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Disruption of Bradycardia During Vigilance: Autonomic Cardiac Dysregulation is Prelude to Disinhibition, Hyperarousal, and Attention Bias in Combat Veterans with PTSD

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Additional information is available at the end of the chapter

Abstract

We propose a model to account for the post-traumatic stress disorder (PTSD) symptoms of disinhibition, hyperarousal, and attention bias. We review the background literature which is the foundation on which our model rests, present key results of our ongoing research, and suggest testable hypotheses for further research. Our laboratory is in a Veterans Affairs (VA) Medical Center, where we began our work with a search for the significant causes and predictors of hyperarousal in combat veterans with PTSD using eyeblink and autonomic conditioning protocols. We believe our studies will lead to integration of a treatment intervention for war veterans (and equally as well for treatment of the traumatically stressed in the general population). Our research has begun to show strong associations between lowered heart rate variability (HRV) and PTSD. Loss of bradycardia during normal vigilance is the cause of lowered HRV, which impairs appraisal of threat value of environmental stimulation, thereby leading to disinhibition, hyperarousal, and attention bias toward and away from threat. The next steps of research we plan are outlined and designed to elucidate how HRV biofeedback is a promising intervention to increase HRV during vigilance of stimuli and restore cognitive appraisal and response selection, thereby reducing PTSD symptoms and normalizing behavior.

Keywords: autonomic cardiac regulation, PTSD, combat veteran, orienting, attention bias

1. Introduction

Brain-based hypersensitivity to environmental stimulation underlies pathological states that have been defined as "disorders of arousal" [1]. "Autonomic tuning" is the term that was historically used to describe the process of normally balanced sympathetic and parasympathetic branches of the autonomic nervous system (ANS), in contrast to the disorders of arousal which are characterized by ANS dysfunction, affective lability, anxiety, stress, and emotional disorders:

> It is a matter of everyday experience that a person's reaction to a given situation depends very much upon his own mental physical, and emotional state. One might be said to be "set" to respond in a given manner … the autonomic response to a given stimulus may at one time be predominantly sympathetic and may at another time be pre-dominantly parasympathetic.([2], pp. 90–91; quoted in [3], p. 179)

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 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 [4]. 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 that chronic autonomic imbalance finally leads to allostasis of affective, cognitive, and behavioral level of function. The effect of heart rate variability (HRV) biofeedback (HRVB) is to manipulate peripheral autonomic state feedback to the central nervous system circuits regulating 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.

2. Key concepts

The chapter is organized into several sections. In Section 3, the role of HRV in autonomic cardiac control as it is found in normal adaptation is described. The specific topic headings in this section are: *Autonomic cardiac regulation; HRV and HRV coherence; Neurophysiological basis of HRV: polyvagal and neurovisceral; HRV and orienting; Executive control of attention and defense;* and *Autonomic cardiac regulation and fear.* In Section 4, the topic headings *Autonomic cardiac dysregulation in PTSD* and *PTSD and attention bias* discuss the derangement of normal ANS cardiac control by PTSD. Section 5 has only one topic heading titled *Applied psychophysiological therapy for PTSD and attention bias: HRV biofeedback* which presents the case that application of the HRVB intervention is intuitively and theoretically sound. In Section 6, *Models of Autonomic Dysregulation in PTSD* is a graphic representation of our ideas of how HRV influences orienting in normal and in the PTSD phenotype. In Section 7, the topic heading *Completed Research on HRVB*

and PTSD and *Planned Research on HRVB and PTSD: The Action Cascade* details the work that has been done in our laboratory and the direction we are taking to further this important line of clinical research.

3. Theories

3.1. Autonomic cardiac regulation

The ANS controls how the individual appraises the valence of environmental stimuli and the responses selection consequent to the appraisal (e.g., maintenance of resting homeostasis, mobilization of defensive response, task performance, tonic immobilization, and/or affiliation) by interplay between sympathetic (accelerative) and parasympathetic (decelerative) influences on the heart. This model of adaptive behavior integrates polyvagal theory [5–8]. Thus, cardiac adjustments to environmental stimuli affect the internal physiological and emotional state of the individual as well as the quality of information processing that the individual can perform during the stimulus appraisal stage of the orienting response. Bradycardia 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 [9–11]. As we have previously modeled, this process occurs during the initial stage of the stimulus orienting response (OR), and it can lead to autonomic and somatic-motor conditioning [12].

3.2. HRV and HRV coherence

The number of studies of the relevance of the ANS to stress and mental disorder has increased markedly in the past 20 years [13, 14]. HRV is the quantification of the variance of inter-beat intervals (ibi) between cardiac pulses. HRV can be measured by electrocardiogram (ECG), fingertip pulse photoplethysmograph (ppg), or beat-to-beat (continuous) changes in arterial blood pressure. *Instantaneous heart rate* in beats per minute (bpm) can be calculated from a single ibi (with unit of seconds) as HR (bpm) = (60 s/min) × (1/ibi) = 60/ibi. On the other hand, neither ibi nor HRV can be calculated from HR in bpm because bpm is an averaged value. We have been studying and recoding HR and HRV in combat veterans for several years.

Quantification of HRV is accomplished in several different ways. The two most common types of HRV variables, and the most easily understood and physiologically interpretable, are the *time-domain* and *frequency-domain* variables [14, 15]. In the time domain, variance of ibi's, or power, across a recording time period is simply derived from the time intervals of either consecutive heartbeats (standard deviation of all N-N intervals, SDNN) or the differences between consecutive intervals (square root of the mean of the sum of squares of differences between adjacent N-N intervals, RMSSD. More variance = more power. In the frequency domain, power in units of ms^2/Hz is derived as the integral (area) under the curve of a given frequency range. Frequency-domain measures are computed with power spectral density (PSD) analysis using fast Fourier transform of the tachygram of HR against time. The PSD

graphically represents how variance or power is distributed as a function of frequency. Three main spectral components are distinguished: very low frequency (VLF, 0.003–0.05 Hz), low frequency (LF, 0.05–0.15 Hz), and high frequency (HF, 0.15–0.50 Hz). There is also an ultra-low frequency (ULF) band of HRV cycle frequency recognized between 0.00001 and 0.003 Hz—that is, a period of months—that has been receiving some attention in recent years. **Table 1** indicates how frequency ranges can be associated with physiologically and behaviorally relevant time periods.

