DYSREGULATION OF AUTONOMIC CARDIAC CONTROL BY TRAUMATIC STRESS AND ANXIETY

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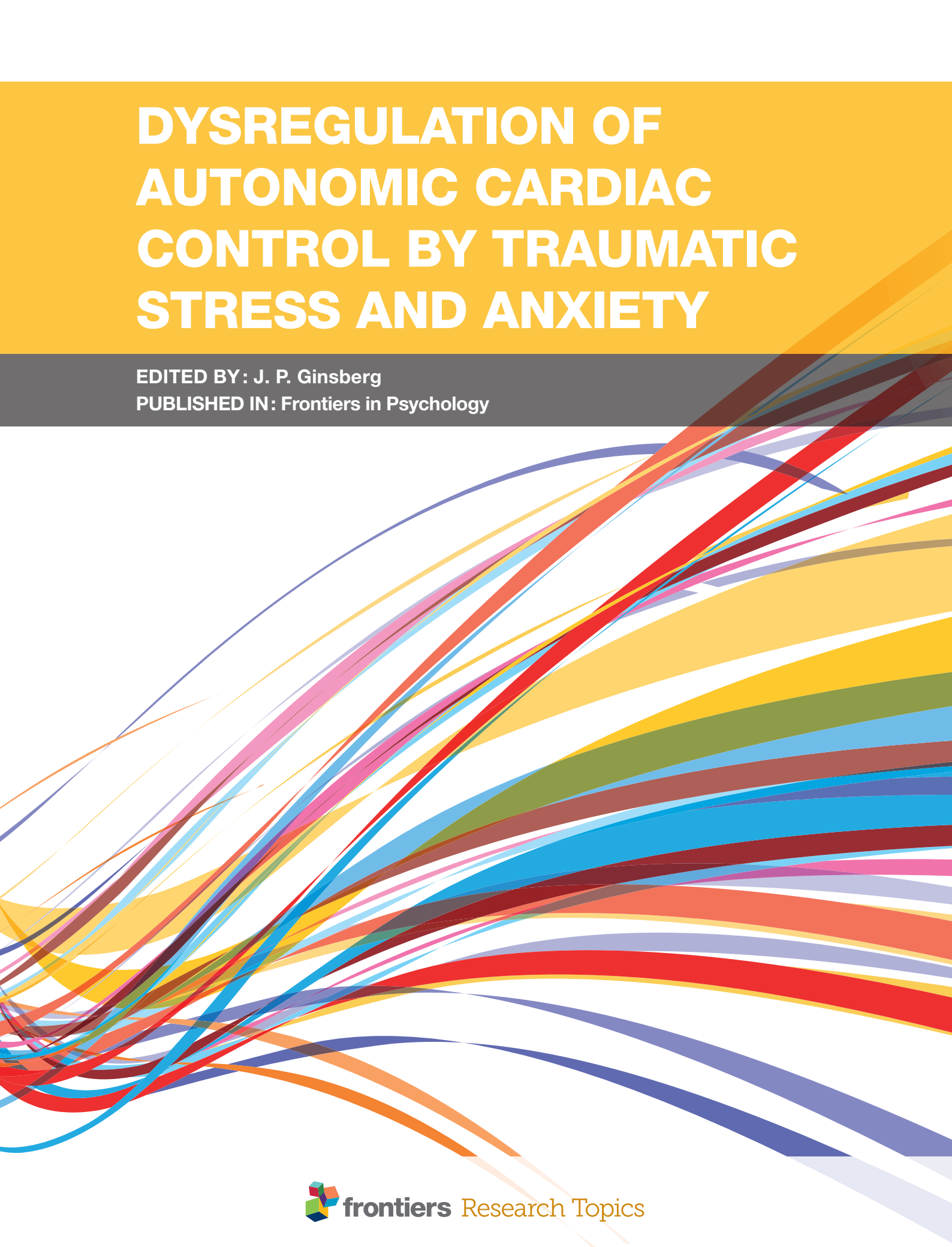

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DYSREGULATION OF AUTONOMIC CARDIAC CONTROL BY TRAUMATIC STRESS AND ANXIETY

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Current understanding of the interplay between sympathetic and parasympathetic influences on cardiac response to environmental stimuli and subsequent response selection (e.g. maintenance of resting homeostasis, mobilization of defensive response, task performance, tonic immobilization, and/or affiliation) will be explored. Reference will be made to how these processes conjoin with proposed polyvagal theory. Cardiac adjustments to environmental stimuli affect the internal physiological state of the organism as well as the quality of information processing that the individual can perform during the stimulus appraisal stage of the orienting response. Bradyrdia is adaptive in early stages of orientation to novel or potential threat, while greater HRV power serves to facilitate self-regulation, stimulus information processing and appraisal, and appropriate response selection. This issue is devoted to current research findings on how normal patterns of cardiac autonomic regulation of HRV are disrupted in PTSD, impairing sustained attention to the environment and increasing the rate of inappropriate responding to stimuli. Origins of our current state of understanding in the 'intake-rejection' hypothesis will be considered, and how the intake-rejection hypothesis has morphed into present-day Optimal Performance practice.

Additionally, empirical data where available will be presented on how dysregulation of the normal pattern of cardiac autonomic regulation by PTSD impairs sustained attention to the environment, and increases the rate of inappropriate responding to stimuli through disinhibition, poor impulse control, emotional withdrawal, over-arousal, and attentional bias. Current research findings are sought that address in controlled, experimental and clinical trials the restorative effects of HRV biofeedback on HRV power, and how increases in HRV power relate to improved attention / immediate memory and self-regulation of affect using outcome measures of cognition, symptoms of PTSD and depression, stress perception, and level of adaptive function.

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EDITORIAL
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Editorial: Dysregulation of Autonomic Cardiac Control by Traumatic Stress and Anxiety

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Keywords: autonomic nervous system, traumatic stress, heart rate variability, Hrv biofeedback, cardiac psychology

The Editorial on the Research Topic

Dysregulation of Autonomic Cardiac Control by Traumatic Stress and Anxiety

"Disorders of arousal" were defined in the past in terms of brain-based hypersensitivity to environmental stimulation (Gellhorn, 1968). Normally balanced sympathetic and parasympathetic branches of the autonomic nervous system (ANS) was historically described as "autonomic tuning," in contrast to the disorders of arousal which are characterized by ANS dysfunction, affective lability, anxiety, stress, and emotional disorder (Gellhorn and Loofburrow, 1963; Everly and Lating, 2012). Recent studies of the relevance of the ANS to stress and mental disorders are becoming increasing in number[1] (Agorastos et al., 2015). ANS dysregulation impacts on both physical (increasing cardiovascular risk) and mental (compromising psychological well-being) health at multiple levels. Loss of regulation of normal autonomic control of cardiac adjustment to environmental stressors thus leads to negative impacts on physiological function affecting arterial blood pressure, heart rate and rhythm, and vagal afference. Allostatic load is a term that has been used for decades to describe "the wear and tear on the body" which grows over time when the individual is exposed to repeated or chronic stress (McEwen and Stellar, 1993). Allostatic load is the physiological consequence of chronic exposure to fluctuating or heightened neural or neuroendocrine response that results from repeated or chronic stress. Thus it is, chronic autonomic imbalance finally leads to allostasis of affective, cognitive, and behavioral level of function. While the older "Disorders of Arousal" model continues to be prevalent in the scientific and clinical literature on stress-related pathogenesis, the field of stress disorders has taken great strides forward in terms of the NIMH-supported Research Domain Criteria (RDoC) initiative[2]. RDoC has successfully redefined "mental disorders" as "brain circuit disorders" using a matrix to organize increasing units of levels of analysis (genes through self-report and paradigms) for studying precisely defined domain constructs describing behavior. Most importantly, is that application of the RDoC approach brings into focus new therapeutics and new targets of therapeutics for brain disorders (Insel and Cuthbert, 2015).

This is exactly where the articles that comprise the *Frontiers Research Topic: "Dysregulation of autonomic cardiac control by traumatic stress and anxiety"* fit into clinical practice and research. Research data over the past two decades are showing that heart rate variability (HRV) is diminished in anxiety and stress-related disorders including PTSD, and lower HRV signals a disturbance

[1]Nagai, Y. (2014). Research Topic: The relevance of the autonomic nervous system to neurological and psychiatric disorders. *Front. Behav. Neurosci.* Available online at: http://www.frontiersin.org/autonomic_neuroscience/researchtopics/The_relevance_of_the_autonomic/2333

[2]National Institute of Mental Health. NIMH Research Domain Criteria (RDoC). Available online at: http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml

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of normal autonomic function and allostatic sympathetic hyperarousal. Furthermore, there is burgeoning and very recent research showing that HRV Biofeedback—the training of resonant frequency breathing, attentional focusing, and positive emotional state—reduces symptoms of anxiety, stress, and PTSD through normalization of autonomic function. HRV biofeedback (HRVB) enables self-regulation of peripheral autonomic state using feedback to the central nervous system circuits that control emotional, cognitive, and sensorimotor activity. The study of HRV and effects of HRVB provide important insights into the mechanisms of autonomic arousal in normal, successful adaptation, and pathological states such as PTSD and anxiety.

All of the individual articles in this ebook can thus be placed into one of three groupings. The papers by Fred Shaffer et al. and Rollin McCraty and Maria Zayas share a descriptive aspect of normal autonomic regulation of cardiac function in the healthy adult human being. Kuan-Hua Chen's contribution is experimental data on fractionation of stages of parasympathetic responding during habituation to repetitive acoustic startle touches on the fundamental process of orienting vs. defensive responses in children, and provides a bridge between early and current perspectives on how derangement of autonomic "tuning" underlies disorders of arousal. Slow habituation of startle to aversive stimuli is a likely factor in development of traumatic stress, which makes for a segue into Susan Wood's paper on biomarkers of autonomic dysregulation in a rodent stress model (the only translational paper in the collection); Wood's review builds the central framework of dysregulation of autonomic cardiac function in anxiety and stress.

All of the papers in the second grouping are connected by their focus on the role of autonomic cardiac *dysregulation* underlying the development and expression of stress in humans. Results of the Steffen et al. clinical research indicate that, with careful monitoring, students receiving psychotherapy at a college counseling center had higher and sustained cortisol and heart rate (HR) during recovery after a clinically-controlled stressor. Importantly, these researchers delved deeper to find that psychotherapy participants experiencing clinically significant levels of distress during the stressor displayed elevated blood pressure and HR, concluding that physiological reactivity to stress is important for psychotherapy clients. Lee et al. calling for the RdoC approach, argue that medication and illicit substance dependence in patients with high-arousal disorders which they associate with a "parasympathetic freeze state" represent output effects of frontal asymmetry activation on *feeling* and a consequent drive for arousal attenuation. Then, Gillie and Thayer use carefully and thoughtfully selected data to bring the argument back to the well-accepted model of executive function and autonomic interactions, based on Thayer's Neurovisceral Integration model of Central Autonomic Networks (CAN) and Anterior Executive Region (AER), and effectively tie it all to PTSD. The groundbreaking thesis, that aging as indexed by poor long-term physical health outcomes and substance abuse, is presented by Williamson et al. Lastly, Conder and Conder extend the utility of HRV as a therapeutic target to treatment of concussion, a topic that is rapidly expanding in importance.

The third group contains overview considerations of the utility of understanding autonomic factors in individual health. Psychobiologic sensors are "a perfect storm" of convenience, affordability, and efficiency, Rob Drury writes; they continue to develop in sophistication of analysis of naturalistic environments and the autonomic responses of individuals, providing new and exciting avenues for health monitoring. Two of the most widely known and respected authorities in the field of HRV Biofeedback, Paul Lehrer and Richard Gevirtz, lay down a blueprint of the inner workings of this integrative medicine intervention. Finally, my colleagues and I (Ginsberg et al.) offer a bird's eye view of the history and current state of the field of study of autonomic cardiac regulation of anxiety and stress, under the unifying term Cardiac Psychology.

This Research Topic is presented with the hope that readers will find it enlightening, stimulating, and a contribution to advancement of the field.

AUTHOR CONTRIBUTIONS

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

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REVIEW ARTICLE
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A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability

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Heart rate variability (HRV), the change in the time intervals between adjacent heartbeats, is an emergent property of interdependent regulatory systems that operate on different time scales to adapt to challenges and achieve optimal performance. This article briefly reviews neural regulation of the heart, and its basic anatomy, the cardiac cycle, and the sinoatrial and atrioventricular pacemakers. The cardiovascular regulation center in the medulla integrates sensory information and input from higher brain centers, and afferent cardiovascular system inputs to adjust heart rate and blood pressure via sympathetic and parasympathetic efferent pathways. This article reviews sympathetic and parasympathetic influences on the heart, and examines the interpretation of HRV and the association between reduced HRV, risk of disease and mortality, and the loss of regulatory capacity. This article also discusses the intrinsic cardiac nervous system and the heart-brain connection, through which afferent information can influence activity in the subcortical and frontocortical areas, and motor cortex. It also considers new perspectives on the putative underlying physiological mechanisms and properties of the ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF) bands. Additionally, it reviews the most common time and frequency domain measurements as well as standardized data collection protocols. In its final section, this article integrates Porges' polyvagal theory, Thayer and colleagues' neurovisceral integration model, Lehrer et al.'s resonance frequency model, and the Institute of HeartMath's coherence model. The authors conclude that a coherent heart is not a metronome because its rhythms are characterized by both complexity and stability over longer time scales. Future research should expand understanding of how the heart and its intrinsic nervous system influence the brain.

Keywords: heart rate variability, psychophysiological coherence, neurocardiology, biofeedback interventions, emotional self-regulation

INTRODUCTION

THE HEART

The heart is about the size of a closed fist, weighs between 250 and 350 g, and beats approximately 100,000 times a day and 2.5 billion times during an average lifetime. The muscular heart consists of two atria and two ventricles. The atria are upper receiving chambers for returning venous blood. The ventricles comprise most of the heart's volume, lie below the atria, and pump blood from the heart into the lungs and arteries. Deoxygenated blood enters the right atrium, flows into the right ventricle, and is pumped to the lungs via the pulmonary arteries, where wastes are removed and oxygen is replaced. Oxygenated blood is transported through the pulmonary veins to the left atrium and enters the left ventricle. When the left ventricle contracts, blood is ejected through the aorta to the arterial system (Marieb and Hoehn, 2013; Tortora and Derrickson, 2014).

THE CARDIAC CYCLE

The cardiac cycle consists of systole (ventricular contraction) and diastole (ventricular relaxation). During systole, blood pressure (BP) peaks as contraction by the left ventricle ejects blood from the heart. Systolic BP is measured during this phase. During diastole, BP is lowest when the left ventricle relaxes. Diastolic BP is measured at this time.

PACEMAKERS

The heart contains autorhythmic cells that spontaneously generate the pacemaker potentials that initiate cardiac contractions. These cells continue to initiate heartbeats after surgeons sever all efferent cardiac nerves and remove a heart from the chest cavity for transplantation. Autorhythmic cells function as pacemakers and provide a conduction pathway for pacemaker potentials.

The sinoatrial (SA) node and atrioventricular (AV) node are the two internal pacemakers that are primarily responsible for initiating the heartbeat. The electrocardiogram (ECG) records the action of this electrical conduction system and contraction of the myocardium (**Figure 1**).

CARDIAC CONDUCTION

In a healthy heart, the SA node initiates each cardiac cycle through spontaneous depolarization of its autorhythmic fibers. The SA

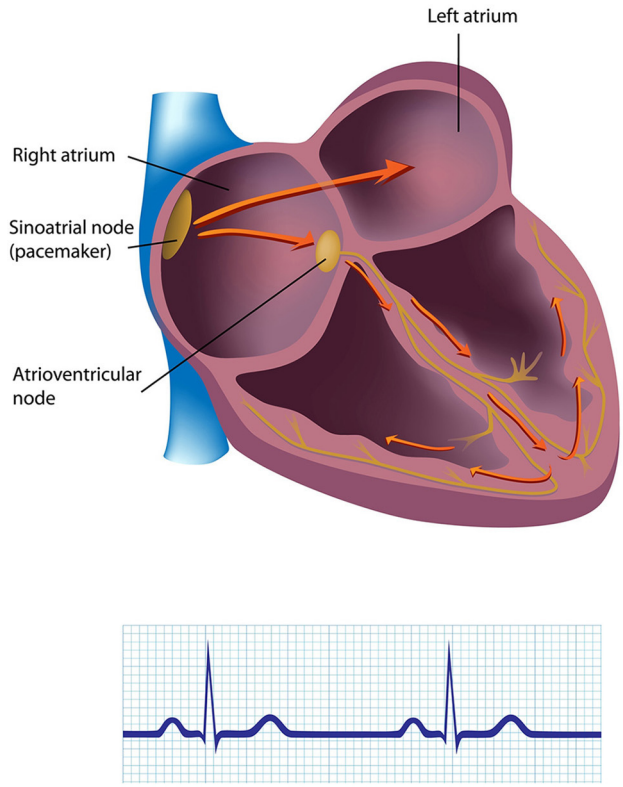

FIGURE 1 | The generation of the electrocardiogram. Credit: Alila Sao Mai/Shutterstock.com.

node's intrinsic firing rate of about 60–100 action potentials per minute usually prevents slower parts of the conduction system and myocardium (heart muscle) from generating competing potentials. The AV node can replace an injured or diseased SA node as pacemaker and spontaneously depolarizes 40–60 times per minute. The SA node generates an electrical impulse that travels through the atria to the AV node in about 0.03 s and causes the AV node to fire (**Figure 2**). The P wave of the ECG is produced as muscle cells in the atria depolarize and culminates in contraction of the atria (atrial systole).

The signal rapidly spreads through the AV bundle reaching the top of the septum. These fibers descend down both sides of the septum as the right and left bundle branches and conduct the action potential over the ventricles about 0.2 s after the appearance of the P wave. Conduction myofibers, which extend from the bundle branches into the myocardium, depolarize contractile fibers in the ventricles (lower chambers), resulting in the QRS complex followed by the S-T segment. Ventricular contraction (ventricular systole) occurs after the onset of the QRS complex and extends into the S-T segment. The repolarization of ventricular myocardium generates the T wave about 0.4 s following the P wave. The ventricles relax (ventricular diastole) 0.6 s after the P wave begins (Tortora and Derrickson, 2014).

REGULATION OF THE HEART

In a healthy organism, there is a dynamic relative balance between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). PNS activity predominates at rest, resulting in an average HR of 75 beats per minute (bpm). This is significantly slower than the SA node's intrinsic rate, which decreases with age from an average 107 bpm at 20 years to 90 bpm at 50 years (Opthof, 2000). The parasympathetic branch can slow the heart to 20 or 30 bpm or briefly stop it (Tortora and Derrickson, 2014). This illustrates the response called accentuated antagonism (Olshansky et al., 2008). Parasympathetic nerves exert their effects more rapidly (<1 s) than sympathetic nerves (>5 s; Nunan et al., 2010).

A major cardiovascular center, located in the medulla of the brainstem, integrates sensory information from proprioceptors (limb position), chemoreceptors (blood chemistry), and mechanoreceptors (also called baroreceptors) from the heart and information from the cerebral cortex and limbic system. The cardiovascular center responds to sensory and higher brain center input by adjusting heart rate via shifts in the relative balance between sympathetic and parasympathetic outflow (Shaffer and Venner, 2013).

In a healthy individual, the HR estimated at any given time represents the net effect of the neural output of the parasympathetic (vagus) nerves, which slow HR, and the sympathetic nerves, which accelerate it. At rest, both sympathetic and parasympathetic nerves are tonically active with the vagal effects dominant. Therefore, HR reflects the relative activity of the sympathetic and parasympathetic systems; with the more important question being, is the relative balance (HR) appropriate for the context the person is engaged in at any given moment? In other words, is HR higher during the daytime and when dealing with challenging tasks, and lower at night, during sleep or when not engaged in challenging duties or activities?

The most obvious effect of vagal activity is to slow or even stop the heart. The vagus nerves are the primary nerves for the parasympathetic system and innervate the intrinsic cardiac nervous system and project to the SA node, AV node, and atrial cardiac muscle. Increased efferent activity in these nerves triggers acetylcholine release and binding to muscarinic (mainly M2) receptors. This decreases the rate of spontaneous depolarization in the SA and AV nodes, slowing HR. Because there is sparse vagal innervation of the ventricles, vagal activity minimally affects ventricular contractility.

The response time of the sinus node is very short and the effect of a single efferent vagal impulse depends on the phase of the cardiac cycle at which it is received. Thus, vagal stimulation results in an immediate response that typically occurs within the cardiac cycle in which it occurs and affects only one or two heartbeats after its onset. After cessation of vagal stimulation, HR rapidly returns to its previous level. An increase in HR can also be achieved by reduced vagal activity or vagal block. Thus, sudden changes in HR (up or down) between one beat and the next are parasympathetically mediated (Hainsworth, 1995).

An increase in sympathetic activity is the principal method used to increase HR above the intrinsic level generated by the SA node. Following the onset of sympathetic stimulation, there is

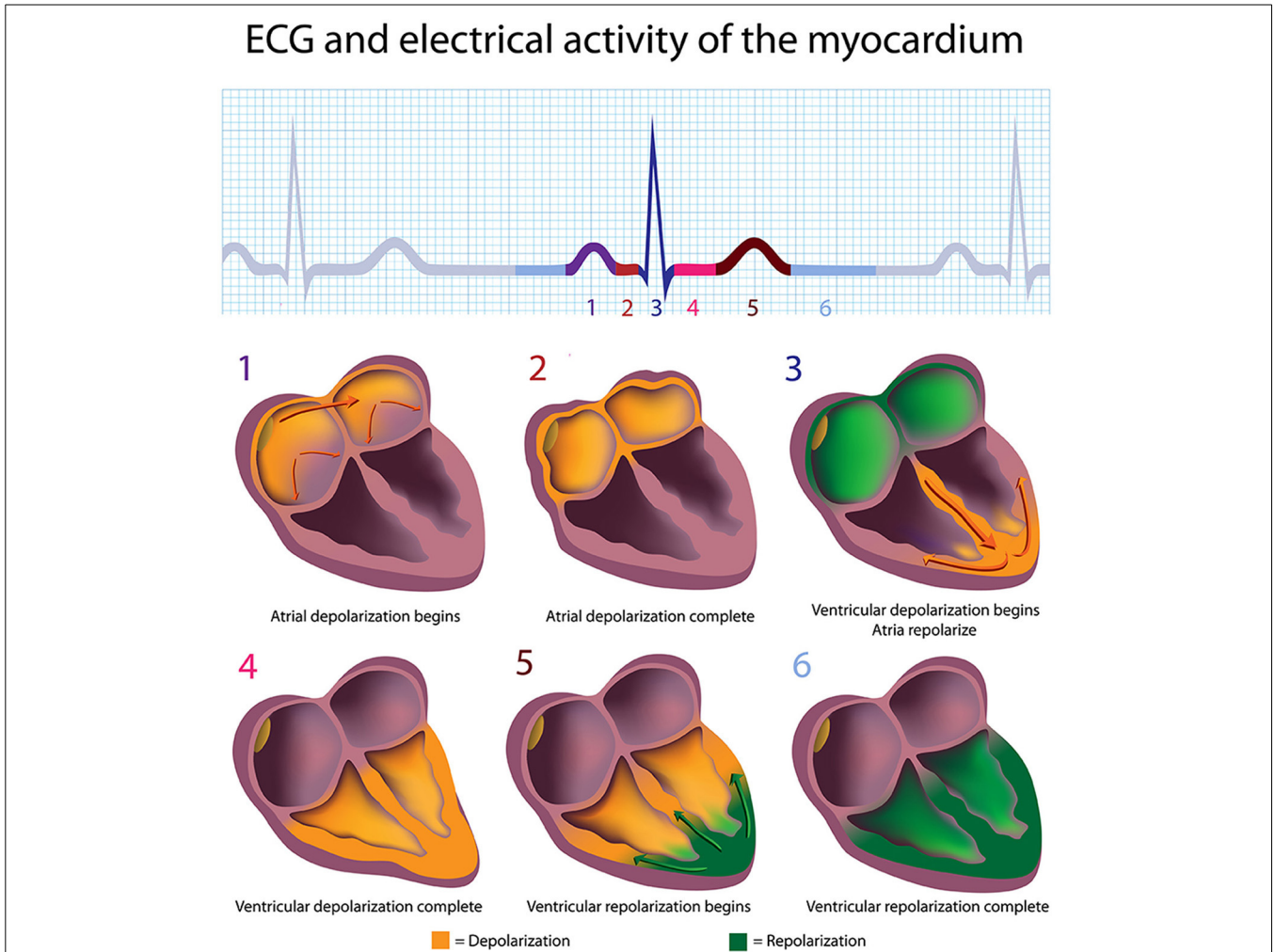

FIGURE 2 | The depolarization and repolarization of the heart. Credit: Alila Sao Mai/Shutterstock.com.

a delay of up to 5 s before the stimulation induces a progressive increase in HR, which reaches a steady level in 20–30 s if the stimulus is continuous (Hainsworth, 1995). The slowness of the response to sympathetic stimulation is in direct contrast to vagal stimulation, which is almost instantaneous. However, the effect on HR is longer lasting and even a short stimulus can affect HR for 5–10 s. Efferent sympathetic nerves target the SA node and AV node via the intrinsic cardiac nervous system, and the bulk of the myocardium (heart muscle). Action potentials conducted by these motor neurons trigger norepinephrine (NE) and epinephrine (E) release and binding to beta-adrenergic (β1) receptors located on cardiac muscle fibers. This speeds up spontaneous depolarization in the SA and AV nodes, increases HR, and strengthens the contractility of the atria and ventricles. In failing hearts, the number of β1 receptors is reduced and their cardiac muscle contraction in response to NE and E binding is weakened (Ogletree-Hughes et al., 2001).

AFFERENT MODULATION OF CARDIAC AND BRAIN ACTIVITY

The field of *neurocardiology* explores the anatomy and functions of the connections between the heart and brain (Davis and Natelson, 1993; Armour, 2003) and represents the intersection of neurology and cardiology. While efferent (descending) regulation of the heart by the autonomic nervous system (ANS) is well known, newer data have suggested a more complex modulation of heart function by the intrinsic cardiac nervous system (Kukanova and Mravec, 2006). These intracardiac neurons (sensory, interconnecting, afferent, and motor neurons) (Verkerk et al., 2012) can operate independently and their network is sufficiently extensive to be characterized as its own "little brain" on the mammalian heart (Armour, 2008, p. 165). The afferent (ascending) nerves play a critical role in physiological regulation and affect the heart's rhythm. Efferent sympathetic and parasympathetic activity are integrated with the activity occurring in the heart's intrinsic nervous system, including the afferent signals occurring from the mechanosensory and chemosensory neurons (**Figure 3**).

Interestingly, the majority of fibers in the vagus nerve (approximately 85–90%) are afferents, and signals are sent to the brain via cardiovascular afferents to a greater extent than by any other major organ (Cameron, 2002). Mechanical and hormonal information is transduced into neurological impulses by sensory neurons in the heart before being processed in the intrinsic

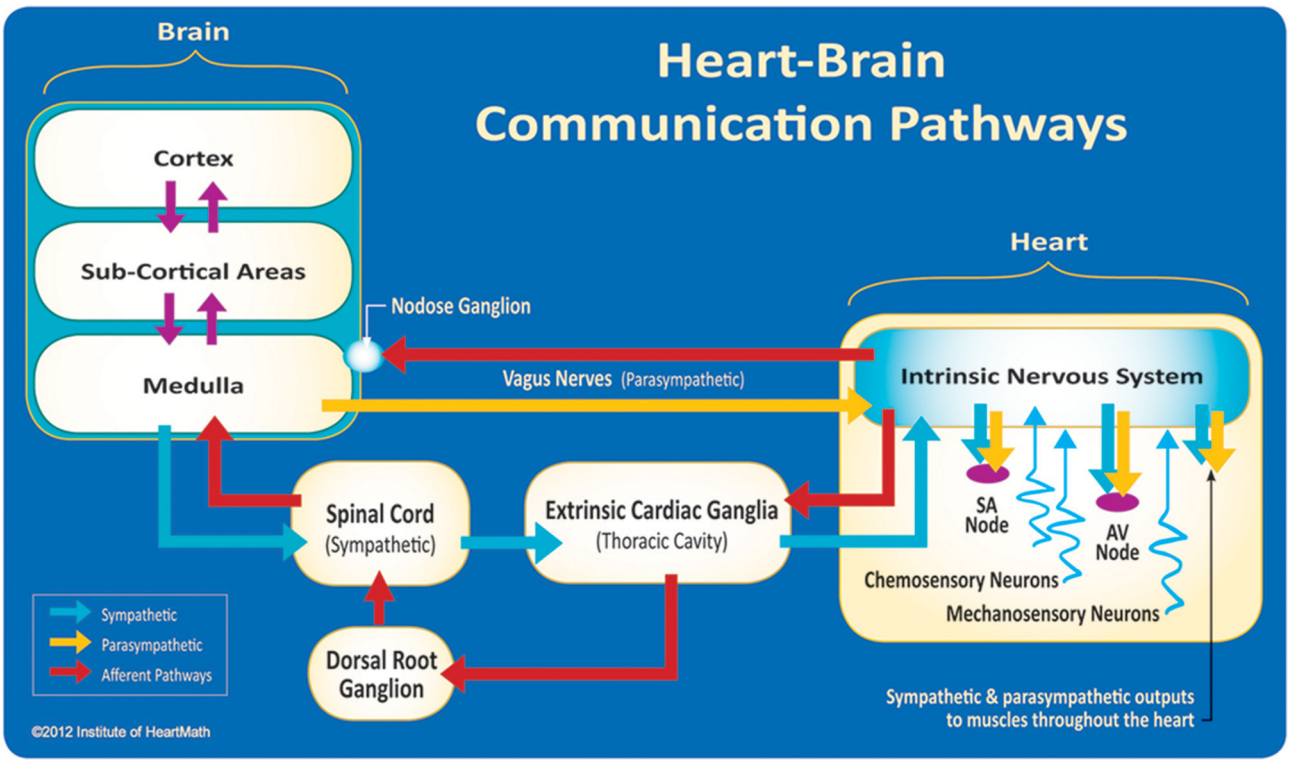

FIGURE 3 | The neural communication pathways interacting between the heart and the brain are responsible for the generation of HRV. The intrinsic cardiac nervous system integrates information from the extrinsic nervous system and from the sensory neurites within the heart. The extrinsic cardiac ganglia located in the thoracic cavity have connections to the lungs and esophagus and are indirectly connected via the spinal cord to many other organs such as the skin and arteries. The vagus nerve (parasympathetic) primarily consists of afferent (flowing to the brain) fibers which connect to the medulla, after passing through the nodose ganglion. Credit: Institute of HeartMath.

nervous system. These impulses then travel to the brain via afferent pathways in the spinal column and vagus nerve (McCraty, 2011).

Short-term regulation of BP is accomplished by a complex network of pressure-sensitive baroreceptors or mechanosensitive neurons which are located throughout the heart and in the aortic arch. Since BP regulation is a central role of the cardiovascular system, the factors that alter BP also affect fluctuations in HR. Intrinsic cardiac afferent sensory neurons (**Figures 4**, **5**) transduce and distribute mechanical and chemical information regarding the heart (Cheng et al., 1997) to the intrinsic cardiac nervous system (Ardell et al., 1991). The afferent impulses from the mechanosensitive neurons travel via the glossopharyngeal and vagal nerves to the nucleus of the solitary tract (NST), which connects with the other regulatory centers in the medulla to modulate SNS outflow to the heart and the blood vessels. There is also some modulation of parasympathetic outflow to the heart via connections to the dorsal vagal complex. Thus, mechanosensitive neurons affect HR, vasoconstriction, venoconstriction, and cardiac contractility in order to regulate BP (Hainsworth, 1995). This input from the heart can also modulate and impact hormonal release (Randall et al., 1981).

The heart not only functions as an intricate information processing and encoding center (Armour and Kember, 2004), but is also an endocrine gland that can produce and secrete its own hormones and neurotransmitters (Cantin and Genest, 1985, 1986; Mukoyama et al., 1991; Huang et al., 1996). For instance, atrial myocytes can secrete atrial natriuretic peptide (ANP), a hormone that promotes salt and water excretion, to lower BP and

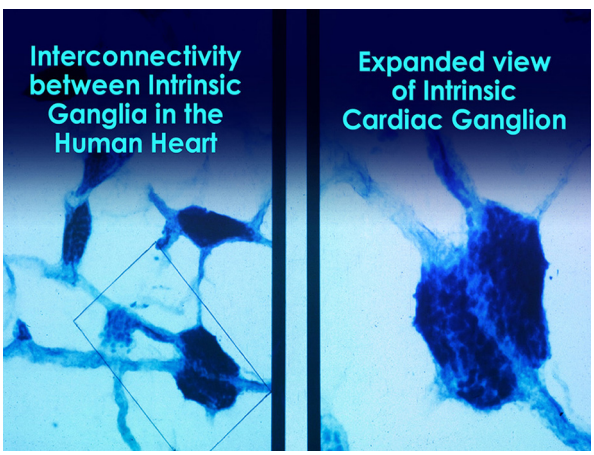

FIGURE 4 | Microscopic image of interconnected intrinsic cardiac ganglia in the human heart. The thin, light blue structures are multiple axons that connect the ganglia. Credit: Dr. Andrew Armour and the Institute of HeartMath.

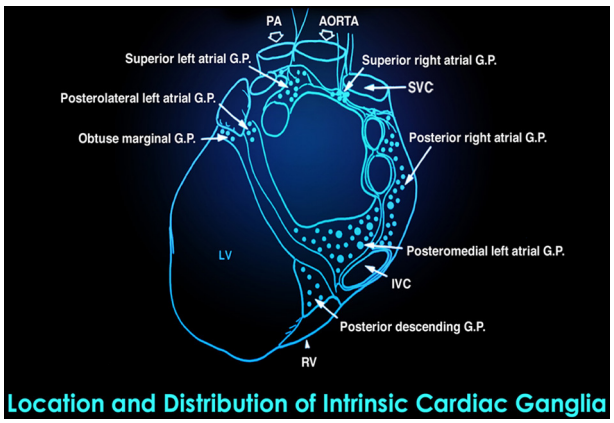

FIGURE 5 | This drawing shows the location and distribution of intrinsic cardiac ganglia which are interconnected and form the "heart brain." Note how they are distributed around the orifices of the major vessels. Credit: Dr. Andrew Armour and the Institute of HeartMath.

produce vasodilation (Dietz, 2005). Additionally, intrinsic cardiac adrenergic cells can synthesize and secrete catecholamines such as dopamine, NE, and E (Huang et al., 1996) in addition to high concentrations of oxytocin (Gutkowska et al., 2000).

Research insights from the field of neurocardiology have confirmed that the neural interactions between the heart and brain are more complex than thought in the past. This research has shown that complex patterns of cardiovascular afferent activity occur across time scales from milliseconds to minutes (Armour and Kember, 2004). This work has also shown that the intrinsic cardiac nervous system has both short-term and long-term memory functions, which can influence HRV and afferent activity related to pressure, rhythm, and rate, as well as afferent activity associated with hormonal factors (Armour, 2003; Armour and Kember, 2004; Ardell et al., 2009).

John and Beatrice Lacey conducted heart–brain interaction studies and were the first to suggest a causal role of the heart in modulating cognitive functions such as sensory-motor and perceptual performance (Lacey, 1967; Lacey and Lacey, 1970, 1974). They suggested that cortical functions are modulated via afferent input from pressure-sensitive neurons in the heart, carotid arteries, and aortic arch (Lacey, 1967). Their research focused on activity occurring within a single cardiac cycle, and they confirmed that cardiovascular activity influences perception and cognitive performance. Research by Velden and Wölk found that cognitive performance fluctuates at a rhythm around 10 Hz. They also demonstrated that the modulation of cortical function via the heart's influence is due to afferent inputs on the neurons in the thalamus which globally synchronizes cortical activity (Velden and Wölk, 1987; Wölk and Velden, 1989). An important aspect of their work was the finding that it is the "pattern and stability" (the rhythm) of the heart's afferent inputs, rather than the number of neural bursts within the cardiac cycle, that are important in modulating thalamic activity, which in turn has global effects on brain function.

This growing body of research indicates that afferent information processed by this intrinsic cardiac nervous system (Armour, 1991) can influence activity in the frontocortical areas (Lane et al., 2001; McCraty et al., 2004) and motor cortex (Svensson and Thorén, 1979), affecting psychological factors such as attention level, motivation (Schandry and Montoya, 1996), perceptual sensitivity (Montoya et al., 1993), and emotional processing (Zhang et al., 1986). Intrinsic cardiac afferent neurons project to nodose and dorsal root ganglia, the brainstem (dorsal root ganglia first project to the spinal cord), the hypothalamus, thalamus, or amygdala, and then to the cerebral cortex (Kukanova and Mravec, 2006; McCraty et al., 2009).

HEARTBEAT EVOKED POTENTIALS

Heartbeat evoked potentials (HEPs) can be used to identify the specific pathways and influence of afferent input from the heart to the brain. HEPs are segments of electroencephalogram (EEG) that are synchronized to the heartbeat. The ECG R-wave is used as a timing source for signal averaging, resulting in waveforms known as HEPs. Changes in these evoked potentials associated with the heart's afferent neurological input to the brain are detectable between 50 and 550 ms after each heartbeat. There is a replicable and complex distribution of HEPs across the scalp. Researchers can use the location and timing of the various components of HEP waveforms, as well as changes in their amplitudes and morphology, to track the flow and timing of cardiovascular afferent information throughout the brain (Schandry and Montoya, 1996).

MacKinnon et al. (2013) reported that HRV influences the amplitude of heartbeat evoked potentials (HEP N250s). In this specific context, self-induction of either negative or positive emotion conditions by recalling past events reduced HRV and N250 amplitude. In contrast, resonance frequency breathing (breathing at a rate that maximizes HRV amplitude) increased HRV and HRV coherence (auto-coherence and sinusoidal pattern) above baseline and increased N250 amplitude. The authors speculated that resonance frequency breathing reduces interference with afferent signal transmission from the heart to the cerebral cortex.

WHAT IS HEART RATE VARIABILITY?

Ever since Walter Cannon introduced the concept of homeostasis in 1929, the study of physiology has been based on the principle that all cells, tissues, and organs maintain a static or constant "steady-state" condition in their internal environment. However, with the introduction of signal processing techniques that can acquire continuous time series data from physiologic processes such as heart rate, BP, and nerve activity, it has become abundantly apparent that biological processes vary in a complex and nonlinear way, even during "steady-state" conditions. These observations have led to the understanding that healthy physiologic function is a result of continuous, dynamic interactions between multiple neural, hormonal, and mechanical control systems at both local and central levels. For example, we now know that the normal resting sinus rhythm of the heart is highly irregular during steady-state conditions rather than being monotonously regular, which was the widespread notion for many years. *A healthy heart is not a metronome.*

With the ability to measure the ECG in 1895, and the later development of modern signal processing which first emerged

in the 1960s and 1970s, the investigation of the heart's complex rhythm rapidly exploded. The irregular behavior of the heartbeat is readily apparent when heart rate is examined on a beat-to-beat basis, but is overlooked when a mean value over time is calculated. These fluctuations in heart rate result from complex, non-linear interactions between a number of different physiological systems (Reyes Del Paso et al., 2013).

The interactions between autonomic neural activity, BP, and respiratory control systems produce short-term rhythms in HRV measurements (Hirsch and Bishop, 1981, 1996; McCraty et al., 2009) (**Figure 6**). The most common form for observing these changes is the heart rate tachogram, a plot of a sequence of time intervals between R waves. Efferent sympathetic and parasympathetic activity is integrated in and with the activity occurring in the heart's intrinsic nervous system, including the afferent signals occurring from the mechanosensitive and chemosensory neurons, all of which contribute to beat-to-beat changes. HRV is thus considered a measure of neurocardiac function that reflects heart–brain interactions and ANS dynamics.

Circadian rhythms, core body temperature, metabolism, hormones, and intrinsic rhythms generated by the heart all contribute to lower frequency rhythms [e.g., very-low-frequency (VLF) and ultra-low-frequency (ULF)] that extend below 0.04 Hz. Due to their long time periods, researchers use 24-h HRV recordings to provide comprehensive assessment of their fluctuations (Kleiger et al., 2005). In concert, these multiple influences create a dynamic physiological control system that is never truly at rest and is certainly never static. In healthy individuals, it remains responsive and resilient, primed and ready to react when needed.

HOW IS HRV DETECTED?

Clinicians use ECG or photoplethysmograph (PPG) sensors to detect the interbeat interval (IBI). While the ECG method had been considered to be more accurate than the PPG method because early software algorithms could more easily detect the sharp upward spike of the R wave than the curved peak of the blood volume pulse signal, newer algorithms have improved peak detection from the pulse wave. The ECG method should be used when recordings are contaminated by frequent abnormal beats (e.g., premature ventricular contractions), since the ECG's morphology and timing properties allow software algorithms to discriminate normal sinus beats from ectopic beats (Mateo et al., 2011).

All HRV assessments are calculated from an IBI file. However, in some cases there can be differences in the IBI files derived from ECG and PPG data. Several studies have shown that when the recordings are taken during a resting state (sitting quietly as done in most resting baseline recordings), the IBI values between ECG and PPG are highly correlated (Giardino et al., 2002; Schafer and Vagedes, 2013). However, during ambulatory monitoring or when a person experiences a stressor strong enough to activate the sympathetic system, there can be significant differences due

FIGURE 6 | Display of short-term HRV activity. Credit: Institute of HeartMath.

to changes in pulse transit time (the time it takes the BP wave to propagate from the heart to the periphery), which result from changes in the elasticity of the arteries. When arteries stiffen due to sympathetic activation, the BP wave travels faster. The accuracy of HRV measurements is primarily determined by the sampling rate of the data acquisition system. Kuusela (2013) recommends a sampling rate of 200 Hz unless overall variability among RR intervals is unusually low, as in case of heart failure. In contrast, Berntson et al. (2007) recommend a minimum sampling rate of 500–1000 Hz. However, for many applications, like HRV biofeedback (HRVB), a sampling rate of 126 Hz may be adequate.

There are many ECG configurations, with varying numbers of leads, used for ambulatory and stationary monitoring. For example, a standard three-lead ECG chest placement locates active and reference electrodes over the right and left coracoid processes, respectively, and a second active electrode over the xiphoid process (**Figure 7**).

WHY IS HRV IMPORTANT?

An optimal level of variability within an organism's key regulatory systems is critical to the inherent flexibility and adaptability or resilience that epitomizes healthy function and well-being. While too much instability is detrimental to efficient physiological functioning and energy utilization, too little variation indicates depletion or pathology.

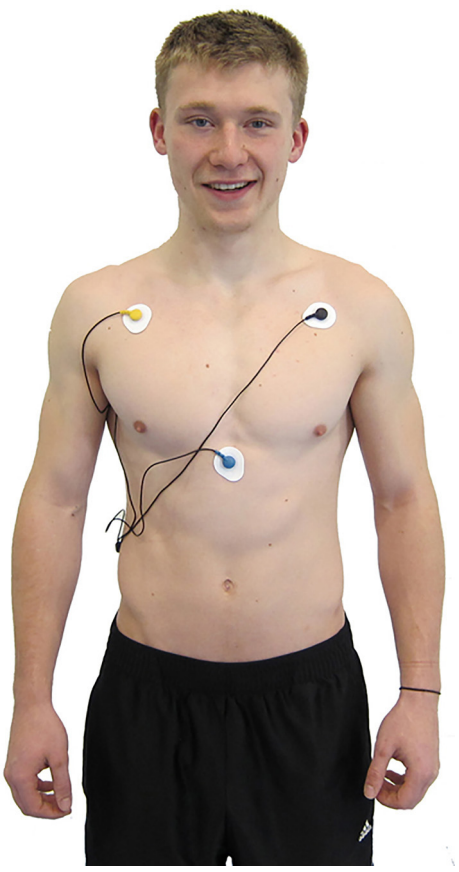

FIGURE 7 | ECG electrode placement. Credit: Truman State University Center for Applied Psychophysiology.

HRV IS A MARKER FOR DISEASE AND ADAPTABILITY

The clinical importance of HRV was noted as far back as 1965 when it was found that fetal distress is preceded by alterations in HRV before any changes occur in heart rate itself (Hon and Lee, 1963). In the 1970s, HRV analysis was shown to predict autonomic neuropathy in diabetic patients before the onset of symptoms (Ewing et al., 1976). Low HRV has since been confirmed as a strong, independent predictor of future health problems and as a correlate of all-cause mortality (Tsuji et al., 1994; Dekker et al., 1997). Reduced HRV is also observed in patients with autonomic dysfunction, including anxiety, depression, asthma, and sudden infant death (Kazuma et al., 1997; Carney et al., 2001; Agelink et al., 2002; Giardino et al., 2004; Lehrer et al., 2004; Cohen and Benjamin, 2006).

Based on indirect evidence, reduced HRV may correlate with disease and mortality because it reflects reduced regulatory capacity, which is the ability to adaptively respond to challenges like exercise or stressors. For example, patients with low overall HRV demonstrated reduced cardiac regulatory capacity and an increased likelihood of prior myocardial infarction (MI). In this sample, a measure of cardiac autonomic balance did not predict previous MIs (Berntson et al., 2008).

Patient age may mediate the relationship between reduced HRV and regulatory capacity. HRV declines with age (Umetani et al., 1998) and aging often involves nervous system changes, like loss of neurons in the brain and spinal cord, which may degrade signal transmission (Jäncke et al., 2014) and reduce regulatory capacity.

Reduced regulatory capacity may contribute to functional gastrointestinal disorders, inflammation, and hypertension. While patients with functional gastrointestinal disorders often have reduced HRV (Gevirtz, 2013), HRVB has increased vagal tone and improved symptom ratings in these patients (Sowder et al., 2010).

The PNS may help regulate inflammatory responses via a cholinergic anti-inflammatory system (Tracey, 2007). While the experimental administration of lipopolysaccharide to healthy volunteers decreases HRV and vagal tone (Jan et al., 2009), HRVB training has reduced the symptoms produced by this intervention (Lehrer et al., 2010).

Hypertensive patients often present with reduced baroreflexes and HRV (Schroeder et al., 2003). HRVB can increase baroreflex gain, which is the amplitude of HR changes, and HRV, and decrease BP (Lehrer, 2013). Several randomized-controlled studies have documented BP reductions in hypertensive patients who received HRVB (Elliot et al., 2004; Reineke, 2008).

HRV is also an indicator of psychological resiliency and behavioral flexibility, reflecting the individual's capacity to adapt effectively to changing social or environmental demands (Beauchaine, 2001; Berntson et al., 2008). More recently, several studies have shown an association between higher levels of resting HRV and performance on cognitive performance tasks requiring the use of executive functions (Thayer et al., 2009) and that HRV, especially HRV-coherence, can be increased in order to produce improvements in cognitive function as well as a wide range of clinical

outcomes, including reduced health care costs (Lehrer et al., 2003, 2008; McCraty et al., 2003; Bedell and Kaszkin-Bettag, 2010; Alabdulgader, 2012).

HRV ANALYSIS METHODS

It was recognized as far back as 1979 that nomenclature, analytical methods, and definitions of HRV measures required standardization. Therefore, an International Task Force consisting of members from the European Society of Cardiology and the North American Society for Pacing and Electrophysiology was established. Their report was published in Task Force (1996).

HRV can be assessed with various analytical approaches, although the most commonly used are frequency domain or power spectral density (PSD) analysis and time domain analysis. In both methods, the time intervals between each successive normal QRS complex are first determined. All abnormal beats not generated by sinus node depolarizations are eliminated from the record.

Analogous to the EEG, we can use power spectral analysis to separate HRV into its component rhythms that operate within different frequency ranges (**Figure 8**). PSD analysis provides information of how power is distributed (the variance and amplitude of a given rhythm) as a function of frequency (the time period of a given rhythm). The main advantages of spectral analysis over the time domain measures are that it supplies both frequency and amplitude information about the specific rhythms that exist in the HRV waveform, providing a means to quantify the various oscillations over any given period in the HRV recording. The values are expressed as the PSD, which is the area under the curve (peak) in a given segment of the spectrum. The power or height of the peak at any given frequency indicates the amplitude and stability of the rhythm. The frequency reflects the period of time over which the rhythm occurs. For example, a 0.1 Hz frequency has a period of 10 s. In order to understand how power spectral analysis distinguishes the various underlying physiological mechanisms that are reflected in the heart's rhythm, a brief review of these underlying physiological mechanisms follows.

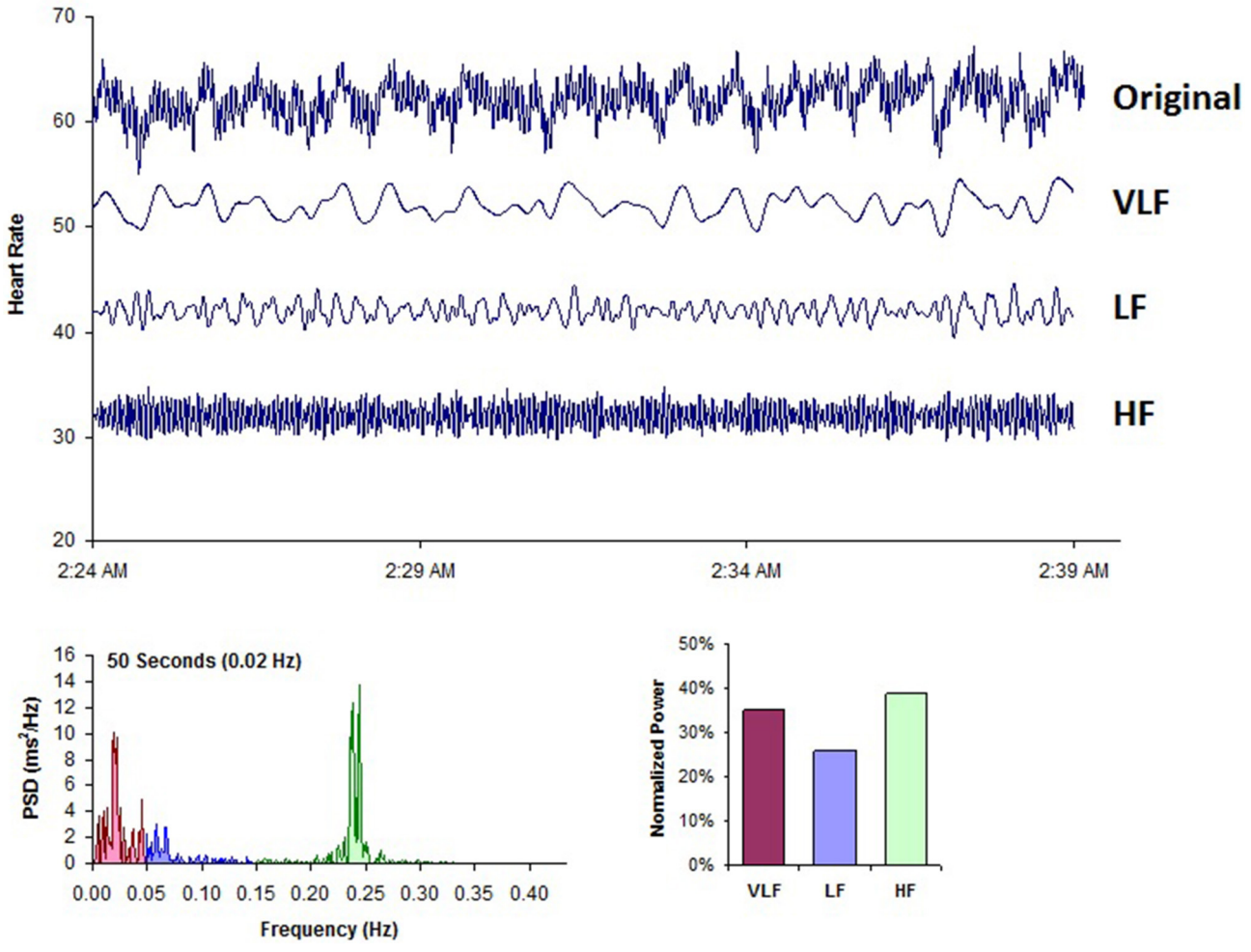

FIGURE 8 | This figure shows a typical HRV recording over a 15-min period during resting conditions in a healthy individual. The top trace shows the original HRV waveform. Filtering techniques were used to separate the original waveform into VLF, LF, and HF bands as shown in the lower traces. The bottom of the figure shows the power spectra (left) and the percentage of power (right) in each band. Credit: Institute of HeartMath.

Figure 8 shows a typical example of an HRV recoding from an adult human at rest. Using filtering techniques, the high-frequency (HF), low-frequency (LF), and VLF bands have been extracted from the original HRV signal and spectral power has been calculated for each band.

SOURCES OF HRV

The Task Force report (1996) divided heart rhythm oscillations into four primary frequency bands. These included the HF, LF, VLF, and ULF bands. The Task Force report also stated that the analysis should be done on 5-min segments, although other recording periods are often used. When other recording lengths are analyzed and reported, the length of the recording should be reported since this has large effects on both HRV frequency and time domain values.

HIGH-FREQUENCY BAND

The HF spectrum is the power in each of the 288 5-min segments (monitored during a 24-h period) in the range from 0.15 to 0.4 Hz. This band reflects parasympathetic or vagal activity and is frequently called the respiratory band because it corresponds to the HR variations related to the respiratory cycle. These HR changes are known as respiratory sinus arrhythmia (RSA). Heart rate accelerates during inspiration and slows during expiration. During inhalation, the cardiovascular center inhibits vagal outflow resulting in speeding the heart rate. Conversely, during exhalation, it restores vagal outflow resulting in slowing the heart rate via the release of acetylcholine (Eckberg and Eckberg, 1982). The magnitude of the oscillation is variable, but can usually be exaggerated by slow, deep breathing.

