANS (SNS) (58, 59). The CNS is also able to control inflammation and contributes to the other anti-inflammatory balancing mechanisms (55).

The cross talk between the immune system and the brain relies, therefore, not only on classical humoral pathways but also substantially on recently discovered neural pathways. Vagus nerve afferent sensory fibers play a vital role in the communication between body and brain when inflammation is occurring. Immunogenic stimuli stimulate vagal afferents both directly by cytokines released from dendritic cells, macrophages, and other vagal-associated immune cells, and indirectly through the chemoreceptive vagal ganglion cells (55).

Acetylcholine plays a major role as neurotransmitter and neuromodulator in the CNS. ACh is an important transmitter substance in ganglion synapses of sympathetic and parasympathetic neurons and is the main neurotransmitter in the postganglionic parasympathetic efferent neurons. Two types of receptors have a high affinity to ACh: muscarinic (metabotropic) and nicotinic (ionotropic). However, like other mediator substances as opioids, ACh is also involved in immune responses. RNA for muscarinic and nicotinic receptors has been detected in mixed populations of lymphocytes and other cytokine-producing cells (60, 61).

A majority of the cells are also capable of producing ACh (62). ACh has an anti-inflammatory effect, beyond others because ACh decreases TNF production *via* a posttranscriptional mechanism. ACh blocks also the release of other endotoxin-inducible pro-inflammatory cytokines, such as IL-1b, IL-6, and IL-18, by same mechanisms; it does, however, not suppress the anti-inflammatory cytokine IL-10 (63, 64). In several experimental models of sepsis, myocardial ischemia and pancreatitis, all characterized by an excessive immune reaction, vagus stimulation was sufficient to block cytokine activity (65–67). The vegetative system may, therefore, play a major role in the immune defense (68). This works in both ways: changed activity of the vagal system modulates the inflammatory response by increasing the release of transmitter substances in the synaptic space like noradrenaline or ACh. On the other hand, inflammatory influences can also enhance or block vagal activity. Pro-inflammatory cytokines activate vagal afferent signaling which again activates efferent vagal signaling directly through the nucleus of the solitary tract (NTS) or indirect through NTS neurons activation of vagal efferents in the dorsal motor nucleus. The vagal system can be considered as an inflammatory control circuit for the inflammatory status in the periphery (69). If this system in animals is destroyed, they are more sensitive to endotoxemic shock (55). The area postrema, a region in the brain stimulated by increased blood concentrations of IL-1 beta can also activate the cholinergic anti-inflammatory pathway (70).

Sepsis is a life-threatening condition, usually caused by invasive bacteria. Success in treatment depends on early identification and treatment with appropriate antibiotics (71). Sepsis is traditionally diagnosed with the help of the clinical picture and blood samples of immunologic parameters (72). HRV changes are sometimes the earliest measurements before the first clinical effects of sepsis are observed (73, 74). This might be based on the close interaction between the PNS and the immune system, as described. HRV parameters change under inflammatory conditions. Soluble TNF-α receptors and IL-6 correlate (negatively) with time-domain HRV variables (SDNN, SDANN) (75–77), also endothelin 1 blood concentration is negative correlated with TP and ULF (78). Although TNF-α might not be associated with HRV variables, a clear relation between IL-6 and decreased HRV has been demonstrated (79). The liver releases CRP as a response to increased IL-1 and Il-6 concentrations, decreased HRV parameters are associated with increased CRP (80–83). In both newly diagnosed and chronic diabetic patients, increased IL-6 is correlated with decreased time domain (SDNN) and frequency-domain parameters (84). In a long-time cohort study with a follow-up of 15 years, linear HRV parameters and DFA was associated with inflammatory parameters at baseline. VLF, LF, TP, and SDNN was negatively correlated with CRP, Il-6, and WBC, DFA had and an inverse association with Il-6 and CRP, and HRT slope to WBC and Il-6 (85).

In conclusion, inflammatory parameters, such as IL-6, CRP, and TNF-alpha, correlate negatively with different HRV parameters. This is not only observed in classical "parasympathetic" parameters like rMSSD or HF but also for more general or "sympathetic" parameters like SDNN, SDANN, TP, VLF, and LF (86). The immune system is a still underestimated physiological and pathophysiological cause of HRV dynamics.

Metabolic Function

Insulin is a major player in metabolic function. In the heart, two different insulin signaling pathways have been identified: the phosphatidylinositol-3-OH kinase pathway, predominant in metabolic tissues and the growth-factor-like pathway (mediated by mitogen-activated protein kinase). Insulin resistance in the heart inhibits the metabolic pathway and stimulates the growth factor-like pathway (87, 88). This leads to decreased glucose uptake with possible consequences for cardiac cell metabolism (88, 89) and is a rather complex process also involving coagulation factors and the immune system (88). Already isolated obesity is associated with increased release of cytokines and other inflammatory markers like the intercellular adhesion molecule-1 (90). The islets with insulin-producing beta cells in the pancreas are innervated by both sympathetic and parasympathetic neurons, making possible a direct control by the CNS. This might also indicate that central nervous circuits have a major role in the functional adaptation to changes in insulin sensitivity. When the ventromedial hypothalamus is lesioned in experiments, increased vagal activity is observed and insulin is released, which can be blocked by vagotomy (91). The PNS effect on the beta cells is mediated by ACh and its effect on the M2 muscarinic receptor. Activation of the SNS through the α2-adrenergic receptor is associated with decreased insulin release, stimulation of β-adrenergic receptors enhance insulin output (92, 93).

There are several factors which can affect HRV in acute and chronic metabolic changes. The direct involvement of the vegetative nerve system can be attenuated in more chronic conditions, when the diabetic autonomous neuropathy, which necessarily occurs after a certain length of illness (94). HRV is an established tool in the diagnoses of diabetic neuropathy. During its subclinical phase, HRV can help in detecting cardiac autonomic neuropathy before the disease is symptomatic (95). Interestingly, reduced HRV in diabetes might be related to increased glycemic variability (96). Theoretically, this could be explained with the help of the concept of coupled oscillators—when the HRV-system as one oscillator fluctuates less, the coupling decreases which again allow the glycemic system to fluctuate independently with less control.

The LF parameter of HRV has been used to predict hypoglycemia (97), this might be even work in patients with advanced diabetic neuropathy (98). Parameters like SDNN and rMSSD are reduced when glucose and insulin are elevated (99). Regarding lipid metabolism, change of diet has been associated with HRV changes (100), but reports are conflicting regarding possible correlations between lipid concentrations in blood and HRV (101, 102).

HRV AS TIME SERIES

Time series show the variation of a parameter during a period. In complexity theory, they are considered as surrogates of the particular system, giving information about the state of the system. Typical time series can consist of a series of blood samples (e.g., CRP, creatinine, white blood cell counts), physical measurements like heartbeats, blood pressure, EEG; or movements like gait, eye blinking or variability of breathing patterns. Even short time series can also give information about a system. Usually, most properties of time series are ignored. They are summarized by simple statistical calculations like the mean and the SD. In the case of HRV, several linear and non-linear algorithms were eventually introduced. The research literature can be roughly divided into three areas. In the first, HRV parameters are used as a prognostic tool. Short-term or long-term results in trials are associated with (usually decreased) HRV parameters. This approach has been very successful providing studies where an analysis of only 2 min of heartbeat predicted all-cause mortality many years later, e.g., in Ref. (103–105). The second approach uses HRV as a proxy for the state of the vegetative system, based on the century-old notion of a balanced situation of the sympathetic and the parasympathetic part. The third approach relies on the complexity paradigm. It considers variability as a proxy for the health of a system and decreased variability as a sign of a pathological condition. In the next section, I will discuss the scientific evidence for associations between HRV and the state of the vegetative system, followed by a section where I present the third approach.

HRV AS PROXY FOR THE VEGETATIVE NERVE SYSTEM

Heart-rate variability is very often used to describe the activity of the SNS and PNS. This is based on the assumptions that there is something like a general activity level of the ANS, that HRV parameters mirror this activity and that SNS and PNS are in the balance, meaning that high SNS activity is associated with low PNS activity and *vice versa*. If this is the case, it should be possible to measure consistent patterns in the activity of different vegetative efferents. But this supposed consistency has frequently not been found. Different other parts of the SNS have not necessarily the same kind of oscillations as the cardiac part of SNS if they have oscillations at all. Cutaneous vasoconstrictor fibers, sudomotor fibers, adrenaline-regulating adrenal preganglionic neurons, and nerves supplying the brown adipose have not oscillations as observed in other parts of the SNS (106–109).

The sympathetic output might also be as similar in different parallel measured subsystems (110). The physiologist William Cannon propose at the beginning of the last century a model of autonomic control, where either sympathetic activation is high and parasympathetic activation is low or *vice versa* (111). In contradiction to this frequently used model evidence has been provided that descending influences from higher neural systems can trigger all patterns of changes in the SNS and PNS, whether reciprocal, independent or even co-active (112, 113). Already early observations indicated that both divisions of the vegetative nerve system could be similar active and work together with the somatic motor system to regulate most behavior, both in normal and in emergency conditions (114). Even when either the SNS or PNS are predominant in the control of an organ or anatomical region (110) and even when the sympathetic and the parasympathetic division have opposed effects on these areas, the balance is more complicated. Coactivation or a degree of opposing activations patterns can both be important to keep homeostasis when external conditions change (22). A major challenge is to interpret experimental approaches which often use isolated organ systems in rather artificial experiments, where other systems are lacking.

The classical description of a stress response of the SNS includes increased heart beat frequency, vasoconstriction, piloerection, and pupillary dilatation (115). However, stress response can be independent of SNS activation.

The increased muscle blood flow, for instance, is triggered by activation of a cholinergic vasodilatation pathway, with only minor involvement of adrenergic pathways (115, 116). Also during the diving reflex, simultaneous activation of the sympathetic and parasympathetic part of the ANS has been observed. When the head is under water, it causes a massive activation of trigeminal afferents nerve fibers which again initiates an intense and simultaneous reaction of SNS and PNS. The SNS triggers massive vascular constriction everywhere (except brain and heart), the vagal activation triggers severe bradycardia and decreases cardiac contractility. The meaning of the diving reflex is to reduce energy demand in a stress situation with an anticipated lack of oxygen in the body (117, 118). Interestingly, the intense simultaneous activation of SNS and PNS is associated with a dramatic loss of fractal properties of the HRV signal (119). Another example is the simultaneous pathological influence of SNS and PNS on AF (120), probably underestimated because HRV usually cannot be used as a tool in these patients. A daily observation in the operation theater is the change of heart rate caused by a sudden nociceptive input in a patient with superficial anesthesia: skilled anesthetists notice a sudden moderate decline of heart rate following by a marked increase some seconds later, most probably caused by simultaneous activity increase of the SNS and PNS, most marked observed in strabism surgery (121). Hundred years after Walter Cannon's insights, we should accept that high SNS activity does not necessarily imply a low PNS activity.

Another important question is if the different parameters of HRV mirror the state of the ANS. It has been shown, that representations of ANS in the brain and brain centers involved in HRV are mainly the same (122–125). However, does HF correlate with the parasympathetic tone? The presented evidence often consists of pharmacologic studies where the sympathetic system is blocked with, e.g., atropine (126–128). In a complex experiment, the relationship between HRV parasympathetic activity was described by a function with an ascending part that goes over to a plateau level (129). These results have been challenged, and some authors argue that HF is a possible, but not optimal index (130), or that it only works out when respiration is controlled (131). Similar in the case of LF and sympathetic activity: several studies confirm the relationship (128, 132, 133), but not in all subjects (134) and some results were challenged (135). Contradictory results are, e.g., when an intense training session in healthy persons (which should usually increase sympathetic activity) is associated with a decrease of HRV parameters (136). High dose atropine is expected to block completely vagal parasympathetic activity and according to Cannon's model increase sympathetic activity, but it nearly all LF power (and HF power) disappeared in an investigation (126, 127). Most of the studies regarding HRV components and different parts of ANS were conducted more than 20 years ago. Since then, the debate has calmed down, and these associations have been assumed by most authors using HRV. The relation between HRV parameters and ANS does certainly exist, but the reality is probably more complicated and more research is needed.

HRV AS SYSTEM INDICATOR

Kauffman, affiliated with the renowned Santa Fe Institute for Complexity Research, proposed the notion of life being generally at the edge of chaos (137, 138). Based on theories of complex (adaptive) systems, life is defined being at the frontier between mathematical chaotic behavior and (some kind of) order. Order is here defined as the possibility to estimate the behavior of the system based on its internal states during the last period. The same argumentation is used of some authors arguing theoretically that "health" is defined not being in complete thermodynamic equilibrium; too close proximity (decreased variation, too little energy dissipation, low entropy) or too far distance (increased variation and energy dissipation, high entropy) would indicate pathology (139). Decreased HRV parameters are usually considered as pathological, according to a notion of Goldberger (140). Changed HRV variability, as seen in elderly individuals is explained as reduced number of system components and reduced coupling between elements in a complexity theories paradigm (141, 142). Many studies seem to support this paradigm, but there are also some contradictory reports where increased variability is associated with illness. In endocrinological diseases, HRV can be increased compared to healthy controls. In patients with acromegaly (caused by increased levels of growth hormone due to hypophysis adenoma), the amount of growth hormone release over 24 h correlates with higher approximate complexity (143). Also in patients with Cushing syndrome, approximate entropy is greater when ACTH and cortisol concentration levels are increased (144). Using the same algorithm on a time series of hormone concentration alone has also shown higher approximate entropy of luteinizing hormone and testosterone concentrations in older males (145). Several diseases have been associated with decreased or increased complexity, compared to healthy subjects (142).

Porges introduced a model with an evolutionary approach (146–149). According to it, the autonomous system has three neural circuits: the myelinated vagus, the unmyelinated vagus, and the sympathetic–adrenal system (**Table 1**). All three circuits are involved in the regulation of physiological states. The sympathetic–adrenal part is mainly involved in mobilization related behaviors (fight and flight) whereas the vagal circuits are related to immobilization related behaviors. This approach can be discovered already in Cannon's classical description (111), but Porges extended it to social behaviors. Initially, a system mainly aimed at homeostasis, ANS became during evolution increasingly important in the regulation of social behavior, according to this theory. The polyvagal theory proposes thus that the development of the mammalian ANS provides the neurophysiological substrates for the emotional experiences and affective processes that are major components of social behavior (147).

Thayer's approach is based on the already mentioned complexity theories paradigm. He proposes to use HRV as a measure of the degree to which a system provides flexible, adaptive regulation of its component systems, with other words as a measure of the adaptivity of the brain–body system (150, 151). They describe their view as follows: "When processes mutually constrain one another, the system as a whole tends to oscillate spontaneously within a range of states. The various processes are balanced in their control of the entire system, and thus the system can respond flexibly to a range of inputs. However, such systems can also become unbalanced, and a particular process can come to dominate the system's behavior, rendering it unresponsive to the normal range of inputs (…) A system, which is 'locked in' to a particular pattern, is dysregulated" (124). This approach has been developed further to a model called Neurovisceral Integration Model (124, 152, 153).

TABLE 1 | Three phylogenetic stages of the neural control of the heart, as proposed of the Polyvagal Theory; modified from Ref. (147).

Phylogenetic state	Autonomic nervous system component	Behavioral function	Lower motor neurons
I	Unmyelinated vagus	Immobilization, passive avoidance	Dorsal motor nucleus of the vagus
II	Sympathetic–adrenal	Mobilization (active avoidance)	Spinal chord
III	Myelinated vagus	Social communication, self-soothing and calming, inhibit sympathetic–adrenal influences	Nucleus ambiguus

Thayer and Lane proposed at the beginning that HRV might be a biomarker for emotion regulation, but they extended it eventually as a surrogate parameter for the more general top-down ability to self-regulation which is again coupled to the vagus nerve to the heart. As a general central nervous base for self-regulation, a Central Autonomic Network (CAN) has been defined (154). This network consists of parts of the prefrontal cortex (anterior cingulate, insula, orbitofrontal, and ventromedial cortex), limbic structure (amygdala and hypothalamus), and brain stem (periaqueductal gray matter, nucleus ambiguus, ventrolateral, and ventromedial medulla). These coupled structures and its oscillatory signal patterns are integrated into the nucleus of the solitary tract (NTS) and again coupled through efferent parts of the vagus nerve with organs outside the brain. The coupling is bidirectional such as peripheral oscillations in the heart, lung, but also in the immunological system (and others) can lead to changes in the CAN. According to the model, this regards especially the parasympathetic activity and should be associated with variations of the HF signal. This model has recently been expanded by defining eight levels of vagal control beginning with intra-cardiac control on the lowest level up to the highest levels where interactions between different parts of the prefrontal cortex shape the vagal tone over longer time periods (152). The model is sophisticated and based on new neuroscientific evidence. Especially on the network level, research is still needed. A recent investigation, for instance, reported no association between different individual levels of HF and general activity in the default mode network or the salience network in the human brain (155).

Besides these two models, other theories have been published. Grossman's biological behavioral model focuses on the regulation of energy exchange by synchronizing respiratory and cardiovascular processes during metabolic and behavioral changes. Also there the main component is vagal signals, reflecting functional energy reserves as adaptive capacity (156). Lehrer and Gevirtz's model is interested in the effects on slow pace breathing to increase vagal tone as a beneficent surrogate for health, mainly as a possible explanation for the effects of HRV biofeedback (157). McGraty and Childre have published a similar model within a broader context of physical and mental health (158).

Based on both approaches several studies have been published, mainly focusing on emotion regulation and executive control. Newer approaches also include sociodemographic co-variables (159), indicating that lower vagal components HRV mirror reduced adaptivity in self-regulation, supposed to be associated with lower sociodemographic status. This would indicate that HRV could be applicated as proxy for executive control and might be even used as measurement for therapeutical inventions. An association of lower sociodemocratic status and lower executive function, however, has been questioned in recent work (160).

An underreported issue is consequences of relatively higher HRV indices, based on the interest for the association between lower HRV and pathological conditions. Some evidence for that relatively higher HRV is associated with better mental and physical health has been reported. For instance, higher rMSSD is associated with better self-rated health (161).

IMPLICATIONS FOR CLINICAL PRAXIS AND FURTHER RESEARCH

A main issue in HRV research is that most studies report HRV parameters, but the main research question was not related to HRV. Frequently, relevant information or non-significant results are not reported. Relevant co-variables beyond age and gender, like Body Mass Index, physical status, or social background are often omitted, at least in the control groups. The well-documented association between immune status and different HRV results, for instance, is rarely reported, e.g., in the form of CRP values.

In the case of time series analysis, linear parameters have been established and are being used reliably. The non-linear part, however, is more difficult. A wide number of different forms of fractal measures, entropy measures or other non-linear indices have been introduced in the last two decades, but their relevance is still unclear. The relation between different HRV indices and the activity of various sympathetic and parasympathetic subsystems is also still unclear. In the last years, HRV parameters (especially HF) mirroring the function of the executive brain, in particular in the prefrontal cortex has been investigated. As pointed out by Holzman and Bridgett (162), a small, but a significant relation between top-down functions of the prefrontal cortex and HRV is now established, but more exact definitions and its clinical relevance remain to be shown.

Heart-rate variability is a fascinating observation and insight in its mechanisms is increasing. One main issue remains that interindividual differences are high and statistical effects are usually shown only on the group level. In particular regarding psychologic functioning, although an association between lower HRV and lower adaptivity is now established (162), the differences are frequently, although significant, very tiny—see as example recent work on HRV and depression (163), which makes its clinical application difficult.

From a systems science perspective, HRV measurement begins to be a sophisticated and relevant tool for both scientific and clinical insights.

AUTHOR CONTRIBUTIONS

GE has elaborated and written the review.

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OPINION
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Opinion: “Heart Rate Variability, Health and Well-Being: A Systems Perspective” Research Topic

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The promotion of health and well-being is a long-standing goal of scientific inquiries. The World Health Organization mission incorporates not only the absence of disease but also an integrative perspective on social, physical, and mental well-being (1). The National Institutes of Health goals are intimately focused on protecting and improving health through funding research and facilitating programs that promote public health (2). Healthy People is an example of a broadly focused, long-range strategic initiative that incorporates results from scientific inquiry into health promotion recommendations (3). Therefore, scientific strategies to understand, describe, and predict health-related issues are important steps in the process of promoting health and welfare.

The Frontiers research topic titled “Heart Rate Variability, Health, and Well-being: A Systems Perspective” is focused on the construct of heart rate variability (HRV) in the context of health and well-being. Autonomic control of peripheral functions involves a complex series of interactions, including the sympathetic and parasympathetic nervous systems as well as central processes, neuroendocrine functions, and reflex arcs. Therefore, studies involving HRV have the potential to provide insight into a wide variety of psychological and physiological processes.

Altered HRV, and its value for predicting dysfunction (or lack thereof), has contributed significantly to our understanding of several conditions [for reviews, see Ref. (4, 5)] such as stress reactivity and resilience (6, 7); emotional reactivity and personality factors (e.g., responses to stress, perception of stress, emotional memory, attention and related cognitive functions, and self-regulation processes) (8–12); emotion-related disorders (e.g., depression, anxiety, and sleep disorders) (13, 14); social behaviors (e.g., social engagement and social–emotional processes) (15–17); cardiovascular functions and risk factors (e.g., hypertension, myocardial infarction, sudden cardiac death, renal dysfunction, and diabetes) (4); and cancer (18). The study of HRV also has provided insight into the interactions of psychological and physiological processes [for review, see Ref. (15)], including stress reactivity following cardiac transplants (8); effects of antidepressants on autonomic function in panic disorder (19); association of depression and cardiovascular disease (13, 20–25); interactions of social factors and cardiovascular function (26–28); treatments for comorbid psychological and physiological conditions (29–32); and novel non-pharmacological treatment strategies for psychological and physiological disorders, such as deep brain stimulation, vagal nerve stimulation, exercise, or yoga (31, 33–35). These brief examples highlight the value of HRV research for describing and predicting several conditions that influence public health.

This integrative research topic on HRV which spans two *Frontiers* journals (*Frontiers in Medicine* and *Frontiers in Public Health*), contributes novel perspectives on the scientific and practical value of HRV research. For example, Kirby and colleagues (12) address the utility of HRV in training exercises to facilitate compassion, highlighting the importance of considering physiological processes in the context of psychological interventions. As discussed, a better understanding of behavioral, social, and emotional factors that contribute to HRV will provide evidence for its utility as an outcome measure, a potential method for manipulating behavioral and emotional states, and an index for understanding the integration of autonomic regulation and emotional reactivity (12). Similarly, Lamb et al. (35) and Steffen et al. (36) present novel findings from techniques that capitalize on altering autonomic function, including the effects of resonance frequency breathing exercises on HRV and mood in healthy humans (36), and the influence of vagal nerve stimulation on HRV and other physiological parameters in combat veterans with posttraumatic stress disorder (35). These concepts are related to those addressed by Ernst (37), who stresses the importance of considering neural–cardiac communication in the context of HRV.

To comprehensively appreciate the role that HRV measurement and manipulation has in health promotion, translation from basic to clinical research strategies is critical. To this end, the prairie vole is an example of an animal model that is used to investigate the integration of social experiences, behavior, and autonomic function (38, 39). This species is reliant on the surrounding social context for the promotion of health and behavior. Prairie voles exhibit several characteristics that mimic human social systems, including social monogamy, living in family groups, displaying biparental care of offspring, and responding negatively to social environmental disruptions (40–42). Given these characteristics, the prairie vole has been considered a useful translational model of social behavior, and the benefits of social monogamy on the endurance of this species have been discussed in the context of studies on parental behavior, pair bonding, and reproductive processes, among others (39, 42–45).

Although there is a large body of literature on prairie vole social behavior and neuroendocrine processes, research questions focused on autonomic and cardiovascular regulation using this model have only been explored over the past 10 years. This research has provided mounting evidence that the prairie vole is a valuable model for the study of social interactions and the heart (39, 46–48). The prairie vole has interesting physiological characteristics that may promote autonomic nervous system health, including a high degree of parasympathetic regulation, which in turn supports a high level of HRV (relative to other rodents, and more in line with larger mammals such as dogs and human infants) and a low resting heart rate (relative to body size scaling) (49).

Recent studies in the prairie vole model have described several autonomic correlates of behavior and physiological processes, including altered heart rate and HRV under different social conditions (50–52). This line of research has provided insight into neurobiological and behavioral processes associated with negative social experiences and stress-related disorders, including isolation, loneliness, depression, anxiety, and cardiovascular disease. For example, prairie voles exposed to social stressors display elevated heart rate, reduced HRV, impairment of endothelial-dependent vascular relaxation, cardiac arrhythmias, and cardiac gap junction protein dysregulation (38, 53–57). Some of these consequences may be due to altered neural control of peripheral processes (e.g., autonomic function, endocrine reactivity, and behavior), including changes in hypothalamic and brainstem autonomic nuclei (54, 58–61).

The issues discussed in this Frontiers research topic coupled with studies using valid and reliable animal models, will inform strategies for preventing and treating disease and facilitating good health practices. Continued dialog—such as that included in the articles focused on this HRV research topic—is crucial for ensuring that the techniques used in the laboratory are theoretically and evolutionarily grounded (37, 62–64) and are fully vetted both from a basic scientific and an applied perspective (65–68). Incorporating HRV measurement and manipulation into studies that include a translation from animal models to humans (and the reverse from human studies to the development of animal models), as well as parallel multispecies experimental protocols, will enhance our understanding of biopsychosocial factors that promote health and well-being.

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AG, the sole author, was responsible for the design of this work and interpretation of findings, drafting the work, final approval of the version to be published, and is accountable for all aspects of the work to ensure its accuracy and integrity.

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An Overview of Heart Rate Variability Metrics and Norms

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Healthy biological systems exhibit complex patterns of variability that can be described by mathematical chaos. Heart rate variability (HRV) consists of changes in the time intervals between consecutive heartbeats called interbeat intervals (IBIs). A healthy heart is not a metronome. The oscillations of a healthy heart are complex and constantly changing, which allow the cardiovascular system to rapidly adjust to sudden physical and psychological challenges to homeostasis. This article briefly reviews current perspectives on the mechanisms that generate 24 h, short-term (~5 min), and ultra-short-term (<5 min) HRV, the importance of HRV, and its implications for health and performance. The authors provide an overview of widely-used HRV time-domain, frequency-domain, and non-linear metrics. Time-domain indices quantify the amount of HRV observed during monitoring periods that may range from ~2 min to 24 h. Frequency-domain values calculate the absolute or relative amount of signal energy within component bands. Non-linear measurements quantify the unpredictability and complexity of a series of IBIs. The authors survey published normative values for clinical, healthy, and optimal performance populations. They stress the importance of measurement context, including recording period length, subject age, and sex, on baseline HRV values. They caution that 24 h, short-term, and ultra-short-term normative values are not interchangeable. They encourage professionals to supplement published norms with findings from their own specialized populations. Finally, the authors provide an overview of HRV assessment strategies for clinical and optimal performance interventions.

Keywords: biofeedback, complexity, heart rate variability, non-linear measurements, normative values, optimal performance

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HEART RATE VARIABILITY

Heart rate is the number of heartbeats per minute. Heart rate variability (HRV) is the fluctuation in the time intervals between adjacent heartbeats (1). HRV indexes neurocardiac function and is generated by heart-brain interactions and dynamic non-linear autonomic nervous system (ANS) processes. HRV is an emergent property of interdependent regulatory systems which operate on different time scales to help us adapt to environmental and psychological challenges. HRV reflects regulation of autonomic balance, blood pressure (BP), gas exchange, gut, heart, and vascular tone, which refers to the diameter of the blood vessels that regulate BP, and possibly facial muscles (2).

A healthy heart is not a metronome. The oscillations of a healthy heart are complex and non-linear. A healthy heart's beat-to-beat fluctuations are best described by mathematical chaos (3). The variability of non-linear systems provides the flexibility to rapidly cope with an uncertain and changing environment (4). While healthy biological systems exhibit spatial and temporal complexity, disease can involve either a loss or increase of complexity (5).

Higher HRV is not always better since pathological conditions can produce HRV. When cardiac conduction abnormalities elevate HRV measurements, this is strongly linked to increased risk of mortality (particularly among the elderly). Close examination of electrocardiogram (ECG) morphology can reveal whether elevated HRV values are due to problems like atrial fibrillation (6).

An optimal level of HRV is associated with health and self-regulatory capacity, and adaptability or resilience. Higher levels of resting vagally-mediated HRV are linked to performance of executive functions like attention and emotional processing by the prefrontal cortex (1). Afferent information processing by the intrinsic cardiac nervous system can modulate frontocortical activity and impact higher-level functions (7).

A BRIEF OVERVIEW OF HRV METRICS

We can describe 24 h, short-term (ST, ~5 min) or brief, and ultra-short-term (UST, <5 min) HRV using time-domain, frequency-domain, and non-linear measurements. Since longer recording epochs better represent processes with slower fluctuations (e.g., circadian rhythms) and the cardiovascular system's response to a wider range of environment stimuli and workloads, short-term and ultra-short-term values are not interchangeable with 24 h values.

Time-domain indices of HRV quantify the amount of variability in measurements of the interbeat interval (IBI), which is the time period between successive heartbeats (see **Table 1**). These values may be expressed in original units or as the natural logarithm (Ln) of original units to achieve a more normal distribution (8).

Frequency-domain measurements estimate the distribution of absolute or relative power into four frequency bands. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) divided heart rate (HR) oscillations into ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF) bands (see **Table 2**).

TABLE 1 | HRV time-domain measures.

Parameter	Unit	Description
SDNN	ms	Standard deviation of NN intervals
SDRR	ms	Standard deviation of RR intervals
SDANN	ms	Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording
SDNN index (SDNNI)	ms	Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording
pNN50	%	Percentage of successive RR intervals that differ by more than 50 ms
HR Max − HR Min	bpm	Average difference between the highest and lowest heart rates during each respiratory cycle
RMSSD	ms	Root mean square of successive RR interval differences
HRV triangular index		Integral of the density of the RR interval histogram divided by its height
TINN	ms	Baseline width of the RR interval histogram

Interbeat interval, time interval between successive heartbeats; NN intervals, interbeat intervals from which artifacts have been removed; RR intervals, interbeat intervals between all successive heartbeats.

Power is the signal energy found within a frequency band. Frequency-domain measurements can be expressed in absolute or relative power. *Absolute power* is calculated as ms squared divided by cycles per second (ms^2/Hz). *Relative power* is estimated as the percentage of total HRV power or in normal units (nu), which divides the absolute power for a specific frequency band by the summed absolute power of the LF and HF bands. This allows us to directly compare the frequency-domain measurements of two clients despite wide variation in specific band power and total power among healthy, age-matched individuals (9).

The *ULF band* (≤0.003 Hz) indexes fluctuations in IBIs with a period from 5 min to 24 h and is measured using 24 h recordings (10). The *VLF band* (0.0033–0.04 Hz) is comprised of rhythms with periods between 25 and 300 s. The *LF band* (0.04–0.15 Hz) is comprised of rhythms with periods between 7 and 25 s and is affected by breathing from ~3 to 9 bpm. Within a 5 min sample, there are 12–45 complete periods of oscillation (9). The *HF or respiratory band* (0.15–0.40 Hz) is influenced by breathing from 9 to 24 bpm (11). The *ratio of LF to HF power (LF/HF ratio)* may estimate the ratio between sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activity under controlled conditions. *Total power* is the sum of the energy in the ULF, VLF, LF, and HF bands for 24 h and the VLF, LF, and HF bands for short-term recordings (12).

Finally, *non-linear measurements* (see **Table 3**) allow us to quantify the unpredictability of a time series (13).

SOURCES OF HRV

This section explores the sources of short-term and 24 h HRV measurements. The authors will not separately discuss ultra-short-term HRV measurements since they are controversial proxies for short-term HRV values and there is an absence of research concerning their physiological origin.

SHORT-TERM HRV

Two distinct but overlapping processes generate short-term HRV measurements. The first source is a complex and dynamic

TABLE 2 | HRV frequency-domain measures.

Parameter	Unit	Description
ULF power	ms^2	Absolute power of the ultra-low-frequency band (≤0.003 Hz)
VLF power	ms^2	Absolute power of the very-low-frequency band (0.0033–0.04 Hz)
LF peak	Hz	Peak frequency of the low-frequency band (0.04–0.15 Hz)
LF power	ms^2	Absolute power of the low-frequency band (0.04–0.15 Hz)
LF power	nu	Relative power of the low-frequency band (0.04–0.15 Hz) in normal units
LF power	%	Relative power of the low-frequency band (0.04–0.15 Hz)
HF peak	Hz	Peak frequency of the high-frequency band (0.15–0.4 Hz)
HF power	ms^2	Absolute power of the high-frequency band (0.15–0.4 Hz)
HF power	nu	Relative power of the high-frequency band (0.15–0.4 Hz) in normal units
HF power	%	Relative power of the high-frequency band (0.15–0.4 Hz)
LF/HF	%	Ratio of LF-to-HF power

TABLE 3 | HRV non-linear measures.

Parameter	Unit	Description
S	ms	Area of the ellipse which represents total HRV
SD1	ms	Poincaré plot standard deviation perpendicular the line of identity
SD2	ms	Poincaré plot standard deviation along the line of identity
SD1/SD2	%	Ratio of SD1-to-SD2
ApEn		Approximate entropy, which measures the regularity and complexity of a time series
SampEn		Sample entropy, which measures the regularity and complexity of a time series
DFA α1		Detrended fluctuation analysis, which describes short-term fluctuations
DFA α2		Detrended fluctuation analysis, which describes long-term fluctuations
D_2		Correlation dimension, which estimates the minimum number of variables required to construct a model of system dynamics

relationship between the sympathetic and parasympathetic branches. The second source includes the regulatory mechanisms that control HR *via* respiratory sinus arrhythmia (RSA), the baroreceptor reflex (negative-feedback control of BP), and rhythmic changes in vascular tone (2). *RSA* refers to the respiration-driven speeding and slowing of the heart *via* the vagus nerve (14).

Dynamic Autonomic Relationship

In a healthy human heart, there is a dynamic relationship between the PNS and SNS. PNS control predominates at rest, resulting in an average HR of 75 bpm. The PNS can slow the heart to 20 or 30 bpm, or briefly stop it (15). This illustrates the response called *accentuated antagonism* (16).

Parasympathetic nerves exert their effects more rapidly (<1 s) than sympathetic nerves (>5 s) (17). Since these divisions can produce contradictory actions, like speeding and slowing the heart, their effect on an organ depends on their current balance of activity. While the SNS can suppress PNS activity, it can also increase PNS reactivity (18). *Parasympathetic rebound* may occur following high levels of stress, resulting in increased nighttime gastric activity (19) and asthma symptoms (20).

The relationship between the PNS and SNS branches is complex (both linear and non-linear) and should not be described as a "zero sum" system illustrated by a teeter-totter. Increased PNS activity may be associated with a decrease, increase, or no change in SNS activity. For example, immediately following aerobic exercise, HR recovery involves PNS reactivation while SNS activity remains elevated (21, 22).

Likewise, teaching clients to breathe slowly when they experience high levels of SNS activity can engage both branches and increase RSA. This is analogous to a Formula 1® driver speeding through a turn while gently applying the left foot to the brake, a maneuver called "left-foot braking." The complex relationship between SNS and PNS nerve activity means that the ratio between LF and HF power will not always index autonomic balance (21).

Regulatory Mechanisms

The autonomic, cardiovascular, central nervous, endocrine, and respiratory systems, and baroreceptors and chemoreceptors influence HRV over a short time period and contribute to the very-low to high frequencies of the HRV spectrum (12). Baroreceptors, which are BP sensors located in the aortic arch and internal carotid arteries, contribute to short-term HRV (23). When you inhale, HR increases. BP rises about 4–5 s later. Baroreceptors detect this rise and fire more rapidly. When you exhale, HR decreases. BP falls 4–5 s later (24, 25). The baroreflex makes this acceleration and deceleration of the heart, called RSA, possible (14).

The baroreflex links HR, BP, and vascular tone. Oscillation in one cardiovascular function causes identical oscillations in the others (26). Baroreceptor firing due to BP changes activates mechanisms that change HR and vascular tone. Rising BP triggers decreases in HR and vascular tone, while falling BP causes increases in both.

TWENTY-FOUR-HOUR HRV

Circadian rhythms, core body temperature, metabolism, the sleep cycle, and the renin–angiotensin system contribute to 24 h HRV recordings, which represent the "gold standard" for clinical HRV assessment (12). These recordings achieve greater predictive power than short-term measurements (10, 27–29). Although we calculate 24 h and short-term HRV measurements using the same mathematical formulas, they cannot substitute for each other and their physiological meaning can profoundly differ (9).

TIME-DOMAIN MEASUREMENTS

Heart rate variability time-domain indices quantify the amount of HRV observed during monitoring periods that may range from <1 min to >24 h. These metrics include the SDNN, SDRR, SDANN, SDNN Index, RMSSD, NN50, pNN50, HR Max − HR Min, the HRV triangular index (HTI), and the Triangular Interpolation of the NN Interval Histogram (TINN, see **Table 1**). Where appropriate, the authors reported accepted minimum short-term and proposed ultra-short-term measurement periods.

SDNN

The standard deviation of the IBI of normal sinus beats (SDNN) is measured in ms. "Normal" means that abnormal beats, like ectopic beats (heartbeats that originate outside the right atrium's sinoatrial node), have been removed. While the conventional short-term recording standard is 5 min (11), researchers have proposed ultra-short-term recording periods from 60 s (30) to 240 s (31). The related standard deviation of successive RR interval differences (SDSD) only represents short-term variability (9).

Both SNS and PNS activity contribute to SDNN and it is highly correlated with ULF, VLF and LF band power, and total power (32). This relationship depends on the measurement conditions. When these bands have greater power than the HF band, they contribute more to SDNN.

In short-term resting recordings, the primary source of the variation is parasympathetically-mediated RSA, especially with slow, paced breathing (PB) protocols (12). In 24 h recordings, LF band power makes a significant contribution to SDNN (9). The SDNN is more accurate when calculated over 24 h than during the shorter periods monitored during biofeedback sessions.

Longer recording periods provide data about cardiac reactions to a greater range of environmental stimulation. In addition to cardiorespiratory regulation, extended measurement periods can index the heart's response to changing workloads, anticipatory central nervous activity involving classical conditioning, and circadian processes, including sleep-wake cycles. Twenty-four-hour recordings reveal the SNS contribution to HRV (33).

The SDNN is the "gold standard" for medical stratification of cardiac risk when recorded over a 24 h period (11). SDNN values predict both morbidity and mortality. Based on 24 h monitoring, patients with SDNN values below 50 ms are classified as unhealthy, 50–100 ms have compromised health, and above 100 ms are healthy (34). Heart attack survivors, whose 24 h measurements placed them in a higher category, had a greater probability of living during a 31-month mean follow-up period. For example, patients with SDNN values over 100 ms had a 5.3 times lower risk of mortality at follow-up than those with values under 50 ms (34). Does this mean that training patients to increase SDNN to a higher category could reduce their risk of mortality?

SDRR

The standard deviation of the IBIs for all sinus beats (SDRR), including abnormal or false beats, is measured in ms. As with the SDNN, the SDRR measures how these intervals vary over time and is more accurate when calculated over 24 h because this longer period better represents slower processes and the cardiovascular system's response to more diverse environmental stimuli and workloads. Abnormal beats may reflect cardiac dysfunction or noise that masquerades as HRV.

SDANN

The standard deviation of the average normal-to-normal (NN) intervals for each of the 5 min segments during a 24 h recording (SDANN) is measured and reported in ms like the SDNN. This refers to IBIs calculated after artifacting the data. SDANN is not a surrogate for SDNN since it is calculated using 5 min segments instead of an entire 24 h time series (9) and it does not provide additional useful information (12).

SDNN Index (SDNNI)

The SDNNI is the mean of the standard deviations of all the NN intervals for each 5 min segment of a 24-h HRV recording. Therefore, this measurement only estimates variability due to the factors affecting HRV within a 5-min period. It is calculated by first dividing the 24 h record into 288 5 min segments and then calculating the standard deviation of all NN intervals contained within each segment. The SDNNI is the average of these 288 values. The SDNNI primarily reflects autonomic influence on HRV. The SDNNI correlates with VLF power over a 24-h period (12).

NN50

The number of adjacent NN intervals that differ from each other by more than 50 ms (NN50) requires a 2 min epoch.

pNN50

The percentage of adjacent NN intervals that differ from each other by more than 50 ms (pNN50) also requires a 2-min epoch. Researchers have proposed ultra-short-term periods of 60 s (31). The pNN50 is closely correlated with PNS activity (32). It is correlated with the RMSSD and HF power. However, the RMSSD typically provides a better assessment of RSA (especially in older subjects) and most researchers prefer it to the pNN50 (35). This may be a more reliable index than short-term SDNN measurements for the brief samples used in biofeedback.

RMSSD

The root mean square of successive differences between normal heartbeats (RMSSD) is obtained by first calculating each successive time difference between heartbeats in ms. Then, each of the values is squared and the result is averaged before the square root of the total is obtained. While the conventional minimum recording is 5 min, researchers have proposed ultra-short-term periods of 10 s (30), 30 s (31), and 60 s (36).

The RMSSD reflects the beat-to-beat variance in HR and is the primary time-domain measure used to estimate the vagally mediated changes reflected in HRV (12). The RMSSD is identical to the non-linear metric SD1, which reflects short-term HRV (37). Twenty-four-hour RMSSD measurements are strongly correlated with pNN50 and HF power (27). Minimum HR is more strongly correlated with LnSDANN than LnRMSSD (Ln means the natural logarithm). Maximum HR is weakly and inconsistently correlated with these time-domain measures (38).

While the RMSSD is correlated with HF power (10), the influence of respiration rate on this index is uncertain (39, 40). The RMSSD is less affected by respiration than is RSA across several tasks (41). The RMSSD is more influenced by the PNS than SDNN. Lower RMSSD values are correlated with higher scores on a risk inventory of sudden unexplained death in epilepsy (42).

NN50, pNN50, and RMSSD are calculated using the differences between successive NN intervals. Since their computation depends on NN interval differences, they primarily index HF HR oscillations, are largely unaffected by trends in an extended time series, and are strongly correlated (9).

HR Max − HR Min

The average difference between the highest and lowest HRs during each respiratory cycle (HR Max − HR Min) is especially sensitive to the effects of respiration rate, independent of vagus nerve traffic. At least a 2-min sample is required to calculate HR Max − HR Min. Instead of directly indexing vagal tone, it reflects RSA. Since longer exhalations allow greater acetylcholine metabolism, slower respiration rates can produce higher RSA amplitudes that are not mediated by changes in vagal firing.

HRV Triangular Index

The HTI is a geometric measure based on 24 h recordings which calculates the integral of the density of the RR interval histogram divided by its height (11). A 5-min epoch is conventionally used to represent this metric (43). HTI and RMSSD can jointly distinguish between normal heart rhythms and arrhythmias. When $\text{HTI} \leq 20.42$ and $\text{RMSSD} \leq 0.068$, the heart rhythm is normal. When $\text{HTI} > 20.42$, the pattern is arrhythmic (43).

Triangular Interpolation of the NN Interval Histogram

The TINN is the baseline width of a histogram displaying NN intervals (11). Like SDNN and RMSSD, contamination by only two artifacts within a 5-min segment can significantly distort its value (8).

FREQUENCY-DOMAIN MEASUREMENTS

Analogous to the electroencephalogram, we can use Fast Fourier Transformation (FFT) or autoregressive (AR) modeling to separate HRV into its component ULF, VLF, LF, and HF rhythms that operate within different frequency ranges. This is analogous to a prism that refracts light into its component wavelengths (11).

ULF BAND

The ultra-low-frequency (ULF) band ($\leq$0.003 Hz) requires a recording period of at least 24 h (12) and is highly correlated with the SDANN time-domain index (44). While there is no consensus regarding the mechanisms that generate ULF power, very slow-acting biological processes are implicated. Circadian rhythms may be the primary driver of this rhythm (12). Core body temperature, metabolism, and the renin–angiotensin system operate over a long time period and may also contribute to these frequencies (11, 45). There is disagreement about the contribution by the PNS and SNS to this band. Different psychiatric disorders show distinct circadian patterns in 24 h HRs, particularly during sleep (46, 47).

VLF BAND

The VLF band (0.0033–0.04 Hz) requires a recording period of at least 5 min, but may be best monitored over 24 h. Within a 5-min sample, there are about 0–12 complete periods of oscillation (9). While all low values on all 24 h clinical HRV measurements predict greater risk of adverse outcomes, VLF power is more strongly associated with all-cause mortality than LF or HF power (48–51). The VLF rhythm may be fundamental to health (12).

Low VLF power has been shown to be associated with arrhythmic death (44) and PTSD (52). Low power in this band has been associated with high inflammation in several studies (53, 54). Finally, low VLF power has been correlated with low levels of testosterone, while other biochemical markers, such as those mediated by the hypothalamic–pituitary–adrenal axis (e.g., cortisol), have not (55).

Very-low-frequency power is strongly correlated with the SDNNI time-domain measure, which averages 5 min standard deviations for all NN intervals over a 24-h period. There is uncertainty regarding the physiological mechanisms responsible for activity within this band (10). The heart's intrinsic nervous system appears to contribute to the VLF rhythm and the SNS influences the amplitude and frequency of its oscillations (12).

Very-low-frequency power may also be generated by physical activity (56), thermoregulatory, renin–angiotensin, and endothelial influences on the heart (57, 58). PNS activity may contribute to VLF power since parasympathetic blockade almost completely abolishes it (59). In contrast, sympathetic blockade does not affect VLF power and VLF activity is seen in tetraplegics, whose SNS innervation of the heart and lungs is disrupted (11, 60).

Based on work by Armour (61) and Kember et al. (62, 63), the VLF rhythm appears to be generated by the stimulation of afferent sensory neurons in the heart. This, in turn, activates various levels of the feedback and feed-forward loops in the heart's intrinsic cardiac nervous system, as well as between the heart, the extrinsic cardiac ganglia, and spinal column. This experimental evidence suggests that the heart intrinsically generates the VLF rhythm and efferent SNS activity due to physical activity and stress responses modulates its amplitude and frequency.

LF BAND

The LF band (0.04–0.15 Hz) is typically recorded over a minimum 2 min period (12). This region was previously called the baroreceptor range because it mainly reflects baroreceptor activity during resting conditions (1). LF power may be produced by both the PNS and SNS, and BP regulation *via* baroreceptors (11, 57, 64, 65), primarily by the PNS (66), or by baroreflex activity alone (67). The SNS does not appear to produce rhythms much above 0.1 Hz, while the parasympathetic system can be observed to affect heart rhythms down to 0.05 Hz (20 s rhythm). In resting conditions, the LF band reflects baroreflex activity and not cardiac sympathetic innervation (12).

During periods of slow respiration rates, vagal activity can easily generate oscillations in the heart rhythms that cross over into the LF band (68–70). Therefore, respiratory-related efferent vagally mediated influences are particularly present in the LF band when respiration rates are below 8.5 bpm or 7 s periods (70, 71) or when one sighs or takes a deep breath.

HF BAND

The HF or respiratory band (0.15–0.40 Hz) is conventionally recorded over a minimum 1 min period. For infants and children, who breathe faster than adults, the resting range can be adjusted to 0.24–1.04 Hz (72). The HF band reflects parasympathetic activity and is called the respiratory band because it corresponds to the HR variations related to the respiratory cycle. These phasic HR changes are known as RSA and may not be a pure index of cardiac vagal control (73).

Heart rate accelerates during inspiration and slows during expiration. During inhalation, the cardiovascular center inhibits vagal outflow resulting in speeding the HR. Conversely, during exhalation, it restores vagal outflow resulting in slowing the HR *via* the release of acetylcholine (74). Total vagal blockage virtually eliminates HF oscillations and reduces power in the LF range (12).

High-frequency power is highly correlated with the pNN50 and RMSSD time-domain measures (10). HF band power may increase at night and decrease during the day (1). Lower HF power is correlated with stress, panic, anxiety, or worry. The modulation of vagal tone helps maintain the dynamic autonomic regulation important for cardiovascular health. Deficient vagal inhibition is implicated in increased morbidity (75).

HF Power and RSA do not Represent Vagal Tone

In healthy individuals, RSA can be increased by slow, deep breathing. Respiration rate changes can produce large-scale shifts in RSA magnitude without affecting vagal tone, which is mean HR change across conditions (e.g., rest to exercise) (76). Grossman (76) proposed an experiment. If you slow your breathing to 6 bpm, you should observe increased HR fluctuations compared with 15 bpm. During this time, mean HR should not appreciably change because vagal tone did not change.

While HF power indexes vagal modulation of HR, it does not represent vagal tone. If shifts in HF power mirrored shifts in vagal tone, they should produce corresponding changes in average HR. But, breathing at different rates within the 9–24 bpm range, which changes HF power, does not change mean HR. RSA and vagal tone are dissociated during large-scale changes in SNS activity, chemical blockade of the SA node, and when intense vagal efferent traffic dramatically slows HR during inhalation and exhalation (73). Shifts in respiration rate and volume can markedly change HRV indices (HF power, RSA, pNN50, RMSSD) without actually affecting vagal tone.

LnHF can Estimate Vagal Tone under Controlled Conditions

The natural logarithm (Ln) is the logarithm to the base e of a numeric value. Under controlled conditions while breathing at normal rates, we can use LnHF power to estimate vagal tone (77).

LF/HF RATIO

The ratio of LF to HF power (LF/HF ratio) was originally based on 24 h recordings, during which both PNS and SNS activity contribute to LF power, and PNS activity primarily contributes to HF power. The intent was to estimate the ratio between SNS and PNS activity (12).

The assumptions underlying the LF/HF ratio is that LF power may be generated by the SNS while HF power is produced by the PNS. In this model, a low LF/HF ratio reflects parasympathetic dominance. This is seen when we conserve energy and engage in tend-and-befriend behaviors. In contrast, a high LF/HF ratio indicates sympathetic dominance, which occurs when we engage in fight-or-flight behaviors or parasympathetic withdrawal.

Billman (21) challenged the belief that the LF/HF ratio measures "sympatho-vagal balance" (78, 79). First, LF power is not a pure index of SNS drive. Half of the variability in this frequency band is due to the PNS and a smaller proportion is produced by unspecified factors. Second, PNS and SNS interactions are complex, non-linear, and frequently non-reciprocal. Third, confounding by respiration mechanics and resting HR creates uncertainty regarding PNS and SNS contributions to the LF/HF ratio during the measurement period.

Shaffer et al. (12) warned that the LF/HF ratio is controversial because different processes appear to generate 24 h and 5 min values, and these values correlate poorly. Furthermore, the SNS contribution to LF power varies profoundly with testing conditions. For example, when LF is calculated while sitting upright during resting conditions, the primary contributors are PNS activity and baroreflex activity—not SNS activity (63, 80). Therefore, interpretation of 5 min resting baseline LF/HF ratios depends on specific measurement conditions.

NON-LINEAR MEASUREMENTS

From Schrödinger's (81) perspective, life is aperiodic (e.g., oscillations occur without a fixed period) and operates between randomness and periodicity. Twenty-four-hour ECG monitoring yields a time series of R–R intervals (time period between successive heartbeats). Non-linearity means that a relationship between variables cannot be plotted as a straight line. Non-linear measurements index the unpredictability of a time series, which results from the complexity of the mechanisms that regulate HRV. Non-linear indices correlate with specific frequency- and time-domain measurements when they are generated by the same processes. While stressors and disorders like diabetes can depress some non-linear measurements, elevated values do not always signal health. For example, in postmyocardial infarction (post-MI) patients, increased non-linear HRV is an independent risk factor for mortality (82). This section reviews S, SD1, SD2, SD1/SD2, approximate entropy (ApEn), sample entropy (SampEn), detrended fluctuation analysis (DFA) α1 and DFA α2, and D_2 non-linear measures (see **Table 3**).

POINCARÉ PLOT

A Poincaré plot (return map) is graphed by plotting every R–R interval against the prior interval, creating a scatter plot. Poincaré plot analysis allows researchers to visually search for patterns buried within a time series (a sequence of values from successive measurements). Unlike frequency-domain measurements, Poincaré plot analysis is insensitive to changes in trends in the R–R intervals (83).

S, SD1, SD2, AND SD1/SD2

We can analyze a Poincaré plot by fitting an ellipse (curve which resembles a squashed circle) to the plotted points. After fitting the ellipse, we can derive three non-linear measurements, S, SD1, and SD2. The area of the ellipse which represents total HRV (*S*) correlates with baroreflex sensitivity (BRS), LF and HF power, and RMSSD.

The standard deviation (hence SD) of the distance of each point from the $y = x$ axis (*SD1*), specifies the ellipse's width. SD1 measures short-term HRV in ms and correlates with baroreflex sensitivity (BRS), which is the change in IBI duration per unit change in BP, and HF power. The RMSSD is identical to the non-linear metric SD1, which reflects short-term HRV (37). SD1 predicts diastolic BP, HR Max − HR Min, RMSSD, pNN50, SDNN, and power in the LF and HF bands, and total power during 5 min recordings (84, 85).

The standard deviation of each point from the $y = x +$ average R–R interval (*SD2*) specifies the ellipse's length. SD2 measures short- and long-term HRV in ms and correlates with LF power and BRS (86–89). The ratio of *SD1/SD2*, which measures the unpredictability of the RR time series, is used to measure autonomic balance when the monitoring period is sufficiently long and there is sympathetic activation. SD1/SD2 is correlated with the LF/HF ratio (83, 90).

APPROXIMATE ENTROPY

Approximate entropy measures the regularity and complexity of a time series. ApEn was designed for brief time series in which some noise may be present and makes no assumptions regarding underlying system dynamics (9). Applied to HRV data, large ApEn values indicate low predictability of fluctuations in successive RR intervals (91). Small ApEn values mean that the signal is regular and predictable (8).

SAMPLE ENTROPY

Sample entropy was designed to provide a less biased and more reliable measure of signal regularity and complexity (92). SampEn values are interpreted and used like ApEn and may be calculated from a much shorter time series of fewer than 200 values (9).

DETRENDED FLUCTUATION ANALYSIS

Detrended fluctuation analysis extracts the correlations between successive RR intervals over different time scales. This analysis results in slope α1, which describes brief fluctuations, and slope α2, which describes long-term fluctuations. The short-term correlations extracted using DFA reflect the baroreceptor reflex, while long-term correlations reflect the regulatory mechanisms that limit fluctuation of the beat cycle. DFA is designed to analyze a time series that spans several hours of data (9).

CORRELATION DIMENSION (CD, D_2)

The CD (D_2) estimates the minimum number of variables required to construct a model of system dynamics. The more variables required to predict the time series, the greater its complexity. An attractor is a set of values toward which a variable in a dynamic system converges over time. CD measures a system's attractor dimension, which can be an integer or fractal (9).

CONTEXT IS CRUCIAL WHEN INTERPRETING HRV MEASUREMENTS

Awareness of the context of recording and subject variables can aid interpretation of both 24 h and short-term HRV measurements. Important contextual factors include recording period length, detection or recording method, sampling frequency, removal of artifacts, respiration, and whether or not there is PB. Important subject variables are age, sex, HR, and health status. In addition, influences of position, movement, recency of physical activity, tasks, demand characteristics, and relationship variables can all affect measurements subtly or even greatly by changing ANS activation, breathing mechanics, and emotions.

CONTEXTUAL FACTORS

Period Length

The length of the recording period significantly affects both HRV time-domain and frequency-domain measurements (93). Since longer recordings are associated with increased HRV, it is inappropriate to compare metrics like SDNN when they are calculated from epochs of different length (11, 94). Generally, resting values obtained from short-term monitoring periods correlate poorly with 24 h indices and their physiological meanings may differ (9).

Detection Method

Electrocardiogram and PPG methods yielded discrepancies of less than 6% for most HRV measures and 29.9% for pNN50 in one study (95).

Sampling Frequency

While a minimum sampling frequency of 500 Hz may be required to detect the R-spike fiducial point of the ECG when RSA amplitude is low, a sampling rate of 125 Hz (93) or 200 Hz (9) may be sufficient when RSA amplitude is normal. Very low RR interval variability, which characterizes some heart failure patients, requires higher sampling rates for adequate temporal resolution (9). Lower sampling rates may threaten the validity of HRV frequency-domain and non-linear indices (96).

Removal of Artifacts

Visual inspection of the raw BVP or ECG signal can help detect artifacts (e.g., missed or spurious beats). Artifacts can significantly distort both time- and frequency-domain measurements (97). Artifacts increase power in all frequency bands. Missed beats produce greater increases than extra beats since deviation from a missed beat equals the mean heart period versus half the mean heart period for extra beats. The bias introduced by even a single artifact can easily eclipse the 0.5–1.0 Ln effect sizes typically found in psychophysiological research (98). When artifacts are present, researchers can select an artifact-free epoch or manually edit the affected RR intervals (99). When a clean segment is shorter than the recommended length for calculating power within a frequency band, values should be valid as long as it contains at least six full periods of oscillations. For example, estimation of LF power requires at least 2.5 min of clean data (9).

Researchers can replace technical artifacts like missed beats through interpolation based on QRS intervals that precede and follow the contaminated segment. Data analysis software like Kubios (8) can help visualize the raw signal and preserve the original record length and synchrony with other physiological signals (e.g., respiration). The editing of ectopic beats and arrhythmias can be challenging because the resulting changes in stroke volume and cardiac output can affect 10–30 beats instead of the two RR intervals that bracket the abnormal heartbeat (9).