Sec/cycle (Period)	86400	600	300	60	15	10	6	5	4	1	.75
Cycles/s (Hz)	0.00001	0.002	0.003	0.017	0.067	0.100	0.167	0.200	0.250	1.000	1.33
Minutes/cycle	1440.0	10.00	5.00	1.00	0.25	0.17	0.1	8	0.07	0.02	0.01
Cycles/min	0.0007	0.1	0.2	1	4	6	10	12	15	60	80
Function	24 h					RFB and BR	Normal respiration				Normal HR

RFB, resonant frequency breathing, BR, baroreflex.

Table 1. Correspondences of period, cycle, and physiological and behavioral functions in the HRV power spectrum.

There is general agreement that efferent parasympathetic output from the vagus cranial nerve is the major contributor to the HF component. HF HRV power is an indicator of respiratory sinus arrhythmia (RSA), the breath-to-breath heart rate fluctuation due to cardiac modulation by vagal parasympathetic output associated with respiration; in the normal state, heart rate accelerates on inspiration and decelerates on expiration during each respiratory cycle. Vagal parasympathetic output results in cardiac deceleration and higher HF HRV power. Although the mediation of HF HRV is complex, the primary source of HF HRV is mediated through the vagus nerve, such that blocking vagal activity removes virtually all HF HRV [16]. RSA results from interaction between lung and brainstem. Lung inflation activates afferent stretch receptors which results in inhibition of vagal parasympathetic cardiac outflow and increased HR; during expiration, the stretch is reduced and vagal inhibition removed leading to reduced HR. The term "vagal tone" has been used to refer to HF HRV although parasympathetic influence on cardiovascular function and HRV, through the baroreflex, extends into the LF range as well.

LF HRV power is a mixture of activity of sympathetic and parasympathetic cardiac efference and afference in feedback loops between heart and brain that control short-term arterial blood pressure changes. "This discrepancy is due to the fact that in some conditions associated with sympathetic excitation, a decrease in the absolute power of the LF component is observed. It is important to recall that during sympathetic activation the resulting tachycardia is usually accompanied by a marked reduction in total power, whereas the reverse occurs during vagal activation" [17]. Furthermore, after reporting complete abolition of the HF and the LF 0.1 Hz peaks as a result of parasympathetic blockade, Akselrod concluded that "our data indicate that

the parasympathetic nervous system (PNS) mediates heart rate fluctuations at frequencies corresponding to the low- and high-frequency peaks of the power spectrum" [16].
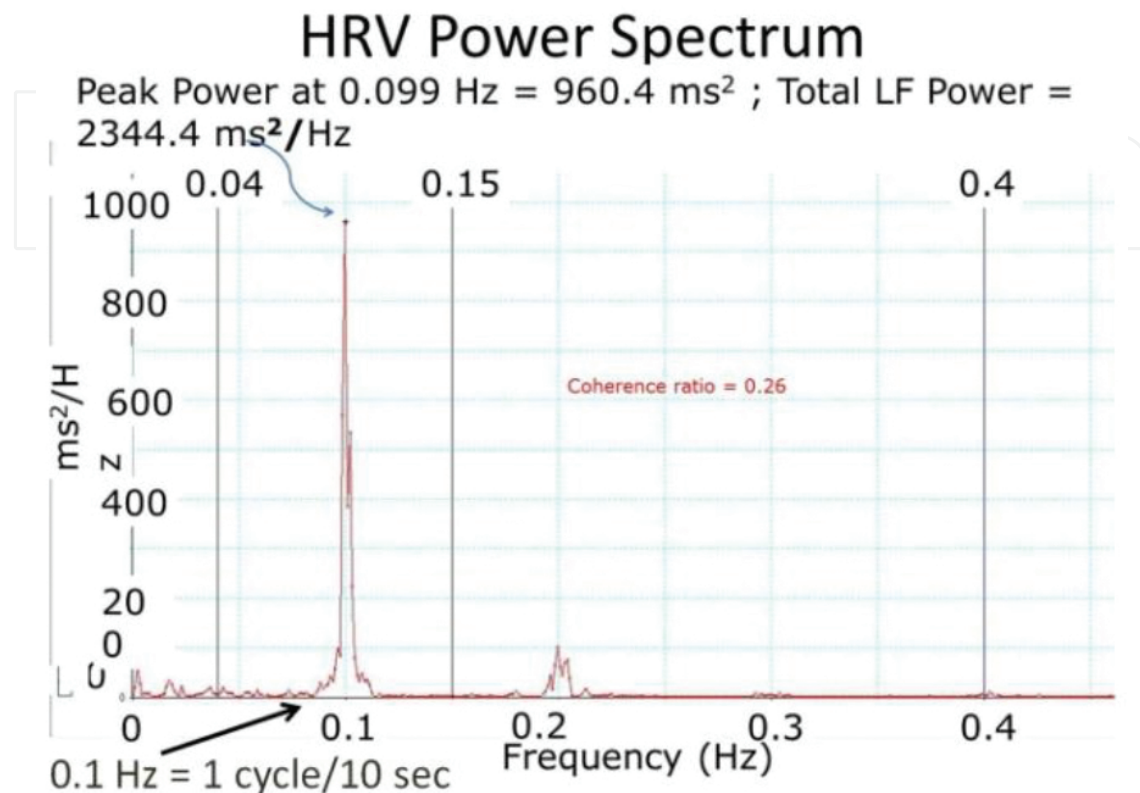
HRV Power Spectrum

Peak Power at 0.099 Hz = 960.4 ms^2 ; Total LF Power = 2344.4 ms^2/Hz

Coherence ratio = 0.26

0.1 Hz = 1 cycle/10 sec

Frequency (Hz)

Figure 1. Example of an HRV spectrum showing HRV coherence.

