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Integrated cardiovascular and neural system processes as potential mechanisms of behavior change

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Integrated cardiovascular and neural system processes as potential mechanisms of behavior change

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Editorial: Integrated cardiovascular and neural system processes as potential mechanisms of behavior change

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Editorial on the Research Topic
Integrated cardiovascular and neural system processes as potential mechanisms of behavior change

Heart-brain communication drives emotion, thought, and ultimately, behavior. This idea has captured the attention of philosophers, physicians, poets, and physiologists throughout the ages. Recently, there has been an explosion of research highlighting the role of autonomic nervous system regulation, not only in physical health and disease, but also in mental health. As a result of this work, clinical science is increasingly recognizing the value of interventions that address mental health issues at the level of the body as well as the brain (1). Unfortunately, research in this area has remained fragmented, with findings typically disseminated in disorder-specific journals, which diminishes progress in translating promising findings to broadly address mental health problems. Given the global health burden of mental disorders, there is a pressing need to better understand mechanisms of body-brain regulation and develop effective and accessible preventive interventions and treatments, as well as tools to sustain holistic health and recovery.

This Frontiers Special Topic focused on heart-brain interactions that support arousal modulation, emotion regulation, and behavioral flexibility, with a special emphasis on the process of heart rate variability (HRV), its mechanisms of action, and clinical implications of HRV biofeedback and episodic resonance-paced breathing (eRPB; 0.1 Hz/~6 breaths per minute) as mental health intervention tools. We start with a consideration of how the body and brain act as a coherent, adaptive system. Steffen et al. propose an evolutionary model of brain development that highlights the operation of adaptive prediction resulting from interdependent brain networks. Interoceptive and exteroceptive information is used to predict future conditions and needs, and to support optimal adaptation to continuously changing internal and external environments. This aligns with current understanding that

the cardiovascular system and the brain continuously signal one another through the baroreflex loop, and that autonomic, cognitive, and emotional regulation share neural circuitry (2).

HRV as both a biomarker and mechanism

Adult emotional life is profoundly influenced by childhood experience. Childhood trauma is related to increased risk during adulthood for anxiety, depression, substance use disorders, post-traumatic stress disorder (PTSD), and intimate partner violence (3). These disorders often co-occur in adulthood and present with commonalities in emotion dysregulation, changes in neural-circuitry, and diminished cardiovascular regulation. Yet, the mechanisms through which integrated cardiovascular and neural processes affect psychiatric symptomology and emotion regulation remain poorly understood. We addressed this gap both in populations exposed to childhood adversity, and in those that were not. Dale, Kolacz et al. examined the influence of childhood adversity on an index of vagal efficiency and probed direct and mediational relations between childhood maltreatment, anxiety and depression symptoms, and autonomic reactivity to emotional and physical challenges in college students. Their results suggested a potential neural pathway through which early mistreatment shapes cardiovascular regulation and increases risk for anxiety and depression. Kwon et al. examined the link between emotion regulation difficulties, drug use, and resting HRV in young adults. Their study highlighted gender differences that may point to a unique inhibitory-motivational pathway in women who had a history of low-level drug use. Holzhauer et al. explored how stress regulation, stress-induced alcohol craving, and alcohol use in female military veterans may be moderated by progesterone. Increased HRV reactivity to a stress induction predicted higher alcohol craving both in lab and daily assessment. Finally, Fink et al. addressed the mechanisms through which co-occurring behaviors of hazardous alcohol use and intimate partner violence operate. This placebo-controlled, alcohol administration study used an emotion regulation task to investigate respiratory sinus arrythmia in distressed and non-distressed violent partners. Findings suggested that when intoxicated, distressed violent partners may use inefficient emotional regulation strategies when attempting not to respond to provocative partner behavior.

Clinical applications

One benefit of probing integrated cardiovascular and neural processes is the identification of new intervention targets to interrupt negative affective states, inefficient coping, and unhealthy behaviors. The idea of affecting "neuromodulation" through self-initiated manipulations of respiratory rate is elegant in its simplicity and accessibility. Clinical and laboratory-based research empirically supports HRV biofeedback and eRPB to enhance cognitive, emotional and behavioral regulation in conditions including substance use disorders (4, 5), affective disorders (6, 7), and PTSD (8). Taking these interventions to scale involves determining who is most likely to use them and perceive them as useful. For example, eRPB significantly dampened craving as an adjunct to substance use disorder treatment, however, there were individual differences in usage rates and within-person variations in perceived usefulness across time (9). In this Special topic, Price et al. identified parasympathetic dysregulation, time-varying exposures to different affective triggers for substance use, and the presence of an alcohol use disorder as potential matching variables for the use of arousal modulation to diminish craving.

COVID-19 disease can cause depression, anxiety and impair autonomic functions (10, 11). Dale, Cuffe et al.' large scale survey in the US showed that people diagnosed with COVID-19, and particularly medical providers, experienced increased autonomic reactivity that was associated with prior adversities and current mental difficulties. Autonomic reactivity mediated much of the relationship between prior adversity and current mental health difficulties. The authors discussed their findings in the light of polyvagal theory suggesting that mental health difficulties following COVID-19 infection may result from autonomic hyper-reactivity.

A novel exploration of whether singing at the resonance frequency of cardiovascular system confers beneficial acute physiological and psychological effects similar HRV biofeedback and eRPB was addressed by Tanzmeister et al.. They examined the relative effects of breathing at 0.1 Hz, singing at 0.1 Hz, and breathing and singing at spontaneous rates. While resonance-paced singing and breathing showed comparable signatures of increased HRV in the low frequency range, their effects on sympathetic activation starkly diverged. This points to the need for further understanding of different forms of 0.1 Hz stimulation and the nuances of effects achieved *via* HRV biofeedback, yogic breathing, muscle tension, singing, meditation and other practices wherein our understanding of physiological mechanisms lags far behind evidence of health benefits.

Finally, Jha et al. addressed the role of neurocardiac modulation in performance anxiety of elite pianists who wore cardiovascular monitors pre-, during, and post-performance. Results highlighted the importance of arousal modulation prior to and during performance in contributing to "flow state" (sustained focused attention, task engagement, negotiation of challenge). Their results suggest that interventions to modulate arousal pre-performance may be useful to enhance music performance, and have implications for intervening in subjective stress, autonomic arousal, and disrupted behavior associated with other forms of social anxiety.

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REVIEW
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The Brain Is Adaptive Not Triune: How the Brain Responds to Threat, Challenge, and Change

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Theory impacts how research is conducted. A popular theory used to conceptualize brain functioning is the triune brain theory. The triune brain theory is an evolutionary theory of brain development that emphasizes three key brain regions consisting of the brainstem, the limbic system, and the cortex that function relatively independently in coping with stress via fight or flight, emotion, and cognition, respectively. However, modern neuroscience research demonstrates that the triune brain theory does not accurately explain how the brain functions in everyday life or during the stress response. Specifically, emotion and cognition are interdependent and work together, the limbic system is not a purely emotional center nor are there purely emotional circuits in the brain, and the cortex is not a purely cognitive center nor are there purely cognitive circuits in the brain. We propose a new evolutionarily based model, the adaptive brain, that is founded on adaptive prediction resulting from interdependent brain networks using interoception and exteroception to balance current needs, and the interconnections among homeostasis, allostasis, emotion, cognition, and strong social bonds in accomplishing adaptive goals.

Keywords: adaptive, triune, prediction, stress response, brain

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"We do not live to think, but, on the contrary, we think in order that we may succeed in thriving."
—Jose Ortega y Gasset

THE TRIUNE BRAIN: AN OUTDATED, INACCURATE MODEL

Theory impacts how research is conducted. An influential theory used to conceptualize brain function and drive research has been the triune brain theory (1–4). The triune-brain approach to understanding the brain takes an evolutionary perspective about how the brain has developed under environmental pressures and how that development impacts our responses, particularly our responses to stress. Describing the triune-brain theory, MacLean (3) states that:

> The human forebrain evolved to its great size while retaining features of three basic formations that reflect an ancestral relationship to reptiles, early mammals, and recent mammals. The three neural assemblies… are radically different in structure and chemistry, and in an evolutionary sense, countless generations apart. Psychological and behavioral functions depend on the interplay of three quite different mentalities. The three evolutionary formations might be popularly regarded as three interconnected biological computers, each having its own special intelligence, its own subjectivity, its own sense of time and space, and its own memory, motor, and other functions." (p. 264).

From the perspective of the triune-brain theory, these three brain regions evolved separately and function somewhat independently: the basal ganglia and brain stem are involved in movement and

basic life functions, the limbic system is involved in emotional responses that are seen more prominently in mammals as compared to reptiles, and the cortex is involved in cognition and executive functions and is most prominent in humans. In this perspective, evolutionary development begins with basic behavioral responses, then adds emotional responses that can alter these basic responses when threat or challenges arise, and then adds on cognition to alter emotional responses using reason, logic, and planning.

There are several key problems, however, with the triune brain theory. First, the brain did not evolve in successive stages as MacLean hypothesized (5). The idea that vertebrate evolution has consisted of "newer brain structures being superimposed over and on top of 'older' brain structures, tracking development of complex cognition," is not evolutionarily justifiable (6). Basic neural regions are shared among all vertebrates. Where they differ is in proportion and extent. Just as an elephant's trunk is not a new structure superimposed over a snout but rather is an analogous structure differing in proportion (and consequently, in functional adaptation to the animal's needs), the human brain is not superimposed on a reptile brain but consists mostly of proportionally different analogous structures. Furthermore, the gradation of proportional shifts is not necessarily a linear progression from reptile to human (7).

Second, brain structures do not function independently of one another (5). During emotional responses, there is activity in the amygdala and in the limbic system, but there is also activity in cortical areas and in the brainstem (8). Additionally, emotion and cognition are not independent events; rather, they are interrelated functions working in concert. For example, Bush et al. (9) and Shackman et al. (10) both note that emotional responses and cognitive responses in the cingulate cortex are interconnected and not separate as previously believed. Perhaps more importantly, the limbic system is not a purely emotional center in the brain. LeDoux (8) notes that the hippocampus is considered part of the limbic system but that it is not considered an essentially emotional brain region; instead, it is a key area involved in memory, which is more closely associated with cognition. Because of these and similar problems, the term "limbic system" is no longer a commonly used term to describe how the brain functions. "Limbic system" also loses its utility in a clinical setting; because affect is a culmination of a wide range of interrelated processes, including synthesis of internal and external stimuli, arousal, and memory, approach to disorders characterized by affect dysregulation is limited by the triune brain approach. And, finally, the brain does not act by simply responding to a stimulus. Instead, it predicts internal and external needs and adapts accordingly. Incoming stimuli interact with the current state in which the brain is (11).

Third, current neuroscience research findings provide further evidence of the inaccuracy of triune brain theory and open new ways of understanding how the brain responds to stress and adapts to changing internal and external environments. Fear research provides an instructive specific example. There is no fear brain circuit that turns on during a fear response but otherwise lies dormant (8). Brain networks always have some level of activity (12) that affects how they process incoming information (11). What changes is the relative activity of different brain networks, with networks being differentially activated based upon need (13–16). As these findings show, triune-brain theory does not match current research findings and using triune-brain theory as a general theoretical approach can lead to faulty hypothesis creation and poorly developed studies.

A more useful evolutionary theory of how the brain works needs to integrate accurate knowledge of brain structure and function. Adaptation, survival, and reproduction are at the heart of evolutionary theory, and interdependent brain networks have evolved to increase adaptation to be able to survive and reproduce. Further, emerging findings suggest that the brain uses interoceptive and exteroceptive information to predict future conditions and needs to enable optimal adaptation to continuously changing internal and external environments (11–20). Based on better understanding of how the brain works, we propose replacing "triune brain" with a term that better captures current understanding of brain function: the adaptive brain. In this conceptualization, the term adaptive brain emphasizes the interdependence and plasticity of brain regions and the brain's ability to predict and adapt to future needs and conditions. Instead of three relatively independent brain regions, or any number of independent brain regions, brain networks work together interdependently; instead of purely "emotional circuits" or "cognitive circuits," the brain uses interconnected networks to optimize maintenance of the body's internal state, emotion, and cognition to adapt to continuously changing needs (11). The brain's summated approach to these priorities regulates affect, and dysregulation of these interdependent circuits has important implications for psychopathology.

THE ADAPTIVE BRAIN: PREDICTION, BALANCE, AND INTERDEPENDENT BRAIN NETWORKS

The adaptive brain developed out of millions of years of evolutionary pressure. Throughout most of their evolutionary history, humans have existed in hunter-gatherer bands, and the evolutionary pressures experienced occurred in this context. This developmental period has been termed the "Environment of Evolutionary Adaptation" because our current adaptations are a direct result of this experience (21). Some of the most important evolutionary pressures experienced were limited resources and dangerous environmental conditions such as predators and extreme weather, and the brain evolved to predict the most adaptive course of action accounting for limited resources and danger, balancing internal needs and external demands (22, 23).

Allostasis, or stability through change that depends on predicting future needs and conditions (17), emphasizes our ability to anticipate and adapt to diverse environmental forces to balance internal needs and external demands (22, 24). Schulkin and Sterling (23) argue that allostasis is basically brain-centered predictive regulation. The brain is continuously

evaluating our internal and external environments based on previous experience, predicting what is likely to occur, and then determining the best course of action based upon this available data. Allostasis, therefore, is about adapting to changing internal and external environments with the goal of stability even when faced with uncertain circumstances, balancing internal parameters essential for life with the changing world around us. Sterling (25) notes that the goal of allostatic balance is not constancy but fitness under the conditions of natural selection. The goal of all organisms is not constancy but survival to reproduce, and the goal of adaptive regulation is reproductive success. Adaptive balance and regulation result from developmental trajectories designed to optimize successful competition.

Challenges, opportunities, and threats can appear quickly requiring rapid responses. Perhaps the most important adaption that evolved during the Environment of Evolutionary Adaptedness is the brain's ability to simulate and predict potential outcomes in coping with challenge and threat (26–28). Predicting likely outcomes increases speed and efficiency of response and improves the brain's adaptivity. To increase the power of prediction and subsequent adaptivity, the brain works to minimize prediction errors; that is, minimizing the difference between predicted outcomes and actual incoming interoceptive and exteroceptive information. The more the brain can minimize prediction error and accurately predict outcomes for different courses of action, the better it will be at anticipating and adequately responding to challenge and threat efficiently and rapidly, thus increasing adaptation and survival (20, 29, 30). Cutting across previously accepted boundaries of the triune brain, Barrett and Simmons (29) propose a neuroarchitecturally distinct brain interoceptive system consisting of visceromotor cortex in the medial and anterior cingulate cortex, the posterior ventromedial prefrontal cortex, the posterior orbitofrontal cortex, and the anterior insular cortex (31). This interoceptive system transmits information through connections in the amygdala, hypothalamus, ventral striatum, and periaqueductal gray to the spinal cord that predicts needed autonomic, hormonal, and immunologic adjustments. According to Barrett's and Simmons' proposal, the frontal interoceptive center also sends this same information to the mid and posterior insula, which can then determine the prediction error to maintain optimal energy use, or homeostasis (29) or initiate allostasis by ongoing adaptation to changing internal and external environments, including internal energy states (17).

Active inference approaches further emphasize the importance of brain adaptivity. These approaches to understanding brain adaptation incorporate prediction and the importance of minimizing prediction errors but also include investigation of how the brain predicts outcomes of different possible behaviors (32, 33) to minimize prediction errors (34). Paulus et al. argue that "the goal of [active inference] is to generate the most complete model of the world to help guide the most adaptive behavior…" [(35), p. 100].

The importance of prediction and minimization of prediction error in brain function has important implications for brain organization. If the brain is not organized in distinct and functionally independent regions, then how is it organized? The organization of the brain reflects the fact that adaptation and survival depend on effectively balancing and predicting often-conflicting needs. Internal needs (i.e., food) must be balanced with external demands (i.e., not being eaten, fight or flight, as well as everyday stressors). The adaptive brain must be able to respond to stress quickly *and* rationally; depending on the context, speed, including automation of response, may be a greater priority than a careful consideration of several outcomes, or vice versa. Our very survival can depend on our ability to change our current course of action to respond to potentially advantageous or threatening events (14), and virtually all situations require an integration of internal and external needs, speed, and rationality. Indeed, internal needs vs. external demands and automated rapidity vs. slower deliberation form key axes informing behavior, and these axes are reflected anatomically.

Fox et al. (15) argue that the brain is organized in interdependent networks along *interoceptive* and *exteroceptive* axes. To best predict need, the brain integrates interoceptive information, or awareness of internal functioning such as blood pressure and heart rate, with exteroceptive information, or awareness of the external environment. As the predicted needs of the moment demand, the brain can then quickly reorient its attention between internally and externally directed activities. For example, the interoceptive system informs response to hunger, temperature, illness, or serum sodium concentration. Through the exteroceptive system, we know if there is food available (an opportunity) or if a predator is looking at us as food (a threat). If we become aware that food is available through our exteroceptive systems, we can put our energy into obtaining that food to meet an existing or predicted internal need. If a predator threatens to eat us, however, we will deprioritize our need to eat and instead focus our energy into fight or flight. Our ability to respond to, and coordinate, attention to external vs. internal stimuli is crucial to survival.

Even when the brain is not attending to an external stimulus or an externally defined task, the brain's networks are active. Historically, however, neuroimaging research has treated a brain that is not attending to external stimuli or an externally defined task as an inactive brain—a baseline to compare activity against. This view of an inactive, unengaged brain (when it is not directly attending to external stimuli), however, is inaccurate, and ignores the interoceptive axis of network organization. Because information from the interoceptive systems informs our brains of internal states and needs such as serum glucose concentration, heart rate, and inflammatory state (29), internally directed "tasks" are ever-present, and the brain is ever active, predicting needs and allocating resources differentially for externally vs. internally motivated tasks. Further, activity typical of "rest," or—more accurately, typical of internally-directed behavior—features distinct recognized patterns on functional neuroimaging. An example of broad network, coordinating activity across historically distinguished "triune" areas, is the default mode network (DMN). Because "rest" is a sophisticated state of coordinated network activity, rather than the absence of activity, it too has the agility to adapt readily to shifting internal needs, or to rapidly adapt to the sudden presence of external

needs. Were "rest" to simply be an "off" state, there would be little room for adaptation within it. In addition, were interoceptive functions to be handled by relatively isolated, much less relatively primitive, modules, it is difficult to explain the complexity of shifting behaviors addressing interoceptive change and how those behaviors can overlap with, and modify, behaviors addressing exteroceptive conditions.