Respiration

Greater tidal volumes and lower respiration rates increase RSA (12, 100). Increasing respiration depth raised HR Max − HR Min and did not reduce time-domain, frequency-domain, or non-linear HRV measures (101, 102). Increasing or decreasing respiration rate from a client's resonance frequency, the breathing rate that best stimulates the cardiovascular system, may lower short-term time-domain measurements and LF band power, while raising or lowering HF power, respectively.

The effect of inhalation-to-exhalation (I/E) ratio on HRV time- and frequency-domain measurements remains unclear. Lin et al. (103) reported that breathing at 5.5 bpm with a 5:5 I/E ratio resulted in higher LF power than with a 4:6 ratio. However, the authors failed to confirm that their subjects actually breathed at the required rates and ratios. Zerr et al. (84, 85) studied different I/E ratios (1:2 and 1:1) at 6 bpm and performed manipulation checks on respiration rate and I/E ratio. They found that HRV time- or frequency-domain values were comparable when healthy undergraduates breathed 6 bpm at 1:2 or 1:1 I/E ratios. A replication study by Meehan et al. (101, 102) also found that HRV time- and frequency-domain values were comparable when healthy undergraduates breathed at 6 bpm at 1:2 or 1:1 I/E ratios.

Paced Breathing

Values obtained during normal breathing and PB can vary significantly (17).

SUBJECT VARIABLES

Age

Heart rate variability time-domain measurements decline with age (17, 104–106). Bonnemeier et al. (104) obtained 24 h recordings from 166 healthy volunteers (85 men and 81 women) ages 20–70. They found the most dramatic HRV parameter decrease between the second and third decades. Almeida-Santos et al. (106) obtained 24 h ECG recordings of 1,743 subjects 40–100 years of age. They found a linear decline in SDNN, SDANN, and SDNN index. However, they discovered a U-shaped pattern for RMSSD and pNN50 with aging, decreasing from 40 to 60 and then increasing after age 70.

Sex

A meta-analysis of 296,247 healthy participants examined 50 HRV measures (107). Women had higher mean HR (smaller RR intervals) and lower SDNN and SDNN index values, especially in 24 h studies, compared to men. They showed lower total, VLF, and LF power, but greater HF power. While women showed relative vagal dominance, despite higher mean HR, men showed relative SNS dominance, despite their lower HR.

Heart Rate

Faster HRs reduce the time between successive beats and the opportunity for the IBIs to vary. This lowers HRV. Conversely, slower HRs increase the time between adjacent heartbeats and the chance for IBIs to vary. This raises HRV. This phenomenon is called *cycle length dependence* (1). Resting HRs that exceed 90 bpm are associated with elevated risk of mortality (108).

Health

Time-domain measurements rise with increased aerobic fitness (109, 110). In general, HRV time-domain measurements decline with decreased health (111, 112). Autonomic cardiac dysregulation is a critical process that underlies the manifestation and perpetuation of symptoms broad spectrum symptoms of poor health. HRV has been shown to be useful in predicting morbidities from common mental (e.g., stress, depression, anxiety, PTSD) and physical disorders (e.g., inflammation, chronic pain, diabetes, concussion, asthma, insomnia, fatigue), all of which increase sympathetic output and create a self-perpetuating cycle that produces autonomic imbalance and greater allostatic load (113–121). Thus, ANS dysfunction is a systemic common denominator of poor health and associated with acute and chronic illness and a risk factor for such serious health issues as cancer survivorship, cardiovascular disease and myocardial infarction, stroke, and overall mortality (49, 75, 122–125).

HRV NORMS

Ultra-Short-Term (UST) Measurement Norms

Ultra-short-term HRV measurements are based on less than 5 min of data (**Table 4**). Four studies reviewed in this section (31, 126–128) measured HRV during resting baselines while sitting upright or lying supine. One study (30) monitored subjects during resting baseline and Stroop test conditions.

The use of ultra-short-term recording to estimate HRV status is important because of its obvious efficiency in both clinical and research settings. However, many of the reviewed ultra-short-term studies (30, 31, 126, 130) suffered from serious methodological limitations. Since only one of the studies (128) specified their minimum criterion for acceptable concurrent validity (e.g., $r = 0.9$), we cannot know the percentage of variability in 5 min values for which their ultra-short-term measurements accounted. Since correlation between measurements doesn't ensure agreement, the authors recommend that investigators utilize the more rigorous Bland-Altman Limits of Agreement (LoA) method (131, 132) like Munoz et al. (129). This procedure calculates the 95% limits of agreement between two methods of measurement for repeated measures.

Review of this emerging literature suggests that differences in contextual factors such as recording method (BVP vs. ECG), age, health, measurement condition, artifacting procedures, and the concurrent-validity criteria used may have greater impact on ultra-short-term measurements than on longer recordings. Nonetheless, for healthy individuals, resting baselines as short as 1 min may be sufficient to measure HR, SDNN, and RMSSD as long as professionals carefully remove artifacts. The standardization of ultra-short-term measurement protocols and establishment of normative values for healthy non-athlete, optimal performance, and clinical populations remain important challenges to their use in place of conventional 5 min and 24 h values.

McNames and Aboy (130) compared 10 s to 10 min resting ECG recordings compared to 5 min recordings using archival data from PhysioNet. The strongest correlations were achieved with HF ms^2, SDSD, and RMSSD. Salahuddin et al. (30) obtained 5 min of resting ECG data from 24 healthy students and noted

TABLE 4 | Ultra-short-term (UST) norms.

Studies	Subjects	HRV monitor	Metrics and minimum epoch required to estimate short-term values
Salahuddin et al. (30)	24 healthy students Age 22–31	ECG	HR and RMSSD-10 s; pNN50, HF (ms^2 and nu), LF/HF, and LF nu-20 s; LF ms^2 and VLF ms^2-50 s; SDNN and the coefficient of variation-60 s; HTI and TINN-90 s to estimate 150 s values
Nussinovitch et al. (126)	70 healthy volunteers Age 42.5 ± 16.1	ECG	10 s and 1 min resting RMSSD values correlated with 5 min RMSSD values, but 10 s and 1 min resting SDNN did not correlate with 5 min SDNN values
Baek et al. (31)	467 healthy volunteers Age 8–69	PPG	HR-10 s; HF ms^2-20 s; RMSSD-30 s; pNN50-60 s; LF (ms^2 and nu) and HF nu-90 s; SDNN-240 s; VLF ms^2-270 s to estimate 5 min values. Minimum values differed by age group
Munoz et al. (129)	3,387 adults (1,727 W and 1,660 M) Mean age 53	Portapres®	Near-perfect agreement of 120 s RMSSD and SDNN values with 240–300 s values. UST RMSSD values achieved stronger agreement with 240–300 s values than UST SDNN for all record lengths and agreement metrics (Pearson *r*, Bland-Altman, and Cohen's *d*)
Shaffer et al. (128)	38 healthy students Age 18–23	ECG	HR-10 s; NN50, and pNN50-60 s; TINN, LF ms^2, SD1, and SD2-90 s; HTI and DFA α1-120 s; LF nu, HF ms^2, HF nu, LF/HF, SampEn, DFA α2, and DET-180 s; ShanEn-240 s; VLF ms^2-270 s to estimate 5 min values. No epoch estimated CD

Coefficient of variation, ratio of the standard deviation to the mean; CD (also D_2), correlation dimension, which is the minimum number of variables required to construct a model of system dynamics; DET, determinism of a time series; DFAα1, detrended fluctuation analysis, which describes short-term fluctuations; DFA α2, detrended fluctuation analysis, which describes long-term fluctuations; ECG, electrocardiogram; HF ms^2, absolute power of the high-frequency band; HF nu, relative power of the high-frequency band in normal units; HR, heart rate; HTI, HRV triangular index or integral of the density of the NN interval histogram divided by its height; LF ms^2, absolute power of the low-frequency band; LF nu, relative power of the low-frequency band in normal units; LF/HF, ratio of LF-to-HF power; NN interval, time between adjacent normal heartbeats; nu, normal units calculated by dividing the absolute power for a specific frequency band by the summed absolute power of the LF and HF bands; pNN50, percentage of successive interbeat intervals that differ by more than 50 ms; RMSSD, root mean square of successive RR interval differences; RR interval, time between all adjacent heartbeats; SampEn, sample entropy, which measures signal regularity and complexity; SD1, Poincaré plot standard deviation perpendicular to the line of identity; SD2, Poincaré plot standard deviation along the line of identity; SDNN, standard deviation of NN intervals; ShanEn, Shannon entropy, which measures uncertainty in a random variable; TINN, triangular interpolation of the RR interval histogram or baseline width of the RR interval histogram; VLF ms^2, absolute power of the very-low-frequency band.

that valid estimation of values from ultra-short-term recordings required differing lengths for different HRV variables: mean HR and RMSSD required 10 s; PNN50, HF (ms^2 and nu), LF/HF, and LF nu required 20 s; LF ms^2 required 30 s; VLF ms^2 required 50 s; SDNN; the coefficient of variance required 60 s; HRV Index and TINN required 90 s; and the Stress Index required 100 s.

Similarly, Baek et al. (31) estimated 5 min resting PPG HRV values from 467 healthy volunteers with ultra-short-term recordings. HR required 10 s, HF ms^2 required 20 s, RMSSD required 30 s, pNN50 required 60 s, LF (ms^2 and nu), HF nu, and LF/HF ms^2 required 90 s, SDNN required 240 s, and VLF ms^2 required 270 s. These minimum periods also differed by age group.

When Nussinovitch et al. (126) compared 10 s and 1 min resting ECG recordings with 5 min recordings from 70 healthy volunteers, ultra-short-term RMSSD measurements achieved acceptable correlations, but SDNN did not achieve acceptable correlations with the longer short-term recordings.

Munoz et al. (129) measured SDNN and RMSSD in 3,387 adults and analyzed data using Pearson's correlation coefficients, the Bland-Altman LoA method, and Cohen's *d*. At 120 s, recordings achieved nearly perfect agreement with 240–300 s values ($r = 0.956$, bias $= 0.406$ for SDNN and 0.986, bias $= 0.014$ for RMSSD).

Shaffer et al. (128) recorded 5 min of resting ECG data from 38 healthy undergraduates and manually artifacted the IBIs. They correlated 10, 20, 30, 60, 90, 120, 180, and 240 s HRV metrics with 5 min metrics. The authors selected a conservative criterion of $r = 0.90$ to ensure that ultra-short-term values would account for at least 81% of the variability in 5 min values. A 10 s segment estimated mean HR. A 60 s segment measured SDNN, RMSSD, NN50, and pNN50. A 90 s segment calculated TINN, LF ms^2, SD1, and SD2. A 120 s segment approximated HTI and DFA α1. A 180 s segment computed LF nu, HF ms^2, HF nu, LF/HF ms^2, SampEn, DFA α2, and DET. A 240 s segment assessed ShanEn. No UST measurement successfully estimated CD.

SHORT-TERM MEASUREMENT NORMS

Short-term measurement norms are based on ~5 min of HRV data (**Table 5**). Because of their relative ease of recording, short-term measurements have been widely used and studied for many years, and appear to be the most commonly found source of published HRV data (11, 60). Short-term values are only appropriate when clients breathe at normal rates (~11–20 bpm). During resonance frequency biofeedback, the only relevant metrics are LF ms^2 or peak frequency since breathing from 4.5 to 7.5 bpm concentrates HR oscillations around 0.1 Hz in the LF band.

Berkoff et al. (133) reported short-term norms from 145 elite track-and-field athletes (87 men and 58 women), 18–33 years, who were measured before the 2004 USA Olympic Trials. The investigators monitored the athletes in the supine position for 2.5 min using ECG after up to 5 min of rest to stabilize HR. These authors used the Fast Fourier transformation (FFT) method to perform power spectral analysis. They reported mean and standard deviation values by sex for the time-domain measures of SDNN, RMSSD, and pNN50 and the frequency-domain measures of LF (ms^2 and nu), HF (ms^2 and nu), LF/HF (LF/HF and LF/HF nu), and total power. Female athletes showed greater values

TABLE 5 | Short-term ECG norms.

Studies	Subjects	Spectral analysis	Breathing	Sample	Position	Metrics
Berkoff et al. (133)	145 elite athletes (87 M and 58 W) age 18–33	FFT	Free	2.5 min	Supine	SDNN, RMSSD, pNN50, LF (ms^2 and nu), HF (power and nu), LF/HF (% and nu), and total power
Nunan et al. (17)	21,438 healthy adults (12,960 M and 8,474 W) age ≥ 40	AR and FFT	Free/paced	Varied	Varied	RR, SDNN, RMSSD, LF (ms^2 and nu), HF (ms^2 and nu), and LF/HF
Abhishekh et al. (105)	189 healthy adults (114 M and 75 W) age 16–60		Free	5 min	Supine	SDNN, RMSSD, LF (ms^{2}and nu), HF (ms^2 and nu), LF/HF, and total power (ms^2)
Seppälä et al. (134)	465 prepubertal children (239 B) and 226 G age 6–8	FFT	Free	5 min	Supine	RR, HR, SDNN, RMSSD, pNN50, HTI, TINN, LF (peak, ms^2, %), HF (peak, ms^2, %), LF/HF, SD1, SD2, SD1/SD2, SampEn, D_2, DFA (α1 and α2) for 5th, 25th, 50th, 75th, and 95th percentiles

D_2 (also CD), correlation dimension, which estimates the minimum number of variables required to construct a model of a studied system; DFA α1, detrended fluctuation analysis, which describes short-term fluctuations; DFA α2, detrended fluctuation analysis, which describes long-term fluctuations; ECG, electrocardiogram; HF ms^2, absolute power of the high-frequency band; HF nu, relative power of the high-frequency band in normal units; HF peak, highest amplitude frequency in the HF band; HF%, HF power as a percentage of total power; HR, heart rate; HTI, HRV triangular index or integral of the density of the NN interval histogram divided by its height; LF ms^2, absolute power of the low-frequency band; LF nu, relative power of the low-frequency band in normal units; LF peak, highest amplitude frequency in the LF band; LF%, LF power as a percentage of total power; LF/HF, ratio of LF-to-HF power; NN interval, time between adjacent normal heartbeats; nu, normal units calculated by dividing the absolute power for a specific frequency band by the summed absolute power of the LF and HF bands; pNN50, percentage of successive interbeat intervals that differ by more than 50 ms; RMSSD, root mean square of successive RR interval differences; RR interval, time between all adjacent heartbeats; SampEn, sample entropy, which measures signal regularity and complexity; SD1, Poincaré plot standard deviation perpendicular to the line of identity; SD2, Poincaré plot standard deviation along the line of identity; SD1/SD2, ratio of SD1 to SD2 that measures the unpredictability of the R–R time series and autonomic balance under appropriate monitoring conditions; SDNN, standard deviation of NN intervals; TINN, triangular interpolation of the RR interval histogram or baseline width of the RR interval histogram; total power, sum of power (ms^2) in VLF, LF, and HF bands.

for pNN50 and HF nu than male athletes. Male athletes showed greater values for LF nu and LF/HF ratio than female athletes. Type of sport (distance runners, field athletes, power athletes, sprinters, and strength athletes) did not affect HRV measures.

Normative data from short-term HRV studies published after the Task Force Report (11) were reviewed by Nunan et al. (17) (**Table 6**). The 44 selected studies meeting their criteria involved 21,438 healthy adult participants. This analysis included three large populations with a minimum age of 40 (135–137) which may explain their comparatively lower HRV values. The authors reported HRV values according to whether breathing was free or paced, sex, and spectral power analysis, autoregressive (AR) or FFT. They reported mean absolute and mean log-transformed values for mean RR, SDNN, RMSSD, LF (ms^2 and nu), HF (ms^2 and nu), and the LF/HF ratio. The selected studies showed greater agreement on time-domain measures (SDNN had the lowest coefficient of variation) than did frequency-domain measures (HF ms^2 and log-transformed HF showed the largest variation). The FFT method resulted in lower LF power, greater HF power (ms^2 and log-transformed), and greater LF/HF ratio than the AR method. PB resulted in higher values on all HRV indices except LF ms^2, which was greatest during free breathing.

More recently, Abhishekh et al. (105) studied 189 healthy participants (114 men and 75 women) who ranged from 16 to 60 years of age. They analyzed 5 min artifact-free supine ECG recordings obtained while participants breathed between 12 and 15 bpm. They reported SDNN and RMSSD time-domain measures, and LF (ms^2 and nu), HF (ms^2 and nu), the LF/HF ratio, and total power frequency-domain measures. The authors found a negative correlation of RMSSD, SDNN, and total power with age. While HF nu was negatively correlated with age, LF/HF ratio was positively correlated. These correlations suggested that sympathetic tone increases with age.

TABLE 6 | Nunan et al. (17) short-term norms.

HRV measure	Mean (SD)	Range	Studies
IBI (ms)	926 (90)	785–1,160	30
SDNN (ms)	50 (16)	32–93	27
RMSSD (ms)	42 (15)	19–75	15
LF (ms^2)	519 (291)	193–1,009	35
LF (nu)	52 (10)	30–65	29
HF (ms^2)	657 (777)	83–3,630	36
HF (nu)	40 (10)	16–60	30
LF/HF (ms^2)	2.8 (2.6)	1.1–11.6	25

IBI, interbeat interval; SDNN, standard deviation of NN intervals; RMSSD, root mean square of successive RR interval differences; LF ms^2, absolute power of the low-frequency band; LF nu, relative power of the low-frequency band in normal units; HF ms^2, absolute power of the high-frequency band; HF nu, relative power of the high-frequency band in normal units; LF/HF, ratio of LF-to-HF power.
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Seppälä et al. (134) monitored 465 prepubertal children (239 boys and 226 girls) 6–8 years of age. They obtained 1 and 5 min resting ECG recordings. They performed power spectral analysis using the FFT method. They reported mean RR interval and HR, SDNN, RMSSD, pNN50, HTI, and TINN HRV time-domain measures, LF (peak, ms^2, and %), HF (peak, ms^2, and %), LF/HF ms^2, and SD1, SD2, SD1/SD2, SampEn, D2, and DFA (α1 and α2) non-linear measures. The authors reported 1 and 5 min reference values for these parameters for the 5th, 25th, 50th, 75th, and 95th percentiles and concluded that the same values could be used for both boys and girls since there were no gender differences. They argued that HRV parameters that reflect parasympathetic HR modulation (RMSSD, pNN50, HF ms^2, and SD1) could be reliably measured using 1 min recordings. However, HTI, TINN, LF ms^2, SD2, and relative LF and HF power, and SD1/SD2, require 5 min recordings due to the longer rhythms that comprise LF-band activity.

TWENTY-FOUR HOUR MEASUREMENT NORMS

Twenty-four-hour norms are obtained using ambulatory HRV monitoring (**Table 7**). The technology for recording and interpreting long-term "naturalistic" HR adjustments is rapidly advancing and the subject of another article in this issue (138). In the classic paper on the subject, The Task Force Report (11) reported 24 h norms for 144 healthy subjects that included cutoffs for moderately depressed and highly depressed HRV and for increased risk of mortality. The authors reported 24 h time-domain measures of SDNN, SDANN, RMSSD, and the HRV HTI, and supine 5 min frequency-domain measures for LF power (LF ms^2 and nu), HF power (HF ms^2 and nu), LF/HF power, and total power (ms^2).

TABLE 7 | Twenty-four-hour HRV norms.

Studies	Subjects	Metrics
Task Force Report (11)	274 healthy subjects (202 M and 72 F), age 40–69	24 h SDNN, SDANN, RMSSD, HTI and 5 min supine LF power (ms^2 and nu), HF power (HF ms^2 and HF nu), LF/HF power, and total power
Umetani et al. (32)	260 healthy subjects (122 M and 148 W), age 10–99	SDNN, SDANN, SDNNI, RMSSD, pNN50, and HR by decade
Beckers et al. (4)	276 healthy subjects (141 M and 135 W), age 18–71	SDNN, RMSSD, and pNN50, total power, LF (ms^2 and %), HF (ms^2 and %), and LF/HF ratio, and non-linear measures, 1/*f*, FD, DFA α1 and α2, CD, S, and LE
Bonnemeier et al. (139)	166 healthy subjects (85 M and 81 W), age 20–70	RMSSD, SDNN, SDNNI, SDANN, NN50, and HTI
Aeschbacher et al. (140)	2,079 subjects (972 M and 1,107 W), age 25–41	HR, SDNN, LF ms^2 and HF ms^2
Almeida-Santos et al. (106)	1,743 subjects (616 M and 1,127 W), age 40–100	SDNN, SDANN, SDNNI, RMSSD, and pNN50

1/f, 1 divided by frequency slope, which characterizes the shape of the HRV frequency spectrum; CD, correlation dimension, which estimates the minimum number of variables required to construct a model of a studied system; DFA α1, detrended fluctuation analysis, which describes short-term fluctuations; DFA α2, detrended fluctuation analysis, which describes long-term fluctuations; ECG, electrocardiogram; FD, signal regularity; HF ms^2, absolute power of the high-frequency band; HF nu, relative power of the high-frequency band in normal units; HF peak, highest amplitude frequency in the HF band; HF%, HF power as a percentage of total power; HR, heart rate; HTI, HRV triangular index or integral of the density of the NN interval histogram divided by its height; LE, Lyapunov exponent, which measures a non-linear system's sensitive dependence on starting conditions; LF ms^2, absolute power of the low-frequency band; LF nu, relative power of the low-frequency band in normal units; LF peak, highest amplitude frequency in the LF band; LF%, LF power as a percentage of total power; LF/HF, ratio of LF-to-HF power; NN interval, time between adjacent normal heartbeats; nu, normal units calculated by dividing the absolute power for a specific frequency band by the summed absolute power of the LF and HF bands; pNN50, percentage of successive interbeat intervals that differ by more than 50 ms; RMSSD, root mean square of successive RR interval differences; RR interval, time between all adjacent heartbeats; S, area of an ellipse fitting a Poincaré plot, which represents total HRV; SampEn, sample entropy, which measures signal regularity and complexity; SD1, Poincaré plot standard deviation perpendicular to the line of identity; SD2, Poincaré plot standard deviation along the line of identity; SD1/SD2, ratio of SD1 to SD2 that measures the unpredictability of the RR time series and autonomic balance under appropriate monitoring conditions; SDNN, standard deviation of NN intervals; TINN, triangular interpolation of the RR interval histogram or baseline width of the RR interval histogram; total power, sum of power (ms^2) in ULF, VLF, LF, and HF bands.

Umetani et al. (32) published 24 h norms for 260 healthy participants (112 men and 148 women) who ranged from 10 to 99 years old. The authors reported means, standard deviations, and 95% confidence intervals for 24 h HRV time-domain measures of SDNN, SDANN, SDNN index, RMSSD, and pNN50, and HR by decade. They analyzed the relationship between each HRV time-domain measure with HR and age, compared HR and HRV measures between decades and two-decade spans. They reported that several HRV time-domain indices declined with age. After age 65, subjects fell below cutoffs for increased threat of mortality. Before age 30, female subjects had lower HRV measurements than their male counterparts. This gender difference vanished after 50 years of age.

Beckers et al. (4) obtained 24 h ECG recordings of 276 healthy participants (141 men and 135 women) 18–71 years of age. They performed power spectral analysis using the FFT method and divided the 24 h recordings into daytime and nighttime. The authors reported day and night time-domain measures, SDNN, RMSSD, and pNN50, frequency-domain measures, total power (ms^2), LF (ms^2 and %), HF (ms^2 and %), and LF/HF ratio, and non-linear measures, 1/frequency slope (1/*f*), fractal dimension (FD), DFA α1 and α2, CD, % of CD difference, S value, and Lyapunov exponent. Both linear and non-linear metrics decreased with age. The authors found that non-linear values were higher at night, did not differ by sex, and decreased with age.

Bonnemeier et al. (139) recorded 24 h ECG for 166 healthy volunteers (85 men and 81 women) aged 20–70. They obtained hourly and 24 h RMSSD, SDNN. SDNNI, SDANN, NN50, and HTI values. All 24 h HRV values declined with age. The attenuation of HRV parameters with age mainly occurred during nighttime. The largest decrease occurred during the second and third decades. Following this drop, the decline was gradual. SDNNI, NN50, and RMMSD correlated most strongly with aging. Mean 24 h RR interval, SDNN, SDNNI (SD for all 5 min intervals) and SDANN were significantly higher in men. Gender differences diminished with age.

Aeschbacher et al. (140) recorded 24 h ambulatory ECGs and assessed the lifestyles of 2,079 subjects (972 men and 1,107) aged 25–41. They obtained HR, SDNN, and LF and HF power. SDNN was 160 ± 40 (men) and 147 ± 36 (women). LF power was 1,337 ms^2 (men) and 884 ms^2 (women). HF power was 289 ms^2 (men) and 274 ms^2 (women). The authors reported that only a minority of their sample had healthy lifestyles and that lifestyle scores were associated with 24 h SDNN values.

Almeida-Santos et al. (106) obtained 22–24 h ambulatory ECGs from 1,743 participants (616 men and 1,127 women) aged 40–100. While their sample included comorbidities like dyslipidemia and hypertension, they were capable of performing the activities of daily living. The authors calculated HRV time-domain measures of SDNN, SDANN, SDNNI, RMSSD, and pNN50. HRV linearly declined with age. SDNN, SDANN, SDNNI, RMSSD, and PNN50 were higher in men than women. RMSSD and pNN50 showed a U-shaped pattern with aging, decreasing from 40 to 60 and then increasing from 70. The authors concluded that global autonomic regulation decreases linearly with aging and is lower in men, diabetics, and obese individuals.

ASSESSMENT IN CLINICAL AND OPTIMAL PERFORMANCE INTERVENTIONS

The selection of HRV time-domain, frequency-domain, and non-linear measurements and norms to assess progress in clinical and optimal performance interventions should be informed by peer-reviewed studies. Professionals training specialized populations (e.g., chronic pain patients) might supplement published norms for the general population with values from their own clients. The rigorous data reporting guidelines proposed by Laborde et al. (93) could guide their efforts to publish their norms to remedy gaps in the literature. The metrics most strongly correlated with clinical improvement and athlete performance gains in these reports could be incorporated in pretreatment/posttreatment, within-session, and across-session assessment. While a full treatment of HRV variables in relation to the HRV biofeedback intervention is beyond the scope of this article, we will briefly touch on the issues that seem to us to be the key ones (141).

In addition to the primary literature, the Association for Applied Psychophysiology and Biofeedback has published two references that identify metrics associated with clinical and optimal performance outcomes, *Evidence-Based Practice in Biofeedback and Neurofeedback* (3rd ed.) and *Foundations of Heart Rate Variability Biofeedback: A Book of Readings* (142, 143). Further, readers might consult Gevirtz, Lehrer, and Schwartz's excellent chapter on Cardiorespiratory Biofeedback in Schwartz and Andrasik's (Eds.) *Biofeedback: A Practitioner's Guide* (4th ed.).

PRETREATMENT/POSTTREATMENT ASSESSMENT

Twenty-four-hour HRV monitoring before and after a series of HRV biofeedback training sessions provides the most valid measurements of ULF, VLF, total power, and LF/HF-domain indices (12). Moreover, 24 h time-domain measurements like SDNN achieve prognostic power that ultra-short-term and short-term measurements cannot. Successful HRV biofeedback should result in increased power in all individual frequency bands, total power, and LF/HF ratio, and relevant time-domain and non-linear values.

Where 24 h HRV assessment is not feasible, short-term (~5 min) resting measurements without feedback or pacing, and while breathing at normal rates can help evaluate physiological change. Successful HRV biofeedback should increase LnHF (which may index vagal tone under controlled conditions), RSA, and possibly LF and total power, and relevant time-domain and non-linear values. Autonomic (finger temperature and skin conductance/potential) and respiratory (end-tidal CO_2 and respiration depth, rate, and rhythmicity) indices can complement HRV measurements. Successful HRV biofeedback may increase finger temperature, decrease skin conductance/potential, increase end-tidal CO_2 to between 35 and 45 torr, increase respiration depth, slow respiration rate below 16 bpm, and increase rhythmicity in respirometer and HR waveforms (144).

WITHIN- AND ACROSS-SESSION ASSESSMENT

Short-term resting HRV, autonomic, and respiratory measurements without feedback or pacing, and while breathing at normal rates can be obtained during pre- and posttraining baselines for within-session assessment or across the pretraining baselines of successive sessions. For both within- and across-session assessment, successful HRV biofeedback training should result in the same pattern of physiological change as described the previous section on short-term resting pretreatment/posttreatment assessment. While increased VLF power in 24 h HRV assessment is consistent with improved health, this change during short-term assessment may indicate training difficulty, *vagal withdrawal*, due to excessive effort (56). Where short-term assessment does not involve physical exercise or stress trials, the LF/HF ratio may not index of autonomic balance since there will be no significant SNS activation to measure (12).

ASSESSMENT DURING HRV BIOFEEDBACK TRIALS

During HRV biofeedback training, adults may be instructed to engage in paced abdominal breathing between 4.5 and 7.5 bpm guided by a real-time display of instantaneous HR and respiration. As clients' breathing approaches their *resonance frequency*, the rate that most strongly stimulates their baroreceptor reflex, RSA will increase (141). Since respiration rate helps to determine the peak HRV frequency (the frequency with the highest amplitude), successful training should produce a lower peak frequency and greater LF power than a resting baseline obtained when clients breathe from 12 to 15 bpm. PB at 6 bpm should result in a spectral peak at 0.1 Hz, while breathing at 7.5 bpm should create a peak at 0.125 Hz. Both 6 and 7.5 bpm rates will also increase power in the LF, which ranges from 0.04 to 0.15 Hz.

SUMMARY

Autonomic efferent neurons and circulating hormones modulate SA node initiation of heartbeats. The interdependent regulatory systems that generate the complex variability of a healthy heart operate over different time scales to achieve homeostasis and optimal performance. Circadian oscillations in circadian variations in core body temperature, metabolism, sleep–wake cycles, and the renin–angiotensin system contribute to 24 h HRV measurements. The complex dynamic relationship between the sympathetic and parasympathetic branches, and homeostatic regulation of HR *via* respiration and the baroreceptor reflex are responsible for short-term and ultra-short-term HRV measurements. Since slower regulatory mechanisms contribute to HRV metrics recorded over longer measurement periods, 24 h, short-term, and ultra-short-term values are not interchangeable.

Clinicians and researchers measure HRV using time-domain, frequency-domain, and non-linear indices. Time-domain values measure how much HRV was observed during the monitoring period. Recording period length strongly influences time-domain values. Shorter epochs are associated with smaller values and poorly estimate 24 h values (17). For example, where 24 h SDNN values predict future heart attack risk, 5 min SDNN values do not (12).

Frequency-domain values calculate absolute or relative signal power within the ULF, VLF, LF, and HF bands. Recording period length limits HRV frequency-band measurement. Minimum recommended periods include: ULF (24 h), VLF (5 min, 24 h preferred), LF (2 min), and HF (1 min). Again, short-term epochs (~5 min) lack the prognostic power of 24 h measurements for morbidity and mortality.

Non-linear indices measure the unpredictability and complexity of a series of IBIs. The relationship between non-linear measurements and illness is complex. While stressors and disease lower some non-linear indices, in cases like myocardial infarction, higher non-linear HRV predicts a greater risk of mortality.

The expanding literature on ultra-short-term, short-term, and 24 h HRV norms requires careful interpretation. Due to the lack of standardization of ultra-short-term measurement protocols, concurrent validity criteria, and normative values for healthy non-athlete, optimal performance, and clinical populations, clinicians should not use ultra-short-term interchangeably with 5 min and 24 h values.

Short-term measurement norms can contribute to assessment before, during, and after HRV biofeedback training for both clinical and optimal performance. Since short-term measurement norm studies vary in detection method (ECG or PPG), frequency-band cutoffs, power spectral analysis method (AR or FFT), position (sitting upright or lying supine), respiration rate, and breathing pacing (paced or free breathing) and subject sex, age, and aerobic fitness, the selection of appropriate norms is crucial. Likewise, 24 h HRV norms can guide HRV biofeedback training for clinical and optimal performance. As with short-term measurement norms, frequency-band cutoffs, power spectral analysis method (AR or FFT), and subject sex, age, and aerobic fitness can help to determine the selection of reference values.

The selection of HRV time-domain, frequency-domain, and non-linear metrics to assess progress in clinical and optimal performance interventions can be guided by peer-reviewed studies and supplemented by values from specialized populations. The HRV metrics most strongly correlated with clinical improvement and athlete performance gains in these reports might be incorporated in pretreatment/posttreatment, within-session, and across-session assessment. Finally, LF-band power and RSA will increase during successful HRV biofeedback trials due to PB in the 4.5–7.5 bpm range.

AUTHOR CONTRIBUTIONS

FS reviewed the literature, revised JG's article outline, wrote the initial abstract, manuscript, and table drafts, and revised the second drafts following feedback from JG. JG reviewed the literature, proposed an article outline, created and maintained an EndNote database, contributed sections of the initial drafts, and made editorial suggestions for the second drafts. Both FS and JG discussed the conceptual issues and themes for the review article.

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New Frontiers in Heart Rate Variability and Social Coherence Research: Techniques, Technologies, and Implications for Improving Group Dynamics and Outcomes

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Concepts embraced by the term coherence have been identified as central to fields such as quantum physics, physiology, and social science. There are different types of coherence, although the term always implies a harmonious relationship, correlations and connections between the various parts of a system. A specific measure derived from heart rate variability (HRV) provides a measure of physiological coherence. Another type of coherence, social coherence, relates to the harmonious alignment between couples or pairs, family units, small groups, or larger organizations in which a network of relationships exists among individuals who share common interests and objectives. A high degree of social coherence is reflected by stable and harmonious relationships, which allows for the efficient flow and utilization of energy and communication required for optimal collective cohesion and action. Social coherence requires that group members are attuned and are emotionally connected with each other, and that the group's emotional energy is organized and regulated by the group as a whole. A number of studies are reviewed which have explored various types of synchronization in infants, pairs and groups, indicating that feelings of cooperation, trust, compassion and increased prosocial behaviors depends largely on the establishment of a spontaneous synchronization of various physiological rhythms between individuals. This article discusses a new application using HRV monitoring in social coherence research and the importance of physiological synchronization in group developmental processes and dynamics. Building on the extensive body of research showing that providing feedback of HRV coherence level at the individual level can improve self-regulation, we suggest the following hypotheses: (1) providing feedback of individual and collective HRV coherence and the degree of heart rhythm synchronization will increase group coherence, and heart rhythm synchronization among group members. (2) Training in techniques to increase group coherence and heart rhythm synchronization will correlate with increased prosocial behaviors, such as kindness and cooperation among individuals, improved communication, and decreases in social discord and adversarial interactions. (3) Biomagnetic fields produced by the heart may be a primary mechanism in mediating HRV synchronization among group members. Data supporting each of the hypothesis is discussed.

Keywords: heart rate variability, social, coherence, self-regulation, synchronization, entrainment

INTRODUCTION

Research in evolutionary anthropology suggests that one of the primary drivers of evolution of the human species is our advanced capacities for social interaction and cooperation (1, 2). This research also suggests that humans are hard-wired to seek social connections and secure attachments, independent of maturational stage, and culture (3). Most people spend a sizeable amount of time communicating, interacting and performing tasks with others. Indeed, being a member of various groups across one's lifespan is an inescapable, and often sought after, aspect of our lives. Some of our most precious moments are those of intimate connection. Terms such as social coherence, social support, social connection, social functioning, loneliness, and social isolation are used to describe various aspects of human social functioning. The importance of developing skills and behaviors and being able to successfully connect, cooperate and collaborate with others is of great importance.

Social incoherence not only affects the way we feel, relate, and communicate with others but also affects physiological processes that disrupt good health. In fact, when it comes to public health, social coherence and connection may be one of the most important public health priorities. The importance of social connections was highlighted by the sobering work of James Lynch who found that loneliness, itself, is a greater risk for heart disease than lack of exercise, smoking, excessive alcohol consumption, and obesity combined (4). Numerous studies have found that individuals experiencing social or cultural changes, or living in circumstances of social instability, disorganization, or isolation are at increased risk of acquiring numerous diseases (5–9). A meta-analysis of social relationships confirmed that when risk for mortality is controlled for based on well-established risk factors, there is a 50% increased likelihood of survival for people with healthy social relationships (10). Furthermore, numerous studies of various populations, regardless of geography or culture, have found that when individuals have close and meaningful relationships, they have reduced risk of mortality and susceptibility to chronic and infectious disease, have improved outcomes in pregnancy and childbirth (11–13) and live happier and healthier lives (10). The importance of social coherence for people's health, as well as for team and organizational performance and societal harmony highlights the need for programs that strengthen people's capacity for mental and emotional self-management and focus on increasing social coherence. Fortunately, to address what ails both individuals and groups in situations of social incoherence, there are practical steps and practices that can help increase and stabilize group coherence and resilience in organizations, teams, schools and communities.

In the context of facilitating social coherence, we (colleagues and collaborators) introduce following hypotheses: (1) Providing feedback of individual and collective heart rate variability (HRV) coherence and the degree of heart rhythm synchronization between group members will facilitate increases in the group's coherence, and heart rhythm synchronization. (2) Training in techniques to increase group coherence and heart rhythm synchronization will correlate with increased prosocial behaviors, such as kindness and cooperation among individuals, improved communication, and decreases in social discord and adversarial interactions. (3) Biomagnetic fields produced by the heart may be a primary mechanism in mediating HRV synchronization among group members.

To support our hypotheses, we briefly review several types of coherence that are relevant to physiological processes and social coherence, and discuss the dynamic interplay between the two. We also explore emerging techniques and technologies to enhance social coherence. More specifically, we discuss a new application using HRV monitoring in social coherence research, and the importance of physiological synchronization in developmental processes and group interactional dynamics. Our primary hypotheses build on extensive research showing that providing HRV coherence feedback to facilitate skill acquisition of self-regulation techniques improves a wide range of health and performance outcomes. See Ref. (14, 15) for a summary.

COHERENCE

As an overarching concept, coherence embraces several related phenomena that we will touch upon throughout the article: cross-coherence, entrainment, auto-coherence, and synchronization (14). Coherence always implies correlations, connectedness, consistency, efficient energy utilization, and typically refers to a global order, where the whole is greater than the sum of its individual parts.

In physics, cross-coherence is the term used to express the amount of synchronized activity among separate oscillating systems. When two or more systems have the same frequency range, they can become phase or frequency-locked as can occur in the human body when respiratory, blood pressure and heart rhythms, shift into an optimal state at the resonant frequency of the cardiovascular system (14). In this case, they are said to be entrained, however, different rhythms can be synchronized to varying degrees and not be entrained. Synchronization is an aspect of coherence that describes the coordination of distinct events that are acting in harmony whether concurrently or sequentially in an enduring patterned organization, between two or more events. In the context of social coherence, various mathematical measures of cross-coherence can be used to assess the degree of pairwise synchronization occurring between physiological rhythms, such as heart rhythms and brain waves of two or more individuals (16).

The term *auto-coherence*, sometimes called auto-correlation in mathematics, describes the order in a single waveform produced by an oscillating system, or the output of multiple complex interacting systems. For example, when the rhythm of the heart, exhibits sine wave-like output, the more stable the amplitude, frequency, and shape of the wave, the higher the degree of auto-coherence. When an oscillatory system has a high degree of auto-coherence and is coupled to other systems, it can pull the other systems into increased synchronization or entrainment, which reflects a more energy efficient and healthier system (17).

Thus, we use the term coherence in the broader sense to describe the degree of order, harmony, and stability in various rhythmic activities, which reflects the regulation of interconnected biological, social, and environmental networks. The assessment of physiological coherence (also referred to as heart coherence, resonance, cardiac coherence, or personal coherence) refers to auto-coherence (stability of a single waveform such as respiration or HRV patterns), and system resonance (18). In the context of this article, we will use the term synchronization to distinguish where we are referring to measures that are used to assess cross-coherence between pairs of individuals.

HRV COHERENCE

The primary measure used to assess physiological or personal coherence is HRV. The most commonly used HRV analysis methods are frequency domain (power spectrums) and time statistical measures of variance in the inter-beat intervals (time domain), which are almost exclusively used to quantify the amount of HRV that occurred over a specific time period. As there are numerous reviews on the various measures of HRV and their underlying physiological mechanisms and interpretations, we will therefore not summarize them here (19–22).

Importantly, we have observed that specific emotional states are reflected in the patterns of the HRV rhythm as opposed to changes in the amount of HRV, and that emotions such as appreciation or compassion are associated with a more coherent rhythm, as opposed to emotions such as anxiety, frustration or impatience. "A coherent heart rhythm is defined as a relatively harmonic (sine wave-like) signal with a very narrow, high-amplitude peak in the low frequency region (typically around 0.1 Hz) of the power spectrum with no major peaks in the other bands (18). Coherence is assessed by identifying the maximum peak in the 0.04–0.26 Hz range of the HRV power spectrum, calculating the integral in a window 0.030 Hz wide, centered on the highest peak in that region, and then calculating the total power of the entire spectrum. The coherence ratio is formulated as: (Peak Power/[Total Power − Peak Power]^2)" (22), p. 55. The association between heart rhythm patterns and emotional states has been demonstrated in studies conducted in both natural and laboratory settings (23–25). Thus, in order to assess physiological coherence in the context of one's heart rhythm, the algorithm needs to detect changes in the pattern or structure of the HRV waveform, independent of how much HRV an individual may have.

HRV AND SELF-REGULATION

Porges (26) has proposed that the evolution of the autonomic nervous system (ANS), or more specifically the vagus nerve, was essential to the development of self-awareness and an expanded range of emotional experience. He also suggests that the vagal branch of the ANS in human beings plays a critical role in the social engagement system. Porges suggests that what he calls the social engagement system gives us the capacity for self-regulation and the ability to initiate prosocial behaviors when we encounter stressors, challenges or disagreements with others and that we are not limited to fight, flight, or freeze responses. He further suggests that the social engagement system acts as a "vagal brake," and that assessment of vagal activity serves as an indicator of one's ability to self-regulate emotions and behaviors. Therefore, lower levels of age-adjusted vagally mediated HRV reflect a low functional status of the social engagement system (26). This is supported by research indicating that higher overall levels of HRV is associated with psychological resiliency, behavioral flexibility and the ability to adapt to changing social demands (27). Furthermore, higher levels of resting state HRV are associated with better cognitive performance on tasks requiring executive functions (28).

SOCIAL COHERENCE

Social or group coherence relates to pairs, families, groups or larger organizations in which there is a stable and harmonious alignment of relationships that allow for an efficient flow and utilization of energy and communication required for optimal collective action (14). Important aspects of group coherence include the degree of physiological synchronization, the capacity for coordinated action, and the number and quality of positive emotional connections, as well as harmonious cooperation, in the relationships of group members.

Individuals who comprise a working group, sports team, family or business organization may be aligned around a common purpose or goal and exhibit a natural tendency toward good communication, cooperation and efficiency (14). They can also share common, broader group identities such as cultural, religious, or political party affiliations and have to interact with individuals who belong to different groups, i.e., groups they are not aligned with. One of the significant challenges, however, in organizations and societies is that people tend to form biases and discriminate between "in-group" and "out-group" members, which can fuel tension, hostility, and unhealthy competition within the larger group (29). Such dynamics may affect families as well, to a lesser or larger degree. When social organization is incoherent and relations are discordant, optimal or even basic coordinated action may not be possible and psychosocial instability and dysfunction are likely consequences (30).

PHYSIOLOGICAL SYNCHRONIZATION IN SOCIAL INTERACTIONS

The smoothness or flow in social interactions depends largely on the spontaneous synchronization between individuals. When people are engaged in conversation, they unconsciously begin to synchronize their movements, vocal pitch, postures, speaking rates, and length of pauses between replies (31). As we are now discovering, important aspects of their physiology also can become synchronized. A number of studies have explored various types of physiological synchronization in infants, pairs, and groups.

In order for physiological activity of separate individuals to synchronize, a signal of some type (light, electromagnetic, sound, tactile, or chemical) must convey information between them. For example, the visual synchronization of physical movements increases feelings of affiliation (32), self-esteem (33), compassion and altruistic behavior (34), rapport (35), and increased prosocial behavior (36), while during arguments, synchrony decreases (37). In groups, synchronization has been shown to increase conformity (38), cooperation and trust (39), and the strengthening of social attachment between group members (39).

The importance of brain activity synchronization between individuals and in groups has recently gained interest in social neuroscience. However, the capacities for studying synchronization between brains during real-world social interactions are limited and tend to be methodologically clumsy, primarily due to the absence of suitable recording set-ups for simultaneous recordings of two or more people, and the lack of tools for multi-subject analysis.

The notion of brain-to-brain synchronization is that the perceptual system of one brain can be coupled to another brain (40). For example, using functional magnetic resonance imaging (fMRI), synchronization between a speaker and listener's brain exhibit joint, temporally coupled response patterns during communication. Importantly, the more extensive the neural coupling between the speaker and listener pairs was, the more successful the communications was (41). The use of magnetoencephalography (MEG), which has a higher temporal resolution than fMRI, also demonstrated more rapid changes in the coupling of the listener's and speaker's cortical signals when interacting (42).

By using the electroencephalography (EEG), which is more practical than fMRI or MEG, in group settings, it has been possible to record multiple interacting participants' brain synchrony and connectivity. For example, multiple participant EEG recordings have been obtained from musicians playing instruments together (43), during spontaneous nonverbal interactions (44) and to assess pairwise synchronization between students' EEGs in a classroom setting (45). The Dikker study simultaneously recorded EEG activity from 12 students as they engaged in natural classroom activities and social interactions over 11 days and found that brain-to-brain synchrony between the students was consistently associated with increased class engagement and improved social dynamics.

HRV AS MEASURE OF INTERACTION SYNCHRONY

Another approach for evaluating interaction synchrony between individuals has done by looking at the synchronization of heart rhythms and HRV. HRV provides a means to evaluate ANS dynamics in real-time and does not practically or technically limit the number of participants that can be simultaneously monitored. As such, it provides an ideal approach for studying real-time dynamics during group interactions, as well as physiological synchronization. An important advantage is that HRV has the potential to reflect participants' emotional states during various types of interactions. We can frequently identify state-specific patterns in the HRV waveforms that reflect real-time emotions, for example, frustration, anger, anxiety, and appreciation. These patterns are independent of the overall amount of HRV in an individual (18). Recent independent work has demonstrated 75% accuracy in discrete emotional state identification from the HRV waveform using a machine learning method for pattern recognition (25). The immediate reflection of emotional states in the HRV pattern is likely due to changes in the outputs of the subcortical structures involved in processing emotions as described by Pribram and Melges (46), Porges (26), and Thayer et al. (28) wherein the subcortical structures influence the oscillatory output of the cardiorespiratory centers in the brain stem. With HRV as a measure, we can simultaneously determine physiological synchronization, and the emotions occurring during the interactions.

MOTHER–INFANT HEART RATE AND HRV SYNCHRONY

Some of the earliest research utilizing HRV to assess interaction synchronization was on parent–infant synchrony and the coregulation of infant physiological process and emotional states through social interaction. Porges has suggested that the maturing of physiological oscillators provides the substrate for the regulation of the sleep–wake cycle, the heart rhythms, arousal, and the real-time registration of shifts in internal states such as hunger, blood pressure, and fatigue (47). Studies conducted by Feldman on infants' biological clocks and cardiac rhythms from mid-pregnancy to term confirmed that the *in utero* development of an infant's biological oscillator systems was critical for later synchronization with their mothers biological rhythms (48).

After birth, further work by Feldman, has shown that during face-to-face interactions, a mother unconsciously adapts her heart rhythms to those of her infant, and the infant adapts his or her heart rhythms to those of the mother in less than a second, resulting in a biological synchronization between the accelerations and decelerations of their heart rates (49). During periods of synchronization between the parent's and child's social interactions, the degree of synchronization between their heart rhythms increased, showing a real-time coordination between the physiological and social processes between separate individuals. The findings of this line of research led Feldman to suggest that biological rhythms provide the foundation for social rhythms (50).

Of further interest is that two forms of interactions were most effective in increasing synchrony between the HRV of mothers and infants: vocal synchronization and emotional state synchronization. The highest degree of HRV synchronization occurred when both emotional and vocal synchrony simultaneously took place, while gaze synchronization did not increase HRV synchronization. This synchronization did not require bodily contact or tactile stimulation as the mothers and infants were not in physical contact and rarely touched each other. Importantly, a more optimal organization or coherence of the biological rhythms between parents and the first months of their infant's life was shown to predict the development of self-regulatory and social interaction capacities later in life (48, 51). Feldman et al. has suggested that the capacity to coordinate physiological rhythms may lie at the heart of human emotional connections and provides the foundation for collaboration and the formation of human societies (49).

ENERGETIC FIELDS AND HRV SYNCHRONIZATION IN ADULTS AND GROUPS

Anyone who has experienced an exceptional concert or watched a championship sports team recognizes that something extraordinary can take place when a group surpasses its normal performance. At those times, it appears that the players are in-sync and communicating on an unseen energetic level. Many teams, such as professional and Olympic sports teams or Special Forces military units, appreciate and strive to increase team coherence although they may refer to it as "team spirit" or "bonding," and often say then can "sense" a palpable "team energy."

As mentioned earlier, in order for the physiological activity of separate individuals to synchronize, a signal of some type must convey information between them. In the previous section, research on the role of visual, auditory and tactile signals in mediating various types of synchronization between pairs was discussed. There are several lines of research suggesting that an energetic field connects individual group members directly, and which simultaneously distributes information between the group members. We have suggested that biologically generated magnetic fields may act as a carrier wave for information transfer between individuals and group members (52). The magnetic field produced by the beating heart, which is radiated externally to the body, provides a plausible mechanism for conveying information to locations external to the body and for how some people can "feel" or "sense" another person's presence (53) or emotional state, independent of body language, or other factors (16).

An interesting study that is also suggestive of an information field connecting group members was conducted during a firewalking ceremony that looked at synchronized heart rhythms between firewalkers and spectators (54). During a 30-min ceremony, they found a high degree of synchronized activity between the firewalkers and spectator's HRV who had an emotional connection to them. The unrelated spectators who did not have an emotional connection to the firewalkers did not have any HRV synchronization with the firewalkers. The researchers concluded that the mediating mechanism must be information that was somehow distributed among the group members. A number of other investigators have found results that are consistent with this hypothesis. For example, a study examining HRV synchronization and coherence levels in 10 groups, each with four individuals, found that being in an HRV coherent state helped others to shift into a more coherent state (55). They also found that HRV synchronization between participant pairs was increased during periods of increased individual HRV coherence and was correlated with the degree of emotional bonding between participant pairs. The authors concluded that "evidence of heart-to-heart synchronization across subjects was found which lends credence to the possibility of heart-to-heart bio-communications."

In a study investigating physiological synchronization during nonverbal compassionate communication, Kemper and Shaltout found significant changes in the receiver's ANS (56) that was correlated with the sender's. A study by Russek and Schwartz also found that cardiac-related information exchange occurs between individuals and that the amount of physiological synchronization between pairs was greater in people raised in a loving environment. They found that the EEG of one person synchronizes to heartbeats (ECG) of another person sitting across from them. Participants who had rated themselves 40 years before the study as having grown up in a loving environment, had significantly more heart–brain synchronization between the pairs than individuals who reported not being raised in a loving environment (57).

In our laboratory (16), we have observed that entrainment (phase or frequency locking) of the HRV patterns between individuals, is rare during normal waking states and that people who have a close working relationship or live together in a bonded relationship are the best candidates for exhibiting this form of HRV synchronization. **Figure 1** shows an example of heart rhythm entrainment between two women who have a close working relationship and who were seated 4-feet apart with their backs to each other and with their eyes closed while they were feeling appreciation for each other.

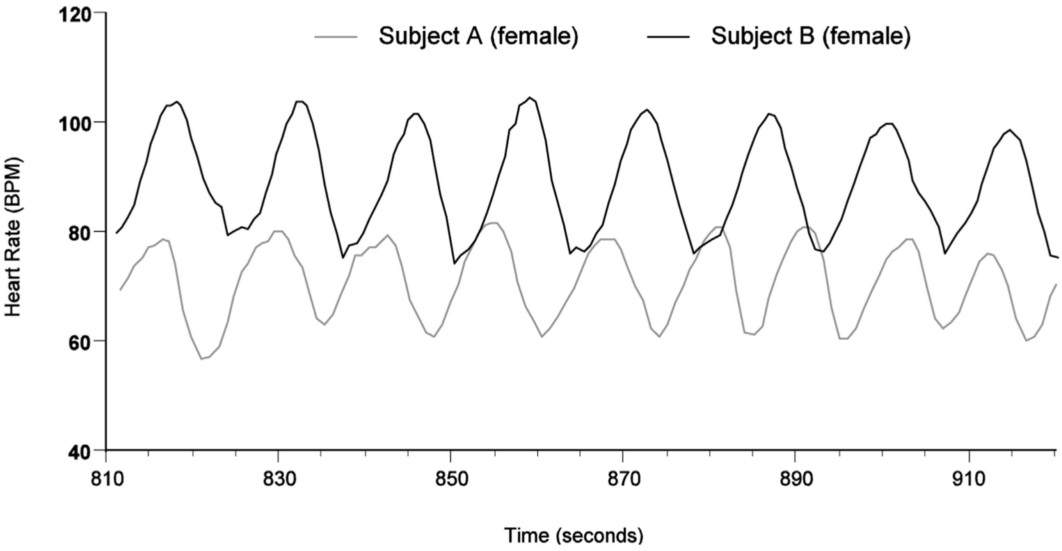

FIGURE 1 | Heart rhythm entrainment between two women. The data were recorded during a period while both participants were consciously feeling appreciation for each other.

Heart rate variability synchronization can also occur during sleep between couples who are in a stable and loving relationship, although entrainment of the two rhythms may not be present as shown in **Figure 1**. **Figure 2** shows an example of a 3-min segment of data from one such couple. Note how the HRV rhythms concurrently change and how heart rates converge.

As with the firewalkers, these examples suggest that a positive emotional connection between people is an important factor in heart rhythm synchronization. Further support for an energetic connection across group members and the importance of positive emotional connections also emerged from research conducted by Raymond Bradley and Karl Pribram. They developed a theory of social communication to explain the arrangements of social organization common to many groups, independent of size, culture, and degree of formal organization (58). By studying numerous groups, they found that most groups have a global organization, structured as a coherent network of emotional connections. By mapping the self-reported relationships between all of the possible combinations of pairs in a given group, they found a strong relationship between the number and structure of reciprocated positive emotional bonds and the structure of the control relationships among group members that predicted group stability and performance 2 years later (59). The theory that best fit the data was one constructed on a field concept where information about the structure of the entire group was simultaneously distributed to all of the group members, a collective consciousness, which they called a "social hologram" (58).

THE HEART'S MAGNETIC FIELD

The various explorations discussed above suggest that a biomagnetic communication system may exist which serves to connect and distribute information among members of stable groups. In the human body, the heart generates the largest rhythmic magnetic field, one that is about 100 times the amplitude produced by the brain. This field, which is measured in the nanotesla range, can be measured several feet outside the body with SQUID-based magnetometers (60). We have found that information reflecting one's emotional state not only is encoded in the patterns of the HRV waveform but also is contained in the heart's electromagnetic field radiated into the environment (16, 18). When an individual is in a heart coherent state, the heart's magnetic field also has a more coherent structure (**Figure 3**). There is a direct mathematical relationship between the HRV patterns and the spectral information encoded in the magnetic field (18).

The heart radiates a series of pulsing magnetic waves, in which the time interval between each pulse of magnetic energy varies in a complex manner. These pulsing waves of magnetic energy produce interference patterns when they interact with magnetically polarizable tissues and substances (18). For example, we have shown that the heart's magnetic field can be detected by the nervous systems of nearby people or animals (16).

Our hypothesis is that biomagnetic fields produced by the heart may be a primary mechanism in mediating HRV synchronization among group members. This perspective is supported by the work of quantum physicists Larissa Brizhik and Emilio Del Giudice. They have suggested that magnetic fields are the most likely physical agent that can continuously provide an exchange of information between living systems within the larger ecosystem. They specifically suggest that magnetic potentials provide the mechanism for establishing self-consistency, coherence, complexity, and non-local information exchange found in any living system and ecosystems (61, 62).