HRV coherence is a physiological state of the individual that is produced when *resonance* occurs in the cardiovascular feedback systems controlling heart rate, arterial blood pressure (baroreflex), and vasomotor tone. When resonance occurs, the difference between the highest and the lowest instantaneous heart rate within one respiratory cycle is maximized [18]. It can easily be seen then that HRV coherence means that HRV of the individual is maximized. HRV coherence is operationalized as the frequency spectrum of a sine wave-like heart rate tachygram that has a narrow, high-amplitude peak in the LF region of the HRV power spectrum, around 0.1 Hz, with no other major peaks in the VLF or HF regions [19, 20]. An example of HRV coherence from our own recording is shown in **Figure 1**. Although there are different ways to calculate a value from the PSD that reflects HRV coherence, one well-known method of calculating a "coherence ratio" is to (1) identify the maximum peak in the 0.04–0.26 Hz range of the HRV power spectrum (which represents parasympathetic function) and calculate the integral in a 0.030-Hz-wide window centered on the highest peak in that region, (2) calculate the total power of the entire spectrum, and (3) divide the parasympathetic power by (total power minus parasympathetic power) [21]. In many if not most individuals who are free from cardiovascular disease, HRV coherence can be reliably produced by diaphragmatic breathing around the 0.1 Hz cycle (six breaths per minute), which is called resonant frequency breathing

(RFB) because that is the frequency when resonance of the cardiovascular system occurs. RFB is integral to the practice of HRVB (see below for more detail). HRV coherence is associated with increased emotional self-regulation and mental alertness [20].

3.3. Neurophysiological basis of HRV: polyvagal and neurovisceral

The polyvagal theory of Porges [7, 22–25] describes the neurophysiological basis of the interface of autonomic state and behavior. Polyvagal theory presents the hierarchical relation among three subsystems of the autonomic nervous system supporting adaptive behaviors in response to the particular features of safety, danger, and life threat in environmental stimulation. The name of the theory "polyvagal" denotes that two vagal pathways operate in mammals. One of the vagal circuits is a vestige of an evolutionarily primordial circuit that associated with defensive responding to threat; the other vagal circuit is a relatively recent evolutionary development, one that is not observed in other animals than mammals. This newer vagal circuit produces physiological states associated with safety and affiliation, and it is crucial for social engagement. Thus, when an individual feels safe the somatic or vegetative conditions are supportive of growth and restoration ("trophotropic" [26, 27]). This newer vagal circuit is characterized by *myelinated* vagal efferent pathways, including the cardiac pacemaker to cause heart rate deceleration and inhibit the fight-flight mechanism of the sympathetic nervous system. The stress response of the hypothalamic-pituitary-adrenal (HPA) axis ("ergotrophic") is dampened, and inflammation is reduced through modulation of cytokine and other immune reactions. Second, integration of nuclei in the brainstem that regulate myelinated vagus with nuclei controlling muscles of the face and head used in facial expressions occurs. As a result, neural pathways are created that enable a social engagement system with bidirectional coupling of bodily states and social behaviors such as facial expressions and prosodic vocalizations [8].

The neurovisceral integration model (NvIM) suggests that vagally mediated HRV (vmHRV) represents a psychophysiological index of cognitive inhibitory control and thus is associated with emotion regulation capacity [25, 28, 29]. Executive brain areas located in prefrontal cortex exert inhibitory influence on subcortical structures, importantly the amygdala, allowing the individual to adaptively respond to demands from the environment and organize responses effectively [30–32]. Thus, at rest, active cortical brain areas are indicative of greater inhibitory and emotion regulation. The NvIM proposes that individual differences in vagal function, as indexed by HRV at rest, reflect the activity of this flexible and integrative neural network which enables effective integration of basic responses (behavioral, cognitive, and emotional) that support goal-directed behavior. The NvIM is founded upon a complex interplay between cortical and subcortical regions of the brain that are grouped under the collective term "central autonomic network" (CAN; [33]). The CAN links the ANS to a higher-order cognitive functioning, especially the prefrontal cortex. Many specific brain nuclei and structures are included and reciprocally interconnected in the CAN: the ventromedial prefrontal cortices, the central nucleus of the amygdala, the anterior cingulate, the insula, the paraventricular nuclei of the hypothalamus, the periaquaductual gray matter, the nucleus of the solitary tract (NST), the nucleus ambiguus, and the medullary tegmental field. Output of the widespread CAN

circuitry extends to autonomic inputs to the heart, including the vagus nerve. By exerting inhibitory control over subcortical pathways, prefrontal cortex functions to enable the individual to perceive and adapt to environmental challenges through higher levels of HRV (i.e., greater vagal tone) at rest.

Converging evidence suggests that these core sets of neural structures are responsible for not only inhibition but also the regulation of the ANS activity and reactivity. The heart and other peripheral organs are under tonic inhibitory control by the ANS. More specifically, this influence is characterized by a relative dominance of the parasympathetic nervous system (PNS) over influences of the sympathetic nervous system (SNS). Vagal parasympathetic control represents the major descending inhibitory pathway (DIP), adaptively regulating physiological functions shaped by psychological processes including emotion regulation. The NvIM posits that vagally mediated HRV may be more than just a simple index of healthy heart function, and also serves as readily available measure and index of the degree to which the brain's integrative system for adaptive regulation provides flexible control over the periphery.

3.4. HRV and orienting

Autonomic cardiac adjustments to environmental stimulation are an integral part of the orienting response (OR) to stimulation in the environment. Deceleration of HR is identifiable during the OR, while acceleration of HR reflects response selection of a defense response after a stimulus is cognitively appraised to be dangerous or threatening. The direction of attention (externally toward environmental information vs internally for information processing) and change in heart rate (deceleration vs acceleration, respectively) are linked. Lacey and Lacey [34, 35] put forward the "intake-rejection hypothesis", proposing that attention to cognitive tasks can be directed toward the environment (intake of the environment) or it can be directed toward internal processing (rejection of the environment). Cardiac deceleration occurs during externally directed tasks (e.g., visual attention and search, empathic listening) due to activation of the parasympathetic branch of the autonomic nervous system. Cardiac acceleration occurs during internally directed tasks (e.g., mental arithmetic or imagery, response selection and output or performance) due to activation of the sympathetic branch of autonomic nervous system via release of norepinephrine from locus coeruleus to stellate ganglion of the heart [36].