Periods of coordinated activation of the DMN are instructive about the brain's shifting focus between internally and externally directed behavior. The DMN is often framed as a "task negative" network, in that it is primarily active in the absence of an externally defined task, including during periods of wakeful rest and/or attention toward self-oriented and social cognition. Its activity is associated with the subjective state of mind wandering and is suppressed for goal-directed, externally oriented cognition characterized by activation of "task-positive" networks such as dorsal and ventral attention networks (13). "Task-negative" and "task-positive" terminology, however, fails to fully reflect the coordination of these sets of networks along interoceptive and exteroceptive *axes* rather than linearity. The brain is not a binary toggle switch, interacting with its environments using its attention networks—or not. In reality, DMN functions are never turned off; instead, these functions are carefully enhanced or attenuated depending on need (12). Rather than use a framework that considers only externally directed cognition as "task," the interplay between DMN and attention networks reflects shifts between internal and externally motivated tasks, both of which are important for survival and both of which are subject to evolutionary pressures (36). Changes in DMN and attention-network cooperativity or reciprocity are associated with maladaptation, including affect dysregulation and affective disorders (37, 38).

Major functional nodes of the DMN include the posterior cingulate cortex and precuneus; the medial prefrontal cortex; and the angular gyrus, with dorsal medial and medial temporal subsystems. These subsystems are themselves broad, expanding from dorsal medial prefrontal cortex to the temporoparietal junction (for the dorsal medial subsystem) and from the hippocampus to the posterior inferior parietal lobe (for the medial temporal subsystem).

Interestingly, though patterns of activation across these areas are typical of "task-negative" activity, there is remarkable overlap across nodes with "task-positive" activity. Here, the example of the midcingulo-insular (M-CIN) and Central Executive (CN) networks is particularly instructive. The M-CIN is often known by an alternate, functionally descriptive name—the salience network (SN)—and, indeed, it is involved in perception of and attentional regulation toward salient stimuli. It is essential to social behavior, including communication; but it is also essential to self-awareness, including integrating interoceptive function. Both the DMN and the M-CIN make extensive use of parietal and temperoparietal structures, and the M-CIN may act as a regulatory switchboard between prioritized use of the DMN or the Central Executive Network (CEN), used for high-cognitive load tasks (39).

A network model of brain activity makes clear that brain "areas" neither behave in isolation nor take charge of tasks which are easily circumscribed into distinct roles. If each area of the brain is active according to the priority of its singular role, the brain is limited in sophistication to the number of possible combinations of active areas. Instead, if each area instead has a very broad range of possible contributions, all modified and molded by the areas with which it is constantly interacting, their functional potential is dramatically expanded. Moreover, they are adaptable, recruited in a wide variety of changing circumstances and in turn recruiting other areas, always participating in the networked brain in novel, and changing ways.

The case of medial temporal lobe structures, specifically, illustrates the limitations of a triune model. Under the triune brain model, these structures are considered paleomammalian and to a large extent functionally separable from neomammalian neocortex. In fact, medial temporal-lobe structures are fully integrated into both task-negative and task-positive systems and across functions historically ascribed to "reptilian," "paleomammalian," or "neomammalian" capability. Indeed, the medial temporal lobe structures share with neocortex their scaffolding of glutmatergic neurotransmission, with circuits evolved to be capable of immediate and dramatic long-term potentiation and long-term depression. Involvement of medial temporal-lobe structures communicating with neocortex is a hallmark of the adaptability of networks—at both molecular and cognitive levels.

Internally focused and externally focused networks also enable the brain to operate in different quadrants of speed and reason. Highly predictable situations require less analysis of external factors to efficiently choose a low-risk behavioral strategy. The DMN enables fast, automated responses to routine situations with learned rules (40). Attention and control networks, in contrast, prioritize increased analysis of external cues and enable slow response systems for situations with harder-to-predict outcomes and fewer or no established rules. The adaptive brain's ability to differentially prioritize these strategies is an instructive example of its overall strategy to assess and address changing needs.

Indeed, whether the adaptive brain's allocation of resources favors activity of the DMN, attention networks, or a combination in any given situation reflects its function as a *predictor* of both the internal and external environment, enabling selection of strategies to maintain homeostasis or to initiate allostasis when needed. Accumulating evidence suggests that the brain uses Bayesian statistical principles to predict environmental states and outcomes based on previous information that the brain has received (20, 30). Structures involved in the brain's Bayesian-like prediction are also implicated in integrating, or differentially prioritizing, brain networks and their adaptive strategies. The insular cortex, for example, has several fundamental roles that seem disparate under a triune-brain model but in fact shed important light on the nature of the adaptive brain. Insular cortex is primary interoceptive cortex activating in response to interoceptive and other stimuli such as self-awareness, pain, heartbeat, gastrointestinal distension, is a key predictive center, and far from functioning in isolation acts as a switch plate or integration center for brain networks (41). Unification of interoceptive, predictive, and integrative roles in centralized

control hubs such as the insula enables brain adaptation to changing environmental and internal circumstances and needs to maintain homeostasis and initiate allostasis. In that it might be part of both the executive-control and emotional-salience networks, the insula might be involved with integrating cognition and emotion (41) in its role in adaptivity. In essence, the brain's interoceptive center promotes adaptation to ever changing internal and external environments through prediction and subsequent adjustment.

Information about the past internal and external environments is used to make predictions about what these environments will be like to adapt to changing internal and external environments (29). As Van den Bergh et al. (20) write, "Prediction signals from models in the brain are matched with sensory input, resulting in prediction errors that are fed back to improve the adaptivity of these models when making perceptual inferences and actively navigating the environment [(20), p. 228]." If the brain's predictions are not correct, it orchestrates adjustments to minimize the difference between what it predicts and the ongoing interoceptive and exteroceptive information it receives. This process of making predictions and initiating adjustments to minimize the differences between prediction and the actual information it receives through the interoceptive system involves both granular and agranular cortices (29). The ongoing process of predicting internal states, receiving updated information about internal states, and adjusting to minimize the differences between prediction and current information enables the brain to anticipate and adapt to regulate changing internal environments, such as heart rate, blood pressure, serum electrolyte concentrations, and levels of glucose and carbon dioxide. As Van den Bergh et al. (20) further note, "according to the predictive-processing framework, a basic task of the brain is to construct an adaptive model of the (external and internal) world, although its only source of information to do so is the spatial and temporal patterning of its own internal activity (p. 229)."

As the role of prediction and prediction errors in homeostasis and allostasis suggests, the adaptivity of the brain to changing circumstances can be rapid. For example, in studies of non-human primates, some neurons in the orbitofrontal cortex make predictions about rewards associated with stimuli. A visual stimulus might predict a certain taste, to which a neuron has assigned a value. When the stimulus no longer predicts the reward, that is, when the prediction is in error, neurons rapidly adapt and no longer propagate the error. Remarkably, this adaptation to the altered association between stimulus and reward can occur in as few as 5 s (42), providing the brain with a fast and continually updating prediction strategy that enables rapid adaptation to changing circumstances. Rolls (42) notes that this rapid change in learning associations between a stimulus and its value has important implications for changing behavior when "expected reinforcers are not obtained, in, for example, feeding, emotional, and social situations (p. 62)," an observation emphasizing the importance of prediction and correction of prediction mistakes in adapting to a continually changing environment (26).

In conclusion, successful human evolution results from successful responses to threat and challenge. A core function of the adaptive brain is to manage the stress response when coping with threat and challenge. We increase survival success by adapting to environmental conditions, which include limited and inconsistent resources, competition for those limited resources, and predators. Successful adaptation involves balancing our time and energy between internal needs (e.g., eating to get more energy) and external demands (e.g., flight/flight to cope with predators and competitors). Therefore, successfully competing for limited resources involves acting in a fast and frugal manner. We need to respond quickly in case of an unexpected attack or opportunity. And we need to be frugal with our energy because consistent meals are not guaranteed limiting caloric availability. The brain's focus on minimizing prediction error and enhancing successful responding has developed to help us be fast and frugal.

EMOTION, COGNITION, AND SOCIAL BONDS: THREE SOLUTIONS TO INCREASING ADAPTATION

Three key adaptations that have developed over human evolution to improve prediction and response are quick emotional responses, slower cognitive responses, and seeking others' help to cooperatively respond to the stressor (21, 43–46). As the brain predicts the best available course of adaptive action, it engages these response systems to enable quick, intelligent, and cooperative responses to life threats and challenges. Brain networks work together interdependently to carry out these adaptations, and all three of these responses work together in an integrated, interdependent manner to increase adaptation (47).

Using the strategic vs. tactical response model of Lang et al. (48), where broad strategies refer to approach and avoidance strategies in general and local tactical responses refer to specific actions taken such as freezing versus fleeing when under threat, the three adaptive response systems of emotion, cognition, and social connection represent broad response strategies, and specific tactical responses in any given situation can be many and varied. Lang et al. (48) note that our strategic state "differentially primes or inhibits subsequent behavior" and the interaction of internal and external information over time provide the "background framework for transactions between the organism and its environment (p. 380)." We are always in some state of affect, cognition, and social connectedness, and our current state impacts how we respond to arising threats and challenges (47, 49). If our current affective state is negative, we are more likely to respond in a defensive manner. Our current negative affective state can adversely impact our cognition and increase the likelihood of a defensive response. And if our perception of our current social connectedness is negative, we are more likely to respond in a defensive manner.

Responding Quickly to Stress

Affect is a representation of how we value our current situation, and our affective reactions arise from whatever we are currently focusing on (50). There are many types of situations that all

animals encounter and confront, many different types of threats, challenges, and opportunities that can lead to gain or loss. Clore and Huntsinger (50) argue that affect and emotions are the embodied representations of how we evaluate and value our situation in ways that are adaptive for the species. Russell (49) argues that affect is how we feel at any given point in time, a combination of valence (pleasant to unpleasant) and arousal (low energy to high energy) (49). Lang et al. (48) argue that affect is more than just a current feeling state; rather, it is a broad strategic approach to coping with life in terms of valence and arousal.

Affect is impacted by the activation of neural circuits that evolved to ensure survival (44, 49). These "motive circuits" or "survival circuits" evolved to address the key needs of avoiding what is dangerous and approaching what is beneficial. Our motivation arises from these circuits, and motivational arousal is the foundation of emotion. Dangerous situations elicit unpleasant affect and beneficial situations elicit pleasant affect, and people usually choose behaviors that increase pleasurable outcomes and decrease unpleasant outcomes. Therefore, our decisions involve predictions of future affect (51). That is, our choices are guided by the expected impact they will have on our affective state. In a sense, "positive and negative affect serve as 'go' and 'stop' signals" [(52), p. 80] for our current decision making.

Our affective arousal results from the intensity of the motivational need that is determined by the degree of danger or benefit (44). Whereas, emotions come and go, we are always in some state of affect. Our core affect results from the integrated awareness of our internal and external worlds, the integration of interoceptive and exteroceptive information (43). Our current affect is like a "'neurophysiological barometer' of our relationship of our internal and external environments at a given point in time." [(43), p. 5].

Emotions, according to LeDoux (8) and Barrett (11), are not what most people think they are. Rather than having dedicated emotion circuits, such as a "fear circuit," emotions are constructed from what LeDoux (8) calls "survival circuits" [see also (44)]. Survival circuits are wired to address basic life needs such as nutrient and fluid regulation, thermoregulation, and defense against harm. LeDoux and Damasio (53) argue that emotions are integrated physiological responses occurring to meet a significant challenge, whereas feelings are the conscious awareness of these physiological responses. From an adaptation perspective, emotions are fast response patterns that allow us to meet a threat or challenge in minimal time, representing an integrated brain response to meet a specific need. There is no "fear circuit" lying dormant in the brain until a threat appears. Rather, interdependent brain networks respond in an integrated manner to meet a basic need, and we experience this as feeling (11).

Responding Intelligently to Stress

When coping with current stressors, it is adaptive to remember past challenging or threatening events that might be like the current situation. Cognition is about gaining, representing, and using knowledge. Hagen and Symons (54) argue that the cognitive mechanisms we have today are evolved adaptations that allow us to solve life challenges. In terms of successful adaptation, cognition is about remembering past events and experiences and then using that knowledge to effectively cope with current environmental challenges. In this sense, cognition is basically about problem solving using existing knowledge to adapt more successfully. With cognition, we imagine possible future events and then plan for possible courses of action to cope more effectively with those possibilities.

Cognition works with emotion in meeting needs. Cognition integrates with emotional responses by including knowledge and experience from previous encounters with similar situations. In terms of brain networks, Raichle (12) compares emotion and cognition to Kahneman's ideas of thinking fast and thinking slow, having quick immediate responses and slower thought-out responses. Cognition and emotion are not independent or conflicting responses; instead, they work together toward the same goals (47). Affect impacts decisions through personal values impacting current mental content (50). Positive and negative affect contribute positive or negative value to whatever might be in the mind at the time. Being happy or sad influences the content and focus of thought, with positive affect validating and negative affect invalidating cognitions (50). Our judgments reflect our current affect, with our core affect resulting from the integration of interoceptive and exteroceptive information (43). Therefore, all our mental states are inseparably interconnected with affective content.

Barrett and Bliss-Moreau (43) note that much of the core affective circuitry of the brain was until recently considered cognitive circuitry. Brain networks integrate exteroceptive and interoceptive information to create an integrated representation of our world now. This integration is like a large-scale neural reference space that presents a neural map of our external and internal worlds built on available sensory information (43). This map is then used to predict best courses of action. Barrett and Bliss-Moreau (43) argue that this core affect neural reference space contains two functional networks: one a sensory integration network that is dependent on values and experience and how current environments might impact homeostasis, and the other a visceromotor network that guides responses via autonomic and endocrine functioning.

Responding Cooperatively to Stress

Finally, strength in social bonds and being able to work with others increases adaptation. Strong social bonds are a key adaptation that developed during the Environment of Evolutionary Adaptation (21). An important problem that early humans likely faced in surviving and reproducing was establishing cooperative relationships (55). Successful human groups were those that most effectively established these cooperative relationships. Being a member of a group can serve many adaptive functions. Evolutionarily, achieving acceptance and status led to better protection, food, and mates, and helping others increases inclusive fitness, with research showing a strong gradient of helping others based on degree of genetic relatedness (55). Interestingly, modern personality theory emphasizes that social acceptance and social status are key foundational principles in personality (56). We all have a desire to "get along and get ahead" (57). We have evolved psychological mechanisms to avoid

being excluded, and the need to belong continues to be a central human motive today (58).

Emotions, cognitions, and strong social bonds have evolved together to maximize the stress response and adaptation. LeDoux and Damasio (53) state that "unconscious emotional states are automatic signals of danger and advantage, whereas conscious feelings, by recruiting cognitive abilities, give us greater adaptability in responding to dangerous and advantageous situations. Indeed, both emotions and feelings also play a major role in social behavior, including the formation of moral judgments and the framing of economic decisions" (p. 1,092). Emotions, cognitions, and strong social bonds are not in competition with each other; in contrast, these adaptations work together to maximize how we cope with stress. Without these adaptations, it is unlikely we would be where we are today.

THE ADAPTIVE BRAIN: APPLICATIONS AND IMPLICATIONS

The brain's organization based on functionally interdependent networks, integration of interoception and exteroception, social bonds, and prediction and minimization of prediction errors indicate that a primary function of the brain is adaptation to internal and external environments in a continual process to maintain homeostasis and implement allostasis as needed. Conceptualizing the brain as an entity one of whose main functions is adaptation has both theoretical and clinical implications.

Theoretical Implications

Viewing the brain as an extraordinarily integrated and adaptive organ implies that investigating a particular brain region in isolation is insufficient to understand how the brain works. While knowing structure and volume of individual brain regions in both health and diseases is critical, it is no longer enough. Rather, knowing how individual structures are connected anatomically and functionally to other brain regions and networks is required, as is knowing the myriad of different configurations brain networks can take in response to incoming internal and external information and in adapting to predicted needs (11). Further, the adaptive brain's integration of interoception, exteroception, emotion, networks such as the DMN suggests that homeostatic and allostatic mechanisms and emotion require integration and inclusion into current models of understanding brain function in both health and disease.

Findings showing that the brain is highly adaptive provide for new theoretical and research models that consider interdependent brain networks, prediction, minimization of prediction errors, and active inference. Evidence implicating the insular cortex, the cingulate cortex, and other frontal regions as elements of interdependent brain regions in integrating interoceptive and exteroceptive input and providing predictions of future homeostatic and allostatic needs illuminates these brain regions and their connections as important regions of interest in functional imaging studies, albeit in relationship to other regions and brain circuits. And, finally, the integration of internal and external information from exteroceptive and interoceptive nerves and regions with predictions and adaptations in the brain and adaptive integration between incoming and outgoing information in some ways might make distinctions between the peripheral nervous system and the central nervous system obsolete (11).

Because a key aspect of the brain is interdependence across multiple networks to optimize adaption to changing internal and external environments, it is important to consider factors that can decrease the brain's adaptability and how a decrease in adaptivity might affect brain function. Anything that impairs the brain's ability to adapt can become critical in understanding putative reasons for impaired adaptability, including conditions such as mental illness (59). For example, among the other adverse effects of chronic stress exposure is the reduced ability to adapt to stress, resulting in a cycle in which stress impedes an animal's ability to appropriately respond to stress (60).

An important implication, therefore, of focusing on the brain's ability to adapt to stress and to adapt to and to predict continuously changing external and internal states is that when the brain's adaptive and predictive systems are not functioning properly, disease states could result (61). Genetic, epigenetic, environmental, and stochastic insults to the frontal, cingulate, and insular interoceptive systems and their output connections that predict and adjust autonomic, hormonal, and immunologic needs and responses, respectively, have the potential to result in disease. Barrett and Simmons (29) argue that improper function of these brain regions interferes with the regulation of the hypothalamic-pituitary-adrenal axis and can lead to depression and to a proinflammatory state. The frontal interoceptive system and the insula enable brain adaptation to changing environmental and internal circumstances and needs to maintain homeostasis and to initiate allostasis. In essence, the brain interoceptive center promotes adaption to ever changing internal and external circumstances through prediction and subsequent adaptation. Impaired adaptive function in these brain regions, therefore, could result in disease, and inadequate active inference could result in mental illness such as panic and depressive disorders (35).