> The messengers should be the electromagnetic fields produced by all the coherent parts of the organism. We recall that a coherent system is one where the phase (namely the rhythm of oscillation of the coupled matter and electromagnetic field) is sharply defined. Here we generalize this approach to a larger scale and show that according to quantum field theory, the electromagnetic field is the messenger that, *via* its electromagnetic potential, governs the dynamics of not only individuals, but of the whole ecosystem to which the individuals

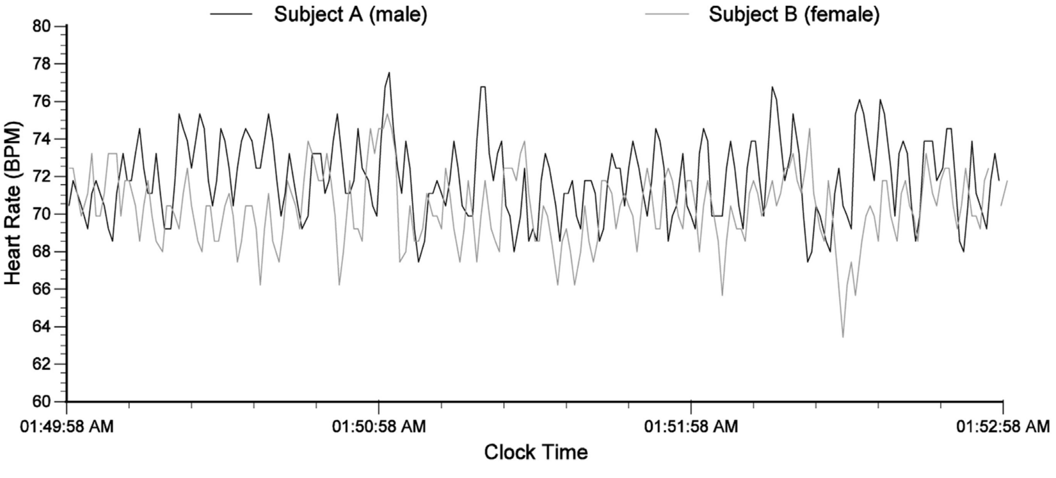

FIGURE 2 | Heart rhythm synchronization between a husband and wife during sleep.

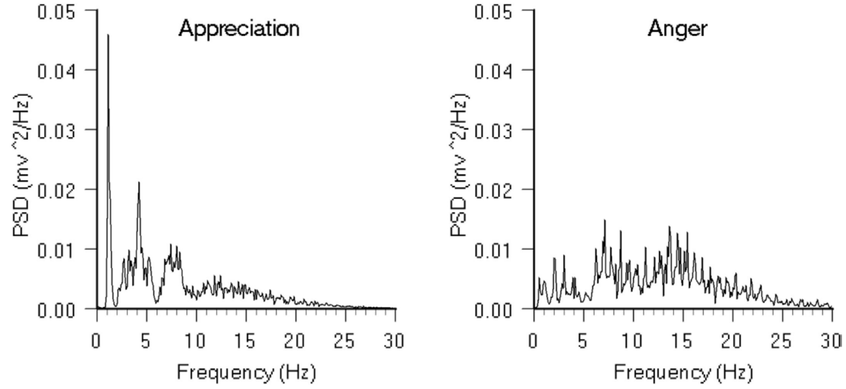

FIGURE 3 | ECG spectra during different emotional states. The above graphs show the average power spectral density (PSD) of 12 individual 10-s epochs of ECG data. The graph on the left is an example of a spectrum obtained during a period of high heart rhythm coherence generated during a sustained heartfelt experience of appreciation. The graph on the right is the spectrum of a disordered heart rhythm recorded during feelings of anger. It can be clearly seen that the spectral patterns in the magnetic fields radiated by the heart have different structures and informational content.

> belong. This generalization is based on the fact that the field causes the emergence of the coherent structures, which, in view of their coherence, openness and nonlinearity, are able to self-organize and form a chain of hierarchical levels of ecosystems (61) (p. 1856).

NEW FRONTIERS

Development of a Group HRV Assessment Platform

There is an extensive body of research showing that providing HRV coherence feedback to facilitate skill acquisition of self-regulation techniques improves a wide range of health and performance outcomes (15, 63–86).

As stated in the Section "Introduction," one of our hypotheses is that providing feedback of individual and collective HRV coherence and the degree of pairwise heart rhythm synchronization will facilitate increases in the group's coherence and heart rhythm synchronization among group members. We are further suggesting that providing HRV coherence feedback to groups about the group's coherence as a whole will help encourage individuals in the group to better self-regulate and engage in more prosocial behaviors. We also propose that it will encourage group members of families, schools, organizations, and communities to learn how to get more in-sync with each other before and during meetings and important communications, while making important decisions or when individuals need to resolve a conflict, etc.

We are in the process of developing new techniques, exercises, and processes for building and sustaining group coherence, which build on the self-regulation techniques used for achieving personal coherence, discussed in the next section.

As discussed above, the experimental paradigms to evaluate the physiological aspects of social interaction have been limited. Typical experiments tend to isolate people from their natural surroundings by placing them in a sealed room where interactions take place through computer games and video or auditor links. Many, if not most social interactions such as meetings, conversations, and other group engagements take place face-to-face and depend on real-time perception of social signals and various forms of physiological synchronization. Given the practicality of recording HRV during group interactions and its usefulness in understanding real-time ANS dynamics, stress and emotional states, and pairwise synchronization among group participants, we have developed a new research system for simultaneously measuring the HRV of group members. The experimental control software provides real-time feedback of group's collective coherence level and degree of HRV synchronization among all the possible pairwise combinations. Each participant is provided with feedback of their own HRV coherence level while simultaneously being presented with a representation of the group's overall coherence score. In other words, there are two types of coherence that are assessed and displayed to the group members. The group's average coherence score (calculated with the algorithm described in the physiological coherence section above) and degree of pairwise HRV synchronization between members grouped into various clusters are presented. We are currently testing several analytic approaches for assessing pairwise synchronization, as well as the most effective approaches for providing feedback to the group members. For example, we have developed and validated a method using near-optimal chaotic attractor embedding techniques to identify specific patterns and clusters of HRV synchronization between people which is described elsewhere (87).

We have also developed custom pulse wave data acquisition modules that allow for analysis of the pulse waves which yields information that complements the information provided by analysis of the HRV waveform, such as changes in arterial wall stiffness, which is affected by sympathetic system activations (88, 89). While currently configured to simultaneously monitor 20 participants, there are no limits on capacity as the system is designed to be easily be scaled up to any number of channels. The system uses an ethernet connection to link the host computers, and considerable effort was invested in time stamping each data channel so that accurate timing of the data collected from each participant is maintained. This allows the group members to be located anywhere in the world as long the host computer has an internet connection.

One of the planned future additions to the system is voice analysis capability which will allow for a more detailed analysis of events that are associated with changes in the HRV during verbal interactions in environments such as business or classroom settings. It will be possible to determine when people are talking over others in meetings and extract information relating to the emotional state of each speaker through spectral analysis of each participants' speech. This will augment the considerable amount of emotional content already detectable in the HRV alone (25). It is also our intention to implement a machine-learning based assessment of emotional state recognition and detection from the HRV and voice signals to aid in detecting pattern in the group dynamics.

The group HRV coherence research system is also designed to interface with the easily available laptop-based emWave Pro (HeartMath, Inc., Boulder Creek, CA, USA) HRV coherence training device which will provide a low cost option for researchers interested in doing group-related HRV experiments. We also plan to develop the capacity for the system to connect to Bluetooth devices such as the Inner Balance Trainer for mobile devices, as well as others, and to develop at least one game in which success is achieved through the combined ability of a group's members to sustain coherent HRV states.

As of summer 2017, we are collecting data during a number of different types of group interactions, such as business meetings, interactive game play, and various heart-based meditations. This research meets all the applicable standards for the ethics of experimentation in accordance with the Declaration of Helsinki, and participants provided written consent prior to participation in data collection. **Figure 4** shows an example of data collected from a group of five individuals seated at a conference table while using a newly developed technique as part of the training program for increasing social coherence called Shift and Lift which is intended to be used before communicating with others. This example is included only to provide a visual reference for

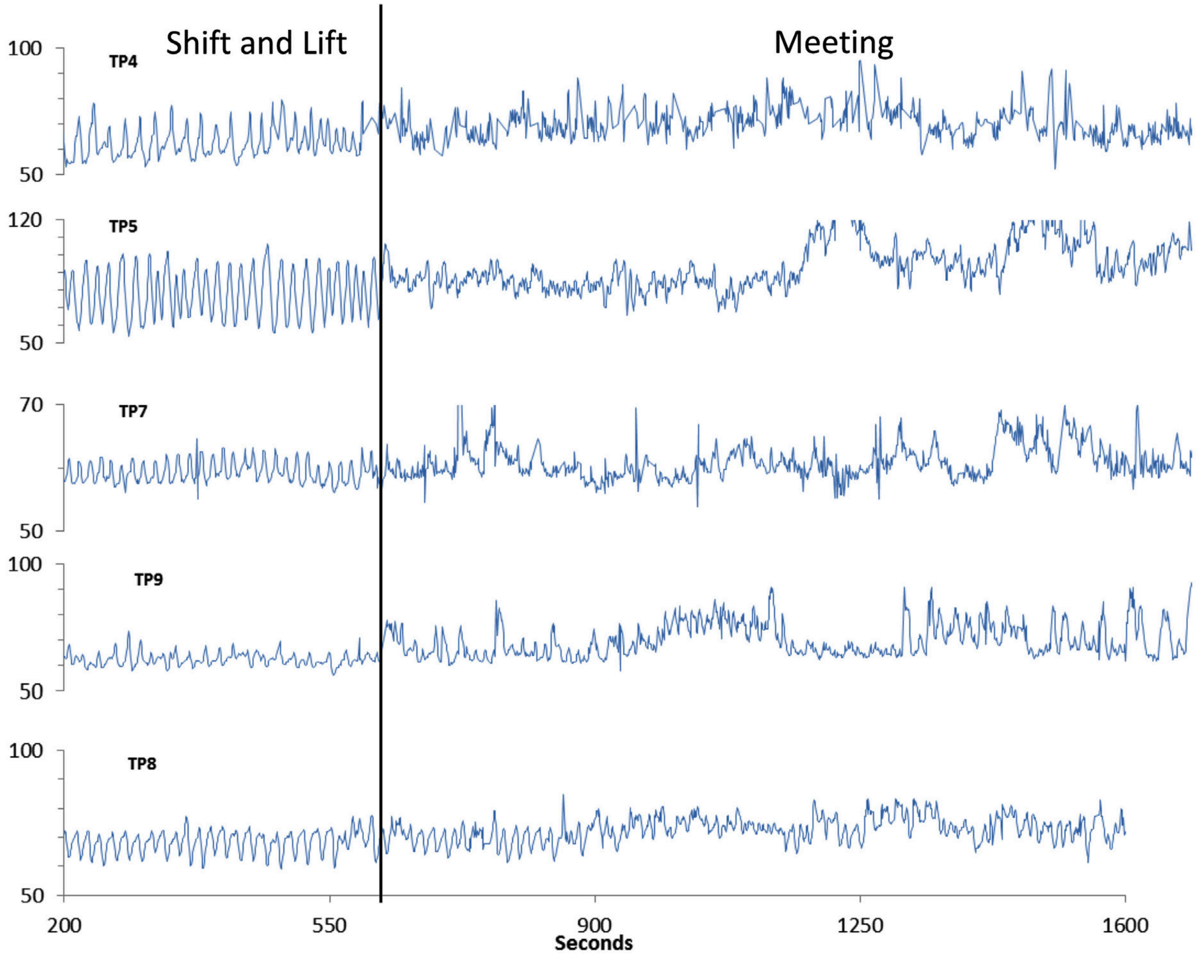

FIGURE 4 | An example of five participants who were simultaneously recorded while using the Shift and Lift technique for approximately 5-min before the start of a business meeting (left side). The second segment is a 15-min period during the meeting. It can be clearly seen that while the participants were using the Shift and Lift technique that four of the five participants were in a more coherent state than during the meeting.

the difference between a coherent heart rhythm as occurred in the first segment labeled Shift and Lift, and the following segment, where the individuals were engaged in a business meeting, where there was not much HRV coherence. It can clearly be seen that during the business meeting segment, that each had much less HRV coherence and there was not any obvious pairwise synchronization between the individuals.

Figure 5 shows an example of 12 participants who were simultaneously recorded.

While they were seated around a long conference table and instructed to use the Heart Lock-In technique for 5 min, which is a heart focused meditation like technique. All of the participants were experienced in using the technique and known from previous experiments to be able to shift into and sustain a coherent HRV rhythm. During this experiment, the pairs were preassigned and instructed to keep their eyes closed during the Heart Lock-In while focusing on actively radiating feelings of appreciation to the other pair partner. The left side of the figure shows an overlay of the HRV waveforms of each pair of participants. The right side of the figure shows an overlay of the HRV power spectrums of each pair. Preliminary results suggest that there is increased HRV synchronization between participant pairs when they focus

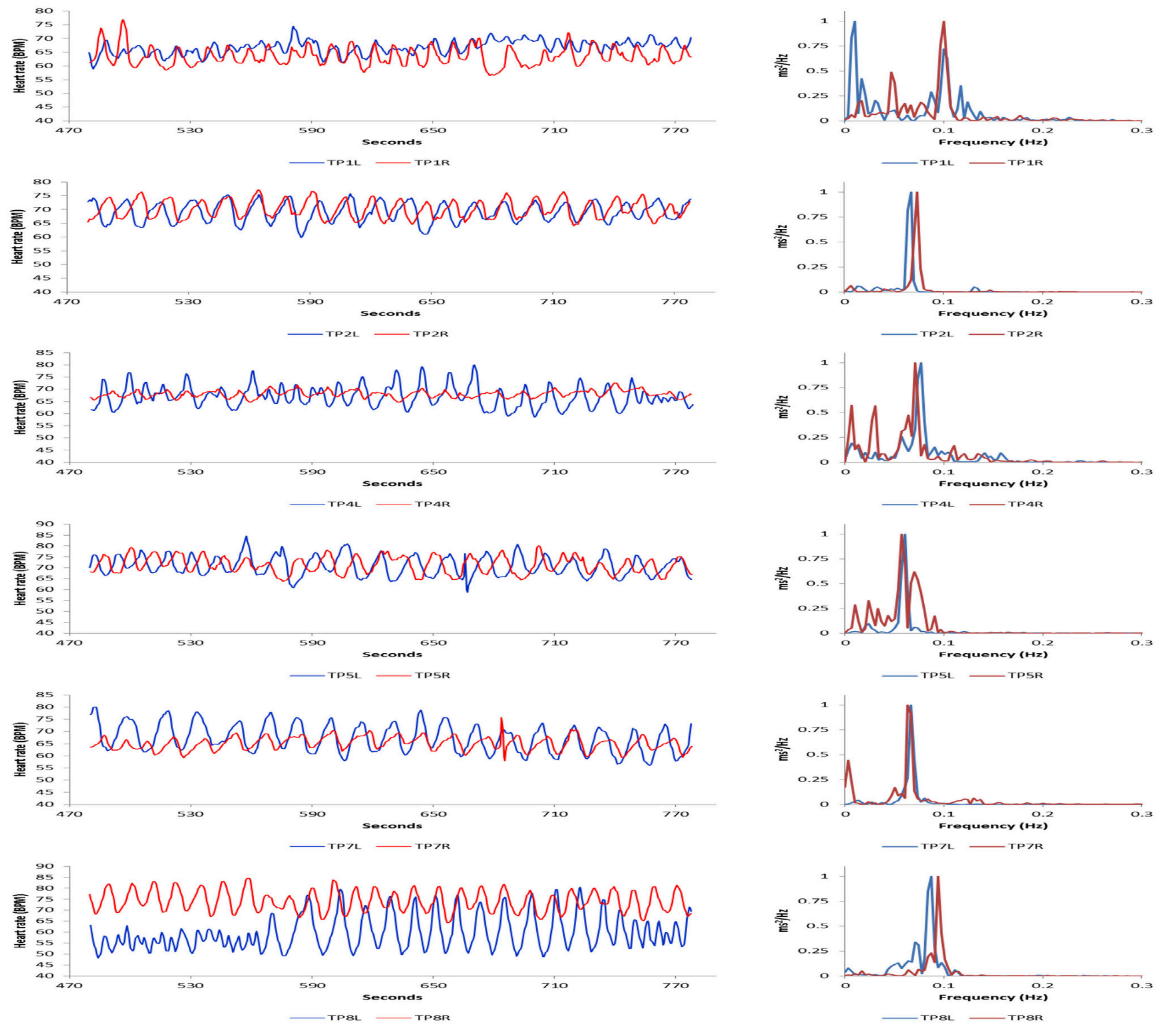

FIGURE 5 | An example of 12 participants who were simultaneously recorded while using the Heart Lock-In technique for 5 min. The pairs were instructed to actively feel and radiate feelings of appreciation to the other pair partner. The left hand side shows an overlay of the HRV waveforms for each pair of participants, while the right hand side shows an overlay of the HRV power spectrums of each pair.

on radiating positive feelings specifically toward each other, as opposed to a more general focus, such as radiating positive feelings or intentions to the people in a remote location, or all the members of the group. The figure is included only as an example of how the platform allows for easier multi-subject data collection than was previously possible, although this example did not utilize some of the other unique features of the platform, such as real-time group coherence feedback, or feedback on pairwise HRV synchronization.

TRAINING PROGRAMS TO INCREASE SOCIAL COHERENCE

In most social contexts, individuals at times form preconceptions or judgments toward one another and hold onto feelings that are often unspoken, but that leads to poor communication and other damaging social dynamics that disrupt optimal team or group performance. Our second hypothesis states that training in techniques to increase group coherence and heart rhythm synchronization will correlate with increased prosocial behaviors, such as kindness and cooperation among individuals, improved communication, and decreases in social discord and adversarial interactions.

Numerous large-scale implementations of training programs for increasing personal self-regulation skills and resilience in hospitals, military and law enforcement, educational, and business environments which included HRV coherence feedback support the hypothesis. It has been shown that providing emotional self-regulation skills combined with heart rhythm coherence training results in significant improvements in communication, employee satisfaction, productivity, problem solving, reduced turnover, and a significant return on investment, both financially and socially (15, 67, 73, 86, 90–92). In our experience, the self-regulation and resilience building training programs are most successful when leadership openly models and support the programs (93). These programs include practical skills that increase self-regulatory capacity and physiological coherence as a key element. Another important lesson, perhaps the most important, is the essential need to implement a robust sustainability strategy. No matter how effective the techniques, exercises, processes or technologies may be for self-regulation and group coherence, their effectiveness cannot be realized if they are not utilized on a consistent basis. As with any new skill, it takes repetition and practice before it becomes routine, especially during challenging situations, when they are needed most. In our experience, the most effective approach to facilitate the ongoing use and grounding of the skills is by providing participants with ongoing support from a team mentor or coach. The main objective of the mentoring is to provide the team members and leadership with continued support, knowledge and tactics to effectively expand and sustain self-regulation and social coherence skills and practices.

We are in the process of developing new techniques, exercises and processes for building and sustaining group coherence, which build on the self-regulation techniques used for achieving personal coherence such as the Heart Lock-In and Freeze Frame, techniques (94–96). It requires effort and energy to shift an incoherent group into a more coherent mode, and an important key is the establishment of more positive emotional bonds, and dissipating negative emotional tensions, interpersonal conflicts and other stressors within the individuals that comprise the group. The newly developed techniques and processes focus on issues such as clearing historical judgments and misunderstandings, appreciating differences, aligning with core values, coherent communication, improving the emotional climate, understanding energetic field environments, avoiding the pitfalls of "groupthink" and utilizing the power of positive "emotional contagion." The majority of the techniques we employ in the social coherence building intervention are designed to be used in the moment one is "triggered" or is experiencing emotional undercurrents or stress. Several of the techniques are designed to be used by groups to "get coherent" and be better prepared for upcoming events that may be challenging such as meetings or interactions with customers or vendors who have a history of being difficult to work with.

We will be conducting a series of field research studies in various groups to refine the social coherence training program content and to evaluate the effectiveness of the HRV based group coherence platform for increasing social coherence. The essence of the hypothesis is that the combination of HRV coherence assessment and feedback at the group level with an educational program focused on increasing a group's coherence will result in a number of benefits. We predict that there will be an increase in positive energy and bonding, care, kindness and cooperation among individuals, creativity and decision-making, appreciation of group members' differences, improved communication, and a decrease in social discord and adversarial interactions resulting in shorter meeting times, fewer mistakes, increased academic performance in schools and increased sense of well-being and collective purpose. In order to assess these types of outcomes, we are also in the process of developing a psychometric assessment specifically for the key constructs of group harmony and coherence.

CONCLUSION

Social coherence was defined as a stable, harmonious alignment of relationships, which allows for the efficient flow and utilization of energy and communication required for optimal collective cohesion and action. Various studies examining synchronization between mothers and infants, pairs and groups, indicate that feelings of cooperation, trust, compassion and prosocial behaviors are facilitated by physiological synchronization between individuals.

Building on the extensive body of research showing that providing feedback of one's HRV coherence level at the individual level can improve self-regulation, we suggest providing feedback of individual and collective HRV coherence and the degree of heart rhythm synchronization will increase group coherence and heart rhythm synchronization among group members.

The development of a new HRV recording system allows for the real-time assessments during group interactions and provides real-time feedback on group dynamics, collective group coherence levels and HRV synchronization among all the possible pairwise combinations. The occurrence of HRV synchronization between clusters of group members has been demonstrated and has been shown to be associated with positive emotional bonds between group members.

We also discussed support for the hypothesis that training group members self-regulation techniques designed to increase group coherence and pairwise HRV synchronization will correlate with increased prosocial behaviors, such as kindness and cooperation among individuals, improved communication, and decreases in social discord and adversarial interactions. Our hope is that this new technology and training program will decrease social discord and increase positive emotional connections, kindness, cooperation, overall social well-being, and sense of collective purpose.

ETHICS STATEMENT

The research met all applicable standards for the ethics of experimentation in accordance with the Declaration of Helsinki. Participants provided written informed consent prior to participation in the study.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Hidden Signals—The History and Methods of Heart Rate Variability

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The understanding of heart rate variability (HRV) has increased parallel with the development of modern physiology. Discovered probably first in 1847 by Ludwig, clinical applications evolved in the second part of the twentieth century. Today HRV is mostly used in cardiology and research settings. In general, HRV can be measured over shorter (e.g., 5–10 min) or longer (12 or 24 h) periods. Since 1996, most measurements and calculations are made according to the standard of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. As the first step, the series of times between successive R-peaks in the ECG are in milliseconds. It is crucial, however, to identify and remove extrasystoles and artifacts according to standard protocols. The series of QRS distances between successive heartbeats can be analyzed with simple or more sophisticated algorithms, beginning with standard deviation (SDNN) or by the square root of the mean of the sum of squares of differences between adjacent normal RR (rMSSD). Short-term HRV is frequently analyzed with the help of a non-parametric fast Fourier transformation quantifying the different frequency bands during the measurement period. In the last decades, various non-linear algorithms have been presented, such as different entropy and fractal measures or wavelet analysis. Although most of them have a strong theoretical foundation, their clinical relevance is still debated.

Keywords: heart rate variability, Holter monitoring, time domain, frequency domain, systems science, complexity theory

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INTRODUCTION

Heartbeat varies over time. This has been observed early in medicine. Variations and patterns of heart beat have been associated with pathological conditions already 2,000 years ago (1). However, first in the last 100 years, conceptual ideas evolved, and understanding of involved mechanisms increased, in particular since 1996 when a standard was established and parameters defined (2).

The increasing interest in heart rate variability (HRV) can partially be explained by the feasibility of the method. Data can in principle be obtained by a simple one-channel ECG or even a pulse watch; data are processed by user-friendly programs. In reality, the issue is more complicated {(3) #2021} {(4) #2317} {(5) #2320}. Whether pulse watch-generated HRV calculations can be used is still a matter of debate {(6) #2326} {(7, 8) #2022} {(9) #2319}. Automated recognition of R-peaks is prone to errors {(10) #2323} and manual editing is still the gold standard, which impairs clinical use. No overall accepted normal values exist. In the beginning, HRV was first usually calculated based on 24-h recordings. Eventually, new algorithms were introduced (explained below) and clinical studies supported the use of short-term measurements. HRV has thus changed to an apparently simple point-of-care method obtained within 2–10 min with potential clinical value for the patients regarding risk stratification, individual therapeutic strategies, and even therapeutically in the form of HRV-biofeedback.

This review intends to give an overview of the developments of HRV in the last decades. It is basically descriptive. In earlier work (11), an extensive literature search was conducted, based mainly on the simple keyword "Heart Rate Variability" in the US National Library of Science (PubMed) and consecutive search in the reference lists of the identified articles. This review extends and updates this work although only the most central publications, chosen by the author will be discussed, for the sake of clarity.

Therefore, in this review, only a brief history of HRV will be presented. In the second part, the methods of signal measurement will be introduced. Most important algorithms for HRV analysis will be explained, but algorithms (still) not being used in clinical research or practice will not be mentioned. In addition, some possible confounding mechanisms of importance will be reported. Finally, a brief perspective of HRV for the future will be offered.

HISTORY

Pulse diagnosis has been early a part of ancient medicine and descriptions include its variation over timeWestern medical historians usually quote Galen as one of the first analyzing pulse patterns in human patients. Pulse diagnosis was, however, an important part of ancient Chinese and Indian medicine, too. In China, pulse diagnosis was investigated as early as between 800 and 200 BCE. For instance, in Chinese Medicine, Bian Que (扁鹊, about 500 BCE, also known as Qin Yueren, 秦 越人), living about one generation before Hippocrates described the "four diagnostic methods" of Traditional Chinese Medicine, in particular tongue and pulse diagnostics. All these forms of historical pulse analysis described patterns qualitatively. Quantitative measurements were first possible after the introduction of exact time measuring devices.

Variations of arterial blood pressure during the respiratory cycle was observed again in the eighteenth century, probably first of Stephen Hales. His observation of HRV was based on conducting measurements of blood pressure in some animal species (mostly dogs) by inserting fine cannulas into arteries and measuring the height to which the column of blood rose (12). Carl Ludwig (1816–1895) described a link between heartbeat fluctuations and respiration [respiratory sinus arrhythmia (RSA)] when investigating the frequency and pulse wave in dogs using a special instrument ("kymograph") (13). One of the founders of experimental psychology, Wilhelm Wundt (1832–1920), made similar observations and introduced the notion of using physiological measures to investigated psychological mechanisms.

The French physiologist, Claude Bernard (1813–1878), introduced the term "milieu intérieur," a basic principle to homeostasis. This internal environment is "constituted, in particular, by the fluids circulating in the body." The American physiologist, Walter Bradford Cannon (1871–1945), expanded Bernards concept of homeostasis, beyond others by the two claims that the regulating system determining the state of the homeostasis consists of several connected subsystems. According to Cannon homeostasis is a consequence of self-organizing systems (termed self-government by Cannon). An important paradigm in HRV is based on Bernard's and Cannon's notion. Stable homeostasis is according to this concept connected to increased variability of HRV (14).

The classical model of autonomic control describes a balance between parasympathetic and sympathetic activation. It was also proposed by Cannon (15) and later expanded by Langley (16) who divided the autonomic outflows between sympathetic and parasympathetic elements, a division used until today. Cannon associated also increased activity in the sympathetic system with the evolutionary notion of "fight and flight." In his seminal book, Langley erroneously defined the ANS as a purely visceral motor system, mediating the consequences of central nervous states to the periphery [today we know that 80% of vagal fibers are in reality afferent, providing important information to the brain regarding the state of the visceral organs (17)]. Hering described the functional relation between the amplitude of RSA and the vagal tone in 1910 (18). His son provided experimental data describing the baroreceptor reflex more exactly in 1927 (19).

Some years later, Adrian et al. published for the first time the behavior of the sympathetic nervous system in anesthetized rabbits and cats (20). At the same time, Maltzberg observed the association between cardiac disease and major depression, at this time termed "involution melancholia" (21), an association leading to important research in the last decades.

In 1965 investigations of the HRV of fetal ECGs revealed diminished variability after contractions when the fetus was distressed (22). This principle is still a cornerstone in monitoring fetus under labor. In cardiology, the relationship between the nervous system status and HRV was described by Wolf (23), 2 years after Valbona et al. described HRV changes in patients with serious brain damage (24).

Katona and Jih (25) introduced a non-invasive approach to measuring cardiac parasympathetic control in anesthetized dogs where they were able to control respiration rate. They introduced the notion that the magnitude of sinus arrhythmia is associated with changes in the vagal tone; assuming a linear association between vagal efferent activity and the change of heart period, and that during inspiration the cardiac vagal input is inhibited. Akselrod et al. applied power spectrum analysis of short-term HRV in an animal model, showing the association between different frequency ranges and the sympathetic and parasympathetic activity (26).

At this time, portable ECG-measurements became more frequent. Until then, HRV was mainly determined by measuring RR-distances with a ruler. Eventually, electrical circuits identifying the peak of R-waves and the time of the intervals with an accuracy of milliseconds were developed. First investigations of HRV were based on 24-h recordings by Holter monitoring. This changed when Axelrod started to analyze the frequency domain of HRV also in humans by using short-term HRV of 10 min or less (27). Earlier, spectral analysis methods were utilized in some study, investigating driver fatigue {(28) #2332}, the effect of aging on HRV {(29) #2333}, or in hypertension {(30) #2334}. Of particular importance at this time was also the increasing interest in non-linear phenomena. In particular Goldberger, the founder of the prominent website "Physionet," began to focus more on non-linear algorithms (31–33). Looking closer on his articles shows relevant influences: he quotes May's important article about evolutionary models (34) and Haken's (35), and Shaw's articles about chaos theory and strange attractors (36). Hermann Haken, physicist conducted research on self-organizing systems and founded at the end of 1960s synergetics, an interdisciplinary science investigating the formation and self-organization of patterns and structures in open systems far from equilibrium—characteristic for most physiological systems {(37) #2327}. Robert May introduced the use of models to test stability and fragility of systems {(38) #2328}. Robert Shaw was one of the pioneers of chaos theory at this time.

The breakthrough of HRV in cardiology occurred when the association between SDNN (explanation, see below) and the mortality after acute myocardial infarction was discovered. Probably, the first observation was made public by Australian group 1978, describing an association between sinus arrhythmia and survival after acute myocardial infarction {(39) #2329}. A landmark study of Kleiger et al. {(40) #1561} and several important cardiologic HRV studies followed, e.g., Ref. (41–44), frequently combining traditional cardiological measures with HRV. Bigger's introduction of short-term measures (45) and Kleiger's study were significant reasons to form the joint Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (2). The Task Force proposed minimal technical requirements, definitions, standardized the areas of Power bands in frequency domain and offered recommendations for clinical research and patient examinations. This article is still the most frequently cited HRV paper. Nearly every study after 1996 is based on this standard, and no major revision appeared until recently—the presentation of currently accepted linear measures is comprehensive, and the clinical signification of the non-linear parameters is still unclear. A recent joint position statement of the European Society of Cardiology and the European Heart Rhythm Association stated a lack of communication between mathematicians and engineers developing new algorithms and clinicians. It recommends, however, the combined use of linear and non-linear measures (46). A recent study provided reference values obtained by healthy individuals (7, 8), with limited relevance because they were recorded with Holter monitoring 24 h and are, therefore, not applicable for short-term measurements. The study was also criticized because of inconsistencies and unrealistic values, beyond others (3).

Already more than one century ago scientists observed and proposed associations between imbalances of the ANS and (pathological) mental states. Notions included that dysfunctional mental states might be associated with excessive vagal outflow (47), with imbalances between the sympathetic and parasympathetic system (48), or with excessive sympathetic outflow (49). Already Lacey and Lacey reported personality traits associated with greater HRV (50). Early work of Porges and Raskin showed mental state associations with HRV (51). This notion was later extended and elaborated by Porges (Polyvagal Theory) and Thayer (Neurovisceral Integration Model) (52–55).

Today, HRV has been used in more than 2,000 clinical trials and has been mentioned in more than 14,000 articles (46). It is used as an algorithm in sports watches and frequently appears in new Apps in electronic devices, mostly for health or training purposes (7, 8). The clinical use, however, is still invariant.

Probably the most relevant use of HRV in clinical practice is risk stratification. Several studies have shown clear associations between decreased HRV and the risk of sudden cardiac death (56–58) and the value of using HRV has been recognized (58–60). In some centers, HRV, together with other variables is used to identify patients at high risk for sudden cardiac death (61). This has consequences for treatment because the identified individuals received Automated Implantable Cardioverter-Defibrillators, an expensive, but a highly effective method. HRV is also established in the identification of cardiac autonomic neuropathy caused by diabetes and part of standardized examination protocols (62, 63). An emerging field is the use of HRV to predict systemic infections in critical care medicine. However, HRV is only utilized in some hospitals, and more often still not implemented in clinical practice (64, 65).

Based on the mentioned models and concepts above, HRV is also increasingly used in psychological research. The general hypothesis there is that higher levels of HRV parameters associated with activity in the parasympathetic system are also associated with better adaptivity to perturbations and better stress response. A recent meta-analysis confirmed this hypothesis, showing significant associations, although the absolute differences were small. Interestingly not only parasympathetic but also higher general HRV parameters were related to greater adaptivity (66). As an example, HRV has been used as a method in anxiety research. According to the neurovisceral model, anxiety disorders can be characterized by a breakdown of the inhibitory processes of the central autonomic network (67). This disinhibition is permanently linked to the continual state of excessive worry and mirrored by the decreased activity of the parasympathetic system. Several studies have investigated individuals with different kinds of anxiety disorders and have supported this notion in general anxiety (68), various forms of panic disorder (69), social anxiety (70), stress-associated anxiety (71), and trait anxiety (72). A closer look at these studies also shows the problems—e.g., in an experimental study looking on correlations between electric skin conductance, startle blink reflex and resting HRV (rMSSD) during conditioned fear inhibition and extinction. Higher rMSSD was associated with pronounced fear inhibition and extinction (indexed with startle blink potentiation), but the effect is most pronounced at the group level, and the scatter plot shows rather a point cloud instead of a clear regression line (73).

The newer history of HRV research is closely associated with the history of complexity research. As already mentioned, Ary Goldberger was inspired by publications of beyond others von Haken. He is one of the European representatives of a research tradition trying to understand systems. A system is regarded as a set of different parts (or subsystems) connected through positive and negative feedback circles. The fundamental notion of complexity science is that the whole system has more properties as the sum of properties of its parts. In other words, if you analyze the parts of the system separately, and add all results, there will be properties which cannot be explained out of this. Another term for this approach is non-linear science. Linear systems can be described by an addition of the equations describing its parts. If the subsystems interact, the system behaves non-linear and its behavior cannot be predicted by analyzing its parts. A set of equations characterizing a non-linear system can usually neither be solved with analytical mathematical methods {(74) #2335}.

Non-linear systems behave different compared to linear systems {(75) #2352}. Key notions are robustness and fragility. System robustness is often defined as the quality of a biological system or network to maintain its components, structure, and function despite both external changes and endogenous fluctuations {(76) #2337} {(77) #2338}. Fragility is connected to robustness. A property of complex systems is a conservation of sensitivity. When robustness is improved in one area, it leads to increased fragility in another {(78) #2339}. Complex systems are, therefore, robust, yet fragile by cascading failures initiated by tiny perturbations which may lead to a complete breakdown, or to a fundamental system change, termed emergence {(79) #2340}. Essential tools to study complexity are mathematical models and time-series analysis. HRV is the most used time-series analysis in medicine. The complexity paradigm has been explicitly used of Thayer and Lane in their neurovisceral model (55). The study of HRV has been influenced by dynamical systems theory, the study of fractal systems and chaos theory. It was also influenced by notions of self-organizing systems, network theories, and by modeling methods {(11) #1498}.

METHODS

Investigating HRV needs a three-step approach. First, a condition should be defined where the measuring of heart rate signals and its variability gives relevant information. For the second, it is important to detect the signal as adequate as possible, to identify potential artifacts and manage them and at the end to obtain a time-series in milliseconds between the heartbeats which can be analyzed. The third step consists of different forms of analysis which again return various parameters to be used to analyze the state of the system.

Preparing a measurement of HRV should involve answers to several questions. The length of measurement is relevant for the kind of parameters of interest. When the focus is on basic parameters, a measurement period of 5 min or even less might be enough. When long-term fluctuations are relevant, a longer measurement period is necessary. Several non-linear parameters do also need a longer measurement period than 5 min. Details are given in **Table 1**. Recently, ultra-short-term analysis has been proposed for some parameters (80). According to these reports, the time domain measure root Mean Sum of Squared Distances (rMSSD) and the frequency domain measure High Frequency Power (HF, both explained in the next sections) can be reliably measured in time-series of 10–30 s.

TABLE 1 | Measurement period and parameters.

Measurement period	Possible parameters
6 s to 2 min	SDNN [Dekker et al. (81) and Carnethon et al. (82)]
5 min	In addition: rMSSD, HF, LF, LF/HF
10 min	In addition: VLF, approximate entropy
hours	In addition: fractal measures
24 h	In addition: ULF

Most algorithms for the analysis of short-term HRV require stationarity of the heart rhythm. The heart rhythm should not increase or decrease during the measurement period. An exact rule of stationarity would demand that the distribution of a time-series is invariant over time. A weaker rule demands only that mean and covariance are stable. When in time-series trends are occurring, they can probably distort the parameter calculation (45). Stationarity in measurement protocols is usually obtained by demanding a resting period for the individuals at least 5, but usually 10 min. In the case of measurements during tests (e.g., physical movement, stress tests) algorithms not needing stationarity should be considered.

Another precondition is of course that the heart rhythm is feasible for HRV analysis. Although some research groups have used HRV analysis in atrial fibrillation (AF) {(83) #1868} {(84) #1719} {(85) #2341}, in most cases individuals with AF have to be excluded. The same applies for participants with a high number of ectopic beats, with exception when heart rate turbulence will be analyzed, where ectopic beats are needed. Individuals with more than 20–30% ectopic beats are usually not feasible for HRV analysis {(86) #2343}. Before HRV parameters can be calculated, preprocessing of the raw data is necessary. Artifacts have to be removed, and ectopic beats have to be identified and handled. Several computer-based algorithms provide automatic identification and managing of ectopic beats, but most protocols include a manual review of the ECG signal {(86) #2343}. A typical way of management is to replace the distances between the QRS complex before and after the ectopic beat by the distance between these two QRS-complexes divided by two {(2) #1505}.

The sampling rate is an important issue. If the sampling rate of the signal is under a certain threshold, the calculated parameters might be distorted. Wittling showed that a sample rate below 256 Hz can already cause significant distortion with the example of a patient investigated after myocardial infarction (87) p 151. The Task Force recommends a sampling rate between at least 250 and 500 Hz. A lower sampling rate is only acceptable if appropriate interpolation algorithms are used, but not lower than 100 Hz (2). A recent exploration described stable measures at sampling rates of 125 Hz or lower (88).

In the last years, heart rate has been increasingly measured by photoplethysmography (PPG), as implemented in newer smart watches {(9) #2319}. For instance, the pulse watch Polar RS800cx, using an electrode belt and PPG measured with a finger cuff, compared with ECG showed moderate to excellent agreement levels. However, some values (LF and HF) had a lower correlation {(89) #2321}. Mobile phone technology showed excellent similarity between ECG signals and finger color changes taped with the camera lens, and the flash turned on {(90) #2324} {(91) #2322}. For instance, SDNN measured by ECG was 92.2 ± 5.3 and 92.3 ± 5.9 by the mobile phone in one study {(91) #2322}. These results seem promising, and this method has been used in some studies, e.g., {(92) #2325}. A recent review concluded that Pulse Rate Variability with PPG seems to work acceptable in healthy younger persons at rest, but not in movement or under stress conditions {(6) #2326}.

Application of pulse watches with breast belts or PPG can only be recommended, if the particular equipment is first validated with a traditional ECG approach.

Several factors influence the measurement results. HRV results are clearly sex and age dependent. Also sleep, physical exercise, fasting, and position might distort HRV parameters. An overview is given in **Table 2**. A comprehensive overview is given in Ref. (11), chapter 4. One major problem regards reference values. Some reference values have been provided by the Task Force {(2) #1505}. In a review, 44 studies with together 21,438 participants were pooled and the results were considerably different {(4) #932}. A recent study provided reference values for 24-h recordings {(7, 8) #2020}, but received massive critic for inconsistencies and the methodological approach {(3) #2021}. Beyond others heterogeneity of study populations, measurement conditions (e.g., stressed or relaxed participants), or time of the measurement can have profound effect. Studies have, therefore, usually control groups instead of relating to reference values. On the other hand, some parameter values, such as SDNN < 50 ms are generally accepted as pathological {(3) #2021}.

Different drugs might influence HRV parameters, but often the evidence is conflicting. Beta blockers are mentioned most frequently (2), but recently a negative study was published (110). In most studies, individuals taking beta blockers are excluded, analyzed separately or included into the statistical model. An overview of some drugs and its effects on HRV is given in **Table 3**. Different antidepressive drugs frequently showed effects on various HRV parameters. Amitryptilin and Doxepin, taken in a period of 2 weeks was associated with general decreased frequency domain parameters (111), the effect of tricyclic antidepressants, selective serotonin reuptake inhibitors and other antidepressants was confirmed in a larger study (112) Also here, a comprehensive overview can be found in Ref. (11), chapter 4.

ALGORITHMS

Linear Algorithms

Time Domain

Time domain analysis measures the variation of the intervals between consecutive normal cardiac cycles. The SD of NN intervals (SDNN) is the most frequently used HRV parameter,

TABLE 2 | Physiological factors on heart rate variability (HRV).

Factor	Effect	Reference
Sex	Most parameters are lower in women	Stein et al. (93) and Bonnemeier et al. (94)
Age	Most HRV parameters decrease with age, except ULF	Bigger et al. (95) and Stein et al. (93)
Weight	Anorexia nervosa: frequency domain↓. Increased BMI: total power (TP)↓. Weight loss >10%: HF↑	Rechlin et al. (96), Poirier et al. (97), and Kimura et al. (98)
Food intake	Few studies. Eating a meal had no influence. Dietary restriction: HF↑, LF↓	Ambarish et al. (99) and Vogele et al. (100)
Ethnicity	Problematic factor. One study showed lower HRV in Afro Americans compared to Caucasians but did not control social class	Choi et al. (101)
Circadian effects	SDNN↑ at night in one study. Most parameters decreased at night	Viola et al. (102) and Bonnemeier et al. (94)
Sleep	REM sleep: TP, VLF, LF↑, LF ↓. Non-REM sleep: TP, VLF, LF ↓, LF↑. In light sleep, SDNN, LF and LF/HF values are similar to wakefulness. Sleep deprivation: LF↑, conflicting results	Busek et al. (103), Zhong et al. (104), Chung et al. (105), Kesek et al. (106), and Ernst (11)
Regular exercise	SDNN, TP, HF, fractal dimension↑	Nakamura et al. (107), Levy et al. (108), and Pardo et al. (109)

TABLE 3 | Effects of drugs on heart rate variability.

Drug	Effect	Reference
Angiotensin II receptor antagonists	Increase of all time and frequency domain parameters	Petretta et al. (113)
ACE inhibitors	Increased total power (TP), HF, LF, ULF, VLF, and SDNN	Binkley et al. (114) and Bonaduce et al. (115)
Beta blockers	TP, HF, LF, and VLF↑, rMSSD, pNN50, SDNN and HF↑, in another study no effect	Pousset et al. (116), van den Berg et al. (84), Lin et al. (117), and Ernst et al. (110)
Antidepressiva	SDNN and frequency domain parameters decreased or unchanged	Rechlin (118), Rechlin et al. (111), Bar et al. (119), Straneva-Meuse et al. (120), and Licht et al. (112)
Caffeine	Increase of SDNN, rMSSD, frequency domain parameters, approximate entropy, detrended fluctuation analysis, or no change	Yeragani et al. (121), Rauh et al. (122), Richardson et al. (123), and Karapetian et al. (124)
Sedatives (midazolam, propofol, thiopental)	Decreased HF and LF	Galletly et al. (125), Michaloudis et al. (126), and Riznyk et al. (127)
Metformin	Increased TP, and HF, decrease in LF and LF/HF ratio	Manzella et al. (128)
Omega-3 fatty acids	Increased SDNN, rMSSD, HF, VLF, or no change	Mozaffarian et al. (129), Mozaffarian et al. (130), and Xin et al. (131)
Digoxin	Increased HF, LF, and rMSSD	Krum et al. (132)

formally the SD of all normal ("NN") QRS distances. It correlates with total power (TP), often $r > 0.9$ (87) {(133) #2347}. Since TP is adjusted to the variance of the analyzed time-series within the particular time frame, this correlation is not surprising. The SD of the average NN intervals (SDANN), usually calculated over 5-min periods, needs longer measuring periods and cannot be applied in short-term HRV measures. pNN50 and rMSSD can be used both in short-term and long-term measurements. NN50 is the number of pairs of successive NNs that differ by more than 50 ms, pNN50, the proportion of NN50 divided by total number of NNs over (normally) a 24h-recording {(2) #1505} and is often interpreted as a proxy for cardiac parasympathetic activity {(134) #2345}. rMSSD stands for the square root of the mean squared differences of successive NN intervals (2, 135). Some reference values for time domain parameters are presented in **Table 4**. Importantly, time domain parameters depend on the length of the recording time. Longer periods generate more variability. Studies can, therefore, only be compared when they use the same measurement period {(136) #2350}.

Geometric Methods

Geometric methods are obtained from sequences of NN intervals. Several algorithms are described as geometric methods, such as the 24-h histogram, the HRV triangular index, the triangular interpolation of NN interval histograms, and the Poincaré-plot.

The *triangular index (TI)* constructs a triangle with the major peak of the histogram, its baseline width corresponding to the amount of RR interval variability, and its height corresponding to the total number of all RR intervals (137). It is based on the density distribution (the number of all NN intervals) divided by the maximum of the density distribution. TI uses time-series of NN intervals on a discrete scale, and the parameter is calculated by the total number of NN intervals divided through the number of NN intervals in the modal bin and dependent on the length of the bin, with other words on the precision of the discrete scale of measurement [Task Force 1996]. It has been used more frequently in the last years, e.g., in Ref. (138, 139).

The *Poincaré-plot* is constructed with pairs of following R–R intervals assumed implicitly that the current one significantly determines the next R–R interval. Under physiological conditions, the difference between the first and following QRS-intervals increases, but less under pathological conditions (135). Poincaré plots can be approached qualitatively by describing their different shapes (140) but they can also be measured by the SD12 index which is based on the length of the axis of a circle having its center at the average RR interval and being related to the plot itself (141). Its additional value to other linear domain parameters is limited since SD1 correlates closely to rMSSD and SD2 to SDNN (142).

TABLE 4 | Reference values for some heart rate variability values provided by the Task Force and Nunan {(4) #2317} {(2) #1505}.

	Task force	Nunan (4)
SDNN (ms)	141 ± 39	50 ± 16
rMSSD (ms)	27 ± 12	42 ± 15
LF (ms^2)	1,170 ± 416	519 ± 291
HF (ms^2)	975 ± 203	657 ± 777
LF/HF	1.5 ± 2.0	2.8 ± 2.6

Frequency Domain

The frequency domain (power spectral density) analysis in humans was introduced by Axelrod et al. (27). It describes the periodic oscillations in different frequencies of the heart rate signal, and quantifies the amount of different frequency bands (137). During preprocessing, the RR intervals have to be resampled to transform it to a real time-series, usually at 4 Hz to capture oscillations up to 2 Hz according to the Nyquist theorem {(143) #2349}. Most frequently, frequency domain is calculated non-parametrically with the fast Fourier transformation (FFT). Parametric methods in the discrete Fourier transformation are more complex and dependent on the used model. The investigated time-series has to be stationary; therefore, it cannot be applicated in patients with fast changing heart rates under the measurement period. Under certain circumstances FFT fails to find structures which can be found with, e.g., wavelet analysis (144).

Usual parameters include TP, VLF (very low frequency, <0.003–0.04 Hz), LF (low-frequency power, 0.04–0.15 Hz), HF (high frequency power, 0.15–0.4 Hz). A frequently used ratio is LF/HF. Frequency domain parameters can be applicated both in short- and long-term measurements, but not ULF (ultra low frequency, <0.003 Hz), which only can be used in Holter monitoring.

HF is frequently interpreted as a marker of the PNS and is influenced by the respiratory rate (135). It is to a certain degree the same as the RSA (45) and correlates with it (145). Parasympathetic regulation of the heart has a fast response after about 0.5 s and returns to baseline within 1 s (67).

LF is modulated both by the activity of the sympathetic and parasympathetic system. A high LF power is often explained as result of high sympathetic activity (mental, physical stress, sympathomimetic pharmacologic agents). Sympathetic input leads to changes in heart rate, however, more slowly as after parasympathetic input, with a peak after about 4 s and return to baseline after about 20 s (146). The LF/HF ratio mirrors the general sympathetic/parasympathetic balance and returns usually in rest a value between 1 and 2. VLF is a general proxy for physical activity and might mirror also sympathetic activity, but the causality is debated (135). Increased inflammatory parameters like CRP, Il-6, and WBC are correlated with low VLF (147). Some reference values for frequency domain parameters are presented in **Table 4**.

Non-Linear Algorithms

The difference between "linear" and "non-linear" methods in HRV is not as straightforward as in the general definition mentioned above. Principally, frequency domain analysis is based on already established patterns. In Fourier transformations, the presumed frame is a sinusoidal wave and in wavelet analysis predefined wavelet function. Both patterns are in principle non-linear, but the methods remain linear because in Fourier transformations the sine waves are added, same as in wavelet analysis the different wavelets. By contrast, non-linear methods are not based on prespecified structures but analyze temporal similarities in the signals. Entropy is frequently, but not entirely, described as a measure for regularity of the signals, whereas fractal methods investigate self-similarities within signals.

Entropy

An influential algorithm in HRV at the beginning of the 1990s was approximate entropy (ApEN) (148). It was first introduced in 1991 (149) and evaluates data sets for repeating structures and for the probability that other time periods in the data set with the same length of runs (*m*), tolerance (*r*), and length of RR intervals (*n*) have the same structures. ApEN returns a number between 0 and around 1. In normal adults, ApEN is around 1. Lower numbers of ApEn indicate higher regularity, higher values less patterns and low uniformity in the data set. ApEN can be used reliably down to 1,000 data points making it feasible for short-term-HRV of 20 min (148). ApEN has been used successfully in such different fields in endocrinology (secretion of ACTH and cortisol in patients with major depressive disorders) (150), HRV behavior in patients with a combination of unstable angina pectoris and depression (151), respiration patterns in panic disorders (152), or HRV of adolescents treated with anti-depressant drugs (153). ApEN and other similar tools are superior to detect unknown relations between seemingly unconnected systems. In one study investigating patients with cachexia due to COPD, they had in contrast to non-cachectic patients with similar disease and healthy controls an absent circadian rhythm of circulating leptin (154). A major problem of ApEN is probably a lack of internal consistency. Therefore, as alternative a different algorithm, termed "sample entropy" (SampEn) has been introduced (155). Similarly, it calculates the probability of identifying specific patterns in a short time-series and is defined as the negative natural logarithm of an estimate for predictability in finding specific matches in a short time-series {(155) #1566}. To set the exactness of pattern recognition, the length (*m*) of the subseries and the tolerance (*r*) for the patterns has to be predefined. It returns results between 0 and around 2, 0 represents, e.g., a sinus curve and a result near 2 complete chaos. SampEn needs far fewer data points compared to ApEN, and it can be applicated in time-series between 200 to 250 data points (156, 157). Several other entropy algorithms have been proposed, like Lempel Ziv entropy (158), Multiscale entropy (159), fuzzy entropy (160), or Renyi entropy (161). All have been used in clinical studies, but their significance is still unclear.

Fractal Analysis

The notion of fractality has been originally introduced and applied by Benoit Mandelbrot on spatial self-similarities in graphical plots of non-linear deterministic iterations (162). Used for heart rate time-series, it refers not to spatial, but to temporal self-similarities over a range of scales {(163) #2351}. A normal series of RR intervals is fractal-like and shows a scale-free 1/f fluctuation typical for self-organizing systems behaving between uncorrelated randomness and highly predictable behavior {(164) #1569} {(165) #1747}.

Detrended fluctuation analysis (DFA) determines the statistical self-affinity of a signal. When used to analyze heart rates, it yields to separate scaling regions, a short-term scaling exponent and a long-term scaling exponent. Peng et al. presented the short-term scaling exponent (also termed $\alpha 1$) calculated by DFA first in genetical data (166) and in the following year also in HRV (167). Its great advantage is that it can be used for non-stationary data from time-series and correlates with the randomness in the heart rate time-series, the lowest values (~0.5) ressembles an entirely random series; high values (1.5) signify a time-series being completely correlated (141). It has been used to predict cardiac mortality in different patient populations (165, 168). Unfortunately, it needs at least 1,000 beats and has, therefore, been used more frequently in Holter monitoring studies.

Other proposed algorithms include coarse grained spectral analysis (169), the Fano factor (170), dispersional analysis (170, 171), fractal dimension (172), correlation dimension (173), or the Largest Lyapunov Exponent (174). Their clinical value is still unclear.

Other Algorithms

Heart Rate Turbulence is normally not considered as a HRV parameter, but it is based, however, on a similar physiological background and can be applicated in comparable ways. Patients need to have ventricular extrasystoles (VES) because HRT is based on the reaction of the system afterward. Healthy individuals without any arrhytmias can not be investigated with HRT. The heart rate directly following a VES increases normally, to decrease a moment later. This pattern is changed or non-existent in patients after myocardial infarction (175). The algorithm returns the parameters turbulence onset and turbulence slope (176).

OUTLOOK

Since the guidelines of the Task Force were published in 1996, the measurement and calculation of linear parameters have been highly standardized, making investigations comparable and meta-analysis possible. After the introduction of different non-linear parameters, expectations were high, but the role of non-linear algorithms is still unclear after more than two decades. As more than 70 different algorithms have been used (177). Today, HRV beyond its use in pulse watches is still not established in the clinical area although the methods are mature and have been tested extensively. The understanding, however, has increased substantially. Several models have extended its use into psychological and mental health research (55, 178, 179). Finally, 20 years after publishing the first globally used standard of measurement (2), a highly recommendable comprehensive methodological hands-on guideline summarizes state of the art and should be used a new standard (180). In addition, the role of non-linear methods has been recently evaluated and recapitulated (46). Also, a useful guideline to present HRV data has been published (181). HRV as a research and clinical tool is still underrecognized. It should be implemented in several clinical areas within a Bayesian paradigm to improve prediction, diagnosis, and therapy (182).

AUTHOR CONTRIBUTIONS

GE has elaborated and written the whole review.

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The PhysioCam: A Novel Non-Contact Sensor to Measure Heart Rate Variability in Clinical and Field Applications

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Heart rate variability (HRV) is a reliable indicator of health status and a sensitive index of autonomic stress reactivity. Stress negatively affects physical and psychological well-ness by decreasing cardiovascular health and reducing quality of life. Wearable sensors have made it possible to track HRV during daily activity, and recent advances in mobile technology have reduced the cost and difficulty of applying this powerful technique. Although advances have made sensors smaller and lighter, some burden on the subject remains. Chest-worn electrocardiogram (ECG) sensors provide the optimal source signal for HRV analysis, but they require obtrusive electrode or conductive material adherence. A less invasive surrogate of HRV can be derived from the arterial pulse obtained using the photoplethysmogram (PPG), but sensor placement requirements limit the application of PPG in field research. Factors including gender, age, height, and weight also affect PPG-HRV level, but PPG-HRV is sufficient to track individual HRV reactions to physical and mental challenges. To overcome the limitations of contact sensors, we developed the PhysioCam (PhyC), a non-contact system capable of measuring arterial pulse with sufficient precision to derive HRV during different challenges. This passive sensor uses an off the shelf digital color video camera to extract arterial pulse from the light reflected from an individual's face. In this article, we validate this novel non-contact measure against criterion signals (ECG and PPG) in a controlled laboratory setting. Data from 12 subjects are presented under the following physiological conditions: rest, single deep breath and hold, and rapid breathing. The following HRV parameters were validated: interbeat interval (IBI), respiratory sinus arrhythmia (RSA), and low frequency HRV (LF). When testing the PhyC against ECG or PPG: the Bland–Altman plots for the IBIs show no systematic bias; correlation coefficients (all p values < 0.05) comparing ECG to PhyC for IBI and LF approach 1, while RSA correlations average 0.82 across conditions. We discuss future refinements of the HRV metrics derived from the PhyC that will enable this technology to unobtrusively track indicators of health and wellness.

Keywords: heart rate variability, non-contact monitoring, arterial pulse, sensors agreement, optics and physiology

INTRODUCTION

Heart rate variability (HRV) frequently has been applied as a reliable indicator of health status, stress, and mental effort. Studies have linked HRV to cardiovascular diseases (1), post-traumatic stress disorder (2), depression (3), and fibromyalgia (4). HRV has been proposed as a sensitive index of autonomic stress reactivity such as in panic disorder (5) and work stress and mental effort (6). The literature on HRV indicates that day-to-day challenges that increase stress and reduce HRV have a negative influence on physical and psychological wellness by decreasing cardiovascular health and reducing quality of life.

Advances in technology have created the opportunity to apply wearable sensors to track HRV during daily activity (7, 8). Movement and light sensors embedded on mobile phones are used as contact sensors to acquire HRV indices (9, 10). These improvements in sensors, coupled with recent advances in mobile technology, have reduced the cost and difficulty of monitoring HRV outside the laboratory in applied contexts. Although sensors are smaller and lighter, they still impose a burden on the human subject. Chest-worn electrocardiogram (ECG) sensors provide the optimal source signal for HRV analysis, but they require an obtrusive electrode or conductive material adherence. A less invasive surrogate of HRV can be derived from the arterial pulse obtained using the photoplethysmogram (PPG), which provides sufficient accuracy to track individual HRV reactions to physical and mental challenges (11). However, sensor placement requirements limit the application of PPG in field research and participant awareness of being monitored is required with both contact sensors (i.e., ECG and PPG).