Autonomic cardiac adjustments to environmental stimulation are furthermore and more basically an integral part of the OR. Orienting is the enhancement of stimulus reception by information processing and appraisal. Early work in this area determined that a deceleration of HR is identifiable during the orienting response, while HR acceleration reflects selection of a behavioral defense response (DR) after stimulus information appraisal indicated the need for it [37, 38]. The history of theory and research on the OR and DR (defense response) includes the role of general psychophysiological measures and phasic cardiac responses in both humans and animals. Obrist called this "cardiovascular learning" [39, 40]. Autonomic substrates of cardiac responding have behavioral significance for the OR and DR, and reveal that cardiac deceleration is necessary for stimulus appraisal after vigilance in orienting, and cardiac acceleration is necessary for defensive response selection [41, 42].

Currently, however, the construct of attention is considerably more complex than is described by intake-rejection hypothesis. Although attention is being defined and measured using varied behavioral tasks, such as spatial cueing, sustained vigilance, and selective focus, the many different types of attention have been grouped into three basic categories, labeled as "alerting," "orienting," and "executive" [43]. Critically, the basic premise that cardiac deceleration is necessary for successful externally directed attention has held up and found new life in the widely accepted practice of employing HRVB for optimal performance enhancement, notably sports preperformance preparation (e.g., [44]).

3.5. Executive control of attention and defense

The human brain is equipped with various executive functions such as selective attention to deal with the vast amount of information flow from the external world in a seemingly effortless manner [45]. Emotional stimuli with their perceptual properties and biological significance must have attentional prioritization in order for adaptation to occur. For example, a dot-probe task was used to investigate whether task-irrelevant auditory emotional information can provide cues for orientation of auditory spatial attention [46]. In this experiment, participants were significantly faster to locate a target when it replaced the negative cue compared to when it replaced the neutral cue, while the positive cues did not produce a clear attentional bias. The results indicate that negative affect can provide cues for the orientation of spatial attention in the auditory domain. By way of possible mechanism for this effect, it has been shown that negative emotion induced by visual stimuli can affect auditory event-related potentials (ERPs) as early as 20 ms after stimulus onset [47], and more generally that scalp potentials are associated reflect autonomic activity associated with behavioral responding [48].

The pressures of evolution have hardwired in humans a set of inborn and automatically activated defense behaviors, termed "the defense cascade." The first step in the defense cascade is arousal; if danger or threat is then perceived, the next step is activation of flight or fight, while freezing is an alternate response at this stage, a "flight-or-fight response put on hold." Tonic, collapsed, or passive immobility (also called fear bradycardia) is the response of last resort, when active fight or flight defense responses have failed and the threat to survival is imminent and inescapable. Each of these defense reactions has a distinctive autonomic pattern mediated by neural pathways. Freezing differs importantly from immobility in the cardiac state: accelerated heart rate characterizes freezing and decelerated heart rate characterizes immobility. The defense cascade is known to activate neural structures that are also central to the CAN: the extended amygdala, hypothalamus, periaqueductal gray (PAG), ventral pontine tegmentum, ventral and dorsal medulla, vagal and sympathetic nuclei, and spinal cord [49].

The hypothalamus (paraventricular nucleus) plays a major role in arousal by increasing sympathetic viscereomotor tone and in striated muscles of the somatomotor nervous system. The body becomes prepared for action by vasoconstriction of blood vessels to the salivary glands (dry mouth) and tension one in the laryngeal muscles of the back. Smooth and striated muscles contract, heart rate and respiration accelerate, and posture is stabilized [49].

3.6. Autonomic cardiac regulation and fear

Fear is an emotion caused by the cognition that a stimulus perceived in the environment is dangerous, threatening, or likely to cause pain. Fear causes a change in brain and autonomic system, and ultimately a change in behavior, such as running away, hiding, or freezing.

Heart rate (HR) conditioning in rabbits (*Oryctolagus cuniculus*) is a widely used model of classical Pavlovian fear conditioning of autonomic responding. Acquisition and retention of conditioned bradycardia (deceleration of heart rate) in the rabbit is useful because the rabbit is a species considered by many as an ideal intact preparation for the study of neural mechanisms of associative learning, and in particular, cardiovascular conditioning. The neural mechanisms underlying HR conditioning have been widely researched in rabbits and other species including humans, with studies concentrating on vagal-mediated, parasympathetic cardiovascular changes, sympathetic-mediated changes, emotional/affective learning components involving the amygdala and prefrontal cortex and extrapyramidal system including some but not all cerebellar structures [50].

Up until his death in 2011, Donald A. Powell was for decades a leading researcher in classical (Pavlovian) conditioning of autonomic and somatomotor function and the founder of our laboratory. His major findings (summarized below) continue to guide the work in our laboratory at the present time. A fear conditioning paradigm was used to concomitantly condition autonomic (cardiac adjustments) and somatic (eyeblink) function [51]. This approach was applied to a classical conditioning model of PTSD in veterans and a parallel translational lesion model of conditioning in rabbits [52, 53]. Dr. Powell's research elucidated two separable neural circuits with different fear conditioning parameters: the cortico-limbic circuit controlling autonomic conditioning and an extrapyramidal neural circuit controlling skeletal, or somatomotor, conditioning.

Lesions of substantia nigra prevented acquisition of the eyeblink conditioned response and had no effect on conditioned bradycardia [54, 55]. While medial prefrontal cortex (mPFC) is not critical for acquisition of somatomotor conditioning [56], post-training lesioning of mPFC impaired performance of the conditioned eyeblink response [57–59]. Moreover, while deep nuclei of the cerebellum are understood to be necessary for eyeblink conditioning [60], manipulation of this extrapyramidal substrate does not affect heart rate conditioning [61].