Behavioral dispositional negativity is a condition that appears to be a vulnerability factor for a variety of psychopathological conditions (20). Both genetic and environmental factors appear to be associated with the development of dispositional negativity, and dispositional negativity appears associated with abnormal function in several brain regions, including the insula, amygdala, mid-cingulate, and orbitofrontal cortex, brain regions that overlap with networks involved with prediction and adaptation. Possibly developing as initially adaptive processing after multiple threats, dispositional negativity appears to be associated with truncating input to the brain and interference with error-prediction reduction, ultimately resulting in worse error prediction. While the truncation of error processing might be adaptive initially in that it makes the environment seem more predictable, it becomes maladaptive in the long term as worsening prediction errors impede brain adaptability (20). Accordingly, factors that affect brain regions involved in prediction error have the potential to result in some types of

psychopathologies such as depression, anxiety (20, 29), fatigue, and autism-spectrum disorders (30).

In addition to associations between dispositional negativity and psychopathology, abnormal functioning in brain regions such as the insula that are involved in prediction and rapid adaptation to continually changing internal states is implicated in the pathogenesis of several anxiety disorders, as well as with obsessive-compulsive disorder. Interceptive information via the glossopharyngeal and vagal nerves reaches the insula and other regions and networks that are involved in interoception. Abnormal function in these regions including the insula appear have been associated with some anxiety disorders and with obsessive compulsive disorder (62). Given the associations between abnormal function in the insula and other regions with some anxiety disorders and with obsessive-compulsive disorder (62) and findings showing the involvement of the insula with error prediction and minimization in influencing rapid adaptation to changing environments (29), it is plausible that abnormal function in adaptation vis-a-vi error prediction is directly associated with some anxiety and obsessive-compulsive disorders, although much additional work is required to identify the brain networks involved with insula function Abnormalities in brain energy function have been associated with autism-spectrum disorders (63), which could be involved with the importance of maintaining and predicting energy needs in the brain in its overall adaptivity (17), implicating dysfunction in the brain adaptivity as possibly associated with some schizophrenia-spectrum and autism-spectrum disorders. Further, functional neuroimaging of individuals with schizophrenia-spectrum, autism-spectrum disorders, and anxiety disorders implicates structural and functional abnormalities of salience networks, disordering how the individual can adapt to changing interoceptive and exteroceptive input, and interfering with the brain's ability to learn functional error prediction algorithms (64). Together, these findings suggest the possibility that dysfunction in brain regions involved in interoception, error prediction, and adaptation affect the pathogenesis of several different types of psychopathologies.

Similar implications arise when considering how malfunction in brain regions involved in error processing possibly might affect function of organ systems in addition to the brain, intimately linking impaired adaptive processing in brain regions involved in interoception, exteroception, prediction, and adaptation to disease in other organ systems. Because brain regions involved in interoception are predicting physiological parameters such as blood glucose concentration, immune states, and heart rate, abnormalities in brain regions involved in interoception and error prediction could be associated with other diseases, such as obesity and diabetes (29). Associations between improperly functioning interoceptive regions such as the insula and related networks provide a common neurological basis to not only some psychiatric disorders but also to some other diseases (29), possibly leading to a novel and more basic understanding of disease and linking psychiatric and medical diseases to dysfunction in the same brain regions and to overall decreased brain adaptiveness.

Both interoceptive and emotional processing with their associated allostatic adaptation appear to rely on predictive coding, wherein the brain including the insula considers previous internal and external conditions in making adaptive changes. Showing how abnormalities in predictive interoceptive and emotional function might be related to other diseases, emotional ability in understanding emotions, interoceptive awareness, and associated activation in the anterior insula were associated with brain white-matter microstructure, providing evidence that abnormalities in adaptation based on faulty predictive coding could result in white-matter disease (65).

Clinical Implications

Given the associations between prediction errors, adaptation, and disease, adaptive brain theory may provide a framework for the understanding and treatment of mental illness (20, 33). Despite significant progress in neuroscience research including information about brain and genetic abnormalities associated with psychiatric disorders and over the last several decades, specifically efforts to advance the prevention and cure of mental illness, little headway has been made (66). Approaching the brain from a triune-brain perspective or similar viewpoints may contribute to hypotheses that are built on inaccurate assumptions about brain functioning. Kozak and Cuthbert (67) note that "there is thus an a priori assumption that the diagnoses refer to real disorders, with ensuing assumptions that they involve a unitary pathophysiology and psychopathology and that the task of a science of disorders is to find the underlying biology of the specific disease entities… [but these] assumptions now [appear] to be false… these approaches have failed to produce significant advances in the understanding or treatment of mental disorders" (p. 287).

To address the disconnection between mental-health diagnoses and neuroscience findings, the NIH initiated a research program, the Research Domain Criteria (RDoC), that uses a dimensional system based upon observable behavior and neurobiological measures, integrating psychology, biology, and neuroscientific findings (66). The key systems under study are negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/modulatory systems. These systems fit well with LeDoux's (8) approach of 'survival circuits' underlying emotional responses, Barrett's (11) constructionist approach to the creation of emotions addressing underlying physiological needs, and Lang's (68) psychophysiological approach to affect and motivation. By combining current neuroscience findings within a broader dimensional framework of mental health, there is potential to improve prevention and treatment of mental illness. Adaptive brain theory builds upon these concepts, providing a theoretically sound framework for understanding mental health and generating effective hypotheses. Research on the neural impact of psychotherapy nicely illustrates how the adaptative brain is malleable and is impacted by treatment for excessive fear and threat responses. For example, MRI studies of patients suffering from panic disorder undergoing CBT show altered brain functioning and decreased fear responses (69, 70). Similarly, CBT for psychosis shows decreased activation

in neural circuits involved in threat responses after successful treatment (71).

CONCLUSION

A primary function of the brain is to make adaptive models (20, 35) of the external and internal environments. Current findings indicate that brain function is based on interdependent networks in contrast to earlier conceptions such as the triune brain in which hypothesized distinct brain centers operated relatively independently of each other. In particular, the brain appears to work by integrating interoceptive and exteroceptive information to make predictions about future metabolic, energy, and other needs while it adapts to continually changing external and internal conditions to maintain homeostasis and to initiate allostasis as needed. As part of this adaptive process, the brain then compares predictions with incoming information and makes adjustment to minimize error prediction further promoting adaptation and health. The brain also might make predictions about potential outcomes from a variety of different possible actions using active inference (33). A triune-brain framework limits understanding of pathophysiology. Conceptualization of the brain's role in adaptation provides new theoretical and clinical insights into brain function in both health and disease. Improper function of brain regions such as the insula and prefrontal cortex and their associated networks leading to impaired adaption and dysregulated affect might be associated with conditions such as depression, anxiety, schizophrenia, and other disease states, possibly indicating an expanded role of the brain in the pathophysiology of disease and providing novel insights into the nature of some diseases as well as potentially identifying and developing new treatment approaches.

AUTHOR CONTRIBUTIONS

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

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Getting Into the Zone: A Pilot Study of Autonomic-Cardiac Modulation and Flow State During Piano Performance

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Background: Music performance anxiety is a common experience among elite and professional musicians and impedes performers from achieving flow state, or a state of focused, sustained engagement that promotes optimal performance.

Objective: The aim of this study was to use heart rate variability (HRV) to determine the psychophysiological underpinnings of optimal music performance.

Methods: We assessed HRV to study how autonomic-cardiac modulation was associated with flow during piano performance. Twenty-two pianists (15–22 years) with at least a Grade 8 Royal Conservatory of Music certification prepared two standardized pieces and a self-selected piece. Performer heart rate data were measured with a Polar 800 watch in 5-min periods immediately before performances, during performances and post-performance. HRV was employed to assess autonomic modulation of cardiac intervals. HRV indices of sympathetic and parasympathetic modulation of the heart were analyzed in 2.5-min segments to monitor short-term autonomic adjustments using the Kubios HRV Software. Flow state was measured using the 36-item Flow State Scale (FSS). Relationships were analyzed using zero-order correlations and multiple linear regressions.

Results: Our sample consisted of 22 RCM Grade 8 certified pianists. Participants achieved the highest level of flow during performance of the Bach piece. Decreased HRV was observed during performance, as indicated by a significant drop in total power. Flow state was positively associated with High Frequency (HF) power during the pre-performance phase, and inversely associated with Low Frequency (LF) power during performance.

Conclusion: Inverse association of flow with LF-HRV during performance affirms the importance of vagal-HR modulation for achievement of flow state. Increased HF-HRV and reduced LF-HRV immediately prior to performance suggests that flow state may

be shaped as much by physiological preparation during pre-performance as it is by physiologic responses during performance. Further research is required to validate the correlation between autonomic modulation of the heart and flow state. Evidence of this correlation between autonomic modulation of the heart and achievement of flow state may pave the way for further research on enhancing musical performance and targeting MPA through HRV-based interventions.

Keywords: flow state, music performance anxiety, heart rate variability, sympathetic nervous system, autonomic-cardiac modulation

INTRODUCTION

Performance anxiety is seen in performative tasks such as public speaking and athletics (1). Music performance anxiety (MPA), colloquially known as "stage fright," is defined as a complex phenomenon involving subjective stress, autonomic arousal, and disrupted behavior upon performing music, usually for an audience, compared to one's baseline state (2). According to the DSM-5, MPA is considered a subtype of social anxiety disorder (3). MPA is a common concern of professional musicians. In a survey of 650 professional musicians, 60% (n = 155) of respondents reported acute symptoms of MPA in anticipation of performances (4). A more recent literature review of 43 studies found that the prevalence of MPA ranged from 16.5 to 60% in diverse musician populations (5). MPA interferes with the performer's ability to achieve flow state, which is a state of focused, sustained attention and engagement in one's task (6), combined with the possession of skills to handle the challenges of the task (7). Flow state constitutes an internal psychological and physiological state associated with the ideal of "peak performance" that performers strive for. To date, the psychophysiological responses that facilitate or maintain flow state are poorly understood.

Non-invasive monitoring of autonomic-heart rate modulation *via* heart rate variability (HRV) analysis may improve our understanding of the physiological underpinnings of MPA and flow state. HRV analysis is a reproducible and accessible non-invasive technique that is widely used to assess sympathetic and parasympathetic modulation of the heart (8).

Marked changes in HRV have been connected to anxiety disorders, and particularly social anxiety disorder (SAD). Multiple studies have shown reduced overall HRV and reduced parasympathetic indicators (9–11). Decreased parasympathetic indicators are associated with increased self-reported symptom severity (10). These findings point toward an association of tonically decreased vagal activity with anxiety disorders.

Several studies have explored heart rates during piano performance. Two studies examining professional musicians' heart rates while performing showed significantly higher heart rates while playing than at rest, as well as significantly higher heart rates during a concert performance than rehearsal (12, 13). Heart rates are also higher while performing higher tempo pieces (14).

Further studies have established a relationship with music and HRV beyond the relationship with heart rate. Firstly, listening to music can affect HRV (15). More specifically, small exploratory studies of HRV during performance have shown a positive relationship between high sympathetic arousal and MPA. A pilot study performed on 11 undergraduate music students showed a shift from high frequency (HF) HRV to low frequency (LF) HRV patterns during high-stress performance, which suggests a shift from parasympathetic to sympathetic modulation of heart rate (16). Similarly, in an observational study that compared rehearsal and competition conditions among 18 pianists, there was increased heart rate and decreased total HRV power during competition, signifying increased sympathetic activity (17).

The physiological manifestation of flow has been assessed with mixed findings. In a study examining flow state in three performance pianists, flow state was positively correlated with HRV markers of sympathetic arousal (18). On the other hand, Harmat et al. observed a pronounced response in HRV indices of parasympathetic activity among three professional pianists during cognitively demanding performances (19). Therefore, while non-invasive monitoring of HRV has provided initial insights into autonomic-cardiac functioning during musical performance, there are limited and conflicting findings regarding the *relationship* between psychological flow and the autonomic-cardiovascular activity in musicians. Further, MPA levels are reported to decrease with pre-performance rituals such as mental rehearsal or meditation (20). This suggests that autonomic activity during the preparatory phase may be as important as during the performance itself in facilitating psychological flow.

The aim of this pilot study was to use non-invasive monitoring of autonomic-cardiac activity and self-reported flow state before, during, and after performance of three separate musical pieces in a group of skilled pianists. We examined the dynamic balance between moderate arousal (reflected by HRV markers of sympathetic modulation and self-reported anxiety levels) and positive valence (reflected by HRV markers of parasympathetic modulation) over the course of performance and their association with self-reported flow state.

MATERIALS AND METHODS

Ethics

This study was approved by the Research Ethics Board of the University of Toronto (protocol number 34638). Participants provided written informed consent.

Inclusion Criteria

We recruited individuals between the ages of 15–22 who had at least a Royal Conservatory of Music (RCM) Grade 8 piano certification, or the minimum amount required to obtain a high school music credit in Canada and apply to a non-piano undergraduate music program. We excluded individuals who reported an acute or chronic medical condition that affects cardio-respiratory function, smokers, and individuals using prescribed medications known to affect cardiac function. Participants were asked to refrain from alcohol and caffeine for at least 12 h prior to their scheduled session.

Music Performance Pieces

Participants were asked to prepare Johann Sebastian Bach's Prelude No. 1 in C Major, Erik Satie's Gymnopedie No. 1, and a piece of their choice 2 weeks in advance. Bach's Prelude No. 1 in C Major and Satie's Gymnopedie No. 1 were chosen due to their clear melodic and harmonic structure and popularity in the world of piano repertoire. Slower pieces were chosen (the Bach piece is usually played at 112 bpm and the Satie at 72 bpm) to avoid the faster heart rate from a faster piece confounding autonomic modulation of the heart brought about by psychophysiological changes. Participants selected a preferred piece as we expected that this performance might yield a higher flow state.

Participant Baseline Characteristics

The RCM grading system (which runs from Grades 1–10 with two higher certifications after level 10, deemed levels 11 and 12 for the purpose of this study) determined participants' piano certification. Immediately prior to testing, participants completed the Godin-Shephard leisure time exercise questionnaire (21) and the Hospital Anxiety Depression Survey (HADS) (22). MPA was not explicitly measured as it was not defined as a disease entity. Our focus was the psychophysiological manifestation of flow state rather than that of music performance anxiety.

Heart Rate Variability

Performer electrocardiogram data was measured with a Polar 800 watch (PolarElectro Oy, Kempele, Finland) for 5 min before performances, during performance and for 5 min immediately post-performance. Its lack of interference with performance made it well-suited to explore MPA. The Polar 800 watch is a non-invasive monitoring device that provides continuous R-R interval data from which autonomic modulation of the heart was assessed. Heart rate variability (HRV) was assessed using Kubios HRV Analysis Software (version 3.0.1, Kuopio, Finland) for 5-min intervals at pre-performance, performance, and post-performance. These intervals were analyzed in 2.5-min segments, in order to detect short-term changes in cardiac-autonomic modulation.

Spectral analysis of the R-R interval segments produced power measures which were interpreted as follows: high frequency peak (HF; 0.15–0.4 Hz) representing primarily parasympathetic modulation, low frequency peak (LF; 0.04–0.15 Hz) reflecting both sympathetic and parasympathetic modulation (23). LF and HF power were each calculated in milliseconds^2 (ms^2) and normalized units (nu) (24). The LF/HF ratio was used as a marker of the relative degree of sympathetic-cardiac modulation (24). Total power (milliseconds^2, ms^2) was used as an indicator of the overall variability of the RR intervals.

Flow State

During the final recovery period, performers completed the Flow State Scale (FSS, **Supplementary Appendix**), a 36-statement questionnaire using a 5 point Likert scale (25). This scale was validated against the State-Trait Anxiety Inventory (STAI) (26) and it has been employed in research with MPA (17, 27).

Experimental Procedures

Resting HRV was established by monitoring heart rate over a period of 5-min prior to beginning performance. Each participant performed the three above-noted piano pieces on a grand piano in random order, as specified using random.org. Performers were instructed to loop or cut their playing of each piece to provide a 5-min recording. HRV was measured for a 5-min post-performance recovery period and participants completed one FSS questionnaire for each piece. A 1–2-min rest period was subsequently taken between each piece.

Statistical Analysis

Baseline characteristics and group differences of the sample were evaluated using Pearson's χ^2 and one-way analysis of variance (ANOVA) in SPSS 25.0. Data were screened for potential covariates, such as baseline anxiety and depression (HADS questionnaire) (22) and physical activity levels (Godin-Shephard) (21). Mean flow was calculated from FSS total score compared across the three pieces using paired *t*-tests. *Post-hoc* comparisons were applied using the least significant difference due to the small sample and exploratory nature of this study. We compared the percentage of participants experiencing positive flow between pieces using paired *t*-tests. Positive flow was defined as a mean score above 3.5 by creating a mathematical division of the 5-point scale. As a rating of "3" denotes "neither agree nor disagree" with the statement, an average score above 3.5 would signify overall agreement with positive statements about the performance. We examined short-term changes in HRV using mean values for each 2.5-min segment within the 5-min intervals for pre-performance, performance, and recovery.

We selected the piece with the highest level of flow to allow for the most direct examination of physiological conditions that correlate with flow. Pearson correlations were used to identify any potential correlations between flow and HRV indices, as well as baseline characteristics including age, sex, anxiety, depression, and pre-performance HRV components: heart rate (HR), LF and HF power in absolute values (ms^2), and LF and HF power in normalized units (nu). Normalized HRV measurements were calculated through division of the index (LF or HF) by the short-term frequency bands summated (LF+HF). We examined partial Pearson correlations to determine if HADS scores affected relationships between HRV indices and flow.

Multivariable linear regression was used to examine the independent association between temporal variation in HRV indices across performance intervals and flow. Predictor variables

of interest were absolute and normalized LF and HF. We examined whether mean values differed between the pre-performance and subsequent segments, including the latter half of pre-performance and both performance segments.

RESULTS

Twenty-five participants were enrolled in this study, three of which were excluded from analysis (two due to technical malfunction during data collection and one for extreme HRV values as the result of being an elite athlete). Our final sample size consisted of nine women and thirteen men, ages 15–22 years old (**Table 1**). There were no significant correlations between age or sex and flow or HRV; therefore, we combined all ages and both sexes into a single group.