This article describes an innovative technology embodied in a novel device, the PhysioCam (PhyC) (12) that overcomes the limitations of contact sensors. The PhyC is a non-contact system capable of measuring arterial pulse with sufficient precision to derive HRV during different physiological challenges. In this article, we explore the science behind the PhyC, the implications of measuring HRV from the vascular periphery, and the future of non-contact sensors.

Non-contact technology is an emerging technology; recent research has explored the use of a basic webcam for measuring multiple physiological parameters. Poh et al. (13) used an inexpensive webcam with automatic face tracking and blind source separation of the color channels into independent components to extract cardiac pulse rate from a video recording. They applied a fast Fourier transform analysis to a 1-min recording of the video to extract the predominant frequency of variation corresponding to the cardiac pulse rate. Subsequently, the same team (14) reported the possibility to obtain the low frequency HRV and respiratory sinus arrhythmia (RSA) components of HRV applying blind source separation and frequency analysis of the components. Phillips released the Vital Signs Camera for iPad 2 or iPhone 4S, an application that uses the webcam capabilities of the tablets to acquire parameters of heart rate and breathing rate from a user who is sitting still in front of the camera. More than 80 applications have been developed that enable smartphone cameras to monitor heart rate. However, these applications use the phones light source and require physical contact with the fingertip. The commercially available applications do not disclose their approach to measure heart rate or breathing rate, but they employ some form of frequency analysis of digital camera data.

Research into non-contact extraction of physiological signals extends beyond pulse measurements with infrared video thermography being employed to accurately estimate breathing rate and relative tidal volume (15) and various forms of radar being explored to locate respiratory signals as well as cardiac activity (16, 17). Wu et al. (18) presented a method to visualize the flow of blood using a standard video sequence as input and applying spatial decomposition, followed by temporal filtering of the frames. The analysis reveals temporal variations in videos that cannot be seen by the naked eye and could represent blood flow; they called their method Eulerian Video Magnification. An evaluation of the literature suggests that non-contact extraction of human physiological parameters is both feasible and of considerable interest for research and commercial applications.

Current approaches to non-contact measures of HRV have limitations, since it is essential to have a high-quality pulse signal and a sensitive algorithm to detect features in the pulse signal to accurately time the sequential interbeat intervals (IBIs) and provide a valid and accurate estimate of IBIs derived from the criterion ECG signal.

In the case of non-contact sensors that utilize videography, the light sensor embedded in the camera limits the quality of the pulse signal. Most video cameras use one of two types of light sensors, the charge-coupled device (CCD) and the complementary metal-oxide semiconductor (CMOS). These photosensors transform light into electrons by the same approach, but use different methods to digitize the information. The CCD sensor digitization process produces high-quality and low-noise images in contrast to the CMOS sensor, which has greater interdependence of pixel level information from surrounding portions of the image array (19), making the CCD sensor an appropriate choice when analyzing biological signals through a Bayer-mapped pixel array.

To optimize frame-by-frame extraction of pulse information to facilitate IBI measurements, we selected a CCD sensor for the PhyC. Conceptually, the frame-by-frame extraction functions similar to digitizing a PPG signal. By contrast, the work of Poh and others is based on webcam with CMOS sensors. As noted, CMOS sensors have greater crosstalk between adjacent pixels of different color sensitivities (e.g., red or green). This may explain why blind source separation is required to extract the underlying physiological variance in the capture image sequences (13, 14).

The PhyC uses a CCD camera as its sensor and can function in ambient (sun, fluorescent, or incandescent) light. The CCD camera operates continuously, capturing images of the subject from a distance of about 3 m, with a field of view that encompasses the shoulders, neck, and face of the individual. From the collected images, a subset of pixels is extracted in each frame that contains the skin area of the upper half of the face. The 3-m distance from PhyC to the target subject in this study is determined by optics, number of pixels of the sensor, ambient light, and area of the body from which the signal is being detected. This distance could be modified for different applications.

The optical properties of human skin are determined by the presence of various chromophores in the layers of skin. The epidermis and the dermis are the predominant layers responsible for the optical properties of the skin. The epidermis is the outermost layer of skin, with a thickness varying from 0.05 to 1.50 mm. The main chromophore in the epidermis is melanin and it is essentially the only pigment affecting the transmittance of light in normal human epidermis (20). The dermis is the intermediate layer of the skin with a thickness varying from 0.3 to 3.0 mm. The predominant chromophores in the dermis are the blood-borne pigments hemoglobin, oxyhemoglobin, beta carotene, and bilirubin. Each of the pigments has different absorption spectra in the range of visible light (from 300 to 1,200 nm). The innermost and thickest layer of the skin is the hypodermis, which is connected to the dermis by collagen and elastin fibers. In between the dermis and the hypodermis is the arteriovenous plexus. The superficial arteriovenus plexus forms a microvascular network typically 0.05–0.50 mm below the skin surface (21) and the deep arteriovenus plexus forms a vascular network typically 1.00–5.00 mm below the skin surface. Thus, the main chromophores determining skin color are the melanin present in the epidermis and the blood-borne pigments present in the dermis/hypodermis vascular plexus.

Within the pixels selected to be processed, the optical characteristics of hemoglobin, an active chromophore in the visible light range, determine the wavelengths of interest. Given the high percentage of hemoglobin in the blood composition (around 45%) (22), it is possible to measure the volumetric blood changes by a light sensor that works in the visible light range (see **Figure 1**). The PhyC decomposes consecutive images to extract the subtle volumetric blood changes from light reflectance changes (i.e., observed color). In addition to the physiological (blood volume) sources of variation in light intensity within these pixels, there are a number of sources of noise in the signal, including inconsistent illumination intensity, movement, shadow, skin color, electrical noise, and failure of the motion tracking algorithms to reliably identify the relevant pixels.

The camera measures the segment of light in the visible band, the portion of the electromagnetic spectrum in the region from approximately 380 to 775 nm. The light captured by the camera is segmented using the red, green, and blue (RGB) Bayer filter pattern into three sub bands: blue (380–500 nm), green (500–600 nm), and red (600–775 nm). The optical properties of the skin, blood, and CCD sensor enable the PhyC to function as a biosensor of cardiovascular activity at the surface of the face.

Figure 1 shows the absorption curve of the hemoglobin (red and blue lines) in relative units. The normalized, relative melanin absorption curve (green line) is superimposed on the hemoglobin absorption curve. At the bottom of the *X*-axis is the range of the spectral response curves for the three color bands of the CCD sensor. Melanin accounts for skin color and predominantly acts in the short wavelength range of the visible light (<500 nm). In this range, differences in skin colors affect the light absorption curve. In the longer wavelength range of light (i.e., above 500 nm), melanin has a notably smaller, more consistent impact on absorbance. The PhyC utilizes wavelengths longer than 500 nm to minimize between subject differences in signal strength due to skin color, green dotted section on **Figure 1**. Only green (500–575 nm) and red (575–750 nm) pixel values are used to estimate relative absorption of light by the blood.

The PhyC utilizes an algorithm integrating knowledge of the physiology of the arterial pulse wave with the capabilities of the camera. The natural or artificial light illuminates the person's face, and some of the light is transmitted through the epidermis and penetrates the skin about 2–3 mm deep into the dermis, where the different components of the dermis reflect, absorb, and/or

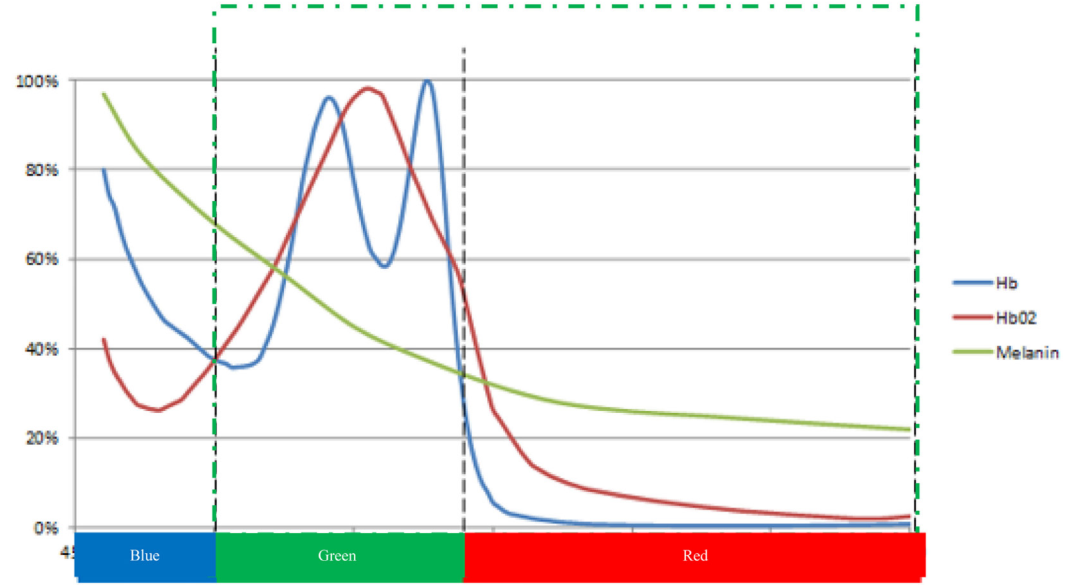

FIGURE 1 | Schematic representation of the relative light absorption of the main chromophores of the human skin: Hb (deoxygenated hemoglobin), HbO_2 (oxygenated hemoglobin), and melanin. Bottom color bar: spectral response range for digital video cameras [adapted from Prahl (23) and Huang et al. (24)].

transmit the light. The main source of rhythmic variation in light absorbance and reflectance in the dermis is the hemoglobin present in the blood vessels. The volume of blood in the arteries and arterioles changes as a function of the beating of the heart. Each heart beat generates a pressure wave that changes the radius of arteries and arterioles. Volumetric changes in the arterial bed cause reflectance and absorbance changes along the transmission and reflection pathways of the incident light. The video camera captures the light reflected by the person's face and the subtle changes in that reflected light due to pulse wave activity. When there is more blood in the arteries and arterioles and more light is absorbed by the blood, the camera detects less reflected red and green light. On the contrary, when there is less blood in the arteries and arterioles, the blood absorbs less light and the camera detects more reflected light (25).

This report evaluates the validity of the derived video pulse wave by comparing it with criterion signals. The precision of PhyC derived beat-to-beat intervals (IBI) were evaluated by contrasting these values with contact measures from an ECG and earlobe photoplythesmogram (elPPG). In addition, derived variables of average heart period (HP), RSA, and low frequency HRV (LF) during specific experimental conditions were contrasted.

MATERIALS AND METHODS

General Approach

Heart rate variability is defined as the variations in time between sequential heartbeats. When HRV is deconstructed through statistical procedures, it is possible to quantify rhythmic components that reflect specific pathways of neural regulation. The most salient components are a respiratory oscillation known as RSA [e.g., Ref. (26)] and a slower frequency (LF) assumed to be related to blood pressure regulation *via* the baroreceptors and peripheral vasomotor activity [for overview see Porges (27) and Reyes del Paso et al. (28)].

Respiratory sinus arrhythmia is assumed to reflect cardiac vagal tone *via* myelinated pathways originating in a brainstem area known as nucleus ambiguus. RSA is due specifically to myelinated vagal efferent fibers and the other HRV components are not specific, and thus may not include both myelinated and unmyelinated vagal fibers. The unmyelinated vagal efferent fibers originate in a brainstem area known as the dorsal nucleus of the vagus and may contribute to the lower frequencies of HRV. Removing RSA from HRV might result in a metric that would be mediated by a contribution of both dorsal and ventral vagal influences. Blockade studies are not useful in differentiating the influence of myelinated and unmyelinated vagal pathways on HRV, since virtually all HRV (i.e., RSA and lower frequencies) is removed with muscarinic blockade (e.g., atropine) (29–31). In addition, HP (i.e., average IBI over a period of time) was monitored, since it reflects the sum of neural, neurochemical, and intrinsic influences on the heart.

The literature, identifying neurophysiological mechanisms and sensitivity of HRV components to behavioral, psychological, and health parameters, is primarily based on the analysis of the heart rate patterns measured with an ECG sensor. ECG has been the signal of choice, since the sequence of times between R-peaks can provide a non-invasive (but not non-contact) measure of the neural regulation of the heart (32).

The PhyC and the elPPG measure heart rate at the periphery, where measures of beat-to-beat heart rate contain the source information from the ECG with added sources of variance. The main source of variance is the vascular system, which acts as a filter modulating the propagation of the heart beat and introducing an additional source of variations in the timing between the sequential pulse-to-pulse interval time series (33). The inherent functioning of the elPPG and the PhyC as photo sensors further introduces movement as a potential source of measurement error. The non-contact nature of the PhyC amplifies the measurement error due to greater variations in movement and light source and a slower sampling frequency of the sensor. To validate the variables derived by the PhyC, an experiment was conducted to identify, describe, and understand the similarities and differences among the values obtained by PhyC, elPPG, and ECG.

Experiment Design

To test the PhyC, we designed an experiment consisting of a resting baseline period followed by several challenges designed to alter the neural regulation of the heart that would be manifested in changes in HRV. By presenting different challenges, it was possible to evaluate whether the PhyC accurately tracked the physiological changes monitored *via* ECG and elPPG.

Physiological Challenges

a. Breathing rate: voluntary or involuntary respiratory rate shifts the neural influence of vagal pathways on heart rate and RSA (34). To evaluate the capability of the PhyC to track changes in autonomic state caused by shifts in respiration rate, two breathing patterns were used (single deep breath and sustained rapid shallow breathing). Single deep breath and hold (SDB) was done by inhaling and holding the volume of air for as long as possible follow by normal breathing. The SDB is accompanied by decreases in heart rate and RSA (34). Shallow rapid breathing (RB) was implemented by restricting the volume of air inhaled on each breath. Shallow breathing decreases the amplitude of the RSA and increases heart rate (35).
b. Cold pressor (CP): the CP test consisted of the immersion of a hand and forearm in ice water for 90 s or as long as tolerated by the participant (36). Due to signal distortions from movement and variations in the duration, immersion data from this condition were not examined for this paper.

Participants

This study was approved by the Institutional Review Board of the University of Illinois at Chicago as protocol # 2012-0206 entitled "Real Time Non-contact Extraction of Human Arterial Pulse." The IRB authorized the recruitment of 20 subjects through flyers, the University of Illinois at Chicago Psychology student subject pool, and *via* email to the UIC students' community. Twenty participants were recruited (10 females and 10 males) between 19 and

71 years of age with a mean of 33.13 years and SD of 14.62 years. 17 subjects reported no preexisting medical condition. Three females had specific medical conditions: one was 6 months pregnant, one was diagnosed with multiple sclerosis and syncope, and one reported an undiagnosed vascular constriction condition. The ethnicity mix of our participants was 60% Caucasians, 25% Hispanics, 10% African-Americans, and 5% Asians.

Data from three subjects were not analyzed for the following reasons: one criterion signal was corrupted making it impossible to access both the ECG and elPPG files, one participant presented with an extreme tonic peripheral vasoconstriction that masked the pulse wave precluding the ability to extract the arterial pulse by the PhyC, and one participant presented sufficiently low HRV that precluded the calculation of the LF component. Data from the remaining seventeen subjects were processed for analysis. Movement-related confounds in some of the criterion variables resulted in an exclusion of segments of data for some participants during specific challenges. For this article, the 12 participants with complete sets of data for the 5 reported tasks are included.

The protocol as approved by the IRB contained two stages:

I. Offline: during the offline stage, video images were recorded and then processed to develop and to optimize the algorithms to process the video signal. The offline stage lasted 15 min, during which participants were asked to perform the following experimental manipulations:
   a. Initial rest baseline (2 min) (1BSL).
   b. SDB (2 min).
   c. Rest (2 min) (2BSL).
   d. CP.
   e. CP recovery (approximately 3 min) (CPr).
   f. Rest (1 min) (3BSL).
   g. Shallow RB (2 min).
   h. Rest (3 min) (4BSL).

II. Online (proof of concept): during the online stage, the PhyC extracted the arterial pulse wave in near real time. The objective of the online stage was to evaluate the factors that may limit applications of the technology such as head and face tracking, processing demands, and time delay between acquisition and output. During this stage, participants were asked to sit quietly during 5 min while the arterial pulse wave was monitored. Data from this stage are not reported in this paper, because of two limiting factors: (1) the slow sampling frequency (30 Hz) at which the signal was collected resulted in greater variations in the estimates of IBIs from the pulse wave and (2) in several participants, the system could not track continuous sequential IBIs for a sufficient duration to calculate HRV, although the estimates of HP over several seconds provided excellent convergence with the ECG signal.

Hardware and Software

To obtain the criterion signals, a BIOPAC MP150 system (BIOPAC Systems, Inc., Camino Goleta, CA, USA) was used. The BIOPAC acquired the criterion data at a 1,000 Hz sampling frequency. The criterion signals acquired by the BIOPAC MP150 system were ECG from a 3-lead configuration on the chest, reflectance earlobe PPG (elPPG), and reflectance fingertip PPG (ftPPG). Breathing frequency was also assessed with a single strain gage respiration band.

To obtain the PhyC signal, a Grasshopper® 03K2C IEEE-1394b (FireWire) digital camera (Point Grey Research Inc., Richmond, BC, Canada) was used. The digital camera serves as the sensor providing the signal from which the arterial pulse wave is extracted. Grasshopper® digital camera monitors color signals with wavelengths between 350 and 750 nm, with a 640 × 480 pixel resolution and transmits the raw 8-bit RGB Bayer data at a sampling rate of approximately 60 frames per second. Subjects were positioned approximately 3 m in front of the camera.

Two software packages were used to acquire and to process the data. AcqKnowledge 4.2 (BIOPAC Systems, Inc., Camino Goleta, CA, USA) was used to collect and archive the BIOPAC data. This program output a text file containing five columns of information: relative time, analog physiological signals (i.e., elPPG, ECG, respiration), and the synchronization signal. LabVIEW™ System Design Software (National Instruments Corporation, Austin, TX, USA) was used to collect and to process the data from the color digital video camera. LabVIEW™ was also used to develop the applications to analyze, compare, and contrast the PhyC with the criterion signals.

Data Quantification

Data quantification was performed at different levels of analysis, due to the hierarchical nature of parameter extraction. For instance, IBIs are first derived from the arterial pulse, and then components of HRV are derived from the IBI time series.

First Level: Raw Signal Processing, Synchronization, and Tasks Segmentation

PhyC—Pulse Extraction

For the offline analysis, images of a seated subject were captured by the camera at specified sampling frequency (approximately 60 Hz). The images were processed by an algorithm that selects a region of interest (ROI, section of the participant's face) and separates the ROI into the RGB color planes. The mean values of each color component are calculated by a histogram function. Mean values of the blue color are not used because they contain the melanin information which varies with skin colors. As noted in **Figure 1**, mean values of green and red are less affected by differences in skin color across subjects. The mean values of the green and red color were divided (green/red) to create a common mode rejection ratio that minimizes common noise signals not related to arterial pulse (e.g., subject's subtle movement, light shifts, and camera artifacts); the resulting signal was labeled $\text{Pulse}_{\text{raw}}$ (37).

The 60 Hz raw values were paired with the time stamp of each frame to create a consecutive time series with inconsistent sampling frequency. This time series was then interpolated and up-sampled to create a constant 1 kHz signal (equivalent to the criterion signals). The inverse signal was calculated to resemble the volumetric changes of the pulse. More light absorption represents higher volume of blood in the arteries, and less light absorption lower volume of blood in the arteries. The signal was filtered using a second order Butterworth Band Pass filter (low cutoff = 0.5 Hz, high cutoff = 2.0 Hz). The cutoff frequencies were established to assure that different heart rate patterns between subjects could be detected. A healthy individual's heart rate at rest is normally between 0.75 and 1.0 Hz (i.e., 60–80 beats per minute). The first derivative of the pulse signal was calculated to augment changes in the slope of the signal. These sequential steps enable the PhyC to generate an analog representation of the arterial pulse wave that is sampled at 1 kHz for synchronization with ECG and elPPG signals from the Biopac.

Ear Lobe Pulse (elPPG)

The elPPG was measured at a 1 kHz through a DC amplifier (no filter settings) to preserve the slower aspects of signal reflecting the sympathetic influences on vasomotor tone. To extract the pulse peak, the elPPG signal was centered on zero by subtracting the first value to the entire trend, next it was filtered using a second order Butterworth Band Pass filter (low cutoff = 0.5 Hz, high cutoff = 2.0 Hz). A first derivative function was applied to translate the signal into slope changes over time and stabilize the estimation of pulse arrival times.

Electrocardiogram

The ECG was sampled at a 1 kHz using the preferred ECG BIOPAC MP-150 analog band-pass filter settings with a gain of 1,000.

Data Segmentation by Task

A time log file documented the start and end of each challenge for each participant and enabled synchronization with the physiological variables. ECG, elPPG, and the resampled (1 kHz) PhyC were aligned by use of a synchronization pulse in the Biopac data. The time log was used to extract the physiological signals associated with the different conditions of the experiment. In this article, segments corresponding to the following tasks were analyzed: initial baseline (1BSL), SDB, rest (2BSL), shallow rapid breathing (RB), and final baseline (4BSL) for ECG, elPPG, and PhyC. Due to variations in tolerance, movement, and the time course of responding, the CP task was not analyzed.

Second Level: Extraction of the IBIs

R Peak and Peak of Pulse Wave Detection

To accurately extract the heart rate pattern, a cardio peak-valley detector (CPVD) was developed. The CPVD is a LabVIEW™ based algorithm that extracts peaks or valleys of different physiological waves, such as the ECG, PPG, and respiration. The CPVD is able to detect peaks or valleys (time position and amplitude) of the signal by an adaptive approach. The algorithm uses a window of data to find a peak, and once the peak is detected the window moves one step and looks into the next window for the next peak. Each window is set to contain at least one physiological peak. For example, the window width for the ECG is around 700 ms and the step size is around 400 ms to assure that and R peak would be present in the analyzed window. For the first three peaks, the window width and step sizes are constant values, after the third peak is extracted, the information of the last two peaks time difference is used to adapt the window width and step size. This ensures that the window width and step size will adapt to the individual's response to the task challenge. If the heart rate increases, the window and step sizes decrease. If the heart rate decreases, the window and step sizes increase. Within each window, a peak detection algorithm is applied.

The peak detection algorithm applied a quadratic fit to identify peaks above a specified threshold determined by the distribution of samples within the window. The peak detector algorithm fits a parabola to a sequence of successive points assuming a specified width pulse wave or the R-wave of the ECG signal. The algorithm checks whether each parabola is at the local maxima by evaluating the sign of the quadratic coefficient, which indicates the parabola's concavity. The number of data points used in the ECG fit is specified by a width of approximately 15 ms. Each peak resulting within the window is tested against the threshold. Peaks with heights lower than the threshold are ignored. Because the algorithm calculates all the peaks above the threshold, it is possible to find two or more peaks within a window, in that case the first peak is compared against the maximum within the window and the one with the greater amplitude is selected as the peak of that window. Because the peak detection algorithm uses a quadratic fit to find the peaks, it functionally interpolates between the data points. Therefore, the timing precision of the peak location exceeds the precision of the original sampling rate of the signal.

The CPVD generates a trend formed by pairs with coordinates of time and peak amplitude. The CPVD has been tested in the analysis of several independent physiological signals, resulting in less than 2% missing peaks for signals with few artifacts. The CPVD has also performed well in extracting peaks from data with periods of low signal to noise ratio (37). The CPVD was used to calculate the R-peaks of the ECG and the pulse wave peaks of the elPPG and the PhyC during the different tasks.

Interbeat Interval

Interbeat interval is the time between consecutives heart beats, expressed in milliseconds. IBIs are calculated by the consecutive differences of the time component of the R-peaks or the pulse peak coordinates.

Third Level: Quantification of HRV Parameters

Time Sampled Mean IBIs from 2 and 5 s Windows (IBI 2sW and IBI 5sW)

The IBI event series was resampled at 2 Hz to generate an equally spaced intervals time series. The 2 Hz time sampled estimates of HP were used for calculating HP, RSA, and LF during each experimental condition and for calculating HP estimates for sequential 2- and 5-s windows. The HP is the average value of the 2 Hz IBI time series within a specific segment or task.

Respiratory Sinus Arrhythmia

Based on the Porges–Bohrer method (38, 39) a third-order, 21-point moving polynomial filter (MPF) was applied to the 2 Hz IBI time series to remove low frequency oscillations and slow trend. The residual detrended output of the MPF was filtered with a Kaiser FIR windowed filter with cutoff frequencies that remove variance not related to spontaneous breathing in adults (0.12–0.40 Hz). The filtered detrended output was divided into sequential 30-s epochs and the variance within each epoch is transformed by a natural logarithm [ln(ms^2)], the mean of these epoch values is used as the estimate of RSA for the specific segment.

LF

Based on the Porges–Bohrer method (38, 39) a third-order, 51-point MPF was applied to the 2 Hz IBI trend to remove extremely low frequency oscillations and slow trend. The residual detrended output of the MPF was filtered with a Kaiser FIR windowed filter with cutoff frequencies (0.04–0.10 Hz). The filtered detrended output was divided in 30 s epochs and the variance within each epoch is transformed with a natural logarithm [ln(ms^2)], the mean of the epochs values is used as an estimate of LF for the segment.

Data Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp.

Bland–Altman (B–A) Plots

Bland–Altman plots were used to compare the PhyC generated IBI values with the IBI values generated by the criterion signals (ECG and elPPG) and also to compare values generated by the elPPG and ECG signals. B–A plots enable the determination of agreement between two sensors, by plotting the mean between pair of measurements against its difference. Visual inspection of the B–A plots was used to identify systematic biases and possible outliers. Paired *t*-tests evaluated whether the differences between the signals were biased (i.e., one signal source generating longer or shorter values). B–A plots and the *t*-test were performed on IBIs collected from all participants during all tasks.

Scatter Plots and Linear Regressions

Scatter plots and linear regression analyses were used to visualize and calculate the level of convergence between the physiological measures derived from PhyC with each of the criterion signals (ECG and elPPG) and between the two criterion signals. Parameters from Mukaka's (40) paper where used to interpret the size of the correlation coefficients.

Size of Effect Repeated Measures ANOVA (RMANOVA)

Value of the partial eta-squared for the TIME effect, obtained by RMANOVA (General Linear Model), of the HP, RSA, and LF for each sensor across the five tasks was used to evaluate if the effect size of the experimental manipulations observed by the three sensors were in the same magnitude and of the same level of significance.

RESULTS

The PhyC Signal

The PhyC produces a physiological signal that resembles the one obtained by the elPPG as observed on the synchronized 15 s segment of data shown in **Figure 2**, elPPG is the top green line and the PhyC is the middle gray line, and the ECG the bottom blue line. The PhyC signal does not look as stable as the traditional elPPG, but follows its pattern. The PhyC signal shows the same offset from the ECG as the elPPG.

B–A Plots

Visual inspection of the B–A plots located in the A panels of **Figures 3–5** indicate excellent agreement and minimal bias between the sequential IBIs measured with ECG and PhyC (color coded by participant) in **Figure 3**, elPPG and PhyC in **Figure 4**, and ECG and elPPG in **Figure 5**. For the three cases, the B–A plots suggest that error magnitude is slightly larger for shorter IBIs, the IBI differences are larger on the left side of the B–A plots and closer to zero on the right side. The 95% confidence intervals are listed in **Table 1**. Note that the mean of the differences are less than 0.1 ms and that there are no significant differences between the metrics in central tendency. The *t*-test results confirm that the pairs of sensors are measuring the same parameter, mean of the differences are not significantly different than zero, indicating that there is no fixed sensor bias.

Scatterplots with regression analyses contrasting the sensor pairs are illustrated in the B panels of **Figures 3–5**. The regression models provide excellent fits to the IBI data with R^2 above 0.90 as shown in **Table 2**.

To stabilize the estimates from the PhyC, IBI data were averaged within 2 and 5 s windows. **Figure 6** illustrates the scatterplots and regression fits for the time windowed estimates of ECG- and PhyC-derived IBI data. Note relatively perfection convergence (i.e., $R^2 = 1.0$) and reduction in dispersion (i.e., reflected in the SD of the differences) as the window for estimating IBI increases from beat-to-beat to 2 s, and then to 5 s.

As observed in **Table 3**, as the window to average IBI measures widens from individual IBIs to 2 and 5 s windows, the SD of the

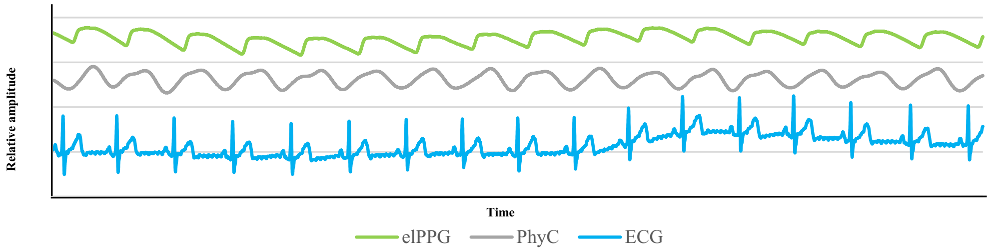

FIGURE 2 | Physiological signals. Plot of 15 s of data for participant #01 during 1BSL, the green line represents the elPPG, the gray line is the PhysioCam (PhyC), and the blue line is the electrocardiogram (ECG).

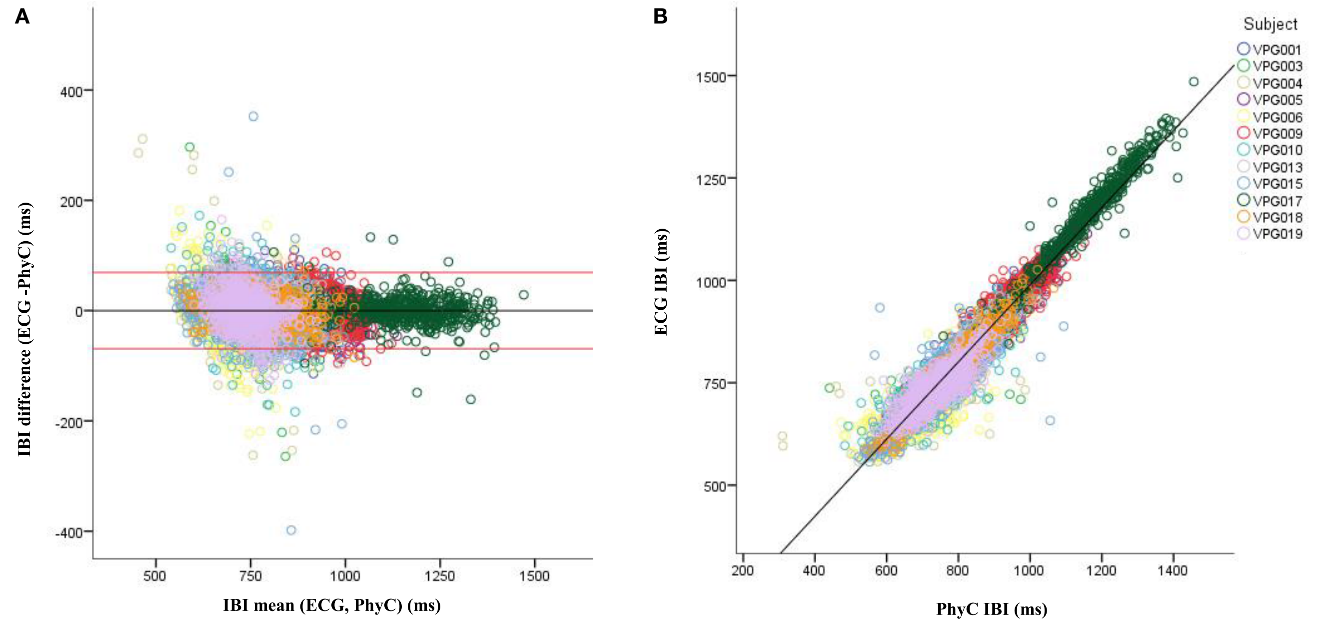

FIGURE 3 | Bland–Altman and scatter plot for interbeat interval (IBI) from the electrocardiogram (ECG) and PhysioCam (PhyC), color coded by participant. **(A)** Plot of the IBI differences vs the means for the ECG and PhyC. Red lines indicate the 95% confidence interval. **(B)** Scatter plot of the PhyC vs ECG IBIs.

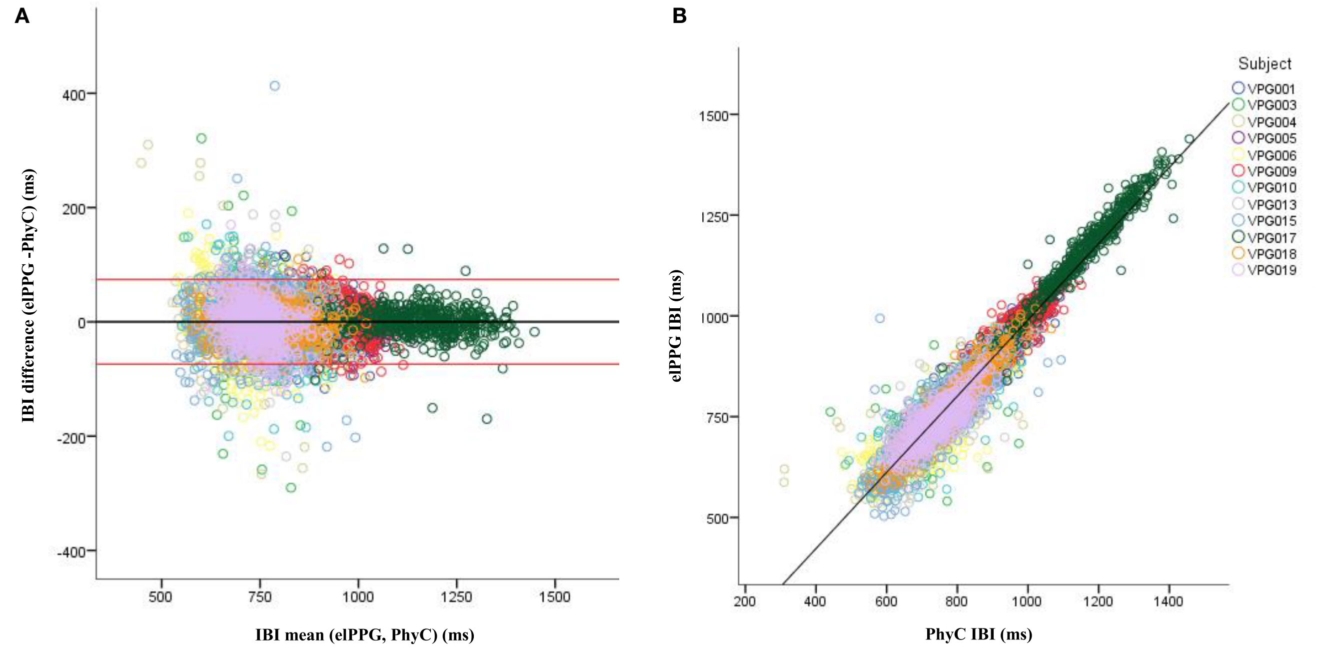

FIGURE 4 | Bland–Altman and scatter plot for interbeat interval (IBI) from the elPPG and PhysioCam (PhyC), color coded by participant. **(A)** Plot of the IBI differences vs the means for the elPPG and PhyC. Red lines indicate the 95% confidence interval. **(B)** Scatter plot of the PhyC vs elPPG IBIs.

differences between the PhyC and the ECG decreases and the R^2 increases reaching unity. The IBI data by subject by sensor shown in **Table 4** are consistent with the scatter plots of **Figure 6**, in which averaging the IBI within a 2 and 5 s window considerably improves the linear regression between the PhyC and both the ECG and the elPPG for all subjects.

Table 4 documents a range of individual differences in which PhyC estimates individual IBIs better in some participants,

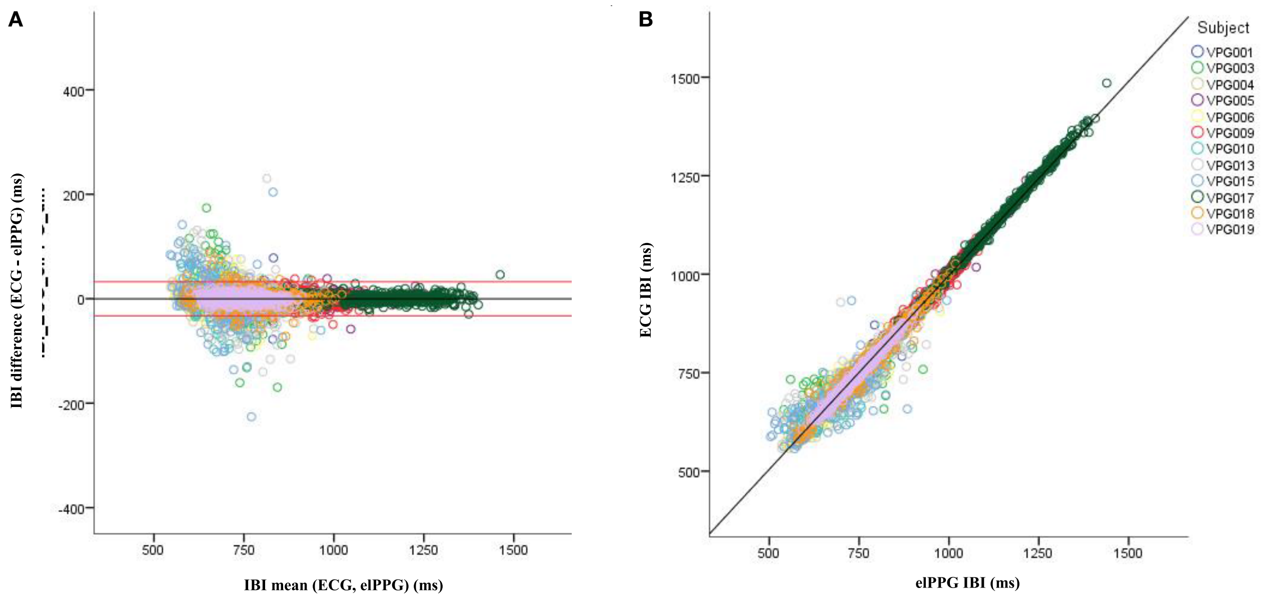

FIGURE 5 | Bland–Altman and scatter plot for interbeat interval (IBI) from the electrocardiogram (ECG) and elPPG, color coded by participant. **(A)** Plot of the IBI differences vs the means for the ECG and elPPG. Red lines indicate the 95% confidence interval. **(B)** Scatter plot of the elPPG vs ECG IBIs.

TABLE 1 | Bland–Altman (B–A) contrast parameters for interbeat interval between sensors.

B–A contrast	95% CI (ms)	Mean of the differences (ms) (SD)	Mean of the differences single sample *t*-test
Electrocardiogram (ECG) vs PhysioCam (PhyC)	±69	−0.07 (35.3)	*t* (8,574) = −0.17, *p* = 0.86
elPPG vs PhyC	±74	−0.02 (37.8)	*t* (8,574) = −0.04, *p* = 0.97
ECG vs elPPg	±33	−0.08 (16.7)	*t* (8,574) = −0.45, *p* = 0.65

Confidence interval, mean of the differences between sensors, single sample t-test of the mean differences.

TABLE 2 | Regression model parameters between sensors when measuring interbeat interval.

Sensors	Regression model	R^2
Electrocardiogram (ECG) vs PhysioCam (PhyC)	$Y = 1.00X + 47.65$	0.94
elPPG vs PhyC	$Y = 0.95X + 44.84$	0.93
ECG vs elPPg	$Y = 0.99X + 12.5$	0.99

R^2 values ranging from 0.64 to 0.96 when compared to ECG. However, these differences are minimized with a 2 s window (i.e., R^2 values range from 0.93 to 1.0) and virtually disappear with a 5 s window (i.e., R^2 values range from 0.98 to 1.0).

Figure 7 indicates convergence around the expected model $y = x$ for all the sensor comparisons for the measures of HP with R^2 of 1.00 for the three cases.

The linear regression of RSA between ECG and PhyC from **Figure 8A** while not in convergence with the model $y = x$ ($y = 1.27x - 2.55$) indicates a moderately strong correlation R^2 of 0.65. The linear regression of RSA between elPPG and PhyC from **Figure 8B** while not in convergence with the model $y = x$ ($y = 1.11x - 1.25$) indicates a moderately strong correlation R^2 of 0.71. The strongest correlation is observed between ECG and elPPG as shown in **Figure 8C** with R^2 of 0.78, close to the 0.8 threshold to be considered a strong correlation.

Figure 9 depicts the linear regression on LF between the different sensors (**Figure 9A**) ECG and PhyC, (**Figure 9B**) elPPG and PhyC, and (**Figure 9C**) ECG and elPPG. The three models show convergence around the expected model $y = x$, with the elPPG and ECG showing the strongest R^2 of 0.97 and the PhyC and elPPG showing the weakest with R^2 of 0.92.

The RMANOVA is used to demonstrate the sensitivity to change across time in each HRV parameter, as observed by each sensor. Results of the partial eta-squared for time in the RMANOVA are shown in **Table 5**. The three sensors measure similar, significant time effects for HP. All three sensors measure a similar, but not significant time effect for LF. While measuring RSA, the PhyC captures a significant, but reduced, effect for time as compared to the ECG, while the elPPG fails to detect a significant time effect for the parameter.

Change Scores for HP, RSA, and LF

Change scores shown in **Figure 10** indicate that the PhyC and the elPPG are able to track the change scores from 1BSL obtained with the ECG (criterion signal sensor) for the HP parameter. While the PhyC and the elPPG do not track the change scores for RSA obtained with the ECG, they both reflect a similar, attenuated

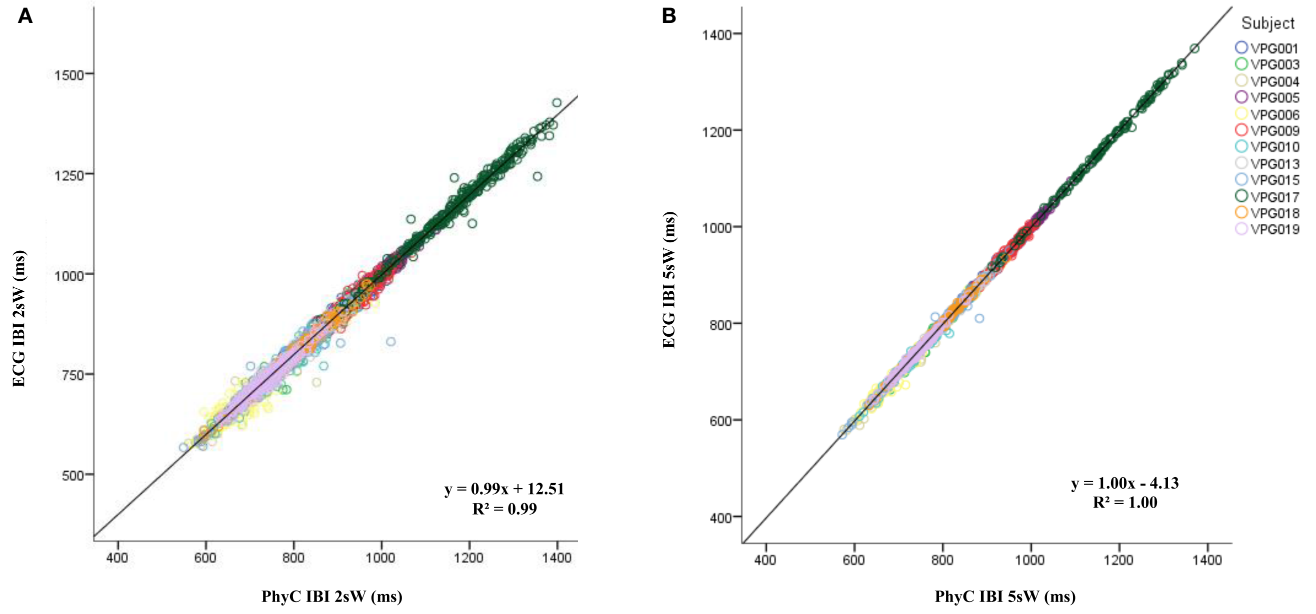

FIGURE 6 | Scatter plot for average window interbeat interval (IBI) from the electrocardiogram (ECG) and PhysioCam (PhyC) color marked by participant. **(A)** Scatter plot of the PhyC vs ECG for 2 s average windows IBIs. **(B)** Scatter plot of the PhyC vs ECG for 5 s average windows.

TABLE 3 | Differences mean and SDs for all subjects, all consditions between the electrocardiogram (ECG) and PhysioCam (PhyC) for interbeat interval (IBI), IBI 2 s windows, IBI 5 s windows, and HP 30; and R^2 of linear regression for PhyC on ECG.

		Differences		Linear regression
PhyC vs ECG	***N***	**Mean**	**SD**	R^2
IBI	8,574	−0.07	35.26	0.94
2 s window IBI	3,501	−1.51	13.03	1.00
5 s window IBI	1,403	−1.50	5.67	1.00
Heart period (30 s epoch)	60	−1.69	1.61	1.00

response for RSA across time. Both sensors track the moderate changes of LF observed by the ECG.

DISCUSSION

The PhyC reliably tracks IBIs when compared to either criterion signal (i.e., ECG or elPPG). As the window of comparison expands from individual heartbeats to 2 and 5 s sequential windows, the modest differences between sensors decreases dramatically and both the PhyC and elPPG converge with the ECG-derived values. Thus, the peripheral measures capture the slower dynamics in heart rate almost exactly, while making small errors in the rapid changes in IBI from beat to beat.

Inspecting the B–A plots reveals greater error in estimating IBIs with either the PhyC or elPPG when IBIs are shortest. Some of this error can be attributed to the shift in signal to noise ratio as the constant measurement error occupies a greater percentage of the interval defining the IBI.

The physical constraints of vascular transmission of the pulse wave also contribute to the deviations between the ECG and the peripheral measures of IBI (elPPG and PhyC). The cardiovascular system acts as a filter, modulating the duration between pulses that define IBIs and the parameters of this filter are non-constant due the neural regulation of vascular tone which has known oscillatory components (41). The conclusion that vascular transmission impacts short-term variation in IBIs is strengthened by: (1) the observation that similar dispersion in deviations from ECG-derived IBIs were observed when comparing elPPG with the ECG (signals collected with the same device at the same sampling frequency) and (2) the fact that similar outcomes have been reported for PPG (42). The error manifested differently across comparisons with the ECG-derived HRV metrics quantified in this study: (1) HP was virtually devoid of error with linear regression documenting the convergence among the HP estimates derived with PhyC, elPPG, and ECG during 30-, 5-, and 2-s epochs; (2) RSA calculation showed modest error magnitude with larger errors during segments with shorter IBIs, as illustrated during the RB condition when RSA estimates from both PhyC and elPPG show similar deviation from the ECG measure; (3) LF was virtually devoid of error documenting that slower components of HRV are relatively immune to the dampening effects of the vascular system.

Other sources of error are due to the physics of the sensor embedded in the PhyC system. Compared to the contact PPG, the PhyC is more sensitive to movements and lighting shifts in the environment, although both measures are based on light absorbance at similar wavelengths. Since the PhyC and the elPPG measure cardiovascular activity at the periphery it would be expected to find more agreement between them then when

TABLE 4 | R^2 of the interbeat interval (IBI) linear regression between sensors by subject considering all the IBI, 2sW, and 5sW.

Subject	Sensors	NO window	2 s window	5 s window
VPG001	ECG_PhyC	0.84	0.96	0.99
	elPPG_PhyC	0.83	0.96	0.99
	ECG_elPPG	0.99	1.00	1.00
VPG003	ECG_PhyC	0.73	0.96	0.99
	elPPG_PhyC	0.64	0.94	0.99
	ECG_elPPG	0.86	0.97	0.99
VPG004	ECG_PhyC	0.69	0.94	0.98
	elPPG_PhyC	0.67	0.94	0.98
	ECG_elPPG	0.96	0.99	1.00
VPG005	ECG_PhyC	0.91	0.98	1.00
	elPPG_PhyC	0.91	0.98	1.00
	ECG_elPPG	0.99	0.99	1.00
VPG006	ECG_PhyC	0.64	0.93	0.98
	elPPG_PhyC	0.65	0.94	0.99
	ECG_elPPG	0.94	0.98	0.99
VPG009	ECG_PhyC	0.80	0.94	0.99
	elPPG_PhyC	0.80	0.94	0.98
	ECG_elPPG	0.98	0.99	1.00
VPG010	ECG_PhyC	0.69	0.94	0.99
	elPPG_PhyC	0.66	0.94	0.99
	ECG_elPPG	0.93	0.99	1.00
VPG013	ECG_PhyC	0.88	0.98	1.00
	elPPG_PhyC	0.79	0.94	0.98
	ECG_elPPG	0.89	0.96	0.98
VPG015	ECG_PhyC	0.81	0.96	0.99
	elPPG_PhyC	0.78	0.96	0.99
	ECG_elPPG	0.92	0.99	1.00
VPG017	ECG_PhyC	0.96	0.99	1.00
	elPPG_PhyC	0.96	0.99	1.00
	ECG_elPPG	1.00	1.00	1.00
VPG018	ECG_PhyC	0.90	0.98	1.00
	elPPG_PhyC	0.87	0.98	0.99
	ECG_elPPG	0.97	0.99	1.00
VPG019	ECG_PhyC	0.65	0.95	0.99
	elPPG_PhyC	0.64	0.95	0.99
	ECG_elPPG	0.98	0.99	1.00

p Values < 0.05.

either is compared individually to the ECG. However, this was not the case with regression analyses of the IBIs suggesting the presence of an additional source of error, likely due to the frame rate consistency of the camera or the complexities of the algorithm used in the PhyC system. The regression analyses between IBIs was slightly stronger between elPPG and ECG (R^2 0.99) than when comparing PhyC-derived IBI values with either the elPPG or ECG (R^2 0.94). In future embodiments, the discrepancy between PhyC and elPPG may be minimized by improving the stability of the sensor system (e.g., optimized Bayer mapping wavelength selection, improved motion tracking) and increasing the sampling rate.

Lessons learned from this study provide guidance for planned improvements to PhyC: (1) reduce movement error by improving the face tracker either through an embedded processor in the camera, external software analysis of the image frames, or a parallel tracking system based on additional sensors, (2) fine tune the selection of the pixels within each frame that contain the physiological information of interest, (3) maximize sensitivity across the range of skin colors by expanding the camera color spectrum to different wavelengths, and (4) use more powerful processors to facilitate the extraction of the pulse signal, enabling online extraction in real time. A combination of these hardware and software modifications will improve the PhyC performance as development continues. Nevertheless, optics of the sensor and available light in the environment (i.e., photons) are key elements in identifying and limiting applications of the PhyC.

In our study, we documented that the PhyC tracks IBI, HP, and LF with sufficient accuracy and precision to be used instead of the traditional contact devices when measuring those components of HRV. However, when measuring HRV from the periphery, the peripheral vascular activity influences the pulse-to-pulse intervals. Although the central tendency (i.e., mean) of pulse-to-pulse intervals converge with the R–R intervals (i.e., IBIs) generated from the ECG, on a beat-to-beat level, vascular rhythms and responses result in variations in the coherence between the two signals. Since the vascular rhythms are frequently slower than RSA, these rhythms tend to blunt the dynamic changes in RSA.

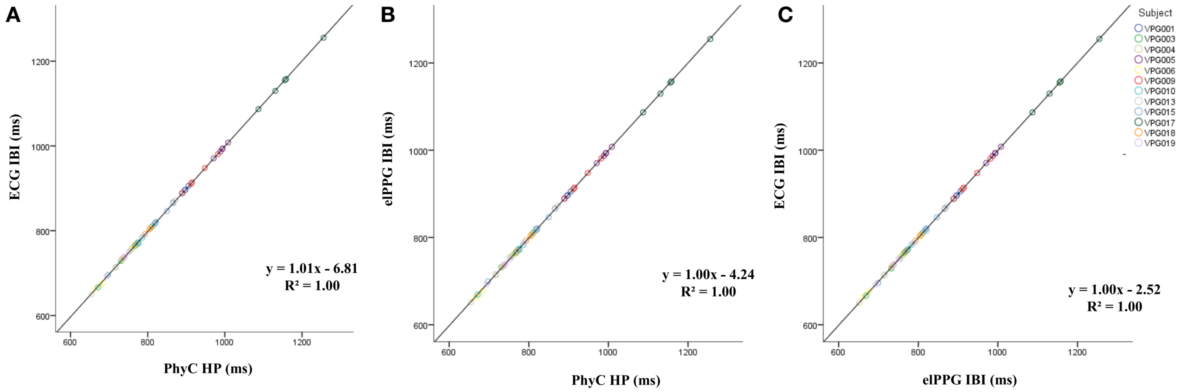

FIGURE 7 | Scatter plots between sensors for heart period (HP), color coded by participant. **(A)** PhysioCam (PhyC) vs electrocardiogram (ECG). **(B)** PhyC vs elPPG. **(C)** elPPG vs ECG.

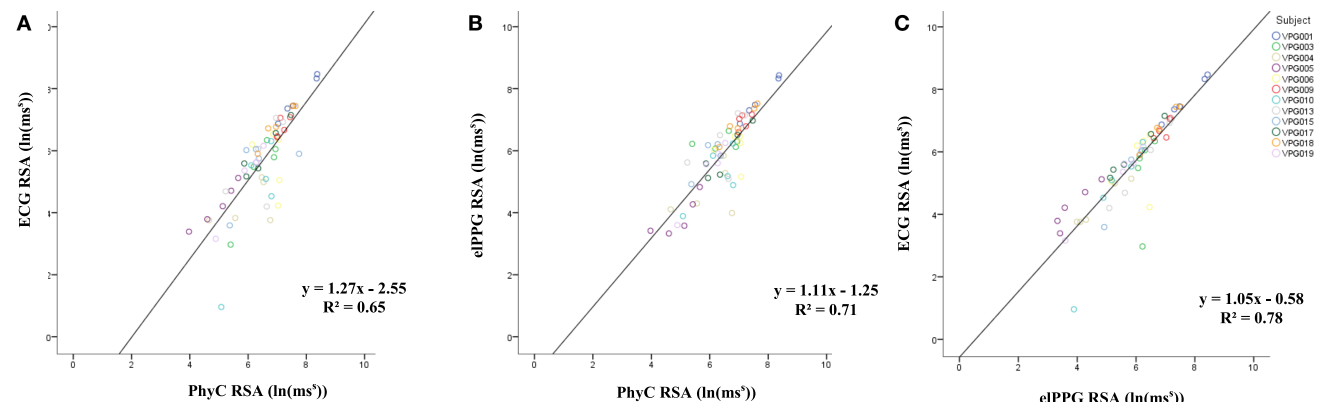

FIGURE 8 | Scatter plots between sensors for respiratory sinus arrhythmia (RSA), color coded by participant. **(A)** PhysioCam (PhyC) vs electrocardiogram (ECG). **(B)** PhyC vs elPPG. **(C)** elPPG vs ECG.

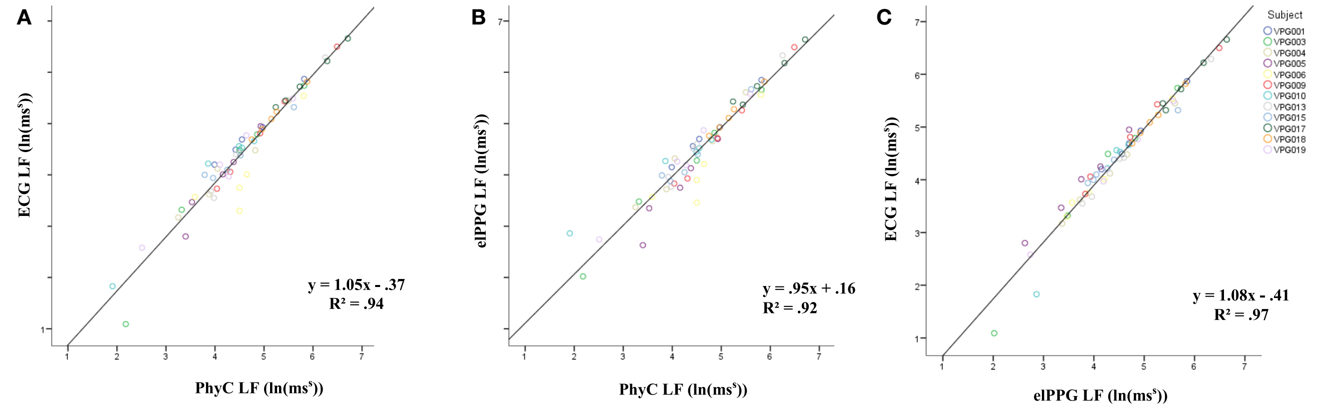

FIGURE 9 | Scatter plots between sensors for LF, color coded by participant. **(A)** PhysioCam (PhyC) vs electrocardiogram (ECG). **(B)** PhyC vs elPPG. **(C)** elPPG vs ECG.

TABLE 5 | Effect size within sensor by heart rate variability parameter.