The modulation of vagal tone helps maintain the dynamic autonomic regulation important for cardiovascular health. Deficient vagal inhibition is implicated in increased morbidity (Thayer et al., 2010). The mechanism linking the variability of HR to respiration is complex and involves both central and reflex interactions. A large number of studies have shown that total vagal blockade essentially eliminates HF oscillations and reduces the power in the LF range (Pomeranz et al., 1985; Malliani et al., 1991).

Reduced parasympathetic (high frequency) activity has been found in a number of cardiac pathologies and in patients under stress or suffering from panic, anxiety, or worry. Lowered parasympathetic activity may primarily account for reduced HRV in aging (Umetani et al., 1998). In younger healthy individuals, it is not uncommon to see an obvious increase in the HF band at night with a decrease during the day (Lombardi et al., 1996; Otsuka et al., 1997).

LOW-FREQUENCY BAND

The LF band ranges between 0.04 and 0.15 Hz. This region was previously called the "baroreceptor range" or "mid-frequency band" by many researchers, since it primarily reflects baroreceptor activity while at rest (Malliani, 1995). The vagus nerves are a major conduit though which afferent neurological signals from the heart and other visceral organs are relayed to the brain, including the baroreflex signals (De Lartique, 2014). Baroreceptors are stretch-sensitive mechanoreceptors located in the chambers of the heart and vena cavae, carotid sinuses (which contain the most sensitive mechanoreceptors), and the aortic arch (**Figure 9**). When BP rises, the carotid and aortic tissues are distended, resulting in increased stretch and, therefore, increased baroreceptor activation. At normal resting BPs, many baroreceptors actively report BP information and the baroreflex modulates autonomic activity.

Active baroreceptors generate action potentials ("spikes") more frequently. The greater their stretch or detection of an increased rate of change, the more frequently baroreceptors fire action potentials. Baroreceptor action potentials are relayed to the NST in the medulla, which uses baroreceptor firing frequency to measure BP. Increased activation of the NST inhibits the vasomotor center and stimulates the vagal nuclei. The end-result of baroreceptor activations tuned to pressure increases is inhibition of the SNS and activation of the PNS. By coupling sympathetic inhibition with parasympathetic activation, the baroreflex maximizes BP reduction when BP is detected as too high. Sympathetic inhibition reduces peripheral resistance, while parasympathetic activation depresses HR (reflex bradycardia) and contractility. In a similar manner, sympathetic activation, along with inhibition of vagal outflow, allows the baroreflex to elevate BP. Baroreflex gain is commonly calculated as the beat-to-beat change in HR per unit of change in BP. Decreased baroreflex gain is related to impaired regulatory capacity and aging.

The existence of a cardiovascular system resonance frequency, which is caused by the delay in the feedback loops in the baroreflex system, has been long established (Vaschillo et al., 2011). Lehrer et al. have proposed that each individual's cardiovascular system has a unique resonance frequency, which can be identified by measuring HRV while an individual breathes between 7.5 and 4.5 breaths per minute (Lehrer et al., 2013). When the

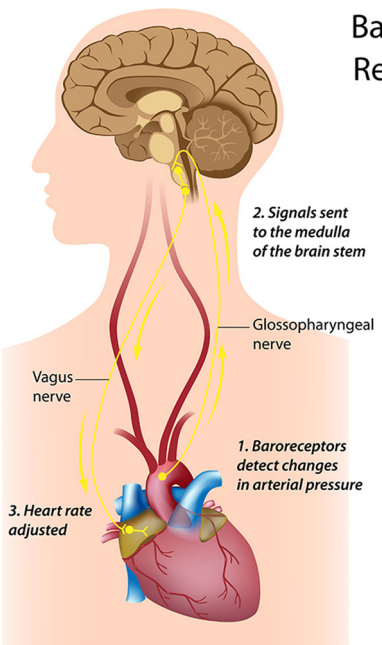

FIGURE 9 | Credit: Alila Sao Mai/Shutterstock.com.

cardiovascular system oscillates at this frequency, there is a distinctive high-amplitude peak in the HRV power spectrum around 0.1 Hz. Most mathematical models show that the resonance frequency of the human cardiovascular system is determined by the feedback loops between the heart and brain (deBoer et al., 1987; Baselli et al., 1994). In humans and many other mammals, the resonance frequency of the system is approximately 0.1 Hz, which is equivalent to a 10-s rhythm.

The sympathetic system 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). During periods of slow respiration rates, vagal activity can easily generate oscillations in the heart rhythms that cross over into the LF band (Ahmed et al., 1982; Tiller et al., 1996; Lehrer et al., 2003). Therefore, respiratory-related efferent vagally-mediated influences are particularly present in the LF band when respiration rates are below 8.5 breaths per minute or 7-s periods (Brown et al., 1993; Tiller et al., 1996) or when an individual sighs or takes a deep breath.

In ambulatory 24-h HRV recordings, it has been suggested that the LF band also reflects sympathetic activity and the LF/HF ratio has been controversially reported as an assessment of the balance between sympathetic and parasympathetic activity (Pagani et al., 1984, 1986). A number of researchers (Tiller et al., 1996; Eckberg, 1997; Porges, 2007; Rahman et al., 2011; Heathers, 2012) have challenged this perspective and have persuasively argued that in resting conditions, the LF band reflects baroreflex activity and not cardiac sympathetic innervation.

The perspective that the LF band reflects sympathetic activity came from observations of 24-h ambulatory recordings where there are frequent sympathetic activations primarily due to physical activity, but also due to emotional stress reactions, which can create oscillations in the heart rhythms that cross over into the lower part of the LF band. In long-term ambulatory recordings, the LF band fairly approximates sympathetic activity when increased sympathetic activity occurs (Axelrod et al., 1987). This will be discussed in more detail in the VLF section. Unfortunately, some authors have assumed that this interpretation was also true of short-term resting recordings and have confused slower breathing-related increases in LF power with sympathetic activity, when in reality it is almost entirely vagally mediated. Remember that the baroreflex is primarily vagally mediated (Keyl et al., 1985).

Porges (2007) suggests that under conditions when participants pace their breathing at 0.1 Hz (10-s rhythm or 6 breaths per minute), which is a component of many HRVB training protocols, the LF band includes the summed influence of both efferent vagal pathways (myelinated and unmyelinated, which reflects total cardiac vagal tone).

AUTONOMIC BALANCE AND THE LF/HF RATIO

The autonomic balance hypothesis assumes that the SNS and PNS competitively regulate SA node firing, where increased SNS activity is paired with decreased PNS activity. While some orthostatic challenges can produce reciprocal changes in SNS activation and vagal withdrawal, psychological stressors can also result in independent changes in SNS or PNS activity. It is now generally accepted that both branches of the ANS can be simultaneously active (Berntson and Cacioppo, 1999). Therefore, the relationship between the SNS and PNS in generating LF power appears to be complex, non-linear, and dependent upon the experimental manipulation employed (Berntson et al., 1997; Billman, 2013).

The ratio of LF to HF power is called the LF/HF ratio. The interpretation of the LF/HF ratio is controversial due to the issues regarding the LF band described above. However, once the mechanisms are understood as well as the importance of the recording context (i.e., ambulatory vs. resting conditions and normal vs. paced breathing), the controversy is resolved. Recall that the power in the LF band can be influenced by vagal, sympathetic, and baroreflex mechanisms depending on the context, whereas HF power is produced by the efferent vagal activity due to respiratory activity. It is often assumed that a low LF/HF ratio reflects greater parasympathetic activity relative to sympathetic activity due to energy conservation and engaging in "tend-and-befriend" behaviors (Taylor, 2006). However, this ratio is often shifted due to reductions in LF power. Therefore, the LF/HR ratio should be interpreted with caution and the mean values of HF and LF power taken into consideration. In contrast, a high LF/HF ratio may indicate higher sympathetic activity relative to parasympathetic activity as can be observed when people engage in meeting a challenge that requires effort and increased SNS activation. Again, the same cautions must be taken into consideration, especially in short-term recordings.

VERY-LOW-FREQUENCY BAND

The VLF band is the power in the HRV power spectrum range between 0.0033 and 0.04 Hz. Although all 24-h clinical measures of HRV reflecting low HRV are linked with increased risk of adverse outcomes, the VLF band has stronger associations with all-cause mortality than the LF and HF bands (Tsuji et al., 1994, 1996; Hadase et al., 2004; Schmidt et al., 2005). Low VLF power has been shown to be associated with arrhythmic death (Bigger et al., 1992) and PTSD (Shah et al., 2013). Additionally, low power in this band has been associated with high inflammation in a number of studies (Carney et al., 2007; Lampert et al., 2008) and has been correlated with low levels of testosterone, while other biochemical markers, such as those mediated by the HPA axis (e.g., cortisol), did not (Theorell et al., 2007).

Historically, the physiological explanation and mechanisms involved in the generation of the VLF component have not been as well defined as the LF and HF components, and this region has been largely ignored. Long-term regulation mechanisms and ANS activity related to thermoregulation, the renin-angiotensin system, and other hormonal factors may contribute to this band (Akselrod et al., 1981; Cerutti et al., 1995; Claydon and Krassioukov, 2008). Recent work by Dr. Andrew Armour has shed new light on the mechanisms underlying the VLF rhythm and suggests that we may have to reconsider both the mechanisms and importance of this band.

Dr. Armour's group has developed the technology to obtain long-term single-neuron recordings from a beating heart, and simultaneously, from extrinsic cardiac neurons (Armour, 2003). **Figure 10** shows the VLF rhythm obtained from an afferent neuron located in the intrinsic cardiac nervous system in a dog heart.

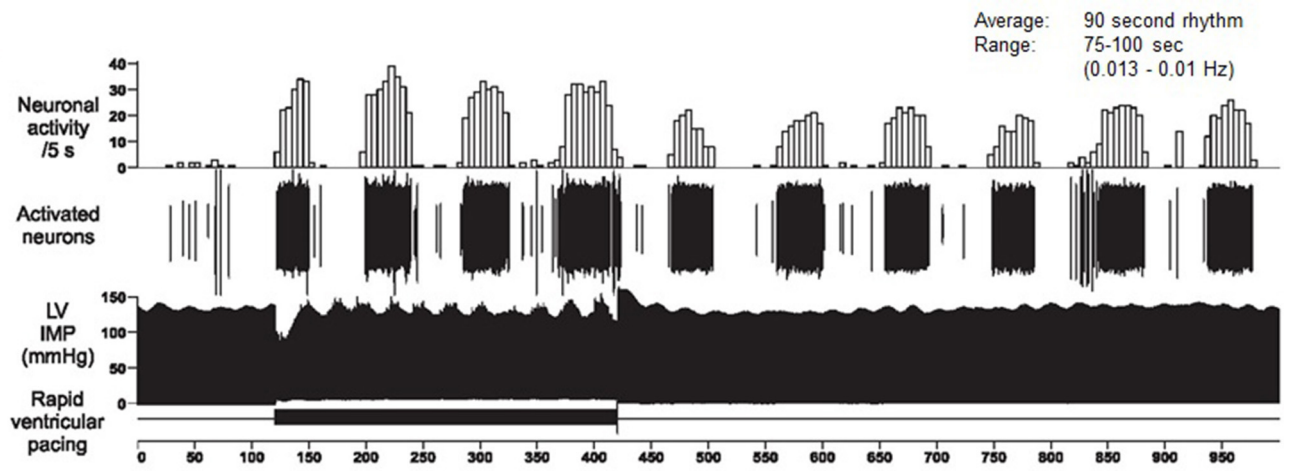

FIGURE 10 | Long-term single-neuron recordings from an afferent neuron in the intrinsic cardiac nervous system in a beating dog heart. The top row shows neural activity, the second row, the actual neural recording, and the third row, the left ventricular pressure. This intrinsic rhythm has an average period of 90 s with a range between 75 and 100 s (0.013–0.01 Hz), which falls within the VLF band. Credit: Dr. Andrew Armour and the Institute of HeartMath.

In this case, the VLF rhythm is generated from intrinsic sources and cannot be explained by sources such as movement. The black area in the bottom of the figure labeled "rapid ventricular pacing" shows the time period where efferent spinal neurons were stimulated. The resulting increase in efferent sympathetic activity (bottom row) clearly elevates the amplitude of the single afferent neuron's intrinsic VLF rhythm (top row).

This work, combined with findings by Kember et al. (2000, 2001), implies that the VLF rhythm is generated by the stimulation of afferent sensory neurons in the heart, which in turn activate 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. Thus, the VLF rhythm is produced by the heart itself and is an intrinsic rhythm that appears to be fundamental to health and well-being. Dr. Armour has observed that when the amplitude of the VLF rhythm at the neural level is diminished, an animal subject is in danger and will expire shortly if they proceed with the research procedures (personal communication with McCraty). Sympathetic blockade does not affect VLF power and VLF activity is seen in tetraplegics, whose SNS innervation of the heart and lungs is disrupted (Task Force, 1996; Berntson et al., 1997). These findings further support a cardiac origin of the VLF rhythm.

In healthy individuals, there is an increase in VLF power that occurs during the night and peaks before waking (Huikuri et al., 1994; Singh et al., 2003). This increase in autonomic activity may correlate with the morning cortisol peak.

In summary, experimental evidence suggests that the VLF rhythm is intrinsically generated by the heart and that the amplitude and frequency of these oscillations are modulated by efferent sympathetic activity. Normal VLF power appears to indicate healthy function, and increases in resting VLF power may reflect increased sympathetic activity. The modulation of the frequency of this rhythm due to physical activity (Bernardi et al., 1996), stress responses, and other factors that increase efferent sympathetic activation can cause it to cross over into the lower region of the LF band during ambulatory monitoring or during short-term recordings when there is a significant stressor.

ULTRA-LOW-FREQUENCY BAND

The ULF band falls below 0.0033 Hz (333 s or 5.6 min). Oscillations or events in the heart rhythm with a period of 5 min or greater are reflected in this band and it can only be assessed with 24-h and longer recordings (Kleiger et al., 2005). The circadian oscillation in heart rate is the primary source of the ULF power, although other very slow-acting regulatory processes, such as core body temperature regulation, metabolism, and the renin-angiotensin system likely add to the power in this band (Bonaduce et al., 1994; Task Force, 1996). Different psychiatric disorders show distinct circadian patterns in 24-h heart rates, particularly during sleep (Stampfer, 1998; Stampfer and Dimmitt, 2013).

The Task Force report (1996) stated that analysis of 24-h recordings should divide the record into 5-min segments and that HRV analysis should be performed on the individual segments prior to the calculation of mean values. This effectively filters out any oscillations with periods longer than 5 min. However, as shown in **Figure 11**, when spectral analysis is applied to entire 24-h records, several lower frequency rhythms are easily detected in healthy individuals. At the present time, the clinical relevance of these lower frequency rhythms is unknown, largely due to the Task Force guidelines that eliminate their presence from most analysis procedures.

TIME DOMAIN MEASUREMENTS OF HRV

Time domain measures are the simplest to calculate and include the mean normal-to-normal (NN) intervals during the entire recording and other statistical measures such as the standard deviation between NN intervals (SDNN). However, time domain measures do not provide a means to adequately quantify autonomic dynamics or determine the rhythmic or oscillatory activity generated by the different physiological control systems.

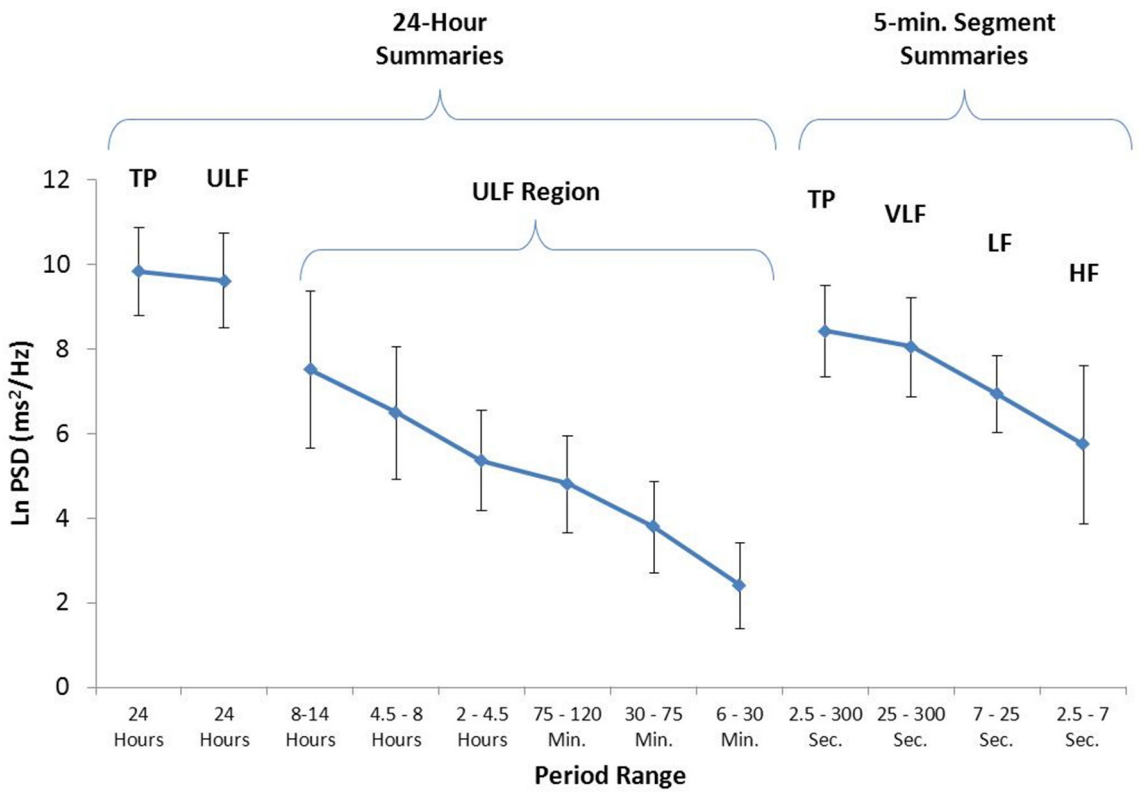

FIGURE 11 | This figure shows the power in the various frequency bands for 24-h HRV and 95% confidence intervals for each of the bands. The left side of the figure reveals a number of slower rhythms that make up the ULF band. The analysis was conducted using the healthy sample described in Umetani et al. (1998). The right side of the figure shows an analysis of the same data performed on 5-min segments as is traditionally done. Credit: Institute of HeartMath.

Since they are always calculated the same way, data collected by different researchers are comparable, but only if the recording lengths are exactly the same and the data are collected under the same conditions.

Time domain indices quantify the amount of variance in the IBI using statistical measures. For 24-h recordings, the three most important time domain measures are the SDNN, the SDNN index, and the RMSSD. For short-term assessments, the SDNN, RMSSD, pNN50, and HR Max – HR Min are most commonly reported.

SDNN

The SDNN is the standard deviation of the normal (NN) sinus-initiated IBI measured in milliseconds. This measure reflects the ebb and flow of all the factors that contribute to heart rate variability (HRV). In 24-h recordings, the SDNN is highly correlated with ULF and total power (Umetani et al., 1998). In short-term resting recordings, the primary source of the variation is parasympathetically-mediated RSA, especially with slow, paced breathing protocols.

SDNN values are highly correlated with the lower frequency rhythms discussed earlier (**Table 1**). Low age-adjusted values predict both morbidity and mortality. Classification within a higher SDNN category is associated with a higher probability of survival. For example, patients with moderate SDNN values, 50–100 ms, have a 400% lower risk of mortality than those with low values, 0–50 ms, in 24-h recordings (Kleiger et al., 1987).

SDANN

The SDANN is the standard deviation of the average NN intervals (mean heart rate) for each of the 5-min segments during a 24-h recording. Like the SDNN, it is measured and reported in milliseconds. This index is correlated with the SDNN and is generally considered redundant.

SDNN INDEX

The SDNN index 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 SDNN Index is the average of these 288 values. The SDNN index is believed to primarily measure

Table 1 | Correlations between time and frequency domain measures in 24-h recordings.

	HR (ms)	N-D delta	SDNN	Ln total power	Ln ULF	SDANN	SDNN index	Ln 5-min total power	Ln 5-min VLF	Ln 5-min LF	Ln 5-min HF	Ln RMSSD	Ln LF/HF
HR (ms)	1												
N-D delta	0.29	1											
SDNN	0.61	0.66	1										
Ln total power	0.55	0.66	0.98	1									
Ln ULF	0.47	0.67	0.95	0.99	1								
SDANN	0.47	0.70	0.96	0.97	0.98	1							
SDNN index	0.72	0.43	0.79	0.73	0.62	0.62	1						
Ln 5-min total power	0.71	0.40	0.78	0.71	0.60	0.61	0.99	1					
Ln 5-min VLF	0.74	0.49	0.83	0.80	0.70	0.68	0.96	0.93	1				
Ln 5-min LF	0.57	0.27	0.63	0.61	0.49	0.48	0.87	0.84	0.81	1			
Ln 5-min HF	0.36	0.38	0.56	0.54	0.44	0.44	0.79	0.75	0.68	0.75	1		
Ln RMSSD	0.54	0.41	0.68	0.64	0.54	0.54	0.90	0.86	0.80	0.82	0.95	1	
Ln LF/HF	−0.02	−0.31	−0.27	−0.24	−0.20	−0.21	−0.37	−0.34	−0.27	−0.20	−0.80	−0.66	−0.20

Credit: Institute Of Heartmath.

autonomic influence on HRV. This measure tends to correlate with VLF power over a 24-h period.

RMSSD

The RMSSD is the root mean square of successive differences between normal heartbeats. This value is obtained by first calculating each successive time difference between heartbeats in milliseconds. Then, each of the values is squared and the result is averaged before the square root of the total is obtained. The RMSSD reflects the beat-to-beat variance in heart rate and is the primary time domain measure used to estimate the vagally-mediated changes reflected in HRV. While the RMSSD is correlated with HF power (Kleiger et al., 2005), the influence of respiration rate on this index is uncertain (Schipke et al., 1999; Pentillä et al., 2001). Lower RMSSD values are correlated with higher scores on a risk inventory of sudden unexplained death in epilepsy (DeGiorgio et al., 2010).

pNN50

The pNN50 is the percentage of adjacent NN intervals that differ from each other by more than 50 ms. 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 (Otzenberger et al., 1998).

HR MAX – HR MIN

HR Max – HR Min is the average difference between the highest and lowest HRs during each respiratory cycle. This measure is especially used for assessment in paced breathing protocols and is highly correlated with the SDNN and RMSSD.

POLYVAGAL THEORY

As previously discussed, increased efferent activity in the vagal nerves (also called the 10th cranial nerve) slows the heart rate, yet has an opposite effect in the lungs as it increases bronchial tone. According to Porges' (2011) polyvagal theory, the ANS must be considered a "system," with the vagal nerves containing specialized subsystems that regulate competing adaptive responses. His theory proposes competing roles for the unmyelinated fibers in the vagus, which originate in the dorsal motor complex, and newer myelinated nerves, which originate in the nucleus ambiguus. He hypothesizes that the unmyelinated fibers are involved in regulating the "freeze response" and respond to threats through immobilization, feigning death, passive avoidance, and shutdown (the freeze response).

In Porges' view, the evolution of the ANS was central to the development of emotional experience and affective processes central to social behavior. As human beings, we are not limited to fight, flight, or freezing behavioral responses. We can self-regulate and initiate pro-social behaviors (e.g., the tend-and-befriend response) when we encounter stressors. Porges calls this the social engagement system and the theory suggests that this system depends upon the healthy functioning of the myelinated vagus, a vagal brake, which allows for self-regulation and ability to calm ourselves and inhibit sympathetic outflow to the heart. This implies that standardized assessment of vagal tone could serve as a potential marker for one's ability to self-regulate.

The theory suggests that the evolution and healthy function of the ANS sets the limits or boundaries for the range of one's emotional expression, quality of communication, and ability to self-regulate emotions and behaviors. The theory describes the details of the anatomical connections from higher brain structures with the centers involved in autonomic regulation and argues that the afferent systems are an important aspect of the ANS. The theory provides insights into the adaptive nature of physiological states and suggests these states support different types or classes of behavior (Porges, 2011).

The SNS, in concert with the endocrine system, responds to threats to our safety through mobilization, fight-or-flight, and active avoidance. The SNS responds more slowly and for a longer period of time (i.e., more than a few seconds) than the vagus system. According to this theory, quality communication and pro-social behaviors can only be effectively engaged when these defensive circuits are inhibited.

NEUROVISCERAL INTEGRATION: THE CENTRAL AUTONOMIC NETWORK MODEL

Thayer and Lane (2000) outline a neurovisceral integration model that describes how a set of neural structures involved in cognitive, affective, and autonomic regulation are related to HRV and cognitive performance. In this complex systems model, the anatomical details of a central autonomic network (CAN) are described that link the NST in the brainstem with forebrain structures (including the anterior cingulate, insula, ventromedial prefrontal cortex, amygdala, and hypothalamus) through feedback and feed-forward loops. They propose that this network is an integrated system for internal system regulation by which the brain controls visceromotor, neuroendocrine, and behavioral responses that are critical for goal-directed behavior, adaptability, and health.

Thayer et al. (2012) contend that dynamic connections between the amygdala and medial prefrontal cortex, which evaluate threat and safety, help regulate HRV through their connections with the NST. They propose that vagally-mediated HRV is linked to higher-level executive functions and that HRV reflects the functional capacity of the brain structures that support working memory and emotional and physiological self-regulation. They hypothesize that vagally-mediated HRV is positively correlated with prefrontal cortical performance and the ability to inhibit unwanted memories and intrusive thoughts. In their model, when the CAN decreases prefrontal cortical activation, HR increases and HRV decreases. The prefrontal cortex can be taken "offline" when individuals perceive that they are threatened. Prolonged prefrontal cortical inactivity can lead to hypervigilance, defensiveness, and social isolation (Thayer et al., 2009).

The CAN model predicts reduced HRV and vagal activity in anxiety. Friedman (2007) argues that anxiety is associated with abnormal ANS cardiac control. HRV indices consistently show low vagal activity in patients diagnosed with anxiety disorders. This finding challenges the completeness of the sympathetic overactivation explanation of anxiety. Friedman observes that "metaphorically, investigators were searching for a 'sticky accelerator' while overlooking the possibility of 'bad brakes'" (p. 186). From his perspective, anxiety disorders can involve varying degrees of sympathetic overactivation and parasympathetic underactivation.

THE PSYCHOPHYSIOLOGICAL COHERENCE MODEL

McCraty and Childre (2010) at the Institute of HeartMath also take a dynamic systems approach that focuses on increasing individuals' self-regulatory capacity by inducing a physiological shift that is reflected in the heart's rhythms. They theorize that rhythmic activity in living systems reflects the regulation of interconnected biological, social, and environmental networks. The coherence model also suggests that information is encoded in the dynamic patterns of physiological activity. For example, information is encoded in the time interval between action potentials and patterns in the pulsatile release of hormones. They suggest that the time intervals between heartbeats (HRV) also encode information which is communicated across multiple systems, which helps synchronize the system as whole. The afferent pathways from the heart and cardiovascular system are given more relevance in this model due the significant degree of afferent cardiovascular input to the brain and the consistent generation of dynamic patterns generated by the heart. It is their thesis that positive emotion in general, as well as self-induced positive emotions, shift the system as a whole into a more globally coherent and harmonious physiological mode associated with improved system performance, ability to self-regulate, and overall well-being.

They use the term "physiological coherence" to describe the orderly and stable rhythms generated by living systems. Physiological coherence is used broadly and includes all of the specific approaches for quantifying the various types of coherence measures, such as cross-coherence (frequency entrainment between respiration, BP, and heart rhythms), or synchronization among systems (e.g., synchronization between various EEG rhythms and the cardiac cycle), auto-coherence (stability of a single waveform such as respiration or HRV patterns), and system resonance.

"A coherent heart rhythm is defined as a relatively harmonic (sine-wave-like) signal with a very narrow, high-amplitude peak in the LF region of the HRV power spectrum with no major peaks in the VLF or HF regions. 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])" (14).

THE HEART RHYTHM COHERENCE HYPOTHESIS

As discussed above, neurocardiology research has established that heart-brain interactions are remarkably complex. Patterns of baroreceptor afferent activity modulate CNS activity over time periods that range from milliseconds to minutes; that is, not only within a cardiac cycle (Armour and Kember, 2004). The intrinsic cardiac ganglia demonstrate both short- and long-term memory. This affects afferent activity rhythms produced by both mechanical variables (e.g., pressure and HR) that occur over milliseconds (single cycles) and hormonal variables that fluctuate over periods ranging from seconds to minutes (Armour, 2003; Armour and Kember, 2004; Ardell et al., 2009). McCraty proposed the heart rhythm coherence hypothesis which states that the pattern and stability of beat-to-beat heart rate activity encode information over "macroscopic time scales," which can impact cognitive performance and emotional experience. For a more detailed discussion, see McCraty et al. (2009).

INCREASING VAGAL AFFERENT TRAFFIC

Mechanosensitive neurons (baroreceptors) typically increase their firing rates when the rate of change in the function to which they are tuned increases. Heart rhythm coherence, which is characterized by increased beat-to-beat variability and the rate of heart rate change, increases vagal afferent traffic from the cardiovascular system to the brain. This perspective is supported by the MacKinnon et al. (2013) HEP study, discussed earlier, which showed that resonance frequency breathing increased the

amount of HRV, HRV coherence, and N250 amplitude in the HEPs. The authors speculated that resonance frequency breathing may have increased vagal afferent traffic and reduced interference with its transmission through subcortical areas to the cerebral cortex.

There has been increasing interest in treating a wide range of disorders with implanted pacemaker-like devices for stimulating the vagal afferent pathways. The FDA has approved these devices for the treatment of epilepsy and depression, and they have been investigated in treating obesity, anxiety, and Alzheimer's disease (Kosel and Schlaepfer, 2003; Groves and Brown, 2005). Neuroradiology research has established that increases in tonic vagal afferent traffic inhibit thalamic pain pathways traveling from the body to the brain at the level of the spinal cord. This finding may explain why studies have shown vagal afferent stimulation can reduce cluster and migraine headaches (Mauskop, 2005) and HRV coherence training reduces chronic pain (Berry et al., 2014).

RESONANCE FREQUENCY BREATHING

Lehrer et al.'s resonance frequency model proposes that the delay in the baroreflex system's feedback loops creates each individual's unique cardiovascular system resonance frequency (Lehrer, 2013). While their theoretical model assumes that taller individuals and men have lower resonance frequencies than women and shorter individuals due to the former's larger blood volumes, height only accounts for 30% of the variance in resonance frequency. Breathing, rhythmic muscle tension, and emotional stimulation at a person's resonance frequency can activate or stimulate the cardiovascular system's resonance properties (Lehrer et al., 2009).

They suggest that when people breathe at this rate, which varies in adults from 4.5 to 6.5 breaths per minute, they "exercise" the baroreflex. They have shown that during this paced period, HR and BP oscillations are 180° out of phase, and HRV amplitude is maximized (deBoer et al., 1987; Vaschillo et al., 2002). They also suggest that this phase relationship between HR, respiration, and BP results in the most efficient gas exchange and oxygen saturation (Bernardi et al., 2001; Vaschillo et al., 2004; Yasuma and Hayano, 2004).

With practice, people can learn to breathe at their cardiovascular system's resonance frequency. This aligns the three oscillators (baroreflex, HR, and BP) at that frequency and moves the peak frequency from the HF range (≈0.2 Hz) to the LF range (≈0.1 Hz). Breathing at the resonance frequency more than doubles the energy in the LF band (0.04–0.15 Hz). This corresponds to the Institute of HeartMath's heart rhythm coherence, which is associated with a "narrow, high-amplitude, easily visualized peak" from 0.09 to 0.14 Hz (McCraty et al., 2009; Ginsberg et al., 2010, p. 54).

Resonance frequency breathing is typically used in the context of HRVB training. Several months of steady practice can reset the baroreflex gain so that it is sustained, even when clients are not receiving feedback (Lehrer et al., 2003; Lehrer, 2013). Increased baroreflex gain is analogous to a more sensitive thermostat, allowing the body to regulate BP and gas exchange more effectively (Lehrer, 2007).

AN INTEGRATIVE PERSPECTIVE

There has been a paradigm shift in the medical treatment of diverse disorders like depression, epilepsy, and pain using vagal nerve stimulation (Kosel and Schlaepfer, 2003; Groves and Brown, 2005; Mauskop, 2005). Instead of exclusively targeting sympathetic activation, physicians also attempt to increase vagal tone. Behavioral interventions like HRVB and emotional self-regulation strategies represent non-invasive methods of restoring homeostasis.

HRVB exercises the baroreceptor reflex to enhance homeostatic regulation. Both the heart rhythm coherence and resonance frequency approaches to HRVB teach clients to produce autocoherent (sinusoidal) heart rhythms with a single peak in the LF region and no significant peaks in the VLF and HF regions (McCraty and Childre, 2010; Lehrer et al., 2013). The coherence model and HEP research (MacKinnon et al., 2013) predict that increased HRV will increase vagal afferent transmission to the forebrain, activate the prefrontal cortex, and improve executive function.

Emotional self-regulation strategies (Forman et al., 2007; McCraty and Atkinson, 2012) can contribute to improved client health and performance, alone, or in combination with HRVB training. McCraty theorizes that emotional self-regulation can increase resilience and accelerate recovery from stressors. From Porges' (2011) perspective, self-regulation through social engagement and bonding can reduce SNS activation while increasing HRV. The CAN model (Thayer et al., 2012) predicts that perception of safety will reduce the activation of the amygdala and increase the prefrontal cortex's ability to exercise top-down control of emotional responses. Finally, from a heart rhythm coherence perspective, emotional self-regulation reduces the SNS activation and/or vagal withdrawal that increase short-term VLF power (Bernardi et al., 1996), decrease shorter-term LF power, and disrupt heart rhythm coherence.

SUMMARY

The SA node normally generates the heartbeat, which is modulated by autonomic efferent neurons and circulating hormones. There is a dynamic balance between sympathetic and parasympathetic nervous outflows in a healthy, resilient, and responsive nervous system. HRV is generated by multiple regulatory mechanisms that operate on different time scales. Recent findings demonstrate the importance of the intrinsic cardiac nervous system and cardiac afferents in generating the heart rhythm and modulating the time interval between heartbeats. Vagally-mediated HRV appears to represent an index of self-regulatory control, such that individuals with greater resting HRV perform better on tests of executive functions.

Since the LF band primarily reflects the vagally-mediated transmission between the heart and the central nervous system in the context of short-term BP regulation, resting measurements should not be used as markers of SNS activity. Based on 24-h monitoring, ULF and VLF rhythms are more strongly associated with overall health status than HF rhythms. When age-adjusted values are low, they are also more strongly associated with future health risk and all-cause mortality.

HRVB exercises the baroreceptor reflex to enhance homeostatic regulation and restore regulatory capacity. Both the heart rhythm coherence and resonance frequency approaches to HRVB train clients to produce auto-coherent heart rhythms with a single peak in the LF region (typically around 0.1 Hz) and no significant peaks in the VLF and HF regions. Emotional self-regulation strategies can contribute to improved client health and performance, alone, or in combination with HRVB training. A coherent heart is not a metronome since its rhythms are characterized by dynamic complexity with stability over longer time scales.

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Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being

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The ability to alter one's emotional responses is central to overall well-being and to effectively meeting the demands of life. One of the chief symptoms of events such as trauma, that overwhelm our capacities to successfully handle and adapt to them, is a shift in our internal baseline reference such that there ensues a repetitive activation of the traumatic event. This can result in high vigilance and over-sensitivity to environmental signals which are reflected in inappropriate emotional responses and autonomic nervous system dynamics. In this article we discuss the perspective that one's ability to self-regulate the quality of feeling and emotion of one's moment-to-moment experience is intimately tied to our physiology, and the reciprocal interactions among physiological, cognitive, and emotional systems. These interactions form the basis of information processing networks in which communication between systems occurs through the generation and transmission of rhythms and patterns of activity. Our discussion emphasizes the communication pathways between the heart and brain, as well as how these are related to cognitive and emotional function and self-regulatory capacity. We discuss the hypothesis that self-induced positive emotions increase the coherence in bodily processes, which is reflected in the pattern of the heart's rhythm. This shift in the heart rhythm in turn plays an important role in facilitating higher cognitive functions, creating emotional stability and facilitating states of calm. Over time, this establishes a new inner-baseline reference, a type of implicit memory that organizes perception, feelings, and behavior. Without establishing a new baseline reference, people are at risk of getting "stuck" in familiar, yet unhealthy emotional and behavioral patterns and living their lives through the automatic filters of past familiar or traumatic experience.

Keywords: coherence, trauma, heart rate variability, HRV, psychophysiological coherence, cardiac coherence, HeartMath, psychosocial well-being

INTRODUCTION

The subjective experience of trauma is unique and varies according to the individual and the type of trauma. What does not vary is the fact that trauma often results in a devastating intrusion into a wished for life of peace, calm, and well-being along with a corresponding unexpected and undesired fragmented sense of self and of life in general. Most would agree that it is a lack of mental and emotional self-regulation that often characterizes stress, anxiety and overwhelm. For some, the lack of self-regulatory capacity is due to immaturity or skill acquisition while for others it can be due to trauma or impairment in the neural systems that underlie one's ability to self-regulate. The degree of impairment in self-regulation that often characterizes trauma makes the possibility of a return to a state of wholeness and well-being appear as distant as an elusive memory. Nevertheless, most people have, at one time or another, likely known a balanced state that is typically characterized by feeling content, happy, in control and in sync within themselves and with others, and irrespective of circumstances and demographic factors, wish to regain this state, and feel good once again.

The quest to understand the mechanisms and dynamics of this sought-after state permeates the scientific and popular literature and gives rise to lines of thought and research that span a number of disciplines. In a broad sense, we call this experience of internal and external intra and interpersonal connectedness "coherence." Through our research at the HeartMath Institute, we have come to identify a specific physiological state associated with optimal cognitive functioning and emotional stability and introduced the psychophysiological coherence model, briefly outlined below. This model is grounded in and consistent with research in the fields of neurocardiology, psychophysiology, and neuroscience (McCraty et al., 2009b).

The psychophysiological coherence model draws on dynamical systems theory. It emphasizes the importance of healthy physiological variability, feedback, inhibition, and reciprocal interactions among a hierarchy of nested neural systems that underlie a complex psychophysiological system for maintaining stability and adaptability to complex changing environments and social demands. Similar to the models proposed by Steve Porges (Porges, 2007) and Julian Thayer (Thayer et al., 2009), the coherence model also suggests that the amount of heart rate variability (HRV) that

is mediated by efferent vagal fibers, reflects self-regulatory capacity and that low age-adjusted HRV indexes a low functional status of the system.

It is our perspective that each of these models introduces important aspects of the neural systems involved in emotional experience and the self-regulation of emotions and behaviors, and together they more fully describe the evolution, anatomy, and functions of these psychophysiological control systems. As these models are discussed in detail elsewhere and in other articles in this issue, they will not be discussed here.

A growing number of studies have linked vagally mediated HRV to self-regulatory capacity (Segerstrom and Nes, 2007; Geisler and Kubiak, 2009; Reynard et al., 2011), emotion regulation (Appelhans and Luecken, 2006; Geisler et al., 2010), social interactions (Smith et al., 2011; Geisler et al., 2013), one's sense of coherence (Miller et al., 1960) and personality character traits of Self-Directedness (Zohar et al., 2013) and coping styles (Ramaekers et al., 1998).

We use the terms cardiac coherence and physiological coherence interchangeably to describe the measurement of the order, stability, and harmony in the oscillatory outputs of the regulatory systems during any period of time. For example, resting HRV data obtained from a population of returning soldiers with a diagnosis of post-traumatic stress disorder (PTSD) found that those with a diagnosis of PTSD had both lower levels of HRV and lower levels of coherence than control subjects without PTSD (Ginsberg et al., 2010). In a study of the effects of playing violent and nonviolent video games, it was found that when playing violent video games, the players had lower cardiac coherence levels and higher aggression levels than did nonviolent game players and that higher levels of coherence was negatively related to aggression (Hasan et al., 2013).

The psychophysiological coherence model predicted that different emotions are reflected in state-specific patterns in the heart's rhythms (HR; McCraty et al., 2009b) independent of the amount of HRV, although state-specific changes in the amount of HRV are of course also important. We can usually identify patterns associated with anxiety versus frustration or anger, for example, by looking at the HRV waveforms. Recent independent work has verified this by demonstrating a 75% accuracy in detection of discrete emotional states from the HRV signal using a neural network approach for pattern recognition (Leon et al., 2010). Several studies in healthy subjects, which help inform the model, showed that during the experience of positive emotions a sine wave-like pattern naturally emerges in the HR without any conscious changes in breathing (McCraty et al., 1995; Tiller et al., 1996). This is likely due to more organized outputs of the subcortical structures involved in processing emotional information described by Pribram and Melges (1969), Porges (2007), and Thayer et al. (2009) in their Central Autonomic Network model in which the subcortical structures influence the oscillatory output of cardiorespiratory centers in the brain stem. Thus, the term psychophysiological coherence is used in the context of when more coherent heart rhythms naturally emerge due to positive experience, or through the self-activation of positive emotions. This is associated with a different subjective inner state that is achieved through techniques such as paced breathing that increase cross-coherence between breathing and heart rhythms via brainstem centers in the medulla, but do not necessarily shift the activity in higher level sub-cortical structures that appear to mediate the structure of different patterns in the HRV waveforms and the increased or decreased coherence related to emotional states (McCraty et al., 2009b). An important aspect of the coherence model (not the specific measure of HRV coherence) is focused on specific approaches to increase people's ability to self-regulate. In this context the HRV coherence measure is intended to be used in the context of facilitating skill acquisition of self-regulation practices that lead to measurable increases in HRV coherence.

The coherence model informed the development of a number of mental and emotional self-regulation techniques, most of which are designed to be used in the moment one is emotionally triggered or is experiencing stress, or to better prepare for upcoming challenging events (Childre and Martin, 1999). The use of these techniques typically shifts the user's physiology into a more coherent and balanced functional state which is reflected in the patterns of the heart's rhythm.

We have found that regular practice of these intentionally simple self-regulation techniques, most of which instruct users to place their attention in the center of the chest and then self-activate a feeling of calmness or a positive emotion, can lead to lasting increases in participants' ability to self-regulate and maintain their composure. Use of the techniques also leads to a state-specific increase in HRV and vagal activity (vagal tone; McCraty et al., 1995; Tiller et al., 1996) and over time can lead to sustained increases in HRV. In a study of high school students who practiced the self-regulation techniques over a three month period, their resting HRV was significantly increased and the pattern of the HRV was significantly more coherent. These improvements in resting HRV coherence were significantly correlated with increased test scores and improved behaviors, suggesting that the practice of the self-regulation skills induces a more coherent heart rhythm, reinforcing the association in the sub-cortical regulatory systems involved in a match/mismatch process between more coherent and stable rhythms in cardiovascular afferent neuronal traffic and feelings we perceive as positive (Bradley et al., 2010).

By reinforcing this natural coupling in the sub-cortical regulatory systems, the self-activation of a positive feeling can automatically initiate an increase in cardiac coherence, while at the same time, a physiological shift resulting from heart-focused breathing can help facilitate the experience of a positive emotion.

An important aspect of the coherence model is the inclusion of cardiovascular afferent neuronal inputs on sub-cortical and cortical structures, which can have significant influences on cognitive resources and emotions. Formally introduced as the "Heart Rhythm Coherence Hypothesis," we proposed that information is conveyed in the patterns of the HR which reflects current emotional states, and that the patterns of afferent neural input (coherence and incoherence) to the brain affect emotional experience, and modulate cortical function and self-regulatory capacity over macroscopic time scales. Furthermore, we proposed that intentional activation of positive emotions plays an important role in increasing cardiac coherence and increasing self-regulatory

capacity (McCraty et al., 2009b). Our findings expand on a large body of research on the benefits of positive emotional states on physical, mental, and emotional health (Isen, 1999; Fredrickson, 2001, 2002; Fredrickson and Joiner, 2002; Fredrickson et al., 2003; Wichers et al., 2007).

This paper provides a brief summary of the psychophysiological coherence model and its implications for improving mental and emotional health and self-regulation. A detailed discussion on the nature of coherence can be found in two seminal articles (McCraty et al., 2009b; McCraty and Childre, 2010). We also provide a brief review of some of the studies that have investigated the coherence-based approach to increasing self-regulatory capacity, physical health, cognitive function, and psychosocial well-being in various populations. Trauma-specific applications with respect to the mechanisms whereby the impact of trauma may be attenuated are considered, with special emphasis on the importance of shifting the internal baseline reference that can be considered a type of implicit memory held in the neural architecture that helps organize perception, feelings and behavior. Of particular relevance to this discussion, is an understanding of the continuum of functions related to mental and emotional self-regulation, and approaches for shifting autonomic nervous system (ANS) activity to one which is increasingly balanced and coherent. As the system becomes more coherent, it becomes possible to reestablish wholeness to the fragmented experience of self and of one's life that is common in individuals who have undergone traumatic events.

PSYCHOPHYSIOLOGICAL COHERENCE OVERVIEW

The coherence model postulates that: (1) The functional status of the underlying psychophysiological systems determines the range of one's ability to adapt to challenges, self-regulate and engage in harmonious social relationships. Healthy physiological variability, feedback systems, and inhibition are key elements of the complex system for maintaining stability and capacity to appropriately respond to and adapt to changing environments and social demands. (2) The oscillatory activity in the HR reflects the status of a network of flexible relationships among dynamic interconnected neural structures in the central and ANSs. (3) State-specific emotions are reflected in the patterns of the HR independent of changes in the amount of HRV. (4) Sub-cortical structures constantly compare information from internal and external sensory systems via a match/mismatch process that evaluates current inputs against past experience to appraise the environment for risk or comfort and safety. (5) Physiological or cardiac coherence is reflected in a more ordered sine wave-like heart rhythm pattern associated with increased vagally mediated HRV, entrainment between respiratory, blood pressure and heart rhythms, and increased synchronization between various rhythms in the EEG and the cardiac cycle. (6) Vagally mediated efferent HRV provides an index of the cognitive and emotional resources needed for efficient functioning in challenging environments in which delayed responding and behavioral inhibition are critical. (7) Information is encoded in the time between intervals (action potentials, pulsatile release of hormones, etc.). The information contained in the inter-beat-intervals in the heart's activity is communicated across multiple systems and helps synchronize the system as a whole. (8) Patterns in the activity of cardiovascular afferent neuronal traffic can significantly influence cognitive performance, emotional experience, and self-regulatory capacity via inputs to the thalamus, amygdala, and other sub-cortical structures. (9) Increased "rate of change" in cardiac sensory neurons (transducing BP, rhythm, etc.) during coherent states increases vagal afferent neuronal traffic which inhibits thalamic pain pathways at the level of the spinal cord. (10) Self-induced positive emotions can shift the psychophysiological systems into a more globally coherent and harmonious order associated with improved performance and overall well-being.

PSYCHOPHYSIOLOGICAL COHERENCE AND WELL-BEING

As discussed earlier, this model was used to develop simple techniques that allow people to quickly self-induce a physiological shift to a more coherent state which takes advantage of the concurrent change in afferent neuronal input to the brain which is associated with increased self-regulatory capacity and thus ability to more successfully handle the demands and challenges of life with more ease and composure. Consequently, there is a greater experience of connectedness, harmony, balance and physical, emotional, and psychosocial well-being.

Outcome studies conducted in laboratory, clinical, educational, and organizational settings with diverse populations have shown sustained reductions in stress and improvements in many dimensions of health, well-being, and performance. For example, a study of middle school students who had a diagnosis of attention deficit hyperactivity disorder (ADHD) demonstrated that the students had a wide range of significant improvements in cognitive functions such as short and long-term memory, ability to focus, and significant improvements in behaviors, both at home and in school (Lloyd et al., 2010). A study of 41 fighter pilots engaging in flight simulator tasks found a significant correlation between higher levels of performance and heart rhythm coherence as well as lower levels of frustration (Li et al., 2013).

Other studies have shown the use of these self-regulation techniques increases parasympathetic activity (HF power) (Tiller et al., 1996) and results in significant reductions in cortisol and increases in DHEA over a 30 day period (McCraty et al., 1998). Studies also show significantly lowered blood pressure and stress measures in a population with a diagnosis of hypertension (McCraty et al., 2003). A study of hypertensive patients showed that those who used the techniques to increase HRV coherence had significantly greater reduction in mean arterial pressure than those who were taking hypertensive medications and using relaxation techniques (Alabdulgader, 2012). A controlled study of pastors found significant improvements in stress and well-being measures with an overall decrease in health care costs of $585 per participant, while the control group had a 9% increase in health care costs. The largest reduction in costs was related to reductions in medications for hypertension (Bedell, 2010). A study of patients with congestive heart failure also showed significant improvements in functional capacity and reduced depression as compared to a control group (Luskin et al., 1999).

While overall health and wellness benefits have been associated with increased coherence, there is also evidence related more specifically to trauma and high stress populations. A study at

the Columbia, South Carolina VA hospital of recently returning soldiers from Iraq who were diagnosed with PTSD, found that relatively brief periods of cardiac coherence training combined with practicing the Quick Coherence technique resulted in significant improvements in the ability to self-regulate along with significant improvements in a wide range of cognitive functions, which correlated with increased cardiac coherence (Ginsberg et al., 2010). In a study of returning veterans with chronic pain, the treatment group showed marked and statistically significant increases in coherence (191%) along with significant reductions in pain ratings (36%), stress perception (16%), negative emotions (49%), and physical activity limitations (42%) (Berry et al., 2014). In a study of patients with severe brain injury, it was found that the emotion self-regulation training resulted in significantly higher coherence ratios and higher attention scores. Additionally, the families' ratings of participants' emotional control correlated with improved HRV indices (Kim et al., 2013b).

A study of correctional officers reporting high work stress showed significant reductions in systolic and diastolic BP, total cholesterol, fasting glucose, overall stress, anger, fatigue, and hostility (McCraty et al., 2009a,b).

Similar results were obtained in several studies with police officers where it was found that the officers' capacity to recognize and self-regulate their responses to stressors in both work and personal contexts was significantly improved. Officers experienced reductions in stress, negative emotions, depression, and increased peacefulness and vitality as compared to a control group. In the qualitative aspect of the study, officers reported improved family relations, better communication and cooperation at work (McCraty and Atkinson, 2012; Weltman et al., 2014).

TRAUMA

Just as the experience of coherence is one of harmonious synchronization and flow, the experience of trauma is often one of disconnectedness, alienation, and dysregulation (Berntsen et al., 2003; Emerson and Hopper, 2011). Neurologist, Robert Scaer (Scaer, 2012) examined the nature of trauma from a neuroscience perspective and paints a picture of a depersonalized reality in which the trauma experience is frozen in time, where procedural and emotion-linked declarative memories become encapsulated elements which are repeatedly brought into one's current consciousness by internal or external cues associated with the traumatic event. These recurring intrusions seem inescapable and threatening and are beyond one's capacity to control them. Being subject to these temporal alterations removes a person from the present moment, resulting in a fragmented experience of life devoid of a sense of control, wholeness or meaningful connections with others. Scaer (2012) also explored the nature of bidirectional interactions between the various parts of the brain during these episodes and highlighted the deactivation of the frontal cortex and the hyper-activity of the limbic system, in particular, the amygdala. Given the role of the frontal cortex in self-regulation, strategic thinking, decision-making, empathy, and relatedness, the necessity for facilitating cortical function and down-regulating activity in the amygdala in order to achieve optimal personal function and psychosocial well-being becomes clear.

While the abundant literature examining the spectrum of trauma has produced numerous conceptualizations of the etiology of trauma, the various correlates of trauma in psychological and social function, and the recommended treatment approaches to address the complex aspects and impact of trauma, there is consensus in the research that trauma is characterized by a disruption in one's ability to respond appropriately to a perceived threat (Levine, 2008) and that physiological factors underlie cognitive, behavioral, and social function (Levine, 2010). Neurological correlates of trauma are well-documented. Emerging research in the field of neurocardiology and psychophysiology provides an expanded understanding of the role of the physiological aspect of trauma, particularly with respect to self-regulation, HRV, and how these relate to restoring optimal function along an integrated continuum (Porges, 2007; Thayer et al., 2009).

Of primary importance in the process of facilitating a return to optimal function is the realization that trauma is associated with emotional dysregulation pursuant to ongoing activation by trauma cues and a corresponding inability to return to physiological homeostasis (Norte et al., 2013). Cardiac function has been clearly implicated in this mechanism, particularly with respect to HRV (Frustaci et al., 2010). For example, it has been shown that elevated psychophysiological baseline scores and heightened physiological reactivity to trauma-related cues are typical features of PTSD which can be objectively measured through cardiac parameters (Keane et al., 1998). A recent twin study (Shah et al., 2013) found a significant relationship between autonomic function and PTSD, independent of other potentially confounding variables such as genetic, familial, and socio-demographics. After adjusting for cardiovascular risks, depression and history of substance abuse, the researchers stated: "...we were able to demonstrate a dose response relationship between PTSD symptom severity and HRV. In contrast, we found a mostly null association between remitted PTSD and autonomic function, suggesting possible reversibility of autonomic dysregulation after PTSD symptom resolution (p. 1106)."