In contrast, lesion studies demonstrated that conditioning of autonomic cardiovascular control requires intact function of a cortico-limbic circuit [62, 63]. Acquisition of conditioned bradycardia in the rabbit is dependent on a prefrontal-amygdala pathway, and the major structures in this pathway are medial prefrontal cortex [64–66] and central nucleus of the amygdala. Interestingly, subiculum of the hippocampus was not found to be necessary for acquisition of conditioned bradycardia in this paradigm [67]. Furthermore, autonomic cardiac conditioning is rapid compared to somatomotor eyeblink conditioning. In animals, conditioned slowing of heart rate was shown to occur within the first 3–5 conditioning trials, whereas eyeblink conditioning requires many more trials, in the range of 50–60 [68]. Similarly, heart rate conditioning in humans was more quickly acquired with shorter interstimulus interval than

eyeblink [69]. At the single neuron recording level, mPFC processing of stimulus information appears to be driving decelerative heart rate-conditioned responding [70].

Since the same set of stimulus contingencies will classically condition both autonomic function and somatomotor behavior, the existence of a process that integrates the two would be expected. The septo-hippocampal system may be the brain circuit that performs this activity. Extinction of classically conditioned bradycardia is delayed by vasopressin, which increases peripheral vascular resistance and arterial blood pressure, a result that seemingly increases the autonomic conditioning cortico-limbic circuit to include hypothalamus and pituitary [71]. Intraseptal injection of the antimuscarinic anticholinergic scopolamine in the concomitant autonomic and somatomotor conditioning paradigm enhanced cardiac deceleration and impaired eyeblink conditioning [72]. Thus, there may be a central border zone cardiac-somatic linkage [39] that couples and uncouples cortico-limbic (stimulus registration and appraisal) from neostriatal (response selection) activities [73]. More research is needed in this area to integrate these crucially important past and current constructs of arousal, attention, and behavior.

4. Clinical implications

4.1. Autonomic cardiac dysregulation in PTSD

Unlike animals, which generally are able to restore their standard mode of functioning once a fear-provoking stimulus is past, humans often are not, and they may find themselves stuck in the autonomic profile associated with response that was tied to the original danger or trauma. This is traumatization of the nervous system. When the nervous system is trauma-tized, current environmental stimuli, or associatively conditioned reminders of the original danger, repetitively trigger the behavioral response to past fearful events. A simple working definition of PTSD then, apart from the formal clinical diagnostic criteria, is that the ANS of the traumatized individual has become stuck in, or is easily shifted into, a state of ergotropic behavioral response to fear, dominated by sympathetic outflow and its accelerative effects on cardiac adjustment. As a result, PTSD influences on autonomic control of heart rate and HRV impact orienting and stimulus appraisal [9].

The effect of PTSD on HRV has been studied since the late 1990s. Our own meta-analysis assessed all available studies of sympathetic and parasympathetic influences on HRV to determine effect sizes and the utility of HRV as a potential psychophysiological indicator of PTSD, summarized below [74]. Using keywords "PTSD" and ("heart rate or HRV or vagal or autonomic nervous system"), 453 potentially relevant studies were identified; after inclusion criteria were added, 39 studies were considered; exclusion criteria reduced the study sample to 19, all of which were then included in the meta-analysis. The meta-analysis was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane Handbook guidelines, using Comprehensive Meta-analysis Software, ver. 2.0. We calculated the Hedges' g effect size with 95% confidence interval (CI), statistical significance (p), and heterogeneity for each effect size estimate. Several HRV variables were considered,

and for each an individual, meta-analysis was performed. Heart rate (HR) was significantly elevated in PTSD patients. The available scientific literature clearly showed that reductions in SDNN, RMSSD, and HF power, and increased LF/HF ratio, have utility as indicators of autonomic effects of PTSD, which can be associated with impaired vagal activity. The positive LF/HF effect size indicates increase in sympatho-vagal function under PTSD as compared with controls, and also reflects, we believe, non-linearity in co-occurring shifts in LF and HF power with proportionately greater reduction in HF than LF [74].

HRV has been shown to be significantly correlated with eyeblink conditioning in normal adults [11, 69]; in combat veterans with and without PTSD (PTSD+ and PTSD-, respectively), EB conditioning was associated with resting HRV. In the PTSD+ veterans, frequency and amplitude of eyeblinks, HRV, and immediate memory on a verbal learning test were all lower than in the control group [12]. Factor analysis revealed four separable factors corresponding to (1) eyeblink amplitude, (2) HRV, (3) immediate memory, and (4) self-report of mood state (depression and anxiety), and eyeblink frequency was significantly predicted by HRV and immediate memory. Furthermore, and importantly, in this study reduced HRV was also shown to be associated with poorer performance on the immediate verbal memory test [12]. Further analysis revealed the effects of eyeblink conditioning on heart rate responding in the same study [10]. In this paradigm, which was discriminative conditioning, a light signal was presented for 5 s followed by a tone conditioning stimulus (CS) that was paired with either an eyepuff (CS+) or no eyepuff (CS-). Thus, there was a 5-s vigilance period before onset of the tone CS. A linear HR deceleration from baseline during the 5-s vigilance period before onset of the tone CS was found in the PTSD- subgroup but was not present in the PTSD+ subgroup. This is strong evidence that PTSD disrupts bradycardia during vigilance.

4.2. PTSD and attention bias

Healthy adaptation requires people to allocate attention to genuine threats in the environment while ignoring other similar stimuli. Traumatic events offset this delicate balance and induce cognitive biases that give rise to threat avoidance and threat-related hypervigilance, among other clinical symptoms. Attentional problems are a common complaint of patients with a PTSD diagnosis, and clinical research data support this. Vietnam veterans with PTSD were found to be significantly worse on controls without PTSD on tasks measuring focused and sustained attention [75]. Using the attentional network test [43], PTSD participants were found to be impaired in inhibiting irrelevant information, a function of the executive attentional network [76].

PTSD may be associated with hypervigilance to salient and threat-related stimuli, but results of attention bias studies in PTSD have found biases both toward and away from threat. Hypervigilance manifest as attention biased toward threat cues while avoidance of threat-related stimuli. Attention bias indexes the degree to which attention fluctuates between vigilance and avoidance and is based on reaction time data derived from variants of the classic dot-probe task. In this task, pairs of threat and neutral (or positive) stimuli are simultaneously presented across repeated trials. Each stimulus pair is followed by a target probe appearing at the location of either the threat stimulus (congruent trials) or the neutral stimulus (incongruent

trials). An attention bias score is calculated as the difference between the mean reaction times of these two types of trials.