Effect size	Electrocardiogram	elPPG	PhysioCam
Heart period	0.23*	0.22*	0.22*
Respiratory sinus arrhythmia	0.39*	0.14	0.28*
LF	0.15	0.16	0.18

**p Values < 0.05.*

This poses the question of whether the pulse-to-pulse intervals can be corrected to account for the vascular filtering effects? The frequency-dependent nature of components of the error suggests that a dynamic algorithm could be developed to adapt to the modulation effect of the cardiovascular system and reduce the rhythmic sources of error. In its current embodiment, PhyC can generate HRV measures from the periphery pulse that can be used interchangeably with those obtained from the ECG. The current PhyC system is capable of HRV estimation when the subject is seated and breathing normally, circumstances that cover a wide range of clinical and research demands. As long as the face is visible to the photosensor, future iterations of the PhyC will be able to deal with greater body movements.

The PhyC provides several advantages over contact measurement of heart rate: (1) the ability to measure HRV by non-contact sensors permits observation of a more neutral baseline by eliminating stressful disruptions caused by placing contact sensors on the participant, (2) the planned ability to measure several participants with the same sensor following further developments on the face tracking algorithm, (3) the collection of additional vascular signals, including sympathetic regulation of vasomotor tone, which are not available in ECG-derived measures, and (4) the system ability to work online in near real time to provide instantaneous measurement and continuous feedback.

These findings provide the basis needed to explore applications of this new methodology in psychophysiological and biomedical research as well as in applied settings. Expanding our understanding of the science behind the PhyC, which includes neurophysiological regulation of the cardiovascular system,

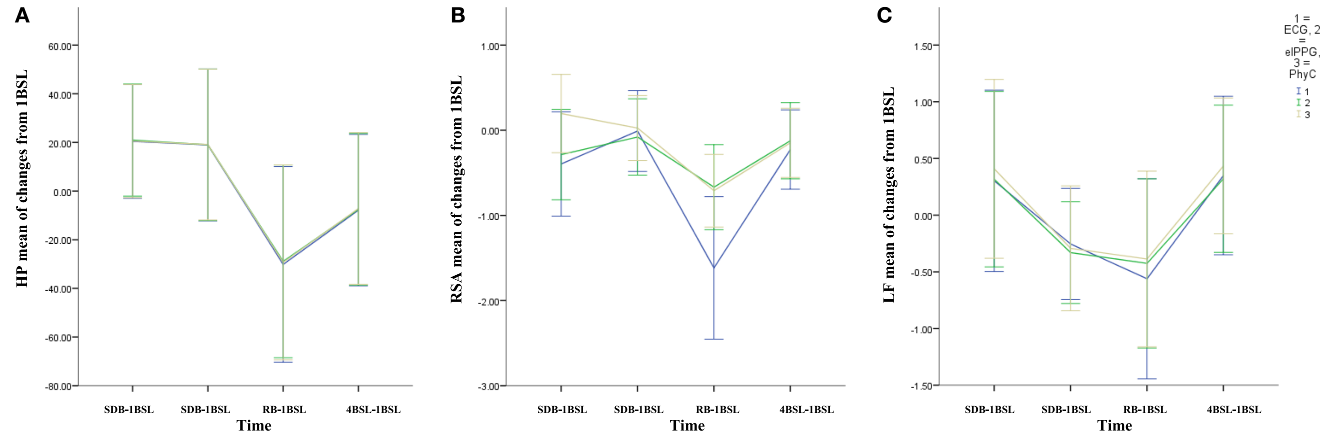

FIGURE 10 | Mean of changes from the 1BSL (error bars: ±2 SE) for the three sensors electrocardiogram (ECG), elPPG, and PhysioCam (PhyC). **(A)** Heart period (HP). **(B)** Respiratory sinus arrhythmia (RSA). **(C)** LF (error bars: ±2 SE).

sensor design, feature extraction, and algorithm development, suggests that an optimized system can extract, quantify, and interpret the neural regulation of the heart and the peripheral vascular system from the optical information collected passively from a subject. The system will continue to expand to accurately recreate the sensitivity and specificity of the ECG and eventually to quantify additional physiological parameters of interest to researchers, doctors, and commercial enterprises interested in neural regulation of the cardiovascular system.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of the University of Illinois at Chicago with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the University of Illinois at Chicago as protocol # 2012-0206 entitled "Real Time Non-contact Extraction of Human Arterial Pulse."

AUTHOR CONTRIBUTIONS

The manuscript is based on MD PhD dissertation work, under SP mentoring, and GL technical guidance. MD, GL, and SP conceived and designed the PhysioCam. MD and GL performed the data acquisition, processing, and statistical analyses. MD, GL, and SP contributed to the selection of the different metrics evaluated in the manuscript and interpreted the results. The intellectual content of the manuscript was jointly created and approved by MD, GL, and SP. All three authors drafted the text, with MD providing the original framework, and all three agreed to be accountable for all aspects of the work.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Diminution of Heart Rate Variability in Bipolar Depression

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Autonomic nervous system (ANS) dysregulation in depression is associated with symptoms associated with the ANS. The beat-to-beat pattern of heart rate defined as heart rate variability (HRV) provides a noninvasive portal to ANS function and has been proposed to represent a means of quantifying resting vagal tone. We quantified HRV in bipolar depressed (BDD) patients as a measure of ANS dysregulation seeking to establish HRV as a potential diagnostic and prognostic biomarker for treatment outcome. Forty-seven BDD patients were enrolled. They were randomized to receive either escitalopram–celecoxib or escitalopram-placebo over 8 weeks in a double-blind study design. Thirty-five patients completed the HRV studies. Thirty-six healthy subjects served as controls. HRV was assessed at pretreatment and end of study and compared with that of controls. HRV was quantified and corrected for artifacts using an algorithm that incorporates time and frequency domains to address non-stationarity of the beat-to-beat heart rate pattern. Baseline high frequency-HRV (i.e., respiratory sinus arrhythmia) was lower in BDD patients than controls, although the difference did not reach significance. Baseline low-frequency HRV was significantly lower in BDD patients (ln4.20) than controls (ln = 5.50) ($p < 0.01$). Baseline heart period was significantly shorter (i.e., faster heart rate) in BDD patients than controls. No significant change in HRV parameters were detected over the course of the study with either treatment. These findings suggest that components of HRV may be diminished in BDD patients.

Keywords: major depression, heart rate variability, respiratory sinus arrhythmia, escitalopram, celecoxib

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INTRODUCTION

Compared to major depressive disorder (MDD) and anxiety disorders, bipolar disorder (BD) is less prevalent, but it represents a significant mental health concern worldwide. BD is one of the most burdensome mental illnesses worldwide with nearly 50 million people suffering from it (1). Although manic episodes represent the distinguishing feature for a diagnosis of BD type I versus other mood disorders, bipolar depression (BDD) causes significant distress and dysfunction for patients and their families and poses major treatment challenges. Because it is often difficult to distinguish BDD from an episode of MDD prior to a distinct episode of mania, it poses significant diagnostic challenges to the clinician. Although episode length and frequency of episodes may be relatively similar between depression and mania in BD, clinical evidence suggests that BD patients are less likely to fully recover from a major depressive episode than from a manic, hypomanic, or even minor depressive episode (2) Therefore, it is imperative to consider BDD patients as being particularly susceptible to treatment resistance. Many symptoms of mood disorders may be reflective of an underlying dysregulation in autonomic nervous system (ANS) function. For example, the increased sympathetic activity with associated elevations in catecholamine and cortisol levels observed in anxiety results in a high comorbidity between anxiety and depression (3). This sustained increase in sympathetic tone can result in changes in blood pressure, decreased blood flow to the gastrointestinal tract leading to weight loss, and insomnia due to sustained pupillary dilation.

Heart rate variability (HRV) is defined as the variation between heartbeats over a period of time; it involves input from both the sympathetic and parasympathetic divisions of the ANS. Short recordings on an electrocardiogram (ECG) produce two primary patterns of oscillation that correspond to HRV (4). One frequency band occurs between about 2 and 8 s (approximately one breath cycle in the general population), which corresponds to 0.12–0.4 Hz (high frequency, or HF-HRV). This oscillation coincides with a physiological phenomenon known as respiratory sinus arrhythmia (RSA), which is characterized by a spontaneous oscillation in the beat-to-beat heart rate pattern that occurs in relation to spontaneous breathing. It is accepted throughout the literature that RSA, or HF-HRV, can be used to estimate cardiac vagal tone (5, 6). A second frequency band occurs between about 10 and 25 s, which corresponds to 0.04–0.10 Hz (low frequency, or LF-HRV). The pattern produced by this frequency band is often known as the Traube–Hering–Mayer wave. Certain studies have attempted to validate the LF measurement as an index of sympathetic activity (7, 8), while other evidence suggests that LF measurements are more reflective of mixed sympathetic and parasympathetic activity (9, 10). A third theory suggests that since atropine, a cholinergic blocker, removes both oscillations in heart rate, the LF-HRV domain is also transmitted through the vagus nerve and represents *another* parasympathetic index (11). Given that abundant evidence has validated RSA as an index of cardiac vagal tone (12) and since there is substantial ambiguity in interpreting other components of HRV (13, 14), we chose to use RSA (i.e., HF-HRV) as our primary index of autonomic function and LF-HRV as a more general index of autonomic state *via* a pathway that is presently not well defined.

The comorbidity between affective disorders and cardiovascular (CVD) and cerebrovascular disease is well documented in the literature. Elucidating the likely pathophysiological links between CVD and mental illness has been a major research focus over the past several decades, and there is growing evidence indicating that one of these links may be HRV. Studies indicate that decreased HRV may be indicative of a myocardial infarction (15, 16) and insulin resistance (17). The relationship between MDD and CVD has been robustly established in the literature (18–20). A decreased RSA and an increased LF-HRV has been associated with MDD (21), and further evidence suggests that increased RSA prior to antidepressant treatment is predictive of a positive treatment response in MDD patients.[1] The literature associating HRV to BD is not as robust, but recent research suggests links between the two (22). In one particular study, both BD and recurrent MDD patients were found to have significantly lower HRV parameters than healthy controls (HCs), despite clinical remission in both groups (23). In BD patients, HRV during a manic episode is significantly higher than HRV during a depressive episode or a euthymic state (24, 25). In the present study, we addressed three specific aims. First, we sought to detect differences in HRV between BDD patients and HC subjects before the initiation of antidepressant drug therapy in BDD patients with documented treatment resistance in regards to depression response. Second, based on our previous findings of treatment response prediction utilizing baseline RSA values in MDD patients, we were interested in determining whether a similar relationship exists between baseline HRV (i.e., RSA and LF-HRV) and treatment response in BDD patients. Third, we were interested in determining whether HRV (i.e., RSA and LF-HRV) changes during the course of treatment of our BDD patients, and if so, would responders differ from non-responders with respect to these components of HRV at the end of treatment.

MATERIALS AND METHODS

Study Population

The study was approved by the Institutional Review Board (IRB) of Loyola University Medical Center and was conducted according to the principles of the Declaration of Helsinki. Males and females 18–65 years of age who met DSM-IV criteria for BD I or BD II without any other psychiatric diagnoses, who were otherwise physically healthy and mentally capable to give informed consent, were considered as candidates. We selected BDD subjects whose depression had failed to remit following at least one adequate trial with an antidepressant, or who were experiencing a breakthrough depressive episode in spite of being maintained on a mood stabilizer and/or an atypical antipsychotic agent. As a condition to enrolling in the study, manic/hypomanic symptoms had to have responded adequately to a mood stabilizer and/or antipsychotic. Subjects were maintained on a mood stabilizer and/or atypical antipsychotic throughout the study. Since we used celecoxib as augmenting agent in one arm of this study, subjects who were being maintained on lithium at the time of screening could not be included due to a potential adverse interaction with celecoxib. If they qualified for the study and were agreeable to having their lithium replaced with a different mood stabilizer, they were enrolled. A minimum score of 18 on their 17-item Hamilton Depression Scale (HAMD-17) was required for study admission. Other Axis I diagnoses, active suicidality, uncontrolled hypertension, dyslipidemia, or diabetes mellitus, and history of smoking or substance abuse in the preceding 6 months. History of heart disease or autoimmune disorder was exclusion criteria. Subjects had to be free of any source of active or chronic inflammation. Female subjects could not be pregnant, lactating, or taking oral contraceptives. Screening blood samples were obtained to determine complete blood count, complete metabolic panel, lipid profile, thyroid function, and urinalysis (including pregnancy test). The presence of any clinically significant abnormalities excluded the prospective participant. Sixty-five treatment-resistant BDD patients who met the inclusion/exclusion criteria and successfully completed the baseline evaluations were randomized into

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one of the two treatment arms: escitalopram + placebo or escitalopram + celecoxib. The primary hypothesis underlying this study was to determine whether modulation of the inflammatory response by co-administration of a specific cyclooxygenase (COX-2) inhibitor would reverse treatment resistance and lead to a better treatment outcome. A total of 37 subjects had complete sets of HRV data to allow meaningful statistical analyses. Their demographic data is shown in **Table 1**.

To quantify the degree to which study patients were treatment resistant we used the Maudsley Staging Method to obtain a resistance score. The scale utilizes a variety of factors to quantify treatment resistance in depression, including duration of depressive symptoms, symptom severity, number of treatment failures, and whether or not the patient had received psychopharmacological augmentation or ECT (26, 27). Each patient was assigned a score with a range of 3 (minimal resistance) to 15 (maximal resistance). Seventy percent of our subjects had scores between 5 and 8, while 30 % had scores between 9 and 13.

HC Subjects

Eligible HC subjects were recruited by advertising and posting of IRB approved flyers. To determine eligibility, identical procedures were used as for the BDD group including a psychiatric diagnostic structured interview and routine laboratory tests. Main exclusion criteria were any medical, inflammatory, or mental illness and substance use (also among first degree relatives). Pregnant or lactating females were excluded. Their HAMD-17 and Beck Depression Inventory scores had to be less than 5. Thirty-six subjects were enrolled resulting in a BDD/HC ratio of about 1:1. Their demographic data are shown in **Table 1**.

Study Design

At the screening visit, subjects underwent a psychiatric interview to establish the diagnosis of treatment-resistant BDD. Subjects who met the screening criteria and signed the IRB-approved consent form underwent comprehensive assessments in order to quantify depression and associated symptoms. Patients then underwent a 2-week washout of their current antidepressant (4 weeks for fluoxetine). After the washout, subjects entered a 1-week run-in phase and received on a single-blind basis escitalopram placebo + celecoxib placebo. The purpose of this run-in was to identify placebo responders. Subjects who continued to meet eligibility criteria at the subsequent baseline visit, were randomized to receive on a double-blind basis escitalopram (beginning at 10 mg/day), +celecoxib (fixed at 400 mg/day), or celecoxib placebo. Escitalopram doses were optimized based on efficacy and tolerability over the first 4 weeks of active treatment but did not exceed a daily dose of 20 mg; no further dose adjustments could be made during the final 4 weeks of the study. Subjects were randomized according to a fixed assignment ratio of 1:1 (escitalopram + celecoxib or escitalopram + placebo). Assignment to groups was based on a pharmacy generated randomization code. The randomization code was kept in the pharmacy and could only be broken if a serious adverse reaction occurred. All study medications were prepared by the pharmacist and were handed to study subjects at each visit. They were instructed to return the empty vials at each visit to determine any amount of unused medication and hence failure to comply.

TABLE 1 | Demographic characteristics of BPD patients versus healthy control (HC) subjects.

	BPD subjects	HC subjects	p/χ^2 value
Study participants	37	36	
Age (±SD)	42.5 (11.8)	39.3 (13.8)	0.28
BMI (±SD)	31.3 (6.4)	26.7 (5.9)	0.003
Female	64.9%	63.9%	0.93
Caucasian	64.9%	75.0%	0.35
Non-Caucasian	35.1%	25.0%	

No discontinuation of medication was permitted throughout the study. Enrolled patients received no other form of therapy for the duration of the study. Follow-up blood draws and assessments using both self-rating and clinician-administered depression and anxiety scales were performed at weeks 0, 1, 2, 4, and 8.

Subjects had to complete at least 6 weeks of active treatment to be regarded as completers. If a subject chose to withdraw from the study on or after 6 weeks of treatment, s/he was expected to complete the end-of-study assessments at that time. Those results were carried forward for the purpose of data analysis.

Collection of HRV Data

Patients were assessed for HRV at weeks 0 and 8 using the SphygmoCor® CPVH system. This test was always carried out between 8 and 11 h in the morning and always in the same examination room to minimize environmental factors and diurnal fluctuations in ANS function. The patient was asked to recline on the examination table and a three-lead ECG was attached to the chest of the subject who had to rest for 10–15 min before the ECG recording was started. ECG data were collected over a 15-min period to ensure consistency in data collection. There is significant evidence that short-term HRV measurements (30 min or less) are stable over a significant period of time as compared to 24-h measurements *via* a Holter monitor (28, 29).

Inter-Beat-Interval Editing and Analysis

Data collected for HRV quantification are subject to artifacts that are related to the function of the ECG. The components of HRV (i.e., RSA and LF-HRV) were calculated from a time series generated by the times between sequential heartbeats (i.e., the time in millisecond between sequential R-wave in the ECG) over a period of 10–15 min. This time series consists of several hundred values that correspond to individual inter-beat-intervals (IBIs). Physiological mechanisms, both related and unrelated to RSA or LF-HRV, can contribute to this time series by distorting the accuracy of the R-wave detection. Influences from a spurious decrease in R wave amplitude, a random abnormally large T wave, single PACs/PVCs, or even patient activity must be removed from the time series before RSA and LF-HRV can be reliably quantified.

To deal with potential anomalies through artifact or ventricular arrhythmia (e.g., RSA is an atrial rhythm and represents the time course of the vagal influence on the sinoatrial node), a software package was used to correct for any of the artifacts in the data collected (30). Editing involved integer arithmetic to adjust the time series by adding IBIs when false invalid intervals occurred and dividing IBIs when R wave detections were missed. These decisions were guided by inspection of the ECG. In order to preserve an accurate representation of the neural regulation of the heart, data were only accepted if less than 5% of the data needed to be corrected.

After visual scanning and editing, the data were analyzed using CardioBatch Software (31). CardioBatch is a program that was created as a companion program to CardioEdit to quantify RSA and LF-HRV based on previously developed procedures by Dr. Stephen Porges (32). Fifteen minutes of ECG data were collected for each individual. Values for heart rate and RSA were calculated in sequential 30-s epochs and then averaged across the 15-min period. RSA and LF-HRV values for each epoch were transformed to their natural logarithmic values to conform to the distributional requirements for parametric analyses (12, 33).

Statistical Analyses

Consistent with the literature that documents HRV decreases with advancing age (34, 35), both the BDD and HC groups exhibited a significant negative relationship between HRV and age. Additionally, the BDD group had a significantly higher BMI than the HC group. To assess the contribution of potential confounding variables (e.g., age, sex, body-mass-index), analyses of covariance (ANCOVA) were used to remove potential confounding effects of age, sex, and ethnicity when comparing RSA and LF-HRV for HC and BD subjects at baseline (**Table 1**). In addition, heart period (HP) was analyzed. HP represents the average interval between heartbeats measured in milliseconds. HP period increases in duration when heart rate decelerates and decreases in duration when heart rate accelerates. Each patient was assigned a Maudsley score with a range of 3 (minimal resistance) to 15 (maximal resistance). A Pearson's correlation was then run between severity of treatment resistance and BL RSA, LF-HRV, and HP.

Repeated measures ANCOVA were conducted to evaluate potential differences in the autonomic parameters (i.e., RSA, LF-HRV, HP) at baseline and week 8 in both the escitalopram + celecoxib group and the escitalopram + placebo group, with controls for week 8 escitalopram dosage and treatment response.

Treatment response in study completers was classified as (a) no response to treatment (less than 50% reduction in HAM-D score from baseline); (b) partial response to treatment (greater than 50% reduction but end-of-study HAM-D score greater than 7); (c) remission (greater than 50% reduction and end-of-study HAM-D score of less than 7). It is generally accepted that for a major depressive episode, patients who have had a partial response to antidepressant treatment are at much higher risk of experiencing physical and mental dysfunction in comparison to patients who achieve remission (36). For purposes of the present analyses, no response and partial response were grouped into the non-response category. ANCOVA compared autonomic parameters at baseline between treatment responders and non-responders.

Level of significance for the analyses was set at $p < 0.05$. p-Values between 0.05 and 0.10 are reported as trends to be investigated in future studies with larger sample sizes (i.e., greater statistical power).

RESULTS

Baseline RSA did not distinguish BDD patients ($n = 37$) from HC subjects ($n = 36$) ($F = 1.44$, $p = 0.23$). However, baseline LF-HRV of BDD patients ($n = 37$) was significantly lower than HC subjects ($n = 36$) ($F = 29.41$, $p < 0.01$). Also, baseline HP of BDD patients ($n = 37$) was significantly shorter than HC subjects ($n = 36$) ($F = 4.70$, $p = 0.03$) (**Figures 1A,B**).

BDD patient Maudsley scores were significantly and negatively correlated with baseline RSA ($r = -0.458$, $p < 0.01$). Maudsley scores also tended to be negatively correlated with baseline LF-HRV ($r = -0.255$, $p = 0.127$) and baseline HP ($r = -0.274$, $p = 0.101$), although the relationship did not reach statistical significance (**Table 2**).

No significant differences in the autonomic parameters were found between BDD patients receiving the escitalopram + celecoxib combination ($n = 21$) and the escitalopram + placebo combination during the baseline assessment ($n = 14$) (data not shown).

For the escitalopram + placebo group ($n = 14$), RSA did not change significantly from baseline to week 8 after controlling for change in escitalopram dosage ($F = 0.42$, $p = 0.53$) and after considering treatment response ($F = 2.89$, $p = 0.12$) (**Figure 2A**). LF-HRV did not change significantly from baseline to week 8 after controlling for change in escitalopram dosage ($F = 0.54$, $p = 0.48$) and after considering treatment response ($F = 1.38$, $p = 0.27$) (**Figure 2A**). HP did not change significantly from baseline to week 8 after controlling for change in escitalopram dosage ($F = 0.00$, $p = 0.96$) and after considering treatment response ($F = 0.00$, $p = 0.98$) (data not shown).

For the escitalopram + celecoxib group ($n = 21$), baseline RSA for patients who were deemed to be end-of-study treatment responders ($n = 13$) was not significantly different than baseline RSA for patients who were deemed to be end-of-study treatment non-responders ($n = 8$) ($F = 2.06$, $p = 0.17$). No significant differences were found between responders and non-responders for baseline LF-HRV ($F = 3.16$, $p = 0.10$) and baseline HP ($F = 0.04$, $p = 0.85$) (data not shown). Visual inspection of these two figures indicates a flat time course of RSA and LF-HRV in the escitalopram + celecoxib group whereas the time course of change in the escitalopram + placebo group indicates a possible trend toward reduction in both components. While neither time course reached statistical significance, it is intriguing to speculate that the celecoxib combination might exert a "protective effect" against RSA and LF-HRV reduction, the latter being possibly associated with one or more of the concomitant medications, these patients were exposed to prior to and during the current study. Clearly an extended time course of observation and a larger sample size would be needed to investigate such a potential protective effect of the anti-inflammatory agent.

For the escitalopram + celecoxib group ($n = 21$), RSA did not change significantly from baseline to week 8 after controlling for change in escitalopram dosage ($F = 2.36$, $p = 0.14$) and between treatment response groups ($F = 0.09$, $p = 0.76$) (**Figure 2B**). LF-HRV did not change significantly from baseline to week 8 after controlling for change in escitalopram dosage ($F = 0.14$, $p = 0.72$) and after considering treatment response ($F = 0.19$,

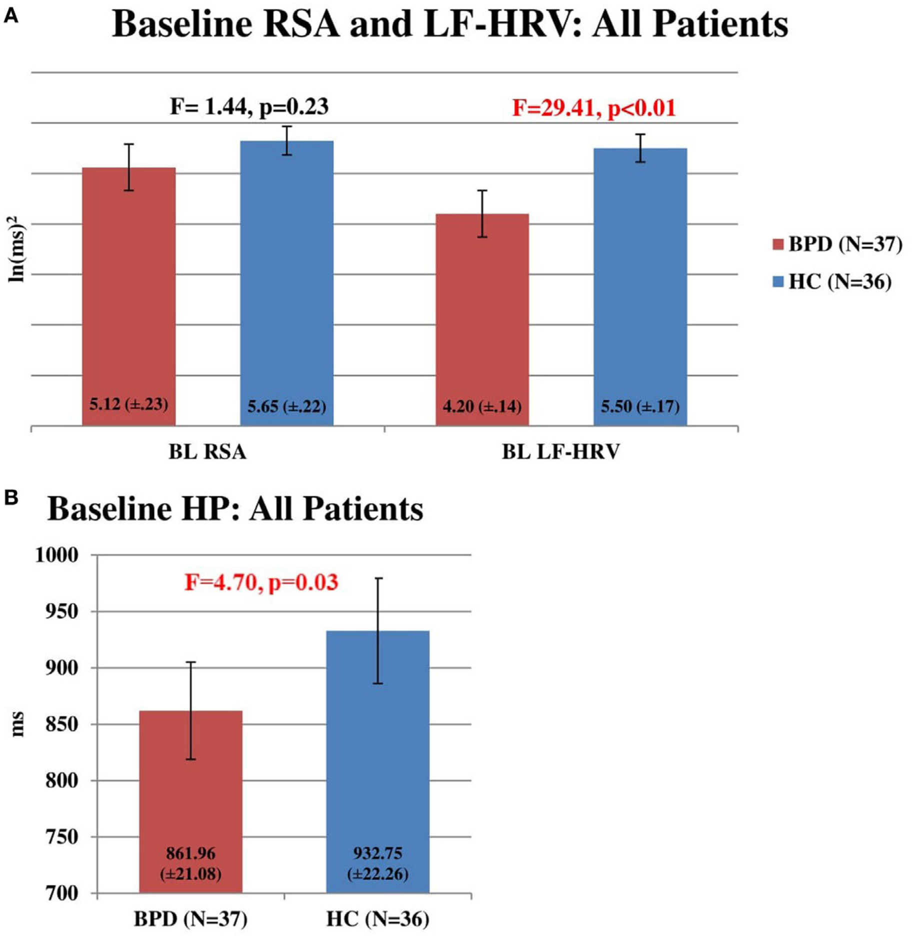

FIGURE 1 | **(A)** Baseline respiratory sinus arrhythmia (RSA) and LF-heart rate variability (HRV) in all patients. Comparison of baseline RSA and LF-HRV in HC subjects (n = 36) and bipolar disorder (BD) patients (n = 37). No significant difference was found between RSA in HC subjects (5.65, SEM = 0.22) and BPD patients (5.12, SEM = 0.23) (F = 1.44, p = 0.23). Baseline LF-HRV was significantly higher in HC subjects (5.50, SEM = 0.17) than in BD patients (4.20, SEM = 0.14) (F = 29.41, p < 0.01). **(B)** Baseline heart period (HP) in all patients. Comparison of baseline HP in HC subjects (n = 36) and BD patients (n = 37). Baseline HP was significantly higher in HC subjects (932.75 ms, SEM = 22.26) than in BD patients (861.96 ms, SEM = 21.08) (F = 4.70, p = 0.03).

TABLE 2 | Correlations between severity of treatment resistance and heart rate variability (HRV) parameters.

	BL RSA	BL LF-HRV	BL HP
Maudsley score	$r = -0.458, p < 0.01$	$r = -0.255, p = 0.13$	$r = -0.274, p = 0.10$

BL, baseline; RSA, respiratory sinus arrhythmia; LF, low frequency; HRV, heart rate variability; HP, heart period.

$p = 0.67$) (**Figure 2B**). HP did not change significantly from baseline to week 8 after controlling for change in escitalopram dosage ($F = 2.18$, $p = 0.16$) and after considering treatment response ($F = 0.16$, $p = 0.70$) (data not shown).

DISCUSSION

As illustrated in **Figure 1**, at baseline, when our BDD patients were at least moderately depressed, but not manic or hypomanic, relative to HC, they had significantly lower LF-HRV, and HP and a trend toward lower RSA. There were negative correlations between treatment resistance severity and baseline RSA, LF-HRV, and HP, with significance reached in the negative relationship between treatment resistance severity and RSA. This significant negative correlation supports the assumption that treatment-resistant BDD may account, at least in part, for reduced RSA. In this context, the role of possible effects of multiple medication trials and specific medications with anticholinergic properties must also be considered. Decreased HRV has been reported in bipolar patients during the manic phase in some studies (37, 38). However, these findings were not confirmed in a more recent study (24, 25) in which the investigators found increased HRV during manic states compared with depressive and euthymic states using a longitudinal study design with repeated measurements. Additionally, these authors reported an inverse relationship between HRV and the severity of depressive symptoms and a positive association between HRV

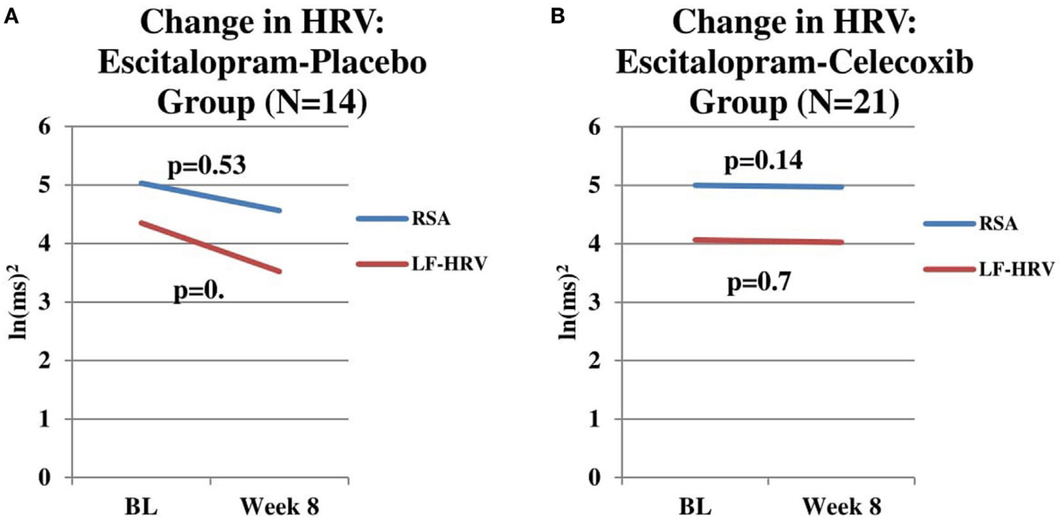

FIGURE 2 | **(A)** Change in respiratory sinus arrhythmia (RSA) and LF-heart rate variability (HRV) in escitalopram-placebo group. Change in RSA and LF-HRV from baseline to end-of-study in patients receiving Escitalopram-placebo combination (*n* = 14). No significant changes in RSA (*p* = 0.54) or LF-HRV (*p* = 0.40) were found. **(B)** Change in RSA and LF-HRV in escitalopram–celecoxib group. Change RSA and LF-HRV from baseline to end-of-study in patients receiving escitalopram–celecoxib combination (*n* = 21). No significant changes in RSA (*p* = 0.14) or LF-HRV (*p* = 0.70) were found.

and the severity of manic symptoms. In another study of bipolar patients studied during a euthymic state, Cohen et al. reported that time domains of HRV (HR, HP) were decreased compared to HCs; however, HF-HRV (also referred to as "vagal tone") was significantly *increased* (39). A recent study comparing bipolar II depressed patients to unipolar major depressed patients and HCs found that BD patients had a significantly lower vagal tone than both HCs and unipolar major depressed patients (40). Specifically, in bipolar I patients, one study found that subsyndromal BD patients had significantly lower HRV parameters than HCs (41). Faurholt-Jepsen et al. (24, 25) recently published data from a systematic and extensive meta-analysis of 15 studies comprising a total of 2,534 patients and showed that HRV is reduced in BD patients compared to HC subjects. They further commented that the discrepant findings among the published studies could be due, at least in part, to factors unrelated to BD *per se*, notably, the heterogeneity of the disorder, phase of the illness at the time of study, sample sizes, and methods used. To this list of variables that must be controlled in future studies, a detailed list of all medications the patient is receiving at the time of the study should be included with special consideration to agents with established anticholinergic activity as well as known noradrenergic properties.

To our knowledge, ours is the first study to find significant decreases in both time and frequency domain parameters of HRV in bipolar I and II depressed patients in comparison to HC subjects. Our findings are suggestive of the following. First, the directionality of both RSA and LF-HRV is supportive of the Polyvagal Theory (11), which proposes that there are two vagal inputs to the heart. The myelinated portion of the vagus nerve originates in the nucleus ambiguus and is responsible for the effects of RSA, whereas the unmyelinated portion of the vagus originates in the dorsal motor nucleus and contributes to bradycardia and the low-frequency (slow) bandwidth of HRV (11). If LF-HRV reflected any sympathetic activity, we would expect to see either no change or possibly even an increase in BDD patients, but the opposite was actually detected in our study. This finding is consistent with similar findings in MDD patients and frequency domain HRV measurements (42). It reinforces the need for further exploration of the physiological mechanism behind LF-HRV and is consistent with the evidence that there is no neural basis to interpret LF-HRV as an index of sympathovagal balance (43).

Current evidence linking depression and HRV is inconclusive and is largely based on the majority of research done in MDD subjects. Initially, MDD appeared to be associated with decreased HRV, and no effect of Selective serotonin reuptake inhibitors (SSRI's) on HRV was detected over a 3–6 week trial period (44). This finding is similar to the lack of effect found in our earlier study with MDD patients (see text footnote 1). However, data obtained over a 2-year period of observation show a significant decrease in HRV in MDD patients receiving antidepressants in comparison not only to HC subjects but also to MDD patients not on antidepressants (45). More recent research has focused on specific medications, and it appears that tricyclic antidepressants (TCAs) are most robust in reducing HRV, followed by serotonin/norepinephrine reuptake inhibitors (46, 47). SSRIs have the least effect on cardiac function and may even *decrease* cardiac sympathetic impact (46). In the present study with BDD patients, we did not observe a change in HRV parameters after 2 months of exposure to escitalopram, and this observation is consistent with the current literature. This finding was obtained with or without the addition of celecoxib to the treatment regimen.

While there is limited evidence linking BDD to HRV, the link between specific medications and vagal tone may offer a glimpse into the findings of our study. TCAs have classically been associated with anticholinergic side effects (e.g., dry mouth, constipation, blurry vision, urinary retention), as well as cardiotoxicity and neurotoxicity in cases of overdose. It is not surprising then that TCAs could exert a deleterious effect on the heart (48). Other medications in psychiatric populations that have been routinely associated with anticholinergic side effects are antipsychotics, particularly, the typical antipsychotics, but also atypical antipsychotics to a degree. Of our 37 patients for whom we have complete HRV data, 10 were placed on a bipolar medication regime throughout the study that included an atypical antipsychotic, while seven were maintained only on an atypical antipsychotic for mood stabilization. The remaining patients were maintained only on a mood stabilizer, most commonly lamotrigine or valproic acid. Atypical antipsychotics most commonly used were quetiapine and aripiprazole, and, less frequently, ziprasidone, olanzapine, and risperidone. Many of our patients had been prescribed several of these medications throughout the course of their lives. We chose not to compare baseline HRV parameters between patients on different mood stabilization medication due to the confounding variables of dosage variations, duration of treatment, and lack of adequate sample size.

Growing evidence indicates that antipsychotic medications can exert an effect on HRV in psychiatric patients. A recent meta-analysis established that clozapine is associated with a significant reduction in HRV (49). Another study determined that, in schizophrenic patients taking olanzapine, patients who gained a significant amount of weight after 1 month had a significantly lower HRV than patients who did not gain weight (50). These findings are not surprising, considering these two atypical antipsychotic agents are most commonly associated with metabolic side effects and are, therefore, more likely to have deleterious effects on the heart (51). These negative effects on HRV also appear to be dose-dependent, with higher doses being associated with further decreases in HRV (52). There have been other findings that atypical antipsychotics decrease HRV, but these papers do not specify which specific medications were used (53, 54). It is worth speculating, however, that atypical antipsychotics with a lower anticholinergic profile may be less prone to reduce HRV parameters. Clozapine, olanzapine, and, to a less degree, quetiapine, have all been shown to have anticholinergic side effects (55). These anticholinergic effects can be hypothesized to decrease vagal tone, reduce overall HRV, and contribute to increased cardiac morbidity and mortality that is often noted in patients taking antipsychotic medication.

Anticholinergic properties of psychiatric medications have resulted in unwanted, unpleasant, or even dangerous side effects for psychiatric patients. There lies the possibility that these properties may also hinder a full treatment response as well. In our pervious study, MDD patients who did not respond to a 3-month trial of either escitalopram or quetiapine monotherapy had significantly lower vagal tone than patients who did respond (see text footnote 1). This finding was not replicated in our BDD patient study, but the theoretical implications are still worth noting. Many of the second line agents used for depression in both MDD and BDD are strongly anticholinergic, including TCAs and atypical antipsychotics, such as quetiapine and olanzapine. Thus, what may actually be happening is that we are making a certain subset of these otherwise treatment-resistant patients *worse*, by giving them medications that exacerbate possible inherent mechanisms responsible for their underlying treatment resistance.

What are the clinical implications of HRV in BDD patients? The primary aim of the BDD study was to assess the role of inflammation in the pathophysiology of bipolar depression and determine if anti-inflammatory adjunctive treatment would aid in remission of depressive symptoms in BDD patients. Not only did patients receiving the escitalopram + celecoxib combination experience a significant decrease in depressive symptoms over a 2-month period in comparison to the escitalopram + placebo group, but they achieved remission much faster than the placebo group ((56); Halaris et al., in preparation).

One possible mechanism underlying the pathophysiology of treatment resistance in either MDD or BDD can be the associated pro-inflammatory state and ANS dysregulation with associated diminution in vagal tone. A decrease in vagal tone likely leads to dysregulation of the body's inflammatory response mediated, in part, by the cholinergic anti-inflammatory pathway (57). It has been demonstrated that efferent vagal fibers originating in the dorsal motor nucleus can modify the release of inflammatory cytokines, such as TNFα, from macrophages, thereby preventing over-activation of the inflammatory process without inducing immunosuppression (58). Loss of vagal tone, therefore, may be crucial to understanding the pro-inflammatory status associated with MDD and BD that has been described in the literature (59, 60). If parasympathetic tone can be maintained at HC levels, reflecting a physiological degree of inflammatory response, antidepressant drug action may proceed unhindered ultimately leading to remission. In our study, we did not see a change in HRV over the course of the study in either the combination treatment group or the placebo group. Celecoxib co-administration modulated inflammation as reflected in significant reduction is specific pro-inflammatory mediators, thereby facilitating and even enhancing the antidepressant efficacy of escitalopram. However, this adjunctive anti-inflammatory treatment did not produce any beneficial cardiovascular effects within the time frame of our study ostensibly due to the anticholinergic properties of the concomitant psychotropic medications used in the present study. Nevertheless, these findings suggest an additional and intriguing theory about the mechanism(s) of treatment resistance and its relationship to both depression and CVD.

FUTURE STUDIES

Although much time and research have been devoted to distinguishing the depressive phase of BD from MDD, a reliable diagnostic distinction often poses serious challenges to the clinician (61). One potential avenue is to utilize HRV assessment and domain analysis as a diagnostic and prognostic biomarker.

Recent evidence suggests that acute HRV measurements can be obtained by only 120 s of ECG recordings (62). Indeed, a recent study compared patients with bipolar II depression and patients with unipolar depression and found significantly lower HF-HRV and a higher LF/HF ratio (used as a measurement of sympathetic tone) in bipolar II depressed patients as compared to unipolar depressed patients (40). Therefore, future studies should take into consideration the length of prior exposure, if any, to pharmacological agents, both psychiatric and non-psychiatric. It will also be interesting to determine if anti-inflammatory medication utilizing selective COX-2 inhibitors can exert beneficial effects on HRV over a longer treatment period. Once the possible effects of pharmacologic agents on HRV domains have been fully clarified, wide utility of HRV as a biomarker will be justified.

LIMITATIONS OF THE STUDY

One limitation to our study is the small sample size. Several of our trending variables might have reached statistical significance with a larger patient and/or HC population. Specifically, given the small heterogeneous sub-groups (age, ethnicity, BMI), it may not be viable within this sample to investigate whether components of HRV at baseline (e.g., RSA and LF-HRV) are related to current episode length and/or previous episodes. Although this does not detract from the importance of our findings, reproducibility with a larger population would be necessary to confirm those findings that did not reach statistical significance. As in any study relying on the collection of data over time, several limitations are to be noted. Current mood state of the patient could have influenced the assigned scores in both the self-assessment and rater-administered scales. To minimize such effects, consistent provider–patient pairings were kept over the course of the study to minimize interobserver bias and to allow the patient to receive a consistent level of care. The fact that our patients had to be fully stabilized on mood stabilizers before being administered antidepressant medication may have blunted any changes in HRV during the course of treatment. In addition, the relatively short duration of our recording (15 min) in the resting state precluded the opportunity to assess HRV during both rest and activity and thereby provide a better measure of cardiac resilience.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Declaration of Helsinki and Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Loyola University Stritch School of Medicine/Loyola University Medical Center.

AUTHOR CONTRIBUTIONS

AH designed the study, wrote the protocol, and oversaw the preparation of the manuscript. BH actively participated in data collection, data analyses, literature search, and preparation of all drafts of the manuscript. BB contributed to data management and data analyses. DD participated in the clinical portions of the study and data collection. KH performed data analyses. SP oversaw data analyses, contributed to manuscript preparation, and acted as a consultant to the co-investigators.

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Biobehavioral Insights into Adaptive Behavior in Complex and Dynamic Operational Settings: Lessons learned from the Soldier Performance and Effective, Adaptable Response Task

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The purpose of this study was to explore the biobehavioral correlates of adaptive behavior in the context of a standardized laboratory-based mission-relevant challenge [the Soldier Performance and Effective, Adaptable Response (SPEAR) task]. Participants were 26 healthy male volunteers (M = 34.85 years, SD = 4.12) with active military duty and leadership experience within the last 5 years (i.e., multiple leadership positions, operational deployments in combat, interactions with civilians and partner nation forces on the battlefield, experience making decisions under fire). The SPEAR task simultaneously engages perception, cognition, and action aspects of human performance demands similar to those encountered in the operational setting. Participants must engage with military-relevant text, visual, and auditory stimuli, interpret new information, and retain the commander's intent in working memory to create a new plan of action for mission success. Time-domain measures of heart period and respiratory sinus arrhythmia (RSA) were quantified, and saliva was sampled [later assayed for cortisol and alpha-amylase (sAA)] before-, during-, and post-SPEAR. Results revealed a predictable pattern of withdraw and recovery of the cardiac vagal tone during repeated presentation of battlefield challenges. Recovery of vagal inhibition following executive function challenge was strongly linked to better task-related performance. Rate of RSA recovery was also associated with better recall of the commander's intent. Decreasing magnitude in the skin conductance response prior to the task was positively associated with better overall task-related performance. Lower levels of RSA were observed in participants who reported higher rates of combat deployments, and reduced RSA flexibility was associated with higher rates of casualty exposure. Greater RSA flexibility during SPEAR was associated with greater self-reported resilience. There was no consistent pattern of task-related change in cortisol or sAA. We conclude that individual differences in psychophysiological reactivity and regulation in response to an ecologically valid, military-relevant task are associated with performance-related adaptive behavior in this standardized operational setting. The implications for modern day warfare, where advancing our understanding of the nature of individual differences in adaptive problem solving is critical to mission success, fitness for duty, and other occupational health-related outcomes, are discussed.

Keywords: adaptability, resilience, problem solving, military-relevant challenge, leadership, autonomic regulation, heart rate variability, electrodermal activity

INTRODUCTION

Modern day warfare requires real-time problem solving to meet changing uncertainties in operational environments. The US military's experiences over the last two decades have illuminated the changing nature of conflict. Adversaries are enabled with technology, lethality has increased over time, and the battlefield is non-contiguous and decentralized. Warfare is more complicated, fast paced, requires less kinetic action, and more often involves the integration of security operations with development programs relative to past eras of conflict. Soldiers and small unit leaders must be resourceful, creative, and adaptively recalibrate to negotiate and succeed on the modern battlefield (1, 2).

The Army's Warfighting Challenge #10 (i.e., first-order problems critical to future capabilities) is to "develop agile, adaptive, and innovative leaders who thrive in conditions of uncertainty and chaos, and are capable of visualizing, describing, directing, leading, and assessing operations in complex environments and against adaptive enemies" (3). As such, *adaptability* is a core capability and is critical to mission success, fitness for duty, and is likely related to other occupational health-related outcomes (e.g., hypertension, sleep disturbance, and depression).

Adaptive leadership involves selective attention to key components of events and the significant information streams linked to those events, while minimizing attentional division caused by irrelevant back-or foreground stimuli. Adaptive leaders are calm and thoughtful under pressure. They are also sensitive to their changing surroundings, absorb what is going on, and comprehend the environment, the situation, and the circumstance. Adaptive leaders also understand and interpret broad high-level strategic mission goals and create and execute action plans that are appropriate for the unique circumstances encountered at the tactical level. They can recalibrate their actions (i.e., fighting vs. negotiating vs. humanitarian assistance) efficiently and effectively, and can sustain high degrees of adaptability across mission duration (4).

Given the dynamic, uncertain and real-time performance requirements in which soldiers need to be able to think, know, respond and do, our research team has proposed a working model that characterizes *adaptability* with respect to the biological, cognitive, and affective resources that are managed in coordination to achieve optimal performance under challenge (5, 6). We anticipate that optimal performance under complex, chaotic, dynamic conditions involves the coordinated reactivity and regulation of environmentally sensitive behavioral, cognitive, and physiological processes (7–9). At the measurement level, our model includes individual differences in executive function (e.g., cognitive inhibition, cognitive flexibility, and working memory) (10, 11) as well as in the flexibility, reactivity, and regulation of the two main components of the psychobiology of the stress response—the autonomic/sympathetic nervous system (ANS/SNS) and hypothalamic–pituitary–adrenal (HPA) axis (7, 12–23). A substantial literature supports the interpretation that individual differences in the HPA response to challenge reflect a "defeat" response, whereas activation of the ANS/SNS to challenge reflects a "defense" response (24). That is, increases in cortisol (the primary product of HPA axis activation) are common when individuals are confronted with unfamiliar circumstances and they are overwhelmed, withdraw, and exhibit high degrees of distress. By contrast, increases in ANS/SNS activation are more likely when individuals experience physiological arousal and are mobilizing that arousal to "fight or flight"—attentional focus, cognitive effort, and taking action-oriented steps in an effort to rise to the challenge.

A central challenge to studying adaptability in the modern American warfighter is the necessity to evaluate inter- and intra-individual differences in a social ecologically valid but standardized setting outside of the operational theater. In an effort to address this challenge, Haufler et al. (6) created the Soldier Performance and Effective, Adaptable Response (SPEAR) task. SPEAR emulates the time-demand, multisensory, multitasking, tactical battlefield challenges requiring adaptive decision making. This 90 min task includes two distinct components/modules consisting of 18 independent embedded mission challenges each. The task was designed to simultaneously engage perception, cognition, and action aspects of human performance like those encountered in the operational setting. Participants engage with text, visual, and auditory stimuli, interpret new information, retain the commander's intent in working memory while calling up training and experience information from memory stores, integrate new experiences with learned behaviors, and compose a response to report their leadership action plan (i.e., adaptive response to the dynamics of the mission challenge). To complete the SPEAR task, the participant must efficiently and effectively negotiate the back and forth of problem engagement, solution development, and dissemination of the action plan, across multiple back-to-back trials. In this manner, the SPEAR task reflects the tactical leader's operational requirement to be able to sustain a psychophysiological response that is supportive of meeting a new challenge, demonstrating adaptive leadership and recovering in order to prepare for the next challenge.

The purpose of this preliminary study was to begin to explore the biobehavioral correlates of adaptive behavior in the context of this standardized laboratory-based mission-relevant challenge task. Participants were 26 healthy male volunteers (M = 34.85 years, SD = 4.12) with active military duty and leadership experience within the last 5 years that included multiple leadership positions, operational deployments in combat zones, had interactions with civilians and partner nation forces on the battlefield, and had experience making decisions under fire. Time-domain measures of heart period (HP), respiratory sinus arrhythmia (RSA), and skin conductance were quantified, and saliva was sampled before-, during-, and post-SPEAR. Saliva samples were assayed for cortisol (HPA axis) and alpha-amylase (ANS/SNS). In this group of experienced military leaders, we expected that individual differences in performance on the SPEAR task would be associated with ANS/SNS, but not HPA axis, task-related reactivity and regulation, as well as with executive function.

MATERIAL AND METHODS

Participants

The participants for this study were qualified volunteers recruited from Fort Meade, MD, USA, The Johns Hopkins University Applied Physics Laboratory, and the greater Washington DC metropolitan area. Volunteers had to have served on active duty in the military within the past five years, held at least one leadership position in any of the following ranks: E-5 (SGT), E-6 (SSG), E-7 (SFC), E-8 (MSG), O-3 (CPT), or O-4 (MAJ), and served in an Army Combat Arms Military Occupation Specialty (MOS). The final study sample consisted of 26 healthy male participants aged 27–41 years (M = 34.88; SD = 3.73) who held multiple leadership positions, had multiple operational deployments in combat, had interactions with civilians and partner nation forces on the battlefield, and had experience making decisions under fire. The participants had high levels of civilian and military education, exercised regularly, and were from combat arms branches to include Infantry, Armor, Artillery, Special Forces, Engineers, and Aviation branches. This study was carried out in accordance with the recommendations of the Johns Hopkins Medical Institution Review Board. This protocol was approved by the Johns Hopkins Medical Institution Review Board.

Apparatus and Measures

The laboratory was configured with two stations each equipped with a Dell laptop personal computer (PC), display monitors, keyboard, and mouse to support the experiment. The experimenter station was used to initiate the experimental protocol and monitor data acquisition. The participant station was configured for the participant to engage with and complete the experimental protocol. Participant responses were acquired usingthe PC keyboard and the five-button Chronos® response box. Koss QZPro Noise Cancellation Sterephone headphones were worn by the participant during the auditory discrimination baseline task and the Soldier Performance and Effective, Authentic Response (SPEAR) adaptability test task. A BIOPAC Systems, Inc. wireless data acquisition system consisting of the MP150 data acquisition hardware (Ethernet-ready data acquisition analysis unit), UIM100C (universal interface module used to connect amplifier modules and signal cables to the MP150), STP100C (safely isolates digital inputs and outputs to and from the MP150; connects the MP150 to the PC running the assessment applications), dual wireless respiration and electrocardiography (ECG) BioNomadix module pair (BN-RSPEC), and electrodermal activity (EDA) BioNomadix module pair (BN-PPGED). Cardiovascular and EDA data were acquired using BIOPAC Systems, Inc. AcqKnowledge software version 4.4. Biophysical data were collected continuously at a sampling rate of 1,000 Hz. Psychology Software Tools, Inc. E-Prime 2.0 (E-Prime) was used to program theexperimental protocol as presented to the participant to include all baseline, executive function and SPEAR task events. Inline code was written in the E-Prime study protocol to designate an event mark (±5 mV excursion) in the AcqKnowledge physiological recording to indicate the onset and offset of specific stimuli events across the study protocol. Absorbent 1 × 4 cm polyolefin swabs (SalivaBio, Carlsbad, CA, USA) were used to obtain the saliva samples. Immediately after collection, saliva samples were stored in a 3.2-cubic-foot Danby upright freezer and samples remained frozen until the day of assay. All saliva samples were assayed for cortisol (Cortisol, CAT# 1-3002) and alpha-amylase (sAA, CAT# 1-1902) using commercially available immune or kinetic assay protocols without modification to the manufacturers recommended instructions (Salimetrics, Carlsbad, CA, USA).

Behavioral Assessments

Demographic, Military Experience and Mental Health Self-Report

Demographic questions consisted of age, gender, education (general and military), race, ethnicity, and physical fitness. Participants also provided information about their rank, military occupation specialty, military training, military deployments, and leadership experience. Measures of mental health were collected to include the Profile of Mood States (POMS-2), Positive Negative Affect Scale (PANAS), State-Trait Anxiety Inventory, and the Dispositional Resilience Scale (DRS).

The POMS is a measure of relatively recent mood state elevations, referred to as Total Mood Disturbance, and differentiates between six clinically important mood state dimensions including fatigue, tension, depression, anger, confusion, and vigor (25, 26). The POMS-2, employed in the present study, also includes a scale for friendliness.

The Positive and Negative Affect Schedule (PANAS) is used to assess current and average human emotion along positive and negative dimensions. PANAS is most commonly used to show relations between positive and negative affect with personality states and traits (27).

The State-Trait Anxiety Inventory for Adults is used to measure levels of anxiety, with separate measures for a person's general trait level, as well as the short-term effect of the state or anxiety at that particular moment (28, 29).

The DRS is an assessment of hardiness which is defined as a resilient stress response pattern (30–33). Hardiness is composed of three sub-components, namely commitment, control, and challenge. Commitment reflects an individual's interest in the world, and the degree to which they believe events have meaning. Control reflects the degree to which an individual believes that they can influence the events occurring around them. Challenge reflects an individual's disposition toward change and new experiences. The DRS-15 consists of 15 questions and was used in the present study.

Baseline Assessments

Three computer-based assessments were completed to establish physiological and performance baseline responses. The first baseline task was a cardiovascular challenge consisting of a sequence of sit and stand periods from which the cardiovascular response to the postural change was used to relate nervous system flexibility to individual physiological adaptability. The initial sit period was 2 min in length, followed by five alternating stand/sit periods each for 1 min in length, and a final 5-min sit period. The second initial assessment was a two-choice reaction time (RT) task (34, 35) which was administered to confirm participants could generate a typical choice RT response and for use as referent data for analysis of the Ericksen-Flanker task. Participants were prompted with either a "1" or "2" stimuli to which they responded as quickly as possible by pressing the corresponding "1" or "2" on the Chronos response box. The stimuli period was 1 s, and the response period was 3 s, with a variable 1–3-s intertrial interval. The choice RT task took a total of 5 min to complete. The third initial assessment was an auditory discrimination task [similar to an auditory odd-ball task (36)] in which participants wore headphones and low and high tones were presented (80/20 ratio, low/high) for 1 s with a variable intertrial interval of 3–5 s. The participant was asked to count the high tones and report the final count number upon completion of the baseline assessment. The series consisted of a total of 60 tones with a delay of 3–5 s between each tone. Seventy-five percent of the tones (45 trials) were low, and 25% of the tones (15 trials) were high. This task took a total of 4 min to complete. This task was a check to assure the participants could distinguish the low and high tones and practice discriminating between the two, in preparation for the dual task requirements of the SPEAR task.

Tests of Executive Function

Three tests of executive function were administered *via* computer to measure cognitive inhibition, cognitive flexibility, and working memory (10, 11). The three tests were the Eriksen Flanker, the Iowa Gambling Task (IGT), and the N-back task (37–44). The Eriksen-Flanker is a test of cognitive inhibition that examines the distractor interference effect from congruency (37). Research shows that attentional control processes in the Eriksen-Flanker are influenced by congruency sequence effects (i.e., the Gratton effect), manifesting as a smaller flanker interference effect after incongruent trials. These results inform the contribution of target flanker and response repetition (38, 39). Participants completed 256 trials that were presented in a balanced, pseudo-randomized design. Specifically, each pattern was displayed for 0.8 s. A fixation cross was displayed for 1 s between trials. The response window for each trial included the intertrial fixation period. The trial structure was generated such that there was an even distribution of trial types [25% Congruent, directed to the right (C), 25% Congruent, directed to the left (C), 25% Incongruent, directed right (I), 25% Incongruent, directed left (I)], congruencies (50% C, 50% I), and previous trial to current trial congruencies (25% II, 25% IC, 25% CC, 25% CI) (39). Participants were given 12 practice trials prior to starting the task. The duration of the task was approximaely 10 min.

The IGT (40) consisted of 200 trials. The goal of the task is to maximize profit while minimizing loss on a loan of virtual money. The participants were shown four decks of cards face down and given a virtual endowment of $2,000. Every card represented a dollar amount, positive, negative, or 0, that would change their total winnings when selected. For each trial, the participants drew a card from one of the four decks, attempting to maximize winnings and minimize loss. The participant is free to switch from any deck to any other deck at any time and as often as they wish across the task period. The decks provide different levels of fixed rewards and punishments. Two decks provide net winnings, while the other two are net losers. After making a selection, participants were shown a feedback display [6 s (41)] of the reward (wins) and punishment (losses) of their selection on that trial as well as their remaining total amount of money. The participants were given an infinite amount of time to make a selection. Participants were not given practice trials for this task. The duration of the entire task was about 12 min.

The N-back task (tested as the 2-back) (42–44) consisted of 75 trials. Participants were required to monitor a series of stimuli and to respond whenever a stimulus was presented that was the same as the one presented n-trials previously, where $n = 2$ in the study's version of the experiment. All participants received trials in the same, pseudo-randomized order. The participants were required to monitor a series of letters and to respond with a 1 if the letter was the same as the one presented two trials previously and a 2 if the letter was not the same as the one presented two trials previously. Each letter displayed for 0.5 s. A blank screen displayed for 2 s between trials. A response could be made from the time the stimuli appear to the end of the 2-s blank screen period. Participants were given 12 practice trials prior to starting the task. The duration of the task was approximately 6 min.