A recent DoD-funded study examined pre-deployment HRV as a predictor of post-deployment PTSD symptoms and compared a HRV coherence biofeedback resilience training to a no-additional training control group in a population of Army National Guard soldiers. Preliminary results demonstrated that lower pre-deployment HRV (SDNN) was a significant predictor of post-deployment PTSD symptoms. The HRV biofeedback resilience training group resulted in lower PTSD symptom severity for soldiers 26 years of age and older (personal communication with Jeff Pyne, Center for Mental Health Outcomes Research Central Arkansas Veterans Healthcare System). Understanding these relationships between physiological baselines as they relate to HRV is essential to developing effective treatment modalities for individuals experiencing trauma. In order to explore this topic at a deeper level, it becomes important to first examine the dynamics of self-regulation in the context of cardiac coherence.

EMOTIONS AND HEART RHYTHM PATTERNS

One of the most salient findings which is of particular relevance to this discussion relates to the association between the quality of emotional experience and the patterns reflected in

HRV waveforms, including coherence. The nature of the emotional experience appears to be related to the level of coherence of the heart rhythm pattern (McCraty et al., 1995, 2009b). **Figure 1** illustrates that emotions typically thought of as positive, such as appreciation and compassion, are related to a more coherent heart rhythm pattern; whereas, emotions that are typically thought of as negative are related to more incoherent pattern, suggesting that positive emotions may have a renewing physiological effect and negative emotions may have a depleting physiological effect.

Although heart rate changes often occur with emotional state changes, we have found that it is more typically the patterns reflected in the heart's rhythm that change in a state-specific manner, especially during emotions that do not evoke large ANS activations or inhibitions of parasympathetic outflow. "These changes in rhythmic patterns are independent of heart rate; that is, one can have a coherent or incoherent pattern at higher or lower heart rates." "Thus, it is the pattern of the rhythm (the ordering of changes in rate over time), rather than the heart rate (at any point in time) that reflects the more subtle ANS and emotional dynamics as well as physiological synchronization" (McCraty and Childre, 2010; p. 12). From a physiological perspective, a coherent heart rhythm is different than the heart rhythm that occurs during the relaxation response, which is associated with a reduced heart rate, but not necessarily a more coherent rhythm.

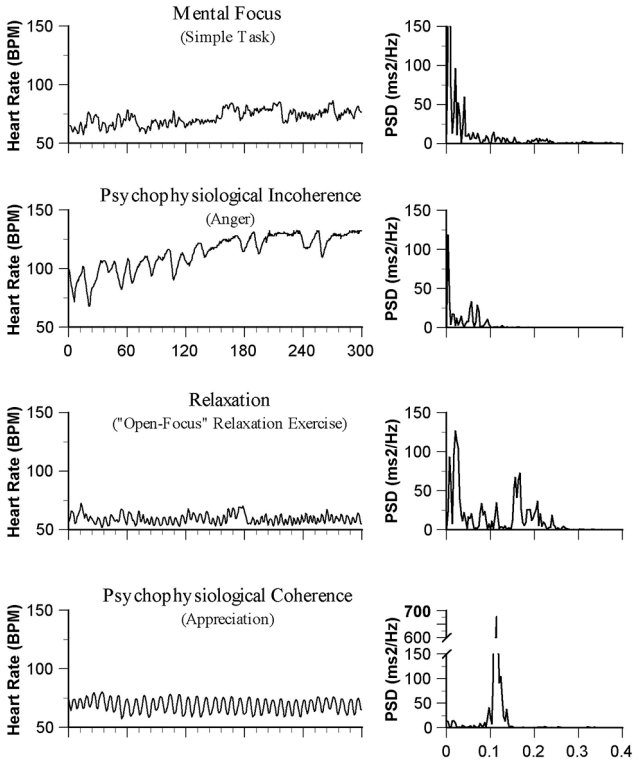

FIGURE 1 | Emotions and heart rhythm patterns. The heart rate tachograms on the left side show patterns in of the HRV waveforms typically observed in differing psychological states. The power spectral density (PSD) analysis of the HRV rhythms for each is shown on the left.

Physiological coherence is reflected in more ordered and sine wave-like HRV patterns at a frequency of around 0.1 Hz (10 seconds rhythm). A coherent rhythm can be defined as "a relatively harmonic (sine wave-like) signal with a very narrow, high-amplitude peak in the LF region of the HRV power spectrum with no major peaks in the VLF or HF regions. 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 0.03 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)]" (McCraty and Childre, 2010; p.14).

HEART–BRAIN COMMUNICATION

The coherence hypothesis suggests that the coherent flow of information within and between the physiological systems and processes in the central and ANS and body plays an important role in determining the quality of the feelings and emotions one experiences.

Heart rate variability analysis, therefore, becomes an important tool that provides a window into the activity occurring between the heart and brain, as well as within regulatory centers in the brain. HRV is generated largely by the interaction between the heart and brain via the neural signals flowing through the afferent (ascending) and efferent (descending) neural pathways of the sympathetic and parasympathetic branches of the ANS (Malik and Camm, 1995; McCraty et al., 1995; Kamath et al., 2013).

Specific HRV variables are used to assess the beat-to-beat changes in heart rate associated with rhythms generated by different physiological mechanisms. The various HRV measures can be used to gain insights into the complex interactions between the central nervous system, the ANS and the heart (McCraty et al., 2009b). An appropriate level of physiological variability in the regulatory systems reflects an organism's flexibility and ability to coherently adapt to stress and challenges (Segerstrom and Nes, 2007). The overall amount of HRV one has, which is best assessed over a 24 hour period, is related to age, with older people having lower levels than younger people (Umetani et al., 1998). Low age-adjusted HRV, especially in the VLF and ULF bands, has been shown to be associated with increased health risk in a wide range of clinical conditions and all-cause mortality (Saul et al., 1988; Arrone et al., 1997; Levy et al., 2002; Lindmark et al., 2003, 2005, 2006). HRV, especially the HF band, provides an index of psychological resiliency, behavioral flexibility and one's capacity to adapt to changing social demands (Beauchaine, 2001). In addition, Thayer and Lane's model describing a dynamic system of neural structures that they call the central autonomic network links cognitive performance with autonomic regulation and HRV. It has been shown in a series of studies that resting levels of HRV are predictive of individual differences in performance on tasks requiring utilization of the prefrontal structures underlying executive functions (Thayer et al., 2009).

CARDIOVASCULAR AFFERENT NEURONS

Porges (2007) also points out that there has been a bias in most text books to focus only on the efferent pathways in the ANS and

neglect the role of the afferent neurons as part of the dynamic regulatory system. Therefore, it is less commonly understood that 85–90% of the fibers in the vagus nerve are afferent (Cameron, 2002) and that cardiovascular related afferent neural traffic significantly affects activity in the majority of higher brain centers, as well as cognitive processes and emotional experience (McCraty et al., 2009b). As shown in **Figure 2**, cardiovascular afferents have connections to numerous brain centers including the thalamus, hypothalamus, and amygdala.

Lacey (1967) and Lacey and Lacey (1970, 1974) were the first to demonstrate a causal relationship between perceptual and sensory-motor performance and cardiovascular afferent neuronal activity. Wölk and Velden (1987) updated their hypothesis after demonstrating that cognitive performance was actually modulated at a rhythm around 10 Hz. In essence, they demonstrated that afferent neuronal activity modulated cortical function by inhibiting or facilitating synchronization of global cortical activity that was mediated by afferent pathways to the thalamus (Velden and Wölk, 1987; Wölk and Velden, 1987, 1989). Importantly, they found it was the *pattern* and *stability* of the rhythm in the cardiovascular afferent neuronal input as opposed to the rate of neural bursts that were important.

Numerous anatomical and neural recording studies in the field of neurocardiology have since shown that the neural communication between the heart and brain is far more complex than has been traditionally understood (Armour and Ardell, 1994). This body of work found that patterns of complex afferent information is continuously sent to the brain (not just within the cardiac cycle) and is related to mechanical and chemical factors over time

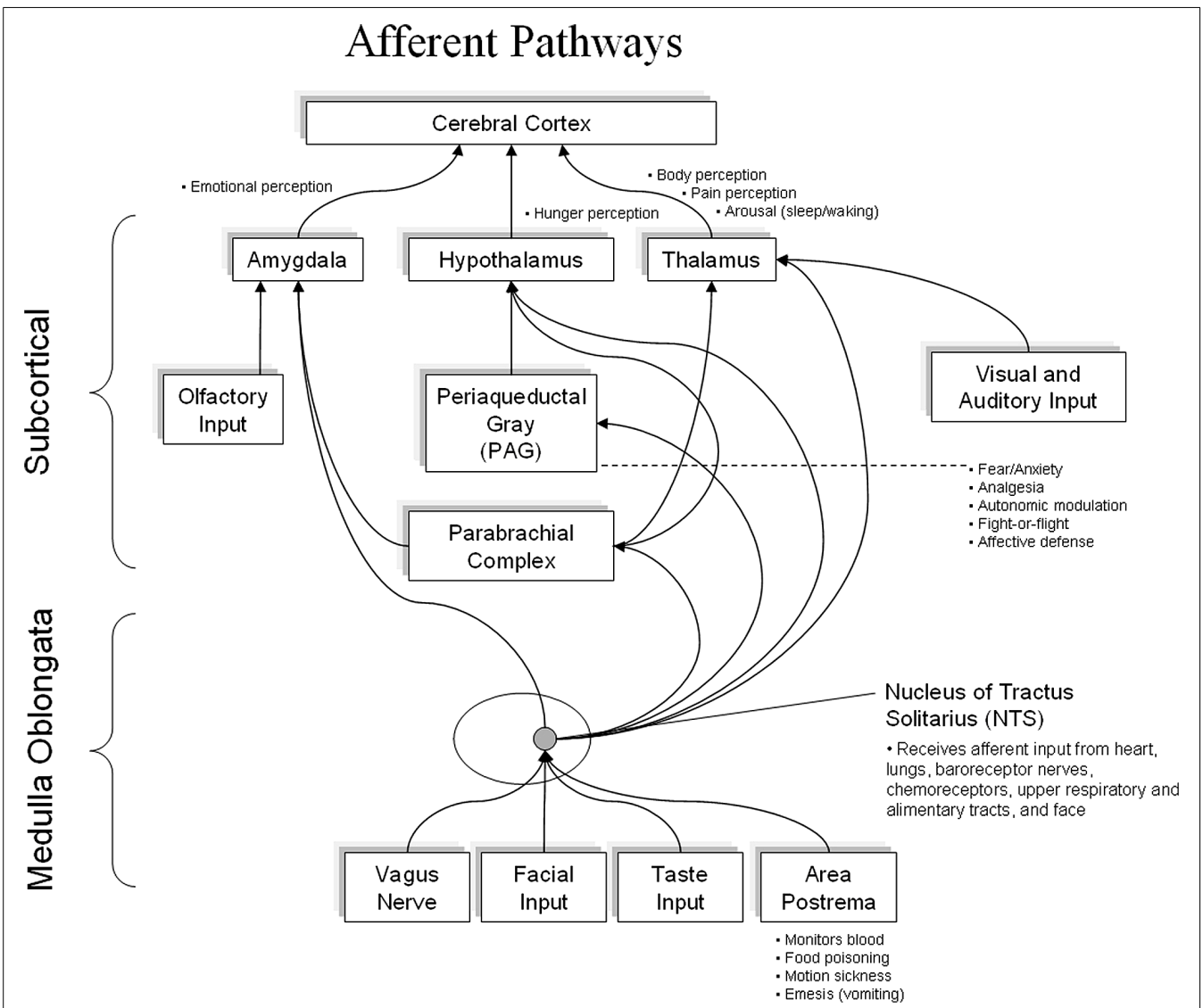

FIGURE 2 | It shows the major afferent inputs from the body to the Dorsal Vagal Complex. Afferent pathways then connect directly to the amygdala, hypothalamus, and thalamus, etc. There is emerging evidence of a direct connection from the NTS to the frontal cortex.

scales ranging from milliseconds to minutes (Armour and Kember, 2004).

Thus, the heart rhythm coherence hypothesis "postulates that the pattern and degree of stability in the beat-to-beat changes in heart rate encodes information over macroscopic time scales which can influence cognitive performance and emotional experience" (McCraty et al., 2009b; p. 16). Several studies have established a relationship between interventions that increase the coherence in the HR and significant improvements in cognitive performance (Bradley et al., 2010; Ginsberg et al., 2010; Lloyd et al., 2010). In a study utilizing an odd-ball audio discrimination task with reaction times and error rates as measures of cognitive performance, participants used a technique to induce either a coherence state or a relaxation state for 5 min prior to the experimental protocol. In the coherence group, there was a carry-over effect on subsequent performance as compared to the relaxation group, and there was a significant correlation between pre-task cardiac coherence and performance across all participants. Additionally, the significant performance improvement was six times larger than that observed due to afferent neuronal effects that occur within a single cardiac cycle (McCraty et al., 2009b).

VAGAL AFFERENT NERVE TRAFFIC

One of the properties of sensory neurons (baroreceptors) is that they are most responsive to increases in rate of change in the function they are tuned to detect (heart rate, pressure, etc.) (Armour and Ardell, 1994). During periods of increased cardiac coherence, there is typically an increased range of variability in both blood pressure and heart rate, which is detected as increases in the rate of change by the sensory neurons, resulting in increased firing rates which increases vagal afferent traffic. There is also a more ordered pattern of activity. A recent study using heartbeat evoked potential showed that using paced breathing at the coherence rhythm increased both the range of HRV and the coherence in the rhythms as expected, and also increased the N200 amplitude potential in the EEG heartbeat evoked potentials indicative of increased afferent input (MacKinnon et al., 2013). Foreman (1989, 1994, 1997) has done a series of anatomical and stimulation studies that have shown the thalamic pain pathways in the spinal cord are inhibited by increases over the normal intrinsic levels of vagal afferent nerve traffic. It has also been demonstrated that vagal afferent nerve stimulation reduces migraine and cluster headaches (Mauskop, 2005). Vagal nerve stimulation has also been shown to improve cognitive processing and memory (Hassert et al., 2004). There has also been a growing number of studies in recent years using afferent vagal stimulation in a wide range of clinical disorders such as epilepsy, obesity, depression, anxiety, autism, alcohol addiction, mood disorders, multiple sclerosis, and traumatic brain injury (Kosel and Schlaepfer, 2003; Groves and Brown, 2005).

Importantly, Lehrer et al. (2006) has shown that regular practice of HRV biofeedback results in lasting improvements in baroreflex gain independent of cardiovascular and respiratory effects, demonstrating neuroplasticity within the baroreflex system, likely in the intrinsic cardiac nervous system. Thus, repeated sessions of heart coherence can reset the baroreflex system gain resulting in increased afferent nerve activity noninvasively.

ESTABLISHING A NEW BASELINE

In order to understand how increased cardiac coherence facilitates self-regulation and helps reset the regulatory systems in cases of trauma, it becomes necessary to examine the emerging perspective in neuroscience that emotions reflect complex somatic states (Cameron, 2002; Damasio, 2003) that become "set points" in the neural architecture which act as a type of implicit memory, or baseline reference (Pribram and Melges, 1969).

Pribram's (1970) theory postulates that emotional information is carried by various internal rhythms, most notably from the heart and facial expressions, in the form of low frequency oscillations produced by these systems. He further proposes that higher frequency oscillations (EEG) relate to the process of making perceptual interpretations of sensory stimuli in the environment. Specifically, he considers the brain's information monitoring role to be a central component of this process. As the brain monitors these inputs, neural patterns are established in nested feedback loops in the neural architecture. This implicit memory functions as a baseline against which we assess all sensory input (Pribram, 1970).

In other words, we establish physiological and behavioral set points or default patterns that, once established, the brain and nervous system strive to maintain. Although more complex, this is analogous to setting the temperature to a specific setting on a thermostat that the heating system works to maintain. It is important to note that the default patterns that are established are adaptive and while appropriate in one context, may not be healthy or optimal in another.

Once a stable pattern is formed and established in memory, all sensory input to the brain from both the internal and external sensory systems is compared to the reference patterns and programs. When the current inputs match the baseline pattern, the brain recognizes them as familiar, which we experience as comfortable and safe. It is important to note that this same process occurs even if the reference pattern is one that is associated with anxiety, chaos, confusion, overwhelm, etc. It becomes comfortable because it is familiar.

In order to maintain stability and feelings of safety and comfort, we must be able to maintain a match between our current experience or "reality" and one of our previously established neural programs (Miller et al., 1960). When we encounter a new experience or challenge, there can be a mismatch between the input patterns of the new experience and the lack of a familiar reference. Depending on the degree of mismatch, it requires either an internal adjustment (self-regulation) or an outward behavioral action to re-establish a match and feeling of comfort. When a mismatch is detected from either external or internal sensory systems, a change in activity in the central and ANSs is produced. If the response is short-lived (one to three seconds), it is called arousal or an orienting reflex. If, however, the stimulus or event is recurrent, the brain eventually adapts and we habituate by updating the memories that serve as the reference. For example, people who live in a noisy city adapt to the ambient noise and eventually tune it out. Subsequent to this adaptation, it is only when they take a trip to the quiet countryside that the actual lack of noise seems strange and is quite noticeable. The mismatch between the familiar noisy background and the quiet setting leads to an arousal reaction that gets

our attention. It is this departure from the familiar that gives rise to a signaling function that creates the experience of an emotion, alerting us to the current state of the mismatch.

In addition to the monitoring and control processes for regulation "in the here-and-now," there are also appraisal processes that determine the degree of consistency or inconsistency between a current situation and the projected future. Appraisals of future outcomes can be broadly divided into optimistic and pessimistic (Pribram, 1970). Appraisals that project an inability to successfully deal with a situation may result in feelings of fear and anxiety. In keeping with the recent research on attentional bias (Olatunji et al., 2013), this appraisal might not be accurate, as it could be the result of hypersensitivity to cues that resemble past traumatic experiences in the current situation. Alternately, an inaccurate appraisal can be due to an instability in the neural systems, or a lack of experience or insight of how to effectively deal with the projected future situation (Pribram, 1970). Despite the lack of accuracy of the appraisal, the familiarity of the input can be sufficient to elicit a pessimistic response. This means we can easily get "stuck" in unhealthy emotional and behavioral patterns and that lasting improvements in emotional experience or behaviors cannot be sustained in the absence of establishing a new set point for the baseline. If behavior change or improved affective states are desired, it is therefore critical to focus on strategies that help to establish a new internal reference. As we successfully navigate new situations or challenges, the positive experience updates our internal reference. In essence, we mature through this process as we learn to more effectively self-regulate our emotions and deal with new situations and challenges. It is through this process that we are able to develop a new, healthier internal baseline reference against which we match inputs so that our assessments of benign inputs are more accurate and result in a feeling of safety and comfort rather than threat and anxiety.

SELF-REGULATION AND STABILITY

Pribram and McGuinness (1975) and others have conducted numerous experiments that provide evidence that the higher brain centers that monitor the pattern-matching process can self-regulate by inhibiting or "gating" the information flowing into the brain. Where we focus our attention, for example, has a powerful effect on modulating inputs and thus on determining what gets processed at higher levels. In a noisy room filled with many conversations, for instance, we have the ability to tune out the noise and focus on a single conversation of interest. In a like manner, we can modulate pain from a stubbed toe or headache or desensitize ourselves to sensations like tickling, and self-direct our emotions (Pribram, 1971). Ultimately, when we achieve control through the process of self-regulation, it results in feelings of satisfaction and gratification. In contrast, failure to effectively self-regulate, and regain control often results in feelings of frustration, impatience, anxiety, overwhelm, hopelessness, or depression.

If the neural systems that maintain the baseline reference patterns are unstable, unsettled emotions, and atypical reactions are likely to be experienced. These neural systems can be destabilized by trauma, stress, anxiety or chemical stimulants, to name a few possibilities. Therefore, it is clear that responding in healthy and effective ways to ongoing inner and outer demands and circumstances, such as daily life situations, depends to a great extent on the synchronization, sensitivity, and stability of our physiological systems (McCraty et al., 2009b; McCraty and Childre, 2010).

Neural inputs originate from numerous organs, and muscles, especially the face. The heart and cardiovascular system, however, has far more afferent inputs than other organs and is the primary source of consistent dynamic rhythms (Cameron, 2002). In addition to afferent nerve activity associated with mechanical information such as pressure and rate that occurs with each heartbeat, continuous dynamically changing patterns of afferent activity related to chemical information is sent to the brain and other systems in the body. In terms of emotional experience, there are afferent pathways to the amygdala via the Nucleus of Tractus and the activity in the central nucleus of the amygdala is synchronized to the cardiac cycle (Zhang et al., 1986; Frysinger and Harper, 1990). Therefore, the afferent inputs from the cardiovascular system to the amygdala are important contributors in determining emotional experience and in establishing the set point to which the current inputs are compared.

In the context of this discussion, it is important to note that the heart's rhythmic patterns and the patterns of afferent neurological signals change to a more ordered and stable pattern when one uses the heart-focused self-regulation techniques. Regular practice of these techniques, which include a shift of attentional focus to the center of the chest (heart area) accompanied by the conscious self-induction of a calm or positive emotional state, reinforces the association (pattern match) between a more coherent rhythm and a calm or positive emotion. Positive feelings then more automatically initiate an increase in cardiac coherence. Increased coherence initiated through heart-focused breathing tends to facilitate the felt experience of a positive emotion. Thus, practice facilitates the *repatterning process.*

This is important in situations where there has been a sustained exposure to truly high risk environments or trauma in the past, but that context is no longer in effect, and the patterns developed at that time no longer serve the individual in current safe environments.

Through this feed-forward process, regulatory capacity is increased and new reference patterns are established, which the system then strives to maintain, making it easier for people to maintain stability and self-directed control during daily activities, even during more challenging situations. Without a shift in the underlying baseline, it is exceedingly difficult to sustain behavioral change, placing people at risk of living their lives through the automatic filters of past familiar experience.

SOCIAL COHERENCE

In social interactions, we also have set points or familiar habitual ways in which we perceive and respond. Consistent with the coherence model, social coherence is reflected in the harmonious quality of the network of relationships shared by individuals. In a socially coherent system, relationships are aligned in such a way as to allow for optimal collective function through efficient communication and shared energy resources (Bradley, 1987). If our familiar social set points reflect a pattern of harmony and support, then optimal social functioning in our interactions leads to an experience of

safety, comfort, and well-being. On the whole, social coherence rests on the ability of group members to remain attuned to the group and the ability of the group to be organized and regulated according to mutually agreed upon norms (Bradley, 1987).

In most social contexts, individuals at times experience incoherent feelings towards one another, such as preconceptions or judgments, which are unspoken and can result in disruptions in optimal social interactions through miscommunication or other damaging social dynamics.

Studies in social incoherence indicate that in addition to generating unpleasant feelings and relational dynamics, physiological processes are engaged which have a direct bearing on our state of health. For example, studies of individuals in incoherent social situations, including social chaos or isolation, suggest that they are more susceptible to disease (Neser et al., 1971; Marmot and Syme, 1976; Berkman and Syme, 1979; Ornstein and Sobel, 1987; Hermes et al., 2009). Research conducted by James Lynch on social isolation indicates that the risks of isolation far exceed the combined risk for heart disease of smoking, obesity, lack of exercise, and excessive alcohol (Lynch, 2000). This is especially sobering and relevant for people suffering from trauma. As stated previously, aside from the experience of inner turmoil, one of the major symptoms of trauma is social alienation that often stems from depersonalization.

In contrast, the protective value of close, meaningful relationships has also become clear. Building upon studies that examine the role of social connection in disease (Cohen and Syme, 1985; Uchino et al., 1996; Ornish, 1998), James Coan and colleagues at the University of Virginia are investigating the role of social interactions and networks in wellness. Coan calls this Social Baseline Theory and suggests that the primary environments to which humans are adapted to are other humans and that the human brain implicitly assumes that it is embedded within a relatively predictable social network characterized by familiarity, joint attention, shared goals, and interdependence. In other words, social proximity is a "baseline" condition, and when proximity is maintained or reestablished, the brain is less vigilant for potential threats because it is familiar with the social environment. Thus, when we are in close proximity to our familiar social environment, and we have a match with our baseline state, we expend less emotional energy. We also expend less energy self-regulating. According to Social Baseline Theory, being alone is more effortful, because a variety of activities require more energy expenditures due to decreased load sharing and risk distribution (Beckes and Coan, 2011; Beckes et al., 2013; Maresh et al., 2013). Given the fragmented psychological state that predominates in trauma, one can speculate that for many, alienation has become the new norm, and even though isolation is innately stressful, a pattern of alienation under these circumstances can become habituated, such that social proximity might be experienced as a mismatch with the existing baseline and therefore add to the perceived stress burden rather than alleviate the burden. This can place the individual in a downward spiral due to a repetitive self-sustaining feedback loop of separation from one of the very resources that has been demonstrated to facilitate healing. This separation may be exacerbated by cultural patterns of marginalization in societies where those with perceived disabilities are shunned, judged and even blamed, sometimes by caregivers themselves (Thomas and Scharzbaum, 2011).

Reestablishing connectedness, whether inner or outer, such as in the case of trauma, is a complicated process, and yet it is one of the most important aspects that allows for reintegration. Levine (2010) speaks about the calming effect of social engagement and how the physiology of trauma compromises the capacity of an individual to be in the present moment and receive social support. Scaer (2012) speculates about the power of "face-to-face empathic attunement" between the client and therapist in a therapeutic setting to activate the limbic centers that are responsible for down-regulating the amygdala, which plays a central role in the physiology of trauma. Scaer notes that the skill of the therapist in establishing this container for reconnection to occur is of paramount importance. Therefore, it is critical for both client and therapist to be able to be present and engaged in an empathic exchange.

Research suggests that when individuals learn to sustain coherence while communicating with others, there is increased physiological linkage, and they become more sensitive to others so as to promote greater empathy and rapport, which allows for the process of heart felt connection to occur (McCraty, 2004).

TRAUMA AND SELF-REGULATION

In considering the importance of reconnecting socially, as well as a few of the basic elements of trauma discussed previously, such as emotional dysregulation, intrusive memories, difficulty returning to homeostasis, inappropriate ANS arousal and reduced HRV, it becomes apparent that simple, straightforward techniques that effectively increase one's self-regulatory capacity would be highly beneficial in bringing wholeness and harmony to not only one's personal experience but also to one's connectedness with others. Although the types and treatment of trauma are a highly complex topic involving many interrelated approaches and modalities, some central elements emerge in the literature. A review by Courtois and Ford (2013) of the principles of complex trauma and how it is expressed across individuals, suggests that crucial components for building a foundation of care includes emotional regulation, attention to wellness and stress management.

SELF-REGULATION TECHNIQUES THAT INCREASE CARDIAC COHERENCE

The HeartMath self-regulation techniques and assistive technologies provide a systematic process for self-regulating thoughts, emotions and behaviors, and increasing physiological coherence (Childre and Martin, 1999; Childre and Rozman, 2003, 2005). Many of them are specifically designed to enable people to intervene in the moment they start to experience stress reactions or unproductive thoughts or emotions. Skill acquisition of the tools and techniques (Heart-Focused Breathing, Freeze Frame, Inner-Ease, Quick Coherence, Heart Lock-In, Prep, Shift and Reset, Getting In Sync, and Coherent Communication) are often supported by heart rhythm coherence feedback technology.

With practice, one is able to use one of the techniques to shift into a more coherent physiological state before, during and after challenging or adverse situations, thus optimizing mental

clarity and emotional composure and stability. As previously discussed, in such a state, most people are able to more quickly find their "center," gain new perspectives, and counter ineffective and maladaptive thoughts, feelings, and behaviors.

Effectively dealing with trauma and instating a new internal reference first involves increased self-awareness and recognizing triggers, reactions, and ongoing emotional undercurrents (fear, negative projection, insecurity, worry, etc.). Once one is more aware, the next step is learning how to consciously self-regulate and increasingly replace these feelings with more neutral or positive attitudes and perceptions.

The first step in most of the techniques is called Heart-Focused Breathing, which includes putting one's attention in the center of the chest (area of the heart) and imagining the breath is flowing in and out of that area while breathing a little slower and deeper than usual. Conscious regulation of one's respiration at a 10 seconds rhythm (0.1 Hz) increases cardiac coherence and starts the process of shifting into a more coherent state. In challenging situations or after a strong emotion has been triggered, Heart-Focused Breathing is often the step that most people can remember and find that it "helps take the intensity out" or "turn down the volume" of the reaction. As we have conscious control over breathing and can easily slow the rate and increase the depth of the breathing rhythm, we can take advantage of this physiological mechanism to modulate efferent vagal activity and thus the heart rhythm. This, in turn, increases vagal afferent nerve traffic and increases the coherence (stability) in the patterns of vagal afferent nerve traffic which influences the neural systems involved in regulating sympathetic outflow, informing emotional experience, and synchronizing neural structures underlying cognitive processes (McCraty et al., 2009b). While rhythmic breathing methods are an effective way to increase heart rhythm coherence, cognitively directed paced breathing is difficult for many people to maintain for more than about a minute before it becomes uncomfortable and distracting (Alabdulgader, 2012).

We have found that self-induced positive emotions can initiate a shift to increased cardiac coherence without any conscious intention to change the breathing rhythm (McCraty et al., 1995; Tiller et al., 1996). Typically, when people are able to self-activate a positive or calming feeling rather than remaining focused on their breathing, they enjoy the feeling shift and are able to sustain high levels of coherence for much longer time periods. However, people who are just learning the techniques or who experience strong emotional triggers may not be able to self-activate a calm or positive emotion. In these instances, using the Heart-Focused Breathing step can be used to start the process of regaining their composure and increasing their coherence. When their thoughts and emotions have slowed down and the intensity reduced, they can move to the next step of the various techniques, depending on the situation. Remembering to use any self-regulation approach requires effort, and ongoing mentoring or coaching can significantly help motivate clients to practice and sustain the use of the techniques (Bedell, 2010).

In addition to the techniques outlined above there are other approaches that also increase HRV coherence. For example, a study of Zen monks found that advanced monks tended to have coherent heart rhythms during their resting recording, while the ones that had been a monk for less than two years did not (Lehrer et al., 1999). A study of Autogenic Meditation also showed increased HRV coherence and found that cardiac coherence was strongly correlated with EEG alpha activity. The authors suggested that cardiac coherence could be a general marker for the meditative state (Kim et al., 2013a). However, this does not suggest that all meditation styles increase coherence, unless the coherence state is driven by a focus on breathing at a 10 seconds rhythm (Peng et al., 1999; Wu and Lo, 2008; Phongsuphap and Pongsupap, 2011) or a positive emotion. For example, a study examining HRV while reciting rosary or bead prayers and yoga mantras found that a coherent rhythm was produced by rhythmically breathing but not by random verbalization or breathing. The authors ascribed the mechanisms for this finding as due to changes in their breathing patterns to a six cycles per minute rhythm and concluded that the rhythm of mantras and rosary prayers were intentionally designed to induce coherent heart rhythms by individuals who had an intuitive understanding of the benefits of this rhythm (Bernardi et al., 2001). In a study of the effects of five different types of prayer on HRV, it was found that all types of prayer elicited increased cardiac coherence; however, prayers of gratefulness and prayers that focused on heart felt love resulted in definitively higher coherence levels (Stanley, 2009). There are also many studies showing that the practice of breathing at 6 breaths per minute, supported by HRV biofeedback, induces the coherence rhythm and has a wide range of benefits (Lehrer et al., 2003, 2006; Siepmann et al., 2008; Hallman et al., 2011; Henriques et al., 2011; Ratanasiripong et al., 2012; Beckham et al., 2013; Li et al., 2013). It has also been shown that tensing the large muscles in the legs in a rhythmical manner at a 10 seconds rhythm can induce a coherent heart rhythm (Lehrer et al., 2009).

HEART RATE VARIABILITY COHERENCE FEEDBACK

In addition to clinical applications, HRV coherence training is often utilized to support self-regulation skill acquisition in educational, corporate, law enforcement and military settings. Several systems that assess the degree of coherence in the user's heart rhythms are available. The majority of these systems, such as the emWavePro, or Inner Balance for iOS devices (HeartMath Inc), Relaxing Rhythms (Wild Divine), and Stress Resilience Training System (Ease Interactive), use a noninvasive earlobe or finger pulse sensor, display the user's heart rhythm, and provide feedback on their level of coherence.

CONCLUSION

The psychophysiological coherence model has informed the development of practical applications and approaches for increasing self-regulatory capacity and vagal tone in a wide range of populations, including individuals who have experienced trauma. Numerous studies have provided evidence that coherence training consisting of intentional activation of positive and calming emotions paired with HRV coherence feedback facilitates significant improvements in wellness and well-being indicators in a variety of populations.

The role of cardiac coherence in facilitating a resetting of adaptive response patterns through a shift in the physiological baseline reference to a healthier pattern appropriate for current contexts was highlighted as central to supporting the process of return to optimal function. While the experience of trauma is associated with a sense of fragmentation and loss of control that emerge from intrusive activations of the trauma stimulus, impairments in self-regulation, and difficulty returning to homeostasis, the practice of techniques that increase cardiac coherence is associated with an experience of intra and interpersonal synchronization, social harmony and wholeness. This is of particular relevance in circumstances where quality of life is significantly impaired, such as in the case of trauma. The process of re-patterning through intentional activation of positive emotions and generating an increasingly consistent state of psychophysiological coherence brings with it the possibility for addressing the primary defining components of the experience of trauma, thus allowing individuals to move out of the "stuck state" of dysregulation and fragmentation into a state of harmonious synchronized healthy function both at the individual and social levels.

DISCLOSURES

Dr. Rollin McCraty is employed by the HeartMath Institute which is a non-profit research center supported by grants, donations, and some fee for service activities such as providing self-regulation trainings, sales of books, and heart rhythm coherence technologies, all is which is focused on services to education, service members, veterans, and non-profit social services agencies. The HeartMath Institute does not manufacture any devices, and if and when they are included in research projects or resold, are purchased from the manufacture in the same way as any other organization.

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Habituation of parasympathetic-mediated heart rate responses to recurring acoustic startle

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Startle habituation is a type of implicit and automatic emotion regulation. Diminished startle habituation is linked to several psychiatric or neurological disorders. Most previous studies quantified startle habituation by assessing skin conductance response (SCR; reflecting sympathetic-mediated sweating), eye-blink reflex, or motor response. The habituation of parasympathetic-mediated heart rate responses to recurrent startle stimuli is not well understood. A variety of methods and metrics have been used to quantify parasympathetic activity and its effects on the heart. We hypothesized that these different measures reflect unique psychological and physiological processes that may habituate differently during repeated startle stimuli. We measured cardiac inter-beat intervals (IBIs) to recurring acoustic startle probes in 75 eight year old children. Eight acoustic stimuli of 500 ms duration were introduced at intervals of 15–25 s. Indices of parasympathetic effect included: (1) the initial rapid decrease in IBI post-startle mediated by parasympathetic inhibition (PI); (2) the subsequent IBI recovery mediated by parasympathetic reactivation (PR); (3) rapid, beat-to-beat heart rate variability (HRV) measured from the first seven IBIs following each startle probe. SCR and motor responses to startle were also measured. Results showed that habituation of PR (IBI recovery and overshoot) and SCRs were rapid and robust. In addition, changes in PR and SCR were significantly correlated. In contrast, habituation of PI (the initial decrease in IBI) was slower and relatively modest. Measurement of rapid HRV provided an index reflecting the combination of PI and PR. We conclude that different measures of parasympathetic-mediated heart rate responses to repeated startle probes habituate in a differential manner.

Keywords: acoustic startle responses, parasympathetic activity, heart rate variability, autonomic nervous system, stress, children, emotion regulation, startle habituation

INTRODUCTION

Brief aversive, acoustic stimuli trigger startle responses. Repeated exposures to the same stimuli further elicit "startle habituation," meaning a reduction of behavioral and psychophysiological responses to the repeated startle stimuli (Turpin and Siddle, 1978a; Mata et al., 2009). Startle habituation is a type of implicit and automatic emotion regulation (Gyurak and Etkin, 2014) and the magnitude of startle response (i.e., eye-blink reflex) has a long history of use as a measure of defensive motivation and physiological index of fear (Bradley et al., 1999).

Recent research suggests that the magnitude of startle responses is meaningfully related to normative variation in adulthood personality and childhood temperament. For example, faster startle habituation has been noted in those who were high in extraversion and sensation seeking in college populations (LaRowe et al., 2006). In contrast, slower startle habituation has been linked to temperamental fearfulness or behavioral inhibition in both child (Quevedo et al., 2010; Barker et al., 2014) and adolescent samples (Reeb-Sutherland et al., 2009).

In clinical settings, diminished startle habituation has been repeatedly observed in patients with psychiatric or neurological disorders including schizophrenia, anxiety disorders, and Parkinson's disease (Lader and Wing, 1964; Messina et al., 1972; Raskin, 1975; Geyer and Braff, 1982; Roth et al., 1990; Rothbaum et al., 2001; Nieuwenhuijzen et al., 2006). Magnitude of startle reflexes has also been useful in distinguishing children with anxiety disorders from controls (Waters et al., 2008) and adolescent males with conduct disorder from controls (Fairchild et al., 2008).

A better understanding of the determinants of the magnitude and rate of habituation to recurring startle stimuli may not only shed light on behavioral, cognitive, and emotional difficulty characteristic of several psychiatric and neurological disorders (Lader and Wing, 1964; Messina et al., 1972; Raskin, 1975; Geyer and Braff, 1982; Roth et al., 1990; Rothbaum et al., 2001; Nieuwenhuijzen et al., 2006) but also facilitate diagnoses and interventions for those conditions. Most previous studies in startle habituation have exclusively focused on examining changes in the electrodermal skin conductance response (SCR;

reflecting sympathetic-mediated sweating; Lader and Wing, 1964; Raskin, 1975; Roth et al., 1990; Rothbaum et al., 2001), eye-blink reflex (Penders and Delwaide, 1971; Messina et al., 1972), and behavioral motor response (Nieuwenhuijzen et al., 2006). The habituation of parasympathetic effect to recurrent startle stimuli is not well understood. Given the strong relationship between parasympathetic activity and psychological and behavioral well-being (Porges et al., 1994; Porges, 2011; Thayer et al., 2012), we felt it was important to investigate the rate of habituation of parasympathetic-mediated heart rate (HR) responses to acoustic startle.

Startle stimuli evokes well-characterized tri-phasic changes in HR [inter-beat intervals (IBIs)], including (1) a rapid, transient decrease in IBI, followed by (2) an increase in IBI within a few seconds, and (3) a delayed decrease in IBI occurring over 20–60 s that dissipates over time (Davis et al., 1955; Graham and Clifton, 1966; Fernández and Vila, 1989; Reyes del Paso et al., 1993, 1994; Vila et al., 2007). In the present study, we focus on the first two components because they are primarily driven by the inhibition and reactivation (recovery) of parasympathetic nerve activity, respectively (in contrast, the third component involves increased sympathetic nerve activity). We refer to the first component as "*parasympathetic inhibition* (*PI*)," and to the second component as "*parasympathetic reactivation (PR)*."

Although habituation of PI and PR has been described previously, the rate and magnitude of habituation have been controversial (Vila et al., 2007). More specifically, early results suggested that PI habituates to a less extent than PR, but the difference was not statistically significant (Davis et al., 1955; Lang and Hnatiow, 1962; Graham and Clifton, 1966). In addition, PI was not always observed in previous studies (Graham and Clifton, 1966). In the present study, we re-visited this issue in a group of normally developing eight year old children.

An advantage of studying eight year old children is their homogeneity in terms of age, health, education, degree of socialization, and other factors that could confound the effect of parasympathetic modulation on HR response during emotion regulation (Byrne et al., 1996; Berntson et al., 1997; Bar-Haim et al., 2000; Hinnant et al., 2011). Previous research suggests that by age eight vagal modulation of HR has matured increasing the likelihood that findings from the current study may generalize to adult populations (Byrne et al., 1996; Berntson et al., 1997; Bar-Haim et al., 2000; Hinnant et al., 2011). In addition, many studies indicate that development of and variation in fear circuitry is relevant to both concurrent and future risk for psychopathology in both internalizing and externalizing spectrum (Degnan et al., 2010). A better understanding of the effect of parasympathetic modulation on HR responses during startle habituation in this age group can help shed light on fear circuitry and emotion regulation.

More recently, heart rate variability (HRV) became a popular measure for quantifying parasympathetic effect on human subjects (Malik et al., 1996; Berntson et al., 1997). HRV can be analyzed from IBIs using either time or frequency domain approaches (Malik et al., 1996; Chapleau and Sabharwal, 2011). In a previous study, Jovanovic and her colleagues examined trial-by-trial changes in HRV during startle habituation. They performed spectral analyses (frequency domain) on 10 s samples post-startle and reported no habituation in both post-traumatic stress disorder patients and healthy control subjects (Jovanovic et al., 2009). In the present study, we used a time-domain approach to re-address this issue. We measured rapid beat-by-beat HRV [root mean square of successive differences (RMSSDs)] from seven IBIs before and after each startle probe. The change/difference between RMSSD pre- and post-startle was then calculated and referred to as Δ*RMSSD7*. Habituation of ΔRMSSD7 was examined trial by trial. We used seven IBIs because preliminary analyses suggested that seven IBI covers the time course of both PI and PR post-startle.

The purpose of this study was to examine the habituation of parasympathetic effect on HR responses during recurring startle probes. Parasympathetic effect was quantified by three different measures: (1) PI, (2) PR, and (3) ΔRMSSD7. We hypothesized that those different measures reflect unique physiological and psychological processes that may habituate differently during repeated startle probes. To compare the three parasympathetic measures with typically used metrics, we also examined the habituation of SCR and motor response.

MATERIALS AND METHODS

PARTICIPANTS

Participants were 81 normally developing children recruited from the eastern Iowa area. They were eight years old at the time of evaluation. Due to procedural error or poor electrocardiogram (ECG) quality, six participants were excluded from data analyses. The remaining 75 participants included 33 boys and 42 girls. The participants are part of a long-term study investigating a variety of psychological and behavioral traits in addition to the physiological assessment (Kochanska and Kim, 2014; Kochanska et al., 2014).

PROCEDURE

Research participation involved one laboratory visit. Parents consented and children provided assent in compliance with the policies of the University of Iowa Institutional Review Board. Children's physiological responses were examined in five tasks presented in fixed order: rest one (3-min), deep breathing (2-min), startle (3-min), rest two (3-min), and anticipation (waiting for gift, 2-min). Only data from the startle task are presented in this report. Participants were seated in a comfortable chair facing a computer monitor. To prevent excessive motion during the startle task, participants were allowed to move around and readjust themselves before the startle task began. Participants and their parents were debriefed before they left the study.

STARTLE TASK

The participants were presented with eight startle probes (**Figure 1A**). The startle probe was an approximately 90 db white noise (8,192 Hz) lasting 500 ms, coming from two loudspeakers in front of the participants. Time between startle probes ranged from 15 to 25 s. In order to keep participant's attention on the task, a series of abstract paintings (for examples, see **Figure S1**) were presented on the screen, changing at random intervals throughout the task. Participants were instructed to simply sit still and watch the pictures presented on a screen in front of them, and were told that they may hear some loud noises.

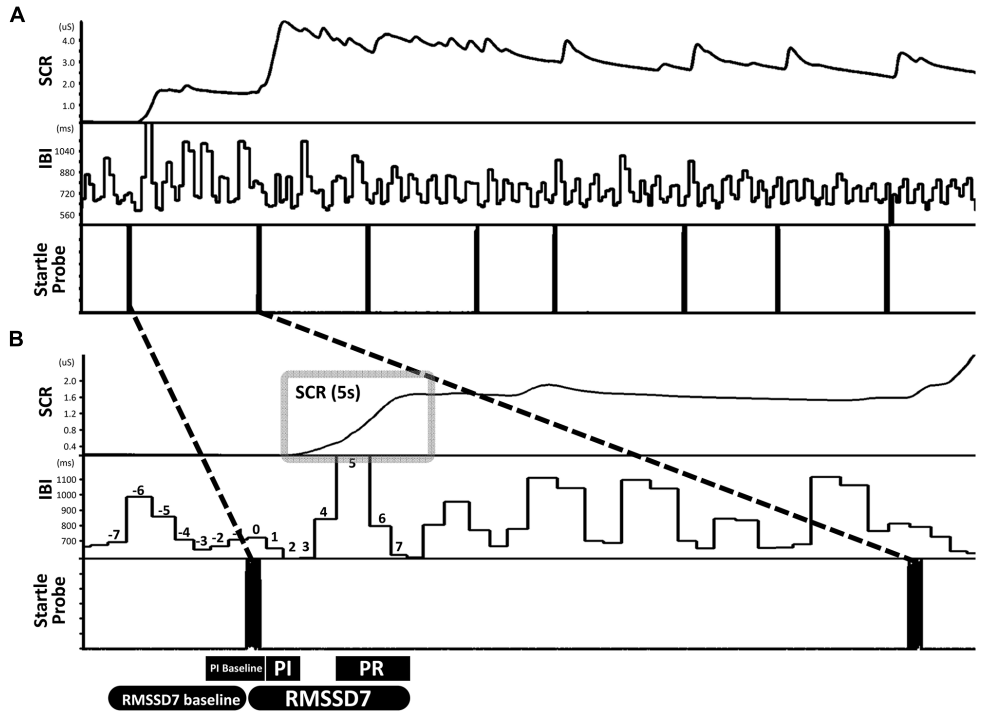

FIGURE 1 | An example illustrating the design of the startle task and the definitions of primary measures. (A) The startle task consisted of eight startle probes. **(B)** Skin conductance response (SCR) was quantified as the area under curve in a 5-s window that begins at the inflection point of the increase from the immediately preceding stable baseline value. Parasympathetic inhibition (PI) was quantified as the change from baseline IBI pre-startle (mean of three IBIs) to the mean of the first two IBIs post-startle. Parasympathetic reactivation (PR) was quantified as the change from PI to the mean of the fifth through seventh IBIs post-startle. ΔRMSSD7 was calculated as the change in RMSSD from the seven IBIs pre-startle (baseline) to seven IBIs post-startle which included the IBI when the startle probe was delivered.

DATA ACQUISITION AND DATA PROCESSING

Heart rate responses

Two foam electrodes were placed, one on the right side of the neck (close to right carotid artery) and the other on the left side of the abdomen, just below the rib cage. ECGs were recorded using a BIOPAC MP100 system at a sampling rate of 1000 Hz. HemoLab software (http://www.haraldstauss.com/HemoLab/HemoLab.php) was used to compute beat-to-beat IBIs from the ECG (R–R intervals). Artifacts in IBI data were corrected manually. For each startle probe, we calculated the following measures: (1) PI (representing the initial decrease in IBI), the difference between a pre-startle baseline (3 IBIs pre-startle, including the IBI when the startle probe was delivered) and the mean of the first two IBIs post-startle; (2) PR (representing the subsequent increase in IBI), the difference between the mean of the first two IBIs and the mean of the fifth through seventh IBIs post-startle. During PR, increases in IBI above baseline were also calculated (referred to as *reactivation overshoot*); (3) ΔRMSSD7, the change of RMSSD from a pre-startle baseline (consisting of seven IBIs) to the first seven IBIs following each startle probe including the IBI when the startle probe was delivered (**Figure 1B**).

Electrodermal activity: skin conductance response

The level of electrodermal activity was acquired by the BIOPAC MP100 system. Two foam electrodes were placed on the thenar and hypothenar eminences of the child's left hand. Electrodermal data were recorded online at 1000 Hz and offline down-sampled to 100 Hz before data processing. We analyzed electrodermal data from the children in which ECGs were analyzed ($n = 75$). Within these 75 children, six had poor electrodermal data quality and therefore were excluded before data processing. For the remaining 69 children, motion artifacts were identified by a trained research assistant (blinded to research hypotheses) and were manually corrected using Ledalab software (Benedek and Kaernbach, 2010). SCR induced by each startle probe was quantified as the change in conductance level measured over a 5-s time period beginning at the inflection point of the increase from the immediately preceding stable baseline value (area under curve, **Figure 1B**). To account for individual differences in general electrodermal reactivity, SCR was normalized by dividing by the range of each child's skin conductance level over the whole testing session (Lykken and Venables, 1971).

Startle behaviors: motor responses

Participants were also video-recorded during the startle task. Due to variation in video recording quality, data from only 59 subjects could be coded for startle motor response by a trained research assistant (blind to the research hypotheses). Due to positioning of the camera, only whole-body startle responses could be coded which were defined as limb, trunk, and/or head movements

evoked by the startle probe coded on a present/absence basis. The coder obtained inter-rater reliability for all judgments concerning startle-evoked movements ($\kappa = 0.92$) with one of the authors (Nazan Aksan).

STATISTICAL ANALYSES

To determine if changes in HR responses and SCR were significant, we performed a set of planned one-sample *t*-tests, examining whether the *change* (before and after startle probe) was significantly higher than 0 (one-tailed). To examine if changes in HR responses and SCR from startle 2 to 8 significantly habituated from startle 1, we performed a set of planned paired *t*-tests, using the contrasts of startle 1 versus 2, startle 1 versus 3, etc. The Bonferroni method was used to correct *p* values for multiple comparisons (net $p < 0.05$).

Motor responses to startle were coded using binary codes (0 = no, 1 = yes). A set of McNemar *Chi-Square* tests were performed to determine if changes in the motor responses to recurring startle probes were significantly different from the response to the first startle probe. *p* values were corrected for multiple comparisons using the Bonferroni method (net $p < 0.05$).

To determine if changes in different psychophysiological measures correlated with each other and with motor responses to startle probes, a set of Pearson correlations were computed for the following measures: changes in (1) PI, (2) PR, (3) reactivation overshoot, (4) ΔRMSSD7, (5) SCR, and (6) motor responses from the first four to the last four startle probes. Statistical significance was considered when $p < 0.05$ (two-tailed test).

RESULTS

MOTOR RESPONSE AND SCR TO STARTLE PROBES

Habituation of motor response and SCR were both robust. Results from McNemar *Chi-Square* tests indicated that, compared to the first startle probe, the fourth through the seventh probes were associated with lower percentage of children showing a motor response and at the eighth probe none of the children showed a motor response ($ps < 0.01$, **Figure 2A**). Regarding SCR, one-sample *t*-tests revealed that the eight startle probes all elicited significant SCR [$ts(68) > 8.60$, $ps < 0.01$, **Figure 2B**]. Paired *t*-tests showed that compared to the first startle probe, SCRs were significantly lower at the second through the eight startle probes [$ts(68) > 3.79$, $ps < 0.01$, **Figure 2B**].

CARDIAC IBI RESPONSES TO STARTLE PROBES

The first startle probe evoked a rapid, transient decrease in IBI followed by a recovery of IBI that exceeded the baseline IBI measured before the first startle probe was introduced (**Figure 3A**). Both the initial decrease in IBI and subsequent increase in IBI triggered by the first startle probe were statistically significant (**Figures 4A,B**). As mentioned above, we refer to the rapid decrease and increase in IBI as PI and PR, respectively (Graham and Clifton, 1966; Fernández and Vila, 1989; Reyes del Paso et al., 1993, 1994; Vila et al., 2007). In addition, we refer to the increase in IBI above baseline as "reactivation overshoot" (**Figure 4C**).

The startle-induced PI (decrease in IBI) was significant for the first three startle probes [$ts(74) > 2.93$, $ps < 0.05$], but was attenuated and no longer statistically significant for startles 4–8 (**Figure 4A**). Comparing with the first startle probe, only the fifth startle probe triggered a significantly less PI [$t(74) > 2.70$, $p < 0.05$].

Regarding PR (the subsequent increase in IBI), the first three startle probes triggered significant PR [$ts(74) > 2.93$, $ps < 0.05$; **Figure 4B**]. Paired *t*-tests revealed that PR was significantly less at startle probes 2–8 than at startle probe 1 [$ts(74) > 2.70$, $ps < 0.05$], which suggests a relatively more rapid habituation of PR than PI.

Reactivation overshoot was only significant at the first startle [$t(74) > 2.79$, $p < 0.05$]. Significant habituation (from the first startle) was observed at startle 2 [$t(74) > 2.59$, $p < 0.05$] as well as startles 5, 7, and 8 [$ts(74) > 2.58$, $ps < 0.05$; **Figure 4C**].

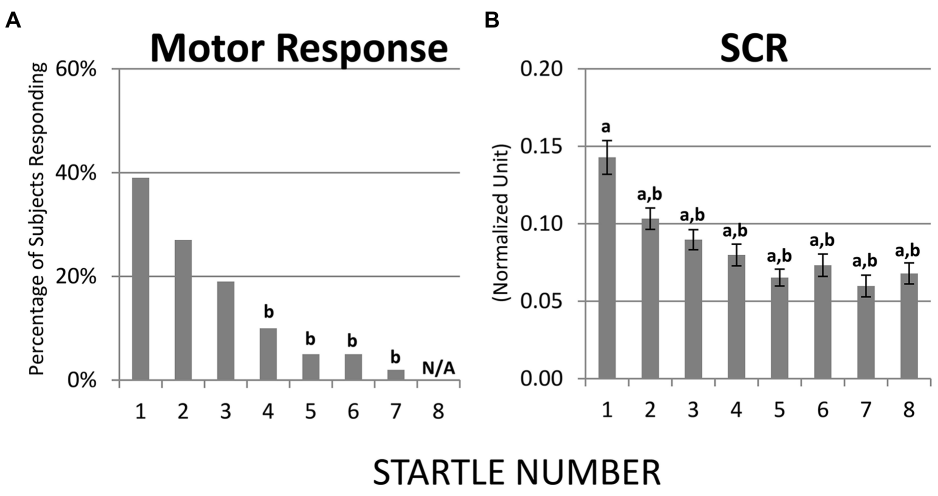

FIGURE 2 | Habituation of motor response and SCR over recurring startle probes. (A) Compared to startle 1, startles 4–7 were associated with lower percentage of children showing a motor response; at startle 8 none of the children showed a motor response. **(B)** SCR habituated immediately at startle 2. a = significantly higher than baseline (0); b = significantly lower than the initial response (i.e., startle 1).