Table 2 displays the mean flow of participants during the performance pieces and the percentage of participants exhibiting positive flow. Psychological flow during performance of the Bach piece was significantly higher than that observed in Satie, $t(21) = -2.51$, $p = 0.02$. Furthermore, the prevalence of positive flow (≥ 3.5) among performers was greater during the Bach performances as compared to the Satie [91 vs. 64%, respectively; $t(21) = -2.81$, $p = 0.01$] while the difference approached significance for the self-selected piece (Own), $t(21) = -2.02$, $p = 0.057$. Given these findings, the Bach piece was chosen for the remainder of analyses of HRV and flow.

Change in HRV indices from the first 2.5-minute pre-performance interval were observed (**Table 3**). The RR-interval decreased significantly in the second half of pre-performance, $t(21) = 4.484$, $p < 0.001$ and it stayed low throughout performance. Total power decreased significantly from pre-performance 1 to performance onset, $t(21) = 4.742$, $p < 0.001$, while there was no significant change observed between pre-performance 1 to pre-performance 2, $t(21) = 0.878$, $p = 0.39$. $LFms^2$ and $HFms^2$ also both decreased in line with the drop in total power. Lastly, the LF/HF value decreased due to the proportionally smaller drop in $HFms^2$ compared with $LFms^2$ over the course of performance.

Correlations were observed among the autonomic indicators at pre-performance, mean flow during the Bach performance, and HADS anxiety score (**Table 4**). Anxiety was negatively correlated with HFnu and positively correlated with LF/HF ratio. Flow was associated with increased parasympathetic (HFnu) and decreased sympathetic ($LFms^2$) influences in the pre-performance condition. Partial correlations controlling for anxiety presented a similar pattern of results (table available upon request).

Peak flow was accompanied by decreased LF $HRVms^2$ in the pre-performance condition (**Table 5**), and with increased HF HRVnu (**Table 6**) prior to performance. Decreased $LFms^2$ values prior to performance were associated with self-reported flow state (**Table 7**). Examination of the second pre-performance condition showed a statistical trend ($p = 0.1$) for a positive association between $LFms^2$ activity and flow.

TABLE 1 | Background characteristics of sample.

Sociodemographic features	Mean	SD
Female/male	(13/9)	
Age (Years)	20	1.5
RCM[a] Qualification (Range: 8–12)	10	1.2
Anxiety: HADS[b] (Range: 0–21)	9.0	4.2
Depression: HADS (Range: 0–21)	3.3	3.1
Godin Phys total leisure time score (>24 = active, <23 = inactive) (40)	38	28

[a] *RCM: Royal Conservatory of Music.*
[b] *HADS: Hospital Anxiety and Depression Scale.*

DISCUSSION

In this pilot study among elite musicians, we observed that autonomic activity in the pre-performance condition significantly predicted psychological flow during the performance of a pre-selected Bach piece across multiple HRV indices. Peak flow was associated with relatively higher vagal-HR modulation (indicated by HFnu) and lower sympathetic modulation (indicated by LF/HF ratio and $LFms^2$). This suggests that increased vagal heart rate modulation and lower sympathetic arousal prior to performance may be necessary to facilitate flow state during performance.

Flow was highest during the Bach piece compared to the self-selected piece and the Satie piece. This is likely primarily due to the popularity of the piece within common piano repertoire, meaning that the majority of participants can satisfy the "challenge-skill balance" dimension of flow (16).

Heart rate variability and RR interval durations decreased significantly from the pre-performance to the performance segment of participant activity. We interpreted this as participants undergoing vagal withdrawal rather than to increased sympathetic drive during this transition, as heart rates increased above 100 bpm but generally remained below 115 bpm (28). The LF/HF ratio was somewhat discrepant with the above pattern, as it decreased from pre-performance to performance. This finding can be attributed to the differential drops in $LFms^2$ and $HFms^2$ activity; the former decreased by 71% from pre-performance 1 to the beginning of performance while the latter decreased by only 53%.

We observed a significant inverse relationship between flow state and the LF/HF ratio in the pre-performance phase, while observing a trend toward significance for a positive relationship between the LF/HF ratio and flow as well as $LFms^2$ and flow during performance. This trend may indicate that sympathetic activity immediately prior to performance and upon onset of performance is beneficial to facilitate flow. As mentioned previously, Manzano et al. (18) found a positive relationship between the LF/HF ratio and flow during performance. However, it is important to note they measured HRV during the performance condition only. As such, the discrepancy between our study and Manzano's et al.'s study could be attributed to the distinction between pre-performance and performance conditions as well as the difference in demographic features that distinguish professional, adult concert pianists from young adult music students.

TABLE 2 | Mean flow and percentage of participants experiencing positive flow during performance of the three different music pieces.

Piece	Mean flow	Standard deviation	*p*-value[a]	% of sample experiencing positive flow (≥3.5 FSS)	*p*-value[a]
Bach	3.87	0.38		91	
Own	3.80	0.56	0.06	68	0.06
Satie	3.64	0.50	0.02	64	0.01

[a] *P-value denotes paired sample t-test as compared to Bach values.*

TABLE 3 | Selected Heart Rate Variability (HRV) measures during each 2.5-min segment in the pre-performance and performance phases.

Time segment	Pre-performance 1–mean (95% C.I[a])	Pre-performance 2–mean (95% C.I)	*p*-value[b]	Bach 1–mean (95% CI)	*p*-value[b]	Bach 2–mean (95% CI)	*p*-value[b]
Total power (ms^2)	3222 (2212, 4233)	2879 (1757, 4000)	0.39	1148 (871, 1425)	<0.001	1647 (1196, 2099)	<0.01
LF (ms^2)[c]	1558 (827, 2290)	1317 (531, 2103)	0.42	446 (282, 610)	<0.001	605 (351, 859)	<0.01
HF (ms^2)[d]	515 (325, 705)	364 (244, 485)	0.03	242 (164, 319)	<0.01	253 (154, 353)	<0.01
HF (nu)[e]	26.9 (20.6, 33.2)	30.9 (24.1, 37.8)	0.19	38.1 (30.5, 45.8)	0.02	32.9 (26.4, 39.5)	0.04
RR interval (ms)[e]	722 (681, 763)	695 (658, 733)	<0.01	697 (652, 742)	0.06	697 (657, 736)	<0.05
HR Range (bpm)[f]	65–117	66–114		66–130		69–129	
LF/HF ratio[g]	3.90 (2.35–5.44)	3.25 (1.85–4.6)	0.47	2.68 (1.02–4.3)	0.03	3.27 (1.31–5.22)	0.22

[a] *C.I (confidence interval).*
[b] *P-value denotes paired sample t-test from corresponding pre-performance measurement.*
[c] *LF (ms^2): low frequency (millisecond squared).*
[d] *HF (ms^2): high frequency (millisecond squared).*
[e] *nu: normalized units.*
[f] *RR interval: beat-beat interval.*
[g] *HR (bpm): heart rate (beats per minute).*

TABLE 4 | Zero order correlations for the first 2.5-min segments of pre-performance HRV, Anxiety and Flow during Bach performance.

Variable	Mean flow		Baseline HADS anxiety	
	r	Sig (*p* value)	*r*	Sig (*p* value)
Baseline HADS[a] Anxiety	–0.42	0.05	–	–
PP $LFms^2$ [b]	–0.72	<0.0001	0.24	0.29
PP $HFms^2$ [c]	–0.41	0.06	–0.43	0.85
PP HFnu[d]	0.40	0.06	–0.43	<0.05
PP LF/HF[e]	–0.29	0.20	0.44	0.04

[a] ***Baseline*** *HADS: Baseline Hospital Anxiety/Depression Survey.*
[b] *PP $LFms^2$: pre-performance low frequency milliseconds squared.*
[c] *PP $HFms^2$: pre-performance high frequency milliseconds squared.*
[d] *PP HFnu: pre-performance high frequency normalized units.*
[e] *PP LF/HF: pre-performance low frequency/high frequency.*

Our findings are consistent with common verbal descriptions of psychological flow. The idea of getting "in the zone" during pre-performance [i.e., a state of confidence and relaxation (29)] matches the negative association of flow with $LFms^2$ and LF/HF, and its positive association with HFnu in the first half of the pre-performance condition. As the time of performance draws closer, seasoned performers "gear up" their senses to perform and become more physiologically aroused and psychologically alert (30). This state of heightened arousal matches the positive association of $LFms^2$ with flow in the second half of pre-performance.

Importantly, the results of our study suggest there may be preventative potential for interventions to exploit autonomic modulation of the heart in order to train performers to facilitate

TABLE 5 | Independent associations of LF/HF ratio with flow during the Bach performance.

LF/HF ratio				
Variable	**β**	**Std. error**	**95% C.I.[a] (lower, upper)**	**Sig (*p* value)**
(Constant)		0.96	3.90, 4.31	<0.001
Pre-performance1	–0.789	0.042	–0.18, –0.005	0.04
Pre-performance2	–0.173	0.028	–0.08, 0.037	0.43
Bach1	0.547	0.057	–0.060, 0.183	0.30
Bach2	0.166	0.053	–0.096, 0.127	0.77

Dependent variable = Mean flow of Bach performance.
[a]*C.I.: confidence interval.*

TABLE 6 | Independent association of HFnu with flow during the Bach performance in a multivariable linear regression.

HFnu				
Variable	**β**	**Std. error**	**95% C.I.[a] (lower, upper)**	**Sig (*p* value)**
(Constant)		0.244	3.824, 4.520	<0.001
Pre-performance1	0.843	0.009	0.006, 0.044	0.01
Pre-performance2	–0.277	0.007	–0.021, 0.006	0.28
Bach1	0.022	0.006	–0.011, 0.012	0.93
Bach2	–0.474	0.008	–0.029, 0.004	0.13

Adjusted R^2 = 0.164.
[a]*C.I.: confidence interval.*

TABLE 7 | Independent association of LF ms^2 with flow during the Bach performance.

LF ms^2				
Variable	**β**	**Std. error**	**95% C.I.[a] (lower, upper)**	**Sig (*p* value)**
(Constant)	4.081	0.099	3.873, 4.289	<0.001
Pre-performance1	-2.58×10^{-4}	5.7×10^{-5}	-1.37×10^{-4}, 0.379×10^{-4}	<0.001
Pre-performance2	8.24×10^{-5}	4.7×10^{-5}	-1.6×10^{-5}, 1.81×10^{-4}	0.10
Bach1	2.06×10^{-4}	2.2×10^{-4}	-2.62×10^{-4}, 6.74×10^{-4}	0.37
Bach2	1.21×10^{-5}	1.39×10^{-4}	-2.82×10^{-4}, 3.06×10^{-4}	0.93

Adjusted R^2 = 0.609.
[a]*C.I.: confidence interval.*

flow state. HRV is a malleable measure that is also affected by several modulators, including overt behavior and cognitive-affective state (15, 31). As the sympathetic nervous system activity has been broadly connected to anxiety responses (9–11, 32), our findings may be particularly useful for those who suffer from music performance anxiety. Acute physiologic arousal associated with stress and anxiety can be mitigated using relaxation or biofeedback-assisted relaxation under conditions that mimic the performance experience (31). One can learn to increase vagal modulation of the heart to counter the effects of stress (33), which suggests it may be possible to use specific targets of vagal-heart rate modulation during pre-performance or performance to improve one's achievement of flow state. Possible procedures include graduated exposure to stressors or the use of a stress-reactivity paradigm to promote a controlled response to the stress of performance, allowing participants to achieve a focused, calm state under performance conditions (31).

Additionally, our participants were typical of young elite musicians with symptoms of anxiety and depression in line with normative HADS values for students or individuals in the early stages of their career (34). This indicates that the results of this study are likely generalizable to early-career musicians. However, further research is needed to assess the application of our findings to non-elite musicians or seasoned professionals.

Overall, despite the small sample size, our HRV measures during the pre-performance phase showed a significant and independent association with the flow state achieved by participants. However, these measures require replication with a larger sample size to observe the robustness of the association. It is important to acknowledge that the interpretation of HRV has been disputed. While some studies validate its use as an indicator of stress (23) and consider the low and high frequency spectral bandwidths to reflect sympathetic and parasympathetic modulation, respectively (35), others have questioned the ability

of the LF bandwidth to reflect sympathetic activity (36). Nevertheless, HRV has been utilized as a clinically relevant tool that can link behavioral modifications to the ANS (31). Moreover, as we did not take a detailed pharmacological history of each participant, one cannot rule out the potential impact of pharmacotherapy on the results. Lastly, the FSS was filled out retrospectively in this trial, which may have impacted the results and would be an important amendment for future trials.

One important future direction concerns the ecological validity of the study. Participants performed in a school classroom with little to no audience (up to three other people, including the experimenters). The lack of a live audience removes one of the key components of a performance that may trigger anxiety. Future studies could make use of a non-invasive measurement apparatus to observe the association between HRV and flow during live performances, such as the study undertaken by Iñesta et al. (13). The setup is easily transferable to a stage and interferes minimally with performance, making it an ideal measurement tool. Future studies may examine the relationship between brain development and flow state, particularly in the context of young adults and teenagers. Lastly, it would be appropriate to repeat this trial with use of questionnaires tailored to music performance anxiety, such as the Kenny-Music Performance Anxiety Inventory (K-MPAI) (37). This would allow for focus and stratification of changes in individuals with high levels of performance anxiety.

Future research could extend to other possible physiological indicators/modulators of flow state, including blood pressure variability or skeletal muscle activity such as frontalis muscle or temporomandibular muscle activity. For example, Manzano et al. (18) found that flow correlated with increased activation of the major facial muscles needed for smiling when examining flow in three performance pianists. Similarly, Kivikangas's study (38) found that flow negatively correlated with EMG activity in the muscles used in facial expression. Such investigations would allow for multifaceted observations that would help to distinguish physiologic responses that are essential to facilitating psychological flow during performance. Furthermore, use of EEG could provide insights into the neurological correlates of flow state or MPA. Katahira et al. reported that increased frontal theta and frontocentral alpha activity, assessed using EEG, may characterize flow state (39).

CONCLUSION

Our pilot study of monitoring of autonomic-cardiac modulation demonstrated sequential shifts in HRV indices that were associated with the achievement of an increased flow state during musical performance, and specifically in the pre-performance or preparatory period. Our results suggest that a global shift toward vagal modulation and relatively lower sympathetic activity during pre-performance may be a necessary condition to facilitate peak flow. The present results contribute to an improved understanding of psychological flow during performance, as well as possible mechanisms to decrease the impact of MPA. Further research is warranted to explore HRV-based therapies for musicians who are required to perform optimally in recurrent stress-evoking situations such as the performance stage.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon request, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Health Sciences Research Ethics Board, Faculty of Kinesiology and Physical Education, University of Toronto. Written informed consent to participate in this study was provided by participants.

AUTHOR CONTRIBUTIONS

All authors contributed to drafting and revising the manuscript and approved its final version. SJ, RN, ST, and AO were involved in the concept and design of the study. SJ and AO were involved in data collection. SJ, AO, and NS were involved in the systematic search, screening of articles, extraction of data, and the statistical analysis. RN, ST, AO, and NS revised the work critically and provided suggestions for improvement.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.853733/full#supplementary-material

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Singing at 0.1 Hz as a Resonance Frequency Intervention to Reduce Cardiovascular Stress Reactivity?

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Slow breathing at 6 breaths per min (corresponding to ∼ 0.1 Hz) has been found to benefit psychological and physical health. In this study, we aimed to examine if paced singing at 0.1 Hz has beneficial acute effects on physiological function as compared to slow breathing. Participants were randomized to one of four experimental interventions prior to performing a mental stress task: paced breathing at 0.1 Hz (n = 26), paced singing at 0.1 Hz (n = 26), spontaneous breathing (n = 24), or spontaneous singing (n = 25). Heart rate, heart rate variability in the low (LF-HRV) and high frequency (HF-HRV) domain, blood pressure and affective wellbeing were assessed. As expected, both paced breathing and paced singing resulted in elevated LF-HRV. Moreover, both singing groups evidenced increases in heart rate, blood pressure and positive affect, thus indicating elevated sympathetic activation. Breathing and singing at 0.1 Hz had no robust effect on cardiovascular stress reactivity. Findings suggest that paced singing could constitute a promising alternative to slow paced breathing as it increases cardiovascular coherence, although more studies are needed to elucidate whether slow breathing and/or singing could ameliorate acute stress responses.

Keywords: cardiovascular resonance, coherent breathing, heart rate variability, mental stress, resonance breathing

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INTRODUCTION

Breathing at around 6 breaths per min (corresponding to 0.1 Hz) has been found to evoke coherent oscillations in various physiological systems, which has been referred to as resonance frequency meaning maximal coherent oscillations with substantial benefits for bodily function [e.g., (1)]. Of note, slow breathing strongly amplifies the variability of cardiac beat to beat-intervals [so-called heart rate variability, HRV; (2)]. Specifically, the link between heart rate (HR) and breathing is indicated by respiratory sinus arrhythmia (RSA), which describes the phenomenon that causes HR to increase during inhalation and decrease during exhalation, ultimately increasing HRV. During resting conditions, healthy adults exhibit breathing frequencies between 9 and 20 breaths per min, which corresponds to 0.15–0.33 Hz [see e.g., (3)]. A lower breathing frequency causes

RSA to shift from the high frequency (HF = 0.15–0.4 Hz) to the low frequency (LF = 0.04–0.15 Hz) domain (4, 5), which is mainly due to vagal influences (6). Hence, breathing at 0.1 Hz leads to a vagally-mediated increase in spectral power in the LF domain, which has been related to baroreceptor reflex sensitivity [e.g., (7)]. Of note, such a kind of slow breathing has been suggested to benefit health and psychological wellbeing [e.g., (8–10)]. Consequently, a slowed breathing rate has been considered a treatment strategy for stress-related diseases and autonomic nervous system dysfunction (4, 6, 11, 12), depression [e.g., (13)], and anxiety and perceived stress [e.g., (14)].