Soldier Performance and Effective, Authentic Response (SPEAR) Task

The SPEAR task was developed to test adaptive decision-making in response to authentic military scenarios based on the Army's definition of adaptability and the study's operational definition of soldier adaptability (6, 45, 46). The SPEAR task was a computer-based task consisting of two blocks of 18 trials each, for a total of 36 trials. Other computer-based tasks, like SPEAR, have been shown to evoke useful measurable responses in decision based training and testing applications (47–50) without compromising authenticity. The block and trial structure was fixed. Each block began with instructions followed by strategic context, mission statement, and commander's intent. Eighteen trials were then presented to closely approximate tactical challenges relevant to the block's strategic context. Participants were expected to retain (increase working load and working memory) the overarching objectives and goals throughout the test and were expected to develop creative ways and new approaches to achieve the commander's intent in the face of changing situations and obstacles to the mission when engaging with the 18 trials in each block. In one block, the mission and commander's intent focused on combat operations (CO) and in the other the mission and commander's intent focused on security force assistance (SFA). These two characterized much of the participant pool's military experience over the last 15 years in Iraq, Afghanistan, and other combatant command areas. COs scenarios included react to contact, react to IEDs, react to casualties, offensive and defensive actions, patrolling, observation post, combat advising, and security and stability operations. The Security Assistance Force block operations included training, advise and assist, and Coalition operations, Embassy relations, human rights issues, and cultural, regional, and political considerations. The block order was counter-balanced across subjects so that one-half completed the COs block first and the other half competed the SFA block first.

Participants were also required to accomplish a secondary auditory discrimination task, similar to the auditory odd ball paradigm (36), while completing each SPEAR block of trials. The purpose of the auditory challenge was to emulate the multisensory and -dimension stimuli environment similar to that encountered on the battlefield. High and low tones were presented for 1 s, with a variable intertrial interval ranging from 3 to 5 s. Tones for the CO block of trials were presented in an 80/20 (low/high) ratio with a variable intertrial interval of 3–5 s. Tones for the SFA block of trials were presented in an 85/15 (low/high) ratio with a variable intertrial interval of 3–5 s. Participants were instructed to keep a running count of all high tones across each block and had to report their total high tone count at the end of the block. The correct number of high tone counts was 111 for CO and 84 for SFA. At the end of each block, participants were also asked to recall the commander's intent from the initial instruction set as a working memory check and to begin to understand the relationship between adaptability and knowledge of mission commands.

Each specific SPEAR trial consisted of a fixation cross (3 s), scenario description (30 s), ensemble video clips (30 s), response prompt (10 s), and response period (105 s). Specific videos, images, and text were selected from the Defense Video and Imagery Distribution System (https://www.dvidshub.net), edited, and reviewed to create the desired intent for each trial scenario. The response prompt instructed the participant to respond to the challenge as if they were reporting their action plan to their higher commanders (Up), adjacent units (=), or subordinates (Down), balanced in random order across each block, to provide a level of uncertainty within each trial and to mitigate any tendency of the participant to anticipate the response prompt or respond passively to the stimulus. Participants typed their action plan.

Each of the trials had one of two stimuli type, consistent (C) or inconsistent (IC), that were presented nine times each in a pseudo-randomized order over the course of each block. A consistent stimulus presented a difficulty to task completion that could be considered "routine" or that might be expected to occur in the accomplishment of the mission task. An inconsistent stimulus presented a challenge to completing the task, one that may have required modifying the task or abandoning it all together in order to achieve the purpose of the mission statement and meet the commander's intent. Inconsistent trials included a higher magnitude of change in the situation and environment, and required a higher level of adaptability to achieve the commander's intent. This aspect of the design provided varying levels of challenge to measure adaptive performance within the test. See **Figure 1** for an illustration of the SPEAR task design and structure.

A scoring rubric (51, 52) was developed to evaluate the participants' responses provided during the SPEAR task. The rubric consisted of an eight category scale in which each category represented a dimension of adaptability ranging from basic recognition of an altered situation to demonstration of an action plan that meets the commander's intent and meets the trial-tactical situation. A participant could earn one point for each category met with a range of possible scores for each trial of 0–8. The participants' responses were scored independently by three trained raters who were military, operations and system engineering subject matter experts. Interrater reliability was checked by computing the intraclass correlation (ICC) coefficient (M = 93.1%, SD = 1.87%) and the Cronbach's Alpha (M = 94.2%, SD = 1.39%).

Procedures

Testing was administered in a laboratory environment at The Johns Hopkins University Applied Physics Laboratory (JHU/APL). See **Figure 2** for an illustration of the protocol. On arrival, the participant was asked a series of questions to confirm eligibility, then read and provided informed consent. The first saliva sample was taken after participants provided informed consent and then periodically (for a total of eight samples) across the testing session. Saliva sample 2 occurred 10-min post-sample number one. After participants completed the demographic and other self-report assessments, they were instrumented with the ECG and EDA sensors. Participants completed the sit-stand, RT and auditory baseline tasks during which all data were collected and signal quality was confirmed. Saliva sample 3 was obtained immediately following the set of baseline tasks.

The tests of executive function were administered in the following order: Ericksen-Flanker, IGT, and 2-Back. Saliva sample 4 was obtained immediately following completion of the 2-Back. Participants were given a 10-min break prior to starting the SPEAR task. Participants completed three practice trials of the SPEAR task and received feedback after each of their responses to assure they understood the instructions, timing, and requirements of the task. Saliva sample 5 was acquired at the completion of the practice trials and prior to the start of SPEAR test task. Following each block of SPEAR trials, participants completed a post-block survey to include ratings of arousal, mental effort and emotion valance [*via* visual analog rating scale (53)], and to record their tone count and recall of the commander's intent. Saliva samples 6 and 7 were acquired just after completing each block of SPEAR trials. A final set of self-report assessments were completed after

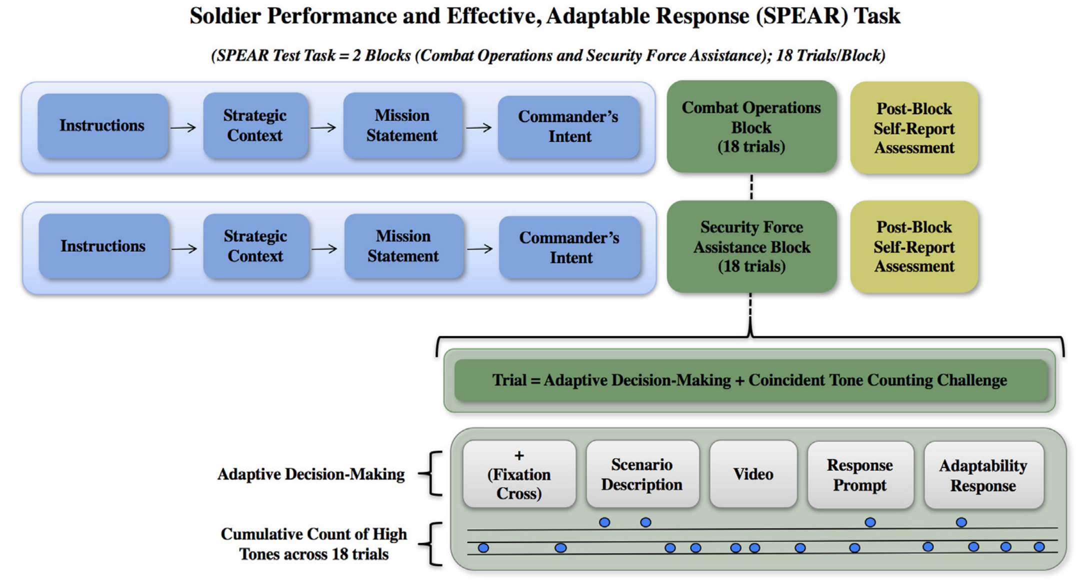

FIGURE 1 | Soldier Performance and Effective, Adaptable Response (SPEAR) task design and trial structure. The initial strategic guidance (i.e., strategic context, mission statement, and commander's intent) is provided at the beginning of a block of trials is show in the blue boxes. This is provided one time at the beginning of each block of trials. The following 18 trials occur within the context of that initial strategic guidance. The Combat Operations and Security Force Assistance blocks are illustrated as green boxes. The gray boxes illustrate the specific trial elements and auditory discrimination task.

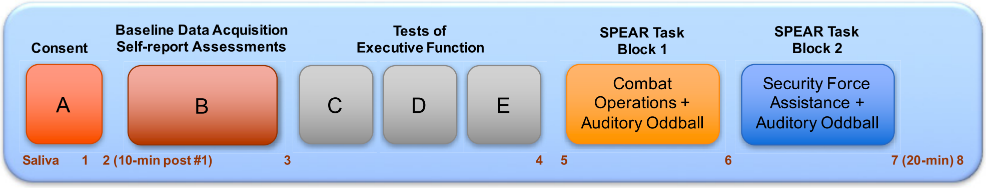

FIGURE 2 | Adaptability protocol. Task events are illustrated and saliva sampling frequency noted. Obtaining the informed consent **(A)** was followed by completion of self-report assessments, instrumentation and the baseline assessments **(B)**. The Ericksen-Flanker, Iowa Gambling Task, and 2-Back tests of executive function were then administered [**(C–E)**, respectively]. The Soldier Performance and Effective, Adaptable Response (SPEAR) task Combat Operations and Security Force Assistance blocks of trials were then completed (orange and blue boxes). Following each of the tests of executive function and both SPEAR blocks of trials, the participant sat quietly for 2-min for a post-task recovery period. The saliva sample acquisition schedule is noted at the bottom of the figure in red text.

all SPEAR trials were completed to obtain the participant's observations on the SPEAR task, identify their referent source for their adaptability responses, and strategy for handling the tone count and adaptability challenge. Participants sat quietly for a 20-min period prior to providing the last saliva sample (sample 8). At the end of the experiment, participants were deinstrumented, debriefed, and escorted to the building entrance.

Signal Processing

Electrocardiogram Signal Processing

Electrocardiogram signals were acquired using a BIOPAC MP150 system with the wireless ECG amplifier module. ECG signals were digitized at 1,000 Hz and stored in a continuous record along with several other channels of information (EDA, and a digital event marker signal). Data were processed within custom-designed Labview software (The Brain Body Center for Psychophysiology and Bioengineering, University of North Carolina at Chapel Hill). The processed data included ECG R-peak detection, interbeat interval (IBI) editing, event marker classification, IBI transformation, and parameter extraction.

The R-wave locations were identified to generate the IBI series for analysis while minimizing artifacts and missing data. ECG quality was evaluated, and the R-wave peak inflection point times were extracted to generate the IBI series sequential R-R intervals data for analysis. Where necessary, preprocessing of the ECG waveform included bandpass filtering and/or inversion of the signal polarity to enhance signal quality. An algorithm was used to fit a second-order polynomial to sequential groups of ECG samples (three to six points). The polynomial fit was tested at each peak against a threshold. Peaks lower than the threshold were ignored. For ECG data with a stable baseline, a single threshold was used through the entire data set. Conversely, for ECG data with variable ECG amplitude and/or quality, an adaptive windowing approach was used in which small temporal windows of

ECG were analyzed. Extracted parameters iteratively updated the length and position of the next analysis window (54).

While editing the IBI, any missing R-wave detections, preventricular contractions, other types of arrhythmias, and erroneous peak identifications were removed by trained editors using visual inspection. Motion artifacts, device communication failures, and natural transient physiological events led to a small number of these types of edits for the recordings. An algorithm was used to inspect the trigger channel from the BIOPAC to identify task segments. The event marks generated by E-Prime were used to identify each task by name, start time, end time, and duration. Events and BIOPAC signals were further separated into two segments of the protocol, each containing multiple tasks: the baseline segment and the adaptability task testing segment. Baseline segments consisted of posture challenge, choice reaction-time, auditory discrimination, Eriksen Flanker, IGT, and 2-back recall tasks. Rest periods were observed before and after each of the aforementioned tasks.

To isolate the RSA component of heart rate variability, the team conducted IBI transformation. This was based on the Porges-Bohrer method (20, 54), which employs a time-frequency method to extract a band-limited component from the HP time series that represents RSA across the full duration of each segment (baseline or adaptability task testing). During this step, a 5-Hz time sampled raw IBI signal and a 5-Hz RSA component were created. From these two series, 15-s windows (epochs) of RSA (magnitude of the oscillation) and HP (mean IBI value) were computed. The set of HP and RSA values within each event (e.g., IGT) were then used to calculate the following parameters of nervous system regulation of cardiac function: mean HP and RSA, HP, and RSA change over time, short-term correlation between HP and RSA, and linear regression slope between HP and RSA. An additional set of parameters investigating the relationship between HP and RSA across all recovery period epochs was also quantified.

EDA Data Processing

To prepare the raw EDA data for analysis, the data were downsampled to 250 Hz. Ledalab (14, 15, 55) was used to compute the number of skin conductance responses (SCRs), as well as the total sum, average, largest value, and the SDs of the amplitudes, areas, and rise times for each the referenced minute during task engagement. Ledalab provides two types of skin conductance analysis: continuous decomposition analysis (CDA), which produces estimates of skin conductance levels, and discrete decomposition analysis (DDA), which produces estimates of SCRs. The DDA methodology, which produces estimates of SCR's, was employed in the current study. DDA was used to predict when SCR stimuli occurred through a method of decomposing the skin conductance data into a distinct phasic component and a distinct tonic component by means of *nonnegative deconvolution* (14, 15). Nonnegative deconvolution captures and explores all unique deviations of the general response shape and computes a detailed full model of all components in the entire data set. When the tonic component and the individual calculated SCRs (each with a calculated rise time, amplitude, and area) are combined (summed), the result can be compared to the original data, and an error (difference) can be calculated. When the error level is within a small acceptable threshold, then the predicted stimuli times can be known. This method is especially suited for psychophysiological models in which the SCR response to stimuli engagement is of interest.

Collection of Saliva and Determination of Salivary Analytes

Across the task series (see **Figure 2** for sample collection timing), eight saliva samples were collected. On each sampling occasion, a 1 × 4 cm oral swab was placed under the participants tongue for 2 min. After collection samples were stored at 4 C until they were frozen (within 15–20 min) at −20 C. All samples remained frozen until the day of assay on which they were thawed to room temperature, vortexed, and then centrifuged for 15 min at 1,500 *g*. Sample volumes were estimated by weight and used to determine saliva flow rate (mL/min). Samples were tested for salivary cortisol using a high sensitivity enzyme immunoassay. The test used 25 µL of saliva per determination, had a lower limit of sensitivity of 0.007 µg/dL, a standard curve range from 0.012 to 3.0 µg/dL, and average intra-assay coefficient of variation (CV) of 5.42%, and an average interassay CV less than 10%. Following Granger et al. (17, 18), all samples were also assayed for sAA by kinetic reaction assay. The test volume was 10 µL of a 1 × 200 dilution, lower limit of sensitivity was 0.4 U/mL, and inter- and intra-assay CVs were on average less than 15 and 10%, respectively. There was no association between salivary cortisol or sAA scores and salivary flow rate. Prior to analyses, cortisol and sAA values that were greater than three SDs from the mean were winsorized. Next, the variables were transformed to meet normality assumptions (natural log and square root transformations for cortisol and sAA, respectively). **Table 1** shows the Pearson correlations and descriptive statistics for all salivary biomarkers.

Analytic Strategy

Descriptive statistics, correlation analyses (parametric and nonparametric), regression analyses, and analysis of variance were computed using Statistical Package for the Social Sciences (SPSS) statistical software (IBM) v24, 64-bit edition. Regression plots were computed using Microsoft Excel v14.0.7106.5003 (32-bit) for visualization. A significance level of $\alpha = 0.05$ was used for all statistical tests. Corrected significance levels are reported to address increased risk of Type 1 error due to multiple comparisons.

To examine if changes in hormonal biomarkers were associated with self-report measures, we computed change scores for sAA and cortisol, separately, between all adjacent scores from time 3 to time 7 (i.e., change between 3 and 4; change between 4 and 5; change between 5 and 6; change between 6 and 7). The change scores could be either positive, indicating an increase in the biomarker, or negative, indicating a decrease in the biomarker.

RESULTS

SPEAR Task Performance

The mean total SPEAR score was 179 (SD = 25.10). The mean score for the CO block was 93.8 (SD = 15.05) and for the SFA block was 85.19 (SD = 12.88). For the purpose of examining the relationship between the biophysical response and SPEAR performance, the response data and SPEAR scores were also analyzed by the

TABLE 1 | Correlations among all cortisol and sAA samples.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Cortisol 1																
2	Cortisol 2	0.85**															
3	Cortisol 3	0.57**	0.81**														
4	Cortisol 4	0.45*	0.54**	0.68**													
5	Cortisol 5	0.64**	0.65**	0.56**	0.72**												
6	Cortisol 6	0.15	0.34	0.38	0.42*	0.44*											
7	Cortisol 7	0.24	0.47*	0.46*	0.48*	0.47*	0.57**										
8	Cortisol 8	0.34	0.50**	0.60**	0.51**	0.52**	0.39	0.74**									
9	sAA 1	−0.04	−0.05	−0.28	−0.27	−0.09	0.07	−0.16	−0.09								
10	sAA 2	0.07	0.02	−0.15	−0.16	0.02	0.06	−0.13	−0.07	0.83**							
11	sAA 3	0.05	0.01	−0.10	−0.15	−0.01	−0.07	−0.14	−0.11	0.86**	0.75**						
12	sAA 4	−0.04	−0.19	−0.34	−0.17	−0.04	0.02	−0.25	−0.24	0.83**	0.77**	0.86**					
13	sAA 5	0.04	−0.02	−0.16	−0.12	0.11	0.05	−0.17	−0.05	0.86**	0.81**	0.88**	0.87**				
14	sAA 6	−0.18	−0.10	−0.18	−0.18	−0.17	0.16	−0.07	−0.14	0.71**	0.68**	0.69**	0.73**	0.67**			
15	sAA 7	−0.14	−0.21	−0.35	−0.23	−0.21	−0.06	−0.21	−0.12	0.86**	0.71**	0.80**	0.84**	0.75**	0.72**		
16	sAA 8	−0.09	−0.17	−0.33	−0.15	−0.07	0.02	−0.26	−0.21	0.77**	0.64**	0.69**	0.86**	0.70**	0.63**	0.89**	
	Mean	0.22	0.22	0.19	0.16	0.13	0.11	0.12	0.11	101.25	88.38	95.17	94.83	164.95	110.06	154.23	145.57
	SD	0.10	0.14	0.09	0.05	0.04	0.04	0.09	0.05	96.29	70.03	76.73	69.55	154.70	90.11	146.84	130.74
	Min	0.08	0.06	0.07	0.09	0.08	0.05	0.04	0.03	12.80	15.10	10.50	8.50	7.90	0.40	11.50	7.20
	Max	0.40	0.59	0.40	0.30	0.19	0.21	0.40	0.23	347.40	281.80	287.30	232.55	555.00	330.30	583.80	528.70

time-ordered blocks completed. The mean and SD for the first and second blocks completed were 92.3 (SD = 14.66) and 86.69 (SD = 14.13), respectively. Paired *t*-tests were computed to test for differences between the time-ordered first and second blocks of the SPEAR task across subjects. Participants performed better on time-ordered block one as compared to block two, $t(25) = 2.03$, $p = 0.05$.

Executive Function and SPEAR Performance

The dependent measure used to detect differential Ericksen-Flanker and SPEAR performance was response time. The consistency of participant response times for the I-C trial pairings was inversely associated with the total SPEAR score. That is, there was a negative correlation, $r(25) = -0.39$, $p = 0.049$, between the SD of the response time for inconsistent (I) to consistent (C) correct response trial pairings of the Ericksen-Flanker and SPEAR total score. No other associations with executive function tasks (i.e., IGT and N-Back) and SPEAR were observed.

Cardiovascular Reactivity, Regulation and the SPEAR Task

Rapid shifts in autonomic state, specifically in cardiac vagal tone as measured by RSA, were observed across the two phases of the SPEAR task. As participants transitioned from the "Information receiving" phase (Scenario description + Video, labeled as "A" phase here) to the "Solution Generation" (Response prompt + Adaptability Response, or "B" phase) phase of each trial, there was a significant decrease in HP of 26.83 ms, $t(21) = 4.45$, $p < 0.001$ and RSA of 0.62 Ln(ms^2), $t(21) = 10.51$, $p < 0.001$, when comparing average levels across the 36 trials for each subject in each phase. The pattern of RSA suppression was particularly regular (see **Figure 3**), which shows the distribution of simple change scores across all 36 trials for all 22 subjects. The median change in RSA was −0.58Ln(ms^2), and 86% of the trials showed a decrease from the A to B phases. A smaller majority, 69.6% of trials, showed a decrease in HP (median change = −21.1 ms, see **Figure 4**).

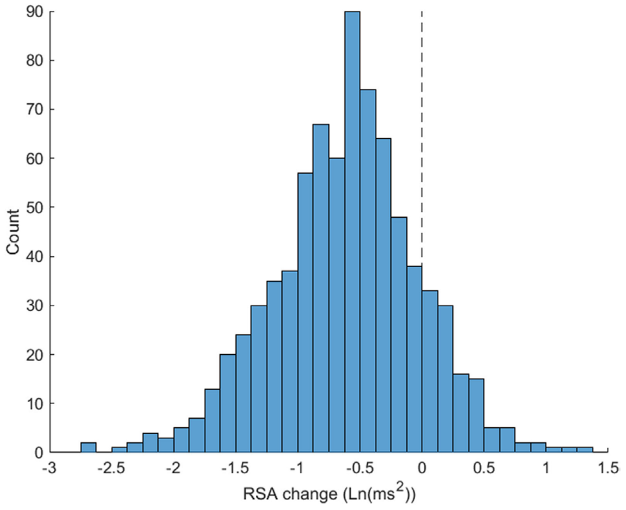

FIGURE 3 | Respiratory sinus arrhythmia (RSA) suppression from Soldier Performance and Effective, Adaptable Response (SPEAR) A to B task phases. Distribution of SPEAR task phases A (Scenario description + Video) to B (Response prompt + Adaptability Response) RSA change scores are illustrated. 86% of trials show RSA suppression from A to B phases (number of trials below 0) indicating shifts in autonomic state to meet "Information Receiving" to "Solution Development" requirements of the task.

While the magnitude of HP and RSA changes were not directly related to performance, the rate of recovery of parasympathetic capacity prior to SPEAR testing was. In the final recovery baseline (FRB) period, prior to the SPEAR tasking (and following the completion of the block of executive function tasks), the rate of

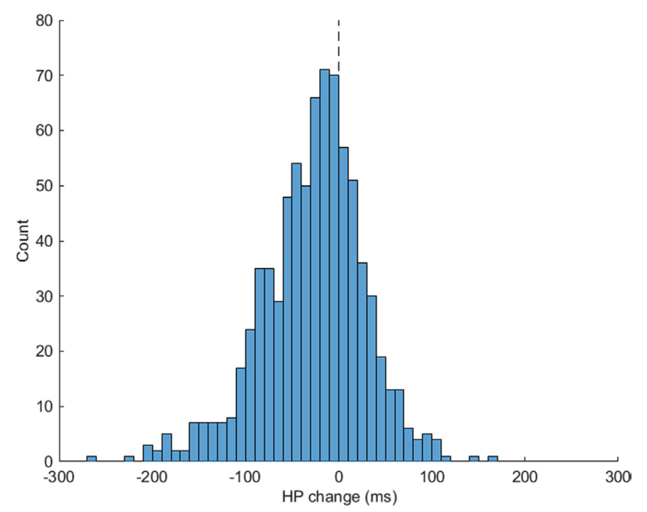

FIGURE 4 | Heart period (HP) change for Soldier Performance and Effective, Adaptable Response (SPEAR) A to B task phases. SPEAR task phases A (Scenario description + Video) and B (Response prompt + Adaptability Response) respiratory sinus arrhythmia change scores are illustrated. 69.6% of the trials show a change in HP from A to B phases (number of trials below 0) indicating shifts in cardiac vagal tone to meet task demands.

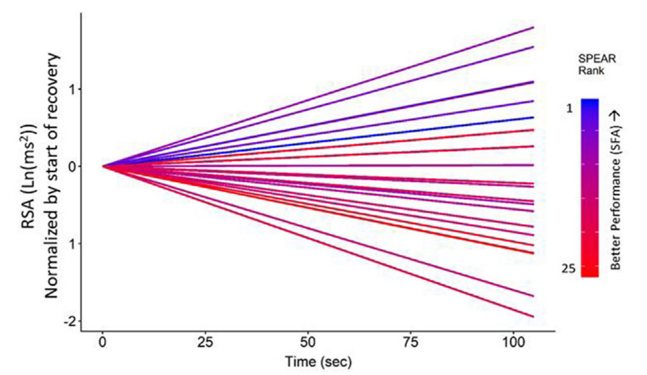

FIGURE 5 | Respiratory sinus arrhythmia (RSA) time trends by Soldier Performance and Effective, Adaptable Response (SPEAR) security force assistance (SFA) ranked score. Recovery of RSA during final recovery baseline prior to the SPEAR task was correlated with greater scores on the SFA block of trials, $\rho(20) = 0.58$, $p < 0.01$. SPEAR performance ranked scores are color-coded on a gradient scale ranging from cool, blue colors (highest scores) to reds (low scores). Highest scores were observed in participants who showed increasing RSA across the 2-min recovery period just prior to the SPEAR task.

RSA change was positively correlated with SPEAR performance and recall of the commander's intent. Soldiers that showed increasing RSA (i.e., recovered vagal inhibition) demonstrated better performance across the subsequent task, $\rho(20) = 0.55$, $n = 22$, $p = 0.007$, while also having a greater recall of the commander's intent, $\rho(20) = 0.47$ and 0.62 for the CO and SFA blocks, respectively, $p < 0.05$. This pattern of RSA recovery is visualized in **Figure 5**. Each line is the slope, shows a subject's average rate of change in RSA during the FRB (just before SPEAR). The lines are all centered at 0 at the start of FRB for visualization, and the performance on Block 2 is used to color code the lines. The highest scores during SFA tasks are observed in those subjects who showed increasing RSA across the 2-min recovery period FRB, $\rho(20) = 0.62$, $p = 0.002$.

In addition to performance relationships, HRV parameters were significantly related to self-reported combat experiences. Frequency of COs during deployments was associated with reduced resting RSA levels. The direction of this effect was consistent across several baseline periods with the highest level of significance observed after the sit/stand challenge [$\rho(22) = -0.47$, $p < 0.05$]. Higher rates of self-reported casualty exposure were also related to reduced HP changes when performing the sit/stand challenge, $\rho(22) = -0.48$, $p < 0.05$. RSA reaction to the posture challenge showed a trend toward the same relationship, $\rho(22) = -0.36$, $p = 0.11$. Higher rates of casualty exposure were also negatively correlated with mean HP in several periods. Specifically, shorter mean HP was observed in those with higher rates of casualty exposure after the sit/stand, $\rho(22) = -0.51$, $p < 0.05$ and executive function challenges, $\rho(22) = -0.50$, $p < 0.05$. Casualty exposure was binned into a three-group classification derived from the self-reported rates (1 = none; 2 = 1–15%; 3 = > 15%), and **Figure 6** illustrates how higher rates of casualty exposure significantly reduced HP response (less of a sawtooth HP pattern, B − A differences averaged across all 36 trials) during SPEAR task engagement, $F(2,19) = 7.49$, $p = < 0.01$. Greater resilience (on the Commitment subscale) as assessed by the DRS was also related to greater decreases in HP from A to B phases of the SPEAR trials, $\rho(22) = -0.44$, $p < 0.05$.

Electrodermal Activity

At the recovery period following the block of tests of executive function and prior to beginning the SPEAR task (called FRB), a paired t-test revealed a significant difference in the SCR counts in minute 1 and minute 2, $t(25) = 3.62$, $p < 0.001$, indicating a decrease in the number of SCR across that recovery period. Further, less SCR mean area in minute 2 relative to minute 1 (computed as a difference score) at FRB was negatively correlated, $r(25) = -0.46$, $p < 0.001$, with total SPEAR score in the second time-ordered block of trials.

Salivary Analytes and Adaptability

Since the change score variables violated the normality assumptions and transformations did not improve the skewness of these variables, we examined Spearman correlations between SPEAR total score and both cortisol and sAA change scores, separately. The results showed no significant relation between any of the cortisol change scores and SPEAR total score. One significant relationship emerged for sAA change scores. The change in sAA between time 4 and time 5 was negatively associated with SPEAR total score, $\rho(25) = -0.41$, $p = 0.04$.

DISCUSSION

In this study of a small group of experienced military leaders, we observed that: cardiac vagal tone demonstrated a predictable pattern of withdraw and recovery during repeated presentation of battlefield challenges, recovery of cardiac vagal tone following

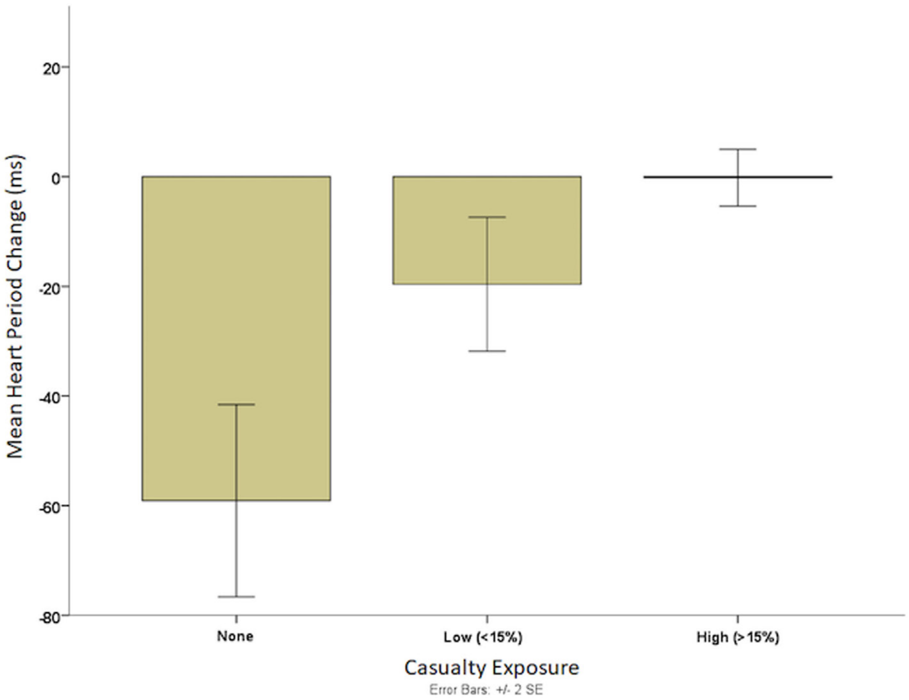

FIGURE 6 | Mean heart period (HP) change during Soldier Performance and Effective, Adaptable Response (SPEAR) task and rates of casualty exposure. A three-group classification derived from the self-reported rates of exposure to combat casualties (1 = none; 2 = 1–15%; 3 = > 15%) is illustrated. The HP value is the change in HP during the SPEAR task. These results illustrate that higher rates of casualty exposure leads to significantly diminished flexibility in cardiac response (less of a saw tooth HP pattern) during SPEAR task engagement.

a set of executive function challenges led to responses that were more adaptive to the battlefield challenges, and executive function was not directly related to adaptive problem solving capacity. These findings suggest that autonomic regulation plays a critical role in facilitating adaptability and tracking RSA would enhance objective measures of adaptability.

The clear pattern of withdrawal and recovery observed in the autonomic activity during the SPEAR task highlights the self-regulatory demands of adaptive problem solving (**Figure 7**). RSA and HP suppression during the transition from "Information Receiving" to "Solution Development" phases of each trial indicate that cognitive processes are demanding different autonomic resources. The vagal break is the quickest means for the body to change arousal state to meet new and demanding situations (22). Rapid recovery of cardiac vagal tone shifts the autonomic system back into normal balance, as at rest, so the soldier is ready for the next problem set. The SPEAR task requires a great deal of cognitive shifting and agile removal of the vagal break and regaining the vagal inhibition. Greater vagal capacity better enables the engagement within and switching between the different demands of the SPEARS task, just as would be encountered on the battlefield.

Furthermore, battlefield experience moderated this pattern of autonomic regulation during the SPEAR task. Specifically, prior exposure to high casualty rates during COs significantly reduced the magnitude of this HP pattern (but not RSA flexibility) during SPEAR task engagement suggesting a reduced self-regulatory capacity or a compensatory reactivity that blunted the impact of cardiac vagal tone on cardiac rate. As such, casualty exposure seems to alter the autonomic nervous system profile by decreasing the efficiency of RSA mediated suppression of cardiac output, which leads to decreased focused attention during SPEAR task engagement and lower levels of adaptive behavior.

The dispositional resilience commitment subscale showed the opposite effect of casualty exposure, with the greater HP suppression during SPEAR task engagement for soldiers with high resilience. A larger sample would be required to test resilience as a mediator of psychological stress (e.g., casualty exposure) on autonomic flexibility and adaptability, but these data suggest that such a relationship is plausible. The study also suggests that simple interventions that could increase recovery of cardiac vagal tone after mentally taxing events, could also increase adaptability or improve recall of mission relevant information (i.e., the commander's intent). The relationship between frequency of COs and autonomic reactivity to the posture challenge suggests that simple protocols could be designed to screen for cardiovascular signatures of psychological stress.

While it was hypothesized that the executive function tasks would represent a dimension of adaptability and therefore be significantly correlated with adaptability, performance on the executive function tasks was not predictive of performance on the SPEAR task. However, the challenges did lead to reduced vagal inhibitory impact on cardiac rate, and recovery of that inhibitory control following the executive function challenges (at FRB) was

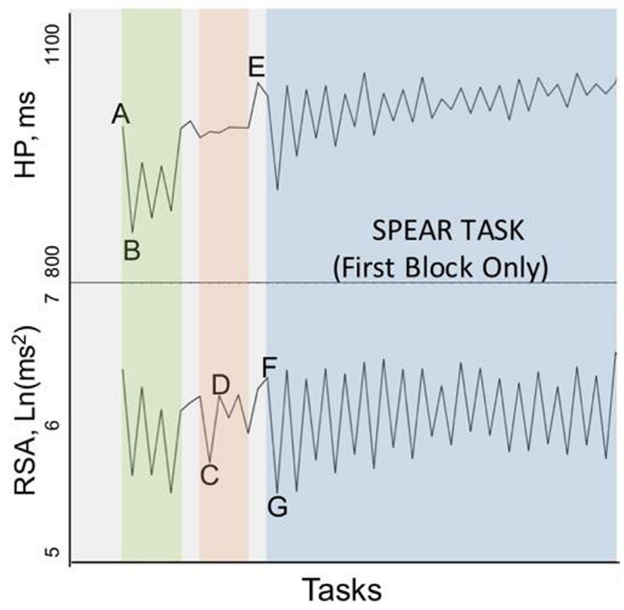

FIGURE 7 | Mean heart period (HP) and respiratory sinus arrhythmia (RSA) cardiac reactivity pattern across the protocol. The mean HP (top) and mean RSA (bottom) over each period in the protocol (A–G) is illustrated. This figure highlights the pronounced cardiac reactivity pattern during the two phases of each trial of the Soldier Performance and Effective, Adaptable Response (SPEAR) task. The first 18 trials of the time ordered SPEAR task are shown to the right of F. The characteristic saw tooth pattern is the heart period (HP) and RSA signal change in response to meeting the demands of the "problem" and "response" phases of the SPEAR task. The regularity persisted in the second time ordered block for RSA but not HP. The tasks notations in the illustration are as follows: A = the initial seated baseline; B = Stand #1; C = Eriksen-Flanker; D = Post Eriksen-Flanker recovery; E = Final recovery baseline (FRB); F = SPEAR Trial 1 (A)—Information Receiving; G = SPEAR Trial 1 (B)—Solution Development.

predictive of SPEAR performance. Recovery of vagal capacity was particularly predictive of performance on the SFA block, which proved significantly more difficult for soldier participants and which required non-kinetic, adaptive solutions. The strong correlation between the rate of RSA recovery and performance on the non-kinetic mission challenges of the SPEAR task suggests that inhibitory capacity is essential to the cognitive processes involved in adaptive problem solving on the modern battlefield. Convergent evidence observed in the EDA data at recovery (at FRB) indicated that declining sympathetic arousal was also predictive of performance on the SPEAR test task.

As expected, we did not find consistent or reliable evidence that HPA reactivity and regulation was associated with SPEAR task performance or executive function. The literature suggests that the HPA axis reacts to circumstances that are novel, when the demands of the situation are unfamiliar, and when individuals who find themselves in such circumstances do not have the capacity or previous experience to adapt to the situation. Given the prior military and leadership experience of this study's participants, it is not surprising that we did not detect changes in cortisol reactivity and regulation in response to the SPEAR task. The "null" result here may be in fact an indirect indication of adaptability and resilience. Follow up studies that explore a more heterogenous sample and a broader range of challenges, both novel and familiar, will be required to establish this hypothesis.

We did expect that the change in sAA would be linked to engagement and active problem solving. We observed associations between sAA levels at specific time points (samples 4 and 5) during the SPEAR task that support this notion. Given these preliminary sAA-related findings, future examination of inter- and intraindividual differences in sAA in a larger sample and in the context of the SPEAR task could predict adaptability.

The combination of the RSA, EDA and sAA findings are supportive of the importance of the recovery response to adaptability. The vagal break appears to be the quickest means for the body to change arousal state to meet new and demanding situations. Rapid recovery of cardiac vagal tone shifts the autonomic systems back into normal balance, as at rest, so the participant is ready for the next problem set. SPEAR required cognitive shifting and agile removal of the vagal break and regaining vagal inhibition to support problem solving. Greater vagal capacity prior to the task appeared to maximize the engagement within and switching between the different demands of the SPEAR task.

Our initial notion of adaptability was constrained to concepts and responses associated with meeting the demands of a challenge. We now understand that the recovery from challenge is crucial to understanding adaptability and performance. The operational setting consists of multidimensional, complex, and often competing demands. The military leader is required to engage, distinguish relevant from irrelevant information, consider options, and refine or create new commands in a timely manner and often under conditions of high stress. Adaptive leadership is meeting such challenges time and again, and until the mission is accomplished. The flexible cardiac response identified in this study provides evidence of a functional and regulatory system response supportive of adaptive problem solving.

With the proper balance of arousal and recovery, individuals and units could better maintain high levels of battlefield effectiveness over extended periods of time. The SPEAR task provides a quantifiable basis on which to determine the optimal amount of rest and recovery needed by units and by individuals to facilitate sustainable adaptability. In addition, the metrics used in the present study could serve as the basis for evaluating supportive training strategies such as biofeedback that could target the autonomic balance directly.

Future work in this domain should include a test battery that taxes multiple processes of cognitive performance to include, for example, math computations, psychomotor vigilance, auditory discrimination, and working memory. Such a task would be expected to evoke a strong regulatory response in all subjects from which recovery would be highly predictive of adaptive problem solving. Beyond laboratory tasks that engage multiple and complex processes, we recommend the development of more authentic, mission relevant test tasks. Such an approach would bridge the current gap between experimentation and field-based training. To advance operational capability, research findings must be validated in large samples in order to address questions of scalability and determine methods to translate evidence-based findings to authentic, field-based training environments.

In order to better understand the generalizability of these finding to adaptability, we recommend extending the study of adaptability beyond the military. We recommend future efforts test a larger military sample representing soldiers across the rank and military occupation specialty (MOS) structure and a large civilian sample representative of the general population. Test tasks could include general cognitive workload, emotion regulation and physical stressors as well as occupational-relevant challenges in order to discern the different aspects of adaptability and confirm the specificity of the adaptability self-regulatory response.

The battlefield is not the only context where adaptive problem solving is critical. First responders, emergency medical teams, disaster relief personnel, fireman, law enforcement officers, and educators, for example, face job-related challenges replete with varying and uncertain performance demands and for which sustained adaptability is required for success. Natural disasters, terrorist attacks, and emergency situations produce the same physiological reactions, tax first responders and victims in the same manner, and require decision-making under stress similar to combat. These same metrics used for military adaptability apply to law enforcement and other stressful public service occupations as well.

These data highlight the importance of a certain response needed to meet the demands of the task and also the importance of recovery as critical to preparation for the next challenge. Military fitness and leader development programs can be developed to increase the recovery capacity of individuals regardless of the individual's physical fitness capacity. Instead of a distinct physical training and task preparation focus, as is characteristic in today's military, it is recommended to shift or augment the focus to psychophysiological training outcomes to achieve higher adaptability and consequently, resilience across the force. In this manner, soldiers would be both physiologically and psychologically equipped to meet the problem solving demands of the battlefield. Leader development programs should include activities that improve the psychophysiological capacity of junior leaders through problem solving and field-based training exercises that demand the pattern of arousal and recovery required for adaptive performance over time (i.e., sustainability). The military must connect the psychophysiological aspects of human performance with its training, education, and mission and battle preparations to optimize human performance in very ambiguous modern warfare that requires more thoughtfulness and less kinetic solutions. Understanding the psychophysiological correlates of battlefield stress could be leveraged to examine dose–response relationships and identify risk factors associated with combat-related disorders.

These indicators should also be incorporated into the military's various selection and assessment programs designed to determine individuals most suited for high risk missions, high stress occupational specialties, and activities that require the most adaptability, such as aviation and special operations activities, and frontline leaders and commanders. This concept applies to any small unit that operates independently across a decentralized and non-contiguous battlefield. Training and advising foreign militaries in austere environments during conflict requires that junior leaders and small unit leaders have a high level of adaptability and resilience. The military would benefit from developing all of its junior leaders in this fashion, so decision-making is adaptable and decision-makers are adaptive and resilient.

In conclusion, these findings indicate flexible autonomic regulation supports recovery following challenge, which in turn supports problem solving or adaptability skills. The response/recovery parameters established in the present study could be applied to predict soldier problem solving as well as resilience to environmental stressors. Autonomic regulation can be enhanced through targeted cardiovascular training designed to increase cardiac vagal capacity. Both the executive function and SPEAR tasks engaged cardiovascular regulatory systems and thus provide a portal to investigate adaptive state regulation. Having identified the neural regulation and balance system associated with problem solving and adaptability, we can now apply these findings to performance enhancement. Cardiac regulation during the SPEAR task was related to psychological resilience, and the interaction between the components of adaptability, autonomic flexibility, and resilience suggests mental (and likely physical) health benefits would result from efforts to increase adaptability.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of applicable Organizational, Local, State and Federal guidelines, as well as The Johns Hopkins Medicine Institutional Review Board (IRB) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Johns Hopkins Medicine IRB-X protocol #00068417 entitled "Soldier Performance and Effective, Authentic Response (SPEAR)" study. The Board determined that the device (BioPac System) was not significant risk (NSR) and meets the requirements for an abbreviated IDE. The IRB also determined that the project involved minimal risk to participants and that a Medical Monitor was not required under DoD Directive 3216.02. The IRB conducted scientific review per Organization Policy 111.5 and determined the research uses procedures consistent with sound research design and the research design is sound enough to yield the expected knowledge.

AUTHOR CONTRIBUTIONS

AH: PI, developed the study concept and protocol, implemented all aspects of the study, results preparation, dissemination, writing. GL: designed cardiovascular aspects of the protocol, ECG signal processing and analysis, results preparation, writing. MD: conducted ECG signal processing, analysis and results preparation. FW: supported SPEAR task development, data collection, signal processing, and results preparation. JG: supported SPEAR task design, data collection, lead the SPEAR task scoring team, interpretation, writing. CB: contributed to the salivary analytes analysis, results preparation, and interpretation. JK: contributed conceptual approach to the analysis and interpretation of HRV data, generated unique visualization of the RSA slope data. DG: contributed to the salivary analytes protocol design, analysis, interpretation, writing. WM: contributed to study implementation, data analysis and results preparation/interpretation, writing. All authors approved the manuscript and agreed to be accountable for all aspects of the work.

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Improvements in Heart Rate Variability, Baroreflex Sensitivity, and Sleep After Use of Closed-Loop Allostatic Neurotechnology by a Heterogeneous Cohort

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Background: Heart rate variability (HRV) is an indicator of dynamic adaptability of the autonomic nervous system. Few interventions target upstream, cerebral cortex components of the heart–brain system for autonomic management. We report changes in HRV and baroreflex sensitivity (BRS), associated with use of a noninvasive, closed-loop, allostatic, computer-guided, acoustic stimulation neurotechnology.

Methods: Over 5 years, 220 subjects with heterogeneous neurological, cardiovascular, and psychophysiological conditions consecutively enrolled in a naturalistic, single-arm study exploring clinical effects associated with use of the neurotechnology. Of those, 202 completed the study protocol and 160 had recordings adequate to analyze HRV and BRS. Mean age was 44.0 (SD 19.4), with 130 women. Participants received a mean of 16.1 (5.2) sessions, over 24.2 days (23.3), with 9.5 (3.8) actual intervention days. Sessions included real-time analysis of brain electrical activity and software algorithm-guided translation of selected frequencies into patterns of acoustic stimulation (audible tones of variable pitch and timing), to facilitate auto-calibration of neural oscillations. Outcomes including 10-min supine, at-rest recordings of blood pressure and heart rate, and inventories for insomnia (ISI) and depression (CES-D or BDI-II), were obtained at baseline and 15.3 (16.7) days after the last session.

Results: Compared to baseline, significant increases (all $p < 0.001$) were observed for measures of HRV across all participants including the mean percentage change for SDNN 24.2% (SE 0.04), and RMSSD, 42.2% (0.08), and BRS [Sequence Up, 55.5% (0.09), Sequence Down, 77.6% (0.23), and Sequence All, 53.7% (0.07)]. Significant improvements were noted in SAP, MAP, and DAP, as well as natural log of HF, and total power. Self-reported ISI was reduced (ISI, −6.4 points, SD 5.6, $p < 0.001$). The proportion reporting clinically significant depressive symptoms reduced from 48.2% at baseline to 22.1% at follow-up. Linear regression showed that rightward asymmetry predicted lower SDNN ($p = 0.02$). Exploratory analysis showed a trend for improved balance of temporal lobe high-frequency amplitudes over the course of initial sessions.

Conclusion: These findings indicate that use of a noninvasive, allostatic, closed-loop neurotechnology appears to have robust potential for public health efforts to support greater flexibility in autonomic cardiovascular regulation, through self-optimization of electrical activity at the level of the brain.

Keywords: neurotechnology, allostasis, heart rate variability, acoustic stimulation, baroreflex sensitivity, closed-loop, neural oscillations, HIRREM

INTRODUCTION

Numerous studies have shown that heart rate variability (HRV) is a useful physiological indicator of dynamic adaptability in the autonomic nervous system. In adults, low HRV is a risk factor for adverse cardiovascular outcomes (1, 2), new onset of diabetes (3), progression of chronic kidney disease (4), and all-cause mortality (5). The ubiquity of diminished HRV in behavioral health disorders has led to its proposal as a transdiagnostic biomarker for psychopathology (6). As a measure that can be obtained easily and noninvasively, HRV merits serious consideration as a target for observation and intervention on a public health basis (7). Furthermore, attention to HRV may support the progress of advanced practices which are beneficial for both physical and mental health or adaptive neurovisceral integration (8).

A wide variety of behavioral, physical exercise, and pharmacological therapies have been shown to increase HRV (9). Especially for interventions that entail relatively non-specific features, it seems likely that effects will depend on the capacity to influence both central and peripheral nervous system pathways. An intriguing question is whether focused engagement of critical central structures, especially those known to have specific roles for autonomic management, may be a way to produce more efficient or pronounced effects on HRV. For example, the bihemispheric autonomic model for management of traumatic stress (BHAM) begins with recognition that the right and left hemispheres are primarily responsible for cortical management of the sympathetic and parasympathetic divisions, respectively (10). The BHAM suggests that temporal lobe electrical asymmetry may be an indication of traumatic stress exposure, associated with health effects including reduced HRV, and the model proposes that intervention to reduce asymmetrical activity may be a way to facilitate a state of enhanced autonomic regulation, including increased HRV.

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®, Brain State Technologies, Scottsdale, AZ, USA), is a noninvasive, closed-loop, allostatic, acoustic stimulation neurotechnology (11), that is designed to facilitate auto-calibration of neural oscillations. The HIRREM brainwave mirroring interventional strategy aims to facilitate more adaptive forms of symmetry at the temporal lobes and other cortical regions. HIRREM is aligned with the BHAM as well as the broader physiological paradigm of allostasis (stability through change), which recognizes the brain as the organ of the central command (12). As a closed-loop neurotechnology (i.e., an intervention whose inputs are objectively measured real-time neurological data), HIRREM is not intended to depend on conscious, cognitive activity, volitional self-regulation, or behavioral monitoring.

The primary objective of this report is to summarize changes in measures of HRV and baroreflex sensitivity (BRS), as well as self-reported symptoms of insomnia (ISI) and depression, in a large, consecutively enrolled, heterogeneous population of subjects who undertook use of HIRREM. Subsets of these data have been presented earlier for patients with menopausal hot flashes (13), postural orthostatic tachycardia syndrome (14), sport-related concussion (15), and post-traumatic stress (16). The secondary objective is to explore the potential role of temporal lobe high frequency patterns of change in temporal lobe asymmetry that were expressed over the course of the initial five sessions of HIRREM.

MATERIALS AND METHODS

Population and Subject Recruitment

Participants were drawn from among those enrolled between 07/16/2012 and 08/05/2016, in a single site, IRB-approved, open label exploratory study to evaluate the feasibility and effects of HIRREM for individuals with one or more diverse neurological, cardiovascular, or psychophysiological conditions (ClinicalTrials.gov NCT02709369). The study was carried out in the Department of Neurology at the Wake Forest School of Medicine, Winston-Salem, NC, USA. Participants were identified by clinician referral or informal networks, and all provided informed consent. Those unable to provide informed consent, attend study visits, or sit comfortably in a chair were excluded, as were those with bilateral total hearing loss, known seizure disorders, or ongoing use of benzodiazepines, opiate, or anti-psychotic medications.

Following informed consent, participants completed a set of outcome measures (below) before beginning their series of in-office HIRREM sessions, which were all conducted at the clinical study site (details below). Post-intervention outcome measures were repeated at a time following completion of the HIRREM sessions that was convenient for the subject, preferably within 2 weeks of the last session.

Assessment of HRV and BRS

Continuous recordings of blood pressure (BP) and heart rate (HR) were acquired from noninvasive finger arterial pressure measurements and electrocardiogram for a minimum of 10-min in subjects lying down quietly, supine, breathing freely.

Recordings were obtained at the enrollment visit, approximately 30 min before the HIRREM assessment, and at the follow-up visit after completion of the HIRREM intervention. Systolic, diastolic, and mean arterial BP, as well as beat-to-beat RR interval files generated *via* the data acquisition system (BIOPAC acquisition system and Acknowledge 4.2 software, Santa Barbara, CA, USA) at 1,000 Hz were analyzed using Nevrokard SA-BRS software (by Nevrokard Kiauta, d.o.o., Izola, Slovenia). Evaluation included measures of BRS including Sequence UP, DOWN, and ALL, and HRV in both the time and frequency domains. All recordings were visually inspected, and the first 5 min of usable tracings were analyzed using Nevrokard Software to identify R waves from the ECG and BP tracing followed by subsequent determination of HRV and BRS in both time and frequency domains. The primary frequency domain variables of interest were low-frequency (LF) power, and high-frequency (HF) power, the ratio of LF to HF (LF/HF), and the total power determined from power spectral analysis using fast Fourier transformations (Hamming window) with band widths 0.04–0.15 and 0.15–0.40 Hz for LF and HF, respectively. The HF is believed to reflect parasympathetic modulation of HR. And the LF and the LF/HF are commonly used to reflect sympathetic regulation and sympathovagal balance, respectively. The primary time domain variables of interest were the SD of all R to R intervals, commonly reported as N to N intervals (SDNN), the square root of the mean of sum of squares of differences in successive N to N intervals (rMSSD). For all of these variables, a higher value suggests greater HRV. Recordings with dropped beats or gross motion artifact were excluded from analysis.

Self-Report Measures for Symptoms of ISI and Depressive Mood

The ISI is a 7-item survey that assesses the severity, nature, and impact of ISI symptoms on quality of life over the previous 2 weeks (17). It is scored on a 5-point Likert scale from 0 (no problem) to 4 (very severe problem) on a composite score range from 0 to 28. Composite scores can be stratified into the following clinical severities of ISI: absence (0–7), sub-threshold (8–14), moderate (15–21), and severe (22–28) (18). The ISI's internal consistency was found to be 0.74 and a correlation with sleep diaries was also established. Depressive mood was measured by the CESD (19) and the BDI-II (20), over the period of the study. Severity of depressive symptomatology was measured dichotomously, using scores of 16 or greater for the CES-D and 14 or greater for the BDI-II.

HIRREM Intervention

Process and procedures for provision of HIRREM have been discussed in detail previously (11). The initial brainwave assessment consisted of two-channel recordings of brain electrical activity from at least six paired locations on the scalp (F3/F4, C3/C4, T3/T4, P3/P4, FZ/OZ, and O1/O2), with the recipient at rest and while carrying out a task, using sensors and amplifiers (Brain State Technologies, Scottsdale, AZ, USA) that sample at 256 Hz. At each location, data were recorded for 1 min each with eyes closed, eyes partially open as a transition in state of arousal, and eyes open while engaging with a mental task (e.g., reading numbers, performing mental calculations, etc.). Trained technologists evaluated assessment data to choose protocols for the initial HIRREM session.

Intervention protocols included recording brain electrical activity through generally two channels, with scalp sensors placed at homologous regions of the hemispheres according to the 10–20 International EEG system. In real-time, software algorithms analyzed specific ranges of the brain electrical frequency spectrum, identified dominant frequencies on the basis of proprietary mathematical formulae, and translated those frequencies to acoustic stimuli (audible tones of variable pitch and timing). The tones were presented to participants through standard earphones (Creative EP-630 or Sony Stereo Headphones MDR-EX58V) with as little as an 8-ms delay. Volume (decibels) of acoustic stimulation was adjusted by each participant in accordance with their preference.

The HIRREM sessions were scheduled to maximize frequency and efficiency with participants generally completing two sessions in a half day, separated by a break of 20–30 min. Each HIRREM session (approximately 90 min each) consisted of 3–10 HIRREM protocols addressing different locations (3–40 min each), some done with eyes closed and some with eyes open, with the participant being asked to relax while sitting or reclining comfortably in a zero-gravity chair. Specific protocols for successive HIRREM sessions were chosen based on brain electrical data from the preceding session, which for purposes of technologist review was aggregated in broad-band frequency ranges (<1.0, 1.0–3.0, 3.0–5.5, 5.5–7.5, 7.5–10.0, 10.0–12.0, 12.0–15.0, 15.0–23.0, 23.0–36.0, 36.0–48.0 Hz). Special attention was given to activity set points suggestive of dominant hemispheric asymmetries and/or suboptimal ratios of energy across the frequency spectrum. Algorithms are designed to support de-establishment of relatively invariant and potentially maladaptive activity patterns. The decision for the total number of sessions to be received was based on impressions of clinical improvement or plateau, including evaluation of the participants' brain pattern evolution over the course of their sessions, as well as the participants' schedules and preferences. All participants continued with their usual medical or behavioral care.

Main Statistical Analyses

All pre- to post-intervention comparisons for autonomic and self-report measures were conducted with Excel, using paired *t*-tests. Variability estimates for time domain measures of HRV, BRS, BP, and self-report inventories were generated as SDs or SEs. Spectral measures of HRV (LF, HF, and total power) were evaluated as natural logarithms.

Exploratory Analyses of Temporal Lobe Electrical Asymmetry

A HF (23–36 Hz) band was selected and filtered as the range of interest for analysis on the basis that activity in this range may be taken as an indication of cortical activation (21). Electrical amplitudes (microvolts) in this range were aggregated as a HF band average. The HIRREM approach is designed to be insensitive to recording artifacts (11). To be consistent with the procedural needs of a point-of-care intervention in a resource-sensitive context, no attempt was made to identify sub-epochs of data that may have reflected noncortical factors (e.g., eye blinks or muscular contractions). A temporal lobe HF electrical asymmetry percentage score (eyes closed) was calculated for each subject by subtracting the value for the HF band average at T3 from the value at T4 and dividing by the lesser of the two, yielding a positive score for rightward (T4) asymmetry. Scalp-measured temporal lobe electrical asymmetry has been proposed as a way to assess autonomic tendencies (22) because temporal regions have relative proximity to the insular cortices, which show a division of labor for management of the autonomic nervous system (23, 24).

Evaluation for a potential relationship between temporal lobe HF asymmetry and SDNN was conducted through a linear regression that tested whether baseline HF asymmetry was a predictor of SDNN. An additional model was tested that included age, gender, current beta-blocker usage, and the revised Charlson comorbidity score (25) as covariates.

Evaluation of change in asymmetry over the first five HIRREM sessions at the bilateral temporal lobes was conducted through an exploratory analysis based on the slope of fitted trend lines for changing asymmetry scores at the start of those successive sessions. Subjects were categorized based on their initial temporal lobe dominance shown during their assessment (eyes closed). Rightward dominance was defined as temporal lobe HF asymmetry of 10% or greater; leftward dominance was defined as asymmetry of −10% or lesser; and symmetry was defined as between −10 and 10%. Except for the first 15-s epoch, data from the first 7 min for each of the first five sessions were analyzed to produce 27 serial asymmetry scores per session (15 s per epoch), which were averaged across all subjects for each dominance group. To assess whether the fitted lines reflected a tendency for change in asymmetry score, a mixed model *F*-test was performed on each slope (SAS, Cary, NC, USA) to account for within-subject temporal correlation, with the null hypotheses being that the slope was 0.