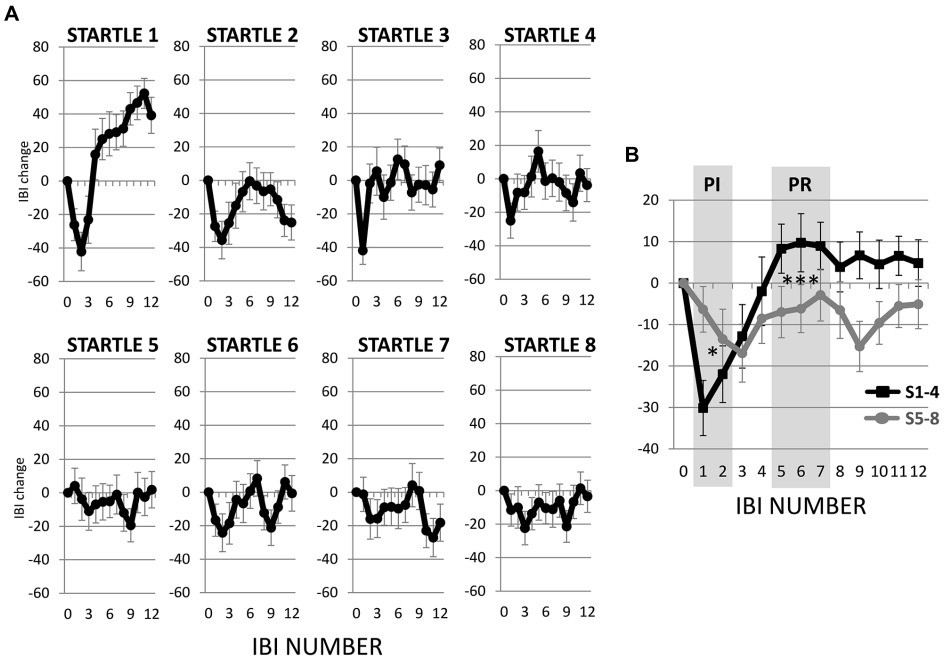

FIGURE 3 | Inter-beat interval (IBI) changes following startle probes. (A) Startle probe 1 evoked a rapid, transient decrease in IBI (PI), which was followed by an increase in IBI (PR) that exceeded the baseline IBI (reactivation overshoot). Both PI and PR habituated over recurring startle probes. **(B)** Average of IBI changes from the first four versus the last four startle probes. Both PI and PR significantly decreased (*p*s < 0.05, **Table 2**). $^{*}p < 0.05$; $^{***}p < 0.001$.

ΔRMSSD7 was significantly increased from the baseline value at startle 1 [$t(74) > 3.28$, $p < 0.01$], which gradually decreased at the startles 2 and 3, and became significantly smaller than startle 1 at startle 4 [$t(74) > 2.52$, $p < 0.05$; **Figure 4D**].

Table 1 summarizes the results described above.

BIVARIATE CORRELATIONS BETWEEN RESPONSES TO STARTLE

To determine if habituation in different psychophysiological measures correlated with each other and with motor responses to startle probes, we first computed the changes in PI, PR, reactivation overshoot, ΔRMSSD7, motor responses and SCR from the first four startle probes to the last four startle probes (**Table 2**). As shown in **Table 2** and **Figure 3B**, habituations of PI and PR were both significant when comparing the average of changes from the first four to the last four startle probes. We then examined the correlations among those measures. As shown in **Table 3**, habituation of PI and PR was strongly correlated ($r = 0.55$). The habituation of ΔRMSSD7 was significantly correlated with habituation of PR ($r = 0.40$), but not with habituation of PI ($r = 0.15$). Additionally, habituation of ΔRMSSD7 was significantly correlated with habituation of reactivation overshoot ($r = 0.27$). Habituation of SCR was significantly correlated with habituation of PR ($r = 0.25$) and was marginally correlated with habituation of the motor response ($r = 0.23$, $p < 0.10$).

DISCUSSION

A variety of parasympathetic, sympathetic, and behavioral responses to recurrent acoustic startle probes were measured in a defined population of eight year old children in this study. The major findings were: (1) The first startle probe induced a significant motor response, SCR, and rapid and transient PI, followed by a PR and overshoot; (2) Habituation of the motor response and SCR was robust and consistent; (3) PR habituated relatively quickly, whereas PI habituated slower, (4) Habituation of ΔRMSSD7 was faster than habituation of PI but slower than habituation of PR; (5) Habituation of SCR was significantly correlated with habituation of PR and marginally correlated with habituation of motor response; (6) Habituation of ΔRMSSD7 was significantly correlated with habituation of PR, but not with habituation of PI. We conclude that different measures of parasympathetic-mediated HR responses habituate in a differential manner during exposure of children to recurrent startle probes.

We discuss below the results of previous studies relevant to our findings, reasons for differences in habituation among the parasympathetic metrics examined, implications for clinical settings, and limitations in the study design.

PREVIOUS STUDIES OF HR RESPONSES TO STARTLE

Early results suggested that PI (the initial decrease in IBI following startle probes) was only evident in some studies. When PI occurred, it habituated to a less extent than PR (the subsequent increase in IBI; Davis et al., 1955; Lang and Hnatiow, 1962; Graham and Clifton, 1966). In the present study, we observed significant PI. Our results also confirm that the habituation of PI was less compared with PR. Of all the parasympathetic metrics we examined, PR showed the greatest habituation which was in part the result of strong overshoot of the increase in IBI at the first startle.

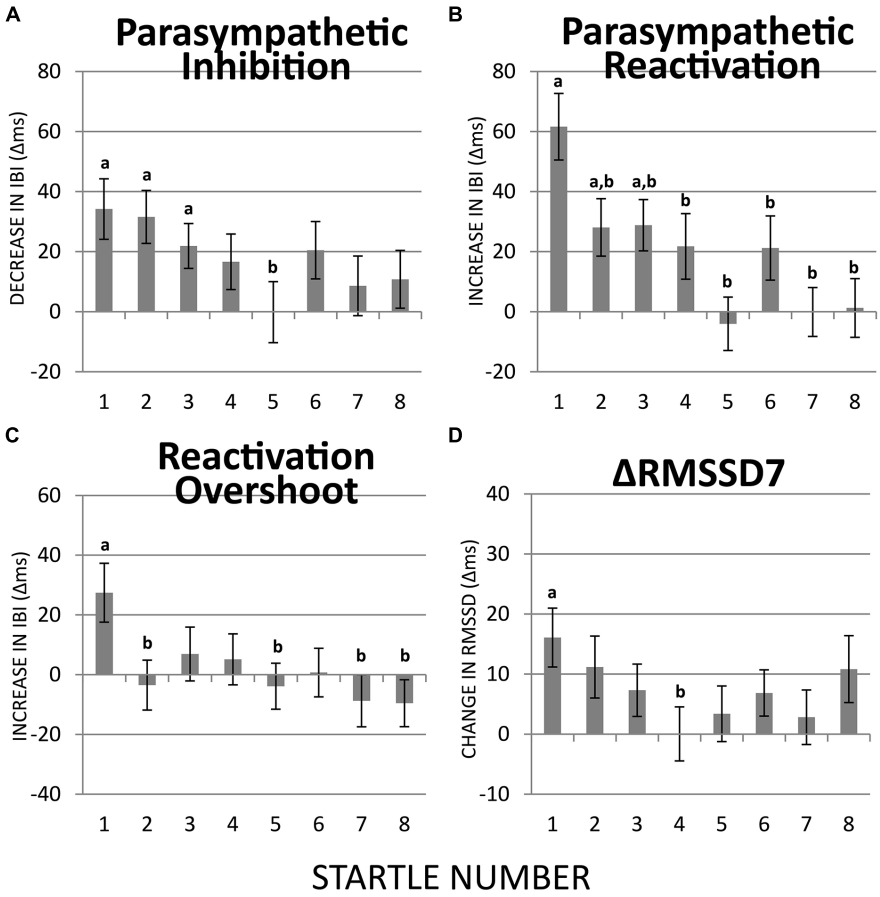

FIGURE 4 | Habituation of PI, PR, reactivation overshoot, and ΔRMSSD7 over recurring startle probes. (A) PI was significant at startles 1–3 but not at the remaining five startle probes. PI at startle 5 was significantly less than at startle 1. **(B)** PR was significant at startles 1–3 but not at the remaining five startle probes. PR habituated at startle 2. **(C)** Reactivation overshoot was significant at startle 1; it habituated at startle 2. **(D)** The first startle probe triggered a significant increase in RMSSD7 from baseline, which habituated significantly at startle 4. a = significantly higher than baseline; b = significantly lower than at startle 1.

Table 1 | Summary of significant responses to startles (S) and significant habituation from the first startle.

	Significant response (Response > 0/baseline[1])	Significant habituated from Startle 1 (Response < S1[2])
Parasympathetic inhibition (PI)	S1, S2, S3	S5
Parasympathetic reactivation (PR)	S1, S2, S3	S2, S3, S4, S5, S6, S7, S8
Reactivation overshoot	S1	S2, S5, S7, S8
ΔRMSSD7	S1	S4
Motor response	–	S4, S5, S6, S7, S8[3]
SCR	S1, S2, S3, S4, S5, S6, S7, S8	S2, S3, S4, S5, S6, S7, S8

[1] *Equals to note "a" in* ***Figures 2*** *and* ***4****;* [2] *Equals to note "b" in* ***Figures 2*** *and* ***4****;* [3] *No participant showed motor response to the startle probe.*

Recent studies provided evidence that low HRV measured during a resting baseline period is associated with decreased startle habituation of the eye-blink response (Gorka et al., 2013a,b). To our knowledge, except for the Jovanovic et al. (2009) study, no other studies have attempted to quantify HRV *during* the process of startle habituation. In this study, we used time-domain based ΔRMSSD7 as an easy-to-measure index of parasympathetic modulated HRV. Our results demonstrate that the first startle probe elicited a significant increase in RMSSD7 from baseline, which gradually decreased at startles 2 and 3, and became significantly smaller at startle 4 compared with startle 1. ΔRMSSD7 during the last four startle probes were less

Table 2 | Mean ± SE of the primary measures, and comparisons between averaged response from the first 4 versus the last 4 startle probes.

	Startle 1–4	Startle 5–8	*t*
Parasympathetic inhibition (ms, PI)	26.06 ± 5.87	9.93 ± 5.74	2.32*
Parasympathetic reactivation (ms, PR)	35.05 ± 6.85	4.58 ± 6.00	4.42***
Reactivation overshoot (ms)	8.99 ± 5.21	–5.35 ± 4.82	2.18*
ΔRMSSD7 (ms)	8.65 ± 2.78	5.97 ± 2.22	0.79
Motor response (frequency)	0.95 ± 0.15	0.12 ± 0.06	6.16***
SCR (n.u.)	0.10 ± 0.01	0.07 ± 0.01	7.14***

*n.u., normalized units. *p < .05, **p < .01, ***p < .001.*

stable, showing a less discernable pattern compared with earlier probes.

REASONS FOR DIFFERENCES IN HABITUATION AMONG PARASYMPATHETIC METRICS

Our results demonstrated that PR showed a rapid and strong habituation after the first startle. In contrast, habituation of PI was slower and relatively modest. We reason this could be a result of the different underlying mechanisms. More specifically, the magnitude of PI (decrease in IBI) immediately post-startle is determined in part by the cardiac vagal tone present during the baseline period prior to startle. In contrast, the subsequent PR (increase in IBI) is dependent on both the magnitude of the initial inhibition and the additional PR and overshoot.

ΔRMSSD7 provides an integrative measure of both inhibitory and reactivating components of parasympathetic modulation. The habituation of ΔRMSSD7 showed a pattern in between PI and PR. ΔRMSSD7 at startle 4 was significantly less than ΔRMSSD7 at startle 1. This habituation was slower than the habituation of PR but faster than the habituation of PI. In addition, ΔRMSSD7 was no longer significantly greater than baseline (measured from 7 IBIs before each startle probe) for startles 2–8, which illustrates the rapid habituation.

IMPLICATIONS FOR CLINICAL SETTINGS

Both PI and PR habituated to recurrent startle probes but at different rates. This result implies that there may have been different mechanisms involved for the individuals to adapt for recurrent aversive environmental stimuli, and those mechanisms may have different time courses for effect.

It has been suggested that PI (decrease in IBI) immediately post-startle reflects a defensive reflex, while PR (increase in IBI) reflects an orienting reflex (Graham and Clifton, 1966). As the task progresses with recurring startles, one might expect a decrease in novelty associated with orienting responses, and an increase in expectation associated with more-controlled defensive responses (comparing to the initial automatic defensive reflex), possibly resulting in decreases in both PI and PR.

Decreases in PI and PR may also reflect the transition from a "passive coping" to an "active coping" phase. According to Obrist (1976), HR deceleration reflects a process of "passive coping," meaning that the heart is passively influenced by the vagus nerve activity rather than by top–down cognitive effort exerted by the individual. "Passive coping" occurs when an aversive stimulus has just been encountered and before the individual has prepared a response to it (Obrist, 1976). In the current study, the high level of PR in the first few startle probes may reflect the process of "passive coping" as participants had little knowledge of what the 'loud sounds' would be like and how frequently they would be delivered. After the individual has encountered the aversive stimuli a few times, he or she may build expectations in the "active coping" phase, a more controlled cognitive process which is associated with increased sympathetic activity, resulting in HR acceleration (Obrist, 1976). In the current study, following repeated exposures to the startle probe, we observed less PR consistent with "active coping".

Results from this study have significant implications for clinical settings. Understanding changes in parasympathetic effect during startle habituation may shed light on both passive and active

Table 3 | Bivariate correlations among primary variables.

	Cardiac measures					
	Parasympathetic inhibition	Parasympathetic reactivation	Reactivation overshoot	ΔRMSSD7	Motor response	SCR
Parasympathetic inhibition (PI)	–					
Parasympathetic reactivation (PR)	0.55***	–				
Reactivation overshoot	–0.48***	0.47***	–			
ΔRMSSD7	0.15	0.40***	0.27*	–		
Motor response	0.20	0.18	–0.01	0.10	–	
SCR	0.15	0.25*	0.11	0.14	0.23$^{\phi}$	–

*SCR, skin conductance response. $^{\phi}p < 0.10$, *p < 0.05, ***p < 0.001.*

emotion regulatory processes during sustained exposure to aversive events. Previous studies have examined parasympathetic effect in responding to environmental changes, such as when the individual moves from rest to a stressful condition or vice versa (i.e., vagal withdraw and recovery, respectively; Porges et al., 1994; Santucci et al., 2008; Gentzler et al., 2009). The findings from the present study speak to this mechanism in a sustained aversive event. This coping process is likely to be automatic and implicit. However, it may require the individual to actively encode the intensity and the timing of the aversive stimuli, and anticipate future events, including the probability, timing, and possible outcomes.

A substantial number of studies have found reduced habituation in sympathetic-mediated and motor responses to recurrent startle probes in several psychiatric and neurological disorders, including schizophrenia, anxiety disorders, and Parkinson's disease (Lader and Wing, 1964; Raskin, 1975; Geyer and Braff, 1982; Roth et al., 1990; Rothbaum et al., 2001; Jovanovic et al., 2009, 2010). Results from the present study demonstrated a significant correlation between habituation of PR and habituation of the sympathetic-mediated SCR. This finding suggests that patients with the above psychiatric/neurological disorders may also exhibit impaired parasympathetic modulation during sustained aversive conditions. We suggest future studies to directly examine the function/dysfunction of parasympathetic modulation during sustained aversive conditions in those clinical populations.

LIMITATIONS IN STUDY DESIGN

There are several limitations in our study to consider. The present study did not control for the depth or frequency of breathing, which could significantly affect the changes in IBI induced by acoustic startle (Turpin and Siddle, 1978b). More specifically, individuals with deeper breathing may exhibit increased HRV than individuals with shallower breathing. In addition, previous studies have found that acoustic startle probes induce a rapid deep breath or gasp in some subjects and that this deep breath may contribute to the initial decrease in IBI post-startle (Smith and Strawbridge, 1969; Hart, 1975; Harver and Kotses, 1987; Reyes del Paso and Vila, 1993). Although we did not systematically analyze the effect of respiration, we did compare a subgroup of children ($n = 12$) who showed exaggerated inspiration post-startle with a subgroup of children whose respiration did not appear to be altered ($n = 14$). Analysis of the IBI responses to the first two startle probes suggests that children exhibiting deeper inhalations post-startle show a trend of greater PI and greater PR than children with unchanged respiration. The between-group difference in PR was significant for startle probe 2 [$t(24) = 2.51$, $p = 0.019$], while the difference in PR was marginally significant for startle probe 1 [$t(24) = 1.84$, $p = 0.078$].

Many startle habituation studies, including the present study, have used relatively short intervals between startle probes (15–25 s; Geyer and Braff, 1982; Jovanovic et al., 2009), while others have used longer intervals (>45 s; Lacey and Smith, 1954; Davis et al., 1955; Lader and Wing, 1964; Raskin, 1975; Rothbaum et al., 2001). One advantage of our design is that use of short intervals facilitates the rate of habituation. However, this design may not allow sufficient time for parasympathetic effect on HR to fully return to the original baseline levels. To test this possibility, we compared baseline RMSSD7 (the index of parasympathetic modulation) before each of eight startle probes. Baseline RMSSD7 did not significantly differ over the period of the first seven startle probes (**Figure S2**). The results suggest that the inter-startle intervals of our study were sufficient for parasympathetic modulation to return to baseline levels prior to the next startle probe.

We also considered that our finding that RMSSD7 increased from baseline at startle 1 and habituated gradually may have been confounded by a possible change in mean HR during the task. Previous studies have demonstrated that changes in HR *per se* can dramatically affect indices of HRV independent of changes in cardiac autonomic regulation (Sacha and Pluta, 2005; Billman, 2013). To address this issue, we compared the means of the IBIs used to calculate the first ΔRMSSD7 (IBIs pre- versus post-startle probe 1) and found no significant difference [$t(74) = 0.03$, $p = 0.98$], which suggested that the increase in RMSSD7 triggered by the first startle probe was not confounded. We also analyzed our data (trial-by-trial habituation in ΔRMSSD7) after correcting for changes in mean IBI as the task progressed (Sacha and Pluta, 2005; Billman, 2013), and the results confirmed our conclusions.

SUMMARY

In summary, we have demonstrated that different measures of parasympathetic modulation of HR responses habituate differentially in children exposed to recurrent startle probes. PR, following the initial PI, shows the most rapid and robust habituation of all of the measures. Our results are consistent with "active coping" hypothesis that has been proposed in adapting to sustained aversive events. We introduced ΔRMSSD7, a simple measure which captures the effects of both PI and PR and demonstrated that it is a valid measure of quantifying parasympathetic modulation during startle habituation. The current findings extend the existing literature on startle responses beyond the motor and sympathetic systems, and inform differences in various measures of parasympathetic modulation. These findings are well-situated to inform future studies that attempt to specify multivariate response profiles in startle paradigms that may come to serve as endo-phenotypes for psychopathology in both normative and non-normative samples.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fpsyg.2014.01288/abstract

Figure S1 | Examples of the abstract paintings used in the startle task. In order to keep participant's attention on the task, a series of abstract paintings were presented on the screen throughout the task.

Figure S2 | Baseline RMSSD7 (measured from seven IBIs prior to each startle probe) did not change significantly until the last startle probe. a = significantly different from the previous startle probe (two-tailed tests, *p* value corrected using the Bonferroni method).

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Cardiac autonomic imbalance by social stress in rodents: understanding putative biomarkers

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Exposure to stress or traumatic events can lead to the development of depression and anxiety disorders. In addition to the debilitating consequences on mental health, patients with psychiatric disorders also suffer from autonomic imbalance, making them susceptible to a variety of medical disorders. Emerging evidence utilizing spectral analysis of heart rate variability (HRV), a reliable non-invasive measure of cardiovascular autonomic regulation, indicates that patients with depression and various anxiety disorders (i.e., panic, social, generalized anxiety disorders, and post traumatic stress disorder) are characterized by decreased HRV. Social stressors in rodents are ethologically relevant experimental stressors that recapitulate many of the dysfunctional behavioral and physiological changes that occur in psychological disorders. In this review, evidence from clinical studies and preclinical stress models identify putative biomarkers capable of precipitating the comorbidity between disorders of the mind and autonomic dysfunction. Specifically, the role of corticotropin releasing factor, neuropeptide Y and inflammation are investigated. The impetus for this review is to highlight stress-related biomarkers that may prove critical in the development of autonomic imbalance in stress -related psychiatric disorders.

Keywords: social defeat, corticotropin releasing factor, neuropeptide Y, inflammation, post traumatic stress disorder, anxiety, depression, heart rate variability

Stress that stems from one's social environment is the most common form of stress encountered by people and is perceived as more intense than other types of stressors (Almeida, 2005). Socially stressful events are well recognized as contributing to the pathogenesis of depression, anxiety and posttraumatic stress disorder (PTSD; Kessler, 1997; Kendler et al., 1999; Javidi and Yadollahie, 2012). In addition to the debilitating consequences these psychiatric disorders have on mental health, they are also strongly associated with cardiovascular disease (CVD). As a result, psychiatric disorders significantly increase the risk of cardiac morbidity and mortality (Anda et al., 1993; Barefoot et al., 1996; Penninx et al., 2001; Rugulies, 2002; Surtees et al., 2008). Despite the clinical association between stress-related psychiatric disorders and CVD, little is understood regarding the pathophysiology or biomarkers underlying these comorbid disorders.

AUTONOMIC IMBALANCE IN PATIENTS WITH PSYCHIATRIC DISORDERS: RELEVANCE TO HEART DISEASE

One physiological change observed in patients with psychiatric disorders thought to contribute to increased CVD risk is dysfunction within the autonomic nervous system as evidenced by changes in heart rate variability (HRV). HRV reveals beat-to-beat changes in heart rate measured by the electrocardiogram. Variability within the heart rate is regulated by the sympathetic nerves, which accelerate heart rate and the parasympathetic (vagus) nerve, which slows it. Therefore, HRV provides a non-invasive measure of the balance between the sympathetic and parasympathetic nervous system. Healthy cardiac activity is characterized by a high degree of parasympathetic input and thus increased variability, protecting the heart against adverse cardiac events such as heart failure and myocardial infarction (Bigger et al., 1988; Hughes and Stoney, 2000; Carney et al., 2001). Alternatively, reductions in HRV that reflect increased sympathetic tone increase the risk of cardiac arrhythmias and sudden cardiac death (Verrier and Lown, 1982; La Rovere et al., 2003). Spectral analysis of HRV has revealed that increased low frequency (LF) measure of HRV and decreased high frequency (HF) reflect enhanced sympathetic and decreased parasympathetic activity, resulting in a marked increase in the LF/HF ratio (Pagani et al., 1986; Berntson et al., 1997; Ramaekers et al., 2002). Importantly, patients suffering from stress-related psychiatric disorders also exhibit autonomic disturbances. Major depression, generalized anxiety disorders and PTSD have all been associated with reductions in HRV (Udupa et al., 2007; Kemp et al., 2010; Pittig et al., 2013) and suffering from two of these disorders concurrently is reported to produce a further reduction in HRV (Chang et al., 2013; Minassian et al., 2014). A shift in HRV of this manner predicts life-threatening cardiac arrhythmias (Huikuri et al., 2009) and in patients lacking preexisting CVD, stress-related disorders such as depression and anxiety are associated with significantly increased risk of adverse cardiac events (Barefoot et al., 1996; Carney et al., 2001). While this association is clearly documented, the molecular systems or biomarkers capable of generating both stress-related psychiatric disorders and CVD are not defined, making treatment challenging. Preclinical models of social stress have provided invaluable clues as to which biological markers may be involved in the pathogenesis of these comorbid diseases and will be the focus of this review.

SOCIAL STRESS-INDUCED DYSFUNCTION IN RODENTS: RELEVANCE TO HUMAN PSYCHIATRIC AND CVD COMORBIDITY

Stress is a common risk factor for both CVD and psychiatric disorders. Therefore, identifying stress-sensitive systems that mediate cardiovascular and behavioral/emotional responses could shed light on the shared pathophysiology that links these comorbid disorders. Two reliable ethologically relevant animal model of social stress have proven particularly useful for studying this link. One is the resident-intruder paradigm of social defeat (Miczek, 1979; Sgoifo et al., 2014). This model involves subjecting a male rat (intruder) to aggressive threats from a larger, unfamiliar male rat (resident) by placing it in the resident's home cage for a short period of time. In the acute sense (minutes to hours) social defeat produces robust sympathetic activation eliciting 30 times the number of arrhythmias (ventricular premature beats) as compared to other non-social stressors such as restraint or foot shock (Sgoifo et al., 1999). Social defeat also produces vagal withdrawal, tachycardia, hypertension, hyperthermia, elevated plasma catecholamines, and increased activation of the hypothalamic-pituitary-adrenal axis (Tornatzky and Miczek, 1993, 1994; Sgoifo et al., 1999; Bhatnagar et al., 2006; Wood et al., 2010). Another valid model is social isolation in the socially monogamous prairie voles. This model involves separating a prairie vole from its opposite-sex partner and is well characterized as producing long-term cardiovascular dysfunction within 2–4 weeks. Under resting conditions, isolated prairie voles exhibit elevated heart rate, decreased HRV (Grippo et al., 2007), and a pronounced increase in circulating corticosterone and adrenal weights (Bosch et al., 2009). The robust activation of the sympathetic nervous system and the HPA axis during social defeat and social isolation are similar to those observed in humans in response to the Trier Social Stress Test, an experimental model of social stress in humans (Hellhammer and Schubert, 2012).

Acute stress responses are adaptive in helping the individual cope with the stressor, however, if unabated in the face of chronic stress this can lead to pathological changes. Therefore, social defeat in rodents and social isolation in prairie voles have behavioral and physiological consequences that are relevant to human pathologies. Cardiovascular telemetry allows for detailed 24 h cardiac monitoring in unrestrained animals and has been critical in establishing cardiovascular repercussions to stress, allowing for direct comparison to humans. From a physiological perspective, social defeat renders rats with disruption of the circadian rhythm for heart rate and core temperature (Tornatzky and Miczek, 1993; Sgoifo et al., 1999, 2002; Meerlo et al., 2002) and maladaptive cardiac hypertrophy (Gelsema et al., 1994). Seven brief exposures to social defeat increased the LF/HF ratio at rest, indicating a shift of sympathovagal balance toward a relative prevalence of sympathetic modulation (Wood et al., 2012). These findings were extended in a recent report where as few as four brief exposures to social defeat produced chronic reductions in both HRV and cardiac baroreflex sensitivity, reflecting a shift toward sympathetic predominance (Sevoz-Couche et al., 2013) which have been shown to be predictive of the occurrence of life threatening arrhythmias (Billman et al., 1982; La Rovere et al., 2003). Similarly, in prairie voles social isolation reduces resting HRV, increases cardiac weight and increases susceptibility to forced swim-induced arrhythmias (Grippo et al., 2007, 2012). Dysfunction within both the HPA axis and the immune system of socially stressed animals are also reported as persistent outcomes and mimic maladaptive changes seen in people with psychiatric diseases (Stefanski, 1998; Buwalda et al., 1999; Bhatnagar and Vining, 2003; Wood et al., 2010). Relevant long lasting behavioral consequences include decreased motivation, increased behavioral despair, anhedonia, anxiety-like behaviors, and decreased social interactions (Von Frijtag et al., 2000; Rygula et al., 2005; Grippo et al., 2007; Becker et al., 2008; Wohleb et al., 2011; Patki et al., 2013). Taken together, these studies provide evidence that repeated social defeat in rodents or chronic social isolation in prairie voles possesses the unique ability to recapitulate the behavioral and physiological changes associated with depressive and anxiety disorders. Taken together, these social stressors represent relevant models to study the comorbidity between psychiatric disorders and CVD, shedding light on mechanisms and biomarkers that may lead to increased susceptibility to psychiatric disorders with comorbid autonomic dysfunction. The following sections of this review report evidence from clinical and preclinical social stress studies highlighting putative biomarkers that should be further evaluated for their role in the pathogenesis of these comorbid conditions.

PUTATIVE BIOMARKER INVOLVED IN PSYCHIATRIC-CVD COMORBIDITY: CORTICOTROPIN-RELEASING FACTOR

There are several stress-sensitive biological molecules that have both pro-depressive or anxiogenic effects and impact the autonomic nervous system. As such, these molecules are classified as putative biomarkers driving the comorbidity between psychiatric disorders and autonomic dysfunction. One potential biomarker is corticotropin-releasing factor (CRF). This neuropeptide is considered the "hallmark" of the stress response (Vale et al., 1981). In stress-sensitive regions of the brain such as the amygdala, locus coeruleus (LC) and dorsal raphe CRF receptor activation is involved in stress-related emotionality and produces behavioral features of the stress response (Heinrichs et al., 1992; Hammack et al., 2003; Ayala et al., 2004; Wood and Woods, 2007; Dunn and Swiergiel, 2008; Valentino et al., 2009). Central administration of CRF in rats also activates the sympathetic nervous system, resulting in a marked pressor response and tachycardia (Briscoe et al., 2000; Nijsen et al., 2000). CRF's influence on the sympathovagal balance also extends into the periphery; intravenous infusion of CRF transiently increased the LF/HF ratio and tachycardia (Arlt et al., 2003). Given CRF's pervasive influence, it plays a central role in the behavioral, neuroendocrine and cardiovascular limbs of the stress response.

Like many elements of the stress response CRF is capable of promoting healthy adaptation to stress (Vale et al., 1981), but when unabated it can lead to pathology. For example, social defeat and social isolation impacts CRF levels as well as CRF_1 receptor distribution and quantity in brain and pituitary (Wood et al., 2009, 2010, 2013; Pournajafi-Nazarloo et al., 2011; Chaijale et al., 2013). Moreover, transgenic mice engineered to over-express CRF in the brain are disposed to exhibiting a depressive- and anxiety-like phenotype as well as decreased HRV (Dirks et al.,

2002; Vicentini et al., 2009; Bangasser et al., 2013). Overproduction of central CRF as evidenced by increased CRF has been identified in CSF of patients with depressive disorders and anxiety disorders such as PTSD (Nemeroff et al., 1984; Bremner et al., 1997; Baker et al., 1999). In post mortem depressed patients, specific changes in CRF within brain regions implicated in psychiatric disorders are also documented. For example, increased CRF protein levels have been documented in the LC and the paraventricular nucleus of the hypothalamus (Raadsheer et al., 1994; Austin et al., 2003; Bissette et al., 2003). Furthermore, CRF receptor mRNA down-regulation was reported in the frontal cortex of depressed patients and was thought to be a secondary consequence of exaggerated CRF release (Merali et al., 2004). Due to the convincing link between CRF dysfunction and psychiatric disorders, clinical trials have evaluated the therapeutic efficacy of CRF_1 antagonists. While the results have been equivocal, there is evidence to support their use as a promising new pharmacotherapy for anxiety and depression (Holsboer and Ising, 2008). The ambiguous nature of clinical results evaluating CRF_1 antagonists is suggested to be, in part, due to testing ineffective doses and the wrong patient population (Belzung, 2014). Preclinical studies have suggested that disorders with a high contribution of stress in the etiology, such as PTSD and stress-induced depression, may benefit from CRF antagonists (Wood et al., 2012; Philbert et al., 2013) however, individuals with stress-induced disorders were not tested (Belzung, 2014). For example, CRF antagonist treatment blocked depressive-like behavior following social isolation in prairie voles (Bosch et al., 2009). Furthermore, our recent studies revealed that social defeat-induced depressive-like behaviors, HPA dysfunction and decreased HRV was blocked by a CRF_1 antagonist during stress (Wood et al., 2010, 2012). Therefore, converging lines of evidence underscore the role of CRF in the development of stress-induced comorbidity between depression or anxiety and CVD.

PUTATIVE BIOMARKER INVOLVED IN PSYCHIATRIC-CVD COMORBIDITY: NEUROPEPTIDE Y

Neuropeptide Y (NPY) is yet another neuroendocrine peptide that has demonstrated central control over both behavioral and cardiovascular responses to stress. NPY is widely distributed in the brain and expressed in regions implicated in psychiatric disorders. NPY is often co-expressed with the neuropeptide CRF and as such, it is poised to impact central regulation of stress-related behavior, neuroendocrine and cardiovascular responses. For example, the LC (Makino et al., 2000), the amygdala (Adrian et al., 1983), and the PVN (Baker and Herkenham, 1995) all highly express both neuropeptides and NPY is reported to oppose the effects of CRF (Heilig et al., 1994; Britton et al., 2000). One such example occurs in the LC, where CRF serves as an excitatory neurotransmitter (Valentino et al., 1983) and NPY reduces the firing of LC noradrenergic neurons (Illes et al., 1993). As a result, central administration of NPY decreases NE overflow by acting on Y_1 receptors (Hastings et al., 2004). Because evidence of elevated LC activity has been linked to depression and PTSD (Wong et al., 2000; Geracioti et al., 2001) this NPY-induced brake on LC over activation may therefore promote stress resilience. The anti-stress effect of NPY is not unique to the LC; decreased levels of NPY were observed in the amygdala, hippocampus and periaqueductal gray of rats that were vulnerable to predator-scent stress versus the resilient phenotype (Cohen et al., 2012). Furthermore, social defeat exposure decreases NPY and NPY receptor mRNA in the hippocampus and hypothalamus (Zambello et al., 2010). Elevated NPY levels have also been associated with resistance to an anxious phenotype; in rats characterized as exhibiting high or low levels of anxiety, NPY mRNA in the amygdala was negatively correlated with anxious behavior (Primeaux et al., 2006). Moreover, central administration of exogenous NPY has demonstrated anxiolytic properties in rodents and is capable of inhibiting the anxiogenic effects of CRF (Britton et al., 1997; Ehlers et al., 1997; Primeaux et al., 2005). Importantly, these preclinical data are relevant to findings in humans; deficiencies within the central NPY system have been demonstrated in patients with major depression (Widerlov et al., 1988). Combat-exposed individuals with PTSD also have significantly lower levels of NPY in CSF (Rasmusson et al., 2000; Sah et al., 2014) and NPY levels recover following remission (Yehuda et al., 2006). Along these lines, high levels of NPY were observed in highly resilient special operations soldiers (Morgan et al., 2000). Therefore, clinical and preclinical data point toward increased NPY promoting resilience, while reduced NPY in the brain is related to psychiatric disorders.

In addition to its cognitive effects, NPY has prominent cardiovascular impact. Like NPY's effect on anxiety, its hemodynamic effects are also in contrast to CRF; central administration of NPY lowers blood pressure and heart rate at rest and in response to social defeat in rats (Klemfuss et al., 1998). The marked depressor and bradycardic actions of NPY occur at doses that have potent anxiolytic properties (Britton et al., 1997; Klemfuss et al., 1998). However, while the central actions of NPY may be cardioprotective, peripheral NPY infusion in rodent and in man acts as a potent vasoconstrictor (Pernow et al., 1987). NPY is co-released with NE during conditions of high-intensity sympathetic nerve activity and studies in mice lacking the NPY_1 receptor revealed that NPY serves to potentiate NE-evoked vasoconstriction (Lundberg et al., 1986; Pedrazzini et al., 1998). As such, peripheral NPY is associated with CVD such as heart failure, hypertension and myocardial ischemia (Zukowska-Grojec et al., 1996). Nonetheless, therapies that increase NPY selectively in the brain may prove effective in treating anxiety or depressive disorders and decrease cardiovascular risk by reducing sympathetic activity. In rodents, the single prolonged stress PTSD model produces many behavioral and biochemical features of PTSD (Liberzon et al., 1997) and in a recent study, intranasal NPY effectively blocked or reversed many of the consequences of this stressor (Serova et al., 2013, 2014). Several lines of evidence link NPY with the psychobiology of resilience to psychiatric disorders and CVD comorbidity. Therefore, investigating the efficacy of intranasal NPY for PTSD and depression as well as mitigating CVD risk in these patients will be critical.

PUTATIVE BIOMARKER INVOLVED IN PSYCHIATRIC-CVD COMORBIDITY: INFLAMMATORY CYTOKINES

Proinflammatory cytokines are another such mediator that can be persistently up regulated as a result of stress in vulnerable individuals and has roots in the pathogenesis of both psychiatric disorders and CVD (Black and Garbutt, 2002). In fact,

inflammation has long been recognized as contributing to CVD and recently, converging evidence implicates inflammatory factors in the pathogenesis of depression and anxiety disorders. Patients suffering from depression exhibit increased levels of the proinflammatory cytokine interleukin-6 (IL-6) while at rest and exhibit greater social stress-induced IL-6 levels, which are normalized following antidepressant therapy (Frommberger et al., 1997; Pace et al., 2006; Fagundes et al., 2013). Furthermore, Infliximab, a monoclonal antibody against tumor necrosis factor-α (TNF-α), exhibited antidepressant efficacy in a subset of patients characterized by elevated plasma cytokines (Raison et al., 2013). Elevated inflammation has also been identified in patients with various anxiety disorders, including PTSD (Vogelzangs et al., 2013; Newton et al., 2014). Interestingly, NPY has an inhibitory influence on neuroinflammation, further supporting the role of NPY in resilience (detailed review in Malva et al., 2012). Preclinical data also support the role of inflammation in depressive-like behaviors; IL-6 knockout mice demonstrate decreased depressive-like behaviors (Chourbaji et al., 2006). In addition to the unique capability of social defeat to produce an anxiety- and depressive-like phenotype with cardiovascular alterations as discussed above, it has been reported to produce persistent increases in the proinflammatory markers IL-6 and TNFα (Kinsey et al., 2008). Furthermore, microglia isolated from the brains of socially defeated mice produced markedly higher levels of the proinflammatory molecules IL-6, TNF-α, and monocyte chemoattractant protein-1 in response to the endotoxin lipopolysaccharide compared with controls (Wohleb et al., 2011). Importantly, antidepressants attenuate inflammation-induced brain cytokine production, as well as depressive-like symptoms, further supporting a role for neuroinflammation in depressive disorders in humans (Castanon et al., 2001; Yirmiya et al., 2001).

Proinflammatory cytokines also possess potent cardiovascular effects. For example, both central and peripheral infusion of the proinflammatory cytokine interleukin-1β induces a pressor response and tachycardia in rats (Kannan et al., 1996). In humans, cytokines are also linked to the autonomic nervous system, as reductions in HRV are associated with higher concentrations of IL-6 and TNF-α (Gonzalez-Clemente et al., 2007; von Kanel et al., 2008). A growing, yet still poorly understood body of evidence points toward neuroinflammation in the psychopathology of stress-related disorders and must be further characterized for the impact anti-inflammatory therapies may have on mitigating CVD risk in these patients (Dantzer et al., 2008; Maes et al., 2009; Rawdin et al., 2013).

There is a large body of evidence to suggest that psychosocial stress plays a prominent role in the etiology and progression of certain CVDs and psychiatric disorders. As such, there is a strong association between psychiatric disorders and increased cardiac morbidity and mortality. This review highlights proinflammatory cytokines, CRF, and NPY systems amongst those capable of generating both depressive or anxiety-like behaviors and reductions in HRV, thereby increasing CVD risk. Targeting these systems in preclinical social stress models and in psychiatric disorder patients with evidence of decreased HRV may prove beneficial and warrant further evaluation.

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Psychotherapy participants show increased physiological responsiveness to a lab stressor relative to matched controls

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Accumulating evidence indicates that psychotherapy participants show increased physiological responsiveness to stress. The purpose of the present study was to examine differences between individuals participating in outpatient psychotherapy and matched controls using an experimental design. Forty-two psychotherapy participants and 48 matched controls were assessed on cardiovascular and cortisol functioning at baseline, during the Trier Social Stress Test (TSST), and during a 20-min recovery period. Psychotherapy participants and matched controls did not differ at baseline or during the TSST on the physiological measures but psychotherapy participants had higher cortisol and heart rate (HR) during the recovery period. In regards to reactivity, cortisol increased during the recovery period for the psychotherapy participants but decreased for those in the matched control group. Psychotherapy participants experiencing clinically significant levels of distress displayed elevated systolic and diastolic blood pressure and HR during the TSST when compared to psychotherapy participants not experiencing clinically significant levels of distress. Overall, physiological reactivity to stress appears to be an important issue for those in psychotherapy and directly addressing this issue may help improve psychotherapy outcomes.

Keywords: stress, physiology, psychotherapy

INTRODUCTION

High levels of psychological distress contribute to elevated physiological activity and negative health outcomes (Steptoe et al., 2005; Chida and Steptoe, 2010; Carroll et al., 2012). In psychotherapy, high levels of psychological distress are related to elevated physiological activity and addressing difficult topics in therapy such as previous trauma leads to increased physiological responses (Lindauer et al., 2006; Ham and Tronick, 2009; Ehrenthal et al., 2010). This is particularly true in more severe pathology and inpatient studies. Lindauer et al. (2006) in a study of posttraumatic stress disorder found that focusing on trauma cues led to increased physiological reactivity. It is not known however if general psychotherapy participants in outpatient settings have elevated stress physiology relative to non therapy controls. The purpose of the present study was to answer this question using a controlled laboratory stress paradigm comparing psychotherapy participants to a psychotherapy naïve control group.

THE IMPACT OF STRESS

Stress is a highly prevalent problem with significant negative consequences (American Psychological Association [APA], 2008). In a nationally representative sample of Americans, approximately one third of Americans reported experiencing high levels of chronic stress (Keller et al., 2012). Research has shown that stress has negative effects on physical and mental health, and chronic stress plays a role in the development and progression of physical illness (Rozanski et al., 1999; Krantz and McCeney, 2002; Rosengren et al., 2004; Carroll et al., 2012). One area of physiological health that seems to be particularly affected by stress is cardiovascular disease. Steptoe et al. (2005) found that unemployment and financial difficulties predicted the development of hypertension at a 3-year follow-up, showing that exposure to stress contributes to deterioration of the cardiovascular system.

Stress reactivity, or the way individuals physiologically and emotionally respond to stressful situations, is central in understanding how we are affected by stress and how it impacts our functioning. Physiological measurements, such as cardiovascular indices and hormonal change, are an integral aspect of evaluating individual's stress reactivity. Increased levels of cortisol have consistently been linked to experienced acute and/or chronic stress (Bohnen et al., 1990; Engert et al., 2012; Aschbacher et al., 2013). Additionally, blood pressure (Juster et al., 2012) and heart rate (HR; Kudielka et al., 2004) are commonly used measures of stress reactivity and recovery. The most commonly used method to assess stress reactivity in the laboratory reported in the research literature is the Trier Social Stress Test (TSST). After establishing baseline levels, participants prepare for an ideal job interview, give the interview, perform math problems, and then rest during a recovery period. The TSST consistently results in elevated blood pressure and cortisol levels and is considered the gold standard of physiological stress reactivity assessment. No studies to date have examined physiological differences between psychotherapy participants and non-therapy controls in their responses to the TSST.

PSYCHOTHERAPY AND PHYSIOLOGY

Individuals engaged in psychotherapy display exaggerated physiological reactivity to stress. Blanchard et al. (2002) in a study of post traumatic stress disorder (PTSD) found that exposure to trauma cues lead to elevated HR reactivity. They also found that PTSD patients who respond positively to cognitive behavioral therapy displayed decreased HR reactivity in response to those trauma cues. Furthermore, PTSD patients provided with eye movement desensitization and reprocessing therapy have lower skin conductance and lower HR during trauma recall after only one therapy session (Aubert-Khalfa et al., 2008). Similarly, mothers who are clinically depressed show increased stress reactivity during a stress-inducing task compared to non-depressed mothers. One session of interpersonal psychotherapy is effective in significantly decreasing stress reactivity of depressed mothers (Cyranowski et al., 2009).

In a more general study about adolescents' externalized behavioral problems, Schechter et al. (2012) found that either low or high cortisol levels of adolescents are correlated with negative multisystemic therapy outcome. Additionally, children and adolescents experiencing stress while in treatment for behavioral problems show worse treatment outcome (Mathijssen et al., 1999). However, patients with panic disorder, agoraphobia, or other phobias actually respond better to treatment when they are more reactive to stress during fear inducing situations, as measured by HR (Lang et al., 1998) and cortisol levels (Siegmund et al., 2011).

To determine if stress reduction techniques enhance therapy outcome, Weiss et al. (2005) had participants receive psychotherapy treatment by itself, or stress reducing mindfulness training in addition to psychotherapy. Even though participants in the mindfulness in addition to psychotherapy group did not differ in distress scores after therapy from the psychotherapy group, the former group did have greater goal achievement scores in average. Psychotherapy related improvements in psychological distress have been correlated with decreased stress reactivity (Blanchard et al., 2002; Aubert-Khalfa et al., 2008; Cyranowski et al., 2009). In a pilot study, Ehrenthal et al. (2010) found that physiological stress reactivity prior to treatment predicts therapy outcome in a sample of inpatients hospitalized for depression. Those with low physiological stress reactivity had significantly better psychotherapy outcome compared to patients with high physiological stress reactivity. However, no studies to date have examined physiological stress reactivity in an outpatient setting.

CURRENT STUDY

The purpose of the present study was to examine whether psychotherapy participants in an outpatient setting would show elevated physiology relative to a matched control group. Three hypotheses were tested. First, psychotherapy participants would show elevated physiology at baseline before beginning the laboratory stressor. Second, psychotherapy participants would show a larger overall response to the laboratory stressor than the control group. And third, the psychotherapy participants would show increased physiological reactivity to the stressor with greater changes from baseline to stressor.

MATERIALS AND METHODS

PARTICIPANTS

Forty-two psychotherapy patients were recruited from the Brigham Young University, Provo Utah, counseling center. Psychotherapy patients entering the study had just begun psychotherapy and had received one to two sessions only. A matched control group of 48 college students not receiving psychotherapy were recruited via a research participation system run by the psychology department. Our sample was comprised of college students only. About 57% of participants were females, and 43% were males. The average age of all participants was approximately 23 (SD = 4.1) and the mean BMI was 23.4 (SD = 3.4). This study received Institutional Review Board approval before beginning and all participants read and signed an informed consent form before participating in the study.

PROCEDURES

Overview

The study proceeded in two phases: (a) completion of preliminary questionnaires, and (b) laboratory physiological stress reactivity measurement. All procedures were approved by the Brigham Young University Institutional Review Board. Preliminary questionnaires involved informed consent, a self-report measures of psychological distress, and demographic information. The second phase of the study involved the laboratory stress task. During the laboratory tasks, participants' physiological measures of stress reactivity were collected. Participants' completion of the study was compensated with 20 dollars cash.

The Trier Social Stress Test

Physiological stress reactivity was assessed through induction of a stressful situation using the TSST (Kirschbaum et al., 1993). The first phase of the TSST involves a baseline rest condition to establish resting blood pressure and levels of cortisol from saliva. During the baseline condition, participants were asked to sit quietly and watch a relaxing video for 15 min. At minutes 11, 13, and 15 of the baseline period BP and HR were measured while and one saliva sample was collected at minute 15. Stress induction occurs during the second phase of the TSST, when participants were asked to prepare for an impromptu speech. Participants were told to prepare mentally for a job interview for their ideal job and to think about how to best present themselves. After 5 min of speech preparation, participants were asked to present their speech in front of an unfamiliar research assistant. They were also told that their speech would be recorded for later analysis by experts. Speech presentation was 5 min. The last phase of the stress indication was a math problem. Participants had to mentally manipulate numbers and solve problems out loud for 5 min. They were told to stop and start over every time they made a mistake. BP and HR were measured at them midpoint and at the end of each task. The last phase of the laboratory tasks was a 20-min rest condition to evaluate how physiological indicators of stress return to normal, with BP, HR, and cortisol being measured at the beginning, midpoint, and end of the recovery period. Presentation of an unexpected speech in the context of evaluation by strangers and mental manipulation of numbers have been shown to significantly increase physiological measures of stress

and to provide an accurate representation of an individual's stress response.

MEASURES

Demographics

Client reported their age and gender, and then were weighed and measured in order to calculate body mass index (BMI).

Psychotherapy outcome

Psychotherapy outcome and participant's progress was monitored using the Outcome-Questionnaire (OQ-45, Lambert et al., 2004). The OQ-45 is a 45-item self-report measure assessing symptom distress, interpersonal relationships, social role, and quality of life in psychotherapy clients (Lambert, 2013). Each item is rated on a 5-point Likert scale ranging from 0-"Never" to 4-"Almost always." The OQ-45 is a valid and reliable measure of change in clients' reported distress. Previous research has determined that a cut-off score of 62 is indicative of clinical distress, those receiving mental health treatment typically score above this point, and community samples typically score below this point. It has an excellent internal consistency of 0.93 and a 3-week test-retest reliability of 0.84. In addition, it has a significant concurrent validity with measures of self-report symptoms and psychopathology such as the Beck Depression Inventory (Beck et al., 1996) and the Spielberger State Anxiety Inventory (Spielberger et al., 1983).

PHYSIOLOGICAL MEASURES

Heart rate, diastolic, and systolic blood pressure (SBP) data were collected using a Dinamap Model 8100 automated blood pressure monitor (Critikon Corporation, Tampa, FL, USA) that capitalizes on the oscillometric method. Readings were obtained following the specifications of the manufacturer using a cuff that was measured and properly sized to fit on the upper non-dominant arm of the participant. Cortisol was measured via saliva samples. Salivary samples were stored at −20°C until analysis. After thawing the samples, the salivettes were centrifuged for 5 min at 3000 rpm. Concentrations of salivary cortisol were measured using a commercially available immunoassay with chemiluminescence detection (CLIA; IBL, Hamburg, Germany).

DATA ANALYSIS

Before analyzing the research questions, experimental groups were first compared to examine whether groups were not significantly different at baseline for demographic, blood pressure, and psychological distress using independent sample *t*-tests and *chi*-square analyses. 2-Group × 7-Time repeated measures analyses of variance (ANOVAs) were used to analyze the research questions. We report partial-eta2 (η_p^2) for ANOVA effect sizes and significant main effects and interactions were decomposed using follow-up contrasts. Main effects for time were calculated to examine the impact of the experiment on blood pressure and HR from baseline to recovery, including the stressor. Time main effects were followed up by analyses of Group × Time interactions and tests of group differences.

RESULTS

SAMPLE CHARACTERISTICS

Table 1 displays the sample characteristics by experimental group. The psychotherapy and control groups were not significantly different on gender composition, age, or BMI. Similarly, there were no differences in baseline physiology between groups. The psychotherapy group scored significantly higher on the Outcome Questionnaire, a measure psychological distress that is related to psychotherapy outcome [Psychotherapy mean = 73.6 (25.7) and control group mean = 43.1 (16.5), $t = 4.280$, $p < 0.001$]. Gender and BMI were related to blood pressure and HR such that men had higher SBP ($t = 6.073$, $p < 0.001$) and lower HR ($t = -3.230$, $p < 0.01$) and those with higher BMI had higher SBP ($t = 4.139$,

Table 1 | Sample characteristics by experimental group.

	Psychotherapy group ($n = 42$)	Control group ($n = 48$)	*p*
Demographics and distress			
Gender (% female)	57%	56%	0.93
Age	22.9 (4.1)	23.0 (4.4)	0.88
Body mass index	23.4 (3.4)	24.3 (5.2)	0.32
Outcome questionnaire	73.6 (25.7)	43.1 (16.5)	<0.001
Baseline physiology			
Systolic blood pressure (mm/Hg)	108 (10)	109 (11)	0.49
Diastolic blood pressure (mm/Hg)	65 (7)	64 (7)	0.71
Heart rate (bpm)	69 (11)	73 (11)	0.10
Cortisol (nmol/l)	11.8 (7.4)	11.4 (7.1)	0.80
Recovery physiology			
Systolic blood pressure (mm/Hg)	112 (13)	112 (12)	0.85
Diastolic blood pressure (mm/Hg)	67 (7)	65 (7)	0.37
Heart rate (bpm)	74 (11)	70 (11)	0.03
Cortisol (nmol/l)	12.7 (10.9)	9.5 (4.9)	0.01

$p < 0.001$). Therefore, gender and BMI were used as covariates in the following analyses because of their significant relationship with the physiological measures.

BASELINE PHYSIOLOGY AND AVERAGE PHYSIOLOGICAL STRESS RESPONSE

The psychotherapy group and matched control group did not differ at baseline on measures of SBP, diastolic blood pressure (DBP), HR, or cortisol. In other words, participants in psychotherapy were not more physiologically aroused than matched controls at the beginning of the experiment. Similarly, there were no differences in average physiological stress responses between groups. During the beginning of the recovery phase, those in the psychotherapy group had elevated cortisol [$F(1,89) = 7.448$, $p < 0.01$, $\eta_p^2 = 0.07$] and HR [$F(1,88) = 4.635$, $p < 0.05$, $\eta_p^2 = 0.05$] relative to the matched control group (see **Table 1**). When examining only those in psychotherapy by level of clinical distress (measured by the Outcome Questionnaire, a score above 62), there were significant differences in average physiological response (see **Table 2**). Psychotherapy participants with high levels of distress displayed larger average physiological stress responses for SBP [$F(1,36) = 4.923$, $p < 0.05$, $\eta_p^2 = 0.12$], DBP [$F(1,36) = 6.280$, $p < 0.05$, $\eta_p^2 = 0.15$], and HR [$F(1,36) = 5.017$, $p < 0.05$, $\eta_p^2 = 0.12$].