There are various methods to produce a breathing frequency of 0.1 Hz, like yogic breathing, during which a person inhales for 4 s and exhales for 6 s (15), or diaphragmatic breathing, where the abdomen expands while the chest stays relatively low (1). Other methods involve specific voice-related activity, like reciting the rosary prayer. Bernardi et al. (16), for example, have shown that reciting one cycle of the rosary prayer lasts exactly 10 s (0.1 Hz). In this respect, singing could also be particularly useful to produce the breathing frequency of 0.1 Hz (11, 17). Vickhoff et al. (17), for example, composed a melody which evoked a breathing rhythm of exactly 10 s corresponding to 6 breaths per min. Specifically, participants were instructed to sing according to the repetitive song structure (with a tempo of 48 bpm) of three subsequent half notes and one half-pause (at which participants had time to breathe). Importantly, this song resulted in a clear LF-HRV power increase.

In addition to the beneficial effects of slow breathing, singing (in groups and solo) was found to go along with beneficial physiological effects, such as decreases of cortisol and increases in immune function, thus suggesting lower stress and improved immunocompetence (18–22). Additionally, singing seems to improve feelings of social connectedness, the sense of self and subjective wellbeing (23). This is in line with the finding that positive emotions resulting from singing could mediate the stress-ameliorating effects of singing, while in the absence of those positive emotions the stress-reducing effect of singing appears to be lowered (19, 20). Hence, singing under individually pleasant circumstances could be a useful tool to buffer stress.

It should be noted that, to the authors' knowledge, studies analyzing the effects of 0.1 Hz breathing or singing on acute cardiovascular reactivity to mental stress are limited to date. Previous studies, for example, suggested that slow breathing may dampen the psychophysiological response to anticipated threat (24, 25). Moreover, Whited et al. (26) found that a 0.1 Hz biofeedback training enduring 4–8 weeks had a rather fragile HRV-enhancing effect during stress in the treatment as compared to the control group and Chin and Kales (27) also reported elevated HRV during a mild cognitive stress task as a result of a single 5 min-slow breathing exercise. Finally, Steffen et al. (28) could observe that a single session of 0.1 Hz breathing training resulted in attenuated systolic blood pressure (SBP) to a mental stress task and recovery period. However, most of the previous studies must be considered underpowered and selective with respect to the variables reported (either HRV or blood pressure).

Based on Vickhoff et al.'s (17) findings that singing at 0.1 Hz could have beneficial physiological effects potentially stimulating vagal efference, this study aimed to examine if singing in combination with slow paced breathing is associated with a more adaptive response to stress. Specifically, we hypothesized that, first, singing at 0.1 Hz and breathing at 0.1 Hz would result in an increase in LF-HRV as compared to the spontaneous (unregulated) groups. We also hypothesized that positive affect would increase more substantially in the singing as compared to the breathing groups. Second, since singing as well as paced breathing have been suggested to have salutary organismic effects [e.g., (16, 19, 29, 30)], we hypothesized that the combined effect of singing and slow breathing (i.e., singing at breathing rate of 0.1 Hz) would result in a lower cardiovascular stress reactivity than spontaneous singing or slow breathing alone. In order to evaluate the presumed adaptive effect of singing in combination with slow breathing in more detail, we established four randomized experimental interventions with a respective duration of 5 min: paced singing at 0.1 Hz, paced breathing at 0.1 Hz, spontaneous singing, and spontaneous breathing. The participating experienced singers completed one of the interventions before being faced with a mental stress task.

METHODS

Participants

An a priori power analysis was conducted to calculate the required sample size. According to Steffen et al. (28), we aimed to detect a medium-sized-interaction effect ($f = 0.25$) at a significance level of 0.05 with a power of 0.80. Specifying a two-way ANOVA with the independent factors time of measurement (baseline, intervention, stressor and recovery) and intervention (0.1 Hz breathing, 0.1 Hz singing, spontaneous breathing and spontaneous singing) a sample size of $N = 100$ was required. We recruited 106 participants, of whom three had to be excluded from further analysis due to suspicion of hypertension at baseline measurement (blood pressure > 149/90 mmHg) and two because of excessive artifacts (one for blood pressure artifacts and one for ECG artifacts), which might have distorted the results of the statistical analyses. Thus, the study comprised of 101 healthy amateur singers (79 women, 22 men) aged 18 to 44 ($M = 25.43$, $SD = 6.21$) with a mean waist to hip-ratio of 0.75 ($SD = 0.07$). Participants were recruited from several Styrian choirs, ensembles, music conservatories, music schools and music universities and hence, were either members of an amateur choir, amateur ensemble or singers of an amateur band. Exclusion criteria included professional singers, cardiovascular diseases, diabetes, psychiatric disorders and pregnancy, as these variables could have influenced cardiovascular activity. The research was approved by the local ethics committee (GZ. 39/61/63 ex 2018/2019). Informed consent was obtained from all participants prior to study entry.

Study Design and Experimental Manipulation

Participants were randomly assigned to one of four experimental interventions. In this phase, the experimental task lasted 5 min. For intervention (1) *paced breathing at 0.1 Hz* (PB; $n = 26$), participants were asked to inhale for 4 s and exhale for 6 s

indicated by a time bar, to produce a breathing rhythm of 0.1 Hz. For intervention (2) *paced singing at 0.1 Hz* (PS; $n = 26$), participants were asked to sing a simple, short song in a loop (see, **Figure 1A**). This song structure was based on the song structure that Vickhoff et al. (17) used in their study. The tempo was 48 bpm, which means that two bars lasted exactly 10 s. Thus, when singing three half notes (which equals exhaling) without pause and only breathing at the indicated half pause (which equals inhaling), participants inhaled 4 s and exhaled for 6 s. In (3) *spontaneous breathing* (SB; $n = 24$), participants were listening to an excerpt of the audio book "The Little Prince". During (4) *spontaneous singing* (SS; $n = 25$), participants were asked to sing the melody of the song "Go Down Moses" (tempo: 120 bpm) in a loop (see **Figure 1B**). This song had no fixed breathing pattern. To avoid any influence of verbal information, participants in the PS and SS interventions were asked to sing both melodies without text, but with syllables of their choice (e.g., "do do"). Both PS and SS were accompanied by a previously recorded piano melody. For interventions 1–3 there was a short training period before the actual intervention began, so that participants could become familiar to the breathing rhythm and/or the songs, respectively. Written instructions and acoustic stimuli were delivered *via* computer screen and loudspeakers.

Stress Task

We used the well-established serial subtraction task as a mental challenge [e.g., (31, 32)]. In this task, participants are asked to mentally calculate serial subtractions and report the results at each step to the experimenter (i.e., subtract 13 from 6,233, then subtracting 13 from 6,220 and so on). Participants were not allowed to use any auxiliary means and were instructed to calculate as fast as possible. If they miscalculated, they had to restart from 6,233. To increase stress, participants were told beforehand that they would be filmed during the whole task and that their performance would be evaluated and compared to others. This phase of the experiment lasted 5 min.

Variables and Instruments

Affective State Assessment

Positive and negative affect (PA, NA) were assessed with the German version of the *Positive and Negative Affect Schedule* [PANAS; (33)]. This schedule includes 10 adjectives to describe PA (e.g., happy, active) and 10 for NA (e.g., angry, nervous). Across study phases, reliability (Cronbach's Alpha) for PA ranged between 0.77 and 0.92 and for NA between 0.72 and 0.86, thus suggesting reliable assessment.

Physiological Measurements

Physiological signals were recorded continuously throughout the entire experimental session and task periods were defined using digital triggers. HR was measured by means of an ECG device (AccuSync® 72, Milford, Connecticut, USA) using a modified Einthoven II-point lead. The ECG was recorded using Ambu BlueSensor® electrodes (Ballerup Sogn, Denmark) with a sampling rate of 1,000 Hz. The signal was recorded with the software AcqKnowledge® 4.3 (Biopac Systems Inc., Goleta, California, USA). HR and HRV were analyzed offline with Kubios premium software [vers. 3.2; University of Finland (34)], thereby applying artifact correction if necessary. LF-HRV and HF-HRV as a sensitive indicator of vagally-mediated HRV [e.g., (4, 35)] were analyzed. HRV variables were log-transformed prior to analysis to account for skewness.

Continuous blood pressure (SBP; diastolic blood pressure, DBP) was measured by non-invasive measurement of arterial finger BP using the Finometer® PRO (Finapres Medical Systems, Amsterdam). The signal was recorded using the software BeatScope® Easy (v2.10). After visual inspection, mean SBP and DBP were calculated for each task period for each participant. **Table 1** shows *M* and *SD* for all interventions and all physiological variables.

Procedure

Upon arrival, participants received informational pages on the study and signed informed consent. Afterwards, their height, weight and abdominal circumference were measured. The physiological sensors were attached and participants were randomly assigned to one of the four experimental interventions. Randomization was accomplished by appearence at the laboratory, irrespective of age and sex. Severe unbalance in the course of the study was monitored and resolved if necessary. The physiological assessment started with a 3-min baseline recording, during which participants were shown landscape photographs. Subsequently, they completed the PANAS. Afterwards they underwent one of the four experimental interventions for a period of 5 min, followed by a second PANAS assessment. Then, the mental arithmetic task was conducted followed by a third PANAS assessment. Subsequently, a recovery period of 3 min was implemented. Throughout the whole experiment, HR, SBP and DBP were recorded. **Figure 2** gives an overview of the study procedure.

Statistical Analysis

In order to examine the effects of the intervention, five 2-way mixed analyses of variance (ANOVAs) were calculated for between subjects' data for each of four levels (paced breathing, paced singing, spontaneous breathing and spontaneous singing) and the within subjects' data over time (at baseline and at intervention). Hypotheses regarding stress reactivity were further analyzed *via* 2-way mixed ANOVAs with intervention (4 groups) and time (baseline, stressor and recovery) as factors. HR, LF-HRV, HF-HRV, SBP, and DBP served as the main dependent variables. Moreover, a 4 (intervention) by 3 (baseline, intervention, stress) ANOVA was conducted for PA and NA, respectively, to track differences in affective wellbeing. *Post-hoc* analyses were carried out using Tukey's honest significant difference (HSD) *post-hoc* tests. Two-tailed significance testing was performed at $p < 0.05$. Degrees of freedom were corrected when necessary, using the Greenhouse-Geisser correction.

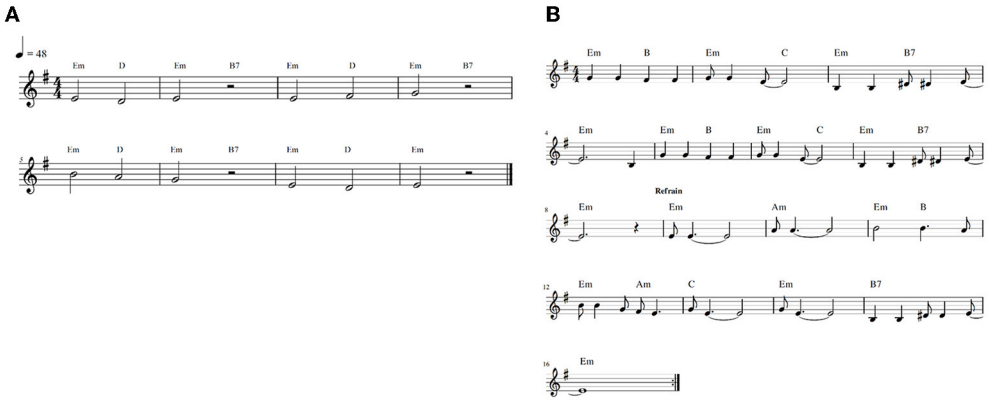

FIGURE 1 | (A) Paced singing melody. **(B)** "Go Down Moses" (spontaneous singing).

RESULTS

Intervention Effects

LF-HRV

Analysis of between-group data reached significance [$F_{(3,97)} = 11.67$, $p < 0.001$, $\eta_p{}^2 = 0.27$], as did within-subject data over time [$F_{(1,97)} = 118.09$, $p < 0.001$, $\eta_p{}^2 = 0.55$], respectively, which however, were further qualified by a significant intervention by time interaction [$F_{(3,97)} = 41.86$, $p < 0.001$, $\eta_p{}^2 = 0.56$], indicating a large effect. Pairwise comparisons showed that LF-HRV increased significantly from baseline to paced singing ($p < 0.001$; Cohen's $d = 1.66$) and paced breathing ($p < 0.001$; Cohen's $d = 2.81$), respectively, with large effect sizes. Conversely, LF-HRV did not change significantly from baseline to both spontaneous singing ($p = 0.595$; Cohen's $d = 0.11$) and spontaneous breathing ($p = 0.600$; Cohen's $d = 0.11$). Furthermore, a Tukey-HSD *post-hoc* test showed that while interventions did not differ significantly from each other during baseline, LF-HRV was significantly higher during intervention in the paced interventions in comparison to the spontaneous interventions ($ps < 0.001$). LF-HRV during paced breathing and paced singing did not differ significantly from each other ($p = 0.099$), while LF-HRV during spontaneous breathing was significantly lower than during spontaneous singing ($p = 0.036$). Results are visualized in **Figure 3A**.

HF-HRV

Analysis of HF-HRV indicated no significant main effects of intervention [$F_{(3,97)} = 0.57$, $p = 0.572$] and time [$F_{(1,97)} = 1.41$, $p = 0.237$], and no significant interaction of time and intervention [$F_{(3,97)} = 0.18$, $p = 0.909$].

HR

Analysis of HR indicated a significant main effect of time [$F_{(1,97)} = 137.52$, $p < 0.001$, $\eta_p{}^2 = 0.59$], but no significant main effect of intervention [$F_{(3,97)} = 1.46$, $p = 0.229$, $\eta_p{}^2 = 0.04$]. However, the main effect of time was further qualified by a significant interaction of time and intervention [$F_{(3,97)} = 25.80$, $p < 0.001$, $\eta_p{}^2 = 0.44$] with a Tukey-HSD *post-hoc* test documenting that HR did not differ significantly between the interventions during baseline. However, during the intervention the spontaneous singing intervention evidenced a higher HR than both the spontaneous breathing intervention ($p = 0.001$) and the paced breathing intervention ($p = 0.003$). Moreover, the paced singing intervention evidenced a higher HR than both the spontaneous breathing intervention ($p = 0.013$) and the paced breathing intervention ($p = 0.041$). Pairwise comparisons revealed that HR significantly increased from baseline to paced singing ($p < 0.001$, $d = 1.23$), spontaneous singing ($p < 0.001$, $d = 1.98$) and paced breathing ($p < 0.001$, $d = 0.97$), respectively, but did not change for spontaneous breathing ($p = 0.307$; $d = 0.10$). Results are displayed in **Figure 3B**.

SBP and DBP

ANOVAs for SBP and DBP revealed significant intrasubject data over time [SBP: $F_{(1,97)} = 72.15$, $p < 0.001$, $\eta_p{}^2 = 0.43$; DBP: $F_{(1,97)} = 139.98$, $p < 0.001$, $\eta_p{}^2 = 0.59$] and between-subjects data for intervention [SBP: $F_{(3,97)} = 5.54$, $p = 0.001$, $\eta_p{}^2 = 0.15$, DBP: $F_{(3,97)} = 7.12$, $p < 0.001$, $\eta_p{}^2 = 0.18$], which however, were further validated by significant interactions of time and intervention for both SBP [$F_{(3,97)} = 28.73$, $p < 0.001$] and DBP [$F_{(3,97)} = 46.46$, $p < 0.001$] with large effect sizes each (SBP: $\eta_p{}^2 = 0.47$; DBP: $\eta_p{}^2 = 0.59$).

As SBP and DBP showed very similar findings, only data for SBP will be reported in the following. A Tukey-HSD *post-hoc* test showed that while SBP did not differ significantly between interventions during baseline, during intervention SBP in both singing interventions was significantly higher than SBP in both breathing interventions (p's ≤ 0.005) as is illustrated in **Figure 3C**. Both breathing interventions and both singing interventions did not differ significantly from each other (breathing interventions: $p = 0.064$, singing interventions: $p = 0.800$). Pairwise comparisons further showed that SBP increased significantly from baseline to paced singing ($p < 0.001$, $d = 1.48$), spontaneous singing ($p < 0.001$, $d = 1.09$) and spontaneous breathing ($p = 0.016$, $d = 0.53$), respectively. Noteworthy, SBP decreased significantly from baseline to paced breathing ($p = 0.023$, $d = 0.47$), indicating a medium-sized effect.

TABLE 1 | Means and standard deviation of all cardiovascular variables for the factors of experimental intervention and time.

		0.1 Hz breathing $n = 26$		0.1 Hz singing $n = 26$		Spontaneous breathing $n = 24$		Spontaneous singing $n = 25$	
		M	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***
SBP (mm/Hg)	Baseline	126.24	9.53	125.14	8.33	128.60	9.31	132.34	12.88
	Intervention	124.31	10.28	140.44	12.55	130.65	9.68	141.29	14.54
	Stressor	148.10	16.16	151.64	14.63	156.53	18.80	149.66	17.99
	Recovery	133.10	13.04	134.19	11.66	139.34	13.16	138.42	15.18
DBP (mm/Hg)	Baseline	74.36	6.55	73.64	6.36	76.51	6.54	77.71	8.32
	Intervention	73.25	6.51	84.07	8.52	77.84	6.80	87.86	8.98
	Stressor	88.84	9.29	91.50	9.71	94.29	10.60	92.05	10.10
	Recovery	79.00	8.63	79.67	7.54	83.01	8.95	83.73	9.07
HR (BPM)	Baseline	72.48	11.58	74.12	9.63	74.78	9.07	73.89	11.56
	Intervention	75.96	10.89	81.51	9.44	74.57	8.85	84.28	9.32
	Stressor	82.32	10.11	89.46	14.56	88.98	11.03	85.28	12.30
	Recovery	71.13	10.06	74.16	9.05	73.62	8.77	71.46	9.72
Log HF-HRV (ms^2)	Baseline	6.67	1.41	6.82	1.16	6.48	1.16	6.77	1.38
	Intervention	6.65	1.31	6.70	0.95	6.26	1.04	6.68	0.77
	Stressor	6.44	1.16	6.15	1.17	6.54	0.66	6.39	0.76
	Recovery	6.55	1.48	6.70	1.09	6.53	1.12	6.80	1.31
Log LF-HRV (ms^2)	Baseline	6.71	1.29	7.04	1.17	6.78	0.94	7.01	0.98
	Intervention	8.95	0.78	8.63	0.73	6.68	0.66	7.11	0.62
	Stressor	7.42	0.81	7.24	0.91	7.48	0.68	7.37	0.46
	Recovery	7.01	1.32	7.11	1.07	6.88	0.86	7.11	0.79

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HF-HRV, high frequency heart rate variability; LF-HRV, low frequency heart rate variability.