RESULTS

A summary of the flow for participant recruitment, screening, enrollment, intervention usage, and follow-up is shown in **Figure 1**. At the screening stage, the need for ongoing usage of a benzodiazepine, opioid, or anti-psychotic medication was the most common reason for ineligibility. Sixty-four percent of the enrolled subjects were women, mean age was 44.0 (SD 19.4, range 13–83). Mean score on the Charlson comorbidity index was 0.9 (SD 1.1, range 0–8), and **Table 1** provides a listing of comorbid health conditions that subjects reported. Clinical diagnoses which subjects gave as their primary motivations for enrolling in the study were ISI (26.7%), traumatic brain injury or concussion (15.8%), menopausal hot flashes (8.9%), post-traumatic stress (8.9%), migraine or headache (7.4%), postural orthostatic tachycardia syndrome (5.0%), or other conditions including anxiety or depression, fatigue or burnout, cancer recovery, autonomic or neurological disorders, and others (27.2%). Participants received a mean of 16.1 (SD 5.2) HIRREM sessions, and there was a mean of 15.3 (16.47) days between the last session and the follow-up visit. There were no serious adverse events reported.

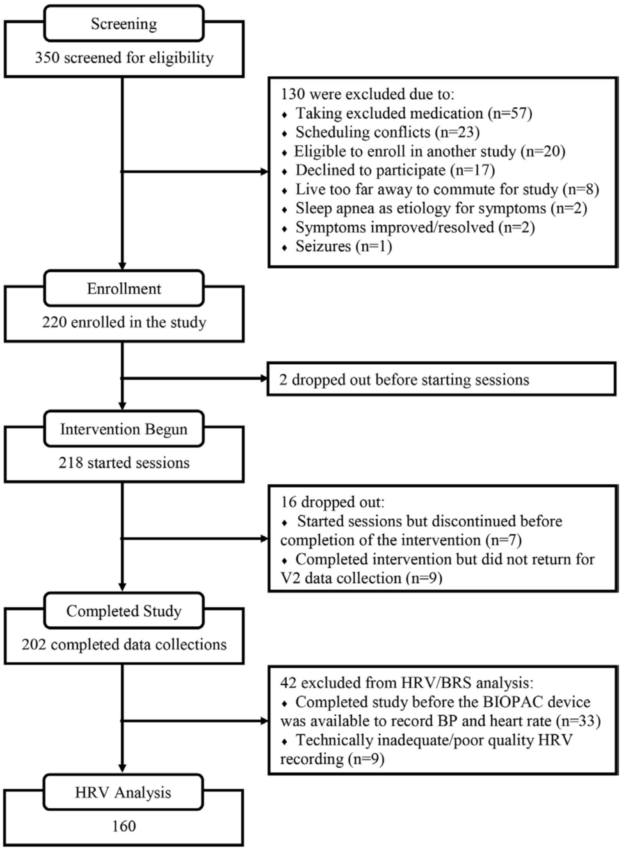

FIGURE 1 | Study participant flow.

TABLE 1 | Self-reported health conditions of study participants.

Condition	Number of participants (percent of $n = 202$)
ADD/ADHD	28 (13.86)
Chronic fatigue	22 (10.89)
Chronic pain	32 (15.84)
Concussion/traumatic brain injury	62 (30.69)
Depression	74 (36.63)
Headaches	84 (41.58)
Hot flashes	44 (21.78)
Hyperlipidemia	25 (12.38)
Hypertension	38 (18.81)
Insomnia	87 (43.07)
Migraines	65 (32.18)
PTSD	29 (14.36)
Stress/anxiety	84 (41.58)

Figure 2 shows percentage changes for measures of HRV in the time domain and BRS, and **Figure 3** shows pre- and post-intervention values for frequency domain HRV measures and BP, before and after usage of HIRREM ($n = 160$). This included significant changes in measures of HRV ($p < 0.001$ for these measures) across all participants including the mean percentage change for SDNN 24.2% (SE 0.04), and RMSSD, 42.2% (0.08), and

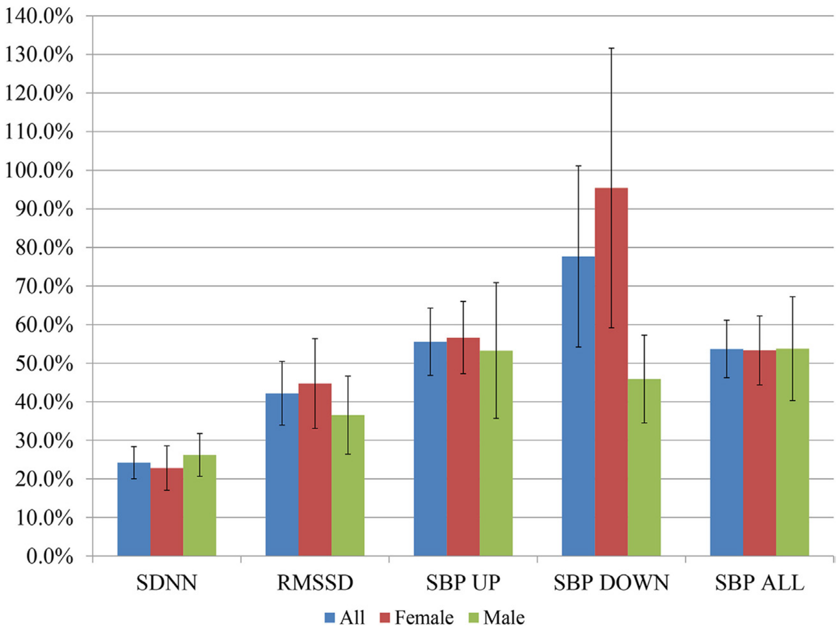

FIGURE 2 | Post-interventional changes in heart rate variability and baroreflex sensitivity on percentage basis. Bars indicate ± SEs for the average percent changes. All changes were statistically significant at $p < 0.001$ except the following, for men: RMSSD, SBP DOWN, SBP ALL ($p < 0.01$ for each), and SBP UP ($p = 0.02$).

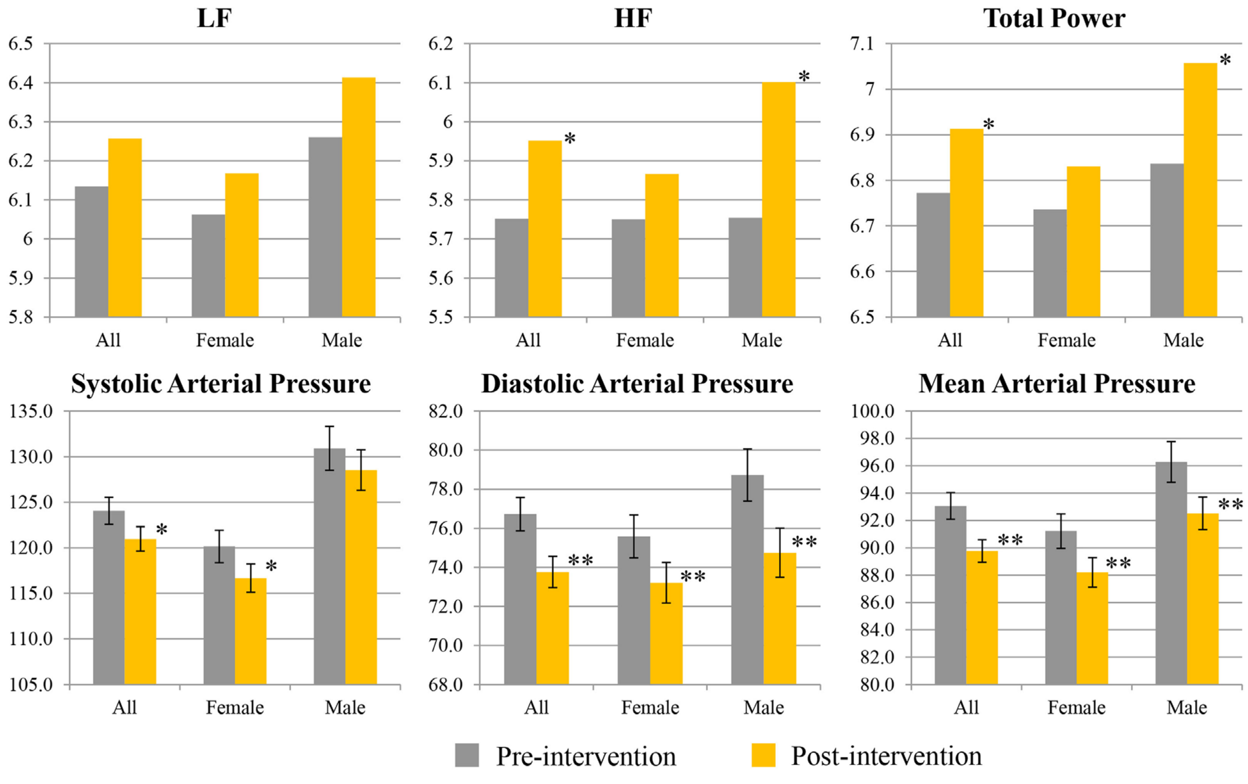

FIGURE 3 | Pre- and post-interventional values for spectral measures of heart rate variability, and blood pressure. Values for low frequency (LF), high frequency (HF), and total power are given as natural logarithms of the absolute values. Values for systolic, diastolic, and mean arterial pressure are given as millimeters of mercury. Single asterisk indicates $0.1 \leq p \leq 0.05$; double asterisks indicate $p < 0.01$.

BRS [Sequence Up, 55.5% (0.09), Sequence Down, 77.6% (0.23), and Sequence All, 53.7% (0.07)]. Significant improvements were also noted in SAP, MAP, and DAP, as well as natural log of HF, and total power. The baseline value for SDNN across all subjects was 44.1 (SD 20.8), and it was 52.0 (SD 25.9) at the follow-up visit. Pre- and post-intervention values for the measures when participants were stratified according to their baseline value for SDNN and LF power are shown in **Tables 2** and **3**, respectively. On average, all baseline SDNN quartiles showed improvements in SDNN and BRS. Those in the lowest quartile for LF power showed an increase in their mean LF power, and those in the highest group showed a decrease. Mean change in the ISI was −6.4 points (SD 5.6, $p < 0.001$), and the proportion of subjects in different clinical categories of ISI symptom severity before and after the intervention are shown in **Figure 4**. At baseline, 48.2% of subjects reported clinically significant levels of depressive mood, while 22.1% did so at follow-up.

Result of a linear regression to explore for the contribution of temporal lobe HF electrical asymmetry toward SDNN is shown in **Figure 5**. Rightward asymmetry was a predictor of lower SDNN (β coefficient = −6.5, $p = 0.023$). In a model for SDNN that included age, gender, beta-blocker usage, and Charlson comorbidity score as covariates, the relationship between temporal lobe HF asymmetry was increased (β = −8.1, $p = 0.002$). **Figure 6** shows the average temporal lobe HF asymmetry values for the first 7 min of each of the first five HIRREM exercises at the temporal lobes (concatenated), when subjects were categorized according to their asymmetry status as measured during the baseline assessment. For subjects who were rightward or leftward dominant at baseline, the slopes of their trend lines for their asymmetry scores over those sessions were negative and positive, respectively; however, analysis did not indicate a statistically significant likelihood of these slopes being non-zero.

DISCUSSION

This report summarizes main findings from an ongoing prospective, single-arm study involving usage of a closed-loop, allostatic

TABLE 2 | Heart rate variability, baroreflex sensitivity, and blood pressure changes by quartile of SDNN.

	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	V1	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**
Ln LF	4.6	4.9	5.8	6.0	6.5	6.7	7.6	7.4
Ln HF	4.1	4.7	5.6	5.6	6.1	6.2	7.2	7.3
Ln TP	5.2	5.6	6.5	6.6	7.1	7.2	8.3	8.2
UP SBP	6.7 (4.4)	9.9 (5.7)	11.9 (5.6)	16.8 (10.5)	15.0 (7.8)	19.2 (12.3)	28.6 (13.8)	32.6 (16.1)
DOWN SBP	7.3 (3.4)	10.1 (6.1)	12.9 (7.4)	16.1 (8.5)	14.2 (6.8)	19.4 (11.3)	23.4 (9.7)	32.2 (20.8)
ALL SBP	6.5 (2.8)	10.1 (5.5)	12.2 (5.3)	16.1 (8.7)	14.4 (6.6)	19.7 (12.1)	26.1 (10.2)	33.4 (17.6)
SDNN	21.6 (5.8)	30.8 (15.8)	35.7 (3.3)	42.8 (16.2)	46.6 (4.3)	53.9 (16.0)	73.5 (14.8)	80.6 (24.0)
RMSSD	12.9 (5.0)	24.3 (19.4)	26.2 (9.4)	31.3 (17.0)	37.0 (13.8)	42.3 (18.6)	65.6 (21.9)	74.2 (30.0)
Heart rate	72.8 (11.0)	70.8 (9.8)	72.1 (17.8)	71.3 (11.0)	67.2 (8.3)	68.2 (10.6)	61.0 (9.8)	60.6 (9.3)
SAP	128.5 (18.4)	124.9 (15.6)	122.9 (18.4)	117.0 (16.8)	127.1 (19.2)	125.1 (18.4)	117.7 (18.0)	116.9 (15.6)
MAP	96.7 (11.4)	93.2 (10.2)	92.1 (11.6)	88.8 (11.1)	94.9 (11.7)	90.9 (10.4)	88.5 (13.7)	86.2 (8.9)
DAP	79.5 (9.0)	76.2 (8.7)	76.2 (10.4)	74.5 (10.7)	77.7 (10.1)	74.0 (11.0)	73.6 (12.8)	70.4 (9.4)

Pre- and post-intervention values are shown for subjects with lower (quartiles 1 and 2) and higher (quartiles 3 and 4) baseline levels of SDNN. Low frequency, high frequency, and total power values are shown as natural logarithms of the absolute power values. SDs are indicated in parentheses. Statistically significant differences between pre- and post-interventional values are shown with colored font (blue for 0.01 ≤ p ≤ 0.05; red for p < 0.01).

TABLE 3 | Heart rate variability (HRV), baroreflex sensitivity, and blood pressure changes by quartile of low-frequency (LF) power.

	Quartile 1		Quartile 2		Quartile 3		Quartile 4	
	V1	**V2**	**V1**	**V2**	**V1**	**V2**	**V1**	**V2**
Ln LF	4.3	5.0	5.8	6.0	6.6	6.6	7.8	7.5
Ln HF	4.3	4.9	5.4	5.5	6.2	6.2	7.1	7.3
Ln TP	5.2	5.7	6.4	6.5	7.2	7.2	8.3	8.2
UP SBP	8.2 (5.6)	10.8 (7.1)	10.9 (6.5)	16.3 (10.2)	17.3 (9.1)	20.0 (14.8)	26.0 (14.8)	31.4 (15.1)
DOWN SBP	8.5 (4.7)	11.7 (7.1)	11.6 (6.6)	15.7 (8.8)	16.2 (8.9)	18.8 (14.0)	21.6 (10.0)	31.5 (19.7)
ALL SBP	7.9 (4.5)	11.3 (6.6)	11.1 (5.7)	15.6 (8.7)	16.4 (8.0)	20.2 (14.3)	24.0 (11.2)	32.2 (17.0)
SDNN	24.7 (9.9)	33.6 (17.0)	36.2 (7.9)	42.4 (17.0)	47.0 (13.3)	52.3 (21.2)	69.4 (17.8)	79.9 (21.6)
RMSSD	18.1 (12.5)	26.8 (18.4)	24.6 (11.7)	32.9 (21.3)	37.3 (18.2)	40.9 (21.8)	61.8 (23.7)	71.6 (30.5)
Heart rate	72.2 (17.5)	69.6 (9.4)	70.9 (11.1)	70.7 (11.6)	70.7 (9.2)	71.3 (10.4)	59.3 (8.4)	59.3 (7.8)
SAP	127.8 (18.5)	125.8 (15.2)	126.3 (19.7)	119.1 (19.4)	122.1 (16.4)	119.7 (15.4)	120.0 (20.0)	119.2 (17.3)
MAP	95.3 (18.5)	92.9 (10.5)	94.9 (11.7)	89.9 (12.0)	91.6 (12.3)	88.9 (10.2)	90.4 (13.4)	87.4 (8.4)
DAP	78.0 (9.9)	75.4 (9.9)	77.9 (9.7)	75.1 (11.1)	76.1 (11.5)	73.3 (10.5)	75.0 (11.9)	71.3 (8.9)

Pre- and post-intervention values are shown for subjects with lower (quartiles 1 and 2) and higher (quartiles 3 and 4) baseline levels of LF HRV power. LF, high frequency, and total power values are shown as natural logarithms of the absolute power values. SDs are indicated in parentheses. Statistically significant differences between pre- and post-interventional values are shown with colored font (blue for 0.01 ≤ p ≤ 0.05; red for p < 0.01).

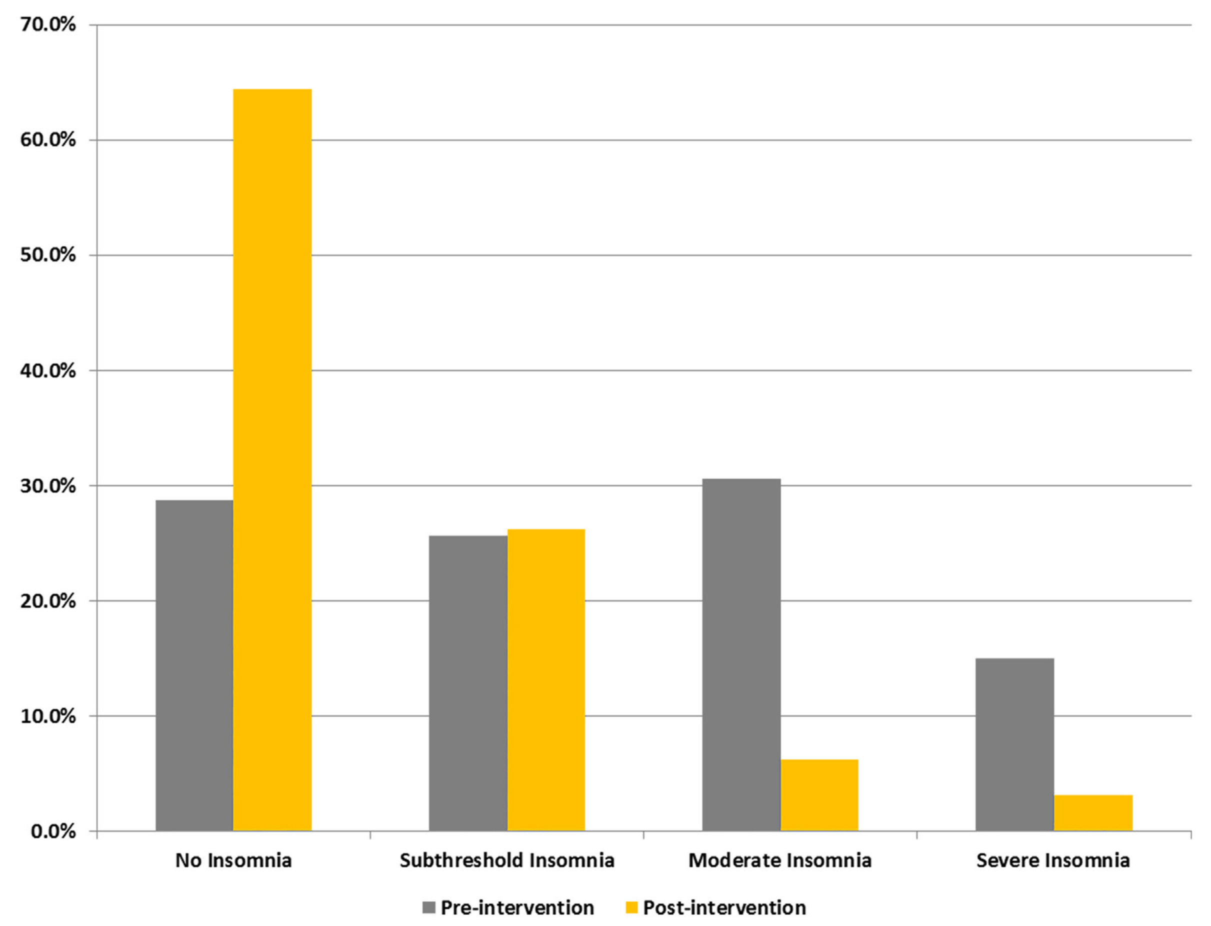

FIGURE 4 | Proportions of subjects reporting different levels of insomnia (ISI) symptom severity. Categorizations are based on self-reported scores on ISI.

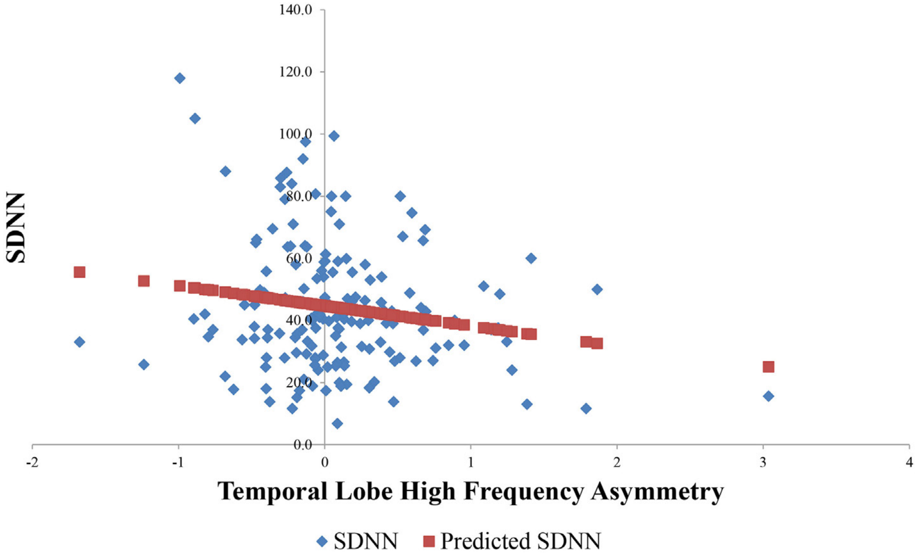

FIGURE 5 | Relationship between baseline temporal lobe high frequency (HF) asymmetry and SDNN. Horizontal axis indicates temporal lobe HF asymmetry score, with positive scores indicating rightward asymmetry and negative scores indicating leftward asymmetry.

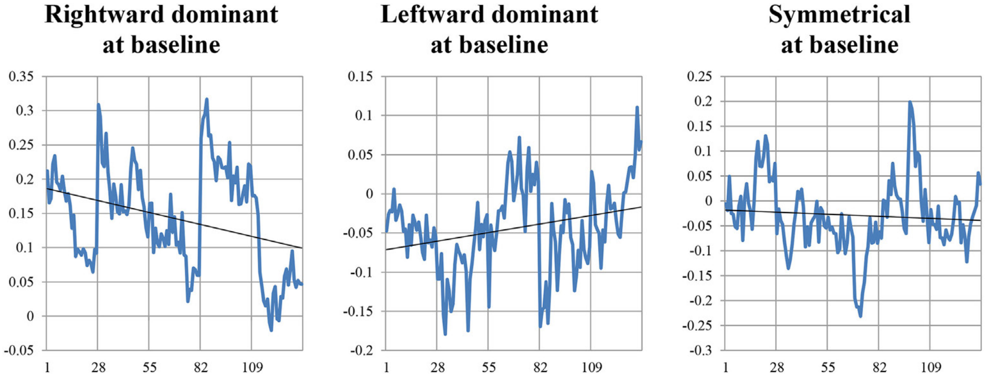

FIGURE 6 | Temporal lobe high frequency asymmetry scores during the initial five HIRREM sessions. Vertical axes indicate values for asymmetry scores calculated from serial 15-s epochs (27 per session), from the first 7 min of a temporal lobe exercise conducted during that session. Gridlines along horizontal axis indicate the start of each session.

neurotechnology. At a follow-up visit that occurred on average just over 2 weeks after intervention completion, individuals with heterogeneous clinical conditions showed statistically significant increases in HRV and BRS; decreases in systolic, diastolic, and mean arterial pressure; and reductions in symptoms of ISI and depression. The results appear to indicate that significant impact on HRV and related measures of autonomic cardiovascular regulation, as well as improvements in sleep and mood, are possible through use of a well-tolerated, noninvasive, and non-pharmacological intervention for auto-calibration of neural oscillations. The expression of these changes in a heterogeneous cohort is encouraging for the prospect of impacting public health without targeting specific clinical diagnoses.

In broad terms, the HIRREM approach is aligned with other closed-loop interventional strategies that are intended as major advances for neurological and psychiatric disorders, sleep enhancement, and potentially for performance optimization (26–29). Closed-loop neurotechnologies leverage real-time analysis of biological functioning to permit direct, precision-guided modulation of the neural substrates of mentation, emotion, or behavior. As components of a potential public health agenda, noninvasive closed-loop interventions may hold special promise if they are shown to be safe, cost-effective, acceptable, and scalable. Recently, a self-care configuration (Braintellect-2®; Brain State Technologies, Scottsdale, AZ, USA) of the closed-loop allostatic neurotechnology evaluated in this study has been developed with support from the United States Army Research Office (30) with sensor placements for temporal and prefrontal cortices only, and integration of this device is envisioned to improve the cost-effectiveness and scalability of neurotechnology-based auto-calibration of neural oscillations.

Given its naturalistic character and in the absence of a control arm, this study was not intended to permit definitive inferences about the specific etiology for changes observed post-intervention. Nonetheless, the relative magnitude and time frame of the HRV increases are noteworthy even if the outcomes were due to nonspecific factors including subjective expectation, social interactions with study personnel, or other components of the placebo effect. For the group as a whole, the increase in SDNN compares favorably to the average improvement of 15.9% that was reported in a meta-analysis of interventions to improve HRV (9). The time interval between the last HIRREM session and the follow-up data collection is likely to have been too long for the HRV changes to reflect a short-term state change through temporary relaxation induction. It is also likely to have been too short to reflect HRV change due to an undocumented behavioral cointervention such as aerobic exercise training, which is typically shown to occur after a period of months (31–33).

Our study population was heterogeneous and the inclusion criteria were deliberately transdiagnostic. Analyses based on autonomic cardiovascular regulation profiles revealed findings which may inform future studies of interventions to promote neurovisceral integration. On average, and when stratified according to baseline quartiles of SDNN, all subjects showed greater SDNN after usage of HIRREM. This finding is consistent with the supposition that autonomic regulation is diminished in a wide range of clinical conditions (34), and that potentially beneficial increases in HRV may be achievable regardless of one's baseline. From the public health perspective, it may be that a campaign for HRV improvement could yield benefits for clinical populations without necessarily targeting those with the lowest HRV. Furthermore, it was intriguing that stratification of subjects by their baseline quartile of LF power showed a post-intervention increase in average power for the lowest quartile, and a decrease in power for the highest quartile. Since LF power comprises both sympathetic and parasympathetic influences (35), this finding gives ground to speculate whether diminished, or high, levels of LF power are a specific reflection of relative activity in one or the other of the autonomic divisions, and whether allostatic neurotechnology can facilitate activity in both divisions to move in healthful directions.

The finding that baseline rightward temporal lobe HF asymmetry was a negative predictor for SDNN is consistent with a cross-sectional analysis we performed previously on a subset of the current subject population (22), which was focused on those individuals with greater degrees of asymmetry. Although the slopes of trend lines for asymmetry did not statistically differ from zero during the first five HIRREM sessions, when comparing individuals who were rightward or leftward dominant at baseline, a similar analysis on a subset of the current group (16) who specifically reported symptoms of post-traumatic stress did show statistical significance. The demographic and clinical heterogeneity of the current sample may have diluted the capacity to detect auto-calibration of neural oscillations, and future studies using larger samples and other analysis strategies may shed additional light on potential mechanisms of HIRREM effects.

CONCLUSION

A heterogeneous clinical population undertook usage of a closed-loop, allostatic neurotechnology, HIRREM, for remediation of a wide range of health concerns. Two weeks after concluding their sessions, they demonstrated significant improvements in HRV and BRS, reductions in systolic, diastolic, and mean arterial BP, as well as decreased symptoms of ISI and depressive mood. The intervention was well-tolerated, and there were no adverse events. In aggregate, the findings suggest that closed-loop allostatic neurotechnology could serve as a valuable component of a public health initiative for enhancement of HRV.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of Wake Forest University Health Sciences, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Parental written consent was obtained for all participants that were minors. The protocol was approved by the Institutional Review Board of Wake Forest University Health Sciences.

AUTHOR CONTRIBUTIONS

Author contributions included conception and study design (CHT, CLT, SL, LG, and HS), data acquisition (CLT, SS and HS), data preparation and analysis (CHT, CLT, HS, SL, HS, SS, and JH), and interpretation of data for this project (CHT, CLT, HS, SL, and LG). All authors have reviewed the manuscript and agreed to be accountable for all aspects of this work.

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Chronic Diffuse Pain and Functional Gastrointestinal Disorders After Traumatic Stress: Pathophysiology Through a Polyvagal Perspective

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Chronic diffuse pain disorders, such as fibromyalgia, and functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome, place substantial burden on those affected and on the medical system. Despite their sizable impact, their pathophysiology is poorly understood. In contrast to an approach that focuses on the correlation between heart rate variability (HRV) and a specific organ or symptom, we propose that a bio-evolutionary threat-related autonomic response—as outlined in the Polyvagal Theory—may serve as a plausible explanation of how HRV, particularly respiratory sinus arrhythmia (RSA), would index the pathophysiology of these disorders. Evidence comes from: (1) the well-documented atypical autonomic regulation of the heart common to fibromyalgia and irritable bowel syndrome reflected in dampened RSA, (2) the neural architecture that integrates the heart, pain pathways, and the gastrointestinal tract, (3) the common physical co-morbidities shared by chronic diffuse pain and FGIDs, many of which are functionally regulated by the autonomic nervous system, (4) the elevated risk of chronic diffuse pain and FGIDs following traumatic stress or abuse, (5) and the elevated risk of chronic diffuse pain and FGIDs in individuals with anxiety and panic disorders. This novel conceptualization points to a pathogenesis rooted in changes to brain-body autonomic feedback loops in response to evolutionarily-salient threat cues, providing an integrated biopsychosocial model of chronic diffuse pain and FGIDs and suggesting new, non-pharmacological treatment strategies.

Keywords: trauma, polyvagal theory, irritable bowel syndrome, functional gastrointestinal disorders, chronic pain, fibromyalgia, heart rate variability, respiratory sinus arrhythmia

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INTRODUCTION

Medically unexplained somatic problems including chronic diffuse pain and functional gastrointestinal disorders (FGIDs) are persistent, disabling, costly, and seen across all medical settings (1–3). However, their pathophysiology is poorly understood. Increasingly, there is a growing awareness that chronic diffuse pain and FGIDs are highly prevalent among those with a history of trauma or abuse (4, 5). Rates of abuse history tend to be highest among patients in pain and gastroenterology clinics (6) and one study found that of all females referred to a gastroenterology clinic, 67% had experienced sexual or physical abuse (7).

Despite this awareness, a pathophysiological mechanism that links trauma and abuse history to chronic pain and FGIDs is lacking. In this review, we use the framework provided by the Polyvagal Theory, an evolutionary neurophysiological model of the autonomic response to safety and threat (8–11). Within this framework, we outline a pathophysiological mechanism rooted in chronic autonomic threat responses that give rise to systemic changes in the regulation of pain pathways and the gastrointestinal tract. We then apply this framework to converging evidence from medicine, psychiatry, physiology, and neuroscience to provide a plausible model for the origins of post-traumatic chronic diffuse pain and functional gastrointestinal disorders in the absence of organic medical cause. While the pathogenesis described here may apply to a range of functional somatic disorders, this review focuses on fibromyalgia (FM) and irritable bowel syndrome (IBS) due to the wide clinical prevalence and abundant research related to these disorders.

Fibromyalgia is a chronic widespread pain condition impacting muscles, ligaments, and tendons. With a prevalence around 2–3%, it is among the most common types of chronic diffuse pain (12). It is estimated that women are about twice as likely to develop the disorder than men (13). A diagnosis is typically made based on the number of tender points in characteristic locations, chronicity, and exclusion of other disorders that may be causing pain. While the etiology of fibromyalgia is unknown and pathophysiology is poorly understood, there is growing understanding that emotional or physical trauma may trigger or aggravate symptoms (13).

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits—diarrhea, constipation, or alternating episodes of both—in the absence of clear anatomical or physiologic abnormalities. The most recent criteria defines irritable bowel syndrome as recurrent abdominal pain, on average, at least 1 day per week in the 3 months before diagnosis that is associated with two more of the following: (a) relation to defecation, (b) association with change in the frequency of stool, (c) association with a change in the form (appearance) of stool (Rome IV criteria) (14, 15). It is the most frequently diagnosed gastro-intestinal condition, accounting for about 30% of all referrals to gastroenterologists (16) and is highly co-morbid with fibromyalgia (17). Based on a meta-analysis of 80 studies involving over 250,000 total subjects, the world-wide prevalence is estimated to be about 11.2% with higher rates in women than men (18). Like fibromyalgia, the etiology and pathophysiology of irritable bowel syndrome remain uncertain although emotional stress intensifies symptoms and hinders positive treatment outcomes (17).

We review evidence for fibromyalgia and irritable bowel syndrome as arising from a chronic autonomic response that may be triggered or exacerbated by evolutionary bio-behavioral processes that regulate the brain and body in response to threat. In pursuit of this, this paper reviews: (1) the elevated prevalence of fibromyalgia and irritable bowel syndrome among sexual abuse and rape survivors, (2) the organizing autonomic threat-response principles drawn from the guiding framework of the Polyvagal Theory that explain the adaptive function of shifts in autonomic state reflected in respiratory sinus arrhythmia (high frequency heart rate variability), (3) the autonomic and neurophysiological systems that regulate pain and gastrointestinal function, (4) empirical evidence of diminished RSA reflecting altered autonomic function in fibromyalgia and irritable bowel syndrome patients, (5) common autonomically-regulated co-morbidities in fibromyalgia and irritable bowel syndrome patients, and (6) evidence for autonomic disruption after trauma. The understanding of fibromyalgia and irritable bowel syndrome as systemic dysfunction produced by a chronic autonomic threat response provides novel opportunities for treatment that targets the brain-body system, including the brain-gut axis, rather than treating individual symptoms.

FIBROMYALGIA AND IRRITABLE BOWEL SYNDROME AFTER SEXUAL ABUSE AND RAPE

Sexual and physical abuse in both childhood and adulthood are a widespread problem. Based on a series of large-scale meta-analyses, international prevalence rates are estimated to be 13% for childhood sexual abuse (8% males, 18% females) and 23% for childhood physical abuse (19). In the US, the Centers for Disease Control and Prevention estimate that the lifetime prevalence of rape is 19% in women and 2% in men and intimate partner violence prevalence is 32% in women and 28% in men (with *severe* intimate partner violence prevalence at 22 and 14%, respectively) (20). Notably, these higher rates of sexual and physical abuse among women are paralleled in the gender-specific prevalence of fibromyalgia and irritable bowel syndrome. Women are about twice as likely to have a fibromyalgia diagnosis (13) and have 1.67 greater odds of having irritable bowel syndrome than men (18).

Converging evidence across many studies shows that abuse history is a strong predictor of fibromyalgia. In a meta-analysis of 18 studies with a total of over 13,000 combined participants, Häuser and colleagues found that sexual and physical abuse in both childhood and adulthood predicted greater odds of fibromyalgia (odds ratio point estimate range: 1.94–3.07) (21). In their meta-analysis, Paras and colleagues found that rape survivors have especially high odds of fibromyalgia diagnosis ($OR = 3.27$) (22). These risk factors are higher in fibromyalgia patients than those with rheumatoid arthritis, highlighting the specificity of the role of abuse and trauma in FM pathogenesis compared to a pain disorder with a known organic cause (23).

Abbreviations: DMX, dorsal motor nucleus of the vagus; DVC, dorsal vagal complex; FGID, functional gastrointestinal disorder; FM, fibromyalgia; GI, gastrointestinal; HRV, heart rate variability; IRS, irritable bowel syndrome; NA, nucleus ambiguous; NTS, nucleus of the solitary tract; PTSD, post-traumatic stress disorder; RAVANS, respiratory-gated auricular vagal afferent nerve stimulation; RSA, respiratory sinus arrhythmia; SNS, sympathetic nervous system; t-VNS, transcutaneous electrical vagal nerve stimulation;VVC, ventral vagal complex.

Rates of gastrointestinal problems such as irritable bowel syndrome are similarly elevated in survivors of abuse. Meta-analytic evidence supports this with childhood sexual abuse being associated with higher risk of gastrointestinal problems (24). It is estimated that individuals with a history of sexual abuse are about twice as likely to develop abdominal pain and gastrointestinal problems than those without an abuse history (25). As seen with fibromyalgia, rape survivors are among those with the highest risk, with meta-analytic methods suggesting their odds of having a functional gastrointestinal disorder are about four times greater than those without an abuse history (22). Those with an abuse history also have higher severity and quantity of GI symptoms and seek medical help more often (26).

Overall, these robust associations suggest that abuse and trauma experiences may be key to understanding the pathogenesis of fibromyalgia and irritable bowel syndrome. However, a comprehensive integrative model to explain the mechanisms through which traumatic experiences affect these chronic disorders is lacking.

THE POLYVAGAL THEORY

The brain-body connection is composed of integrated sensory, interoceptive, and regulatory systems that monitor internal body conditions and the external environment, coordinating homeostatic processes required for maintenance of biological functions as well as responses to threats from inside and out (27–30). Within the body, interoceptive signals continuously provide homeostatic information about the body's physiological condition to the brain. In complement, exteroception (evaluation of external conditions) provides information about environmental challenges and threats, to allow for the flexible shifting of resource allocation to meet external demands. Detection of both internal and external threats or perturbations can disrupt homeostatic processes in the interest of allocating resources for addressing the threat.

The Polyvagal Theory (8–11) provides a neurophysiological framework for understanding the evolutionary history of mammalian nervous system and its relation to the anatomic and functional organization of the human brain-body connection. Over the course of evolution, vertebrate nervous systems have elaborated on and appended to the earliest and most primitive of these brain-body systems. With time, newer systems increased precision, speed, and complexity, as well as evolved new functions that respond to novel environmental and social needs. These newer neurophysiological systems did not replace older systems, but instead became integrated with older functions.

Some of the first of these regulatory systems, observed in the earliest vertebrates, were powered by hormones and facilitated relatively slow, diffuse reactions in the brain and body. However, with time, the evolution of the autonomic system afforded more rapid and targeted control. With the heart serving as a key metabolic structure, the earliest neural regulatory pathways evolved to provide control over its function. These efferent pathways emerged from an area of the brainstem known as the dorsal motor nucleus of the vagus (DMX), adjacent to the target site of the sensory afferent pathways that provides information from the heart and target organs. Together, this coordinated efferent-afferent system formed the dorsal vagal complex (DVC). This regulatory circuit was well developed in early vertebrate evolution and emerged in primitive vertebrates such as cartilaginous fish, integrating information arising from the body and higher brain structures. In humans, this system has few fibers innervating the heart, with most efferent projections innervating organs below the diaphragm, including the gastro-intestinal tract, to regulate digestive and metabolic functions.

The emergence of a spinal sympathetic nervous system (SNS) in bony fish, with its broad scope and target specificity, provided a rapid and coordinated fight/flight system for mobilizing the body in response to threats. This system built on the architecture of the DVC, utilizing information traveling from the body and exteroceptive higher brain regions to coordinate threat-related response needs. In humans, this system regulates a wide range of tissues and structures including the digestive tract, heart, and lungs.

The phylogenetically newest autonomic system is the ventral vagal complex (VVC), which emerged during the transition from primitive extinct reptiles to mammals. Like the SNS before it, this system built on the integration of afferent information arising from the body and descending signals from higher brain structures to respond to internal and external needs. Its efferent arm emerged as cell bodies of vagal efferent source nuclei of the DMX migrated ventrally, forming a second and distinct cardioinhibitory nucleus known as the nucleus ambiguus (NA) and became integrated with circuits that regulate the bronchi and muscles of the face and head. Unlike earlier systems, which promoted defense-related survival responses, this new autonomic face-heart connection formed in concert with the mammalian dependence on social-affiliative behaviors. It provided a substrate for communication of defense or affiliative states via vocalization acoustic features (via regulation of the larynx and pharynx) (31, 32) and facial expressions, as well as providing capacity to dampen older survival-based response systems.

In mammals, all three systems contribute to maintaining homeostatic function and coordinating responses to internal and external perturbations. Information from within is integrated in signals arising from afferent pathways and converging on brainstem structures, most prominently the nucleus tractus solitarius (NTS), while top down signals from higher brain regions, including sensory systems, provide information about external threats. This integrated interoceptive and exteroceptive information is projected to higher-level brain structures and to visceral organs via the source nuclei of the motor pathways involved in the DVC, SNS, and VVC to coordinate responses. This integrated information also interacts with neuroception, the subconscious assessment of threat and safety in the environment (named in contrast to consciously experienced sensory perception) (33, 34). Importantly, the non-conscious threat detection that occurs in both the body and higher-level brain centers suggests that individuals may not be aware of threat-response triggers. However, they may consciously experience the threat-related changes in brain and body regulation (e.g., urge to defecate, feelings of anxiety).

The Polyvagal Theory proposes that the evolution and individual anatomical pathways of the DVC, SNS, and VVC give rise to an ordered response hierarchy that promotes coordinated responses to threats. Under normal homeostatic conditions, each system is involved in basal functions for organism maintenance. However, under threat conditions, the function of individual systems can be recruited to regulate metabolic resources as needed. Phylogenetically newer systems are primary responders; older systems are recruited as threat persists. This phylogenetically ordered response hierarchy is consistent with the Jacksonian principle of dissolution (35). First, under threat, the VVC, the most rapidly responsive system, withdraws its inhibitory influence on mobilization. Since a component of HRV, known as respiratory sinus arrhythmia (RSA; see below), is primarily a product of this circuit, it is often used as an index of the strength of this circuit. Second, the SNS can further ramp up mobilization and promote fight/flight behaviors. Finally, when recruited for defense responses, the DVC produces an efferent vagal surge that inhibits metabolic functions by slowing heart rate, reducing digestive processes, and promoting behavioral shut down. Notably, all three autonomic systems feature cardio-regulatory pathways; modulating cardiac function is key to altering metabolic resources for body responses. Calm, affiliative social engagement requires dampening of threat-related bodily mobilization (this mobilization brake must be removed for efficient body mobilization), fight/flight mobilization requires ratcheting up available resources, and behavioral shut down requires reduction of metabolic function.

Though acute neural threat reactions are adaptive and necessary, chronic state shifts that maintain threat responses can be a risk factor for body dysfunction and disease. The brain-body connection is composed of multiple integrated feedback loops and the chronic maintenance of threat responses can lead to a "compromised" functional state. Chronic compromised states may give rise to the emergence of functional gastrointestinal disorders and altered pain signaling as part of a chronic systemic, rather than an event related organ- specific, pathophysiology. These changes in homeostatic functions may be self-maintaining or cascading even after the threat has been lifted due to long-term alterations in set points, learned responses to threat cues, and the symptoms themselves propagating threat-reaction.

NEURAL CIRCUITS INVOLVED IN PAIN AND GASTROINTESTINAL REGULATION

Neural Pain Regulation in the Periphery

The detection and appropriate responses to noxious or dangerous stimuli from without and within relies partly on the propagation of pain signals through the nervous system (nociception). Mechanisms integrating nociceptive sensory signaling, spinal pathways, and central regulation allow dynamic flexibility for acute and long-term safety- and danger-related functions. Pain signal regulation is a normal part of a nervous system defense response, such as the body's illness reaction that activates and sensitizes afferent nociceptive neurons (36). This adaptive pain signal modulation, which relies on integrated afferent-efferent brain-body feedback loops may be compromised in chronic-long term states of threat response.

Spinal nociceptive pathways are not passive conveyors of information from the body to brain, but rather under dynamic endogenous regulatory control that includes mechanisms contributing to sensitization and inhibition. During typical homeostatic states, active inhibition of pain signals modulates the strength of nociceptive response levels, silences nociceptive neurons in the absence of noxious stimuli, and impedes the spread of excitatory signals between sensory modalities and somatotopic borders (37). These inhibitory signals are prepotent, typically tonically active, crucial for constraining spinal nociceptive signaling, and have a large portion of the spinal neural architecture dedicated to them (38, 39). Dampening of these inhibitory mechanisms or facilitation of pain-related signaling can lead to hyperalgesia, allodynia, or spontaneous pain (37, 39). Somatic and interoceptive systems provide constant dynamic input from the body to the brain, and pain signaling from these system is highly integrated with homeostatic threat-responsive systems (40). Changes in homeostatic and threat-response feedback loops thus may interact with these incoming afferent signals, altering efferent (motor) output and perceptual qualities.

The sensitization and inhibition of spinal pain pathways is under the influence of brain-body feedback loops. These include multiple brain areas related to survival and threat related functions as well as the sympatho-adrenal system and vagal afferent pathways in the periphery. Descending modulation from the brain includes the periaqueductal gray, the rostroventral medulla, the lateral and caudal dorsal reticular nucleus, and the ventrolateral medulla (39, 41). Notably, several of the brainstem areas that are involved in pain modulation–including the medullary raphe and ventromedial reticular region-are also involved in the regulation of autonomic sexual functions and defense behavior (42), providing the substrate for functional coupling of survival- and threat-related states with pain.

Peripheral mechanisms that include vagal and spinal pathways are also involved in regulating nociception. Under normal homeostatic conditions, active nociceptive inhibitory control is maintained by spontaneous tonic vagal afferent activity (36, 43). Threat-related subdiaphragmatic vagal afferent signaling or disruption of tonic activity to the brain can trigger defense reactions that affect pain not just in the viscera but in the superficial and deep somatic tissues as well (36, 44). These signals can activate second-order NTS neurons, leading to an illness response cascade that facilitates nonciceptive impulse transmission in the spinal cord, inhibition of digestion, and biobehavioral state changes including immobility and sleep increase (36). In rodents, the nociceptive sensitivity induced by severing vagal afferents shows an extended time delay, with maximum sensitization of the paw-withdrawal threshold being reached by about 1–3 weeks post-surgery and involving interactions with the sympatho-adrenal system (45). In this study, this level sensitization endured over the course of the study, which lasted 8 weeks, indicating that the sensitization was chronic. In light of the present model, vagal afferent severance may mimic an extreme loss of vagal afferent flow and feedback loop, promoting a state of heightened autonomic threat response. This slow time frame to reach maximum sensitization may reflect complex, slow acting processes that give rise to latent sensitization emerging some time after the initial traumatic insult.

Neural Gastrointestinal Regulation

The digestive tract is innervated by a rich complex of afferent, efferent, and inter-neurons. Most of these neurons form the enteric nervous system, the intrinsic gastrointestinal network containing approximately an equal number of neurons to the spinal cord (47, 48). The enteric nervous system produces local reflex loops that coordinate gastrointestinal functions. The neural brain-gut connection is formed by spinal and vagal afferent pathways and projections from the DVC and SNS. Visceral afferent vagal and spinal projections carry chemical, mechanical, and, inflammatory, immune, toxicity, and noxious information. DVC and SNS efferent projections synapse mostly with the neurons of the enteric system, rather than the digestive tract itself (though several sites are directly innervated, such as those mediating defecation by the DVC and vasoconstriction by the SNS).

For the most part, under normal conditions, basic digestive functions are delegated to intrinsic enteric processes (though spinal and vagal pathways are employed for reflexes to coordinate GI function across wide or multiple regions) (46, 47). However, under conditions of internal and external threat, SNS and DVC pathways can override typical gastrointestinal local reflexes as part of coordinated organism responses (48, 49). In such situations, digestion can be inhibited or bowels can be cleared to facilitate more energy for other metabolic needs. These functions are executed by alterations to digestive secretions, motility, and—via the DVC—defecation. Sympathetic outflow to the gut is inhibitory, slowing transit and diminishing secretions. The DVC includes both excitatory and inhibitory functions. Gastrointestinal function changes induced by DMX stimulation in animals co-occur with heart rate and respiration slowing (50), consistent with the view that in contrast to the fight-flight functions of the SNS, recruitment of the DVC during challenge may promote bio-behavioral shut down.

These gastrointestinal function circuits are coordinated with afferent information arising from the body to the NTS (51) as well as the function of the VVC. Although the VVC does not directly innervate the gut, the stimulation of its efferent source nuclei (the NA) in rodents inhibits digestive function via feedback through the subdiaphragmatic vagal pathways that include the DVC (52). This suggests that monitoring of VVC function, via indices like RSA, can provide an indirect window into the state-related modulation of GI function.

FIBROMYALGIA AND IRRITABLE BOWEL SYNDROME: MANIFESTATIONS IN VAGAL REGULATION OF THE HEART

Respiratory Sinus Arrhythmia (RSA): An Index of Ventral Vagal Complex Activity

Multiple neural mechanisms influence the heart's internal pacemaker. While heart rate is a global measure of metabolic state, understanding the neural mechanisms mediating dynamic changes in cardiac output provides information for metrics capable of indexing the influence of vagal pathways on the heart. Although the intrinsic firing rate of the sino-atrial node, the heart's pacemaker, may be relatively fixed, the heart does not beat at a constant rate in healthy individuals. The heart beat is modulated by the transitory inhibition of the pacemaker by vagal pathways. When the spontaneous respiration rate is manifested in the heart rate pattern it is called respiratory sinus arrhythmia (RSA).

References to RSA were made in the early twentieth century. Wundt observed that "respiratory movements are … regularly accompanied by fluctuations of the pulse, whose rapidity increases in inspiration and decreases in expiration." (53) Hering described the functional relation between the amplitude of RSA and cardiac vagal tone, stating "It is known with breathing that a demonstrable lowering of heart rate is indicative of the function of the vagi" (54) (see (55, 56) for historical perspectives on heart rate variability and the autonomic nervous system). Since the neural mechanisms mediating RSA are well understood as the functional output of myelinated efferent vagal pathways, we focus on RSA and not on other metrics of heart rate variability, the origins of which have yet to be clearly defined.

Contemporary neurophysiology has supported these early reports and provided increased detail on their mechanisms. Humans and non-human mammals have cardioinhibitory neurons housed within the nucleus ambiguus of the VVC (55). These cardioinhibitory neurons receive excitatory input from the NTS (facilitating heart beat slowing) and inhibitory influences from brainstem reflexes linked to the respiratory rhythm (57, 58). This process gives rise to heart rate slowing during exhalation, mediated via vagal efferent outflow from the nucleus ambiguus. Thus, respiratory sinus arrhythmia, heart rate variability in the frequency of spontaneous respiration (also termed high frequency heart rate variability), provides an index of nucleus ambiguus cardioinhibitory function that separates its effect from that of other cardio-regulatory influences that lack a respiratory rhythm.

As described in the Polyvagal Theory, the mammalian nucleus ambiguus is a component of the VVC that is involved in facilitating affiliative social behavior and dampening threat-related reactivity (see above). It integrates the regulation of the body with safety- and threat-related states, forming an afferent-efferent system. Changes in signaling within the NTS (an area receiving information from the body vagal and spinal afferents) alter functional output of cardioinhibitory neurons in the nucleus ambiguous (58) and gastrointestinal regulation via the DMX (51). If the outflow of the VVC system is dampened or withdrawn (giving rise to low RSA), principles of dissolution would predict that more primitive threat-reactivity systems would be activated, reflecting a threat-response bodily profile marked by poorer homeostatic digestive function and potentially sensitized pain signaling.

Evidence for Dampened RSA in Fibromyalgia and Irritable Bowel Syndrome

In accordance with this prediction, several reviews and meta-analytic analyses document that fibromyalgia is associated with depressed heart rate variability including RSA, which is often reported as high frequency HRV (59–61). Furthermore, there is mounting evidence that interventions that decrease pain in fibromyalgia also result in increased HRV. A recent study reported that individuals whose fibromyalgia symptoms benefited from resistance training also responded with an increase in HRV (62), while an intervention that used breathing biofeedback documented that practice increased participant RSA and decreased pain (63).

Similarly, irritable bowel syndrome has also been linked to reduced VVC control of the heart as indexed by RSA. A meta-analysis based on 7 studies found that RSA was depressed in irritable bowel syndrome patients compared to healthy controls (64). This dampened VVC control may be especially pronounced in the subtype of irritable bowel syndrome characterized by predominant constipation, severe abdominal pain, and a comorbidity of anxiety or depression (65).

That both fibromyalgia and irritable bowel syndrome are marked by low amplitude RSA supports the hypothesized role of dampened VVC control in these disorders and suggests these disorders are associated with a state of heightened threat-related autonomic state. This link is so consistently observed that low heart rate variability has even been proposed as a "biomarker" of fibromyalgia (61, 66). However, the lack of specificity of low HRV as unique to fibromyalgia and the functional relation between VVC function to broad safety- and threat-related functions warrants a more systemic autonomic interpretation of this link.

Polyvagal Theory proposes an alternative interpretation of the covariation of HRV with both fibromyalgia and irritable bowel syndrome. Consistent with the integrated model of the autonomic nervous system described in the theory, atypical heart rate variability is not interpreted as a biomarker of any specific disease. Rather, depressed respiratory sinus arrhythmia (high frequency heart rate variability) is proposed as a neurophysiological marker of a diffuse recalibration of the autonomic nervous system following an adaptive complex autonomic reaction to threat. We propose that an initially adaptive neural response to threat, via visceral afferent feedback from the visceral organs to the brainstem, may result in a chronic reorganization of autonomic regulation observed in vagal regulation of the heart (i.e., depressed RSA) in conjunction with altered subdiaphragmatic organ function and afferent pain signaling (see **Figure 1**).

FIBROMYALGIA AND IRRITABLE BOWEL SYNDROME CO-MORBIDITY AND CO-OCCURRING AUTONOMIC SYMPTOMS

In addition to the shared VVC dampening in both fibromyalgia and irritable bowel syndrome, these disorders also share a high co-morbidity and overlap in autonomic symptoms. Fibromyalgia occurs in about 49% of irritable bowel syndrome cases (17). Both diagnoses are also associated with other autonomic and state-regulation problems. Irritable bowel syndrome patients have increased rates of non-digestive pelvic pain, chronic fatigue, sleep problems, syncope and dizziness (67), as well as heightened visceral and cutaneous pain perception (68). Fibromyalgia co-morbidities are similar and include chronic fatigue, sleep problems, elevated rates of visceral pain and sensory hypersensitivities (13). Furthermore, self-reported autonomic problems - including issues with subdiaphragmatic organs, orthostatic, vasomotor, and secretomotor functions - are elevated in fibromyalgia patients and overall severity of fibromyalgia symptoms is associated with severity of these problems (69).

Fibromyalgia and irritable bowel syndrome are both associated with elevated sexual and reproductive system problems that may be a manifestation of general autonomic function. Individuals with irritable bowel syndrome have elevated rates of vulvodynia, dysmenorrhea, amenorrhea, and irregular menstruation (67). Likewise, fibromyalgia is related to increased incidence of dysmenorrhea (13). In addition, women with fibromyalgia experience blunted sexual desire and arousal, fewer experiences of orgasm, and increased pain during intercourse (70).

The co-occurrence of fibromyalgia and irritable bowel syndrome with their overlapping autonomic co-morbidities suggest a role for a general systemic dysfunction as an underlying pathophysiology that gives rise to chronic diffuse pain and functional gastrointestinal problems. This points to the possibility that integrated brain-body reactions may produce long-term systemic changes that give rise to chronic disease and dysfunction related to evolutionary threat responses. Abuse or psychological trauma provides an especially potent experience that may re-tune the nervous system toward a chronic threat response.