PHYSIOLOGICAL REACTIVITY TO THE LABORATORY STRESSOR

Because cortisol was not different between groups at baseline but did differ during recovery, there was a significant difference in terms of physiological reactivity following the stressor. The overall within subjects analysis was $F(3,282) = 5.471$, $p < 0.01$, $\eta_p^2 = 0.06$ indicating different response patterns for the psychotherapy and matched control groups. Specifically, the psychotherapy participants displayed an increase in cortisol following the presentation of the laboratory stressor whereas the control group trended lower [$F(1,94) = 6.749$, $p < 0.05$, $\eta_p^2 = 0.07$; see **Table 1**]. For SBP, there was a non significant trend for those clinically distressed to have more physiological reactivity [$F(1,210) = 4.923$, $p = 0.082$, $\eta_p^2 = 0.050$; see **Table 2**]. This difference was most strongly seen during the math portion of the laboratory stressor with the clinically distressed participants in the psychotherapy group still showing relatively high levels of SBP, whereas the non-clinically distressed participants showed a significant drop in SBP [$F(1,36) = 4.083$, $p = 0.05$, $\eta_p^2 = 0.10$; see **Figure 1**].

DISCUSSION

The purpose of this study was to examine whether physiological response to a laboratory stressor would be higher in psychotherapy participants relative to a matched control group. It was hypothesized that psychotherapy participants would have elevated baseline physiology, elevated average physiological response, and greater reactivity to a speech and math stressor relative to baseline levels. No group differences in physiology were found at baseline. Those in psychotherapy did report higher levels of psychological distress as might be expected. There were no differences between groups in average physiological response; however there was a significant difference when comparing those with high levels of clinical distress with those with low levels. Those high in clinical distress displayed higher overall SBP, DBP, and HR to the TSST than did the low distress group. In regards to physiological reactivity, the psychotherapy group showed greater cortisol levels following the TSST relative to the control group indicating a stronger stress response.

There are three key implications of these findings. First, not everyone engaged in psychotherapy has clinical levels of distress and it appears that overall level of clinical distress is an important factor in physiological response to stress. However, most of those who qualified as clinically distressed were in the psychotherapy

Table 2 | Sample characteristics by level of clinical distress for those in the psychotherapy group only.

	High distress ($n = 28$)	Low distress ($n = 12$)	p
Demographics and distress			
Gender (% female)	58%	56%	0.90
Age	23.2 (4.5)	22.8 (4.1)	0.60
Body mass index	23.1 (3.7)	24.3 (4.8)	0.20
Overall physiology (average across all tasks)			
Systolic blood pressure (mm/Hg)	117 (10)	110 (11)	0.03
Diastolic blood pressure (mm/Hg)	66 (7)	62 (7)	0.02
Heart rate (bpm)	76 (12)	69 (10)	0.03
Baseline physiology			
Systolic blood pressure (mm/Hg)	109 (10)	108 (11)	0.94
Diastolic blood pressure (mm/Hg)	66 (7)	64 (7)	0.19
Heart rate (bpm)	72 (12)	70 (10)	0.40
Physiological stress reactivity (math)			
Systolic blood pressure (mm/Hg)	126 (16)	123 (15)	0.082
Diastolic blood pressure (mm/Hg)	77 (9)	73 (8)	0.395
Heart rate (bpm)	81 (15)	80 (12)	0.757

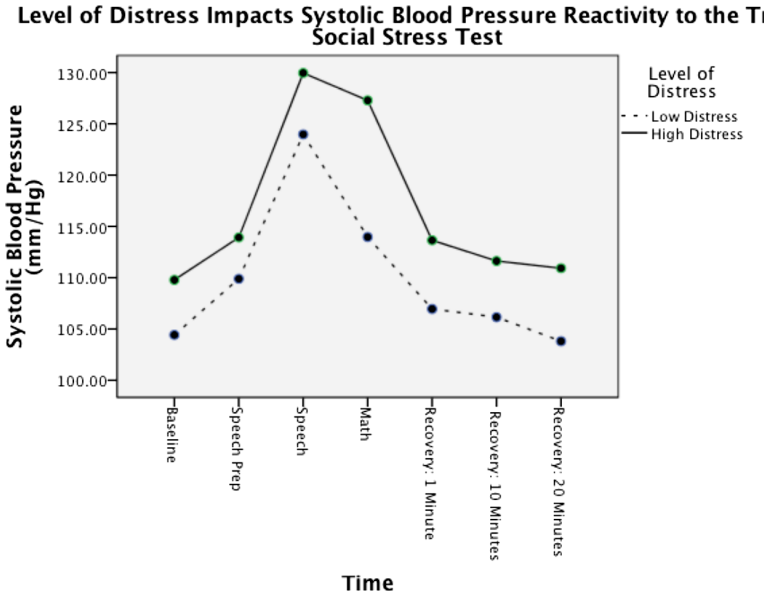

FIGURE 1 | Psychotherapy participants with high levels of clinical distress (an Outcome Questionnaire score above 62) show higher levels of blood pressure reactivity to the Trier Social Stress Test.

group. Given the limited size of this study and the small number of controls with clinical distress, there was insufficient power to see whether there was an interaction between psychotherapy participation and clinical distress.

The second implication is that psychotherapy participants may look normal physiologically at rest but have an exaggerated response to stressful situations. To examine the impact of stress in psychotherapy, it is insufficient to measure just baseline physiology. Rather, it is the reaction to and recovery from stressful situations that are important (Zautra, 2009). This finding is in line with Heim et al. (2000) who found that those with depression and trauma did not appear different physiologically at baseline but had a large physiological stress response relative to controls. Resilience may play a key role here (see Connor and Davidson, 2003; Zautra, 2009). Those higher in resilience may handle stress more effectively and thereby recover from stress more quickly. It is also possible that successful psychotherapy increases resilience and thereby decreases physiological reactivity to stress (Lane et al., 2009; Thayer et al., 2012).

The third implication is that stress reduction strategies may be a useful adjunct for those in psychotherapy. High levels of stress can interfere with attention and focus and stress reduction may help improve psychotherapeutic efforts by reducing physiological stress symptoms. Marci and Riess (2005) and Riess (2011) argue for the clinical relevance of using psychophysiologic measures as an important adjunct in psychotherapy that has the potential to improve therapy quality and help guide therapeutic decisions. It is also possible that the current focus on mindfulness approaches in cognitive behavioral psychotherapy is at least partially driven by its success in reducing stress. Additionally, HRV biofeedback has shown promise as an adjunctive treatment in depression and anxiety, with stress reduction likely playing a key role in this affect (Karavidas et al., 2007; Lehrer and Eddie, 2013).

There are several limitations to this study. First, this study was cross sectional in nature so it is not clear how stress physiology impacts long term outcome in psychotherapy. Second, the sample consisted of relatively young, healthy college students with psychotherapy being administered in a counseling center. It is not known if these results will generalize to other age groups, conditions, or different clinical settings. Strengths of the current study were the inclusion of a matched control group with no previous psychotherapy experience and a controlled experimental design. Future studies could build on these findings by conducting controlled experimental longitudinal studies to examine how reducing stress physiology is related to psychotherapy outcome and by looking at different age groups and different clinical settings. Additionally, focusing on the role of resilience in the relationship between psychotherapy and psychophysiological stress reactivity may be especially fruitful (see Connor and Davidson, 2003). It is possible that psychotherapy increases resilience in the face of significant stress (Lane et al., 2009; Thayer et al., 2012).

In conclusion, people with who are clinically distressed display greater physiological response and greater physiological reactivity to a laboratory stressor relative to a matched control group. Distressed individuals did not differ at baseline physiologically indicating resting physiological measures may be insufficient to identify those who may be at risk of stress related problems in psychotherapy. Rather, examining stress response as well as ability to recover from stress once the stressor is over is crucial. Stress reduction techniques may be a beneficial adjunct to psychotherapy and future studies could examine this possibility using a longitudinal controlled experiment.

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A bihemispheric autonomic model for traumatic stress effects on health and behavior

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A bihemispheric autonomic model (BHAM) may support advanced understanding of traumatic stress effects on physiology and behavior. The model builds on established data showing hemispheric lateralization in management of the autonomic nervous system, and proposes that traumatic stress can produce dominant asymmetry in activity of bilateral homologous brain regions responsible for autonomic management. Rightward and leftward dominant asymmetries are associated with sympathetic high arousal or parasympathetic freeze tendencies, respectively, and return to relative symmetry is associated with improved autonomic regulation. Autonomic auto-calibration for recovery (inverse of Jacksonian dissolution proposed by polyvagal theory) has implications for risk behaviors associated with traumatic life stress. Trauma-induced high arousal may be associated with risk for maladaptive behaviors to attenuate arousal (including abuse of alcohol or sedative-hypnotics). Trauma-induced freeze mode (including callous-unemotional trait) may be associated with low resting heart rate and risk for conduct disorders. The model may explain higher prevalence of leftward hemispheric abnormalities reported in studies of violence. Implications of the BHAM are illustrated through case examples of a military special operations officer with history of traumatic brain injury and post-traumatic stress disorder, and a university student with persisting post-concussion symptoms. Both undertook use of a noninvasive closed-loop neurotechnology – high-resolution, relational, resonance-based, electroencephalic mirroring – with ensuing decrease in hemispheric asymmetry, improvement in heart rate variability, and symptom reduction. Finally, the BHAM aligns with calls for researchers to use brain-behavioral constructs (research domain criteria or RDoC, proposed by the National Institutes of Mental Health) as building blocks for assessment and intervention in mental health science.

Keywords: autonomic nervous system, hemispheric asymmetry, trauma, traumatic brain injury, post-traumatic stress disorder, polyvagal theory, violence, RDoC

INTRODUCTION AND OVERVIEW

Though studies of the autonomic nervous system (ANS) have historically been dominated by focus on anatomically inferior neural structures or body organs including the heart, gut, skin, and blood vessels, there has also been increasing appreciation for how the ANS is regulated by pathways of the central nervous system that are anatomically and functionally more "upstream" (Saper, 2002; Cechetto and Shoemaker, 2009). The present paper begins on the foundation of multiple studies that have reported lateralization in hemispheric management of arousal or ANS functioning, with the right and left hemispheres being principal managers for the sympathetic and parasympathetic divisions of the ANS, respectively. We propose that the finding of hemispheric laterality in ANS management may be productively integrated with recent thinking that suggests a hierarchical structure in ANS responsivity to stress or trauma (Porges, 2011). The resulting synthesis is a novel ANS model of traumatic stress effects on health and behavior that may have explanatory, predictive, and interventional implications as a new paradigm in trauma studies.

In one way or another, trauma undoubtedly affects the entire brain. To gain initial traction on this complex problem, the bihemispheric autonomic model (BHAM) explains and predicts traumatic stress effects on health and behavior in terms of shifts in hemispheric asymmetry in the activity of bilateral homologous brain regions responsible for autonomic management. Asymmetrical activation in these regions is associated with different forms of physiological arousal and behaviors. Rightward asymmetry in salient regions is associated with acute threats and sympathetic high arousal (fight-or-flight) behaviors. Leftward asymmetry is associated with repeated or severe traumas (or trauma that produces a sense of futility) and a parasympathetic freeze state (physiological and behavioral immobilization). Production of these asymmetries and their associated arousal states is viewed as the expression of relatively autonomous drives for autonomic auto-calibration. That is to say, when the brain "neurocepts" a

threatening environment, the ANS will tend to calibrate for high arousal without an individual's conscious deliberation. Similarly, if the brain neurocepts a stressful or traumatic state that produces no possibility of successful escape (including serial stressors, an overwhelming stressor, or emotional abandonment), then the ANS will tend to calibrate for a freeze response, again without the subject's thinking or willing.

Autonomic auto-calibration, demonstrable at the level of cerebral hemispheres, may occur in response to trauma, but also as processes or behaviors to support recovery (or attempted recovery) from trauma. Drives for autonomic auto-calibration out of traumatic stress states may explain some behavioral repertoires associated with traumatic life experience, and this aspect of the BHAM is developed in alignment with the hierarchical structure of ANS behavioral responsivity proposed by polyvagal theory (Porges, 2011). Polyvagal theory posits that vagal inhibition of sympathetic arousal, in safe contexts, is the highest-order mode of ANS operation, followed by sympathetic high arousal for acute threats, and finally parasympathetic freeze mode for persistent or severe trauma, as mode of last resort. An inverse view of this hierarchy – in conjunction with postulated existence of autonomous drives for recovery – suggests that individuals in parasympathetic freeze mode may be at risk for generating compensatory high-arousal behaviors to depart the freeze mode, including conduct disorders and substance abuse, to generate greater experience of subjective *feeling*. Individuals in sympathetic high-arousal mode may be at risk for arousal-attenuating behaviors including substance abuse or medication dependence or abuse. Evidence from criminology appears to support the BHAM explanation for history of traumatic life events and high-arousal behavioral risk, in that individuals with propensity for violence have increased prevalence of leftward hemispheric asymmetry or left-hemispheric aberrancy.

The paper illustrates the model through two case examples of individuals with histories of traumatic stress including mild traumatic brain injury, in which reduction of asymmetrical activity in brain regions associated with autonomic management appeared to reflect improved upstream regulation in the ANS. Comment on these cases includes suggestion that the BHAM is in alignment with calls from the National Institutes of Mental Health (NIMH; Cuthbert and Insel, 2013) for researchers to focus on biologically valid brain-behavioral constructs, rather than symptom checklists and population statistical criteria, to make meaningful progress in mental health science. The discussion concludes by proposing that recently proposed hierarchical understanding of ANS responsivity integrated with appreciation of hemispheric lateralization in ANS management, may support a new scientific paradigm (Kuhn, 1962) for research and intervention related to the ANS with broad implications for health and behavior.

STUDIES REPORTING HEMISPHERIC ASYMMETRY IN MANAGEMENT OF AROUSAL OR AUTONOMIC FUNCTIONING

Many studies have reported hemispheric asymmetry in management of arousal levels, either demonstrating or potentially implying a distinct form of ANS activity associated with each hemisphere. We review representative studies in four categories: consequences of unilateral brain dysfunctionality on measures of arousal, studies involving direct stimulation or inactivation of brain structures, psychophysiological studies in healthy subjects, and studies related to stress effects on hemispheric or neurocardiac functioning. Several of the studies have converged on the bilateral insular cortices as being key sites for lateralization in hemispheric management of the ANS, and implications of this finding are addressed in the case study section. For purposes of this literature review we highlight hemispheric laterality as the common unit of analysis.

Gainotti (1972) compared 80 patients with left-sided lesions to 80 patients with right-sided lesions, with respect to their behaviors during neuropsychological exams. He found that those with left-sided lesions were more likely to demonstrate emotional tendencies for "catastrophic reactions" (anxiety, tears, swearing), and those with right-sided lesions were more likely to show "indifference reactions" (indifference, minimization, or anosognosia). Other teams (Heilman et al., 1978; Morrow et al., 1981) extended his findings with psychophysiological measures showing decreased galvanic skin resistance with a stimulus, indicative of hypoarousal, in patients with right-hemispheric lesions, compared to patients with left-hemispheric lesions or controls without brain injury. The above authors largely refrained from positing a causal role of the left hemisphere to explain findings in patients with right-sided lesions, proposing instead injury to thalamo-cortical loops (Heilman et al., 1978) or disruption of right hemispheric functionality for emotional processing (Gainotti, 1972; Morrow et al., 1981). More recently, Daniele et al. (2002) reviewed electrocardiograms of 352 hospitalized individuals with completed ischemic strokes and found that those with right-hemispheric injuries were more likely to have cardiac arrhythmias than those with left-sided injuries. They postulated that right-sided injuries were more likely to disinhibit right-sided neural mechanisms for sympathetic regulation of heart rate. Finally, Avnon et al. (2004) reported that in a group with unilateral migraine, those with left-sided headache were more likely to have augmented parasympathetic responses – vasodilatation and bradycardia in response to a mild stressor (soapy water to the eye) – than were those with right-sided symptoms. In contrast to the earlier studies, this report suggested a direct role of the left hemisphere in producing parasympathetic responses.

Peri or intra-operative epilepsy surgeries have allowed more direct inferences about the causal role of brain structures. Zamrini et al. (1990) investigated cardiovascular responses from unilateral hemispheric inactivation by intra-carotid amobarbitol, in 25 epileptics undergoing preoperative evaluation for epilepsy surgery. Heart rate increased after left hemisphere inactivation, and decreased after right hemisphere inactivation. Spurred by interest in possible mechanisms of cerebrogenic sudden death in epileptics, Oppenheimer et al. (1992) performed intra-operative stimulation of the insular cortex prior to temporal lobectomy for seizure control. They found that stimulation of the left insula (in comparison to the right) produced more bradycardia and blood pressure depressor responses than tachycardia and pressor effects. The opposite was true of right insula stimulation. Other studies (also based on unilateral intra-carotid amobarbitol infusion in epileptics) corroborated opposing hemispheric roles for autonomic cardiovascular control using spectral analysis of heart rate (Yoon et al.,

1997) and measures of blood pressure and baroreflex sensitivity (Hilz et al., 2001). Collectively, these studies lend stronger evidence that neural mechanisms in the left hemisphere have an independent, efferent, and parasympathetic role in autonomic modulation.

Evidence that hemispheric lateralization of autonomic management exists for human subjects without neurological disease has been provided through two sets of experiments by Wittling (1990) and Wittling et al. (1998a,b). In the first study, Wittling (1990) and Wittling et al. (1998a,b) showed a romantic film to 50 young adults through a technique of stimulus presentation to a single hemisphere at a time. Right hemispheric film presentations caused significantly greater increases to blood pressure, especially for the female subjects. In the subsequent study, they used the same single hemisphere stimulation technique to show two different films (to control for the effects of emotionality as such, independent of lateralized presentation effects) to 58 young adults. One film was emotionally challenging ("Schindler's List," a film about the pogrom of Jews in Germany), while the second was a scenic film of peaceful pictures. Right hemisphere stimulation was found to be associated with increased ventricular myocardial activity, and left hemispheric stimulation was found to be associated with higher values for the high-frequency spectral component of heart rate variability, a commonly used metric for parasympathetic activation. These studies have represented an important step towards a BHAM by further showing independent roles of the hemispheres, and in subjects without brain injury.

The fourth category of studies supporting a two-hemisphere view of ANS management includes reports that relate to the topic of stress effects on hemispheric or neurocardiac functioning. Rabe et al. (2006) compared electroencephalographic activity of 22 individuals with post-traumatic stress disorder (PTSD) due to motor vehicle accident, 21 individuals who had been through a motor vehicle accident but without PTSD, and 23 healthy controls. Those with PTSD showed greater right-hemispheric activation than the other groups (decreased alpha band on the right compared to the left), when exposed to trauma-related material, and the degree of their asymmetry was correlated with PTSD symptom severity. The same researchers went on to show that rightward asymmetries tended to be reduced after a successful cognitive-behavioral therapy intervention (Rabe et al., 2008). Right-temporal lobe activation has also been reported in a magneto-encephalography study of PTSD (Engdahl et al., 2010), though no inference was made by the authors to associate asymmetry with autonomic mechanisms. In an acute stressor paradigm (performance of rapid calculations), Gray et al. (2007) studied scalp-derived electrical potentials associated with cardiac function, in ten men with heart disease. They found that negativity of a heart-evoked potential (HEP, an electrical signal from the scalp, synchronized with the heart beat) at left temporal and left lateral frontal regions was correlated with changes in cardiac output and cardiac repolarization homogeneity. While this report appears to add to the case for a bihemispheric model of autonomic management, perhaps even more significantly it showed that cortical signals related to autonomic cardiac regulation could be detected through noninvasive measures at the scalp. And though the authors approached the study as a means to better understand afferent cardiac signaling to the cortex, they were careful to recognize that the cortical potential they measured could instead be representing efferent signaling from the cortex to control the heart rate. Finally, recently we have reported (Tegeler et al., 2013) in a heterogeneous cohort of individuals with stress-associated conditions, that leftward asymmetry in temporal lobe high-frequency electrical activity measured from the scalp is negatively correlated with heart rate and positively with heart rate variability.

It should be noted that not all learned opinion is in agreement regarding the defensibility of a consistent model of lateralized cortical cardiovascular sympathetic and parasympathetic representation. One general refutation of this hypothesis has been presented in the discussion of a retrospective study of individuals hospitalized for video-EEG monitoring whose medical records included evidence of bradycardia or bradycardia-related clinical events (Britton et al., 2006). The authors identified 13 cases that met their inclusion criteria, out of 6168 who underwent video-EEG monitoring over a 14-year period, and they found no consistent hemispheric lateralization of seizure activity in these patients. This study by Britton et al. (2006) is a helpful counterpoint, though it bears mentioning that lack of evidence for correlation between an autonomic effect and a specifically hypothesized form of asymmetry (e.g. lateralized seizure activity) permits a weaker type of inference – only that the autonomic effect being studied was not associated with that specific form of asymmetry – and does not constitute evidence that lateralization in autonomic management does not exist.

THE BIHEMISPHERIC AUTONOMIC MODEL

The studies reviewed in the preceding section collectively suggest that an accurate and comprehensive view of autonomic functioning requires consideration of the independent roles of the left and right hemispheres, and especially patterns of asymmetrical hemispheric activation in brain regions responsible for autonomic management. In this section, we integrate the above data into a BHAM that encompasses the above findings while also proposing a way to understand the dynamics of trauma effects on the brain and brain influences on behavior. We propose the existence of relatively autonomous drives for autonomic auto-calibration that may find expression as shifting forms and degrees of asymmetrical hemispheric activation. For purposes of this paper, the model is deliberately qualitative and conceptual. We hope the model will encourage empirically precise, quantitative, and hypothesis-driven studies, even as we hope it facilitates additional conceptual and theoretical innovations across health and behavioral sciences.

FOUR THESES OF THE MODEL

Thesis One. *Relative symmetry in activation of bilateral cerebral hemispheric regions responsible for management of the autonomic nervous system is likely to be associated with an organismal state of relative autonomic optimality, characterized by relatively small and healthy fluctuations between leftward and rightward asymmetry of activity in those regions.* This state of relative symmetry,

fluctuating towards either leftward or rightward asymmetry but not to extreme degrees or for prolonged lengths of time, corresponds to a relative capacity for healthy and adaptive fluctuation. In a complex and changing environment, it is healthy, needful, and subjectively enjoyable, to move smoothly and fluidly between parasympathetic states of rest and calm, and sympathetic states of increased arousal, action, and overt excitement.

Thesis Two. *Rightward dominant asymmetry may arise in hemispheric regions responsible for management of the autonomic nervous system, in association with traumatic experience or perception of threat, producing a tendency for high arousal physiology that is likely to be maladaptive in its persistence.* The right hemisphere-dominant autonomic state may be adaptive, for example in a military serviceperson in armed combat, or in an individual living in close quarters with someone who behaves abusively. However, the persistence of such asymmetry and associated high-arousal physiology is likely to be maladaptive for non-threatening contexts. The same soldier returning from war will predictably have difficulties in maintaining the calm and restful parasympathetic state needful for civilian life. Similarly, the individual under threat of abuse in their home may feel maladaptively aroused when they go to the workplace or attempt to enjoy low-risk social encounters. Individuals in this state may be at risk for compensatory behaviors to attenuate the high arousal associated with right-dominant autonomic asymmetry, for example substance abuse or medication dependence or abuse.

Thesis Three. *Leftward dominant asymmetry may arise in hemispheric regions responsible for management of the autonomic nervous system, especially in association with severe trauma or perception of futility, producing a risk for compounded maladaptations – tendencies both for persistent immobilization physiology, as well as compensatory high arousal behaviors.* A leftward dominant state may be characteristic of an individual faced with stress or trauma that overwhelms the utility of high arousal (for fight or flight) or otherwise presents no exit options, thereby inducing a state of behavioral freeze or shutdown. For example, leftward asymmetry might characterize a soldier who has had severe traumatic stress and is now emotionally numb (frozen), or an individual who feels abandoned by a care-giver or loved one. Such a state may be adaptive as a way to withdraw from complex environments (and decrease risk of further injury), but if persisting it will prevent healthful engagement with life by most any reasonable measure. Paradoxically, high-arousal behaviors may also be expressed by those with immobilization physiology as compensatory processes (to depart the freeze state). Risk for producing these behaviors, which may include conduct disorders, rage, or substance abuse, is predicted to represent a significant burden of suffering for those in the parasympathetic freeze state (see Autonomic Auto-calibration May Explain Increased Risk for High-Arousal Behavior in Individuals who are in a Parasympathetic Freeze State).

Thesis Four. *Movement between the states of symmetry and asymmetry described in Theses One through Three is a function of two main influences – relatively autonomous drives for autonomic auto-calibration, and higher-order self-regulatory processes managed by the prefrontal cortex.* Exposure to stressors or trauma will be associated with relatively autonomous drives for autonomic auto-calibration from relative symmetry to rightward dominance, and/or leftward dominance, whereas processes for recovery will tend to be associated with auto-calibration from leftward or rightward dominance, toward relative symmetry. Autonomous drives for autonomic auto-calibration may be guided by conscious choice-making and other capacities associated with the executive role of the prefrontal cortex, that represent a rudder and decision-making apparatus for navigation and management of environmental contexts and neural energetics that together produce asymmetries.

The distinction made in the model between stresses that produce rightward or leftward asymmetry owes much to polyvagal theory (Porges, 2011), which has reconceptualized autonomic responsivity in hierarchical terms, distinguishing between self-calming (typically healthful) and immobilizing (trauma-induced and typically maladaptive when persisting) functionalities of the vagus nerve. Roughly, the first three theses of the BHAM may be considered to correspond to functionality of the myelinated ("smart" or "social") vagus, the sympathetic division, and the unmyelinated ("vegetative") vagus, respectively. Polyvagal theory is discussed further in Autonomic Auto-calibration May Explain Increased Risk for High-Arousal Behavior in Individuals who are in a Parasympathetic Freeze State.

We reiterate that the BHAM as presented in this paper is qualitative and conceptual. It is intended to explain and predict tendencies and risks, not causality, and in its current form is a deliberate simplification. Many individuals in a right-hemispheric autonomic state (Thesis Two) may be "driven high-achievers" without pathological high arousal. Similarly many individuals in a left-hemispheric autonomic state (Thesis Three) may have relatively withdrawn personalities that are not necessarily dysfunctional. Individuals may also have mixed forms of trauma history (producing both sympathetic high arousal and parasympathetic freeze tendencies) associated with mixed forms of right/left overactivation that masks the underlying hemispheric dynamics. With these cautions and caveats, the main elements of the BHAM theses are illustrated in **Figure 1**.

Notably, Craig (2005) has proposed a model of forebrain emotional management that similarly depends on lateralization of hemispheric management of the ANS, and in a broad sense his conceptualization overlaps with Thesis One. The Craig model helpfully articulates the roles of the right and left hemispheres for homeostatic opponent processes, permitting catabolic and anabolic energy management through the sympathetic and parasympathetic divisions, respectively. In contrast to the BHAM, the Craig model tends to focus on afferent over efferent pathways for the brain's interaction with the peripheral ANS and views the parasympathetic role of the left hemisphere primarily in terms of its role for self-calming and interoception. Thesis Two of the model overlaps with discussion from Rabe et al. (2006), who also propose a model correlating rightward hemispheric asymmetry with increased arousal. Davis et al. (2013) recently showed that individuals with post-traumatic stress disorder and comorbid substance use disorder had decreased startle responses compared to those with post-traumatic stress disorder alone (self-medication hypothesis), lending support to the idea that autonomic auto-calibration to recover from high arousal may

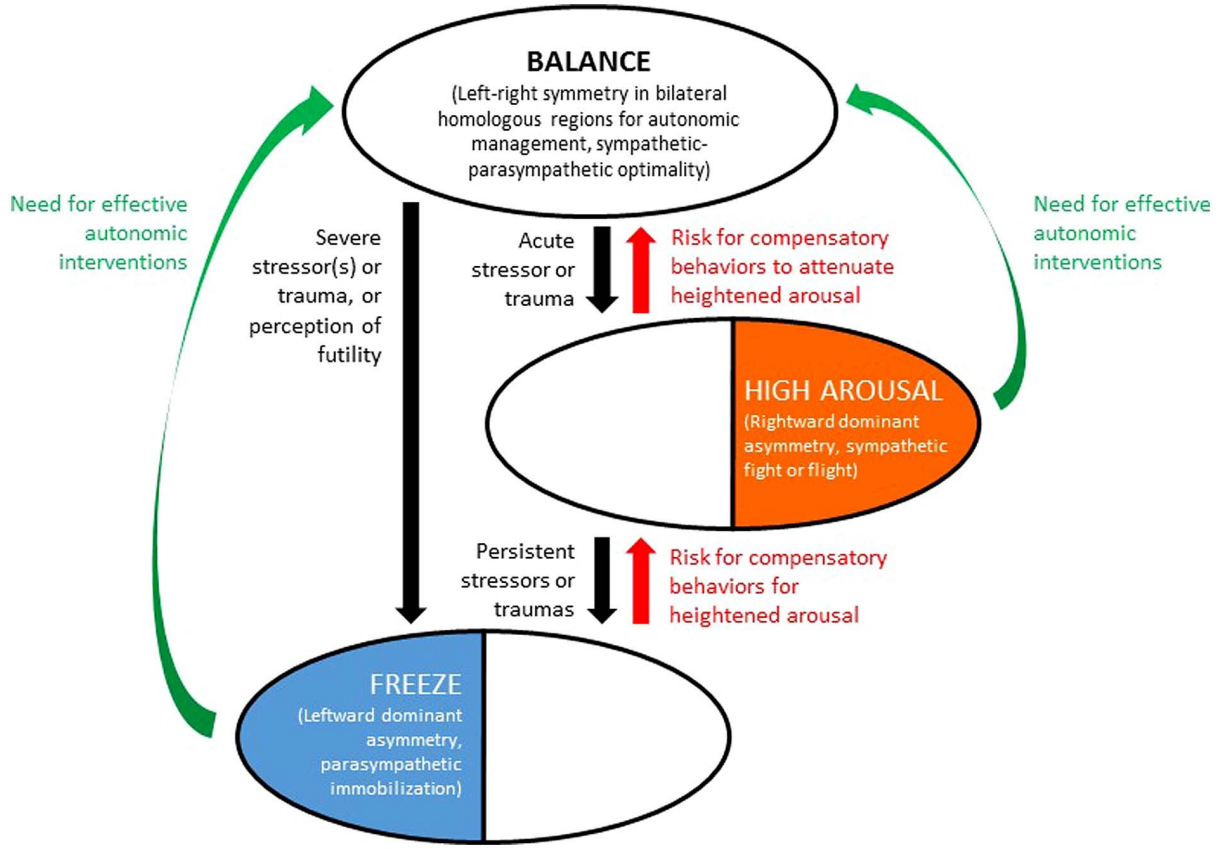

FIGURE 1 | Bihemispheric autonomic model (BHAM) for traumatic stress effects on health and behavior through auto-calibration of arousal. Top oval denotes state of relative symmetry (balance) in activity of bilateral homologous brain regions responsible for autonomic management. Middle oval denotes rightward dominant asymmetry in activation of the same brain regions, indicative of traumatic stress associated with high arousal. Bottom oval denotes leftward asymmetry in activation of the same regions, indicative of traumatic stress associated with parasympathetic freeze mode. Recovery from trauma may be associated with compensatory adverse behaviors (including but not limited to conduct disorders, especially from freeze state to progress to high arousal; and varying forms of substance abuse or medication dependence, to achieve state of balance). Effective autonomic interventions are needed, that can support recovery of balance and decrease likelihood of compensatory adverse behaviors.

be a driver for adverse compensatory behaviors. We are not aware of other writings that advance the ideas contained in Theses Three or Four.

EXPLANATORY VALUE OF THE MODEL

Model subsumes earlier findings related to hemispheric lateralization of arousal or autonomic management

The BHAM subsumes the reports cited in Section "Studies Reporting Hemispheric Asymmetry in Management of Arousal or Autonomic Functioning." Gainotti's (1972) early finding that individuals with right-sided lesions were more likely than those with left-sided lesions to have "indifference" reactions, can be re-interpreted to implicate efferent left-hemispheric influences for freeze behaviors – avoidance or lack of engagement – disinhibited by the right-sided injury. Similar re-interpretations can be offered for the findings of Heilman et al. (1978) and Morrow et al. (1981). The findings of Avnon et al. (2004) also align with the model, suggesting that left-sided migraine carries a burden of greater parasympathetic shutdown physiology – in the form of bradycardia and vasodilatation – after a stressor, perhaps due to enhanced excitably of left-hemispheric circuits. Bradycardia or vascular depressor responses reported by several of the other studies (Zamrini et al., 1990; Oppenheimer et al., 1992; Hilz et al., 2001; Tegeler et al., 2013) are also consistent with the idea that the left hemisphere mediates a parasympathetic freeze response.

Autonomic auto-calibration may explain increased risk for high-arousal behavior in individuals who are in a parasympathetic freeze state

In this section, we further develop the explanation of behavioral risks associated with a history of trauma exposure (Thesis Three). Fuller explanation of this idea is supported by review of the polyvagal theory. The polyvagal theory proposes that the vagus nerve includes branches that are anatomically and functionally distinct, deriving from different periods of vertebrate evolutionary phylogeny. A myelinated branch is associated with fine-tuned self-calming, social communication skills and physiological regulation, and inhibition of sympathetic arousal in environments perceived to be safe. An unmyelinated branch is associated with

neurogenic bradycardia and other freeze-mode behaviors in the presence of severe stressors, when movement may appear to be futile or dangerous, or in the setting of novel stimuli. In traumatic context, the freeze-mode produces hypoarousal, subjective emotional numbness, avoidant behaviors and social disengagement, and in severe form dissociation.

Polyvagal theory conceives autonomic regulation in hierarchical terms, in contrast to dominant models that view sympathetic and parasympathetic functions as opponent processes (or as being in paired antagonism). The myelinated vagus is normatively "on top," functional in safe and restful environments and inhibitory of sympathetic mobilization. In the setting of an acute threat that requires mobilization or otherwise overwhelms the capacity for self-calming, sympathetic arousal is "second in command" and can provide fight or flight responses. If sympathetic mobilization behaviors are inadequate for the stressor or otherwise not adaptive for the presented need, then the unmyelinated vagus may be engaged as the mode of last resort, producing freeze or shutdown behaviors and physiology. These relationships are explained to be consistent with the Jacksonian principle of dissolution wherein evolutionarily more primitive structures rise to dominance when the higher are rendered inadequate.

The existence of *relatively autonomous drives for autonomic auto-calibration* has been proposed in our model as a way to describe dynamics of movement between different autonomic states. This postulate overlaps with polyvagal theory's incorporation of the concept of Jacksonian dissolution. Shifts to sympathetic high arousal or parasympathetic freeze states associated with stress exposures may represent needful, automatic, and calibrated responses to perceived threats. Whereas Jacksonian dissolution explains trauma effects to produce relatively more primitive functioning, the concept of autonomic auto-calibration can also be used to explain behaviors associated with *recovery* (or attempted recovery) from stress or trauma in the direction of reconstitution or greater order. The ubiquity of relaxation strategies (from formal introspective meditation habits to alcohol or sedative-hypnotic use), can be understood as the response to the need of stressed or traumatized individuals to inhibit sympathetic arousal (Thesis Two).

The adverse effects of excess sympathetic arousal – and medical or self-directed strategies to dampen arousal – are commonly recognized by both health professionals and much of popular culture. In contrast the parasympathetic freeze state is less well known, less obviously amenable to intervention, and perhaps even more problematic as a health risk. In extreme cases, neurogenic bradycardia can lead to cardiac arrest (including fetal demise in obstetric contexts), and it may be a mechanism for cerebrogenic sudden death in epileptics. Unmyelinated vagal freeze-mode mechanisms likely contribute to asthma (Porges, 2011). Furthermore, a persisting freeze state may be associated with burdens of suffering independent of the risks of acute cardiac or respiratory shutdown, and also independent of the psychosocial disturbances or discontinuities that accompany emotional numbness or avoidant behaviors as such.

In explication of Thesis Three, we propose that an important burden of suffering associated with the freeze mode is related to autonomic auto-calibration in the direction of recovery from trauma. The hierarchical logic of polyvagal theory appears to suggest that recovery from a traumatic freeze state that may be associated with disproportionate engagement of the unmyelinated vagus requires some degree of transition through a sympathetic high-arousal state, before one can regain (or gain) the self-calmed state of the myelinated vagus. *Autonomic auto-calibration to depart a parasympathetic freeze state may be expressed as a drive for movement towards high-arousal states, which may be socially dysfunctional but nonetheless experienced as a "step-up" in the hierarchy of autonomic states described by polyvagal theory.* It is established for example that a history of early life abuse or neglect confers a risk of anti-social behaviors or conduct disorder (Weiler and Widom, 1996; Maniglio, 2014). Autonomic auto-calibration may explain this risk as the expression of relatively autonomous drives, in individuals who are in a parasympathetic freeze state, to engage in behaviors associated with heightened arousal. Broadly, we hypothesize that heightened-arousal behaviors driven by a need to depart a parasympathetic freeze state may take a variety of forms, from conduct disorders including rage, to drug abuse (especially, but not only, stimulants) and possibly suicidality.

Autonomic auto-calibration in relation to the freeze state would appear to have specific salience for research on the psychological trait called "callous-unemotional." Callous-unemotional traits have been found greater in children with experience of trauma, with the relationship being mediated by self-reported numbness to emotions (Kerig et al., 2012). In turn, a higher degree of the callous-unemotional trait in early adolescence has been shown to be a strong predictor of anti-social outcomes during adolescence and adulthood, including delinquency and arrests (McMahon et al., 2010). Callous-unemotional traits may be a function of traumatic stress that produces the parasympathetic freeze state, and the resulting greater risk for conduct disorders may arise from a drive to be unfrozen, to experience *feeling*.

Corroborative evidence for the physiological dimension of Thesis Three appears to exist in the association between low resting heart rate in children and adolescents, and anti-sociality. In reviews spanning nearly twenty years, the criminologist Adrian Raine has concluded that low resting heart rate is the best-replicated biological correlate of anti-sociality in children and adolescents (Raine, 1996, 2002; Glenn and Raine, 2014). Low resting heart rate correlates with anti-sociality independently of multiple other risk factors, and the significance of the relationship has been confirmed in prospective studies. Raine has invoked both psychological and neural functional explanations for this relationship, and his reference to "stimulation-seeking theory" is of special pertinence to the BHAM being proposed in this paper. Low resting heart rate may represent a subjectively unpleasant low-arousal state that encourages behavioral processes including anti-sociality to mitigate or depart the experience of that state. This explanation is essentially identical with the concept of auto-calibration of arousal to depart parasympathetic freeze mode. Intriguingly, Raine (2002) has further noted that the finding of low resting heart rate (increased parasympathetic efferent control) seems to be at odds with other findings showing that anti-social children have decreased vagal tone (decreased

respiratory sinus arrhythmia or heart rate variability, indicative of decreased parasympathetic efferent modulation). However, this paradox is entirely consistent with the existence of two distinct forms of vagal functionality proposed by polyvagal theory. As to the cause for low resting heart rate, the construct of auto-calibration of autonomic arousal encompasses early life traumatic exposures and thus may explain developmental aspects of anti-sociality more robustly than can explanations based on strictly genetic heritability.

The challenge of the freeze state and the relatively autonomous drive for autonomic auto-calibration is perhaps most sharply illustrated by the plight of many US veterans who have returned from the wars in Iraq and Afghanistan. Many or most of these servicemen and women will have experienced significant degrees of stress or trauma. Depending on individual factors, their autonomic physiology is likely to be characterized by significant sympathetic mobilization tendencies, but also marked degrees of parasympathetic freeze mode. Some expressions of high arousal may reflect intrinsic elevation in sympathetic activity, while others may represent a drive to disengage from the freeze state. The latter expressions might include propensity for violence, substance abuse, and suicidality – all of which are highly prevalent in these veterans (Institute of Medicine, 2013).

The bihemispheric autonomic model may explain left-hemispheric asymmetries or abnormalities associated with violence

A recurrent question in criminology is whether or to what degree biological factors may influence propensity for criminal behavior. This topic has been pursued intermittently over the twentieth century with respect to cerebral asymmetry, unilateral hemispheric dysfunctions, and laterality preferences (Nachson and Denno, 1987). One finding that emerged from early work is that left hemispheric EEG abnormalities, especially in the temporal lobe, tend to be more frequent in violent compared to non-violent subjects, and more recent studies have corroborated that finding. Using positron emission tomography, Volkow and Tancredi (1987) reported left temporal lobe metabolic abnormalities in four psychiatric patients with a history of repetitive, purposeless, violent behavior. Convit et al. (1991) recorded EEG's of 21 violent male psychiatric inpatients and found that increased leftward fronto-temporal and temporal asymmetry in the low frequency range (delta band) was correlated with increased violence. Wong et al. (1994) studied 372 subjects in a maximum security mental hospital and reported that those categorized to be in the highest tertile for violence had a markedly higher number of temporal lobe EEG abnormalities (without mentioning whether asymmetries were present). Pillman et al. (1999) reported that, among 222 defendants in a state court who were seen for pretrial psychiatric assessment, the ten individuals with focal left temporal lobe EEG abnormalities had a significantly higher number of violent offenses, than those without abnormalities. More recently, leftward temporal lobe EEG slowing and diminished arousal to emotional stimuli were reported in a case study of a serial killer (Ostrosky-Solis et al., 2008), and leftward temporal lobe high-frequency brain electrical asymmetry was observed in a group of five violent inmates in a medium-security prison (Gerdes, unpublished observations). In some of these studies, left-sided electrical abnormalities or leftward asymmetries have been interpreted to indicate deficits in language or cognitive processing skills that led the individuals to rely on violence as instrumental means for social interaction.

It should be pointed out that the above studies include reports of both left-sided abnormalities of EEG and leftward asymmetry of electrical activity. While equivalence should not be presumed between abnormalities and asymmetries, nonetheless on a preliminary basis we interpret these studies to suggest that, as with the patients with left-sided migraine symptoms (Avnon et al., 2004), that aberrant or excess left-sided electrical activity represented in these subjects was an indicator of augmented parasympathetic freeze physiology. Review of these data from the perspective of the BHAM, including its concept of autonomic auto-calibration from freeze state, suggests an explanation for the violence of individuals with left-sided defects or excess in brain electrical activity that is independent of the left hemisphere role for language or analytic cognition. Individuals prone to violent behavior may disproportionately have a history of severe life stress adequate to promote the parasympathetic freeze state, associated with leftward asymmetry in the activity of brain regions responsible for autonomic management. A relatively autonomous drive for autonomic auto-calibration may have been expressed, in the individuals in these studies, as propensity for violence.

The BHAM interpretation that risk for violence associated with leftward asymmetry or left-sided abnormality does not contradict the idea that cognitive or language deficits associated with left-sided aberrancy contribute to violent tendency. The combined influence of these factors could easily be greater than either on its own. Furthermore, study design and statistical aspects of the above findings permit a conclusion no stronger than to suggest that leftward dominant asymmetry merits ongoing investigation as a possible relative risk factor for violence, not a determinant of violence. Even if leftward dominant asymmetry is validated as a risk factor for conduct disorder or violence, we hypothesize that only a minority of individuals with leftward dominance will manifest flagrant behavioral disturbance. We reiterate the role of the prefrontal cortex for supporting an individual to steer behaviors and navigate environments, whatever one's prevailing asymmetry. With those caveats, we propose that the BHAM, including the concept of autonomic auto-calibration, may explain previously unexplained portions of the likelihood to enact dysregulated behaviors, among individuals with a history of severe traumatic stress. The model also has implications for intervention, and these are explored in the following section.

ILLUSTRATIONS OF THE BIHEMISPHERIC AUTONOMIC MODEL INCLUDING IMPLICATIONS FOR INTERVENTION

A PARADIGM OF INTERVENTIONAL RESEARCH BASED ON THE BIHEMISPHERIC AUTONOMIC MODEL

The two case examples below are drawn from participants enrolled in an IRB-approved, open label, feasibility study at Wake Forest School of Medicine, exploring use of a noninvasive computer-guided neurotechnology for individuals with a variety of conditions, many associated with stress or psychophysiological

dysregulation. The technology is called high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM®, or Brainwave Optimization®), and it is a non-medical device designed to facilitate relaxation and auto-calibration of neural oscillations (Gerdes et al., 2013). The technology produces closed-loop acoustic stimulation (audible tones of variable pitch and timing) such that the brain tends to self-optimize its electrical activity patterns, shifting towards greater symmetry between left and right hemispheres, and more optimized ratios of energy along the brain electrical frequency spectrum. For these subjects, the technology was provided as a series of sessions, typically 90–120 min duration (and up to two sessions per day), with each session composed of a series of 4–9 protocols (6–40 min per protocol), conducted predominantly with eyes closed while at rest. Protocols target multiple brain regions including temporal, frontal, frontal pole, central, parietal, occipital, cerebellar, and occipital lobes and locations. The technology is a "whole-brain" approach, but for purposes of explicating the BHAM, attention is paid in the case illustrations to temporal lobe activity only. As reviewed above, surface readings of brain electrical activity from temporal locations have been found to correlate with peripheral measures of autonomic cardiac control (Gray et al., 2007; Tegeler et al., 2013), and temporal scalp locations have specifically been proposed to be sites for recording or influencing afferent or efferent autonomic activity in the insular cortex (Gray et al., 2007; Montenegro et al., 2011; Gerdes et al., 2013; Okano et al., 2013).

Participants completed a variety of measures at baseline and again after completing the sessions. Self-reported symptom inventories included the Insomnia Severity Index (ISI), a 7-item survey that assesses the severity, nature, and impact of insomnia symptoms on quality of life over the previous two weeks, with possible scores ranging from 0 to 28 (Morin et al., 1993). Scores of $\geq$8 suggest clinically relevant symptoms of insomnia, and a change of seven points reflects a meaningful change. The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item survey, with possible scores from 0 to 60, that assesses affective depressive symptomatology to screen for risk of depression (Radloff, 1977). Scores of $\geq$16 suggest clinically relevant symptoms of depression, and a change of eight points reflects a meaningful change. The Post-traumatic stress disorder (PTSD) Checklist-Civilian Version (PCL-C), is a 17-item inventory to evaluate multiple symptoms of post-traumatic stress, with scores ranging from 17 to 85 (Weathers et al., 1993). Scores of $\geq$44 points suggest clinically relevant symptoms of PTSD for the PCL-C, and a change of 16 points reflects a meaningful change.

Baseline data collection also included continuous recordings of blood pressure and heart rate (bpm) data, acquired from noninvasive finger arterial pressure measurements, for a minimum of 5 min while subjects were in the supine position. Systolic blood pressure and RR interval data acquired (BIOPAC acquisition software, Santa Barbara, CA, USA) at 1000 Hz were analyzed using Nevrokard BRS software (Nevrokard BRS, Medistar, Ljubljana, Slovenia) to produce measures of heart rate variability, reported here as the standard deviation of the normal beat to beat interval (SDNN, ms), and baroreflex sensitivity (BRS, ms/mmHg), which we report according to the sequence method.

Each participant had a baseline assessment to obtain information regarding electrical frequencies and amplitudes (Gerdes et al., 2013). The assessment included 3 min recordings obtained from at least six standard locations on the scalp (using placements from the 10–20 system, F3/F4, C3/C4, P3/P4, T3/T4, FZ/OZ, and O1/O2, 1 min each for eyes closed, partially closed, and eyes open), with the participant at rest (eyes closed, partially closed) and while carrying out a cognitive task (eyes open). The assessment is intended to provide a "snapshot" of relative symmetry between homologous brain regions, as well as the distribution of amplitudes among different frequency bands at each location. Data from the assessment were used to identify the protocols for the first intervention session, and data from each intervention session were used to guide protocol selections for subsequent sessions. For purposes of the following case illustrations, spectrographs of 1 min averages of amplitudes at bilateral temporal lobes, eyes closed, are shown for the assessment and the penultimate minute of the temporal lobe protocol for the penultimate HIRREM session.

CASE 1: LEFTWARD TEMPORAL LOBE BRAIN ELECTRICAL ASYMMETRY IN A SPECIAL OPERATIONS MILITARY OFFICER WITH MILD TRAUMATIC BRAIN INJURY AND POST-TRAUMATIC STRESS DISORDER

A 29-year-old man, deployed as part of a US military special operations unit, experienced a mild traumatic brain injury (mTBI) when he was in close proximity to an exploding rocket-propelled grenade. He was diagnosed with mTBI and post-traumatic stress disorder. He had been in good overall health prior to the mTBI, with the exception of several years of insomnia, requiring medications. He reported that his primary symptoms were severe insomnia, headaches, and impaired memory, both short and long term. The traumatic event occurred 15 months prior to enrollment. During the period between the mTBI and enrollment, he reported having tried numerous treatments including both medical therapies and non-traditional approaches (cognitive processing therapy; prolonged exposure; group therapy; antidepressant medication; adrenal optimization; dietary changes; fitness changes; nerve blocks; nerve ablations; acupuncture; transcranial magnetic stimulation; meditation; massage therapy; pain medication; ketamine infusions; bio-feedback; sleep medications; service dog) from which results had been by his estimation "mixed and relatively limited." At the time of enrollment, pertinent medications included eszopiclone (3 mg nightly), melatonin (30 mg nightly), venlafaxine XR (225 mg daily), and thyroid hormone (2 grains daily).

On baseline assessment, at homologous temporal lobe regions (T3/T4) with eyes closed (**Figure 2**), there was a leftward (T3) dominant pattern in the higher frequencies (amplitudes 20–74% greater than the right, at T4). Scores for the ISI, CES-D, and PCL-C were 28, 34, and 78, respectively. Resting heart rate, SDNN, and BRS were 53 bpm, 65 ms, and19.2 ms/mmHg, respectively. The subject received a total of 22 HIRREM sessions over 12 days, during which time he self-tapered and/or discontinued his various medications. He reported no adverse events in association with the sessions.

Figure 3 shows a one-minute snapshot of temporal lobe (again T3/T4) brain electrical activity from the penultimate minute of a protocol during the penultimate session, to illustrate the

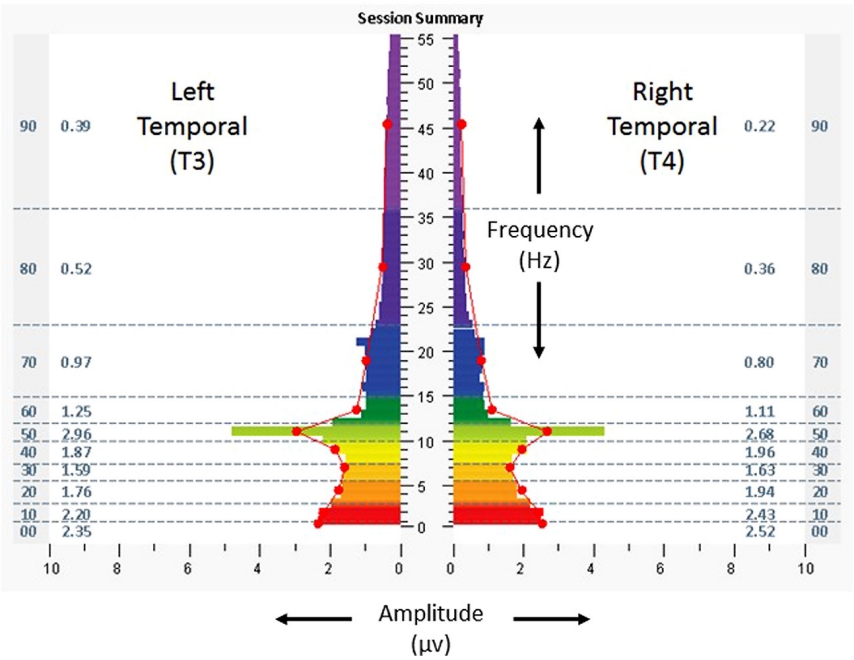

FIGURE 2 | Spectrographs of left and right temporal lobe brain electrical activity for 29-year-old US military special operations officer with history of mTBI and PTSD (Case 1) at baseline, before undergoing neurotechnology intervention for auto-calibration of neural oscillations. Data were collected from T3 and T4 in 10–20 system, with frequency (Hertz, Hz, vertical axis), plotted against amplitude (microvolts, μv, horizontal axis). Individual color bars reflect amplitude averages for one minute of recording, eyes closed, at rest, without stimulation. Columns to the left and right of the color bars denote ten frequency bands of aggregated data (00: < 1.0 Hz; 10: 1.0–3.0 Hz; 20: 3.0–5.5 Hz; 30: 5.5–7.5 Hz; 40: 7.5–10.0 Hz; 50: 10.0–12.0 Hz; 60: 12.0–15.0 Hz; 70: 15.0–23.0 Hz; 80: 23.0–36.0 Hz; 90: 36.0–48.0 Hz) and numerical values for averages in those ranges.