Attentional bias toward threat in PTSD could reflect either difficulty disengaging from threat-related stimuli or facilitated engagement of such stimuli, although there is some evidence that attentional bias toward threat in PTSD reflects difficulty disengaging as opposed to facilitated engagement [77]. Early dot probe studies in PTSD in adults and children reported mixed findings. Some studies found bias toward trauma or threat-elated stimuli in PTSD [78–82], while others reported an association between PTSD and a bias away from trauma or threat [83, 84]. Still others have failed to find significant attentional bias differences between PTSD and control groups, consisting of healthy individuals and a group of recent trauma survivors that included individuals both with and without acute stress disorder [85, 86]. Difficulty disengaging from threatening stimuli has been associated with the 5-HTTLPR serotonin transporter gene polymorphism [87], although the significance of this finding has not been explained.

Iacoviello [88] derived a measure of attention bias by grouping, or "binning," consecutive 20-trial sequences on the dot-probe task and calculating a bias score for each bin. The standard deviation of the bias scores across bins was then divided by the participant's mean reaction time to generate the measure of attention bias for each subject throughout the session. Results of this study revealed greater attention bias in participants with PTSD than in trauma-exposed participants without PTSD and nonexposed healthy participants. Attention bias was also positively correlated with PTSD symptom severity.

Different selective attentional orienting mechanisms underlying anxiety-related attentional bias have been identified, such as engagement and disengagement of attention [89]. These mechanisms are thought to contribute to the onset and maintenance of general anxiety disorders and have relevance for the study of attention bias in PTSD. General anxiety seems to be associated with a preferential bias for negativity. The measure of attention bias has recently been refined by employing a moving average technique, rather than the previously employed binning method, to generate a more stable index that is influenced less by the number of trials in any particular study [90]. However, attention bias is still something of a novel measure, and we know of no reports of test-retest reliability. Overall, attention bias may be best conceptualized as reflecting natural plasticity built into the threat-monitoring system that is influenced by different contexts and situations, rather than indexing a stable trait.

Attentional training (sometimes called attention bias modification, ABM) is aimed at reducing symptoms and behaviors associated with anxiety by systematically reducing negative attentional biases and training selective attention to orient away, or to disengage, from threat [91]. Attention control training, but not attention bias modification, was found to significantly reduce attention bias and reduce PTSD symptoms [92]. Thus, further study of treatment efficacy for attention bias, and its underlying neurocognitive mechanisms, seems warranted.

5. Applied psychophysiological therapy for PTSD and attention bias: HRV biofeedback

The scientific and clinical data supporting the facts of diminished vagal and increased sympathetic activity in PTSD increased notably in the past decade and continue to mount [13]. In developing a treatment intervention, it is important to understand the signature patterns of normal and deranged stimulus processing and appraisal, and response output type, whether immobility, defense, or affiliative. Effective interventions aim to activate, deactivate, or modify one or more components of the abnormal cardiac adjustment pattern. Because the process of treatment intervention pertains to humans, we may speak of an intervention that shifts the response pattern of cardiac adjustment as being a "mind-body intervention."

In our clinical research, we use HRVB as a psychophysiological intervention to study the effects of psychological trauma and its potential amelioration. HRVB is a very well-tolerated, easy-to-use, and effective mind-body technique that appears to have achieved acceptance as an integrative health procedure for routine healthcare. HRVB training teaches the practitioner to self-regulate his or her own HRV by monitoring visual feedback indicating whether or not HRV coherence is attained, and then associating that feedback with self-regulation of emotional state. With practice, the individual learns how to voluntarily and quickly produce HRV coherence using RFB, focused attention, and conscious voluntary positive emotional state. HRVB is an interactive procedure that uses hardware/software systems to monitor and display the individual's HRV patterns in real time. Visual feedback of HRV (either quantitative display or animated challenge games) is provided as participants practice techniques of attention focusing (such as mindfulness), RFB, and induction of a positive emotional state. Acquisition of the skill of self-regulation of HRV coherence takes anywhere from 1 to 6 weekly sessions of about 45 min each. Summaries of the evidence for the efficacy of HRVB in reducing mental and physical symptom burden are available [93–95].

6. Models of autonomic dysregulation and treatment of PTSD

Figure 2 is a model of HRV, orienting, and PTSD. The process begins in the upper left corner of the figure, when a stimulus in the environment is registered A normal OR is initiated in less than a second, and proceeds (blue arrow) to appraisal through cortical processing with an output of cardiac adjustment that depends on the appraisal: stimulus is not further perceived with return to baseline vigilance *or* appraisal of life threat with no escape (immobilization) *or* appraisal of affiliative engagement *or* appraisal of danger with freeze, fight, or flight response. Each of the latter appraisal outcomes is associated with an autonomic state, respectively: return to preregistration baseline, bradycardia modulated by dorsal vagal nucleus, bradycardia modulated by ventral vagus and nucleus ambiguus, cardiac acceleration modulated by withdrawal of rostroventral lateral medulla, and activation of sympathetic nervous system. This process is shown in schematized and highly simplified form in the right upper portion of **Figure 2** (for more detail of the vagal afferent and efferent neural circuits controlling cardiac

function, see [19, 31]; see [96] for a thorough discussion of the centrally key role of the paraventricular nucleus of the hypothalamus in autonomic dysfunction). In the individual with PTSD, however, cortical appraisal is short-circuited (red arrows) with repetitive activation of sympathetic nervous system and freeze of fight/flight. We propose that the beneficial effects of HRVB on PTSD symptoms, including attention bias, occur according to the model shown in **Figure 3**.

Figure 2. Model of HRV, orienting, and PTSD.

Figure 3. Dysregulation of heart rate deceleraton by PTSD and reduction if PTSD symptoms by HRVB.

7. Research

7.1. Completed research on HRVB and PTSD

In our meta-analysis of PTSD and HRV [74], we also examined the effects of treatment of PTSD on various HRV parameters. The first finding was that very few controlled studies examining changes in HRV variables pre- and posttreatment on PTSD have been published [97–100]. However, all of these studies employed some form of HRV biofeedback as the treatment intervention. The study by Lande [98] was excluded because HRV data were not included in the study report. Using conservative random effect modeling for the meta-analysis, a significant increase in RMSSD could be discerned and a decrease in HR was nearly significant (p 1-tailed = 0.08).