TRAUMATIC STRESS IS RELATED TO ALTERED AUTONOMIC FUNCTION

As reviewed above, the human autonomic nervous system is tuned to rapidly respond to a wide range of external and internal conditions. Many mild events that challenge the nervous system's resources are part of everyday life and trigger adaptive acute reactions. However, traumatic

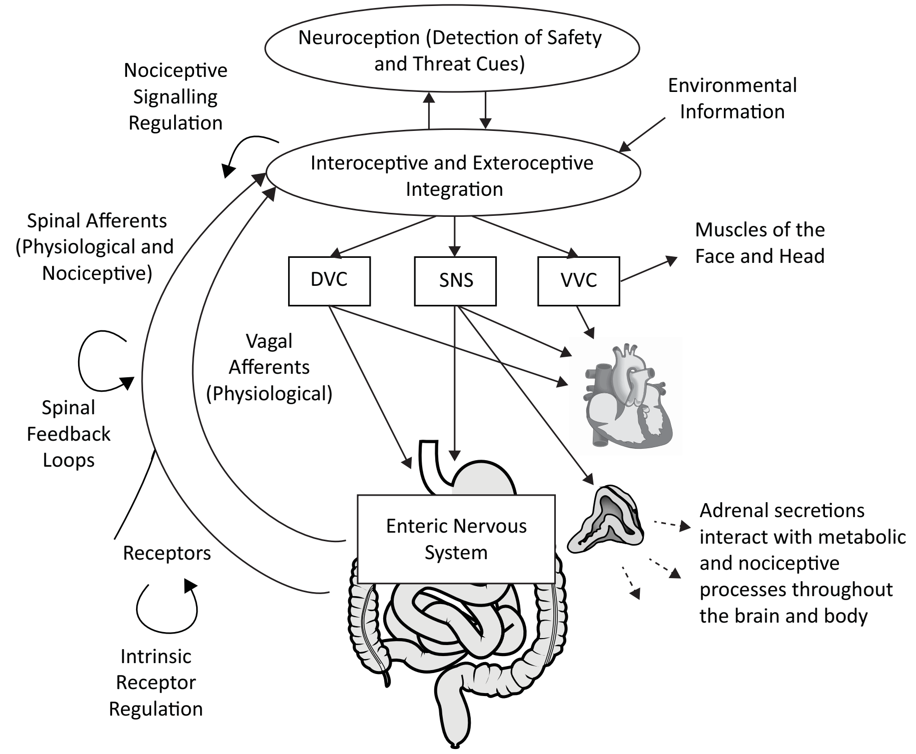

FIGURE 1 | A polyvagal perspective on autonomic regulation of nociceptive signaling and gastrointestinal function. Interoceptive and exteroceptive information is constantly monitored and interacts with neuroception, the non-conscious process of detecting safety and threat cues. These signals are used to regulate adaptive biobehavioral responses to current conditions. Nociceptive signaling is regulated in concert with top-down processes involving the brainstem and higher brain structures, vagal afferent signaling, spinal feedback loops, and the sympatho-adrenal system. The gastrointestinal tract is regulated by the dorsal vagal complex (DVC) and sympathetic nervous system (SNS), partly via actions on the enteric nervous system. The heart can serve as an index of autonomic circuits, with respiratory sinus arrhythmia (high frequency heart rate variability) providing an index of ventral vagal complex (VVC) function. Acute and chronic threat responses can alter neural feedback loops. Anatomical graphics are drawn from Wikimedia Commons and used in accordance with the Creative Commons license. |Adrenal gland by DBCLS 統合TV, CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=55201790 | Heart by Sheldahl, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=53328950 | Digestive tract by Olek Remesz (public domain), CC 2.5, https://commons.wikimedia.org/wiki/File:Tractus_intestinalis_esophagus.svg.

experiences may be especially potent in re-calibrating the autonomic nervous system toward a state that supports chronic defense responses. These long-term chronic changes, which affect autonomic regulation and the function of the brain and body, are observed across a range of traumatic events, including physical and sexual abuse in both childhood and adulthood.

These traumatic experiences may trigger a chronic threat-related brain-body response. A recent meta-analysis showed that RSA is dampened in individuals with Post-Traumatic Stress Disorder (PTSD) (71). This is consistent with a model of dampened VVC activity, as part of a chronic threat response, being implicated in long term effects following a trauma. Emerging evidence also suggests that a range of interventions including biofeedback and mindfulness that improve PTSD symptoms also increase heart rate variability (72–74). Importantly, however, VVC regulation may be dampened and trigger somatic problems even in the absence of a PTSD diagnosis. Although empirical research in this domain is currently scant, one study found that women with an abuse history have low RSA compared to health controls even when they do not meet diagnostic criteria for PTSD (75).

FIBROMYALGIA AND IRRITABLE BOWEL SYNDROME COMORBIDITIES WITH ANXIETY, PANIC DISORDERS, DEPRESSION, AND SOMATIC FUNCTION

Anxiety disorders and depression are common sequelae following traumatic events. Both fibromyalgia and irritable bowel syndrome co-occur with panic disorder, generalized anxiety disorder, and PTSD (13, 76). It is estimated that 30–50% of fibromyalgia patients also have anxiety and/or depression at the time of diagnosis (12). A meta-analysis shows that across studies, depression symptoms are elevated in fibromyalgia and irritable bowel syndrome and anxiety is elevated in irritable bowel syndrome (77). Patients with GI dysfunctions, who have an abuse history, have higher rates of panic symptoms and depression as well as autonomically-related somatic symptoms such as sleep disturbance and pelvic pain than those without abuse history (26), suggesting a higher likelihood of systemic brain-body dysfunction.

A NEW MODEL OF POST-TRAUMATIC CHRONIC PAIN AND FUNCTIONAL GASTROINTESTINAL DISORDERS

The reviewed converging evidence, viewed through the lens of organizing principles derived from Polyvagal Theory, proposes a plausible pathway through which chronic subdiaphragmatic organ disease and pain may be based in the evolutionary neurophysiological defensive states elicited by abuse and life threat. These chronic systemic functional problems are reflected in regulation of the heart by the VVC (as measured by RSA), providing a portal for identifying disorders of visceral organ function. This novel model describes a possible mechanism through which trauma may lead to the pathophysiology of chronic pain and functional gastrointestinal disorders. When organic cause is not evident, functional GI problems or chronic diffuse pain may be a marker of a traumatized nervous system.

Although the link between sexual and physical abuse is well documented, there are many other experiences that may trigger chronic neurophysiological defense responses in chronic pain and FGIDs. Other traumas that trigger defense states, including invasive surgical procedures, may have similar effects. Many infants born prematurely require chronic intensive medical interventions to survive. These interventions, although enhancing survival, are marked by repeated pain-inducing procedures, surgery, medication, and maternal separation at a time when the regulation of the autonomic nervous system, particularly the VVC, is still developing. These experiences may all have the capacity to trigger a life-threat challenge to the nervous system, which may alter ANS function in the long term. Adolescents who were born premature have more tender points and lower tender thresholds than those born full term (78) and a recent study found that 62% of female fibromyalgia patients reported a gestation of <38 weeks (this gestational age cut off is based on the study sample median and provides preliminary evidence for the proposed model until a study with more clinically meaningful criteria is conducted) (79).

Our review has focused on the chronic pain disorder fibromyalgia, since it is among the most common types of chronic diffuse pain and has been widely researched. However, at least 10% of the general population has chronic diffuse pain that is not diagnosed as fibromyalgia, with little specific disease or obvious abnormality to explain symptoms (12). Notably, sexual abuse history is also associated with elevated rates of pelvic and nonspecific chronic pain (22). It is possible that these non-specific pain problems may have an underlying autonomic mechanism involving both vagal efferent and afferent pathways conveying information between the brainstem and subdiaphragmatic organs.

Similarly, our review of functional GI disorders has been limited to irritable bowel syndrome since this is the most widely reported and studied GI disorder. However, it is possible that the range of functional gastrointestinal disorders lacking obvious anatomical or physiologic causes that do not meet irritable bowel syndrome criteria—including functional constipation, diarrhea, abdominal bloating, and distension (15)—may have a pathophysiology rooted in chronic defense states. For instance, functional dyspepsia, a disorder marked by bloating, upper abdominal pain or discomfort, and indigestion in the absence of organic disease, may also be part of a chronic subdiaphragmatic immobilization or shut down response. Notably, the risk of functional dyspepsia is elevated among childhood sexual abuse and war survivors (80), co-occurs with elevated rates of depression and anxiety (77), is marked by a lack of the typical gastric antral motility reactivity to mental stress exhibited by healthy controls (81), is associated with decreased RSA (81, 82), and successful symptom treatment by acupuncture concurrently increases RSA (83).

EXPERIMENTAL EVIDENCE FOR THE PROPOSED MODEL AND INSIGHTS FOR THE DEVELOPMENT OF NEW TREATMENT APPROACHES

A conceptualization of pain and GI regulation as part of an integrated nervous system that is capable of dynamic state-related shifts provides an optimistic opportunity for new treatment targets. Rather than focusing on disease symptoms as organ, tissue, or pathway-specific, the understanding of the organizing principles through which the nervous system regulates visceral organs and afferent signals may lead to novel approaches that draw on evolutionary neurophysiological feedback loops. Treatments that target the autonomic nervous system, rather than the digestive system or a pain source, provide a direct test of the proposed model. With the rising availability of vagus nerve stimulation devices, there is increasing evidence that targeting ANS function can indeed improve symptoms.

Recent applications of electrical vagus nerve stimulation show promise for both treatment of pain and functional gastrointestinal disorders. These treatments stimulate afferent vagal signaling, rather than the GI tract or painful regions. This signaling may increase VVC regulation and strengthen the body's natural safety-related feedback loops that inhibit pain signaling and promote efficient GI function. A pilot study showed that an implanted vagal nerve stimulator had positive effects in a small sample of treatment-resistant fibromyalgia (84). This suggests that vagal nerve stimulation likely influences general noxious- and pain-related pathways and may have benefits for a range of neurophysiologically-linked problems. Promising results have been observed for respiratory-gated auricular vagal afferent nerve stimulation (RAVANS) in chronic pelvic pain patients, which include reductions in anxiety (85). Benefits have also been observed for GI function. In healthy participants, non-invasive transcutaneous electrical vagal nerve stimulation (t-VNS) with deep slow breathing increased both musculoskeletal pain threshold and gastroduodenal motility (86). The stimulation also increased heart rate variability, consistent with a model of VVC activation inhibiting pain pathways and stimulating efficient gastrointestinal functions. In addition, a randomized, sham-controlled double-blind study found that an ear-attached cranial nerve stimulator (which includes the vagus nerve as a target) improved GI pain symptoms in adolescents with pain-related FGIDs (87). These studies provide preliminary experimental evidence for the proposed model of ANS afferent signaling as a part of the pathophysiology of FGIDs and FM.

Beyond vagus nerve stimulation, a polyvagal approach also predicts that evolutionary cues that trigger neurophysiological safety responses and remove threat cues may likewise have treatment potential. Empirical work based on these evolutionary neurophysiological cues is needed. However, there is mounting evidence that mammalian safety-cueing acoustic features are embedded in frequency bands and spectro-temporal modulation (31, 32) and preliminary work demonstrates that these properties may be effective in promoting VVC activation for clinical applications (88). Other sensory modalities may also offer promising non-invasive portals for influencing nervous system function.

CONCLUSION

The evolutionary neurophysiological framework of the polyvagal theory provides a plausible model for post-traumatic chronic pain and functional gastrointestinal disorders based on systemic brain-body responses to safety and threat. This framework provides an integrative perspective that unites multiple co-occurring phenomena across perceptual and neurophysiological reports, though much individual variability still remains. While FM and IBS share a neurophysiological substrate with threat-response systems, symptom heterogeneity is the rule rather than the exception, which likely reflects interactions with higher level brain structures, neuroendocrine, and immune processes [e.g., (89)]. However, this review highlights the potential for the autonomic nervous system to be the basis for the organization and synthesis of observations made made by physicians, mental health practitioners, and neuroscientists to piece together the mechanisms that link traumatic experiences, threat-related nervous system function, and multiple somatic disorders. Conversations about trauma history between patients and medical practitioners may be critical for interpreting symptoms and developing treatment plans, but these conversations are rare (26). By building a better understanding of the systemic chronic nervous system alterations that can be induced by trauma, the medical community can move toward explaining co-morbidities and developing targeted treatments.

AUTHOR CONTRIBUTIONS

JK and SWP both contributed to the conceptualization and writing of this work.

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Corrigendum: Chronic Diffuse Pain and Functional Gastrointestinal Disorders After Traumatic Stress: Pathophysiology Through a Polyvagal Perspective

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In the published article, there was an error regarding the affiliations for Stephen W. Porges. As well as having affiliation 2, Dr. Stephen W. Porges should also have affiliation 1. The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way.

The original article has been updated.

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ORIGINAL RESEARCH
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School-Aged Children With Higher Reflective Functioning Exhibit Lower Cardiovascular Reactivity

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Despite extensive theorizing regarding the regulatory role of reflective functioning (RF), few studies have explored the links between RF and physiological indices of emotion regulation, and none have examined these associations in children. Further, while scholars contend that RF promotes resilience via enhanced ability to process emotional experiences, including those occurring in attachment relationships, this argument has seldom been tested empirically in children. In the current study, we explore the association between RF and physiological measures of emotion reactivity and regulation, as well as the interaction of RF and attachment insecurity. We test these associations by examining children's ($N = 76$; 8–12 years old) cardiovascular responses [respiratory sinus arrhythmia (RSA)] to a standardized paradigm designed to evoke reactions regarding the experience and expression of attachment-related needs. Children also completed a semi-structured attachment interview, which was later coded for children's attachment insecurity (operationalized as attachment dismissal and preoccupation) and RF. Our findings were largely consistent with theory and our hypotheses, suggesting that higher RF is associated with lesser cardiovascular reactivity (higher levels of RSA) during the stressor task and better recovery following the task. These links were especially strong for children with greater attachment preoccupation but did not vary as a function of children's levels of attachment dismissal. These findings contribute to developmental theory in suggesting that RF is closely linked to physiological emotion regulation in children.

Keywords: reflective functioning, mentalization, children, respiratory sinus arrhythmia, attachment

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INTRODUCTION

Emotion serves an important role in orienting us to attend to internal or external stimuli (1, 2). Regulation of emotions, which involves conscious and unconscious processes (3, 4), is a key developmental milestone and transdiagnostic protective factor against psychopathology (5–7). Emotion is a multifaceted construct comprised of experiential, behavioral, and physiological components, with each factor revealing unique information (3). Measuring these different components has the potential to give insight into those unique streams of information. Physiological measures of emotion can be particularly useful in measuring autonomic arousal, a metric that is less susceptible to reporting biases or social desirability effects than other assessments (e.g., self-report). Heart rate variability (HRV), an index of the change in time invervals between heartbeats, is a measure of physiological reactivity that reflects the interplay of different physiological systems that enable us to adapt to challenges in the internal and external environment (8). Respiratory sinus arrhythmia (RSA) is a short-term measure of HRV that reflects the vagus nerve's influence on the slowing and speeding of the heart. RSA captures parasympathetic nervous system activation in response to environmental stimuli (9). Higher levels of task-related changes in RSA indicate lower levels of sympathetic reactivity (10–12). While the initial response to a stimulus indexes emotion reactivity, observed recovery or return to baseline RSA can be used to infer emotion regulation, as has been done in prior studies (13, 14).

ATTACHMENT

Attachment security, or the felt sense that others will be responsive to one's expression of needs for comfort and support, is thought to develop as a result of a history of receiving sensitive care from attachment figures (15). The internal working model, a cognitive-affective schema that emerges from a history of interactions between infant and caregiver, contains important beliefs regarding the experience and expression of emotion (15): when children's expressions of emotional need have been met consistently with empathy and assistance in regulating emotion, children internalize the message that painful emotional experiences can be experienced, expressed, and resolved, resulting in optimal self-regulation of emotion later in development (16). In contrast, when children's needs have been rejected or ignored or when caregivers have responded inconsistently or with alarm to children's needs, children resort to defensive emotion regulation strategies, such as deactivation or hyperactivation, which while adaptive in the short-term, can result in negative outcomes over the long-term (16).

Decades of research substantiate this theorizing by documenting links between attachment security and emotion regulation in adults [e.g., (17, 18)]. Although middle childhood remains an understudied developmental phase with respect to attachment and its links with emotion (19), emerging evidence suggests that school-aged children with secure attachment have better emotion regulation than their insecure counterparts [e.g., (20, 21)].

The association between attachment and emotion regulation is thought to depend on early parent-child interactions involving physical/embodied regulation by the parent (22, 23). These interactions serve to calibrate the infant's developing stress regulation system so that over time, physiological *self*-regulation is established (24), with the presence of the parent needed and sought only in contexts of threat or higher levels of distress. In addition, expectancies regarding the parent's availability to respond to distress are reflected at a representational level. By middle childhood, attachment processes (1) have facilitated emotional regulation through their early physiological impact on the development of the stress regulation system; (2) continue to facilitate emotional regulation through the actual availability of, support from, and protection offered by attachment figures in times of distress (25); and (3) promote regulation at a representational level regarding the imagined responsiveness and trustworthiness of attachment figures and others in times of need (26). In line with this perspective, longitudinal evidence suggests that the quality of early parenting, through its impact on epigenetic regulation and DNA methylation, has long term implications on self-regulation and interpersonal processes into adulthood (27–29).

MENTALIZATION

As conceptualized by Fonagy et al. (24), *mentalization* refers to the process of interpreting the reactions of others in terms of psychological experience, imagining the mental states and intentions that underlie behavior, and being cognizant of one's own emotional reactions and their impact on others. Mentalization has been operationalized for research purposes as reflective functioning (RF). RF includes a self-focused dimension of one's own mental states, as well as an other-focused dimension concerning others' experiences (30–32).

Mentalization develops alongside attachment when infants are treated as individuals with minds and are responded to as if their behavior communicates something about their psychological experience (33). Through being treated as intentional agents, children discover their minds and come to think of themselves as having thoughts, desires, and feelings (34). Consistent with this argument, parental mentalization predicts school-aged children's own mentalization (30).

People with higher RF are more likely to have secure attachment (35), perhaps as a result of the association between sensitive parenting and parental mentalization, but the two constructs are not synonymous. Evidence suggests that adults with secure attachment are more likely to have higher RF (36–38), but the effect sizes obtained in these studies are not large, suggesting the distinctiveness of the two constructs. However, to date only one study has explored the links between attachment security and RF in children, finding that lower RF is associated with dismissing and disorganized, but not preoccupied attachment (Bizzi et al. in press).

MENTALIZATION AND EMOTION REGULATION

Scholars contend that there is a bidirectional association between RF and emotion reactivity and regulation (24). Having access to representations, metacognitive reflection, and semantic processing regarding one's own emotions facilitates the ability to make sense of and modify emotional expeirence. Fonagy et al. (24) describe a particular type of early non-verbal communication involving marked mirroring of the infant's peak affects and ostensive cueing, suggesting that this type of interaction provides the infant with an external representation of his/her emotions that is important for the consolidation of an early sense of self (39). Thus, mentalization is thought to serve a powerful regulatory function, helping individuals make sense of their own and others' behaviors, thoughts, and feelings, and in so doing, create an environment in which emotions are viewed as predictable, meaningful, and controllable (24). At the same time, mentalization is impacted by emotional arousal—higher levels of arousal may inhibit effortful and deliberate RF (31, 40).

Despite the rich theorizing regarding the regulatory role of mentalization, the links between RF and emotion have seldom been examined empirically, and have not yet been explored in children. Although there is no direct evidence of the link between children's RF and children's emotion regulation, several studies provide indirect support for this association. First, there is evidence that mentalization in parents predicts parenting behavior that is associated with better emotion regulation in children. For instance, parents with higher RF engage in more sensitive (41–45) and less intrusive or frightening parenting than parents with lower RF (41, 46). We see this as consistent with the theorized association, given that more sensitive or controlled parenting may in and of itself be evidence of better emotion regulation (47). Second, in a series of studies on parental mentalization and school-aged children's emotional adjustment (48, 49), Gottman and colleagues find that parents who show greater awareness of their own and their children's emotions have children who exhibit better emotion regulation. Conversely, lower RF confers risk for a variety of forms of psychopathology, including autism, depression, psychosis, PTSD, eating disorders, substance abuse [for a review see (50–55)], as well as forms of psychopathology chiefly characterized by emotion dysregulation [e.g., borderline personality disorder; (56, 57)], suggesting that the two may be linked. Similarly, in adolescents, lower RF is a general risk factor for psychopathology, including borderline and narcissistic personality traits, as well as internalizing and externalizing symptoms (58). Finally, in children, lower RF is associated with more depressive, externalizing, and somatic symptoms [Bizzi et al., under revision, (59, 60)].

RF AS A RESILIENCE FACTOR IN THE CONTEXT OF ATTACHMENT

According to theory, mentalization can assist individuals in the processing of life experiences, including those that occur in attachment relationships (24, 61). Mentalization can help individuals understand and make sense of their past experiences, which is thought to be central to resilience. This conceptualization of mentalization converges with the notion of resilience as a "reintegration of self that includes a conscious effort to move forward in an insightful integrated positive manner as a result of lessons learned from an adverse experience" [(62), p. 3].

In support of this argument, research finds that among adolescents who report having experienced parental neglect (adverse early experience), those with higher RF were less likely to be classified as having insecure attachment (outcome) compared to their lower-RF counterparts (63). Similarly, another study found that among parents with childhood experiences of maltreatment (adverse early experience), those with higher levels of RF regarding trauma were less likely to have infants who were disorganized in their attachment [outcome variable; (64)]. In the current study, we examine whether the link between RF and RSA is stronger among children with greater attachment insecurity (more attachment preoccupation or dismissal), who are likely to have experienced greater distress in the context of attachment related needs than children with lesser attachment insecurity, thereby assessing whether RF can promote resilience in the context of attachment experiences.

CURRENT INVESTIGATION

We pursue two central aims—first, we test the concurrent associations between school-aged children's RF and their physiological reactivity to and recovery following a stressor task related to attachment needs. Second, we explore whether RF interacts with attachment insecurity in its associations with physiological reactivity and recovery.

To these ends, a community sample of school-aged children completed an attachment interview, which was later coded by independent teams of raters naïve to study hypotheses for attachment security and RF. Approximately 1 week later, children completed a standardized laboratory paradigm used in previous studies of attachment (65), in which they read hypothetical vignettes of other children encountering situations that are likely to evoke attachment-related needs (e.g., being sick, feeling afraid). During and following the presentation of these vignettes, we monitored children's RSA, which we used as measures of reactivity and regulation, respectively.

We tested the following hypotheses. First, consistent with prior work, we sought to replicate the association between higher attachment insecurity (dismissal and preoccupation) and lower RF. Second, we predicted that higher RF would be associated with lower reactivity and regulation (higher RSA during and following the stressor task). We followed this prediction with an exploratory test of the pathway between RF and emotion regulation, testing whether RSA during the stressor (emotion reactivity) mediates the association between RF and RSA following the stressor (emotion regulation). Third, we tested the theory that RF buffers the effects of attachment insecurity; we predicted that RF and attachment insecurity would interact in their association with RSA during (emotion reactivity) and following the stressor (emotion regulation), such that for children higher in attachment insecurity, higher RF would be more strongly associated with attenuated reactivity and regulation. Similar to above, we followed this hypothesis-driven prediction with an exploration of a moderated mediation model in which RF moderates the link between attachment insecurity and RSA following the stressor, as mediated by RSA during the stressor.

METHODS

Participants

The protocol for this study was approved by the Institutional Review Board at Pomona College. Children ($N = 76$; 50% boys, $M_{age} = 9.82$, $SD_{age} = 1.47$) between the ages of 8 and 12 participated in this study of children's development. The principal investigator calculated the targeted sample size based on a power analysis using effect sizes obtained from her prior work on attachment in school-aged children, which suggested a sample size of $N = 70$ would be sufficient to detect an effect. The participants were recruited from the community through advertisements posted online, flyers, and word of mouth. The sample was racially/ethnically (40% of caregivers identified as Hispanic, 36% Caucasian, 13% African American, 4% Other, 1% Asian, and 1% Native American) and socioeconomically diverse (50% of families reported an annual income <\$40,000; 8% >\$120,000).

Procedure

The study took place over two sessions occurring ∼2 weeks apart. Caregivers provided consent to participate in a study, while children provided informed assent. Participants were informed that they could choose to opt out of any portion of the study at any time. Then children completed the Child Attachment Interview [CAI; (66)], from which two non-overlapping teams of coders scored children's attachment security and RF. On the second visit, children completed a laboratory stressor and recovery task during which we monitored their cardiovascular reactivity.

Measures

Attachment Security

Children completed the CAI, a semi-structured interview for 8–13 year olds, designed to assess the quality of their attachment to their caregivers. The interview consists of 19 questions about children's current and past experiences with their caregivers. Responses are coded on 8 scales (e.g., Idealization, Preoccupying Anger, Balance of positive/negative references to attachment figures), as well as on the Overall Narrative Coherence scale, a dimensional measure of attachment security (67). A certified CAI coder coded all interviews, with reliability performed on 16 randomly-selected cases coded by a second certified coder. The Intraclass Correlation Coefficients (ICC) for CAI scales ranged from 0.72 to 0.97. The average ICC across all CAI subscales was 0.87.

The CAI manual provides guidelines for using scale scores to place children into one of four best-fitting attachment classifications with respect to each caregiver: secure, dismissing, preoccupied, and disorganized. However, in line with the argument that attachment is best reflected using dimensional, rather than categorical, metrics (68, 69), we used factor analytically-derived scales of dismissing and preoccupied attachment. This procedure has previously been used with studies using the CAI (70–72). The details of the factor analysis conducted within the larger sample are reported elsewhere (73), but in brief, the analysis revealed the presence of two factors. Scales loading on the first factor (eigenvalue = 4.83) signified attachment dismissal, with high scores indicating high dismissal of attachment needs and idealization of relationships with caregivers. Scales loading on the second factor (eigenvalue = 1.86) signified preoccupation, with high scores indicating high involving/preoccupying anger (communalities above 0.70). A high level of inter-rater reliability was achieved on these factor scales, dismissal ICC = 0.92, preoccupation ICC = 0.96.

Reflective Functioning

Children's RF was coded from their responses to the CAI using the Child Reflective Functioning Scale [CRFS; (30, 74)]. The CRFS is a modification of the Adult Reflective Functioning Scale [ARFS; (75)], which is used to measure RF on the Adult Attachment Interview [AAI; (76)]. The CRFS involves coding children's ability to articulate their own and others' internal experiences while describing current and past experiences with their caregivers. Coders rate RF on each CAI question; these scores are then averaged to create a global RF score. Although relatively recently developed, the CRFS has already shown promising psychometrics—the item-total correlations ranged from 0.57 to 0.79, and Cronbach's alpha was 0.94 (36). Due to our interest in children's general reflective capacities, in the current study we use children's global RF scores in analyses. In this study, internal consistency in RF scores across items was high, $\alpha = 0.96$. The coder of all of the CAIs in this sample was trained by and was demonstrated to have excellent reliability with the developer of the CRFS measure (ICC = 0.92). The CRFS coder was unaware of all information regarding the children in the study (including their attachment classifications) and was not part of the attachment coding team.

The CRFS manual contains descriptions and examples of different levels and types of children's RF. Children's narratives are coded on an 11-point scale (1–9) descriptively anchored at six points in terms of their propensity to consider interpersonal interactions and personal reactions in mental state terms. To obtain a general indicator of children's RF (CRF-G), the mean RF of all the coded responses was used. The scale alpha was 0.94, and item-total correlations ranged from 0.57 to 0.79, confirming that the total score (CRF-G) could be used as a good indicator of overall RF. Because of theoretical considerations and previous findings with adults indicating that self- and other understanding may have distinct implications, self and other items were treated as separate scales. A factor analysis is not reported given that the sample was composed in part of children with histories of sexual abuse involving their fathers and that this may have had an effect on their mentalization regarding fathers that may be particular to this sample and would be unlikely to be replicated in other samples.

Laboratory Stressor: Distress Vignettes Paradigm

Children completed a standardized laboratory stressor task in which they were presented with multiple vignettes in text form regarding same-sex hypothetical children experiencing mildly emotionally and physically distressing situations (sadness, fear, sick, and hurt) on a computer screen (65). They were asked to reflect on their thoughts and feelings in reaction to each vignette (e.g., *[Child's name] hurt her/his knee when (s)he was playing basketball. It hurt all day long*). We used two different counterbalanced conditions to control for order effects of the presentation of the different situations (Order 1: hurt, sad, afraid, sick, neutral; Order 2: neutral, sick, hurt, sad, afraid). For each distressing situation, three vignettes were presented (order randomized within counterbalanced block) to represent increasing levels of severity of distress. All stimuli were presented using E-Prime. Prior data using this paradigm suggest that

TABLE 1 | Descriptive statistics of key variables by children's gender.

Measures	Total ($N = 76$) M (SD)	Boys ($n = 38$) M (SD)	Girls ($n = 38$) M (SD)	Gender differences t
Age	9.82 (1.47)	9.24 (1.38)	10.39 (1.33)	−3.72***
Attachment dismissal[a]	0.05 (1.00)	0.36 (1.01)	−0.27 (0.88)	2.89**
Attachment preoccupation[b]	0.11 (0.98)	0.10 (0.97)	0.12 (1.00)	−0.11
RF	3.09 (0.84)	2.71 (0.69)	3.47 (0.80)	−4.45***
RSA-baseline	6.85 (1.24)	6.63 (1.38)	7.08 (1.05)	−1.60
RSA–stressor	6.75 (0.90)	6.68 (0.94)	6.83 (0.85)	−0.70
RSA–recovery	6.79 (0.90)	6.77 (0.91)	6.80 (0.90)	−0.16

*RF, Reflective functioning; **$p < 0.01$. ***$p < 0.001$.*

[a] *Attachment dismissal, Factor analytically derived dismissing attachment score (Child Attachment Interview); Higher score means highly dismissing.*

[b] *Attachment preoccupation, Factor analytically derived preoccupied attachment score (Child Attachment Interview); Higher score means highly preoccupied.*

TABLE 2 | Correlation matrix for key variables.

Variable	1	2	3	4	5	6	7	8
1. Age	–							
2. Gender	0.40***	–						
3. Attachment dismissal[a]	−0.18	−0.32**	–					
4. Attachment preoccupation[b]	0.03	0.01	−0.04	–				
5. RF	0.40***	0.46***	−0.58***	−0.10	–			
6. RSA-baseline	−0.01	0.18	0.02	−0.07	−0.05	–		
7. RSA–stressor	−0.22	0.08	−0.09	−0.02	0.10	0.58***	–	
8. RSA–recovery	−0.25*	0.02	−0.04	−0.06	0.13	0.53***	0.84***	–

*RF, Reflective functioning; Gender coding: 1, boys; 2, girls; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

[a] *Attachment dismissal, Factor analytically derived dismissing attachment score (Child Attachment Interview); Higher score means highly dismissing.*

[b] *Attachment preoccupation, Factor analytically derived preoccupied attachment score (Child Attachment Interview); Higher score means highly preoccupied.*

children experience significant increases in self-reported negative emotion in response to these vignettes (65).

Cardiovascular Physiology

RSA data were collected before, while, and after the laboratory stressor was presented. Baseline RSA was collected while children sat quietly and watched a 290 s nature video. During the laboratory task, RSA-stressor was collected while each of the vignette ("story") and reflection periods were presented (60 s for each vignette). Following each distress block (e.g., afraid), which included the presentation of three separate vignettes and reflection periods, children completed a 30 s RSA recovery period during which they were asked to sit quietly and wait until the next "story" appeared on the screen. Thus, for the purposes of this study, we considered RSA recordings taken during the vignettes to be measures of reactivity, whereas we considered RSA measures taken during the recovery periods following each block of vignettes to be measures of regulation.

We collected HRV data using disposable Mindware 1.5-in foam EKG electrodes with 7% chloride wet gel and touchproof snap leads, which were connected to a BioNex 8 slot chassis equipped with an impedance cardiograph (Mindware Technologies, Gahanna, OH). Data were collected using BioLab 2.5 acquisition software and were later edited for peak errors and noise using BioLab HRV 2.0 application (Mindware Technologies, Gahanna, OH). Prior to conducting data analysis, we computed mean RSA across the baseline assessment, and the reactivity and recovery sessions of the four distressing vignette types.

Data Analytic Plan

To evaluate our hypotheses, we used hierarchical linear regressions in which we controlled for children's age and gender on an initial step. For analyses involving moderation, mediation, and moderated mediation, we used Hayes' PROCESS macro (77). In analyses in which reactivity and recovery levels of RSA were the dependent variables, we included baseline RSA as an additional covariate.

RESULTS

Descriptive Statistics

Descriptive statistics for key variables, overall and by child gender, are reported in **Table 1**. Independent samples t-tests revealed that girls were significantly older, less dismissing, and higher in RF than boys. Zero-order correlations indicated that older children had higher RF ($r = 0.40$, $p < 0.001$) and higher RSA-recovery ($r = -0.25$, $p = 0.03$; see **Table 2**). Children with more dismissing attachment had lower RF ($r = -0.58$, $p < 0.001$).

Based on the results of these preliminary analyses, we controlled for children's age and gender in all subsequent analyses.

Hypothesis 1. Association Between Children's RF and Attachment Security

After controlling for children's age and gender ($R^2 = 0.27$, $p < 0.001$), attachment dismissal was negatively associated with children's RF ($\Delta R^2 = 0.22$, $b = -0.40$, $SE = 0.08$, $p < 0.001$; see **Table 3**). In a subsequent analysis, when we controlled for attachment preoccupation ($R^2 = 0.28$, $p < 0.001$), attachment dismissal was still negatively associated with children's RF ($\Delta R^2 = 0.21$, $b = -0.40$, $SE = 0.08$, $p < 0.001$), but preoccupation was not.

Hypothesis 2. Association Between Children's RF and RSA

Table 4 depicts the results of two hierarchical linear regressions testing the association between children's RF and RSA-stressor, as well as children's RF and RSA-recovery. After controlling for children's age, gender, and baseline RSA ($R^2 = 0.38$, $p < 0.001$), children's RF was significantly positively associated with RSA-stressor ($\Delta R^2 = 0.05$, $b = 0.28$, $SE = 0.11$, $p = 0.01$; Hypothesis 2a). Thus, in support of Hypothesis 2, higher RF was associated with lesser reactivity.

Second, after controlling for the same set of covariates ($R^2 = 0.34$, $p < 0.001$), children's RF was significantly positively associated with children's RSA-recovery ($\Delta R^2 = 0.09$, $b = 0.37$, $SE = 0.11$, $p = 0.002$; Hypothesis 2b). Therefore, in support of our hypothesis, higher RF was associated with greater parasympathetic activation during the recovery period.

Exploratory Mediation

Figure 1 presents the results of a hierarchical regression testing the mediation model. PROCESS Model 4 revealed that after controlling for children's age, gender, and baseline RSA in the first step ($R^2 = 0.43$, $p < 0.001$), children's RSA-stressor acted as an indirect effect in explaining the link between child RF and RSA-recovery (point estimate = 0.21, 95% CI [0.03, 0.42]). Controlling for the indirect effect, the direct effect between child RF and RSA-recovery was not significant (point estimate = 0.16, 95% CI [−0.004, 0.33]).

TABLE 3 | Child attachment dismissal associated with child RF.

	Dependent variable: child RF			
Step	***b***	**SE**	**β**	**CI**
Step 1 R^2	0.27***			
Constant	0.79	0.57		[−0.34, 1.92]
Age	0.14*	0.06	0.25	[0.02, 0.27]
Gender	0.60**	0.18	0.36	[0.24, 0.96]
Step 2 ΔR^2	0.22***			
Attachment dismissal[a]	−0.40***	0.08	−0.48	[−0.55, −0.25]
Attachment preoccupation[b]	−0.11	0.07	−0.13	[−0.25, 0.04]

*RF, Reflective functioning; *p < 0.05; **p < 0.01 ***p < 0.001.*

[a] *Attachment dismissal = Factor analytically derived dismissing attachment score (Child Attachment Interview); Higher score means highly dismissing.*

[b] *Attachment preoccupation = Factor analytically derived preoccupied attachment score (Child Attachment Interview); Higher score means highly preoccupied.*

Hypothesis 3. Association Between Children's RF and RSA Moderated by Attachment

We tested whether attachment dismissal or preoccupation moderated the link between children's RF and RSA-stressor (Hypothesis 2a) or RSA-recovery (Hypothesis 2b), after controlling for covariates. The results of these moderation analyses revealed that neither attachment dismissal ($\Delta R^2 = 0.01$, $b = -0.13$ $p = 0.21$), nor attachment preoccupation ($\Delta R^2 = 0.01$, $b = 0.09$, $p = 0.28$), moderated the link between children's RF and RSA-stressor. However, after controlling for children's age, gender, baseline RSA, and the main effects of attachment dismissal and preoccupation ($R^2 = 0.48$, $p < 0.001$), attachment preoccupation moderated the link between children's RF and RSA-recovery ($\Delta R^2 = 0.05$, $b = 0.21$, $p = 0.01$). Among children with mean ($b = 0.43$, $p = 0.002$), and high levels of attachment preoccupation ($b = 0.63$, $p = 0.0001$), RF was positively associated with RSA-recovery. Among children with low attachment preoccupation, the association between children's RF and RSA-recovery was not significant ($b = 0.23$, $p = 0.15$; see **Figure 2**). Attachment dismissal did not moderate the association between child RF and RSA recovery after the stressor task ($\Delta R^2 = 0.004$, $b = -0.07$, $p = 0.52$); therefore, we elected not to examine a moderated mediation using attachment dismissal.

Exploratory Moderated Mediation

After controlling for children's age, gender, baseline RSA, and attachment dismissal ($R^2 = 0.43$, $p < 0.001$), the examination of conditional effects revealed that among children with mean ($b = 0.22$, $p = 0.02$) and high attachment preoccupation ($b = 0.36$, $p = 0.002$) RSA-stressor mediated the link between children's RF and RSA-recovery (point estimate = 0.20, 95% CI [0.003, 0.39]; see **Table 5** and **Figure 3**). Among children with low attachment preoccupation, there was no significant mediation effect ($b = 0.08$ $p = 0.45$).

DISCUSSION

Despite extensive theorizing regarding the regulatory role of RF, prior to the current investigation, extremely few studies had explored the links between RF and physiological reactivity or regulation, and none had examined these associations in children. In the current study, we tested these associations by exploring children's physiological responses to a standardized paradigm designed to evoke reactions regarding the experience and expression of attachment-related needs. Consistent with theory and hypotheses, the key findings of

TABLE 4 | Hierarchical regressions examining associations between children's RF, RSA-stressor and RSA-recovery.

	Dependent variable: RSA–stressor				Dependent variable: RSA–recovery			
Step	***b***	***SE***	**β**	**CI**	***b***	***SE***	**β**	**CI**
Step 1 R^2	0.38***				0.34***			
Constant	5.22***	0.73		[3.76, 6.67]	5.62***	0.76		[4.10, 7.13]
Age	−0.15*	0.06	−0.24	[−0.27, −0.02]	−0.15*	0.06	−0.25	[−0.28, −0.02]
Gender	0.13	0.18	0.07	[−0.23, 0.50]	0.04	0.19	0.02	[−0.34, 0.42]
RSA–Baseline	0.41***	0.07	0.56	[0.27, 0.54]	0.38***	0.07	0.52	[0.24, 0.52]
Step 2 ΔR^2	0.05*				0.09**			
RF	0.28*	0.11	0.26	[0.06, 0.51]	0.37**	0.11	0.34	[0.14, 0.60]

*RF, Reflective functioning. *p < 0.05. **p < 0.01. ***p < 0.001.*

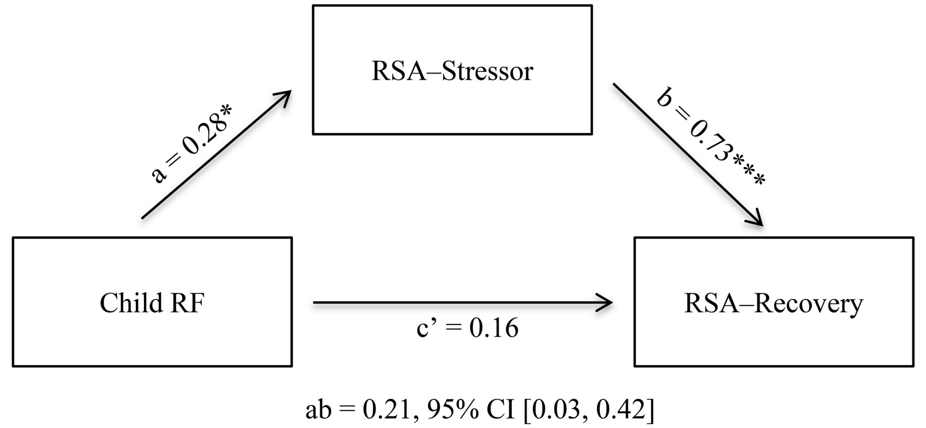

FIGURE 1 | RSA-stressor as a mediator for the association between Child RF and RSA-recovery. Figure shows unstandardized *b* values. Analysis includes the following covariates (not pictured here): child age, child gender, RSA-Baseline. RF, Reflective functioning; *$p < 0.05$. ***$p < 0.001$.

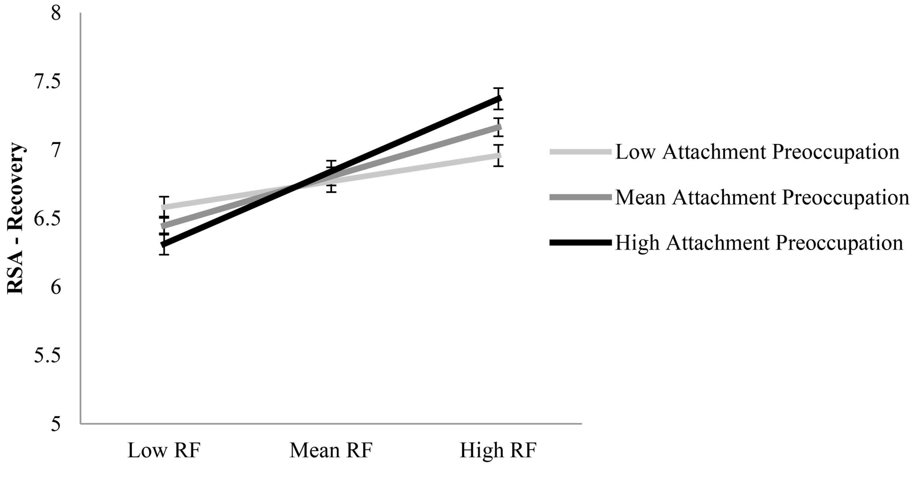

FIGURE 2 | Attachment preoccupation moderates the association between children's RF and RSA-recovery, but not RSA-reactivity. RF, Reflective functioning; Attachment preoccupation, Factor analytically derived preoccupied attachment.

this study were that higher RF was associated with lower cardiovascular reactivity and better regulation, links that were especially strong for children with greater attachment preoccupation.

The findings of our first analysis revealed that greater attachment dismissal was associated with lower RF, but that attachment preoccupation was not significantly associated with child RF. Thus, using ratings derived from independent

TABLE 5 | Regressions examining the moderated mediation model: attachment preoccupation as a moderator of the mediation of the children's RF to RSA-recovery by RSA-stressor.

	Independent variable: children's RF		
	Dependent variable: RSA–recovery		
Predictor variables	***b***	***SE***	**CI**
Low attachment preoccupation	0.08	0.11	[−0.13, 0.30]
Mean attachment preoccupation	0.22*	0.09	[0.03, 0.41]
High attachment preoccupation	0.36**	0.11	[0.14, 0.59]

*RF, Reflective functioning; Attachment preoccupation, Factor analytically derived preoccupied attachment score (Child Attachment Interview); Higher score means highly preoccupied. *p < 0.05, **p < 0.01.*

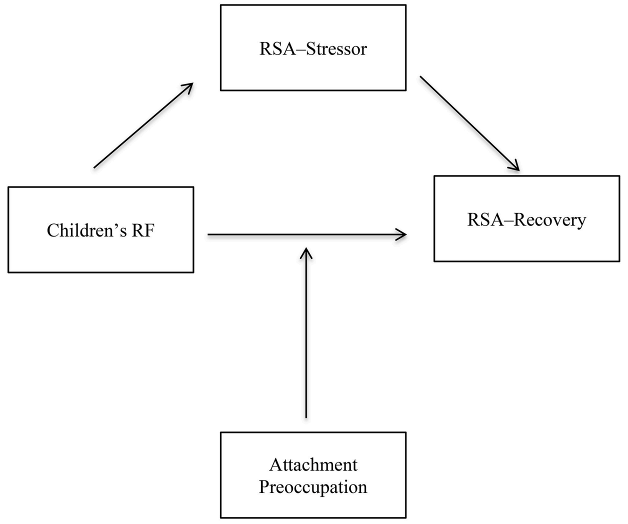

FIGURE 3 | Visual depiction of the proposed moderated mediation: Attachment preoccupation moderates the association between children's RF and RSA-recovery mediated by RSA-stressor. RF, Reflective functioning; Attachment preoccupation, Factor analytically derived preoccupied attachment score (Child Attachment Interview); Higher score means highly preoccupied.

teams of coders, we found that children classified as having high attachment dismissal had lower RF, demonstrating the limitations in their abilities to hold in mind their own and their parents' mental states. However, our findings revealing a unique link between dismissing attachment and RF are in line with results from other studies finding a specific association between dismissing attachment and lower RF in children and parents [Bizzi et al., under revision; (73), but see (36), for an association between lower RF with dismissal and preoccupation]. One potential reason for the lack of association between RF and preoccupation is that preoccupied children may use more emotion words than dismissing children, and may potentially use comparable numbers of emotion words as secure children. The use of emotion words constitutes part of the global RF score and thus could inflate the RF ratings of preoccupied children, despite their relatively infrequent use of attributions or actual mentalization. However, for preoccupied children, the use of mental state language may not be as emotionally regulating as it is for secure children, or perhaps preoccupied children use mental state language but do not achieve higher levels of mentalization (e.g., drawing connections between mental states and behavior). An alternate explanation is that preoccupied children, who are likely to be more open to experiencing and expressing negative emotion than dismissing children (16), may engage in a type of hypermentalizing in an attempt to regulate emotion, but are unable to use their mentalization in an organized way to regulate and contain negative effects and anger in relation to attachment figures (Bizzi et al., under revision).

Our central study hypotheses concerned the interrelations of RF and physiological reactivity and regulation, operationalized as RSA during the task and the recovery period, respectively. RF was associated with higher RSA during the stressor and recovery period, supporting our hypotheses and suggesting that RF is associated with lower reactivity and better regulation. Interpreting these findings in terms of theory would suggest that for children with higher RF on the CAI, contemplating attachment needs (being physically hurt, sick, sad, or frightened) did not require as much physiological regulatory effort as this task demanded from children with lower levels of RF. Thus, at least in the context of the current attachment-based task, RF was associated with superior physiological regulation. According to mentalization theory, a child's experience of the benign interest of parents in their subjective experience can improve emotion regulation, as it opens a space where they can communicate their concerns, fears, and difficulties to their parents, allowing them to develop a mutually elaborated understanding of themselves and their emotions (26, 33, 60).

However, much remains to be understood about these effects as, given the correlational design in which measures were assessed at a single timepoint, causal conclusions elude us. Further, RF could be associated with emotion reactivity and regulation via several channels. For instance, children may have been less reactive owing to a sense of confidence that emotions can be safely experienced and shared. Higher RF may in part be associated with lower stress activation because of early experiences in which children's subjective experience was responded to first through marked affect mirroring when they were young (24) and later through the parents' creation of a shared mental space where the children's subjective experience can be elaborated. Further, interactions in which the parent actively helped the child understand affective experience could have positively impacted the development of the child's stress regulation system. Alternatively, higher RF youth may not have found the vignettes emotionally taxing, as, by virtue of their abilities to mentalize, contemplating attachment needs and emotions may not be as daunting. Via mentalization, children have learned to mentally represent emotions, symbolize subjective experience, and put these experiences into words, a process which facilitates the understanding and regulation of emotions. When children develop symbolic and semantic representations of emotion, children's neurobiological pathways of stress regulation and mentalization may be more effectively connected, thus promoting the effective regulation of emotion. We tentatively suggest that the outcome of interpersonally developed mentalization about self and others, evident at the level of physiological regulation, may reflect an integration of symbolic and affective processes that are likely evident at the level of neurobiology but may also be seen from the perspective of self and identity. At this level of development, higher RF may be seen as an index of the child's emerging sense of self and attachment figures, and as central to identity.

Finally, we found that attachment preoccupation, but not attachment dismissal, moderated the link between RF and RSA during recovery, but not RSA reactivity. Specifically, the positive association between RF and RSA was only statistically significant among children with mean or higher attachment preoccupation, and not among children with low levels of attachment preoccupation. Children who are low in attachment preoccupation may not need RF to regulate themselves when considering attachment needs and feelings, as contemplating these topics may have evoked less intense reactions. On the other hand, for preoccupied children, for whom the contemplation of attachment needs may have caused higher reactivity, RF appears to have helped in their recovery. We have previously speculated whether the higher measured RF found among preoccupied children was indicative of hypermentalizing (repetitive, unproductive contemplating about mental states), but the current findings suggest that RF does in fact facilitate regulation among preoccupied children.

This finding can be understood in terms of its contribution to the notion that RF promotes resilience—children whose mental representations are characterized by preoccupation, who were nonetheless simultaneously engaged in the process of making sense of these experiences (evidenced by high RF), demonstrated superior physiological recovery from the stressor task. As resilience can be conceptualized as the capacity of a system to adjust to disturbances that could threaten it, or the attempt to continually derive meaning and insight from experiences (62), it aptly characterizes the process of mentalization co-occurring with preoccupied attachment. The link between RF and physiological reactivity did not vary as a function of dismissing attachment; at all levels of dismissing attachment, higher RF was associated with better emotion reactivity and regulation. Thus, no matter how low the attachment dismissal, RF confers regulatory protection.

Strengths and Limitations

As the first empirical test of the links between RF and physiological reactivity in children, we believe that this study contributes to the literature in significant ways. By using robust observational measures of attachment and RF, and by employing a standardized laboratory stressor designed to present to children situations in which attachment needs are evoked, we offer an important, highly controlled examination of research hypotheses. Further, our use of a highly racially and ethnically diverse sample of children increases the generalizability of the findings we report.

However, it is also important to contextualize the contributions of this study in light of its limitations. One limitation of the study is that the assessment occurred at a single timepoint, leaving open the possibility that lower physiological reactivity or better regulation could cause higher levels of RF, or that a shared third variable drives the association between RF and emotion reactivity and regulation. Longitudinal designs will be able to identify whether RF predicts emotion regulation later in development, which would strengthen the argument that children's RF promotes resilience. Further, we examined attachment and RF using the same instrument (CAI). Although we used non-overlapping coders who were blind to all participant information, the fact that these indices were derived from the same measure may limit the extent to which we can accurately conceptualize them as separable constructs.

Further, measuring children's RSA in response to the distress vignettes task did not permit us to examine the types of negative emotion reactivity and regulation that are associated with RF (e.g., we cannot make an argument regarding discrete emotions), nor can we speak to children's subjective emotional experience more generally; this is an area ripe for future inquiry. Relatedly, for the purposes of this study, we attempted to distinguish between physiological measures of reactivity (RSA measured during the presentation of the vignettes) and regulation (RSA measured during the 30 s following each vignette block); however, this distinction contains some error in that children can employ regulation before and during the presentation of the distress vignettes. Thus, it is impossible to conclude that these measures indexed reactivity and regulation, but we can state that they assessed early and later measures of cardiovascular activation. In terms of the use of RSA, we note that some researchers suggest that greater decreases in RSA during a demanding task connote greater activation to stimuli and thus more optimal use of coping strategies (78–80), while others suggest that higher RSA during a stressor signifies lower emotional reactivity, which serves an adaptive function (10–12). Thus, it is important to note that our interpretation that lower stressor- and recovery-RSA signifies greater reactivity is consistent with one way of conceptualizing task-related changes of RSA, but this view is not universally held.

In addition, we did not measure or control for children's reading or learning abilities, which leaves open the possibility that the effects found here are biased to some extent by children's cognitive functioning. Finally, in future studies, it would be informative to measure task-specific or state-like RF regarding the laboratory task, as has been done in at least one other investigation (46), as this would enable us to get closer to identifying the processes occurring during the stressor task for high RF children.

CONCLUSIONS

This study provides new physiological evidence that children's mentalization is associated with more efficient stress regulation, as higher RF was associated with less physiological reactivity during and more efficient recovery from a stressor. When confronted with attachment stress, children with higher RF regulated their autonomic nervous systems with less effort than children with lower RF. Consistent with the argument that

RF promotes resilience, the association between RF and higher RSA was only significant among children with higher levels of attachment preoccupation.

AUTHOR CONTRIBUTIONS

JB designed the study, developed the hypotheses, oversaw the data collection, conducted data analyses, and was the chief contributor to the writing of the manuscript. KE developed the coding system for children's reflective functioning, oversaw the coding of the data, and contributed to the writing and editing of the manuscript. KH assisted with data analyses, editing and writing of the manuscript, and the preparation and checking of references. ATS conducted the coding of the reflective functioning data and assisted with the literature review of the manuscript. RD provided conceptual guidance regarding the framing of the manuscript. PF assisted with the conceptual framing of the mentalization aspect of the manuscript.

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Heart Rate Variability in Dental Science

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Dentistry has made progress as a profession by integration with both medicine and other human sciences, especially when it uses empirical metrics to study process and outcome variables. Notably, progress in our understanding of genomic, biomic, and other molecular biological phenomena has been valuable. As has been identified by Drury (1, 2), it is proposed in this commentary that the inclusion of heart rate variability (HRV) as a biomarker of health may further this integrative progress. HRV is derived by various linear and non-linear statistical analyses of the R-R, beat-to-beat ECG interval in microseconds. Over twenty three thousand reports are identified in a recent PubMed search of the term heart rate variability, most of which demonstrate HRV's sensitivity to a wide diversity of physical and psychosocial pathologies. The small literature of dental use of HRV in both assessment and treatment will be selectively reviewed and relevant exemplars for other important health applications of HRV will be discussed. This will lead to a proposed agenda for researching HRV's value to professional dentistry as a human health and wellness profession.

Keywords: heart rate variability, research priorities, dental assessment, dental procedures, dental science

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Before HRV was specifically identified, it was well-known that dentistry involved negative affective states such as fear, stress, and pain. Indeed, "painless dentistry" was a key marketing feature of some practitioners, and "gentle dentistry" is still a frequent practice name. Although originally using rather unsophisticated unidimensional approaches, our increasing knowledge of biomedicine, neuroscience, and psychosocial issues has led to recent findings summarized by Flaten and al Absi (3) on the cardiovascular and neuroendocrine elements of response to stressful dental treatments. Similarly, the effects of dental surgery on cardiovascular and sympathetic responses have been observed (4), as well as deep pressure input on the parasympathetic system in wisdom tooth extraction (5).

As awareness and understanding of HRV have matured, as in this Research Topic, it has been used in a variety of ways to aid in both assessment and treatment of dental issues and conditions (6). For example the suppression of HRV in malocclusion has been demonstrated by Ekuni et al. (7) and the non-linear characteristics of HRV during endodontic treatment have been identified (8). HRV has been used to monitor orthostatic dysfunction during postural change in the dental chair (9). Several studies have used HRV analysis in the treatment of burning mouth syndrome (10, 11).

In an especially salient study, the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) case-controlled study followed 1633 Tempero Mandibular Dysfunction-free controls and 185 TMD cases for several years at multiple dental universities. The primary finding that emerged from the initial studies of potential risk factors was relative to controls, TMD cases displayed a dysfunction in autonomic activity characterized by reduced HRV at rest and in response to both physical and psychological stressors (12). This was reflected by a decrease in all HRV measures in both time and frequency domain during each of the test epochs. There is emerging evidence that somatosensory disorders such as TMD and Fibromyalgia are associated with a reduction in HRV and an overall dysfunction in autonomic activity (13). The association between TMD and headaches (14) coupled with the evidence that headache patients also have increased sympathetic nervous system activity and decreased parasympathetic activity compared to non-headache controls (15), clarifies the emerging need to measure and monitor HRV in dentistry. TMD, being one of the most common chief complaints a dentist may encounter, has always been thought of as a "stress" syndrome, but HRV now provides a quantitative method to assess, diagnose, and measure treatment effectiveness. Addressing, and possibly improving a biomarker such as HRV via a common dental disorder such a TMD, will allow for the potential improved understanding of comorbid symptoms such as migraine and tension headaches, myofascial pain, and fibromyalgia. With the decreasing cost and increasing accuracy of modern biosensors, it is realistic to expect HRV monitoring to become ubiquitous within the dental profession to enhance and measure treatment process and efficacy.

Beyond the use of HRV in assessment of dental processes and interventions, it has been used in applications which include treatment for physical disorders and psychosocial conditions. HRV Biofeedback (HRVB) has been studied in a number of clinical applications in cardiac rehabilitation and impaired sleep quality (16). HRVB has also shown value in modulating emotional response (17, 18) and treating disorders such as depression (19), stress (20), pain (21), post-traumatic stress disorder (22), and substance use disorder (23). Conversely, exercise therapy has been studied empirically and found to improve HRV (24) and some pharmacological agents have been shown to improve HRV (25, 26), as has hypnosis (27), message (28), and yoga (29). These results are encouraging but they have not been applied to dental treatment issues as of yet.

This general commentary has highlighted the rapidly emerging body of findings showing HRV to be a significant biomarker of various human health conditions, diseases and important functional states. Applications of such findings to dental practice have not been made in the dental literature and this should be a high priority. Not only is HRV of great potential use in assessing and evaluating various dental conditions and procedures, but it has also been helpful in treating a wide variety of non-dental conditions, and may well-generalize in dental treatment. In particular, rapid advances in wearable biosensors, networked algorithmic streamed data analysis and feedback, machine learning, artificial intelligence, and epigenetics will strongly contribute to the overall development of the fields of human health and well-being. This period of rapid technological development (2, 30) has been identified in the current Research Topic and presents a major opportunity for dental science.

AUTHOR CONTRIBUTIONS

RD conducted the overview of heart rate variability literature relevant to dental practice. He identified contributions and the need for additional research in this area. SS reviewed the manuscript.

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