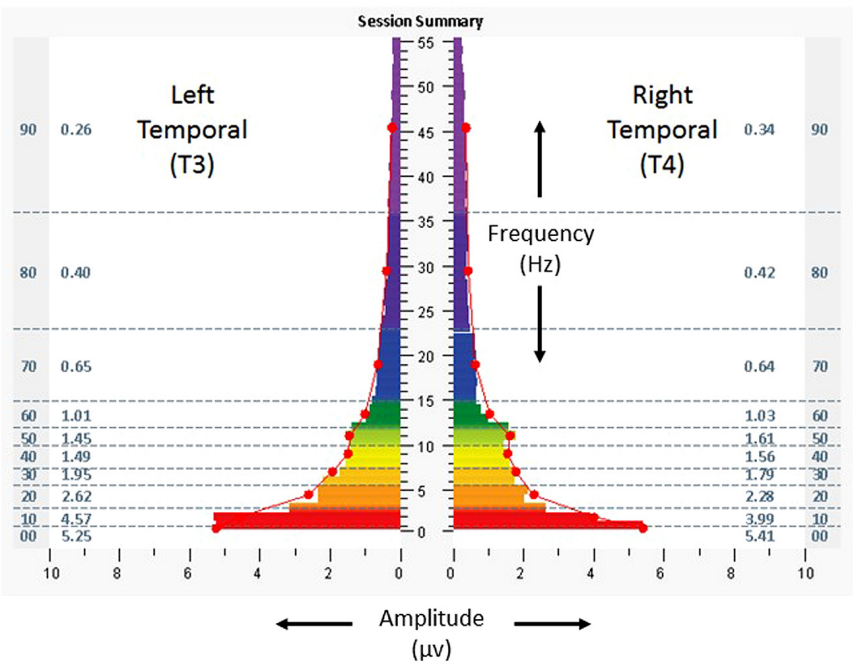

FIGURE 3 | Spectrographs of left and right temporal lobe brain electrical activity for 29-year-old US military special operations officer (Case 1), during penultimate session of neurotechnology intervention, penultimate minute. Data reflect subject's brain activity with eyes closed, at rest, while listening to audible tones. See **Figure 2** legend for detailed explanation of data elements.

movement towards symmetry which had begun early in the course of sessions (less than 5% asymmetry in higher frequencies). At exit, the subject reported having slept 6 h the preceding night, and scores for the ISI, CES-D, and PCL-C decreased to 19, 22, and 60, respectively. His written comments were that "[I have] discontinued all prescription medication, started sleeping with steady improvement, have reduced pain, increased focus and concentration, and [have had] an improved dynamic with anxiety and depression." After completing the sessions, the resting heart rate, SDNN, and BRS were 61 bpm, 83.6 ms, and 24.1 ms/mmHg, respectively.

CASE 2: RIGHTWARD TEMPORAL LOBE BRAIN ELECTRICAL ASYMMETRY IN A FEMALE UNIVERSITY STUDENT WITH PERSISTING POST-CONCUSSION SYMPTOMS INCLUDING DEPRESSION

A 23-year-old woman, a graduate student at a local university, enrolled in the same research study referenced in Case 1, due to persisting post-concussion symptoms. She played soccer and suffered from five concussions during a six month period at age of 13. She then suffered additional, non-athletic concussions at 10 and 5 months prior to enrollment in the study, due to a fall and a mishap while dancing, respectively. She reported persisting headaches and dizziness as primary complaints, was unable to exercise at all, and was in the process of dropping out of graduate school since she was not able to read, study, and learn as needed. She mentioned having migraines during high school but denied other medical problems. She had started amitriptyline (25 mg nightly) three days prior to enrollment in the study but discontinued that medication upon beginning the intervention. Her other medications were oral contraceptives, sumatriptan (25 mg tablet as needed migraine), and ibuprofen (prn).

The baseline assessment at T3/T4, eyes closed (**Figure 4**), revealed T4 dominance (15–29%) in the highest frequencies. Scores for the ISI, CES-D, and PCL-C were 5, 31, and 22. Resting heart rate, SDNN, and BRS were 79 bpm, 55.5 ms, and 13.5 ms/mmHg. She received 23 HIRREM sessions over 34 days and reported no adverse events.

Figure 5 shows temporal lobe brain electrical activity (eyes closed) from the penultimate minute of a protocol from the penultimate intervention session, with asymmetry reduced to 3–6% in the direction of T3, in the same frequency ranges. During and following the sessions, she reported that she was able to engage in more activities including walking, reading, and watching movies. She also reported improved mood, fewer headaches, increased stamina, better appetite, and improved quality of sleep. Scores for the ISI, CES-D, and PCL-C were 3, 9, and 19. Resting heart rate, SDNN, and BRS were measured at 68 bpm, 83 ms, and 35.7 ms/mmHg.

COMMENT ON CASE ILLUSTRATIONS

The above cases illustrate asymmetries of brain electrical activity measured at temporal scalp locations. In accordance with our findings that brain electrical asymmetry measured at this location appears to allow assessment of relative sympathetic or parasympathetic activation (Tegeler et al., 2013), subjects reported symptoms related to a number of clinical issues that can manifest as dysregulation of arousal, including insomnia, depressiveness, post-traumatic stress, and pain. McGrath et al. (2013) found that

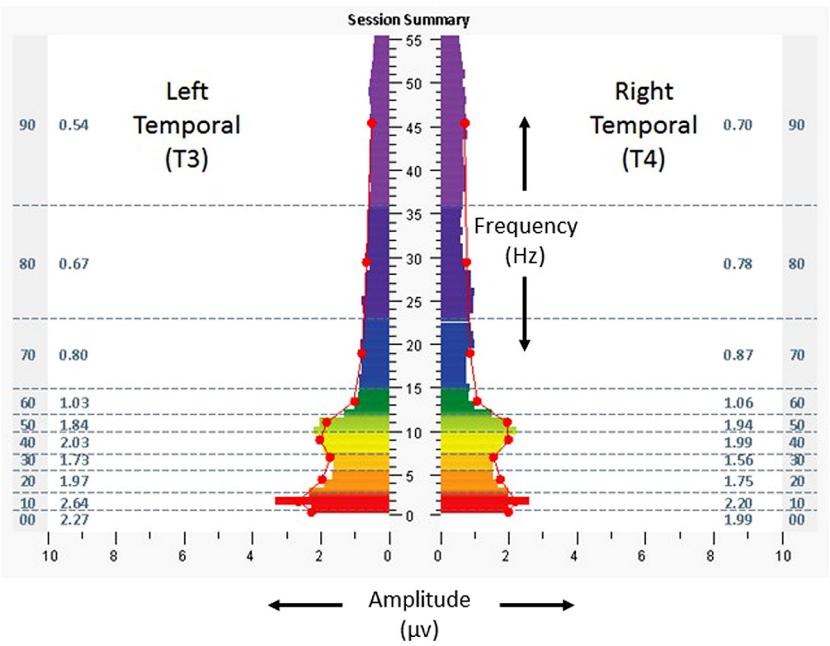

FIGURE 4 | Spectrographs of left and right temporal lobe brain electrical activity for 23-year-old woman with history of persisting post-concussion symptoms (Case 2), before undergoing neurotechnology intervention for auto-calibration of neural oscillations. Data were collected from T3 and T4 in 10–20 system, with frequency (Hertz, Hz, vertical axis), plotted against amplitude (microvolts, μv, horizontal axis). See **Figure 2** legend for detailed explanation of data elements.

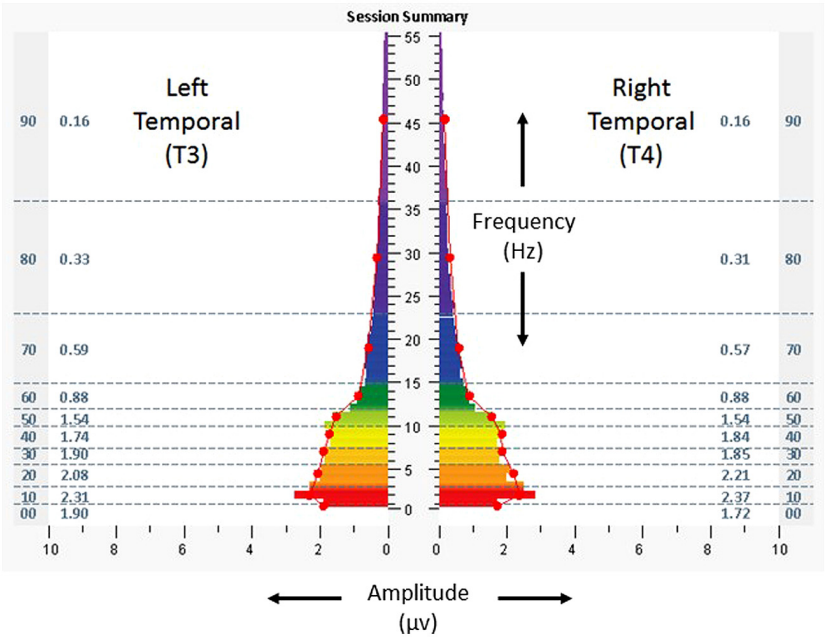

FIGURE 5 | Spectrographs of left and right temporal lobe brain electrical activity for 23-year-old woman (Case 2), during penultimate session of neurotechnology intervention, penultimate minute. Data reflect subject's brain activity with eyes closed, at rest, while listening to audible tones. See **Figure 2** legend for detailed explanation of data elements.

increased right anterior insula activation helped predict treatment response in major depression, and it has been suggested that the asymmetry reported in that study may have been due to differences in autonomic arousal that are detectable through surface measures of brain electrical activity (Tegeler et al., 2014). Traumatic brain injury itself is well appreciated to be associated with autonomic dysregulation (Hilz et al., 2011). For both subjects, use of a noninvasive neurotechnology for auto-calibration of neural oscillations was associated with shifting of temporal lobe brain electrical activity toward greater symmetry, especially in higher frequency ranges. Both subjects reported significant reductions in clinical symptom inventories and overall improvement in functionality.

Cardiovascular measures were consistent with predictions of the BHAM and its incorporation of polyvagal theory. In Case 1, the subject with leftward (T3) dominance was found to have increased resting heart rate after completing the intervention, possibly reflecting release from the "hold" of a parasympathetic freeze state, allowing increased sympathetic activation. In Case 2, the subject with rightward (T4) dominance was found to have decreased resting heart rate post-intervention, possibly reflecting increased functional parasympathetic inhibition from the left hemisphere. In both subjects, heart rate variability (reflected as higher SDNN values) was increased after the intervention, possibly reflecting greater capacity of the myelinated vagus to maintain calm and emotionally well-regulated states as would be predicted by polyvagal theory. Whereas both heart rate and heart rate variability are known to be under vagal regulation (Task Force for the European Society of Cardiology, and the North American Society of Pacing Electrophysiology, 1996), the dissociation of the direction of changes in these two variables for the subject in Case 1 is consistent with recovery of a higher level of autonomic functioning as conceived by polyvagal theory. That is to say, the subject may have demonstrated a shift away from unmyelinated toward myelinated vagal activity, permitting both increased resting heart rate and increased heart rate variability.

We do not presume that the epochs of temporal lobe brain electrical activity shown in the figures are exhaustive and unqualified indicators of ANS management. In the first place, other cortical regions may be of interest. Foster et al. (2008) reported a correlation between frontal asymmetry and heart rate, while other investigators have reported null findings when testing for correlation between heart rate variability and frontal asymmetry (Chang et al., 2012; Balle et al., 2013) or parietal asymmetry (Balle et al., 2013). The possibility cannot be excluded that medication or supplement effects (including changes to regimens) contributed to the brain electrical activity findings in these case studies. Differences in asymmetry between the states of eyes closed and eyes open (at task) may be of particular interest, given that both spectral and topographical aspects of brain electrical activity are known to change between those states (Barry et al., 2007). Moreover, the comparison of brain electrical activity "snapshots" from the assessment and the penultimate intervention session is not meant to imply a linear transition from dominant asymmetry to symmetry. Conceptually, the neurotechnology provided to these subjects is allostatic ("stability through change") in its intention (Sterling, 2012), aimed to facilitate brain activity to become "un-stuck" from maladaptive set-points (Gerdes et al., 2013). Though the end result tends to be greater hemispheric symmetry and more optimality of

ratios between low and high frequencies, every recipient is recognized to demonstrate unique and complex neural oscillatory patterns throughout their process. Whether the BHAM may be better defined by the addition of asymmetry measures for regions other than the temporal lobes, to what degree asymmetry in key regions may be influenced by the state of eyes closed or eyes open or concurrent medication use, and the temporal and spectral dynamics of measured asymmetry (including their reproducibility) over the course of an intervention, are all questions for further study.

Being uncontrolled case examples and in consideration of the variables involved, the above case examples are adduced not as proof of the BHAM but rather as illustrations of its application and as preliminary explorations of phenomena that may be meaningful targets for ongoing study. The neurotechnology used in these case studies has also been associated with reduction of insomnia and depressive symptoms in a pilot clinical trial (Tegeler et al., 2012), but to our knowledge there has otherwise been little attempt to leverage hemispheric lateralization of autonomic management for clinical purposes. In trained cyclists, Okano et al. (2013) have reported that transcranial direct current stimulation over left temporal cortex may modulate sensory perception of effort through delay of parasympathetic withdrawal, to permit increased exercise performance.

We propose that the clinical improvements reported by these subjects may be understood in a way that is highly convergent with the imperative for new frameworks to advance mental health sciences. Specifically, we suggest that these subjects' symptom clusters, diagnostically differentiated under the schema of the Diagnostic and Statistical Manual but physiologically related under the BHAM, exemplify the need to reconceptualize mental health as the integrated expression of core and interlocked modules of brain-behavior functionality. The NIMH has been vocal in directing mental health researchers to view individuals in such brain-functional terms, rather than through checklists of behavioral and symptom clusters that are compared to population averages (Cuthbert and Insel, 2013). The NIMH RDoC (Research Domain Criteria) initiative has preliminarily identified arousal, positive valence, negative valence, cognitive systems, and social processes as being five core brain-behavioral domains which are operative in both health and disease, and which may serve as more biologically valid units of analysis for future progress in mental health research. We propose that the BHAM is a promising vehicle for fresh efforts in the direction of RDoC and related endeavors.

DISCUSSION

The present paper has proposed a BHAM that may explain and predict a range of phenomena related to traumatic stress and arousal, mediated partially through relatively autonomous drives toward autonomic auto-calibration. The model proposes that relative symmetry in activity of hemispheric brain regions responsible for autonomic management represents a state of relative optimality in autonomic functioning, whereby sympathetic and parasympathetic functionalities fluctuate naturally and are adaptive for the ongoing needs and changing circumstances of life. Rightward dominant asymmetry in activity of brain regions responsible for autonomic management may reflect a state of sympathetic mobilization which may develop as an adaptive response to a given context, but is likely to be maladaptive if it is persistent despite changing and especially non-threatening environments. Leftward dominant asymmetry in the same brain regions may be indicative of a parasympathetic freeze mode, also adaptive for certain contexts, but also likely maladaptive if persistent. Exposure of an individual to varying degrees and types of traumatic stress, and recovery from the associated traumatic states, produces (or reflects) processes of autonomic auto-calibration toward and away from varying degrees of dominant rightward or leftward asymmetry.

The BHAM concept of autonomic auto-calibration proposes to explain the increased risk for behavioral disturbances (including conduct disorder and substance abuse) among individuals with a history of traumatic stress. For an individual with a history of severe stress or trauma leaving them in a parasympathetic freeze state, compensatory high-arousal behaviors may represent options for *feeling*, despite being at odds with accepted societal norms. Those in a state of traumatic high arousal may be at risk for compensatory behaviors for arousal attenuation, including substance abuse and medication dependence. The model does not imply that relatively autonomous drives for autonomic auto-calibration are not subject to regulation by the prefrontal cortex.

We have illustrated potential interventional implications of the BHAM through case examples of a military veteran with traumatic stress, and a university student with persisting post-concussive symptoms, both of whom had asymmetries of temporal lobe brain electrical activity, and both of whom experienced symptom reduction after using a noninvasive technology designed for auto-calibration of neural oscillations. The subjects' improvements in arousal-related symptom clusters that cut across diagnostic categories appear to exemplify the value of the RDoC framework proposed by NIMH. Furthermore the traumatic stress history incorporated by the BHAM reflects a sensitivity to neurodevelopmental trajectories that is an advantage of RDoC (Cuthbert, 2014).

Many questions can be asked of the model, to confirm its validity or to explore potential mechanisms or ramifications. We consider that data-collection paradigms based on scalp measures of brain electrical asymmetry are likely to be productive, especially because of their high temporal resolution and ease of implementation, permitting serial measures. Both those advantages may be critical with respect to the capacity of the brain – and the ANS – to shift activity patterns quickly, in the context of rapidly changing and newly anticipated needs. In contrast, some of the core advantages of more complex experimental methodologies, especially their high spatial resolution, are of less consequence if a key parameter of interest is instantaneous hemispheric activation asymmetry.

Within the paradigm of brain electrical measures, it may be asked if there are particular scalp locations most likely to produce reliable indications of autonomic signaling. With respect to the measured signals themselves, studies could be carefully designed to tease apart whether they represent efferent or afferent signals or both, or even one rather than the other depending on the instantaneous context. Spectral components of brain electrical signals

may also hold meaningful information. Just three of the testable hypotheses that derive from the BHAM include the following. Nominally healthy and trauma-free individuals who experience an acute (but not overwhelming) stressor, will have greater rightward hemispheric asymmetry in brain regions responsible for autonomic management and greater peripherally measured heart rate, than matched controls who do not experience the stressor. Individuals who have a history of severe or extended exposure to stress or trauma, or children with a history of severe childhood trauma and evaluated to be callous-unemotional, will be more likely to demonstrate left-hemispheric autonomic asymmetry, and they will have on average a lower resting heart rate, than matched controls. In cases of either rightward or leftward asymmetry, it may be hypothesized that degree of asymmetry will correlate with the magnitude of heart rate differences. Third, one may hypothesize that use of interventions to support greater hemispheric symmetry in brain regions responsible for autonomic management will be associated with more optimal autonomic regulation and associated subjective and behavioral improvements.

If the BHAM is valid, then questions should be raised about its generalizability. A new and non-trivial insight about ANS functioning should have new and non-trivial consequences, given the pervasive and critical role of the ANS across organ systems and behaviors (Rees, 2014). It may be that polyvagal theory represented the beginning of a *paradigm shift* for understanding the ANS. And although the phrase "paradigm shift" is now often used loosely to refer to any subjective shift of perspective, we use the phrase in a manner consistent with its original use by the historian and philosopher of science Kuhn (1962). A scientific paradigm shift begins when normal science is met with an anomaly. In the case of the ANS, understanding of the stress-buffering role of the parasympathetic nervous system did not cohere with understanding about the potential lethality of neurogenic bradycardia. Polyvagal theory explained that anomaly by articulating two different forms of vagal activity, especially identifying distinct features of the parasympathetic freeze state, and proposing that autonomic activity is expressed in a hierarchical way in accordance with environmental context and individual variations. New scientific paradigms require new tools and procedures for collecting and interpreting empirical data, and we suggest that measurement of brain electrical asymmetry may represent a productive new approach for autonomic neuroscience. If a paradigm shift for assessment and intervention on autonomic dimensions of brain-behavior relationships is now in the making, we hope for the BHAM to support productive explorations of the new worldview.

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Individual differences in resting heart rate variability and cognitive control in posttraumatic stress disorder

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Post-traumatic stress disorder (PTSD) is characterized by deficits in cognitive functioning, particularly cognitive control. Moreover, these deficits are thought to play a critical role in the etiology and maintenance of core PTSD symptoms such as intrusive thoughts and memories. However, the psychophysiological concomitants of cognitive control remain largely unexamined. In this article, we suggest that individual differences in heart rate variability (HRV), a physiological index of self-regulatory capacity, may underlie the association between cognitive control ability and intrusive cognitions in PTSD. We review evidence showing that individual differences in HRV at rest are related to prefrontal cortical activity and performance on a broad range of cognitive control tasks. We highlight the importance of inhibition as a mechanism by which HRV promotes successful cognitive control. In addition, we summarize recent research linking individual differences in HRV to performance on laboratory tasks that assess the ability to control unwanted memories and intrusive thoughts. We conclude by suggesting that future studies should examine the role of low HRV as a risk factor for developing PTSD.

Keywords: cognitive control, individual differences, heart rate variability, posttraumatic stress disorder

INTRODUCTION

Traumatic experiences can greatly alter an individual's cognitive, emotional, and physiological functioning as demonstrated by those with post-traumatic stress disorder (PTSD), who experience avoidance, hyperarousal, and re-experiencing symptoms (American Psychiatric Association, 2013). While current models of PTSD have emphasized the role of psychological processes such as attentional bias toward potential threat, enhanced recall of trauma-relevant material, and appraisal of the trauma event and its sequelae as mechanisms that underlie PTSD symptom expression (for review, see Ehlers and Clark, 2000; Brewin and Holmes, 2003), there has been less focus on the role of cognitive control. However, researchers have recently suggested that the re-experiencing symptoms of PTSD, such as intrusive thoughts and memories, may stem from deficits in cognitive control that exist prior to the onset of trauma (Dalgleish et al., 2008; Levy and Anderson, 2008; Bomyea et al., 2012a). Yet, the physiological underpinnings of such a relationship remain unclear. We propose that individual differences in heart rate variability (HRV), a physiological index of self-regulatory capacity, may underlie the association between cognitive control ability and intrusive cognitions in PTSD. To begin, we briefly summarize the model of neurovisceral integration (Thayer and Lane, 2000, 2009), which suggests a role for individual differences in HRV in the regulation of cognitive processes.

HEART RATE VARIABILITY: THE NEUROVISCERAL INTEGRATION MODEL

Thayer and Lane (2000, 2009) developed the neurovisceral integration model, which suggests that individual differences in vagal function, as indexed by heart rate variability (HRV) at rest, reflect the activity of a flexible and integrative neural network, which allows the organism to effectively organize emotional, cognitive, and behavioral responses in the service of goal-directed behavior and adaptation. An important part of the neurovisceral integration model is the complex interplay between cortical and subcortical regions collectively termed the central autonomic network (CAN; Benarroch, 1993). The CAN serves as the neuroanatomical link between the autonomic nervous system and brain areas associated with higher order cognitive functioning (e.g., the prefrontal cortex). The neural structures of the CAN include the anterior cingulate, the insula, the ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaquaductual gray matter, the nucleus of the solitary tract (NTS), the nucleus ambiguous, and the medullary tegmental field, among others (Thayer and Lane, 2009; Thayer et al., 2012). These components are reciprocally interconnected, allowing the prefrontal cortex to exert inhibitory control over subcortical structures in order to generate cognitive, behavioral, and physiological responses that support goal-directed behavior and adaptability. Critically, the output of this inhibitory cortico-subcortical circuit extends to autonomic inputs to the heart, including the vagus nerve. In this model, higher levels of HRV (i.e., greater vagal tone) at rest are a product of a system in which the prefrontal cortex exerts inhibitory control over subcortical circuits thus allowing the organism to respond to environmental challenges in a controlled and adaptive manner when needed. For this reason, examining the parasympathetic influence on the heart via HRV can provide an index of an individual's capacity to effectively function in a complex and challenging environment.

Studies using pharmacological and neuroimaging approaches demonstrate that prefrontal cortical activity is associated with vagally mediated HRV (Ahern et al., 2001; Lane et al., 2009; Thayer et al., 2012). For example, pharmacological inactivation of the prefrontal cortex increased heart rate and decreased vagally mediated HRV (Ahern et al., 2001). These findings establish that the prefrontal cortex tonically inhibits cardioacceleratory circuits and changes in cortical activity are reflected in HRV. Neuroimaging studies have linked HRV to activity in a number of prefrontal brain regions including the ventromedial prefrontal cortex, superior prefrontal cortex, and dorsolateral prefrontal cortex (Lane et al., 2009); these associations were further supported by a recent meta-analysis of neuroimaging studies that included HRV (Thayer et al., 2012). Together, these findings provide a conceptual model of individual differences in HRV as a marker of self-regulatory capacity. Next, we review evidence linking HRV at rest to specific cognitive control functions including attention, working memory, and inhibition.

INDIVIDUAL DIFFERENCES IN HRV AND COGNITIVE CONTROL ABILITY

Cognitive control refers to the mental processes involved in keeping desired information active while inhibiting irrelevant or unneeded information (Braver, 2012). While cognitive control is subsumed within the broader construct of "executive function," the general purpose control mechanisms that regulate thoughts and behaviors (Miyake and Friedman, 2012), it may not reflect the capacity for higher order functions, such as organization, sequencing, reasoning. Miller and Cohen (2001) proposed that successful cognitive control stems from the active maintenance of patterns of activity in the prefrontal cortex that represent goals and the means to achieve them. In addition, the extent to which prefrontal control areas exhibit greater connectivity with other functional networks is associated with increased cognitive control ability. Given that resting HRV has been shown to index important aspects of prefrontal neural function, it follows that individual differences in HRV may be a useful predictor of cognitive control ability. It is worth noting that cognitive control is not a unitary construct. In support of this idea, Miyake et al. (2000) used latent-variable analysis to identify three specific functions that underlie the construct of cognitive control: information *updating and monitoring, attentional set-shifting*, and *inhibition*. However, recent perspectives suggest that inhibition may be a "basic function" that underlies other aspects of cognitive control (Thayer et al., 2009; Miyake and Friedman, 2012). Put another way, control over working memory and attentional set-shifting may require some degree of inhibition. Conceptual views of HRV parallel these ideas, as inhibition is seen as the core mechanism by which individuals produce context appropriate responses; individual differences in HRV reflect the extent to which these inhibitory processes are effective (Thayer, 2006). Thus, although HRV is largely an index of inhibitory control, it should also be associated with performance-based measures of working memory and attention.

A growing body of research has found that individuals with higher levels of HRV at rest demonstrate enhanced performance on cognitive control tasks that require working memory, attentional control, and inhibition. Hansen et al. (2003) found that individuals with higher levels of HRV performed better on a standard two-back working memory task compared to those with lower levels of HRV. Another study replicated and extended these results by showing that high HRV individuals maintained enhanced working memory capacity even in the context of a stressful environment (i.e., under threat of shock; Hansen et al., 2009). Moreover, aerobic training/detraining produced concomitant changes in working memory performance and HRV; those who continued aerobic training over a 4-week period showed increased accuracy on a working memory task and higher levels of HRV post-task relative to those who discontinued exercise (Hansen et al., 2004). These findings provide support for a causal relationship between individual differences in HRV and working memory capacity.

Resting levels of HRV are also associated with performance on tasks that require attentional control (Park and Thayer, 2014). Park et al. (2012) found that individuals with low levels of HRV were less able to inhibit their attention away from locations where fearful faces were previously presented. A subsequent study demonstrated that the previous findings likely reflected both automatic and voluntary deficits in attentional control as those with low HRV showed increased attentional engagement to and decreased disengagement from fearful faces (Park et al., 2013). In addition, among individuals with dental anxiety, those with lower levels of HRV were less able to regulate their attention when presented with threat-related dental words relative to those with higher levels of HRV (Johnsen et al., 2003). Thus, individual differences in HRV are associated with the capacity to control attention, especially in the presence of emotional stimuli.

Consistent with perspectives that suggest a relationship between prefrontal inhibitory processes and HRV (Thayer and Lane, 2000, 2009), studies have found associations between individual differences in HRV and performance on tasks that require motor response-inhibition and inhibitory control more broadly. Using an emotional stop-signal task that required individuals to withhold their motor response in the presence of negative emotional cues, those with higher levels of HRV activated and inhibited their responses faster than those with lower levels of HRV (Krypotos et al., 2011). A recent study by Hovland et al. (2012) found that higher levels of HRV at rest were associated with better performance on the *Wisconsin Card Sorting Task* and the *Color-Word Interference Task*, two measures of general cognitive flexibility and executive function. Importantly, although resting HRV predicted general performance on the tasks, it was most strongly associated with aspects of the tasks that reflected inhibitory control (Hovland et al., 2012). Altogether, there is considerable evidence suggesting that individual differences in HRV are linked to the specific mental processes that underlie cognitive control, particularly inhibition.

COGNITIVE CONTROL DEFICITS IN PTSD

Deficits in cognitive control that have been observed in patients with PTSD appear to parallel those that have been associated with individual differences in HRV. However, it is worth noting that the association between cognitive control ability and PTSD

is complex and evidence for broad cognitive control deficits in PTSD remains mixed. For example, while some have found that those with PTSD perform worse on neuropsychological measures that require a combination of sustained attention, inhibition of habitual responses, and set shifting, compared to trauma-exposed individuals without PTSD and healthy controls (Stein et al., 2002; Polak et al., 2012; Cohen et al., 2013) others have failed to show such associations (Barrett et al., 1996; Crowell et al., 2002; Kanagaratnam and Asbjørnsen, 2007). Moreover, some have noted that comorbid conditions such as depression, anxiety, and substance abuse, rather than PTSD symptoms, may account for group differences in cognitive control ability between those with PTSD and healthy controls (Barrett et al., 1996). In light of these findings, researchers have begun to investigate whether PTSD may be best characterized by deficits in specific cognitive control functions, rather than widespread cognitive impairment (Leskin and White, 2007; Aupperle et al., 2012).

Relative to other aspects of cognitive control, deficits in inhibitory control have been most consistently observed among individuals with PTSD (Aupperle et al., 2012). For example, Leskin and White (2007) found that while college undergraduates with PTSD were less able to inhibit their attention to irrelevant distractors relative to trauma-exposed controls, the groups performed similarly on tasks assessing attentional set-shifting, alerting, and orienting. Similarly, others have shown that those with PTSD perform significantly worse than healthy controls on tasks that require inhibitory control (e.g., the stroop test) but not those tasks that assess attention span and working memory capacity (Flaks et al., 2014). Moreover, individuals with PTSD show deficient motor response control as evidenced by high inhibition-related error rates on the Go/No-Go and Stop-Signal tasks (Casada and Roache, 2005; Falconer et al., 2008; Wu et al., 2010; Swick et al., 2012). Because inhibition is often required for adaptive self-regulation, individual differences in inhibitory control should be associated with PTSD severity.

Indeed, evidence suggests that deficits in inhibitory control are associated with elevated PTSD symptoms, particularly the experience of unwanted memories and thoughts (Vasterling et al., 1998; Leskin and White, 2007; Bomyea et al., 2012a). Laboratory investigations have focused on the relationship between proactive interference control, an inhibition-related function that taps the ability to resist information that was previously relevant to the task but has since become irrelevant (Friedman and Miyake, 2004), and the frequency of intrusive memories and thoughts. Those who display lower levels of proactive interference control, assessed through a variety of neuropsychological tests, self-report a greater frequency of intrusive thoughts (Friedman and Miyake, 2004; Bomyea et al., 2012a). Individual differences in proactive interference control also play a role in the experience of unwanted thoughts and memories following stressful events. Wessel et al. (2008) found that greater proactive interference control predicted less self-reported intrusive cognition 24 h after viewing an emotionally evocative trauma film clip. Others have shown that the relationship between proactive interference control and intrusion frequency after stress is consistent across longer time intervals (1 week) and cannot be accounted for by neuroticism and gender (Verwoerd et al., 2011). These findings provide initial evidence that deficits in inhibitory control may serve as a vulnerability factor for experiencing intrusive thoughts and memories. A related topic is the extent to which individual differences in cognitive control correlate with the effectiveness of attempts to control intrusions via mental control strategies.

Along these lines, researchers have investigated the association between cognitive control ability and suppression, a strategy commonly used to manage the experience of intrusive cognitions. Suppression is widely considered to be a maladaptive strategy as it sometimes serves to paradoxically increase the frequency of unwanted cognitions (for review see Wenzlaff and Wegner, 2000). Attempts at thought suppression among those with PTSD are often unsuccessful as evidenced by a paradoxical increase in trauma-related intrusive thoughts following instructed suppression in a laboratory setting (Shipherd and Beck, 1999, 2005). In a similar manner, individuals with PTSD who attempt to suppress trauma memories typically experience enhanced remembering of the trauma and other negative personal material, as well as a lack of specificity in the recollection of the personal past (Dalgleish et al., 2008). Ineffective suppression of unwanted thoughts and memories is associated with deficient cognitive control ability. For example, individuals with reduced working memory capacity are less able to suppress intrusive thoughts relative to those with higher levels of working memory capacity (Brewin and Beaton, 2002; Brewin and Smart, 2005). In addition, those with low levels of inhibitory control show a reduced capacity to stop retrieval of unwanted memories (Depue et al., 2010; Wessel et al., 2010). Dalgleish et al. (2007) have shown that reduced specificity of autobiographical memory, a consequence of unsuccessful memory suppression, is largely a function of reduced cognitive control. Thus, individual differences in cognitive control may influence both the tendency to experience intrusive cognitions and the extent to which such intrusions are controllable.

While there is growing evidence suggesting that the re-experiencing of symptoms and intrusive cognitions experienced by individuals with PTSD are associated with deficits in cognitive control, two issues remain unsettled. One question concerns the nature and organization of cognitive control deficits observed in PTSD. Specifically, it remains unclear whether these deficits are the result of disruptions in broadband cognitive ability or impairment in more specific functions such as inhibition. Another issue is that few studies have examined the psychophysiological correlates of cognitive control ability among those with PTSD. Adopting a psychophysiological perspective may provide greater insight into the relationship between cognitive control and the severity of PTSD symptoms and lead to new research directions focused on the etiology and treatment of PTSD. Individual differences in resting levels of HRV are associated with cognitive control ability, particularly inhibitory processes. Moreover, the neurovisceral integration model suggests that low HRV at rest may serve as an endophenotype for some forms of psychopathology, including anxiety disorders (Melzig et al., 2009; Thayer and Lane, 2009). By examining individual differences in resting HRV, researchers may be better able to elucidate the relationship between cognitive control ability and re-experiencing symptoms among those

with PTSD. One interesting possibility is that individual differences in HRV may underlie the association between cognitive control ability and intrusive cognitions in PTSD. Although this idea has yet to be directly examined, researchers have begun to recognize the role of autonomic dysfunction (i.e., low HRV) among those with PTSD. In addition, studies have started to investigate associations among individual differences in HRV, cognitive control processes, and re-experiencing symptoms. Next, we review evidence demonstrating that individuals with PTSD tend to be characterized by low resting HRV. In addition, we show that low resting HRV is also associated with deficits in cognitive control processes and the tendency to re-experience unwanted thoughts and memories.

ASSOCIATIONS AMONG HRV, PTSD, AND RE-EXPERIENCING SYMPTOMS

Given that individual differences in HRV index the degree to which the prefrontal cortex exerts a tonic inhibitory influence over subcortical circuits, one would expect that disorders characterized by psychological inflexibility and impaired inhibitory control, as is the case for PTSD, would also be associated with low resting levels of HRV. Indeed, a number of studies show that individuals with PTSD display lower levels of HRV at rest compared to healthy controls and trauma-exposed individuals without PTSD (Cohen et al., 1998; Sack et al., 2004; Jovanovic et al., 2009; Hauschildt et al., 2011; Nagpal et al., 2013; Norte et al., 2013). Blechert et al. (2007) found that individuals with PTSD exhibited lower levels of vagally mediated HRV at rest relative to healthy controls and patients with panic disorder, another anxiety disorder also characterized by low resting HRV (Friedman and Thayer, 1998). Importantly, other investigations have shown that individuals with PTSD are characterized by reduced levels of HRV even after accounting for important covariates such as traumatic brain injury and levels of depression (Minassian et al., 2014). A limitation of the extant literature is that a majority of studies are cross-sectional. Thus, it is unclear whether reduced levels of HRV observed in patients with PTSD represent a pre-trauma vulnerability factor or result from exposure to trauma. However, given that resting levels of HRV appear to be relatively stable over time (Li et al., 2009), it seems more likely that low resting levels of HRV may precede the onset of a traumatic event. In support of this idea, evidence suggests that low levels of HRV prospectively predict increases in anxiety among women diagnosed with breast cancer (Kogan et al., 2012). In addition, a recent study found that HRV measured soon after trauma exposure predicted the development of PTSD 6 months later; those with lower vagally mediated HRV at rest were more likely to develop PTSD and show greater severity of symptoms relative to those with higher vagally mediated HRV (Shaikh al arab et al., 2012).These findings provide initial support for the notion that low HRV at rest increases an individual's vulnerability to develop PTSD. If having low HRV increases an individual's susceptibility to develop PTSD, it may do so by way of its relationship to cognitive control processes.

Individual differences in HRV influence the effectiveness of cognitive control processes involved in managing the experience of intrusive memories and thoughts. A recent study (Gillie et al., 2014) examined whether HRV at rest predicted the degree to which individuals are able to suppress unwanted memories, assessed via the Think/No-Think Task (Anderson and Green, 2001). In this task, participants learn a series of a word pairs and later intentionally and repeatedly attempt to stop retrieval of the memory of the words when presented with a cue. Successful suppression of a target memory should reduce its accessibility at a later point; therefore, recall for the response words is assessed at the end of the experiment. Moreover, effective suppression is thought to require a high degree of inhibitory control (Levy and Anderson, 2008). Gillie et al. (2014) found that higher levels of resting HRV were associated with more successful suppression, as indicated by lower recall of the to-be-suppressed stimuli relative to control stimuli. Another study by this group examined the association between HRV and control over unwanted thoughts using a standard laboratory thought suppression paradigm (Gillie et al., submitted for publication). Participants were randomly assigned to either a suppression or free-thought control condition and asked to monitor the occurrence of a personally relevant intrusive thought. Among those instructed to suppress, higher levels of HRV were associated with greater declines in thought intrusions across the monitoring periods. Moreover, when HRV was low, higher spontaneous suppression effort ironically predicted greater persistence of intrusive thoughts over time. Taken together, these findings demonstrate an association between individual differences in HRV and the ability to exert control over unwanted thoughts and memories. It is worth noting that these studies included only healthy, college-aged participants. Thus, it remains to be seen whether these findings generalize to individuals with PTSD.

CONCLUSION AND FUTURE DIRECTIONS

A large body of evidence suggests that PTSD is characterized by cognitive control deficits, which in turn have been linked to the re-experiencing of symptoms such as intrusive thoughts and memories. Moreover, these deficits in cognitive control are primarily the result of impaired inhibitory processes. Building from the common neural basis for cognitive regulation and physiological regulation of the autonomic nervous system, the neurovisceral integration model suggests that individual differences in HRV may be a peripheral marker of cognitive control ability. Indeed, low resting HRV is associated with poorer performance on tasks that require cognitive control processes, especially those that tap inhibition. Initial findings suggest that individual differences in HRV may also index the extent to which individuals are subject to re-experiencing symptoms such as intrusive thoughts and memories. Understanding the relationships among individual differences in HRV, cognitive control, and re-experiencing symptoms is critical, as it may help to refine theoretical models describing the etiology and maintenance of PTSD. Perhaps more importantly, identifying and manipulating the mechanisms that underlie PTSD symptomology may lead to improvements in preventative and therapeutic approaches. Because HRV is able to index the activity of brain networks that support goal-directed behavior, some have advocated its use as a research tool to better understand basic cognitive and psychopathological processes, such as those involved in the etiology and maintenance of PTSD (Appelhans and Luecken, 2006;

Thayer and Lane, 2009). We echo this statement and posit that individual differences in HRV play a central role in the relationship between cognitive control and re-experiencing symptoms among those with PTSD. The evidence reviewed in this article suggests interesting possibilities for future research.

Identifying risk factors for developing PTSD has been a major focus of previous research. A number of studies have found that particular biological and cognitive individual characteristics observed prior to the onset of trauma heighten an individual's risk of developing PTSD (for review, see Bomyea et al., 2012b). Among the pre-trauma cognitive vulnerabilities, proactive interference, a type of inhibitory process, has been specifically linked to the occurrence of re-experiencing symptoms (Verwoerd et al., 2011). Given that HRV taps an individual's capacity for effective inhibitory processing, it seems plausible that reduced HRV may promote poor proactive interference control which could in turn lead to more severe PTSD symptomology, especially intrusive thoughts and memories. As mentioned previously, a recent study found that HRV measured soon after trauma exposure predicted PTSD development and severity (Shaikh al arab et al., 2012). Future studies should aim to replicate and extend these findings by prospectively investigating the relationship between individual differences in HRV and cognitive control ability both before and after trauma exposure. By using prospective study designs, researchers can more fully investigate the causal pathway between HRV and the severity of PTSD symptom expression and perhaps better understand the underlying mechanisms (e.g., poor cognitive control).

The associations among HRV, cognitive control, and re-experiencing symptoms may also help to inform treatments for PTSD. If low HRV acts as a vulnerability factor for developing PTSD in the manner that we suggest, it follows that enhancing HRV through medical or psychological interventions may promote more effective cognitive control and thus reduced occurrence of re-experiencing symptoms. A number of interventions including mindfulness mediation (Tang et al., 2009), applied biofeedback (Tan et al., 2011), and aerobic exercise (Jurca et al., 2004) have been shown to increase HRV over either short-term or longer term intervals. Of particular interest are studies demonstrating that improvements in HRV as a result of aerobic fitness training are associated with concomitant increases in cognitive control ability (Luque-Casado et al., 2013; Alderman and Olson, 2014). In addition, Hansen et al. (2004) found that aerobic detraining decreased both levels of HRV and cognitive performance. These findings provide further support for the association between HRV and cognitive control and demonstrate that exercise training may influence both factors. Yet, few studies have examined whether inventions attempting to improve HRV and cognitive control affect PTSD symptom severity (but see Tan et al., 2011). Thus, future studies should examine whether interventions designed to increase resting HRV also enhance cognitive control ability and reduce PTSD symptom severity.

In this review, we sought to highlight the associations among individual differences in HRV, cognitive control, and re-experiencing symptoms that characterize PTSD. Empirical evidence suggests that these factors are intimately related, though we emphasize the importance of considering HRV given its role as a peripheral marker of organism adaptability and self-regulatory capacity. We hope that our suggestions, derived from a model of neurovisceral integration, will help researchers to develop hypotheses regarding the etiology and maintenance of PTSD symptoms.

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Maladaptive autonomic regulation in PTSD accelerates physiological aging

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A core manifestation of post-traumatic stress disorder (PTSD) is a disconnection between physiological state and psychological or behavioral processes necessary to adequately respond to environmental demands. Patients with PTSD experience abnormal oscillations in autonomic states supporting either fight and flight behaviors or withdrawal, immobilization, and dissociation without an intervening "calm" state that would provide opportunities for positive social interactions. This defensive autonomic disposition is adaptive in dangerous and life threatening situations, but in the context of every-day life may lead to significant psychosocial distress and deteriorating social relationships. The perpetuation of these maladaptive autonomic responses may contribute to the development of comorbid mental health issues such as depression, loneliness, and hostility that further modify the nature of cardiovascular behavior in the context of internal and external stressors. Over time, changes in autonomic, endocrine, and immune function contribute to deteriorating health, which is potently expressed in brain dysfunction and cardiovascular disease. In this theoretical review paper, we present an overview of the literature on the chronic health effects of PTSD. We discuss the brain networks underlying PTSD in the context of autonomic efferent and afferent contributions and how disruption of these networks leads to poor health outcomes. Finally, we discuss treatment approaches based on our theoretical model of PTSD.

Keywords: PTSD, aging, polyvagal theory, chronic stress, autonomic nervous system

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a common diagnosis following trauma exposure. In a survey of 23,936 people with trauma exposure conducted by the World Health Organization World Mental Health Surveys across 13 countries, 6.6% evidenced clinical or subclinical PTSD symptoms consistent with DSM-V criteria (McLaughlin et al., 2014). In military samples, nearly 40% of people who experienced mild traumatic brain injuries developed symptoms of PTSD or depression (Tanielian et al., 2008).

Despite the prevalence of PTSD diagnoses, the consequences of trauma exposure, in particular in the context of PTSD, are far from deterministic. Exposure to trauma has varied outcomes between individuals, and repeated exposures may have different outcomes in the same person. At present, the underlying differences between individuals who appear to be resilient in the face of exposure to such trauma and those who are more likely to develop PTSD or another psychological disorder are not well understood. These individual differences in resilience and vulnerability are an important area of focus and may underlie chronic differences in health outcomes.

Current research is documenting the important mediating effects of several factors including genetics, developmental history, age, prior and present environment, and context. In this review, we will focus on the impact of chronic PTSD on the trajectory of health. Although PTSD is a categorical designation, there are varying degrees of severity of trauma-elicited perturbation of stress responses and disposition. Not everyone who is exposed to a traumatic experience develops symptoms that meet the categorical designation of PTSD. Furthermore, of those that do, many do not develop chronic dispositional shifts—i.e., they recover fully. Likewise, those that do not meet the criteria for a PTSD diagnosis may experience chronic effects of trauma exposure. In this review paper, we use "PTSD" as shorthand for PTSD continua symptoms as opposed to just the categorical designation.

The American Psychiatric Association (2013) recently revised the diagnostic criteria for PTSD [Diagnostic and Statistical Manual of Mental Disorders (5th Edition), 2013]. In order to be diagnosed with PTSD, one must have been exposed to one or more traumatic events that may include direct exposure, witnessing in person, indirect exposure, or repeated extreme indirect exposure to death, actual or threatened serious injury or actual or threatened sexual violence. The symptoms of PTSD are clustered into four categories: (1) intrusion symptoms (2) avoidance symptoms (3) negative alterations in cognition and

mood and (4) alterations in arousal and reactivity [Diagnostic and Statistical Manual of Mental Disorders (5th Edition), 2013]. Related to these symptoms are shifts in autonomic state to deal with perceived threat. Specifically, the autonomic nervous system can shift state to efficiently promote mobilization for fight or flight behaviors or shift to a metabolically conservative state of quiescence that can manifest as extreme social withdrawal or even vasovagal syncope (i.e., fainting). Reaction to perceived threat takes precedence and displaces autonomic states that support social behavior, health, growth, and restoration. This automatic bias to prioritize potential (though often improbable, in the context of PTSD) threat is not entirely suppressed or easily modified by the higher cortical processes that we associate with voluntary behaviors, intentions, and learning. It is this loss of modulation of autonomic state that compromises a full range of functions from an ability to immobilize without fear in the presence of others, mobilize without rage or anger, and socially engage others. We conceptualize a loss of the range of autonomic state in response to social and environmental cues as a core component of PTSD itself (Williamson et al., 2013).

Chronic PTSD symptoms are related to several apparently disparate poor health outcomes including metabolic disease (e.g., possible increased diabetes risk; Miller-Archie et al., 2014), cardiovascular disease, asthma, cancer, back pain, peripheral vascular disease, gastrointestinal problems, thyroid disorders (Glaesmer et al., 2011) to mental health factors including loneliness (Kuwert et al., 2014) and hostility (Miller et al., 2013), which themselves are associated with physiological health consequences. However, through the lens of the autonomic nervous system, these disorders are related to an interaction between the autonomic nervous system and the regulation or modulation of myriad neurophysiological functions, from cognition to the immune responses. Below we discuss the contributions of autonomic dysregulation to deteriorating health. Within this context, we describe how autonomic functioning is related to central and peripheral inflammatory factors, immunologic functions, and psychosocial impairments (e.g., hostility and loneliness) in mediating and often exacerbating deleterious health outcomes.

PTSD AND AUTONOMIC BEHAVIOR: CHRONIC THREAT AND THE PERPETUAL STATE OF FIGHT, FLIGHT, OR IMMOBILIZATION

Post-traumatic stress disorder manifests as a disorder across multiple systems in which there are atypical expressions of social engagement behaviors as well as disruptions in the regulation of emotional and cognitive processes. From an autonomic perspective, these processes and behaviors are consistent with a dispositional state of chronic mobilization or withdrawal in response to perceived threat. Affect, cognition, and autonomic functioning are interconnected via shared cerebral anatomy including cortical and subcortical structures and the white matter structures that connect them. The state of the autonomic nervous system is a component of nearly every function in which humans engage, including mobilization of cerebral hemodynamic resources to perform simple thinking tasks and mobilization of peripheral nervous system resources to engage with the environment, including through neurophysiological functions that involve muscle activity. The autonomic nervous system is integrated in all behavioral and physiological functions that are dependent on smooth, cardiac, and striated muscles.

Patients with PTSD process environmental stimuli differently than people without PTSD. For example, in a functional neuroimaging study comparing 23 patients with PTSD and 42 healthy controls, the patients with PTSD showed greater activation of the amygdala, a key limbic structure, in response to photographs of emotional facial expressions of fear (Felmingham et al., 2010). In another small study comparing 15 patients with PTSD and 15 age and sex matched controls, patients with PTSD demonstrated no ERP differences between processing of neutral and angry faces, suggesting reduced capacity to distinguish between threat and non-threat (Felmingham et al., 2003). Further, there is preliminary evidence that patients with PTSD have decreased high-frequency heart rate variability, likely indicative of an autonomic state that would support the mobilization necessary for fight or flight behaviors and resulting in lower vagal tone to the heart. This is perhaps due to the perception of a threat condition manifesting as a combination of increased sympathetic drive and/or parasympathetic withdrawal (Tan et al., 2011). Moreover, patients with PTSD also have altered acoustic startle responses, typically probed with brief but loud auditory stimuli. This alteration is not unimodal, as some people express greater physiological reactivity (increased startle reflex) whereas others, often those with severe or repeated trauma exposure, express physiological hyporeactivity (McTeague et al., 2010; D'Andrea et al., 2013).

Thus, PTSD may be understood as a deficit in autonomic adaptation that is often expressed as an incongruity between physiological state and environmental demands (Williamson et al., 2013). In the appropriate environment, a fight or flight state is adaptive. However, in environments that normally should be considered safe (e.g., sitting in an office or trying to sleep in one's bedroom), such a state is maladaptive. When chronic, this incongruity may be pathological, even when only components of the mobilization response are chronic. For example, in Cushing's syndrome there is a chronic state of elevated cortisol, and this disease is correlated with emotional and cognitive changes along with other health issues, including hypertension, diabetes, immunologic dysfunction, and sleep disturbances. As we will discuss, this is not unlike the health outcomes observed in patients with PTSD. Although an acute shift to a defensive physiological state can be an appropriate and effective response to environmental demands, a chronic fight or flight state is damaging. This damage includes metabolic, immunologic, and cardiovascular effects. Also, the psychological effects include impairment of close relationships with other humans. Thus, we propose that PTSD is associated with a pathological resetting of the autonomic nervous system that is manifest as an autonomic disposition to optimize defense reactions to danger and life threat.

POLYVAGAL THEORY

Autonomic reactivity and the construct of autonomic disposition can be conceptualized within the framework of the Polyvagal Theory. The Polyvagal Theory, by providing a neurophysiological basis of how autonomic state and behavior interface, enables a better understanding of several behavioral and physiological

features observed in PTSD. The theory emphasizes a hierarchical relation among three subsystems of the autonomic nervous system that support adaptive behaviors in response to the particular environmental features of safety, danger, and life threat (Porges, 1995, 2001, 2007, 2009).

The theory is named "Polyvagal" to emphasize that there are two vagal circuits. One is an ancient vagal circuit associated with defense. The second is an evolutionarily newer circuit, only observed in mammals, that is associated with physiological states related to feeling safe and spontaneous social behavior, and is important for social engagement. Consistent with this, potent regulators of our physiological state that mediate emotional expression are embedded in relationships (Cozolino, 2006; Siegel, 2012). Hofer (1994) employed a similar concept to explain the role of mother–infant interactions in facilitating the health and growth of infants. The core of the social engagement system in mammals is reflected in the bidirectional neural communication between the face and the viscera. Through reciprocal interactions via facial expressivity, gesture, and prosodic vocalizations, attunement occurs between the social engagement systems of two individuals. This attunement, consistent with Hofer's insights, regulates behavioral states (i.e., emotional regulation), and simultaneously promotes health, growth, and restoration.

According to the Polyvagal Theory, when the individual feels safe two important features are expressed: first, bodily state is regulated in an efficient manner to promote growth and restoration. Functionally, this is accomplished through an increase in the influence of myelinated vagal efferent pathways on the cardiac pacemaker to slow heart rate, inhibit the fight–flight mechanisms of the sympathetic nervous system, dampen the stress response system of the hypothalamic–pituitary–adrenal (HPA) axis (e.g., cortisol), and reduce inflammation by modulating immune reactions (e.g., cytokines). Second, the brainstem nuclei that regulate the myelinated vagus are integrated with the nuclei that regulate the muscles of the face and head. This integration of neuroanatomical structures in the brainstem provide the neural pathways for a functional social engagement system characterized by a bidirectional coupling between bodily states and the spontaneous social engagement behaviors expressed in facial expressions and prosodic vocalizations (Porges, 2011; Stewart et al., 2013). Thus, the behavioral manifestation of this integrated social engagement system emerged specifically as a consequence of the neural pathways regulating visceral states becoming neuroanatomically and neurophysiologically linked with the neural pathways regulating the muscles controlling gaze, facial expression, head gesture, listening, and prosody (see Porges, 2001, 2007, 2009).

The autonomic subsystems responsible for defensive mobilization or restoration and social engagement can be conceptualized as phylogenetically ordered and behaviorally linked to three global adaptive domains of behavior including: (1) social communication (e.g., facial expression, vocalization, listening); (2) defensive strategies associated with mobilization (e.g., fight–flight behaviors); and (3) defensive immobilization (e.g., feigning death, vasovagal syncope, behavioral shutdown, and dissociation). These neuroanatomically based subsystems form a response hierarchy consistent with the construct of dissolution proposed by John Hughlings Jackson (Jackson, 1958) in which more recently evolved neural circuits regulate the function of older circuits. Therefore, the newest autonomic circuit associated with social communication has the functional capacity to inhibit the older involuntary circuits involved in defense strategies of fight/flight or shutdown behaviors.