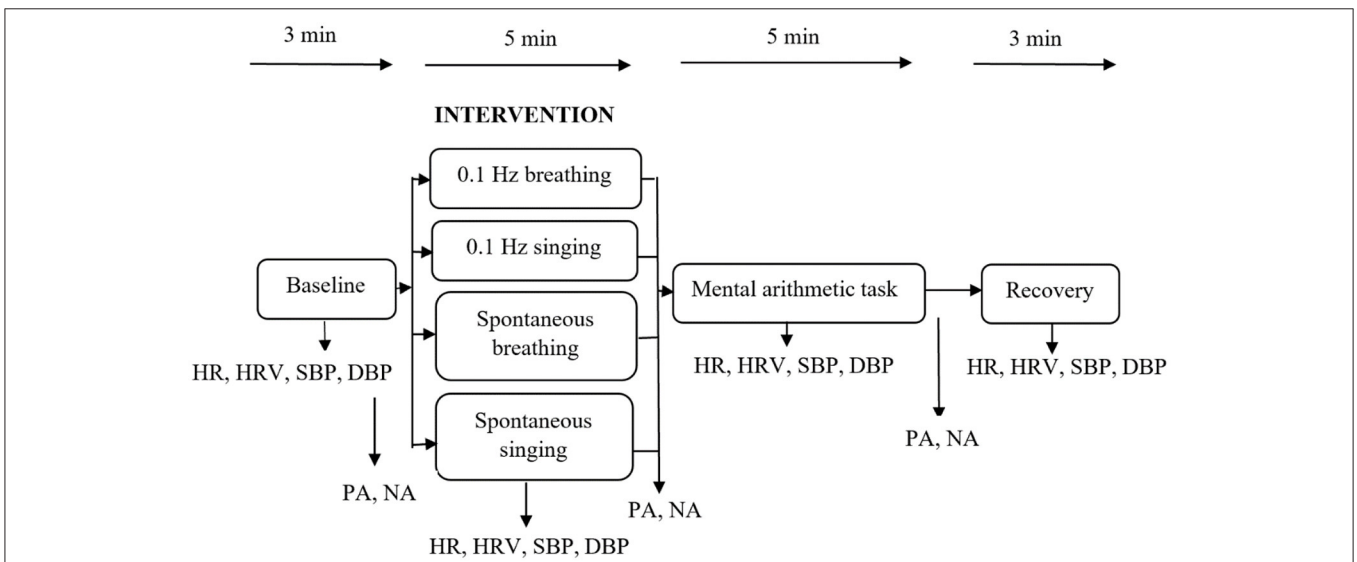

FIGURE 2 | Study procedure and main variables. HR, heart rate; HRV, heart rate variability; SBP, systolic blood pressure; DBP, diastolic blood pressure; PA, positive affect; NA, negative affect.

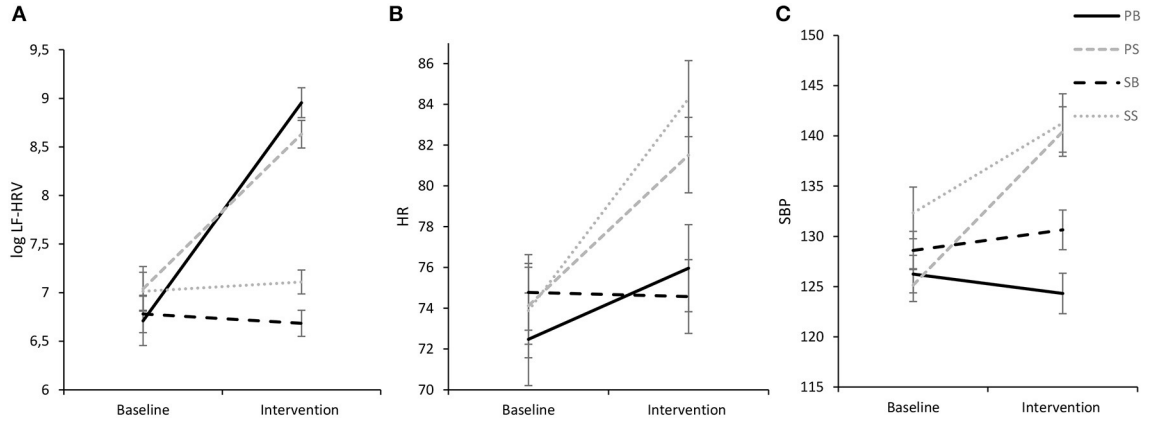

FIGURE 3 | Experimental intervention effects for log LF-HRV **(A)**, HR **(B)**, and SBP **(C)** (M ± 1 SE). log LF-HRV, low-frequency HRV; HR, heart rate; SBP, systolic blood pressure; ln, natural logarithmic transformation. PB, paced breathing at 0.1 Hz; PS, paced singing at 0.1 Hz; SB, spontaneous breathing; SS, spontaneous singing. This figure show elevated LF-HRV for both paced interventions and increases in cardiovascular activity for both singing interventions.

Cardiovascular Stress Reactivity

LF-HRV

Analysis of LF-HRV only revealed a significant intrasubject effect of time [$F_{(1.725,167.369)} = 14.46$, $p < 0.001$, $\eta_p{}^2 = 0.13$] with pairwise comparisons indicating that LF-HRV significantly increased from baseline to the stress task ($p < 0.001$, $d = 0.45$). The reduction of LF-HRV from stress to recovery was also significant ($p < 0.001$, $d = 0.36$). Between-subjects effect of intervention did not reach significance [$F_{(3,97)} = 0.14$, $p = 0.936$, $\eta_p{}^2 = 0.004$] and there was no significant interaction of time and intervention [$F_{(5.176,167.369)} = 1.06$, $p = 0.388$, $\eta_p{}^2 = 0.03$]. Results are visualized in **Figure 4A**.

HF-HRV

For HF-HRV there was a significant intrasubject effect of time [$F_{(1.671,162.065)} = 7.58$, $p < 0.001$, $\eta_p{}^2 = 0.07$], while there was no between-subjects effect of intervention [$F_{(3,97)} = 0.07$, $p = 0.974$] and no intervention by time interaction [$F_{(5.012,162.065)} = 1.92$, $p = 0.093$, $\eta_p{}^2 = 0.06$], although a trend toward a more pronounced vagal withdrawal to stress was evident in the paced singing intervention with a subsequent rebound (**Figure 4B**).

HR

The ANOVA revealed only a significant intrasubject effect of time [$F_{(1.230,119.353)} = 191.73$, $p < 0.001$, $\eta_p{}^2 = 0.66$] with pairwise comparisons showing that HR was significantly higher during the stressor in comparison to baseline ($p < 0.001$, $d = 1.28$) and recovery ($p < 0.001$, $d = 1.59$), respectively. Furthermore, HR was significantly lower during recovery in comparison to baseline ($p = 0.002$, $d = 0.31$). No other effects were significant (see **Figure 4C**). In particular, there was no significant time by intervention interaction [$F_{(3.691,119.353)} = 1.53$, $p = 0.203$, $\eta_p{}^2 = 0.05$].

SBP and DBP

The ANOVA for SBP revealed a significant intrasubject effect of time [$F_{(1.599,155.086)} = 262.02$, $p < 0.001$, $\eta_p{}^2 = 0.73$], which was further qualified by a significant interaction of time and group [$F_{(4.796,155.086)} = 2.74$, $p = 0.023$], indicating a medium effect size ($\eta_p{}^2 = 0.08$). In general, all groups evidenced a stress response with significant increases from baseline to stressor with large effect sizes (all p's < 0.001; PS: $d = 2.50$, PB: $d = 1.89$, SS: $d = 1.15$, SB: $d = 2.06$) and a significant decline from stressor to recovery (PS: $d = 1.96$, PB: $d = 1.81$, SS: $d = 1.25$, SB: $d = 1.57$). In general, recovery values exceeded baseline values with medium to large-sized effects (PS: $d = 1.01$, PB: $d = 0.81$, SS: $d = 0.59$, SB: $d = 1.58$). Of note, the spontaneous singing group showed a significantly lower response than the other groups and particularly the paced singing group [$F_{(1.623,79.546)} = 4.91$, $p = 0.015$, $\eta_p{}^2 = 0.09$], which became evident by decomposing the two-way interaction between time and group. Results are visualized in **Figure 4D**.

For DBP there was a significant intrasubject effect of time [$F_{(1.597,154.873)} = 427.33$, $p < 0.001$, $\eta_p{}^2 = 0.82$] and no significant interaction of time and intervention [$F_{(4.790,154.873)} = 1.87$, $p = 0.106$, $\eta_p{}^2 = 0.06$] as well as no between-subjects effect of intervention [$F_{(3,97)} = 1.58$, $p = 0.199$, $\eta_p{}^2 = 0.05$].

State Affect in the Course of the Experiment

For PA (**Figure 5A**), the ANOVA revealed no significant intrasubject effect of time [$F_{(1.796,174.198)} = 1.23$, $p = 0.291$, $\eta_p{}^2 = 0.01$] and no between-subject effect of intervention [$F_{(3,97)} = 0.85$, $p = 0.470$, $\eta_p{}^2 = 0.03$], respectively, while a significant interaction of time and intervention [$F_{(5.388,174.198)} = 4.77$, $p < 0.001$] indicating a medium effect size ($\eta_p{}^2 = 0.13$) was found. Tukey-HSD *post-hoc* tests further showed that while interventions did not differ during baseline ($p = 0.678$) and stress ($p = 0.849$), respectively, PA was significantly higher following paced singing than both paced breathing ($p = 0.010$) and spontaneous breathing ($p = 0.019$). Likewise, following spontaneous singing, PA was significantly higher than after

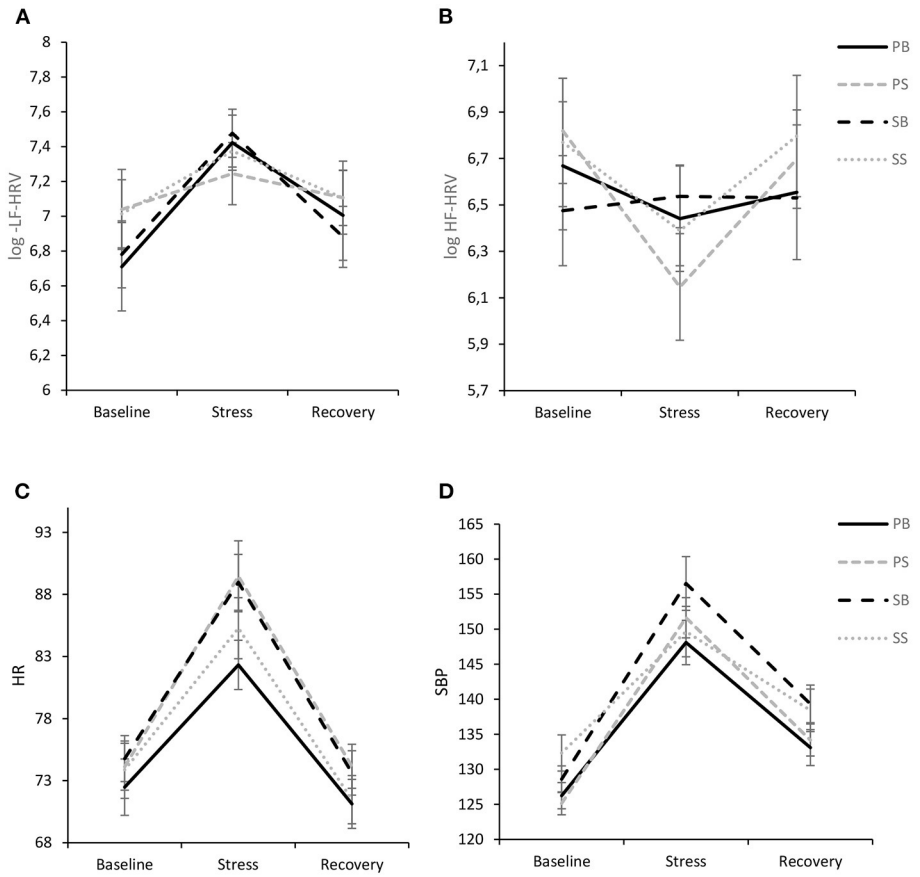

FIGURE 4 | Interaction of experimental intervention and time (M ± 1 SE) for log LF-HRV **(A)**, log HF-HRV **(B)**, HR **(C)**, and SBP **(D)**. PB, paced breathing at 0.1 Hz; PS, paced singing at 0.1 Hz; SB, spontaneous breathing; SS, spontaneous singing. This figure show pronounced cardiovascular stress reactivity, but no differences between interventions.

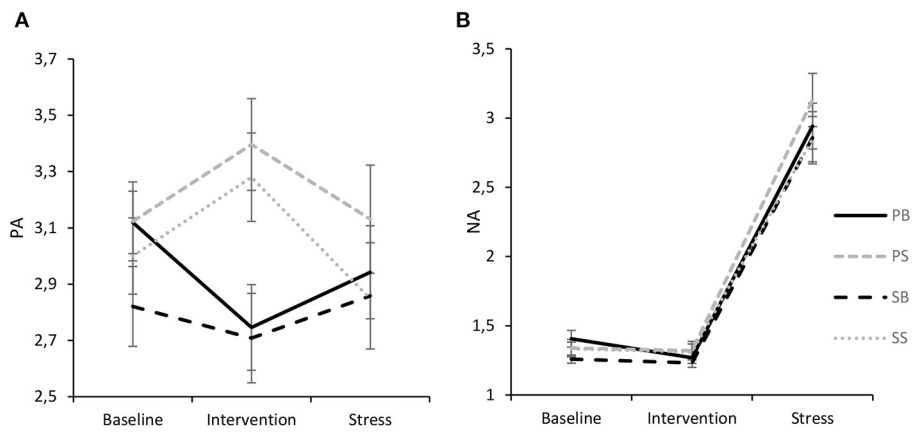

FIGURE 5 | Interaction of experimental intervention and time (M ± 1 SE) for PA **(A)** and NA **(B)**. PB, paced breathing at 0.1 Hz; PS, paced singing at 0.1 Hz; SB, spontaneous breathing; SS, spontaneous singing. It is shown that both singing interventions increased PA, while paced breathing led to a deterioration of PA. NA only evidenced a pronounced stress effect.

spontaneous breathing ($p = 0.027$) and paced breathing ($p = 0.015$), respectively. Pairwise comparisons showed that PA increased significantly from baseline to spontaneous singing, indicating a medium-sized effect ($p = 0.012$, $d = 0.55$). For paced singing, a similar increase could be observed ($p = 0.009$, $d = 0.50$). On the contrary, paced breathing led to a significant

decrease in PA ($p = 0.003$, $d = 0.64$) while spontaneous breathing was not associated with a reliable change from baseline ($p = 0.192$, $d = 0.27$). Moreover, a significant reduction in PA from intervention to stress could be observed for spontaneous singing ($p < 0.001$, $d = 0.79$), while the reduction was not reliable for the other interventions ($ps > 0.05$).

For NA (**Figure 5B**), there was no significant interaction effect of time and intervention [$F_{(3.356,108.495)} = 0.18$, $p = 0.924$, $\eta_p{}^2 = 0.006$] and no significant between-subject effect of intervention [$F_{(3,970)} = 0.74$, $p = 0.529$, $\eta_p{}^2 = 0.02$]. However, a significant intrasubject effect of time [$F_{(1.119,108.495)} = 270.34$, $p < 0.001$, $\eta_p{}^2 = 0.74$] indicated that NA marginally significantly decreased from baseline to intervention ($p = 0.060$, $d = 0.19$) and significantly increased from intervention to stressor ($p < 0.001$, $d = 1.71$). Finally, after the stressor NA was significantly higher than after baseline ($p < 0.001$, $d = 1.67$). It should be noted though that NA levels in general were rather low.

DISCUSSION

The main aim of this study was to investigate the effects of slow singing and breathing at 0.1 Hz on cardiovascular function and to evaluate their respective impact on cardiovascular stress reactivity in a sample of experienced singers. First, it turned out that paced singing at 0.1 Hz resulted in a similar increase in LF-HRV to slow breathing. However, it also provoked comparably stronger increases in SBP, HR and PA, while 0.1 Hz breathing led to a significant decrease of blood pressure. Second and unexpectantly, spontaneous singing resulted in a lower SBP stress reactivity as compared to singing at 0.1 Hz, while there were no reliable intervention differences for the other cardiovascular variables.

Both Paced Singing and Paced Breathing Increased Resonance Frequency

Research suggests that vagal activity during slow breathing (respiratory frequency of 0.1 Hz) can produce RSA oscillations that extend into the LF frequency band of HRV (36). Our findings confirm that singing at 0.1 Hz provoked similar changes in RSA as 0.1 Hz breathing. In particular, while HF-HRV did not change from baseline to intervention, LF-HRV strongly increased with large effect sizes. This pattern of finding generally indicates that the manipulation of breathing produced positive results in both paced interventions, thus suggesting that singing at 0.1 Hz could be considered a similarly powerful tool to evoke resonance frequency and thus, to stimulate baroreceptor function (7). Hence, this finding further supports previous research (11, 16, 17), which suggests that 0.1 Hz singing, humming or chanting mantras that follow a specific musical structure could constitute suitable alternatives to 0.1 Hz breathing for inducing cardiovascular resonance [e.g., (29)]. Other previous research found a similar elevated HRV pattern during slow singing without words, in low pitch and not requiring effort (37).

It should be noted that LF-HRV during 0.1 Hz breathing has been attributed to vagal origin (6), thus suggesting a parasympathetic stimulation. Importantly, while LF-HRV was similarly enhanced in individuals performing paced singing and paced breathing, HR and SBP differentiated between interventions. In particular, singing also induced substantial increases in blood pressure and HR, while 0.1 Hz breathing reduced blood pressure. While the decrease in blood pressure in the latter intervention could indicate the effect of baroreceptor stimulation, the reason for the blood-pressure increasing effect during 0.1 Hz singing could be attributed to enhanced bodily (muscles) activation by producing sounds in comparison to (soundless) breathing. Importantly, Lehrer et al. (7) showed that rhythmic muscle contractions paced at 0.1 Hz resulted in elevated LF-HRV and pronounced SBP oscillations. Of note, the marked increase in both HR and blood pressure in addition to the strong increase in RSA during 0.1 Hz singing might reflect a combined influence of both sympathetic and parasympathetic nerve fibers. In contrast, higher HR and blood pressure during spontaneous singing without alterations in HRV are compatible with the assumption of a stronger sympathetic efference. Although the health effect of a more general activation of both branches of the autonomic nervous system during paced singing remains to be elucidated in future research, it should be noted that it was also associated with higher wellbeing (elevated PA), which may argue for a generally beneficial activation pattern.