Our small-scale controlled study of the co-occurrence of reduction in HRV parameters and sustained attention in Iraq combat veterans with and without PTSD. We [97] tested the effects of HRVB using as outcomes HRV coherence and a small battery of attentional tests patterned on Mirsky's model of attention [101]. Veterans met with an HRVB professional once weekly for 4 weeks for HRVB. HRV coherence was achieved in all participants, and the increase in coherence ratio was significant post-HRVB training. Furthermore, significant improvements were observed as increased digit span backwards and fewer commission errors on continuous performance testing, with a significant interaction of training with PTSD on word list learning that demonstrated combat veterans with PTSD were able to benefit from HRVB to a greater degree than veterans without PTSD.

Based on the findings of that small-scale study, we recently performed a 3-year study of HRV and HRVB in combat veterans with PTSD, funded by the US Department of Defense. Below are some of the key findings from that study which have not been previously published anywhere else. Operation Iraqi Freedom (OIF)/Operation Enduring Freedom (OEF) veterans 21–45 years old with and without PTSD were recruited from our veterans' hospital outpatient population. PTSD+ veterans receiving standard of care for PTSD were assigned to one of two treatment groups: active HRVB training and sham HRVB training. PTSD- veterans served as a baseline control group only and did not receive any HRVB training. The length of training was 6 weekly sessions. A follow-up assessment was made 8 weeks post-training to test for persistence of effects (no HRVB was administered during the 8-week period post-training until follow-up). Pre-training (baseline), post-training, and follow-up PTSD symptom levels were assessed by licensed clinical psychologist raters using the Clinician Administered PTSD Scale (CAPS). Raters were blind to the training assignment groups. The study used DSM-IV-TR criteria, not DSM-5 criteria, because the latter were not in existence at that time. Enrollment was planned for 30 PTSD+ veterans in each of the two HRVB groups (active and sham), and 15–20 PTSD- veterans in the control group; final results included 29 and 32 PTSD+ combat veterans in the active and sham HRVB subgroups, respectively, and 12 PTSD- combat veterans in the control group.

Some of the important findings from this study are summarized here and are being prepared for submission as a research article elsewhere. HRV coherence was quantified as log10 of the

peak LF power, thus the measures of HRV analyzed were SDNN, RMSSD, log10 HF, and log10 peak LF. Nonparametric statistical tests revealed that all four pre-training HRV measures were significantly intercorrelated; overall, SDNN was most strongly correlated to the other three HRV variables, and the largest correlation coefficient with log10 peak LF was SDNN (rho = 0.765, p(1-tailed)<0.001). Pre-training SDNN, RMSSD, and log HF were all significantly lower in the PTSD+ compared to the PTSD- subgroup (Mann-Whitney U, all ps < 0.020); however, SDNN discriminated best between groups with and without PTSD.

Data showing correlations between HRV variables and measures of PTSD in a sample this size have not, to the best of our knowledge, been previously published. When the four pre-training HRV variables were tested for associations with pre-training PTSD, we found that Log10 HF power was most closely correlated with severity of PTSD measured as total CAPS score (p = -0.370, p(1-tailed) = 0.001); HF power is a traditional measure of parasympathetic activity and consistent with the research hypotheses, the correlation between parasympathetic activity (which indicates vagal tone) was negative. Thus, as vagal tone increased, total PTSD severity decreased. Closer examination revealed that the pre-training HRV variables associated differentially with the three pre-training CAPS clusters: intrusive thoughts (e.g., nightmares, daytime memories), avoidance/numbing (e.g., depression, avoidance behaviors), and arousal (e.g., irritability, exaggerated startle). Log10 HF power was also the only HRV variable to significantly correlate with all three clusters (p(1-tailed) < 0.05, all correlations negative). The time-domain HRV variables SDNN and RMSSD were both significantly negatively correlated with the arousal cluster. The intrusive thoughts cluster was negatively correlated with log10 HF power, yet was not correlated with either of the time domain variables. The pre-training coherence indicator, log10 peak LF, did not correlate significantly with CAPS total or any of the clusters, presumably because none of the subjects had received any training at that point in time.

With respect to differences between the active and sham HRVB subgroups, whereas pre-training differences in the two HRVB subgroups were nonsignificant (p = 0.913), the post-training active HRVB active group had significantly higher coherence compared to the Sham group (p = 0.007). This is strong evidence that active HRVB training produced coherence in those veterans who received it.

Active HRVB produced increased HRV SDNN and RMSSD post-training, and reduced PTSD, while sham HRVB produced little or no change. Results showed that the interaction of group (Sham vs HRVB+) x time period of assessment (pre-, post-, follow-up) interaction effect was significant, with clinically significant improvements in PTSD severity in the active HRVB subgroup relative to the sham HRVB subgroup. The mean CAPS score of PTSD+ subgroup receiving active HRVB training improved from 79.4 to 57.3. Within the active HRVB group, the mean PTSD severity did rebound between post-training and follow-up 8 weeks later to 60.8, but this increase was not statistically different from the post-training mean, and at follow-up, the PTSD severity mean was statistically lower and clinically improved relative to the pre-training mean. Within the sham HRVB group, there were no statistical or clinical improvements in the mean PTSD severity score post-training or at follow-up.