Effective social communication is easier during states when we experience safety because our defense strategies are inhibited. This system is dependent on myelinated vagal pathways and fosters inhibition of sympathetic influences on autonomic behavior including dampening of the HPA axis (Bueno et al., 1989; O'Keane et al., 2005; Hostinar and Gunnar, 2013). Depending on when trauma occurs, there may be an interruption in the development of these social situations that impact cumulative life stress and health (Hostinar and Gunnar, 2013). Input to the nucleus ambiguus, which has direct output to the heart and bronchi via the newer myelinated vagus, promotes a state conducive to social engagement. As the dynamic process of threat detection increases, stage 2 (mobilization) or stage 3 (immobilization) responding occurs. Mobilization is characterized by sympathetic activation and parasympathetic withdrawal such that blood pressure increases and respiratory sinus arrhythmia (i.e., high-frequency heart rate variability) decreases. These physiological behaviors support high-energy actions including fighting or fleeing. Immobilization is an ancient defense strategy shared with most vertebrates and is facilitated by unmyelinated vagal pathways or "vegetative" vagus that slows the heart and inhibits subdiaphragmatic processes (e.g., digestion). This response strategy might be considered our most primitive defense system, and more severe trauma is associated with less physiological (i.e., sympathetic) reactivity and often complete collapse to threat stimuli (D'Andrea et al., 2013).

The Polyvagal theory has stimulated research across several disciplines (e.g., neonatology, obstetrics, bioengineering, pediatrics, psychiatry, psychology, exercise physiology, human factors, etc.) and has been used as a theoretical perspective to generate research questions and explain findings by numerous research teams (Travis and Wallace, 1997; Beauchaine, 2001; Beauchaine et al., 2007; Egizio et al., 2008; Hastings et al., 2008; Schwerdtfeger and Friedrich-Mai, 2009; Weinberg et al., 2009; Perry et al., 2012; Ardizzi et al., 2013). This theory has informed stress researchers of the important role the parasympathetic nervous system and its component vagal circuits play in neurophysiological mechanisms related to defensive strategies associated with reactivity, recovery, and resilience (Brown and Gerbarg, 2005; Kogan et al., 2012; Wolff et al., 2012; Evans et al., 2013; Kim and Yosipovitch, 2013).

NEUROCEPTION

The Polyvagal Theory proposes a process, neuroception, which evaluates risk without awareness (Porges, 2003, 2007). Unlike perception, which involves a cognitive appraisal, neuroception involves brain processes that function outside the realm of awareness, although the individual may immediately become aware of consequences of these reactions when there are major shifts in autonomic state, such as palpitations, tachycardia, bradycardia, vasovagal syncope, nausea, or light headedness (Porges, 2003, 2007). Neuroception is supported by sensory and association cortices including temporal cortex, fusiform gyrus (face detection),

and limbic structures including the amygdala (Adolphs, 2002; Pessoa et al., 2002; Winston et al., 2002) and orbitofrontal cortex (Grèzes et al., 2014). Neuroception is viewed as an adaptive mechanism that can either turn off or turn on defenses to engage others. Moreover, as this process triggers shifts in autonomic state, it may also bias perception of other people in a negative or positive direction. If our physiological state shifts toward behavioral shutdown and dissociation, mediated by the unmyelinated vagal pathways, we lose contact with the environment and others. The resulting observation in PTSD would be an autonomic disposition that would support defensive behavioral strategies.

Our nervous system continuously monitors and evaluates risk in the environment. When features of safety, danger, or life threat are detected, areas of the brainstem that regulate autonomic structures are activated. When features of safety are detected, autonomic reactions promote open receptivity with others, but when features of threat are detected, autonomic reactions promote a closed state limiting the awareness of others (Porges, 2003, 2007). For example, in the presence of someone with whom an individual feels safe, a person experiences the sequelae of positive social engagement behaviors consistent with a neuroception of safety; their physiology calms and their defenses are inhibited. Defensive strategies are then replaced with gestures associated with feeling safe and with this state of safety there is a perceptional bias toward the positive. Appropriately executed prosocial spontaneous interactions reduce psychological and physical distance. However, activating a sense of safety is greatly challenged in PTSD.

RESETTING THE AUTONOMIC NERVOUS SYSTEM TO SUPPORT ADAPTIVE RESPONSES TO DANGER AND LIFE THREAT

Autonomic dispositions, or adaptive or maladaptive autonomic dynamic responses to external and internal environment cues, may be reset by trauma-related disruptions to the hierarchically organized neural regulation of the autonomic nervous system. This disruption may occur via physical trauma (e.g., TBI) injuring relevant systems (Williamson and Harrison, 2003; Smith-Bell et al., 2012), by genetics (Koenen, 2007; Glatt et al., 2013), or by a combination of factors, e.g., the diathesis-stress model (Edmondson et al., 2014).

Patients with PTSD may have a lower threshold to move from a neutral to a defensive state. PTSD alters threat detection such that information that may be identified as innocuous by someone who does not have PTSD (e.g., a car backfiring) is identified to be a threat by someone who does (e.g., a car backfiring is interpreted to be a gunshot). Their perception of threat is a manifestation of individually endogenous variables (personality, trauma history, sleep/arousal status, current transient stress levels, perceived control) and environmental variables (accessibility of exits, lighting levels, presence of strangers). Some aspects of PTSD may be a defensive strategy to environmental features that are outside of conscious awareness. For example, many people with PTSD, seemingly habitually, position themselves in a room with their back to a wall (i.e., no one can approach from behind), optimize access to an exit, and monitor visibility to directions of potential threat. To shift from this chronic defensive disposition, the patient with PTSD must be able to not only perceive, but to have an accurate neuroception of safety, which would inhibit limbic structures that mobilize defensive visceral states.

Though a person with PTSD may be able to consciously state that a given situation is safe, they may be unable to shift to the appropriate physiological state due to a disconnect between their cognitive appraisal and their bodily (e.g., autonomic) reactions. Perhaps an apt analogy is the difference between anosognosia and anosodiaphoria; in the former, the patient is unaware of a deficit, whereas in the latter, the patient is able to express the deficit, but cannot realize the emotional consequences of the issue. Both of these are more likely with right hemisphere lesions and there may be a right hemisphere bias in the process of neuroception such that sympathetic drive and mobilization defense strategies are supported preferentially by right hemisphere systems.

CHRONIC STRESS, LONG TERM HEALTH CONSEQUENCES

The chronic stress associated with PTSD is a critical health issue as the physiological reaction to threat detection is metabolically costly. Although an invaluable survival tool in short-term, contextually appropriate situations, chronic engagement of threat response systems may lead to deterioration of health and social relationships, and ultimately, accelerate the aging process including decreasing age of onset of cognitive decline and early disability. Several features in the resting heart rate spectra (very low frequency, low frequency, and high frequency) are correlated with mortality (Williamson et al., 2010). In particular, low frequency heart rate variability is an independent predictor of death (Tsuji et al., 1994). Furthermore, reduced low frequency baseline (rest) heart rate variability is also linked to coronary artery disease (Kotecha et al., 2012), and lower nighttime heart rate variability as indexed by the standard deviation of RR internals is linked to increased stroke risk even in apparently healthy people (Binici et al., 2011). Allostatic load (McEwen and Wingfield, 2003) from incongruent threat detection and chronic defensive autonomic disposition is a chronic stress with cumulative consequences, however, it may be treatable. In a study of twenty PTSD discordant twin pairs (one having PTSD and one not), reduced heart rate variability was evident in the twins that had PTSD. Furthermore, patients who had recovered from PTSD (no longer reporting symptoms) were not different from the matched healthy twin in the heart rate variability measures. This suggests that at least a portion of the negative health consequences of PTSD may be reversible if treated early (Shah et al., 2013).

This is important because PTSD is associated with poor health outcomes. Patients with PTSD subsequent to the World Trade Center attacks have a tendency to develop diabetes (Miller-Archie et al., 2014) and have a higher likelihood of developing cardiovascular disease (Jordan et al., 2013). Also, in a sample of 52,095 people surveyed by the World Health Organization, patients with PTSD or other disorders of emotional regulation (e.g., depression) have an increased risk for developing cancer (O'Neill et al., 2014).

In addition to being associated with poor physical health outcomes, PTSD is associated with other mental illnesses and poor health behaviors, suggesting that health outcomes in this population are likely multifactorial. Miller et al. (2008) examined

personality structure in patients with PTSD and found, using a structured clinical interview, that PTSD was best characterized by two internalizing factors, anxious-misery (correlating with PTSD and depression), and fear (correlating with panic disorder and obsessive compulsive disorder), along with one externalizing factor associated with antisocial personality disorder traits and substance abuse. The multifactorial basis of poor health outcomes is exemplified by PTSD's association with alcohol dependence, as when PTSD is comorbid with a substance use disorder, it has been found to be the primary disorder in 60–85% of patients (Epstein et al., 1998). Even though PTSD is the primary disorder, alcohol dependence drives myriad poor health and social outcomes. In addition, patients with PTSD are more likely to smoke cigarettes (Gabert-Quillen et al., 2014; Lombardero et al., 2014), smoke at higher rates (Calhoun et al., 2011a) and show greater dependence (McClernon et al., 2005; Fu et al., 2007). It is not clear if the predisposition to substance use and abuse in the context of PTSD is driven by PTSD itself or if both are driven by shared underlying factors. In the case of cigarette use, for example, smoking rates are associated with a greater likelihood of developing PTSD possibly due to enhancement of memory (memory quality is associated with the development of PTSD) and/or differences in prefrontal-executive functions predisposing dysregulation of limbic circuitry after trauma. Smoking may exacerbate symptoms of PTSD as evidenced by enhanced acoustic startle in patients with PTSD after smoking (Calhoun et al., 2011b).

In addition to higher substance use and abuse rates, patients with PTSD have higher rates of aggression and anger, in particular amongst combat Veterans (Novaco and Chemtob, 2002). For example, a recent study examining the prevalence of intermittent explosive disorder in patients with trauma exposure ($n = 232$) reported that 24% met criteria for lifetime intermittent explosive disorder diagnosis and that PTSD severity was a significant predictor of intermittent explosive disorder diagnosis (Reardon et al., 2014). This violence can also manifest as hostility, a dispositional-like trait that may be characterized by cynical/hostile attributions, anger, and aggressive behaviors (Brummett et al., 1998). Hostility, as measured by personality scales such as the Cook-Medley Hostility Scale [Minnesota Multiphasic Personality Inventory (MMPI)-derived tool] is associated with cardiovascular disease and also with body mass index, waist-to-hip ratio, insulin resistance, lipid ratio, triglycerides, alcohol use, and smoking (Bunde and Suls, 2006). Anger/hostility is related to stress exposure (e.g., trauma), exaggerated autonomic reactivity to stress including cognitive (Williamson and Harrison, 2003) and pain stressors (Herridge et al., 2004), and reduced heart rate variability (Sloan et al., 2001).

Hostility, independent of PTSD, is related to loneliness. Even at an early age, lonely children are hypervigilant to social threat (Qualter et al., 2013), thus there is some counter co-morbidity to PTSD constellation symptoms. These co-morbid symptoms/traits rely on the same brain systems, supporting the idea that shifts in autonomic states impact aspects of mood/personality in a predictable manner and suggesting that intervention in these systems would likely affect all of those behaviors. Loneliness predicts reduced physical activity (Hawkley et al., 2009) and increased blood pressure in older adults (Hawkley et al., 2009, 2006). Thus, the driver of health outcomes after trauma is not necessarily the categorical presence of PTSD, but rather a reaction to trauma that perturbs the dynamic homeostasis of the social engagement system such that some aspect of chronic defensive disposition is elicited. That could be a constellation of symptoms that manifests primarily as anger, sadness, isolation or an interaction/fluctuation amongst these states and dispositions that results in a more severe presentation of symptoms, chronic stress, and deleterious health outcomes.

Patients with PTSD, relative to non-PTSD patients, have reduced heart rate variability in response to trauma cues, require an exaggerated recovery time after exposure (Norte et al., 2013), and have higher blood pressure (Paulus et al., 2013). Furthermore, chronic PTSD increases in catecholamines (e.g., epinephrine and norepinephrine) suggest increased sympathetic load in patients with PTSD (Lemieux and Coe, 1995). Norepinephrine enhances attention and memory formation and increased norepinephrine levels in cerebrospinal fluid are associated with the severity of presentation of symptoms of PTSD (Geracioti et al., 2001). Baseline levels of catecholamines due to trauma history may influence responses to stressors. For example, women with a history of abuse, in response to a mild physical challenge (1 mile stationary bike ride), demonstrated significantly greater reduction in parasympathetic tone than a control population (Dale et al., 2009). An investigation into plasma cortisol concentrations of rape victims revealed that those who reported a history of previous sexual trauma to a new assault did not respond with the same increase in plasma cortisol that first time victims did (Resnick et al., 1995). These findings suggest a direct relationship between stress responses, autonomic nervous system behavior, the manifestation of PTSD, and a mechanism of health decline. It should be noted that characterizing trauma presence and response is a challenge. Since the perception of an event as being traumatic depends not only on the physical features of the event but also on personal history and individual neurobiological differences, several sources of variance contribute to individual subject experiences.

Chronic stress, such as is present with PTSD and depression, has a negative impact on hippocampal characteristics in both animal models (Uno et al., 1989; Magariños and McEwen, 1995; Luo et al., 2014; Tse et al., 2014) and in humans (Childress et al., 2013). Furthermore, mood disorders such as PTSD and associated comorbidities (e.g., depression) are associated with hippocampal atrophy (McEwen and Sapolsky, 1995; Smith, 2005) as well as cognitive disorders such as dementia, as has been demonstrated in former prisoners of war with PTSD (Meziab et al., 2014). This may be in part due to shared neurobiological factors associated with the development of PTSD and dementia or other neuroanatomical changes associated with aging. For example, recent evidence suggests that the presence of apolipoprotein E4 allele (ApoE4), a risk factor for the development of Alzheimer's disease, moderates the relationship between trauma exposure and the development of PTSD (Lyons et al., 2013). In animal models, ApoE4 also affects lipid factors that influence the development of atherosclerosis (Ewart et al., 2014).

In addition to neuroanatomical impacts, PTSD also negatively influences sleep. In a recent laboratory sleep study, 13 veterans

with PTSD were compared to 17 trauma-exposed controls and 15 healthy controls (van Liempt et al., 2013). Patients with PTSD showed more frequent awakenings during both nights of the study compared to both control groups. Further, heart rate was higher in patients with PTSD compared to both control groups. Finally, adrenocorticotropic hormone and cortisol levels were inversely related to the presence of slow wave sleep (van Liempt et al., 2013). Patients with PTSD, in comparison to those with Panic Disorder and healthy controls, show lower respiratory sinus arrhythmia (Woodward et al., 2009), suggesting persistent vagal withdrawal during sleep. PTSD is also associated with low brain gamma-aminobutyric acid (GABA) levels and higher insomnia severity scores, which are correlated with lower GABA, and higher glutamate levels in parieto-occipital cortex (Meyerhoff et al., 2014). These results suggest that the chronic defensive dispositions of patients with PTSD manifest even during sleep. Poor sleep quality is an independent contributor to poor health outcomes including impairments in cognition (Aricò et al., 2010), white matter (Kumar et al., 2014), and cardiovascular disease factors independent of sleep apnea (Tosur et al., 2014).

The literature suggests that chronic throttling of social engagement systems such that defensive reactions are dominant results in poor health outcomes. The mechanisms of these outcomes are multifactorial and include damage from health behavior choices that may be attempts to self-regulate autonomic tone (e.g., stimulating nicotinic acetylcholine receptors by smoking cigarettes and modulating GABA receptors by drinking alcohol in large quantities), direct effects from chronic changes in cardiovascular behavior (e.g., decreased heart rate variability and increased blood pressure), and metabolic inflammatory responses as indicated by the presence of diabetes.

TREATMENTS OF THE SOCIAL ENGAGEMENT SYSTEM AND EFFICACY IN PTSD

Numerous therapeutic strategies have been employed to treat PTSD utilizing different targets of the disordered system. These targets include cognitive schemas, behavioral techniques, relaxation strategies, and pharmacological interventions. Cognitive interventions include methods such as cognitive processing therapy (CPT), in which automatic thoughts are challenged via learning different thinking strategies. Behavioral techniques include exposure methods such as prolonged exposure therapy or flooding (Bluett et al., 2014). Relaxation strategies include interventions such as mindfulness-based stress reduction (MBSR) and paced breathing. Pharmacological interventions include propranolol and serotonin reuptake inhibitors, among others. Further, electrical stimulation and direct nerve interaction techniques are also available including stellate ganglion blockade and trigeminal nerve stimulation. All of these likely have an effect either directly or indirectly on threat detection and autonomic disposition. For the purposes of this review, we focus our discussion on the impact of treatment on modulation of the autonomic nervous system as this treatment outcome (reduction of chronic stress responses and facilitation of shift to a state conducive to social engagement) may be mechanistically the most germane to health outcomes and also appears to be a central component of the presentation of PTSD. These stress-modifying strategies can be broadly categorized as parasympathomimetic or sympatholytic.

There are few empirically supported psychotherapy treatments for PTSD. The details of these treatments are generally outside of the scope of the purpose of this review, however, the effects on the social engagement system are germane. Briefly, most empirically supported psychotherapies for PTSD have, at their core, an exposure component. Exposure-based therapies are commonly used for the treatment of anxiety disorders including PTSD, both with and without pharmacological adjuvants. The basic premise is that presentation of conditioned fear-eliciting stimuli without presence of an aversive event will result in extinction of the conditioned fear response. This type of approach is very effective with conditions such as specific-phobia. Exposure is more complicated in the case of PTSD and scaffolding has been created to deliver an effective extinction-based treatment paradigm. Empirically supported treatments include prolonged exposure and CPT. Eye movement desensitization and reprocessing (EMDR) does have empirical support for efficacy, but there are few data supporting the eye movement component. Unfortunately, there are scant published studies examining physiological efficacy of these psychological therapies or changes in attentional systems. Prolonged exposure therapy has been shown to improve symptoms of irritable bowel syndrome in a case study of a patient with PTSD (Weaver et al., 1998). Sympathetic arousal does impact GI function, thus this suggests the possible effectiveness of modifying the stress response (Weaver et al., 1998). EMDR has been shown to increase heart rate variability, again suggesting a possible mediating effect of vagal mechanisms in alleviating symptoms of PTSD (Sack et al., 2008). Additional research is needed to explore the impact of these treatments on the core symptoms of PTSD, specifically startle-responses, vigilance-attention behaviors, and baseline and task-dependent autonomic responses.

A second category of treatments that have demonstrated efficacy in the treatment of PTSD, or potential efficacy as shown in animal models, work via direct modulation of the autonomic nervous system. Within this domain of autonomic modulation, strategies fall broadly into two categories: sympatholytic (i.e., down-regulating sympathetic nervous system tone) and parasympathomimetic (i.e., up-regulating parasympathetic tone).

Sympatholytic approaches that directly dampen sympathetic reactivity are a promising route of therapeutic intervention. Beta blockers (e.g., propranolol), a class of compounds that are antagonists of β1- and β2-adrenergic receptors, inhibit the action of norepinephrine and epinephrine at these sites and have shown promise in both animal models and humans when administered during the acute phase of trauma, however, results have been mixed (Cahill et al., 1994; Vaiva et al., 2003; Hoge et al., 2012; Bailey et al., 2013). Capitalizing on the fact that norepinephrine levels tend to be higher in patients with PTSD, in a case study and a preliminary pilot study, Lipov et al. (2012) demonstrated the utility of stellate ganglion blockade in alleviating symptoms of PTSD. This method prevents lateralized sympathetic input from the stellate ganglion to the peripheral nervous system. However, there is evidence that the stellate ganglion blockade affects intracranial activity such that

there may be increased risk of cerebral ischemia due to reduced blood flow of the non-blocked hemisphere (Kim et al., 2013a). The stellate ganglion blockade is a direct sympathetic nervous system intervention, however, some reports of decreased vagal tone measured by respiratory sinus arrhythmia (i.e., high-frequency heart rate variability) have been reported to occur concurrently (Fujiki et al., 1999), possibly suggesting that there may be a potential positive influence on the social engagement system.

Two parasympathomimetic approaches with promise include (MBSR; Kabat-Zinn, 1982) and Vagal nerve stimulation (VNS). VNS has been an FDA approved treatment for epilepsy since 1997 and treatment resistant depression since 2005. More recently it has shown promise for numerous other disorders including PTSD. At the moment, this human work has limited interpretability due to inadequate subject numbers and lack of control groups, but a pilot study did demonstrate a significant improvement in treatment resistant anxiety disorders (George et al., 2008). Rodent models of PTSD treated with extinction learning and VNS have yielded very encouraging results (Fanselow, 2013; Peña et al., 2013). Peña et al. (2013) demonstrated rodents trained on auditory fear conditioning showed rapid extinction of the conditioned response when the exposure training was done in conjunction with VNS. Mechanistically, they attributed this to a localized release of norepinephrine in limbic CNS structures, and VNS stimulation has been demonstrated to increase norepinephrine output in the amygdala (Hassert et al., 2004). Norepinephrine relased in limbic structures including the amygdala and hippocampus is thought to facilitate memory formation, and, in the case of PTSD, to facilitate new associations with stimuli used in extinction paradigms. On the other hand, data on the consequences of VNS stimulation on parasympathetic tone are sparse and somewhat contridictory. In children with epilepsy, for example, VNS stimulation caused a reduction in respiratory sinus arrhythmia (DeGiorgio et al., 2009). However, it may be the case that stimulation parameters in many of these patients were intense enough to directly stimulate vagal efferents, as respiration was dramatically reduced as well. It may also be the case that epileptic children, who are known to have atypical autonomic regulation, may be a unique population in their response to VNS. In a porcine model, right VNS resulted in an increase in parasympathetic tone and a decrease in low frequency heart rate variability, which is associated with decreased sympathetic tone. In canines who received 1 week of low level VNS, stellate ganglion nerve activity (sympathetic) was reduced (Shen et al., 2011).

Mindfulness-based stress reduction (Kabat-Zinn et al., 1992) was originally used to treat chronic pain, but has become a subject of much interest as a potential treatment for PTSD. The efficacy of MBSR for PTSD symptoms has been largely positive (Kimbrough et al., 2010; Dutton et al., 2013; Kearney et al., 2013; Omidi et al., 2013; Earley et al., 2014), though much of this research has suffered from design weaknesses such as a lack of active control groups, i.e., waitlist control groups are often used or, in some cases, no control at all. Despite this limitation, these findings are encouraging. MBSR borrows from both traditional and more contemporary practices including mindfulness meditation, body scan medication, and Iyengar Yoga. Two portions of this practice have explicit focus on breathing (i.e., mindfulness mediation and Iyengar Yoga). Both the mindfulness meditation and Iyengar Yoga components of MBSR are introduced to participants with a focus on one's own breath (Kabat-Zinn, 1982). During these components, explicit instruction to slow ones breath is not given, however, it has been reported in multiple investigations that breath slows during the practice (Ditto et al., 2006; Ahani et al., 2014). Given the influence of slow breathing and especially expanding the duration of exhalation upon vagal afferents, it is not a surprise that increases in parasympathetic tone as indexed by respiratory sinus arrhythmia have been reported in a recent pilot study (Krygier et al., 2013). Yoga, as a standalone intervention not integrated into MBSR, has been reported to have efficacy as a PTSD treatment (Descilo et al., 2010). However, yoga is not a standardized practice and is administered via widely divergent procedures. For example, in a pilot study, Hatha Yoga and Iyengar Yoga, closely related styles that encourage attention to breathing, have been demonstrated to increase parasympathetic tone in healthy populations (Papp et al., 2013). On the other hand, other yoga interventions for PTSD have employed rapid breathing and hyperventilation, but those interventions failed to elicit an increase in parasympathetic tone (Telles et al., 2010). Given the heterogeneity of yoga procedures that have been employed for the treatment of PTSD, drawing conclusions of mechanism and efficacy for PTSD are difficult (see Kim et al., 2013b for review of mind-body practices in PTSD treatment, including Yoga). Although, interventions involving slow, paced breathing, either explicitly or implicitly, tend to enhance parasympathetic tone.

CONCLUSION, PTSD AND ACCELERATED AGING

Post-traumatic stress disorder is heterogeneous and, while many people with PTSD often spontaneously recover, many others struggle with chronic symptoms. While there is variability in presentation, the core symptoms are well conceptualized as a disruption in the social engagement system such that threat detection is over-generalized and patients are chronically in a defensive autonomic disposition. This defensive autonomic disposition may support either mobilization (i.e., lower respiratory sinus arrhythmia, increased blood pressure, heightened cardiovascular reactivity to perceived-threat stimuli, and elongated recovery to baseline) or immobilization (i.e., blunted cardiovascular responses to emotional stimuli and a generalized profile of avoidance and apathy), or a fluctuation between these defensive strategies. These chronic defense responses appear to be related to deterioration in health as characterized by early morbidity and mortality, most commonly via cardiovascular disease. Further, a cascade of psychological and physiological responses influences these health outcomes such that poorer quality social interactions contribute to the deterioration of social support networks. This compounds the situation, functioning as a negative feedback loop, aggravating the chronic stress response and further impairing the ability of the person to recover.

Chronic disorders such as cardiovascular disease and diabetes increase in prevalence with age. Diseases of the vasculature including the heart and brain are primary age-related diseases

(Corella and Ordovás, 2014). In healthy aging, there is a reduction in respiratory influences on heart rate variability (Nemati et al., 2013), and these are exacerbated by cardiovascular risk factors. Further, there is a link between decreased heart rate variability associated with stress and the risk for vascular disease (Borchini et al., 2014). Thus, the chronic stress from trauma in young adults as they age may accelerate the normal aging process in part by prematurely introducing heart dynamics associated with older age.

Together, the PTSD related cardiovascular, metabolic, and inflammatory systemic changes affect the body in a manner consistent with accelerated aging. Further, pre-trauma exposure characteristics that predict future diseases of aging (e.g., ApoE4 status), are associated with vulnerability to the development of PTSD. Several groups have hypothesized early Alzheimer's disease onset due to chronic changes associated with PTSD (Weiner et al., 2013; Greenberg et al., 2014), and linkages between PTSD diagnosis and dementia have been demonstrated in large samples. For example, in a sample of more than 180,000 veterans, those that were diagnosed with PTSD were more than twice as likely to develop dementia (Yaffe et al., 2010). PTSD has been linked to many brain changes including structural and functional shifts in medial prefrontal cortex, amygdala and hippocampus, with some studies showing longitudinal changes (Uno et al., 1989; Magariños and McEwen, 1995; Smith, 2005; Bremner, 2007; Childress et al., 2013; Luo et al., 2014; Tse et al., 2014). These regions, in particular frontal-temporal structures, are also particularly vulnerable in normal aging; e.g., limbic white matter tracts are amongst the structures that deteriorate the earliest and fastest with aging. (de Groot et al., 2014). Further, these regions are primary areas of amyloid deposition in Alzheimer's disease (Fjell et al., 2014).

Due to potential chronic effects of both PTSD and aging on limbic areas and their cortical mediators, there is a possibility of a progressive decline of social engagement systems such that delaying intervention may affect the viability of treatment effectiveness. In normal aging, resting respiratory sinus arrhythmia is lower with age (De Meersman and Stein, 2007; Capuana et al., 2012) and task-dependent autonomic response reflects heightened sympathetic response (Capuana et al., 2012). Paralleling this, young adult patients with PTSD show task-dependent differences in respiratory sinus arrhythmia response such that RSA does not change in response to cognitive challenge in comparison to healthy age matched adults (Sahar et al., 2001). However, if the autonomic dysregulation associated with PTSD is addressed, interrupting the cascading effect of metabolic, autonomic, neuroimmunologic, and health behavior interactions, then we can dramatically improve health outcomes and greatly improve quality of life in these individuals. In particular, studies of early intervention in both comparative and human patients with trauma exposure focusing on treatments with parasympathomimetic effects may yield the best effect sizes for attenuating or arresting the impact of trauma on the acceleration of the aging processes in these patients.

Overall, focus on early treatment of trauma victims is a public health concern with great potential for economic impact. Interventions that focus on supporting physiological states, thus providing a neural platform for spontaneous social engagement behaviors by optimizing autonomic regulation and functionally dampening defensive mobilization and immobilization strategies, should have the highest impact. As is the case with interventions focused on improving health trajectories with aging, the earlier the treatment, the greater the eventual effect is likely to be. Assessing which defensive strategy is dominant may be key to the selection of effective interventions. Research on efficacy of treatment should treat the category of PTSD as heterogeneous and should examine differential response based on personality factors in the expression of PTSD symptoms and dispositional differences in chronic stress profiles. Ideally, treatment should result in normalization of cardiac vagal tone, reduction of overgeneralization of or faulty neuroception, and facilitate social engagement responses. These treatment targets show the greatest promise for assuaging the acceleration of physiological aging in chronic PTSD.

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Heart rate variability interventions for concussion and rehabilitation

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The study of heart rate variability (HRV) has emerged as an essential component of cardiovascular health, as well as a physiological mechanism by which one can increase the interactive communication between the cardiac and the neurocognitive systems (i.e., the body and the brain). It is well-established that lack of HRV implies cardiopathology, morbidity, reduced quality-of-life, and precipitous mortality. On the positive, optimal HRV has been associated with good cardiovascular health, autonomic nervous system (ANS) control, emotional regulation, and enhanced neurocognitive processing. In addition to health benefits, optimal HRV has been shown to improve neurocognitive performance by enhancing focus, visual acuity and readiness, and by promoting emotional regulation needed for peak performance. In concussed athletes and soldiers, concussions not only alter brain connectivity, but also alter cardiac functioning and impair cardiovascular performance upon exertion. Altered sympathetic and parasympathetic balance in the ANS has been postulated as a critical factor in refractory post concussive syndrome (PCS). This article will review both the pathological aspects of reduced HRV on athletic performance, as well as the cardiovascular and cerebrovascular components of concussion and PCS. Additionally, this article will review interventions with HRV biofeedback (HRV BFB) training as a promising and underutilized treatment for sports and military-related concussion. Finally, this article will review research and promising case studies pertaining to use of HRV BFB for enhancement of cognition and performance, with applicability to concussion rehabilitation.

Keywords: heart rate variability, concussion, mild TBI, biofeedback, neurofeedback, rehabilitation

Heart rate variability (HRV) has emerged as an essential component for study, research and clinical applications in physiology and psychophysiology (Moss et al., 2013). Research has shown implications for HRV in physiology, pathophysiology, psychology, psychopathology, cognition, and neurocognitive impairment (Gevirtz, 2013). Within the physical domain, HRV has been postulated as a measure of not only cardiac health, but of cardiac pathology and as a marker of possible mortality from cardiopathology (Bigger et al., 1995). Psychologically, given its connections with the autonomic nervous system (ANS) and limbic system, HRV can be a marker for anxiety disorders, such as a generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), or a general predisposition to react sympathetically to external or internal stressors (Blechert et al., 2007). Cognitively, persons with high HRV have shown superior performance on neurocognitive measures of attention, concentration, working memory, and executive functioning (Hansen et al., 2003). Alternatively, HRV can be adversely affected by concussions or any degree of traumatic brain injury (TBI; Goldstein et al., 1998). However, there is research that HRV and HRV impairment can be modified and trained through exercise (Hedelin et al., 2001; Hansen et al., 2004; Hautala et al., 2009), diet (Lima-Silva et al., 2010), and biofeedback interventions (Lehrer et al., 2013). This article will first review theoretical models of the heart–brain ANS interaction, with specific emphasis on the adverse effects of sport and military concussions on HRV. Second, this article will review studies suggesting that heart rate variability biofeedback (HRV BFB) is a promising intervention for treatment of sport and military concussions.

EPIDEMIOLOGY AND DIAGNOSIS OF TRAUMATIC BRAIN INJURY

First, it is necessary to review the etiology and severity of TBI to understand where concussions fall along the continuum of severity of injury and how they may affect HRV. TBI is defined as an injury to the brain resulting from blunt trauma to the head or body, or acceleration or deceleration forces transmitted to the brain (Barr and McCrae, 2011). TBI severity is classified as Mild, Moderate, or Severe based on degree of injury severity, including presence and length of loss of consciousness (LOC) and number and degree of post-traumatic symptoms. These three categories are based on assessment with the Glasgow Coma Score (GCS; Teasdale and Jeanette, 1974). The GCS measures a patient's level of functioning based on eye opening and verbal and motor responses, resulting in a score ranging between 3 (minimum) and 15 (maximum). The Mild GCS group has a score of 13–15, and typically will have minimal or no permanent neurologic sequelae, with typical recovery expected in 1–3 months (Levin et al., 2012). The Moderate TBI group has a GCS score of 9–12 and may have permanent sequelae impacting personal life, school or

work; finally, the Severe TBI group has a GCS score of 8 and below, and will almost always present with permanent neurologic damage at a moderate level or greater, affecting all aspects of life. It is the "Mild" group that is the primary focus of this article, as these are the athletes and soldiers that most often will be seen clinically and who may have cardiac correlates of concussion sufficient to interfere with cognitive and cardiovascular resources needed for athletic and military performance. Generally, patients with a GCS in the 13–15 range will not have LOC, but may have episodic cognitive confusion, transient amnesia, dizziness, slow reaction time, and balance problems (McCrory et al., 2013). When assessed in the Emergency Room, the traditional physical neurologic exam will be negative and non-focal for pathology, as will the Head CT. The traditional Emergency Room concussion evaluation protocol may not elucidate underlying neuropathology, which is being seen in controlled research studies of athletes with sophisticated neuroimaging including magnetic resonance spectroscopy, fMRI, or diffusion tensor imaging (DTI; Bluml and Brooks, 2006; Pardini et al., 2011) or neuroelectrical assessment including EEG and ERP (Broglio et al., 2009; McCrea et al., 2010; Barr et al., 2012). If someone with a presumed Mild TBI does present with greater neuropathology, such as a basilar skull fracture, intracerebral bleed, or cerebral hematoma, then they are generally referred to as a "complicated" Mild TBI and the severity of injury is noted, with implications for a more complicated recovery.

Giza and Hovda (2001) have elucidated an animal neurometabolic model of mild TBI or concussion, in which there is a significant mismatch between glucose metabolism and regional cerebral blood flow, with a concomitant influx of glutamate and other ionic changes in the cell membrane. Their studies have repeatedly shown a return to baseline neurometabolism around seven days post-injury, presumably without permanent cellular damage. These animal studies have provided the basis for predicted return to baseline functioning in athletes in 7–10 days. This neurometabolic model may be useful to explain the quick recovery typical of non-refractory concussions. However, refractory concussions (the focus of this article) may be better explained by a model of neuronal deformation induced by the biomechanical force of the injury (Abolfathi et al., 2009).

McCrory et al. (2013) postulate that concussions may overlap with the lower end of the Mild TBI spectrum, and may extend to a lesser degree of severity labeled Minimal TBI. The terms "concussion" and "Minimal TBI" may be used interchangeably and as an alternative to Mild TBI but "concussion" will be used in this article, consistent with its usage in sports medicine.

Bigler (2008) points out that a concussion from a football tackle, automobile accident or blast injury does not solely affect the brain. The concussive forces can affect all organs, including the heart (Cernak and Noble-Haeusslein, 2009). Cardiac sequelae of a primary blast injury may produce arrhythmias, ischemia or a myocardial infarction (Garner and Brett, 2007), even in the absence of cerebral concussion. For example, comotio cordis is an unfortunate and often fatal cardiac event from a direct blow to the chest wall, usually in baseball, and without a concomitant cerebral concussion. Additionally, Palma and Benarroch (2014) reviewed non-traumatic cerebral illnesses which impair HRV, including epilepsy, ischemic, and hemorrhagic stroke and neurodegenerative diseases, such as Parkinson's. They postulate that these neuropathologies involve the insula, basal ganglia, and brainstem and may impair HRV, leading to secondary cardiac illness.

While there have been studies measuring actual G-force on the playing field (Guskiewicz and Mihalik, 2011), few such studies have been done for the most common cause of concussion in adults: automobile accidents. In children, the most common cause of concussion presenting at emergency departments is bicycle accidents (Gilchrist et al., 2011), followed by sport-related injuries. The change in momentum (impact) and transfer of kinetic energy in low impact auto accidents can produce a concussion, and these kinetics and V-max are presumed to produce greater forces than those experienced on the playing field.

Other factors that can impact concussion recovery include protective health status and motivation. Athletes and soldiers tend to have greater cardiovascular and aerobic fitness, which has been postulated as a protective factor for recovery from complicated concussion (Kontos et al., 2006), as opposed to the general, sometimes deconditioned, population. Psychosocial factors, such as motivation, also can impact recovery trajectory. Ponsford et al. (2000) tracked emergency room TBI admissions by mechanism of injury (MOI). After three months, the athletes who presented at the emergency room were significantly less symptomatic than those who presented with a motor vehicle accident as their MOI. Data is not currently available on quantification of blast injury for soldiers in theater, or their outcomes regarding concussion. Nevertheless, typical sequelae of a refractory Mild TBI include problems in attention, concentration, working memory, and executive functioning. Even though the MOI is different between blast injuries (Garner and Brett, 2007) and athletic injuries, the neuropsychological outcomes are similar (Belanger et al., 2009; Cooper et al., 2012) and symptom differences may be due to PTSD in the military group (Lippa et al., 2010). Tan et al. (2009) report a complex, synergistic relationship between PTSD, pain, Mild TBI, and HRV in OEF/OIF veterans.

HEART RATE VARIABILITY

As this article focuses on the relationship between HRV, cognition, and concussion, an explanation of HRV is necessary. While a full explication of HRV assessment and treatment is beyond the scope of this article, for our purposes we are interested in the measures traditionally cited in the research literature that are amenable to measurement and intervention in the clinic and in exploring the cardiac correlates of concussion. HRV is measured as part of the cardiac QRS complex. The Inter-Beat Interval (IBI) measured between R-waves is the basis for measurement of HRV. HRV was initially felt to be more artifacts, but now is itself the focus of intense study (Lehrer, 2013). HRV is also useful in that it can be measured with minimal hardware and software. A traditional EKG with as few as three chest leads or a three-lead wrist placement with electrodes can be used (Thought Technology, Montreal, Canada). A Blood Volume Pulse sensor (photoplethysmograph) attached to the distal phalange of a finger or the earlobe can be used with appropriate hardware and software to also calculate the IBI (HeartMath, Boulder Creek, CA, USA; StressEraser, New York, NY, USA).

There are two standard metrics for measuring HRV for analysis and treatment. One is the time domain (changes over time) and the other is the frequency domain (measurement of a spectrum of oscillatory components of the heart). While there are multiple measures of time domain, the most common used statistical method is measuring the Standard Deviation of the Normal-to-Normal interval (SDNN). The SDNN is basically normalization of the standard deviation of the R-to-R interval, with artifacts removed. Comparisons of data should be with equal epochs, usually 5 min for SDNN. The power spectrum measurements are fractionations of all the oscillatory frequencies contained within a specific epoch. The frequencies are generally calculated over the same epoch as the SDNN metric. There are three frequency subbands of particular interest within HRV. The very low frequency (VLF) is composed of frequencies less than 0.04 Hz. The low frequency (LF) is composed of frequencies between 0.04 and 0.15 Hz. The High Frequency (HF) band investigates frequencies between 0.15 and 0.4 Hz. There are both physiologic and cognitive correlates of these frequency bands. The VLF band is considered to reflect mainly sympathetic activity. The LF band is considered to show parasympathetic activity, as well as the baroreflex and enhanced cognitive processing. The HF band is considered to reflect respiratory sinus arrhythmia, and activity from the vagus nerve (Combatalade, 2010).

These same hand-held HRV monitoring devices can provide visual and/or auditory feedback to train HRV. HRV training begins with breathing exercises to increase respiratory sinus arrhythmia, and help one find their resonant frequency – the frequency at which greatest HRV occurs. Breathing rates between 4.5 and 6.5 breaths per minute will produce the greatest HRV in most persons. The biofeedback instruments can provide a visual pacer for breathing rates and informs the person when they have achieved the greatest coherence between respiratory rate and heart rate. A more detailed training protocol is reported by Lehrer et al. (2000).

NEURAL RELATIONSHIP BETWEEN BRAIN AND HEART

Thayer et al. (2009, 2012) and Thayer and Lane (2009) have postulated an intricate Neurovisceral model of the relationship between the prefrontal cortex of the brain and the heart. In the Thayer model, prefrontal brain areas, including the orbitofrontal cortex and the medial prefrontal cortex tonically inhibit the amygdala, with disinhibition of the central nucleus of the amygdala. The deactivation of inhibitory nuclei leads to a net increase in sympathetic activity which eventuates in decreased HRV and increased heart rate. The central nucleus of the amygdala is believed to be the major efferent source of modulation of autonomic, endocrine, and cardiovascular responses. Three routes are postulated. One involves the activation of tonically active sympathoexcitatory neurons of the rostral ventrolateral medulla due to decreased inhibition from neurons in the caudal ventrolateral medulla, resulting in an increase in sympathetic activity. The second involves inhibitory neurons in the nucleus of the solitary tract, which can lead to a decrease in overall parasympathetic activity. The third postulated pathway involves direct excitation of sympathetic rostral ventrolateral medulla neurons, further leading to an increase in sympathetic activity. The overall result, regardless of the pathway, would be an increase in sympathetic output and overall heart rate, with a concomitant decrease in HRV. While these pathways have not been validated either electrophysiologically or with physiologic staining techniques, Lane et al. (2007) used positron emission tomography (PET) to measure medial prefrontal activity along with simultaneous measurement of spectral HRV. In these studies, subjects were shown film clips depicting emotional situations, involving happiness, sadness, or disgust. In all experimental conditions, HF HRV was correlated with activation of the right prefrontal cortex.

Thayer and Lane (2009) also elucidate hemispheric differences in cardiac activation. Aron et al. (2004) postulate that the right prefrontal cortex may have more potent input for cardiac modulation. This is not surprising, given the functional neurology of the right prefrontal cortex involved in emotional regulation and dysregulation. Nevertheless, the models propose that prefrontal activity will modulate cardiac output, including general heart rate and HRV. However, Mild TBI or concussion injuries are rarely lateralized, typically being more diffuse in etiology and MOI.

Williamson et al. (2013) propose a similar model. They propose a model of connections between the orbitofrontal cortex through the uncinate fasciculus to the amygdala, terminating in the sympathetic nervous system. The importance of these white matter tracts for this model is that they communicate from the prefrontal cortices to the brain stem, then to the heart. Disruption of the white matter tracts may induce a loss of inhibitory control upon theANS. Not only does this loss of inhibitory control result in impairment of cognitive abilities, but it also can result in loss of emotional regulation, as seen in soldiers and civilians with PTSD. This review cites similar neuroimaging studies to Thayer et al. (2009) as well as citing neurotransmitter involvement.

Studies using DTI assess the integrity of the white matter tracts, whereas typical MRI including T1, T2, and FLAIR protocols may not show neuropathology in white matter. In DTI studies, fractional anistrophy (FA) and mean diffusivity (MD) are measures of white matter integrity noted to be impaired in concussion. Disruption may result in loss of neural transmission or in reduction in transmission time due to neural deformation from physical trauma (Bazarian et al., 2007).

MECHANISM OF INJURY IN CONCUSSION

As noted above, children from pre-school to senior high school are most often injured in bicycle accidents. Among teen sports, American football is the next most frequent concussion generator. By gender in this age group, American football is the greatest concussion generator for males, while soccer is the greatest concussion generator for females. Both sports can provide blunt trauma at high velocity, either directly through head-to-head strikes, foot- or knee-to-head strikes, or striking the ground or another object, such as the goal. Due to the jagged cranial cavity, most often the physical injury to the brain impacts the orbitofrontal and anterior temporal areas. Linear forces are more often involved in head-to-head contact of athletes and persons in motor vehicles with straight-line acceleration, then impact, followed by rapid deceleration. In contrast, rotational injuries may be seen in open-field tackles or checking or boarding on the ice of a hockey rink.

While traditional neuroimaging will not show white matter attenuation, a recent study of Division I Ivy League football players

with subconcussive injuries (not diagnosed with a formal concussion) revealed changes in FA and MD DTI after a season of play (McAllister et al., 2014). The groups compared contact sports, such as American football and soccer versus non-contact sports, including cross country and track and field. There were significant changes in FA and MD in the contact sport group over the course of a season. Long-term follow up is needed to ascertain if these changes are reversible (some data points to this) or if they are non-reversible. However, this does validate the concerns about the integrity of white matter tracts as being the conduit between the heart and brain.

Thompson and Hagedorn (2012) report alterations in HRV in patients with concussion or mild TBI, including low amplitude and poor rhythmicity. Decrease in HRV has been seen among patients with all levels of TBI severity, from Severe TBI (Baugley et al., 2006) to concussion (Goldstein et al., 1998; La Fountaine et al., 2009). Disruption in cardiovascular reactivity was noted after sports concussion, with interruptions of middle cerebral artery blood velocity after oxidative stress (Len et al., 2011). Len et al. (2011) studied HRV in Canadian Junior Hockey League players with and without concussion and matched for demographic characteristics. In the resting condition, there were no differences noted. However, upon exertion, there were significant differences in total HRV, as well as LF and HF power for the concussed group. This has implications for elite athletes who quickly need to respond with greater cardiovascular output to perform well in their sport (Gall et al., 2004). By extension, this cardiovascular output dysfunction may also hold true for soldiers concussed in IED blasts. Similarly, Leddy et al. (2007) fully reviewed the ANS changes from concussion, including "greater sympathetic and lower parasympathetic activity . . ." and cerebrovascular dysregulation. These concussive changes may affect multiple organ systems, including pulmonary, hepatic, and renal. They suggest an individualized aerobic exercise program that is below the threshold of symptom onset.

HRV AND EEG

As multiple models postulate a heart–brain connection in HRV, measurement can empirically validate this neurovisceral relationship. Searches of both Medline and PsychInfo revealed only a few studies that addressed measurement of EEG changes with HRV intervention. Sherlin et al. (2010) measured EEG variables during HRV training. They assessed 19-channel QEEG and sLORETA variables in a group of laboratory stressed-induced (non-injured) subjects undergoing HRV training. Significant changes in either alpha increase or beta decrease were found at Brodman's areas 24, 30, and 31, all associated with the limbic system and cingulate gyrus. The authors postulate these measured EEG changes from HRV BFB reflect a decrease in autonomic arousal in brain areas critical for stress regulation.

Prinloo et al. (2013) examined EEG correlates of HRV intervention in stressed senior managers, further exposed to experimental laboratory stress. In this study, five EEG sites were monitored. Two frontal sites (Fp1 and Fp2) were monitored for muscular artifacts. The important midline sites of Fz, Cz, and Pz were monitored, as they are thought to reflect brain attention and arousal mechanisms. After a single session of HRV BFB, significant changes were found with reduced beta and increased theta at all three central sites. The authors suggest these EEG changes are reflective of ". . . increased relaxation, decreased anxiety and decreased mental effort . . . (p. 31)." These EEG changes were associated with increases in LF and SDNN HRV variables.

Reid et al. (2013) assessed EEG changes in 40 clinical subjects, half of whom were athletes undergoing optimal performance training, including HRV BFB. For this study, only one EEG site was utilized: Cz, the primary central site of the vertex, reflecting the sensorimotor rhythm (SMR) at 12–15 Hz. Clients showing successful HRV training (peak frequency heart rate between 0.05 and 0.15 Hz) also showed significant increases in SMR amplitude. The authors conclude that the SMR increase reflects a state of relaxed anticipatory focus (Sterman, 1966) useful for athletes who need to perform better in stressful sport competitions, with greater flexibility and regulation over their ANS. By extension, soldiers might also benefit from this approach.

Collura (2009) developed a software and hardware protocol (BrainMaster, Bedford, OH, USA) that combined HRV and Alpha EEG training. Each parameter could be trained independently or simultaneously for greater HRV and Alpha enhancement. Bazanova et al. (2013) trained high Alpha EEG (10–12 Hz) to measure its effect on HRV. They found that healthy male subjects with low resting levels of Alpha who increased Alpha had lowered EMG, greater HRV and showed increases in cognitive performance. They also noted that these changes were not present in a control group that did not receive any feedback, thus validating the need for actual feedback for self-regulation.

To date, only case studies have been conducted on concussed patients using either HRV or Neurofeedback interventions. Lagos et al. (2013) used a 10-week HRV BFB protocol on an adult athlete with post-concussion syndrome. At the end of treatment, the patient showed greater HRV, and greater LF power, as well as significant reduction in severity of post-concussion headaches and overall post-concussive symptoms. Thompson et al. (2013) report the case of an athlete who received a sport-related concussion and was treated with a multi-modal intervention, including both HRV BFB and neurofeedback. Bhandari et al. (2013) used both HRV and neurofeedback to treat an adult male with a Severe TBI. While this patient was much more severely injured than a person with a concussion, after a lengthy course of treatment he showed improvement on multiple QEEG parameters, as well as three HRV parameters, and was able to function successfully in his personal and work life. Lagos et al. (2012) provide a comprehensive rationale for HRV BFB in prolonged PCS from hyperactivation of the sympathetic nervous system and hypoactivation of the parasympathetic nervous system. In addition to changes in HRV as an outcome measure for BFB intervention, they also recommend multimodal measures, such as cardiovascular and neurovegetative functioning, and quality of life indicators.

NEUROCOGNITIVE ENHANCEMENT AND REHABILITATION WITH HRV BFB

Several compelling studies have implicated HRV BFB in neurocognitive enhancement, particularly executive functioning and working memory. In studying non-injured persons, Hansen et al. (2003) divided military personnel on the basis of low or high HRV

groups and then assessed sustained attention and working memory. As would be expected, the higher HRV group had superior performance on both measures. Other studies of executive functioning, including the ability to make decisions, plan, and benefit from feedback, have linked executive skills to high HRV. Murray and Russoniello (2012) divided university students between exercise or control groups. HRV including instantaneous changes of heart rate and spectral analysis of HRV were measured. Results indicated optimal performance with the peak inverted-U curve for both the complex Trail Making B task and a four-choice reaction timed complex test. Optimal neurocognitive performance was obtained in the LF band. These studies suggest that HRV training may be a viable intervention to promote executive function rehabilitation in PCS.

Collegiate basketball players with high-state anxiety levels were given ten minutes of HRV training for ten days to increase coherence and respiratory sinus arrhythmia (Paul and Garg, 2012). The premorbidly anxious collegiate basketball players showed improvement on objective measures of dribbling, passing, and shooting with increases in HRV, especially the LF range. This study has implications for HRV BFB training in the rehabilitation of autonomic and emotional dysregulation as a critical component in PCS recovery. In a study with military relevance (Saus et al., 2006), Norwegian Police Academy cadets with higher HRV were noted to have greater situational awareness, and to perform more accurately in complex shooting drills requiring focused attention and executive abilities. A compelling study not yet undertaken would be to investigate whether pre-deployment training in HRV could possibly reduce anxiety-related aspects of combat, including PTSD.

SUMMARY AND CONCLUSION

In summary, this article has attempted to elucidate the relationship between the brain, particularly the prefrontal cortices, the ANS, and the heart. There can be top-down or bottom-up interaction to both, such that the prefrontal cortices' judgment of ambiguity for threat attenuates HRV. Similarly, baseline higher levels of HRV, especially LF HRV, are associated with greater performance on complex neurocognitive tasks of concentration, working memory, and executive functioning, requiring prefrontal integrity. Further, as sports-related and perhaps military-related concussions interfere with optimal levels of HRV, interventions to restore or increase these optimal HRV levels are needed. Diet, endurance/cardiovascular exercise, and biofeedback are effective interventions. Of these three, HRV BFB can be accomplished with minimal hardware, software, time, cost, and effort constraints upon an individual over a period of a few days. Additionally, biofeedback provides real-time feedback for the attribute of interest, allowing the athlete or soldier to exercise cognitive control over their physiology.

Future research is needed to assess the EEG correlates of HRV intervention on randomized, controlled groups of symptomatic post-concussion athletes and soldiers. As Tan et al. (2013) noted, HRV intervention can be more acceptable for veterans with PTSD than the emotionally charged psychotherapies, and this same logic may hold true for athletes and soldiers with PCS. Data currently available regarding HRV BFB efficacy raise a compelling argument for the need for further empirical validation, not only for treatment of refractory sport and military concussions, but possibly pre-deployment stress inoculation training for soldiers, and pre-game training for athletes.

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Wearable biosensor systems and resilience: a perfect storm in health care?

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We begin by placing our discussion in the context of the chronic crisis in medical care, noting key features, including economic, safety and conceptual challenges. Then we review the most promising elements of a broadened conceptual approach to health and wellbeing, which include an expanded role for psychological, social, cultural, spiritual and environmental variables. The contributions of positive and evolutionary psychology, complex adaptive systems theory, genomics and neuroscience are described and the rapidly developing synthetic field of resilience as a catalytic unifying development is traced in some detail, including analysis of the rapidly growing empirical literature on resilience and its constituents, particularly heart rate variability. Finally, a review of the use of miniaturized ambulatory data collection, analysis and self-management and health management systems points out an exemplar, the Extensive Care System (ECS), which takes advantage of the continuing advances in biosensor technology, computing power, networking dynamics and social media to facilitate not only personalized health and wellbeing, but higher quality evidence-based preventive, treatment and epidemiological outcomes. This development will challenge the acute care episode model typified by the ER or ICU stay and replace it with an ECS capable of facilitating not only healthy autonomic functioning, but both ipsative/individual and normative/population health.