No Reliable Acute Effects of 0.1 Hz Singing or Breathing on Cardiovascular Stress Reactivity

Our findings could not confirm a robust ameliorating effect of 0.1 Hz singing or breathing on cardiovascular reactivity to mental stress. Conversely, spontaneous singing led to a lower SBP reactivity as compared to 0.1 Hz singing. It could be speculated that the combination of slow breathing and singing might have increased burden as it may represent a dual task. However, also breathing alone at 0.1 Hz did not result in a reliable modification of the cardiovascular stress response. Hence, this study deviates from previous research suggesting attenuated physiological stress reactivity of 0.1 Hz breathing [e.g., (24–28)]. For example, Whited et al. (26) found evidence for a mild stress buffering role of slow breathing on HRV and Steffen et al. (28) reported attenuated SBP reactivity and recovery resulting from slow breathing. It should be noted though that Steffen et al. (28) used a longer training phase of 15 min, while the individual resonance frequency for each person was determined. Whited et al. (26) even implemented a 5- to 8-week slow (biofeedback) breathing training with 30 min each week. Hence, it could be speculated that the 5-min intervention in the present study (in individuals not previously familiar with this kind of paced breathing) was insufficient to reliably modulate cardiovascular stress responses. It should also be noted that some of the previous studies applied rather mild stress tasks that did either not reliably induce stress responses (28), found reliable effects only for a particular cardiac measure [pNN50; (26)], or examined rather small samples in each intervention seldom exceeding $n = 12$, thus challenging the robustness of the findings [e.g., (24, 25, 27)]. Nonetheless, it could be speculated that the pacing during singing

and breathing could have been problematic in that it might have provoked additional demands on the participants, thus undermining a general stress-relieving effect.

Singing Raises PA

Previous research (20, 21) showed that singing improves wellbeing. We found that singing increased PA for both paced and unpaced singing with medium effect sizes. Noteworthy, PA remained rather the same after spontaneous breathing and even decreased significantly after paced breathing. It must be noted though that while singing resulted in elevated PA, this effect was rather short-lived as PA after the stress task decreased to the same level in all four interventions. However, it should be kept in mind that participants sung for only 5 min and that an increase in PA could be found even after this short time period, although in almost all other studies that explored this effect (19–21), participants engaged in singing for at least half an hour. Importantly, the findings suggest that due to the stimulating effect of singing on PA, combining slow breathing with singing could be beneficial for ensuring participants' compliance during long-term breathing interventions to benefit health.

Limitations of the Study

Although this study provides support for acute coherence enhancing effects of combining 0.1 Hz breathing with singing, some limitations should be discussed. First, in the literature the impact of singing on mood or physiological stress indicators has usually been measured in the context of a rehearsal lasting at least half an hour (21). In the present study, however, individuals sang/breathed for only 5 min, so it may well be that the positive physical and psychological responses usually elicited by singing and/or 0.1 Hz breathing could not have been elicited to the full extent. Future research should thus strive for longer intervention periods and/or a higher dosage. In this respect, there is evidence that professional singers might particularly benefit from the physiological effects of singing [i.e., exhibit a particularly pronounced increase of LF-HRV; (38)], which further suggests that a more extensive singing engagement could prove particularly positive for health. Second, the study sample was quite homogeneous, consisting mainly of academics (ungraduated and graduated students). Moreover, the sample was composed of hobby singers (who may have been very positive about singing), since otherwise random assignment to the interventions would have been impossible or very difficult (possibly imposing a stress induction due to singing for many naïve individuals). Interestingly, Grape et al. (38) could also show that amateur singers were particularly enthusiastic when engaging in singing. Hence, it needs to be evaluated in future research if the beneficial physiological and psychological effects of 0.1 Hz singing and breathing, respectively, can be generalized to individuals without singing experience. Finally, although both sexes were examined, men were underrepresented, thus precluding generalizability of the results.

CONCLUSION

Our study confirms a growing body of scientific research on the immediate positive psychological as well as physiological effects of (slow) singing. Specifically, by analyzing cardiovascular activity and subjective affect throughout the study period, we found that paced singing at 0.1 Hz was associated with a similarly elevated LF-HRV like 0.1 Hz breathing, which is in accordance with studies suggesting vagally stimulating effects of slow breathing, humming or singing. Moreover, higher HR, SBP and PA resulted during both 0.1 Hz singing and free singing, which confirms the activating effect of singing in general. Although it has been suggested that slow paced breathing could counteract cardiovascular disease [such as chronic hypertension (16, 39, 40)] and generally benefit physical and mental health [e.g., (2, 8, 10, 36)], acute effects of a brief intervention on cardiovascular reactivity could not be supported. More studies are certainly needed in order to examine dosage-response effects in more detail.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Graz Local Ethics Committee (GZ. 39/61/63 ex 2018/2019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ST: study conceptualization, manuscript writing, and data analysis. CR: study conceptualization, data parametrization, study implementation, and manuscript writing. BW: study implementation, study realization, and paradigm programming. JMT: data visualization, manuscript writing, and data parametrization. ARS: manuscript writing, study funding, manuscript writing, and statistical analysis. All authors contributed to the article and approved the submitted version.

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Increased Autonomic Reactivity and Mental Health Difficulties in COVID-19 Survivors: Implications for Medical Providers

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Background: Because there is a relationship between mental health (MH) and medical adversity and autonomic dysregulation, we hypothesized that individuals infected with COVID-19 would report greater current autonomic reactivity and more MH difficulties (emotional distress, mindfulness difficulties, and posttraumatic stress). We also hypothesized that individuals diagnosed with COVID-19 who are experiencing difficulties related to their prior adversity and those providing medical care to COVID-19 patients would be more negatively impacted due to their increased stress and infection rates.

Method: US participants (N = 1,638; 61% female; Age M = 46.80) completed online self-report measures of prior adversity, current autonomic reactivity and current MH difficulties, and COVID-19 diagnosis history. Participants diagnosed with COVID-19 (n = 98) were more likely to be younger and providing medical care to COVID-19 patients.

Results: Individuals diagnosed with COVID-19 reported increased current autonomic reactivity, being more negatively impacted by their prior MH/medical adversities, and currently experiencing more MH difficulties with an increased likelihood of clinically-significant PTSD and depression (p <0.01 – p <0.001). Current autonomic reactivity mediated 58.9% to 85.2% of the relationship between prior adversity and current MH difficulties; and COVID-19 diagnosis moderated and enhanced the effect of prior adversity on current autonomic reactivity ($p < 0.01$). Being a medical provider was associated with increased current autonomic reactivity ($p < 0.01$), while moderating and enhancing the relationship between current autonomic reactivity and emotional distress and posttraumatic stress symptoms ($p < 0.05$). Combining COVID-19 diagnosis with being a medical provider increased likelihood of clinically-significant PTSD and depression ($p < 0.01$).

Conclusion: Individuals diagnosed with COVID-19, particularly medical providers, have increased current autonomic reactivity that is associated with their prior adversities and current MH difficulties.

Keywords: COVID-19, autonomic reactivity, adversity, mental health, PTSD, healthcare providers

INTRODUCTION

The outbreak of the COVID-19 pandemic has placed stress on society that relates to worry of being infected, losing access to necessities and medications, financial instability, and social isolation (1, 2). The potential impacts and effects of these stressors may be explained through polyvagal theory (3). Polyvagal theory suggests there is a neurophysiological framework rooted in human phylogenetic heritage for the body to determine whether an environment is safe. Through the process of neuroception, the autonomic nervous system can detect threats outside of conscious awareness. When in danger, the sympathetic nervous system triggers mobilization (fight or flight) or immobilization (freeze) response to disengage from social interaction. Mobilization may manifest into chronic anxiety or irritability, whereas immobilization may lead to death feigning, syncope, dissociation, withdrawal, loss of purpose, social isolation, and depression (2).

Along with societal stressors that may retune the autonomic nervous system to react to a potential threat, there may be a link between COVID-19 diagnosis and autonomic dysregulation that may relate to the body's reorganization to fight the disease. One study found the COVID-19 patients in the acute and chronic phase experienced tachycardia, labile blood pressure, muscular fatigue, and shortness of breath (4). Given that autonomic dysregulation can also contribute to these symptoms, the author called for testing, research, and interventions that target the autonomic nervous system (ANS). Another study found significant differences in autonomic functioning in severe and mild COVID-19 patients compared to the control group, as indicated by their heart rate and blood pressure variability and lower baroreceptor sensitivity which put them at risk for sudden cardiac death (5). Research also suggests that the changes in the autonomic nervous system may persist after the infection has dissipated (6). Amongst COVID-19 survivors, symptoms include orthostatic hypotension, postural tachycardia syndrome, orthostatic intolerance, and sudomotor, gastrointestinal and pupillomotor dysfunction (6). Thus, the COVID-19 infection may alter the functioning of the autonomic nervous system, suggesting a need to look at how the COVID-19 infection, outside of societal stressors, may relate to autonomic reactivity.

In addition to medical consequences associated with the infection, there have been numerous reported mental health effects such as depression, anxiety, insomnia, and executive functioning and psychomotor difficulties, as well as decreased quality of life (7–14). In a study examining brain scans pre and post COVID-19 infection, the virus was found to be associated with a reduction in gray matter thickness in fronto-parietal and temporal regions of the brain as well as significant cognitive decline, which persisted even when only examining mild cases (15). The effects of the COVID-19 infection also include difficulties with thinking, concentrating, and memory, known as brain fog, which is hypothesized to be a result of infection and inflammation of cells of brain vessels (16). Considering autonomic reactivity is an indicator of overall physical and mental wellbeing (17), it is important to take this into account as it may further explain how the COVID-19 infection may relate to MH difficulties.

A particularly vulnerable group to autonomic dysregulation may be those who have experienced prior adversity, as their ANS may be retuned to be more reactive, and thus more sensitive to future threats. One study found that in uninfected participants during the pandemic increased autonomic reactivity mediated the relationship between prior MH adversity and current MH difficulties that were not medically related (1). However, there is a need to go beyond asking about the occurrence of an event, such as emotional abuse, and to focus on the perceived impact of the experience as it may relate to the frequency and severity of the events. This is important as individuals who are more impacted by their adversity history may experience greater alterations in their ANS.

Medical adversity may also impact autonomic regulation. Changes in autonomic functioning are present in fibromyalgia, which is characterized by chronic, widespread pain and symptoms of fatigue and dizziness (18). Autonomic dysregulation among fibromyalgia patients include hyperactivity at rest (associated with cold extremities, irritable bowel syndrome, interstitial cystitis), hypoactivity during stress (associated with persistent fatigue, low blood pressure, dizziness, and faintness), sleep disruption, and postural orthostatic tachycardia syndrome (POTS) (18, 19). POTS, a common abnormality of the autonomic nervous system frequently diagnosed with fibromyalgia, consists of autonomic failures such as dysregulated blood flow and orthostatic tachycardia (19).

One mechanism for autonomic dysregulation may be through the immune system as the level of activity and responsivity of discharges in the sympathetic and parasympathetic nerves is affected by cytokines and other immune factors (20). This connection between the ANS and the immune response is discussed in gut-microbiome homeostasis (21) and in theories behind the etiology of depression that link elevated pro-inflammatory cytokines with major depressive disorder (22).

The interaction between the immune system and ANS is evident in multiple sclerosis (MS), an autoimmune disease involving dysregulation of both sympathetic and parasympathetic systems (23). The parasympathetic nervous system is largely driven by the vagus nerve (10th cranial nerve) activity that interacts with the acetylcholine receptors in the body and is involved in anti-inflammatory pathways and cellular immune function (23). This is important for MS, as the pathophysiology of this disease involves over-activation of immune cells that begin to attack the body's own cells, producing symptoms including but not limited to pain, fatigue, loss of sensation, difficulty swallowing, and depression. When communication between the ANS and immune system is dysregulated, inflammatory responses may influence the progression of MS activity, which may induce or worsen a flair of MS (23). Thus, it may be that ANS dysfunction contributes to MS disease progression, specifically through changes in communication with the immunological system (23). Similarly, individuals impacted by their prior medical adversities who are infected with the COVID-19 virus may exhibit increased autonomic reactivity because

their ANS may be "retuned" to optimize reactivity to threat and consequently experience MH difficulties associated with autonomic dysregulation.

With healthcare providers being the frontline workers during the COVID-19 pandemic, there has been an increasing concern about their mental and physical health. The results of a large systemic review of the literature suggest that medical providers are at risk of reporting MH difficulties such as anxiety, depression, distress, and sleep problems, which may relate to their work demands, COVID-19 exposure, and lack of personal protective equipment (24). A review study found healthcare workers reported these mental health problems in addition to emotional exhaustion, depersonalization, lack of personal accomplishment, and somatic symptoms such as decreased appetite, indigestion, and fatigue (25). COVID-19 work related stressors such as caring for infected patients, witnessing patient deaths, shortages of equipment, and increased professional demands, may also contribute to a decline in their mental health (26, 27). One study found significantly higher rates of anxiety about spreading the virus to loved ones, mental exhaustion, and posttraumatic stress symptoms in healthcare workers placed in the COVID-19 unit compared to healthcare workers in other units (28). Another study found high rates of moral injury in healthcare providers that were related to how much COVID-19 impacted their work life, concerns about COVID-19 protective equipment, and how supported they felt by their administrative leadership (29).

The worries of the medical providers are founded in reality as they have an increased risk of contracting COVID-19 (2,747 cases per 100,000 people) compared to the general population (242 cases per 100,000 people); suggesting the need to look at related outcomes of the diagnosis itself on this population (30). Given the mental health consequences associated with a previous COVID-19 infection in the general population (7–14), one would anticipate similar or more severe outcomes in medical providers. However, little research has been done on how being infected with COVID-19 may influence this population's mental health. One study found that medical workers with a history of a COVID-19 infection had significantly higher prevalence of stress, anxiety, depression, and PTSD compared to medical workers with no COVID-19 infection history (31). Therefore, both the COVID-19 diagnosis and stress that healthcare providers experience may result in increased levels autonomic reactivity that retune their autonomic nervous systems and worsen their mental health.

The current study investigates whether individuals infected with COVID-19 are experiencing higher levels of self-reported current autonomic reactivity and more MH difficulties, and whether their difficulties would relate to their prior MH and medical adversities. Polyvagal theory would suggest that individuals more impacted by their prior adversities would be more vulnerable to and impacted by the COVID-19 virus, and that their COVID-19 infection exacerbating their prior vulnerabilities and leading to more MH difficulties (i.e., emotional distress, mindfulness difficulties, and posttraumatic stress symptoms). Specifically, the increased autonomic reactivity associated with their prior adversity and the COVID-19 infection would be associated with greater negative MH difficulties. Thus, we hypothesized that

- Individuals infected with the COVID-19 virus will report higher levels of current autonomic reactivity and having been more impacted by their prior MH and medical adversities.
- Individuals more impacted by their prior MH and medical adversities will report experiencing higher levels of current autonomic reactivity.
- COVID-19 diagnosis will interact with prior adversity to impact current autonomic reactivity.
- COVID-19 diagnosis will moderate the relationship between prior MH and medical adversity and current MH difficulties, with individuals infected by the COVID-19 virus who are more impacted by their prior adversities reporting more current MH difficulties (i.e., emotional distress, mindfulness difficulties, and PTSD symptoms).
- Increased current autonomic reactivity will mediate the relationship between prior MH and medical adversity and current MH difficulties.

In addition, this study will explore whether medical providers, who are on the frontline of caring for COVID-19 patients and at greater risk of contracting COVID-19, may be more negatively impacted. Specifically, it explores whether they report higher levels of current autonomic reactivity and current MH difficulties, and if their increased current autonomic reactivity relates to their MH difficulties beyond the general population effects reported for COVID-19 diagnosis.

METHOD

Procedure

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. After receiving Institutional Review Board approval, data collection began on March 29, 2020. Data was collected through fall of 2020, which coincides with the first wave of COVID-19 in the United States. The only inclusion/exclusion criteria was that individuals needed to be 18 years or older. Participants were recruited *via* social media postings on Reddit, Twitter, Facebook, Instagram, and email lists. To increase the percentage of male, low income, and non-Caucasian responders in the U.S., additional individuals were recruited *via* Qualtrics Panels and paid according to their compensation plan (e.g., cash, airline miles). On the study landing page, participants read the consent form and decided whether to participate. The survey data underwent quality analysis *via* automated checks.

Constructs and Measures

The survey asked participants whether they have been diagnosed with COVID-19 and if they had experienced physical symptoms related to COVID-19. The latter information was used to eliminate participants from the sample who may have had COVID-19 but did not get an official diagnosis, as data collection

began at a time when testing for COVID-19 was not readily available. Demographic factors, such as their age, gender, racial identity, and education and income level, were additionally collected. Below is a description of the constructs and measures and the analyses assessing internal consistency of the measures *via* Cronbach alpha (α).

Current autonomic reactivity was assessed *via* the Body Perception Questionnaire Short Form (32, 33), a 20-item measure that assesses self-reported experiences of reactivity in organs and tissues regulated by the ANS. The respondent indicates frequency of bodily sensations using a 5-point Likert scale (1 = *never* and 5 = *always*). Higher scores indicate destabilized autonomic reactivity and have been found to relate to lower parasympathetic activity, higher resting heart rate, and less parasympathetic and sympathetic flexibility in response to challenges (Kolacz, Lewis et al., in preparation). This measure has good convergent validity, internal consistency, high test-retest reliability, and consistent factor structure across samples (34–36).

Mental and medical health history represents participant's reported diagnostic history and how impacted they were by their mental and medical health experiences. Two questions asked whether they had a medical diagnosis believed to increase their COVID-19 risk (e.g., heart condition, chronic lung disease, moderate to severe asthma) or had a prior psychiatric diagnosis.