7.2. Planned research on HRVB and PTSD: the action cascade

The basic results presented above provide evidence that HRVB reduces formal DSM-IV symptoms, yet there remains a gap in our understanding of stimulus appraisal, attention, and orienting aspects of PTSD. The orienting reflex could facilitate attention and perception toward a stimulus on one hand, whereas it could bias attention away from the percept on the other hand. Our planned research on the autonomic stages of the OR in combat veterans with PTSD uses the action cascade, a software program of our own creation. The action cascade is a computerized test that presents the subject with stimulus trials that produce an experimental analog of the naturalistic stages of orienting and response: Rest, Alert, Vigilance, Orienting and Appraisal, and Response Selection and Output. Each trial lasts about 25 s (**Figure 4**). Heart rate and HRV are recorded continuously and simultaneously with task performance on the action cascade by linking the physiological recorder to the computer stimulus presentation program.
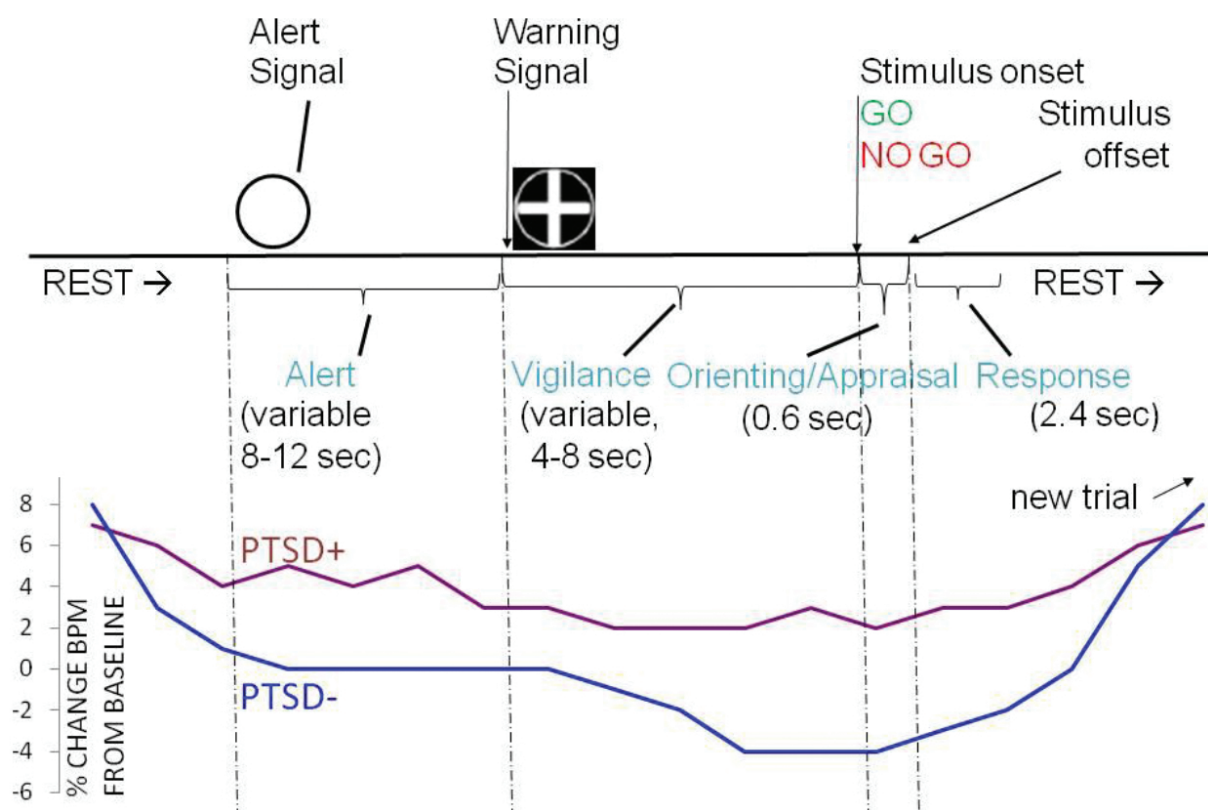

Figure 4. Action cascade: HRV during stages of rest, alert, vigilance, stimulus orienting/appraisal and response.

We have developed HRV Cascade Action Software to measure HRV during the stages of Rest, Alert, Vigilance, Orienting/Appraisal and Response. Durations of the Rest, Alert, and Vigilance stages vary to reduce the anticipatory predictability of the task. The action cascade is a close analog of the defense cascade paradigm, but modified stimulus valence (e.g., pleasant, unpleasant or fear-provoking)—which would provoke emotionally laden ANS responding—to be instead only informational (Go, No Go) and thereby guiding the action of stimulus

appraisal into the cortical (mPFC) portion of the cortico-limbic circuit controlling autonomic cardiac regulation. The action cascade protocol is in preliminary data collection stage at this time. The working hypothesis, illustrated in **Figure 4**, is that cardiac deceleration will be absent or at least attenuated in the PTSD+ subjects pre-training HRVB, and this deficit will be normalized or at least improved post-training HRVB. Results may bridge the gap in understanding the role that ANS dysfunction plays in the adverse effects of PTSD on arousal, attention, and response disinhibition.

8. Summary and conclusions

Our chapter has reviewed evidence underlying the theory that ANS control of cardiac adjustments to environmental stimulation is a central factor in the symptom complex of PTSD. HRV is measured and quantified in terms of power (variance) and the coherence ratio of parasympathetic to total variance in the tachygram. Understanding of vagus nerve as the major control point of responsivity to environmental stimulation, with inputs and outputs affecting emotions, cognition, and behavior, fits into the evolutionary framework that includes the range of response outputs—fight or flight, freezing, tonic immobility, and affiliation. The neurovisceral integration model specifies the neuroanatomical networks of vagal afference and efference which control the rhythm of cardiac acceleration and deceleration. The entire system of ANS-regulated defense cascade is due to the executive ability of prefrontal cortex. Fear is a normal and adaptively healthy aspect of the defense cascade, well-understood and modeled by translational models. Dysregulation of the normal fear response by traumatization deranges the ANS and its control of HRV and subsequent defense cascade. As a result, attentional bias both toward and away from reminders and fear-provoking stimulation occurs. HRVB is theoretically and intuitively beneficial in the restoration of ANS function to adaptive parasympathetic and sympathetic levels. While these complex relations can be heuristically modeled, the reader is cautioned that PTSD is a very heterogeneous and multifactorial disorder and numerous other approaches to modeling and treatment (epigenetic, neuro-inflammatory, cognitive-behavioral, to name a few) are certain to add to our understanding and successful treatment outcomes. Our research provides preliminary evidence that HRVB improves HRV and reduces PTSD symptoms, and we intend to further develop our model with an experimental paradigm.

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