Keywords: resilience, heart rate variability, psychobiological health marker, complex adaptive systems, risk vs. resilience factors, consilience, digital epidemiology

The laudable goal of this special issue is to further elucidate the role of autonomic dysregulation in important conditions including anxiety disorders such as PTSD. We endeavor to present an integrated view of a particular combination of conceptual, methodological and technological resources which are related to these important issues and, at the same time, reach beyond it, to overarching scientific and social issues. This broad perspective is warranted, I believe, because we, as a national society and even world confluence of cultures are experiencing a crisis regarding the provision of effective, affordable and safe health care and support of well-being. During a recent invited presentation to the Chinese Academy of Science's Institute of Psychology, I was reminded that the ancient Chinese pictograph for crisis combines danger and opportunity. A pointed example of this is the situation in the United States where we spend huge amounts of money to provide services which frequently have very limited and sometimes dangerous outcomes. Not only is this danger tangible to millions of patients but the fiscal danger to our country is significant. If health care costs continue to escalate at the present rate, our Federal government may be bankrupt by 2040 (Longman, 2013)

Financial catastrophe is only one danger related to the current system, most often described as a procedure and profit driven disease treatment approach. Patients routinely face dangers of both improper and inadequate treatment of iatrogenic disease (Institute of Medicine, 1999, 2006). While these problems persist in the face of polarized political ineptitude and massive vested interests which are frequently inimical to both safety and efficacy, the major obstacle is adherence by most health care professionals, including their suppliers and vendors of medical supplies and equipment to the tenants of the infectious disease biomedical model (Drury, 2013; Emmaneul, 2014). While Emmanuel's proposals are the basis of the Affordable Care Act, and include adoption of the electronic medical record, use of social media and other personal communication technologies, changing reimbursement for providers from procedure to outcome based and stringent quality of outcome measures, they don't include the scientific elements to be described here. These scientific constituents represent a major opportunity to contribute to human health and well-being.

We are now on the cusp of a progressive transformation which some have identified as revolutionary or true Kuhnian paradigm succession, based on evolutionary and systems science approaches in biology, psychology, neuroscience and other disciplines. Originating in mathematics, the study of complex adaptive systems has gradually spread to biology and then the psychosocial sciences. This continuing development places the person in a hierarchy of nested systems from the subatomic to the cosmological (Strogatz, 1994; Johnson, 2001; Mitchell, 2009). Rather than sole focus on pathology and aggressive treatment, this approach gives recognition to the factors that promote human resilience and positive adaptive outcomes. In the health area this has been

described a personalized medicine, prescriptive medicine and 4P medicine, well-articulated by Hood (2014) of the Institute for Systems Biology. It has proven a generally integrative force, although the process of radical scientific discovery and subsequent translation into practice has frequently progressed in Max Planck phrase "one funeral at a time." Eric Topol (2012) has advocated the "creative destruction of medicine" to indicate the degree of transformation needed. These developments have even led one of our most distinguished scientists, Wilson (1998) to proclaim the goal of consilience, which is the comprehensive unification of knowledge. The rapid development of omics also turns toward systematization of broad areas of inquiry from genomics to connectomics [the Human Connectome Project (National Institutes of Health, 2012)]. Our understanding and ability to intervene to promote health and well-being will be greatly enhanced by these conceptual developments in science with psychology functioning as a central hub science, since our understanding of human life and human nature is the primary lens through which we view all other phenomena.

This special issue focuses on an area of huge conceptual and empirical significance, since our understanding of human nature from a complex systems perspective emphasizes the complicated interactive dynamics of the many constituent systems that comprise the person and their sociocultural environment. In particular the role of the autonomic nervous system is increasingly understood as a major contributor to systems regulation and intermodulation of multiple systems beyond the central nervous system, including the cardiovascular, digestive, respiratory and immune systems. The major significance of Porges' polyvagal theory (2011) and Thayer et al.'s (2009) neurovisceral integration model is illustrated not only by their frequent citation, but the invited presence of their work in this issue.

Both Porges and Thayer have emphasized the important role played by the vagal nerve complex in bidirectional mediation of CNS-cardiac interaction from a neurobiological perspective. Porges use of the term polyvagal highlights the several functions of the vagal nerve complex, especially in facilitating the social engagement system. Thayer et al. (2012) suggests that heart rate variability (HRV) is an excellent indicator of vagal regulatory activity in the service of ongoing dynamic neurovisceral integration and concludes his recent meta-analysis of HRV (2012) proposing that HRV may function as "a proxy for 'vertical integration' of the brain mechanisms that guide flexible control over behavior with peripheral physiology, and as such provides an important window into understanding stress and health." A recent Frontiers of Psychology article by Park and Thayer (2014) describes how cardiac vagal tone modulates perceptual and attentional processes in response to emotional stimuli and he comments on implications of HRV for health and well-being. Following the work of both Porges and Thayer, the role of the vagal nerve is not confined to only CNS-cardiac interaction, since it is anatomically connected with a variety of other important systems such as the immune, respiratory and digestive systems and the facial expression of emotion. Thus, HRV seems to be implicated in a wide variety of important relationships regarding health maintenance and disease processes. It is a sensitive indicator of both the presence of a wide variety of disease and illness conditions and health and well-being, and has been used as a measure for assessing the effects of treatment interventions as well. Some of the conditions using HRV recently published include sepsis, sudden cardiac death, diabetes, insomnia and sleep apnea, cerebral palsy, infection post coronary artery bypass surgery, dysauatonomia, effects of air pollution, need for air evacuation in triage and syncope.

This rapidly growing line of research is contributing empirically and theoretically to the overall neuroscientific literature on the role of structure and dynamics of the central nervous system and its complex regulatory interactions with other bodily systems. This area was recently reviewed by Pessoa (in press) focusing on brain networks, rather than individual regions. In addition to HRV studies, some important emerging areas will be cited. The study of the adaptive function of the brain's default network (Andrews-Hanna, 2012) is giving a more nuanced understanding of previously "dark areas" of the CNS. Basar's (2013) studies of brain oscillations emphasize the importance of multimethod studies to most adequately understand the function of the brain, and his comments apply as well to this chronobiological approach to the interaction of all biological systems. The work of Gotlib's group (Hamilton et al., 2013) highlights the neural systems approach to psychopathology, but this approach is equally relevant and germane to other elements of illness. The recent work of Sandman's group (Pincus et al., 2014) ties the use of systems and network conceptualization to the emergence of resilience, emphasizing the use of non-linear dynamics as a previously neglected tool to elucidate biological functions that do not meet the requirements or assumptions of traditional linear methods inherited from classical physics. The work of Calhoun's group (Stephen et al., 2013) identifies independent component analysis as a viable contributor to the study of such complex phenomena.

The two major elements of the complex systems analysis approach advocated here are resilience and HRV. Resilience is a conceptual development that integrates the many critiques of the tradition pathology-oriented medical treatment system. Zautra and his colleagues have described resilience as the vehicle for the emergence of a new model of health (Reich et al., 2012). Zautra's group and other prominent scientists (Lukey and Tepe, 2008; Southwick and Charney, 2012; Spira and Drury, 2012) and well informed popular writers such as Andrew Zolli (2012) have presented well supported descriptions of resilience with a transdisciplinary emphasis. Resilience is generally defined as the ability of an individual, group, organization or culture to "bounce back" adaptively after experiencing a challenge, stressor or trauma and maintain its mission, purpose or goal structure. Rather than identify risk factors for adverse outcomes, it uses the massive data accumulated by the sciences to explore resilience factors which promote positive adaptational outcomes such as growth development and optimal functioning, as summarized in the citations above. Important methodological and conceptual elements such as extensive longitudinal data collection, multimethod studies and appropriate statistical approaches have been emphasized (Reich et al., 2012). Other elements of central scientific importance are the roles of emotion regulation (Gross, 2007; Kring and Sloan, 2010) and stress and allostasis (Drury et al., 2010; Karatsoreos and McEwen, 2013).

Some of the key resilience factors that have been identified (Drury, 2013) are cognitive coping and appraisal, realistic optimism, social support, religion and spirituality and sense of meaning and purpose in life, and psychophysiological self-soothing and affect regulation. It should be noted that resilience is not strictly an individual characteristic, but also applies to groups, communities, and cultures. Morality, defined by Greene (2014) as a "set of psychological adaptations to allow otherwise selfish individuals to reap the benefits of cooperation," is a resilience characteristic at various levels. The work on compassion, empathy and altruism by the Stanford Center for the Study of Compassion and Altruism Research and Education (CCARE, 2014) is contributing to our understanding of resilience, as does the work of Peterson and Seligman (2004) on character strengths, virtues and positive psychology. As exemplified by Kabat-Zinn (2013), Mindfulness-Based practices have been associated with positive resilience outcomes as have practices that develop Emotional Intelligence (Goleman, 2005). Further research is needed to refine our understanding of interrelationships between various resilience factors.

One of those resilience factors is HRV, a rapidly growing field of inquiry which has led to over 16,000 peer reviewed references in a recent Pub Med search. While disturbance of HRV is associated with a huge variety of disorders and conditions, increased HRV is associated with higher levels of health, well-being and optimal performance. HRV refers to the variation in interbeat interval which is characteristic of the heart, with diminished HRV most often representing impaired function, and greater HRV showing greater health and functional ability. Notably, HRV disturbance is not only an indicator of physiological and biomedical functioning, but also reveals the effects of psychosocial disturbances and conditions. The majority of articles assembled by Dr. Ginsberg in this special issue use HRV as a central variable in studying both autonomic function and dysfunction, especially as it relates to important problems such as PTSD and mTBI. HRV is both an element in the treatment of PTSD (Gewirtz and Lehrer, this issue), but is also a highly sensitive marker of psychobiosocial health status which can be applied in diagnosis/treatment and health promotion, disease prevention and performance optimization.

Resilience and HRV are poised to be key components in the nascent Personalized Health and 4P Health movements, which are premised on an entirely different approach to cultivating and supporting human assets, including health and well-being. Not only does it sometimes take multiple episodes of "scientific" discovery to break paradigmatic logjams, which are by nature conservative, but as in Plank's quotation above, there is sometimes active resistance to new and innovative approaches.

The traditional model has focused on massively expensive and "heroic" episodes of disease treatment, epitomized by the urgent visit to the ER and Intensive Care Unit. The emerging integral approach (Rakel, 2012; Drury, 2013) suggests the following components: ongoing frequent, or even continuous monitoring of health status, using unobtrusive microelectronic data acquisition and analysis devices, networked with cloud-based high throughput analytic algorithms to track ongoing psychobiosocial functioning. The 4P model described by Hood (2014) highlights personalized, predictive, prescriptive and participatory systems of care, with each individual involved in self-regulation activities closely related to their current health status, including both assets and challenges. This approach can be mediated through the use of smart phones, social media, sophisticated non-linear algorithms and other rapidly growing technologies that synergize this important field. As mentioned earlier, the use of a evolutionarily-grounded complex adaptive systems overall framework will obviate many of the structural impediments to the transition from traditional to integral health and wellbeing.

This unfolding development is based on a biobehavioral understanding of human nature informed by current evolutionary science. From that perspective, the various challenges thrust upon contemporary individuals can be seen as dramatically different from those of the last two million years of hominid experience. A telling example of this issue is the challenge of modern treatment to "cure the disease epidemic of obesity." While some treatments claim temporary benefit, most often scientific study has revealed yo-yo patterns with little long term weight loss. The long term evolutionary success of the savanna based gorge and starve model which has been historically conserved is strongly implicated in the limited success of conventional approaches and suggests again, that we must shift our understanding and be historically acute and informed about our nature and the limits and limitations on adaptation.

Another salient aspect of the emerging model is its recognition of the central role in human and other mammalian life of attachment phenomena (Bowlby, 1988). Long ignored by psychology and other relevant disciplines, attachment was dismissed as too ethereal and fuzzy to be studied scientifically. Both Bowlby and Harlow fired the opening shots across the bow of organized science and we are now in a very generative phase of exploring the development and problem issues surrounding attachment issues. The recent volume by Gillath et al. (2012) has reinforced the importance of the conceptual and methodological issues described here in their focus on relationship science. They specifically emphasize the role of neuroscience, evolutionary biology and socio-cultural studies to gain a more complete understanding of human relationships. Examples are the contribution of neurobiology in the area of neuroplasticity (McEwen and Gianaros, 2011) and neurochemistry in the area of oxytocin (Carter, 2014), both of which stimulate much current research relevant to human health and its upper limits.

The perfect storm alluded to in my title, occurs when a set of individual factors produce a seemingly unexpected and potentially very disruptive synthesis. If you happen to be in a fishing boat in the middle of such an event, or a patient in a modern medical care system, the situation can become more that disruptive and actually dangerous, even life-threatening. The synergy involves not only many classes of environmental factors, but individual behaviors as well. I will sketch only one example of the type of process/outcome that offers an alternative to the limitations of traditional medicine. The maintenance of the traditional system has been sustained for only the briefest historical moment from an evolutionary standpoint despite the tremendous costs, financial and human.

An urgent symptom leading to an ambulance transport to an ER and then ICU is the archetype of dramatic and aggressive health care mediated by high technology. Its high priority in the attentional focus of many consumers is shown by the great popularity of the TV show with that title. Here I will suggest an alternative that may not have the same appeal to viewers of reality TV, but will use technology in a more nuanced and potentially large scale manner creating an Extensive Care System (ECS). An exemplar of a functional ECS would include a longitudinal data acquisition and analysis system for a population sample based on unobtrusive microelectronic hardware to obtain continuous HRV data which functions as a highly sensitive marker of psychobiological status. Using the rapidly growing abilities of high throughput and cloud based computing, mediated through smart phones, this data could be used algorithmically to not only scan for potential impairment but also encourage increasingly greater levels of wellness. The use of advanced data analyses, including fractal and other non-linear approaches is increasingly recognized as optimal for detecting some organic life function and dysfunction that is not detectable apparent standard statistical methods, especially the puny methods that are sometimes paraded as "gold standard" clinical trials. The use of sophistication technology with innovative analytic methodology may give us much more effective interventions for both treatment and prevention, as Vodopivec-Jamsek et al. (2012) have proposed in their Cochrane Database Systems Review of mHealth. An ECS approach is an ideal vehicle to increase our use and understanding of self-control and its evolution (MacLean et al., 2014) in encouraging patient participation in the maintenance of health and well-being.

Following the tradition of learning theory based psychology, such a system would offer positive reinforcement, social or tangible, for objective indications of positive health behavior as indicated in either accelerometer-based activity level or high level of HRV. Consistent with our understanding of behavior change and maintenance, immediate reinforcement is the most effective approach to encouraging health behaviors. A second category of impaired health status information would also be used to prompt an individual to engage in adaptive preventive and health promoting activities, which could also be subsequently reinforced. Of note many health insurers, companies and local governments are exploring methods to reinforce positive health behaviors, although the lack of an agreed upon metric is problematic. As pointed out above, weight loss, even when reinforced by reduced health premiums or other reinforcers, may be ineffective and/or lead to gaming the system. Beyond prompting of individual, the ECS is capable of notifying designated health professionals of decreases in health status with decision support for triage and intervention options. Of note, King et al. (2009) has recently conducted research using brief HRV data analysis generated at crash sites to improve decision support efficiency of triaging Life Flight evacuations, potentially saving both lives and money.

This ECS approach borrows from health psychology and epidemiology the necessity of longitudinally repeated measures of the same individual to create an ipsative/normative data base very sensitive to potential disruption common in complex adaptive systems, which are notoriously "sensitive to initial conditions." While needing to protect personal health information, this approach would collect literally millions of data points from which firm baselines of healthy functioning could be obtained, possibly for the first time ever. The acceptability and popularity of such an approach is suggested by the millions of individuals who voluntarily participate in the "Quantified Self" and other social media movements, which like other forms of self and alternative care, are funded directly by the participant with no government or business based subsidy. In addition to the values of longitudinal data collection, use of small world network dynamics and analytics, transdisciplinary study and electronic health data acquisition and archiving, this approach is easily tasked to study populations in pursuit of public health and epidemiology goals. Especially in poor regions where smart phones are leapfrogging older communication strategies, this example of the ECS could massively impact the attainment of both prompt intervention through Digital Epidemiology (Wolfe, 2011) and assessing and supporting higher levels of positive health status with little traditional infrastructure. In particular, this example avoids some of the pitfalls of approaches that rely on self-report or low fidelity molar measures such as weight or BMI.

All the components of the proposed ECS currently exist, awaiting a more complete integrative dialectical synthesis. Similar to climate change, it is not clear how difficult and disastrous the consequences of maintaining the current system through inaction will be. Highlighting the central functions and dysfunctions of the autonomic nervous system addressed in this issue, the ECS will be difficult to operationalize and systematically deploy, dependent on zeitgeist readiness but offers a relatively distinct way forward. Of course this path forward needs focused resources to accomplish such a translational research and development objective but the time may be right for the self-organizing emergence of existing conceptual, empirical and technological resources in a prosocial Perfect Storm.

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Heart rate variability biofeedback: how and why does it work?

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In recent years there has been substantial support for heart rate variability biofeedback (HRVB) as a treatment for a variety of disorders and for performance enhancement (Gevirtz, 2013). Since conditions as widely varied as asthma and depression seem to respond to this form of cardiorespiratory feedback training, the issue of possible mechanisms becomes more salient. The most supported possible mechanism is the strengthening of homeostasis in the baroreceptor (Vaschillo et al., 2002; Lehrer et al., 2003). Recently, the effect on the vagal afferent pathway to the frontal cortical areas has been proposed. In this article, we review these and other possible mechanisms that might explain the positive effects of HRVB.

Keywords: heart rate variability, biofeedback, resonance, baroreflex, homeostasis

INTRODUCTION

In recent years there has been substantial support for heart rate variability biofeedback (HRVB) for a variety of disorders and for performance enhancement (Gevirtz, 2013). Since conditions as widely varied as asthma and irritable bowel syndrome seem to respond to this form of cardiorespiratory feedback training, the issue of possible mechanisms becomes more salient. The most supported possible mechanism is the strengthening of homeostasis in the baroreceptor (Vaschillo et al., 2002, 2006; Lehrer et al., 2003). Recently, the effect on the vagal afferent pathway to the frontal cortical areas has been proposed. In this article, we review these and other possible mechanisms that might explain the positive effects of HRVB.

In the 1990s Lehrer et al. (2000) began experimenting with a form of cardiorespiratory intervention that has subsequently been labeled HRVB, respiratory sinus arrhythmia (RSA) biofeedback, or resonance frequency feedback (RFF). The procedure consists of feeding back beat by beat heart rate data during slow breathing maneuvers such that the participant tries to maximize RSA, create a sine-wave-like curve of peaks and valleys, and match RSA to heart rate patterns. RSA is the heart pattern that occurs when heart rate increases during inhalation and decreases during exhalation. Thus as can be seen in **Figure 1**, the participant uses feedback or a breath pacing device to produce the characteristic maximized RSA.

Gevirtz (2013) recently reviewed all of the available literature on the outcomes of HRVB. He looked at the following application categories: asthma, COPD, IBS, cyclic vomiting, recurrent abdominal pain, fibromyalgia, cardiac rehabilitation, hypertension, chronic muscle pain, pregnancy induced hypertension, depression, anxiety, PTSD, insomnia, and performance[1]. While few areas have extensive support by way of controlled studies, the overall picture seems to be very promising for this intervention. As can be seen, the applications are quite varied. We have begun to explore what physiological and/or psychological mechanisms might be contributing to these positive outcomes.

MECHANISMS BY WHICH HIGH-AMPLITUDES OF HRV ARE ACHIEVED DURING HRV BIOFEEDBACK

Heart rate variability (HRV) has a complex structure, often referred to as "chaotic," involving various superimposed oscillation frequencies, non-linearly related to each other (Ivanov et al., 1999; Pikkujamsa et al., 1999). Some processes involved in this pattern are caused by known reflexes, some with modulatory functions, often controlled by different autonomic pathways. These can be described as "negative feedback loops," which operate as closed loop system components that help maintain allostatic balance, while allowing adaptation to environmental demands (Lehrer and Eddie, 2013). During HRV biofeedback, the amplitude of heart rate oscillations grows to many times the amplitude at rest, while the pattern becomes simple and sinusoidal. This pattern occurs in almost everyone, and is often achievable within a fraction of a minute even in persons who have never previously been exposed to the technique. The mechanism for this effect lies in a confluence of processes: (1) phase relationships between heart rate oscillations and breathing at specific frequencies, (2) phase relationships between heart rate and blood pressure oscillations at specific frequencies, (3) activity of the baroreflex, and (4) resonance characteristics of the cardiovascular system.

PHASE RELATIONSHIPS BETWEEN HEART RATE OSCILLATIONS AND BREATHING

During normal breathing, one of the many oscillations in heart rate usually occurs at the same frequency as breathing. People often breathe at differing frequencies at different times, and various

[1] See Gevirtz (2013) for citations.

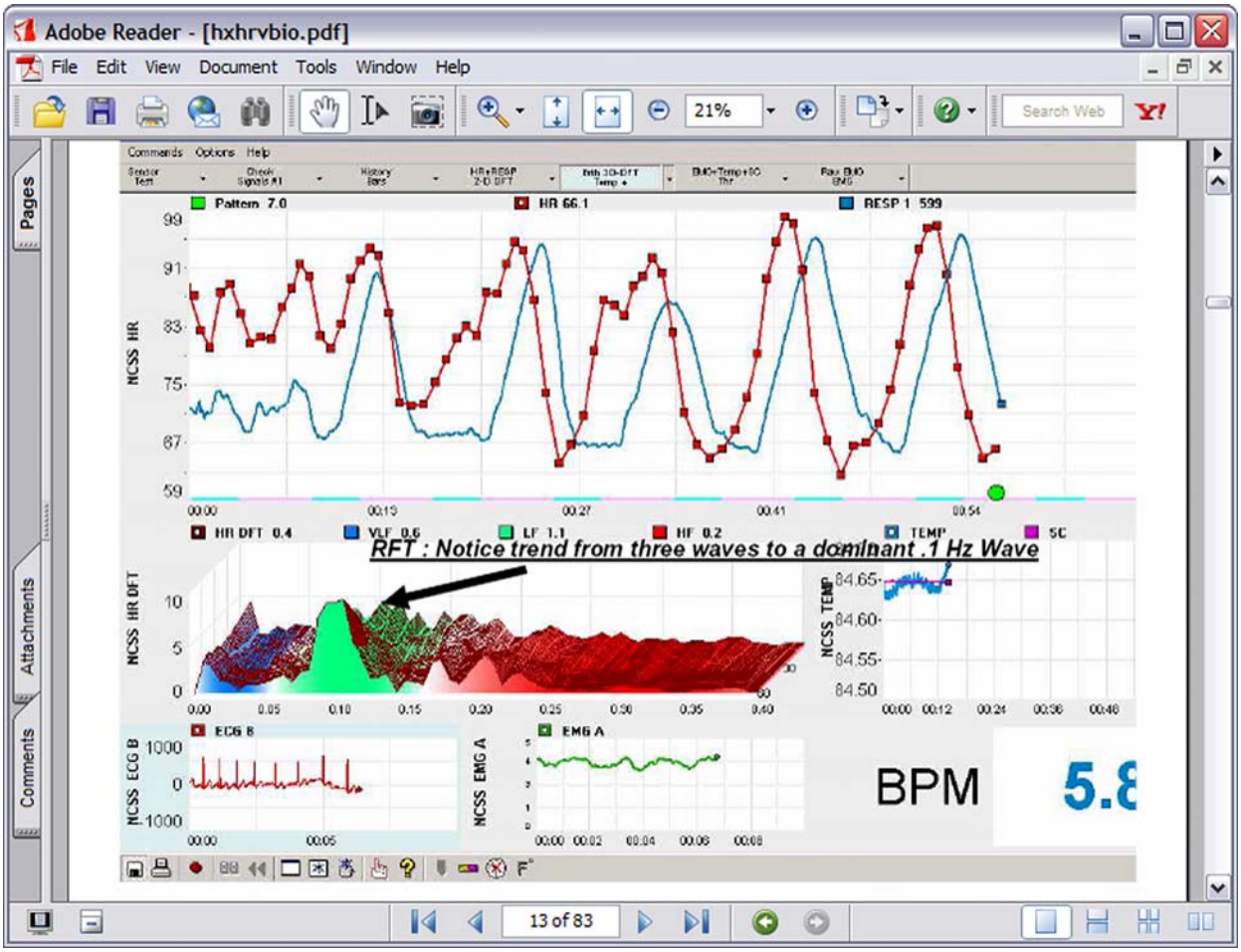

FIGURE 1 | A typical HRVB screen showing the transition from normal breathing to 7 breaths per minute breathing.

individuals tend to breathe at different rates. For most people, most of the time, breathing frequency is between 0.15 and 0.4 Hz, or 9 to 24 breaths per minute. The corresponding oscillations in heart rate are called RSA, which can be interpreted as influences of respiration on the sinoatrial node of the heart. The frequency range of 0.15–0.4 Hz is the "high frequency" (HF) band in the HRV spectrum, and spectral amplitude within this range is often used as an index of RSA (Berntson et al., 1997). However, although RSA is often driven by breathing, it also may be influenced by respiratory pacemaker oscillations in the central nervous system, which occasionally differ from actual breathing. These processes might be influenced by external factors (e.g., sudden exercise or stress, sighs, etc.), where both pacemaker and actual respiration may both produce heart rate oscillations. These can sometimes occur at different frequencies and with different patterns, as shown in dissociation between RSA and breathing during mechanical ventilation (Van de Louw et al., 2010), apnea (Passino et al., 1997), and paced breathing (Song and Lehrer, 2003). At resting respiratory rates, the phase relationship between breathing and HR is far from synchronous, such that heart rate increases tend to follow inhalation at about the mid-breath point, and heart rate decreases follow exhalation also at about the mid-breath point (Vaschillo et al., 2002).

Respiratory sinus arrhythmia is known to have important regulatory functions. It controls the rate of gas exchange at the alveoli, such that heart rate tends to be higher when air in the lung is richest in oxygen, and exhalation occurs when carbon dioxide in the lung is highest. It is notable, however, that the partial out-of-phase relationship between heart rate and breathing is *not* the most efficient pattern for gas exchange. Animal experiments by Hayano et al. (1996) in Japan have found that gas exchange at the alveoli is most efficient when heart rate starts increasing at the beginning of inhalation, and starts decreasing just as exhalation starts, i.e., a 0° phase relationship. In these studies, denervated dogs were artificially ventilated, and heart rate oscillations were entirely controlled by a cardiac pacemaker, such that the phase relationship between respiration and heart rate could be experimentally manipulated, in three phase relationships: 0, 90, and 180° (the last of these corresponding to a pattern where heart rate started increasing at the beginning of each exhalation, and started decreasing at the beginning of each exhalation). They measured gas exchange in the alveoli, and

found that it was greatest at the 0° phase relationship, at an intermediate level at the 90° phase relationship, and lowest at the 180° phase relationship. Perhaps the function of a partially out-of-phase phase relationship is to allow the greatest degree of flexibility to the organism, such that greater efficiency can be achieved during greater metabolic need, and less during decreased need. Phase relationship studies at various levels of metabolic need have not yet been done, so this interpretation must remain speculative.

Respiratory sinus arrhythmia also can reflect aspects of autonomic function. It is controlled entirely by the vagus nerve, such that vagus nerve outputs to the sinoatrial node primarily occur only during exhalation. Greater vagus nerve traffic will therefore produce greater amplitudes of RSA, such that many scientists equate RSA (or HF HRV) with "cardiac vagal tone," or parasympathetic influence on the heart (Berntson et al., 1997). However, longer exhalations (Strauss-Blasche et al., 2000) and slower respiration (Eckberg et al., 1985; Grossman et al., 1991; Song and Lehrer, 2003) also may increase RSA amplitude, possibly independently of vagus nerve traffic, since vagus nerve output occurs for relatively longer periods of time with each breath.

Indeed, it has long been known that amplitude of HRV is systematically related to breathing frequency, with higher amplitudes achievable with slower respiration (Eckberg et al., 1985; Brown et al., 1993; Badra et al., 2001; Eckberg, 2003; Song and Lehrer, 2003). However, most studies find that maximum effects usually are achieved when breathing at a rate of approximately 0.1 Hz (six breaths per minute). Working in St. Petersburg, Russia, Vaschillo systematically studied relationships between breathing and heart rate, using a "transfer function analysis," whereby the interplay between two oscillations is studied at different frequencies – i.e., different respiration rates. The maximum heart rate oscillations at respiratory frequency occurred at approximately 0.1 Hz (six breaths per minute), the one frequency at which heart rate oscillates with breathing at a 0° phase relationship, i.e., exactly in phase. Thus breathing at this frequency produces both the highest amplitude of RSA and the most efficient gas exchange.

It should also be noted that respiratory-induced changes in HRV may function as a positive feedback loop, spiraling further increases in HRV, by feedback from the heart to the central nervous system, through the vagal afferent system, as described below.

These results also suggest that, where HRV biofeedback produces a 0° phase relationship between heart rate and breathing, conditions requiring better gas exchange efficiency could show improvement. Consistent with this, there is evidence for better athletic performance after training in HRV biofeedback (Strack, 2003; Shaw, 2011; Paul and Garg, 2012) and that HRV biofeedback may help improve breathing symptoms and quality of life among patients with emphysema (Giardino et al., 2004).

PHASE RELATIONSHIPS BETWEEN HEART RATE AND BLOOD PRESSURE

Vaschillo's early studies also showed systematic changes in phase relationships between heart rate and blood pressure, when the system was stimulated at various frequencies. For each person, he found, there was a specific frequency where heart rate changes per unit change in blood pressure were greatest. This frequency varied from individual to individual, but was ∼0.1 Hz. (In later research we refined the average frequency for highest heart rate oscillations to be at about 0.09 Hz, or 5.5 breaths per minute, with breath duration of about 11 s; Vaschillo et al., 2002.) When he examined phase relationships between heart rate and blood pressure, he found that, at this frequency, heart rate and blood pressure oscillated in a 180° phase relationship: i.e., completely out of phase, such that blood pressure began falling as soon as heart rate began rising, and blood pressure began rising as soon as heart rate began falling. This phase relationship strongly suggested that the mechanism for the high-amplitude heart rate oscillations was the baroreflex.

THE BAROREFLEX

The baroreflex is a reflex mediated by blood pressure sensors in the aorta and carotid artery that help modulate blood pressure fluctuations (Eckberg and Sleight, 1992). Baroreceptors in the walls of these arteries detect stretching of the arteries as blood pressure increases. When blood pressure increases, the baroreflex causes immediate decreases in heart rate. As blood pressure falls, the baroreflex causes immediate increases in heart rate. Thus, when the system is stimulated at the specific frequency causing maximum heart rate oscillations and a 180° phase relationship between heart rate and blood pressure, effects of the stimulator are compounded by effects of the baroreflex. As external stimulation causes heart rate to rise, it also causes blood pressure to fall, thus causing an additional stimulus for heart rate to rise further; and as external stimulation causes heart rate to fall, it also causes blood pressure to rise, thus causing an additional stimulus for heart rate to fall further.

Because of the 0° phase relationship between heart rate and breathing at approximately the same frequency that external stimulation causes maximal stimulation to the baroreflex, breathing becomes a natural way to provide external stimulation to increase HRV. Conversely, each breath then stimulates the baroreflex. We have found large increases in baroreflex gain (number of beats per minute change in heart rate per 1 mm Hg change in blood pressure) during HRV biofeedback: i.e., the baroreflex operates more strongly (Lehrer et al., 2003). When HRV biofeedback is practiced twice daily at home over about a 3 month period, we also find increases in *resting* baroreflex gain (i.e., before people start practicing biofeedback in a given session; Lehrer et al., 2003). This demonstrated neuroplasticity in the baroreflex, and suggested that regular exercise of the reflex rendered it stronger. It also suggested that various conditions affected by blood pressure lability and baroreflex control may be affected by HRV biofeedback. Thus, there is a growing body of evidence that a course of HRV biofeedback can help hypertensive patients lower their blood pressures (Nolan et al., 2010; Wang et al., 2010; Lin et al., 2012).

Pathways of baroreflex neural control suggest other possible HRV biofeedback applications. The baroreflex is mediated through the nucleus tractus solitarius, located in the brain stem

(Raven et al., 1997; Rogers et al., 2000; Polson et al., 2007; Arnold et al., 2009). This center communicates directly with the amygdala, a center for emotional control, in a pathway extending through the insula (Volz et al., 1990; Henderson et al., 2004). Perhaps it is for this reason that various studies have shown positive HRV biofeedback effects for treating anxiety and depression (Karavidas et al., 2007; Reiner, 2008; Siepmann et al., 2008; McCraty et al., 2009; Nada, 2009; Zucker et al., 2009; Henriques et al., 2011; Tan et al., 2011; Patron et al., 2013).

THE BAROREFLEX, HRV, AND RESILIENCE

There is a large amount of evidence that people are more resilient – physically and emotionally – when HRV oscillation amplitudes are higher and more complex. Greater complexity, as measured by various calculations of fractal entropy, suggest the operation of multiple regulatory feedback loops. One can think of this as the system having multiple backup systems to regulate the body, and finely tune it to environmental and internal need. Thus individuals with low HRV have generally impaired function: i.e., they are physically (Volz et al., 1990; Henderson et al., 2004) or emotionally (Friedman and Thayer, 1998; Gorman and Sloan, 2000; Carney and Freedland, 2009; Kemp et al., 2010) sick, are older (Fukusaki et al., 2000; Valentini and Parati, 2009; Nunan et al., 2010; McNarry and Lewis, 2012), are less aerobically fit (De Meersman, 1993; Hautala et al., 2003; McNarry and Lewis, 2012; Boutcher et al., 2013), and, when greatly physically compromised, at greater risk of dying (Kudaiberdieva et al., 2007; Laitio et al., 2007; Chan, 2008; Politano et al., 2008; Ranpuria et al., 2008; Stein, 2008; Ahmad et al., 2009; Thayer et al., 2010; Christensen, 2012; Handa et al., 2012; Huikuri and Stein, 2013). Total HRV in these studies generally is measured by the standard deviation of normal beat-to-beat intervals, i.e., intervals controlled by central nervous system input to the sinoatrial node of the heart, rather than by abnormal cardiac function). People with simpler patterns of HRV appear to be similarly compromised (Otsuka et al., 1997; Srinivasan et al., 2002; Yeragani et al., 2002; Skinner et al., 2008a,b, 2009; Huikuri et al., 2009). For this reason, HRV is often seen as a measure of physical and emotional resilience. We have found that HRV biofeedback restores autonomic function that is suppressed when people are exposed experimentally to inflammatory cytokines (Lehrer et al., 2010). *All* frequencies are suppressed by these cytokines, much as happens when we catch the flu or are subjected to another inflammatory condition.

RESONANCE

It is a physical principle that all oscillating feedback systems with a constant delay have the characteristic of resonance. A resonant system is one that, when stimulated, produces high-amplitude oscillations at a single frequency, recruiting or overshadowing other frequencies, to produce a sine wave oscillation with very high-amplitude (Başar, 1998). An example of this from everyday life is the so-called Larsen effect, where a high pitched squeal at a single frequency results from placing a microphone in front of a speaker, and stimulating the system with sound (Weaver and Lobkis, 2006).

The same thing appears to happen in the cardiovascular system. The constant delay appears to be caused by amount of blood in the system, although, theoretically, flexibility, and diameter of the blood vessels also should play a role. We have found that taller people and men, who have a greater blood supply than, respectively, shorter people and women, have lower resonance frequencies (Vaschillo et al., 2006). That is, independently, stimulation at lower frequencies causes heart rate oscillations with the highest amplitude in taller people and men. Independently of height, age, and weight have no effect on resonance frequency, nor does experience with repeated system stimulation by HRV biofeedback.

If resonance occurs in the cardiovascular system at approximately 0.1 Hz, it should not occur exclusively in response to breathing. Rather, any source of rhythmic stimulation that affects the cardiovascular system should produce the same effect. This has, in fact, been found for rhythmic muscle tension (Lehrer et al., 2009; Vaschillo et al., 2011), and rhythmical presentation of emotion-inducing pictures (Vaschillo et al., 2008).

There also is evidence that resonance may occur at lower frequencies than 0.1 Hz. There is some evidence for resonance at about 0.02–0.03 Hz. While the source of this resonance is not completely known, it is known that the highest amplitudes of blood pressure oscillations are achieved when the system is stimulated at approximately this frequency (Vaschillo et al., 2002). Oscillations in this range are thought to be controlled primarily by the alpha sympathetic system, and related to oscillations in vascular tone, which also is affected by the baroreflex (Vaschillo et al., 2012). Thus, when blood pressure increases, the blood vessels dilate; when blood pressure falls, blood vessels constrict. This causes an oscillation in both blood pressure and vascular tone, but at a lower frequency than for the heart rate limb of the baroreflex, because dilation and constriction of blood vessels is a slower process than speeding or slowing the heart. Little is known about biofeedback training to stimulate the system in this frequency range. However, it is known that experienced Zen monks tend to breathe in this very slow range (Lehrer et al., 1999). Oscillations in this range are also thought to be involved in reflexes controlling thermoregulation (Fleisher et al., 1996; Thayer et al., 1997; Matsumoto et al., 1999).

THE VAGAL AFFERENT PATHWAY

Several studies have reported that HRVB might be effective in reducing symptoms of depression and/or anxiety (Karavidas et al., 2007; Reiner, 2008; Siepmann et al., 2008; McCraty et al., 2009; Nada, 2009; Zucker et al., 2009; Henriques et al., 2011; Tan et al., 2011; Patron et al., 2013). These results led to speculation that some other mechanism might be at work beyond the baroreflex gains. One possible clue came from the recent research using vagal nerve stimulation for severe depression (and seizure disorders; Sackeim et al., 2001a,b; Nahas et al., 2005; Daban et al., 2008; George et al., 2008; Cristancho et al., 2011). An implanted electrical stimulation device is used to stimulate the vagal afferent pathways resulting in reduction of depressive symptoms. While this technique has not been subjected to larger random controlled trials, the preliminary pilot studies do raise interesting possibilities. It is known that the vagal afferent pathways affect brain areas known to be involved in affect regulation and mood (locus

coeruleus, orbitofrontal cortex, insula, hippocampus, and amygdala; Grundy, 2002). In addition, there has been speculation that stimulation especially of the sub-diaphragmatic pathways through slow deeper breathing techniques might be stimulating these same pathways and thus having an effect on depressive/anxiety symptoms (Brown and Gerbarg, 2005a; Porges, 2011; Brown et al., 2013). We discovered some literature that offered the possibility that these pathways could be investigated using a technique called heart period evoked potentials (HEPs). Schandry and his colleagues had used this procedure to study interoception some years ago (Schandry, 1981, 2003; Schandry et al., 1986; Montoya et al., 1993; Critchley et al., 2004; Pollatos et al., 2005a,b; Gray et al., 2007). The HEP is a unique version of the usual evoked response (ERP) in that the R-wave of the ECG is used as a signal rather than being filtered out. Each heart beat then creates a large electrical signal to the brain which can be measured with surface electrodes. The above mentioned studies discovered that those subjects that had better interoception (ability to perceive their heart rates) produced a larger evoked potential presumably by way of the vagal afferent system. So if HRVB is, in fact, stimulating beneficial brain structures, we might see it reflected in the HEP. Thus far, two studies have supported this idea. In the first (MacKinnon et al., 2013), we examined the HEP waveform (it's called an N250 because it produces a negative deflection at about 250 ms) at baseline in a resting state, during a negative emotion induction, during a positive emotion induction, and during a slow resonance breathing period. **Figure 2** shows the results.

As can be seen, the slow breathing condition was significantly more negative than the other conditions.

In a second study (Huang et al., 2014), we trained a group of 12 participants in HRVB over four sessions and compared them to a group of 13 participants who received EMG/relaxation training again over four sessions. As expected the HRVB group improved their HRV substantailly whereas the EMG comparison group did not (see **Figure 3**).

More importantly, only the HRVB group showed changes in their HEP (see **Figure 4**).

These results support our speculations and those of Brown and Gerbarg:

> "... voluntary control of breath patterns can affect ANS functions via vagal afferents to brainstem nuclei (nucleus tractus solitarius, parabrachial nucleus, locus coeruleus)...Our neurophysiologic model postulates that vagal afferents activate hypothalamic vigilance areas and enhance and enhance attention and alertness, whereas pathways through the thalamus quiet frontal cortical activity and reduce anxious worrying" (Brown and Gerbarg, 2005a,b, p. 713).

Of course, there are many other possible explanations for why the complex process that occurs with HRVB might reduce depression and/or anxiety (distraction, self-efficacy, etc.). However, HEP method might give us a tool to disentangle possible mechanisms of the intervention.

OTHER POTENTIAL MECHANISMS FOR THERAPEUTIC EFFECTS

Because HRV biofeedback is apparently helpful to conditions involving various physiological systems (pain, anxiety, depression, COPD, blood pressure control, athletic performance, etc.), it is probable that a number of mechanisms are involved in various effects, in addition to baroreflex stimulation and effects of vagal afferents. Most of them have received little empirical attention, but they all deserve investigation at this point. Possible mechanisms include:

EFFECTS OF VAGAL EFFERENTS

Parasympathetic activity is usually a component in the "relaxation response." Stimulation of parasympathetic reflexes by HRV biofeedback may produce body autonomic activity characteristic of relaxation, and thus directly counter stress effects. One way this may occur is a mechanism that has been labeled "Accentuated Antagonism." "Vagal 'tone' predominates over sympathetic tone at rest. Under normal physiological conditions, abrupt parasympathetic stimulation will inhibit tonic sympathetic activation and its effects at rest and during exercise. This response is known as 'accentuated antagonism' (Olshansky et al., 2008, p. 863)". Presumably this aspect of the parasympathetic efferent system is strengthened with HRVB training. This may be at play in inhibiting sympathetic output to myofascial trigger points (Hubbard and Berkoff, 1993; Gevirtz et al., 1996; Hubbard, 1998). The work of the Aziz group in London (Hobson et al., 2008) has also demonstrated that slow breathing almost immediately prevents esophageal pain thresholds from dropping dramatically when acid is introduced to the stomach.

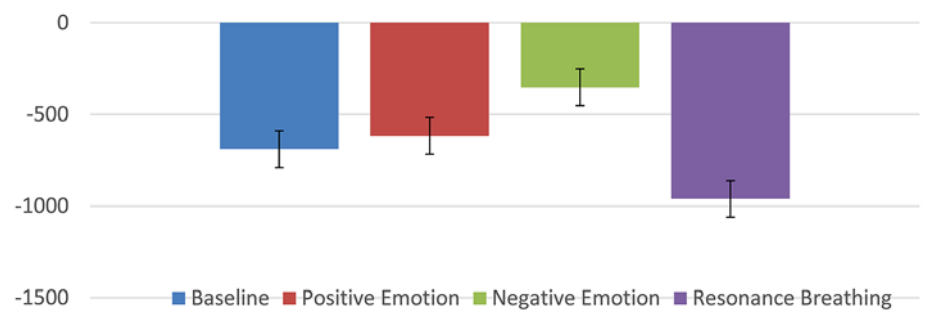

FIGURE 2 | N250 (in microvolts) evoked potential during various conditions.

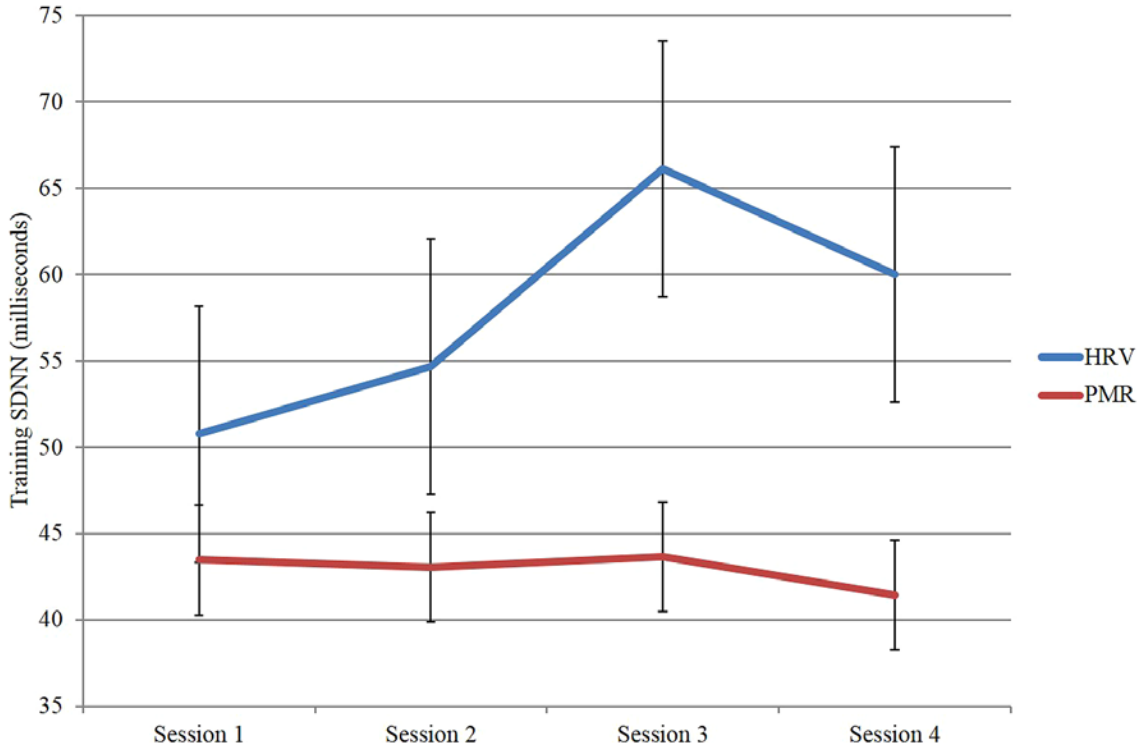

FIGURE 3 | Heart rate variability as measured by SDNN across sessions for the heart rate variability biofeedback group compared to the EMG/relaxation group.

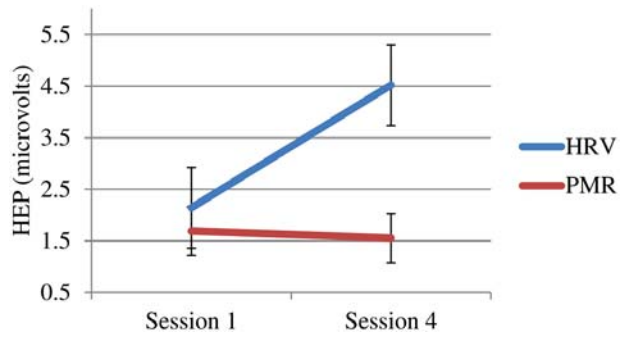

FIGURE 4 | Heartbeat event related potential (HEP) at 250 μs for both groups pre vs. post-training (sign reversed).

INCREASED GAS EXCHANGE EFFICIENCY

Because of the 0° phase relationship between breathing and heart rate during resonance frequency breathing, improved gas exchange may help people with respiratory diseases, and may even decrease respiratory drive in people with stress-induced hyperventilatory reactions.

MEDITATION EFFECT

Heart rate variability biofeedback involves paying close attention to nuances in breathing. This is very similar to what is done in mindfulness meditation exercises. The pathway here would be primarily mental: i.e., one cannot simultaneously worry about various concerns of the day while concentrating on relaxed breathing.

MECHANICAL STRETCHING OF AIRWAYS

Effects on asthma may occur indirectly through effects of stretching epithelial tissue in the lung by deep breathing. It is known that only a single deep inhalation during a methacholine challenge can decrease airway reactivity to methacholine in asthma patients (Pellegrino et al., 1996; Marchal et al., 2002).

ANTI-INFLAMMATORY EFFECTS

It is known that the vagal system interacts closely with the inflammatory system, such that increases in vagus nerve traffic (usually produced by electrical vagal stimulation) are associated with decreases in serum levels of various inflammatory cytokines (Borovikova et al., 2000; Tracey, 2002). One study did find a decrease in C-reactive proteins among hypertensive patients treated with HRV biofeedback (Nolan et al., 2012). In another study, we experimentally exposed healthy subjects to an inflammatory cytokine, lipopolysaccharide (Lehrer et al., 2010). Usually both sympathetic and parasympathetic activity is blocked by lipopolysaccharide. Although no biofeedback-induced decreases in inflammatory cytokines were found, the autonomic effects of inflammation were greatly modulated, indicating that a greater resiliency was preserved among individuals given HRV biofeedback.

CONCLUSION

In this paper we have tried to summarize possible mechanisms for the effectiveness of HRVB. We have been working under the assumption that increases baroreflex represented a viable marker of improved autonomic homeostasis or increased complexity. We have reviewed the evidence that led us to this conclusion, w*hich now are somewhat established* by our labs and others. We now speculate that in conjunction with this class of mechanisms, stimulation of the vagal afferent system may also play a role, especially in disorders of negative affectivity.

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Treating the mind to improve the heart: the summon to cardiac psychology

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The link between the heart and mind has been studied over the centuries in many fields, such as medicine and psychology (Thayer and Lane, 2009; Allan, 2012). Different terms have been used recently to identify this research and clinical area: e.g., Behavior Cardiology (Rozanski et al., 2005), Psychocardiology (Jordan et al., 2007), and Cardiac Psychology (Allan, 2012). Many risk factors for coronary heart disease have been studied: thus, age, gender, and family history are considered as typical unmodifiable risk factors, whereas diabetes, weight, life stress, type A behavior, social isolation, depression, sedentary lifestyle, cholesterol/HDL ratio, hypertension, and cigarette smoking are the typical modifiable and clinically treatable risk factors (Allan, 2012).

Mental stress is now also recognized as a risk factor in cardiac dysregulation. Due to an "epigenetic psychobiologic susceptibility-the nexus of psychophysiologic reactivity and biopsychosocial vulnerability" (Fischer and Collins, 2012, p. 58), acute emotional traumas could "trigger a panic attack in some and transient or permanent cardiac damage or life-threatening arrhythmias or death in others" (Fischer and Collins, 2012, p. 58). Moreover mental stress could be an important trigger of cardiovascular events with clinical relevance, taking into account that stress responses can be mediated or moderated by psychological variables, such as coping skills or personality characteristics, and by social aspects such the presence of family or systemic support (Krantz et al., 2012). In many situations multiple stressors could be involved in generating cardiovascular events (Menezes et al., 2011). Natural calamities, such as earthquakes, and human-made extreme disasters, such as war and terrorism, can precipitate cardiovascular events (Mittleman and Mostofsky, 2012).

A typical field of intervention for the Cardiac Psychology is Posttraumatic Stress Disorder (PTSD), classified as an anxiety disorder in the latest version of Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). The essential feature of PTSD is the development of specific symptoms, following exposure to one or more traumatic events, such as recurrent and intrusive memories or dreams about the trauma (re-experiencing symptoms), flashbacks, emotional numbing, or heightened physiologic arousal. PTSD affects significant organic outcomes too (Doerfler and Paraskos, 2012). A typical example is reported in Shemesh et al. (2004), where a group of patients with PTSD followed one year after a myocardial infarction (MI) were more than twice as likely to be submitted to another hospitalization because of cardiovascular reasons than individuals with MI but without PTSD. Taking into account that many effective interventions are available nowadays to treat and reduce PTSD in different populations (Arnberg and Johannesson, 2013; Barrera et al., 2013; Gillies et al., 2013; Warner et al., 2013; Cukor and Difede, 2014), it appears to be the case that research into cardiac effects of PTSD is not highly developed, in fact in 2012 Doerfler wrote that "Research on CBT (Cognitive Behavioral Therapy)

for cardiac-related PTSD is in its infancy, and the literature consists of only a few uncontrolled case studies, but these reports may be instructive in stimulating treatment development" (Doerfler and Paraskos, 2012, p. 260).

So the study of psychosocial factors and interventions in the field of Cardiac Psychology and PTSD is a growing need and challenge in our clinical and scientific community (Ginsberg et al., 2008, 2010; Chen et al., 2014; Conder and Conder, 2014; Drury, 2014; Gillie and Thayer, 2014; Lee et al., 2014; Lehrer and Gevirtz, 2014; Mccraty and Zayas, 2014; Shaffer et al., 2014; Steffen et al., 2014; Wood, 2014). In cardiovascular rehabilitation protocols it is important to evaluate different clinical psychology-based program types, such as psychological interventions, psycho-educational programs, psychotherapies, educational training, stress management, biofeedback, counseling sessions and relaxation techniques (Jordan et al., 2007; Dornelas, 2008, 2012; Manzoni et al., 2008; Castelnuovo, 2010a,b). New approaches have to be tested, such as Acceptance and Commitment Therapy (Spatola et al., 2014a,b) or expressive writing (Manzoni et al., 2011a), improving the study of rehabilitation programs on patients with comorbidities such as obesity (Manzoni et al., 2011b; Pietrabissa et al., 2012), improving the study of psychosocial and cognitive features related to the cardiac pathology with or without complications (Capodaglio et al., 2010, 2013; Manzoni et al., 2010, 2011a; Proietti et al., 2012, 2014; Cazard and Ferreri, 2013; Castelnuovo et al., 2014), and opening to the growing opportunities provided by new technologies and mHealth approach (Castelnuovo et al., 2003, 2014; Nguyen et al., 2004; Rubel et al., 2005; Riva et al., 2006; Roth et al., 2009; Castelnuovo and Simpson, 2011).

The study of the relationship of autonomic cardiac adjustment to stress and mental disorder—the heart-mind connection—is the challenge that Cardiac Psychology has accepted. This *Frontiers* Research Topic special is devoted to providing a foundation for the development of the scientific study of these relationships, and the discovery of the propositions that govern them.

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