Impact of prior MH and medical adversity was assessed *via* a preliminary version of the Adverse and Traumatic Experiences Scale (1, 37). This instrument asks about prior MH adversity (19 items; $\alpha = 0.86$), which includes caregiver adverse experiences, caregiver maltreatment, non-caregiver maltreatment, life-threatening situations, sudden death of close ones. It also asks about prior medical adversity (6 items; $\alpha = 0.78$), which includes serious chronic health condition (e.g., diabetes), severe asthma attack that did not respond to medication, life-threatening illness (e.g., cancer), life-threatening injury requiring hospitalization, traumatic brain injury, invasive surgery with general anesthesia. For all the items, the participants indicate how impacted they were *via* a 5-point Likert scale (0 = *event did not occur*, 1 = *occurred and no impact on my life*, 2 = *minimal impact on my life*, 3 = *some impact on my life*, and 4 = *big impact on my life*).

Current Mental Health

We focused on measures assessing emotional distress, mindfulness difficulties, and posttraumatic stress symptoms. In addition, two measures were used to determine if the participants scored above the clinical cutoff for PTSD and depression. The specific measures used are described below:

Emotional distress was measured *via* a 12-item instrument designed to assess extent of distress symptomatology listed in the Center for Disease Control Website. The respondent indicated *via* a 5-point Likert scale (0 = *not at all*, 1 = *a little bit*, 2 = *moderately*, 3 = *quite a bit*, and 4 = *extremely*) if they were experiencing signs of distress (e.g., anger/fear, sadness, bothered by things that did not bother them before, everything feels like an effort, feelings of disbelief, and increased substance use). The internally consistent items ($\alpha = 0.92$) were combined to form a total score, with higher scores representing greater emotional distress.

Mindfulness difficulties was measured *via* the Mindful Attention Awareness Scale (38), which includes 15-items that assess dispositional mindfulness, such as open and receptive awareness of what is presently occurring. The respondent rates frequency of everyday experiences *via* a 6-point Likert scale (1 = *almost always*, 2 = *very frequently*, 3 = *somewhat frequently*, 4 = *somewhat infrequently*, 5 = *very infrequently*, and 6 = *almost never*). For the current study, the items were reverse scored so that higher total scores reflect higher levels of mindfulness difficulties. This measure has strong psychometric properties (38) and was found to be internally consistent with the current sample (α =0.90).

Posttraumatic stress symptoms were measured using the PTSD Checklist Civilian Version (39), which is a 17-item self-report measure assessing posttraumatic stress symptoms over the past month related to a traumatic event using a five-point Likert-type scale (0 = *not all*, 1 = *a little bit*, 2 = *moderately*, 3 = *quite a bit*, 4 = *extremely*). This measure has good convergent validity, internal and temporal stability, and test-retest reliability (40), and was found to be internally consistent with the current sample (α =0.96). For the current study, we also focused on the categorization of whether participants scored above or below the clinical cutoff, which is reached by endorsing at least one re-experiencing item, three avoidance items, and two hyperarousal items (41).

Depression was assessed *via* the Patient Health Questionnaire-2 (42, 43), which assesses frequency of depressed mood and anhedonia over the past 2 weeks *via* a 4-point Likert-type scale (0 = *not at all*, 1 = *several days*, 2 = *more than half the days*, and 3 = *nearly every day*). The scores for the two items are summed to determine if the respondent meets clinical cutoff (total score is 3 or greater), which suggests the need for further assessment for depressive disorder.

Statistical Analyses

To assess differences in current autonomic reactivity and prior mental health histories in individuals infected or not infected by COVID-19, ANOVA and chi square analyses compared the groups with regard to their current autonomic reactivity, mental health history (prior diagnosis and impact of MH and medical adversity), and current MH difficulties (emotional distress, mindfulness difficulties, and posttraumatic stress symptoms). To investigate whether individuals more impacted by their prior MH and medical adversities report experiencing higher levels of current autonomic reactivity, linear regression analyses were run. To test the hypothesis that COVID-19 diagnosis interacts with prior adversity to impact current autonomic reactivity, hierarchical linear regression analyses were run. The first model included as predictors the individual and combined impact of prior MH adversity and COVID-19 diagnosis in step 1, and then included medical adversity in step 2 to determine if its inclusion influenced the predictive power of the variables entered in step 1. Similarly, the second model included as predictors the individual and combined impact of prior medical adversity and COVID-19 diagnosis in step 1, and then included MH adversity in step 2 to

determine if its inclusion influenced the predictive power of the variables entered in step 1.

Moderated mediation analyses *via* SPSS Process model 7 explored whether autonomic reactivity mediated the relationship between prior adversity and the current MH difficulties, and whether the relationship between prior adversity and current autonomic reactivity was moderated by COVID-19 infection group status and thus was different for the two groups. The hypothesized moderated mediation model (see **Figure 3**) was tested using a bootstrapping approach in multiple models to assess the significance of the indirect effects at the two levels of the moderator (44). Previous MH and medical adversity were the predictor variables, with current autonomic reactivity as the mediator. The outcome variables were current MH difficulties (i.e., mindfulness difficulties, emotional distress, and posttraumatic stress) and COVID-19 diagnosis was the proposed moderator. Moderated mediation analyses test the conditional indirect effect of a moderating variable (i.e., COVID-19 diagnosis) on the relationship between a predictor (i.e., MH or medical adversity) and an outcome variable (i.e., mindfulness difficulties, emotional distress, or posttraumatic stress) *via* potential mediators (i.e., COVID-19 diagnosis). The "PROCESS" macro, model 7, v2.16 (44) in SPSS version 23 with bias-corrected 95% confidence intervals (n = 10,000) was used to test the whether the indirect (i.e., mediated) effects were mediated by current autonomic reactivity (i.e., conditional indirect effects). This model explicitly tests the moderating effect on the predictor to mediator path (i.e., path a). An index of moderated mediation was used to test the significance of the moderated mediation or the difference of the indirect effects for the COVID-19 diagnosis groups. Significant effects are supported by the absence of zero within the confidence intervals.

To investigate whether medical providers report a higher level of current autonomic reactivity and if their increased autonomic reactivity relates to more MH difficulties, various analyses were run. First, chi square analyses evaluated whether the individuals diagnosed with COVID-19 were more likely to be providing medical care to COVID-19 patients. Next, ANOVA analyses explored the contributions and potential interaction of medical provider role and COVID-19 diagnosis on levels of current autonomic reactivity while considering age. Moderation analyses with age entered as a covariate investigated whether medical provider role moderated that relationship between current autonomic reactivity and emotional distress. Lastly, binary logistic regression analyses examined the contributions of medical provider role and COVID-19 diagnosis in predicting individuals who score above or below the clinical cutoff for PTSD.

RESULTS

Participants

Participants (N = 1,638; 61% female; Age M = 46.80, SD =16.29, range 18–88 years old) were individuals living in the US that either reported no prior diagnosis or physical symptoms related to COVID-19 (n = 1,540) or having been diagnosed with COVID-19 (n = 98) currently (n = 61) or previously (n = 37). We found that 47.1% of the participants previously diagnosed with COVID-19 reported currently having symptoms that could be related to COVID-19, whereas 52.9 of participants that reported currently having COVID-19 reported currently having symptoms that could be related to COVID-19.The participants infected with COVID-19 were younger (M = 37.98, SD = 12.51) than those not infected by COVID-19 (M = 47.37, SD = 16.35), $F_{(1,1586)}$ = 30.53, p <0.001; eta square = 0.019. The groups did not differ with regard to educational level or income.

Aim 1: Assess Differences in Current Autonomic Reactivity and Prior Mental Health Histories in Individuals Infected or Not Infected by COVID-19

As reported in **Table 1**, the COVID-19 diagnosis and no COVID-19 diagnosis groups differed in terms of level of their current levels of autonomic reactivity and the distributions within the groups are virtually non-overlapping. When focusing only on the 98 participants diagnosed with COVID-19, the 47 participants currently infected reported experiencing more autonomic reactivity (M = 70.01, SD = 11.13) than the previously infected (M = 64.14, SD = 13.60), $F_{(1,95)}$ = 5.44, p =0.022; η^2 =0.05. However, as evident by the eta square coefficients, the magnitude of these effects was noticeably smaller than the COVID-19/no COVID-19 contrasts.

Table 1 also shows that the COVID-19 diagnosis and no COVID-19 diagnosis groups differed in their likelihood of previously being diagnosed with depression and a medical disorder that increases COVID-19 risk. While these differences are significant, the most striking differences are with regard to how impacted they were by their prior MH and medical adversities. Similar to current autonomic reactivity, the distributions within the groups are virtually non-overlapping.

Thus, we investigated the relationship between reported impact of prior adversity, current autonomic reactivity, and likelihood being infected with COVID-19. **Figure 1** shows ROC curves for current autonomic reactivity, prior MH adversity, and prior medical adversity on the probability of COVID-19 diagnosis. The probability of COVID-19 infection dramatically increases as scores increase for prior MH and medical adversity and for current autonomic reactivity.

Aim 2: Investigate Whether Individuals More Impacted by Their Prior MH and Medical Health Adversities Report Experiencing Higher Levels of Current Autonomic Reactivity

Linear regression analyses evaluated how prior MH and medical adversity is associated with current autonomic reactivity. The combination of variables accounted for 57.9% of variance for the COVID-19 diagnosis group, $F_{(2,94)}$ = 64.66, p < 0.001, with prior medical adversities being a stronger predictor than prior MH adversities (B =0.49, p <0.001 and B =0.32, p = 0.004). In contrast, for the no COVID-19 diagnosis group, the combination of variables only accounted for 24% of the variance, $F_{(2,1529)}$ = 247.20, p < 0.001, with prior MH adversities being a stronger predictor than prior medical adversities (B =0.34, p <0.001 and B =0.22, p < 0.001).

TABLE 1 | Vulnerability factors by COVID diagnosis groups.

	COVID diagnosis (n = 98)	No COVID diagnosis (n = 1,540)	F or X^2	$\eta 2$
	M (SD)	*M (SD)*		
Autonomic reactivity	67.02 (12.73)	46.47 (9.42)	$F = 417.09^{***}$	0.20
Mental health history				
Prior psychiatric diagnosis	0.98 (0.82)	0.77 (1.04)	$F = 3.78$	0.00
Depression diagnosis	33.7%	24.2%	$X2 = 4.48^{*}$	0.00
Anxiety diagnosis	21.4%	26.8%	$X2 = 1.34$	0.00
PTSD diagnosis	14.3%	14.5%	$X2 = 0.00$	0.00
Impact of MH adversities	30.99 (14.47)	12.03 (10.08)	$F = 303.42^{***}$	0.16
Medical health history				
Prior COVID medical risks	50.0%	22.2%	$X2 = 39.16^{***}$	0.05
Moderate to severe asthma	25.5%	7.3%	$X2 = 34.44^{***}$	0.02
Diabetes	28.6%	8.1%	$X2 = 45.52^{***}$	0.03
Impact of medical adversities	9.71 (4.90)	2.99 (3.68)	$F = 294.24^{***}$	0.15

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Aim 3: Determine Whether COVID-19 Diagnosis Interacts With Prior Adversity to Impact Current Autonomic Reactivity

Table 2 reports the results of two models that used hierarchical linear regression analyses to predict autonomic reactivity. For model 1, the hierarchical regression analyses determined that all three predictors (MH adversity, COVID-19 diagnosis, and interaction of MH adversity and COVID-19 diagnosis) entered in step 1 significantly predicted current autonomic reactivity and account for 39% of the variance. Although the inclusion of prior medical adversity in step 2 significantly increased the variance accounted for to 42%, it did not decrease the impact of the variables found to be significant in step 1.

Model 2 determined that the individual and combined impact of medical adversity and COVID-19 diagnosis accounted for 37% of the variance in autonomic reactivity and that the significant predictors were COVID-19 diagnosis and the interaction of medical adversity and COVID-19 diagnosis. Although the inclusion of prior MH adversity in step 2 significantly increased the variance accounted to 43%, it did not decrease the impact of the variables found to be significant step 1.

Aim 4: Determine Whether Increased Current Autonomic Reactivity Mediates the Relationship Between Prior Adversity and Current Mental Health Difficulties

As reported in **Table 3**, compared to those not infected with COVID-19, those infected with COVID-19 reported currently experiencing more emotional distress, greater mindfulness difficulties, and more posttraumatic stress symptoms, and were more likely to score above the clinical cutoff for PTSD and depression. With considerably large effect sizes, the greatest difference between the COVID-19 diagnosis groups was with regard to their level of emotional distress and posttraumatic stress symptomatology.

The hypothesized moderated mediation model was tested using the PROCESS macro model number 7. As reported in **Figure 2**, COVID-19 diagnosis moderated the effect of both prior MH and medical adversity on current MH difficulties (i.e., mindfulness difficulties, emotional distress, and posttraumatic stress). Zero is not within the CI in any of the models, indicating that COVID-19 diagnosis significantly moderates the direct effects of prior MH and medical adversity on current autonomic reactivity. These significant moderation results are displayed in **Figure 3** *via* density plots and heat maps that are useful for visualizing areas where observations are more common.

Separate analyses indicated that current autonomic reactivity mediated a large percentage (between 58.9 and 85.2%) of the relationship between prior MH and medical adversity and current MH difficulties. However, as presented in all models in **Figure 2**, the moderated mediation results indicated that the conditional indirect effect was stronger in those diagnosed with COVID-19 and weaker in those without COVID-19 diagnosis.

Aim 5: Investigate Whether Medical Providers Report Higher Level of Current Autonomic Reactivity and if Their Increased Autonomic Reactivity Relates to More MH Difficulties

The participants who had been diagnosed with COVID-19 were more likely to be providing medical care to COVID-19 patients, $X^2_{(1,n=1,638)} = 164.35$. Specifically, 34.3% of these medical providers were infected with COVID-19, whereas only 4.0% of the general population. Because of the higher rates of COVID-19 infection, the medical providers appeared to have a higher probability of having higher levels of current autonomic reactivity. ANOVA analyses indicated both COVID-19 diagnosis, $F_{(1,1635)} = 339.17$, $p < 0.001$, and medical provider role, $F_{(1,1635)} = 10.14$, $p = 0.001$, were significant predictors of current autonomic reactivity (Both Risks $M = 69.27$, $SD = 11.41$; Only COVID-19 Diagnosis $M = 65.65$, $SD = 13.37$; Only Medical Provider $M = 49.41$, $SD = 12.74$; No Risks $= 46.33$, $SD = 9.12$).

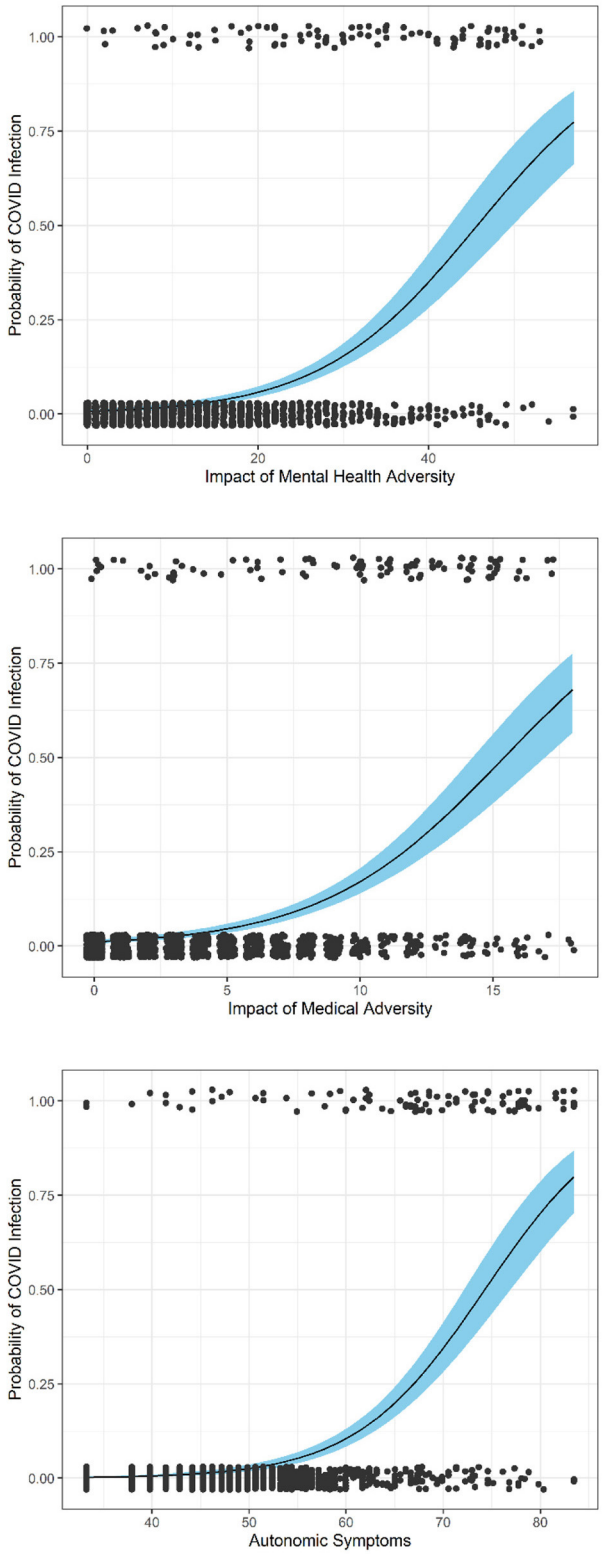


FIGURE 1 | ROC models.

There was an incremental increase in levels of current autonomic reactivity from the individual with both risks to the individuals with no risk factors. These differences remained when taking into account the significant age differences between the medical providers and the general population (medical providers $M = 39.13$, $SD = 12.77$ and general population $M = 47.34$, $SD = 16.38$), $F_{(1,1586)} = 25.03$, $p < 0.001$.

Moderation analyses with age entered as a covariate indicated that the medical provider role moderated the relationship between current autonomic reactivity and emotional distress, $F_{(1,1583)} = 5.45$, $p = 0.020$. Similar moderation results were found for overall posttraumatic stress symptoms, $F_{(1,1582)} = 3.98$, $p = 0.046$, and the components of re-experiencing, $F_{(1,1582)} = 4.19$, $p = 0.041$; and avoidance, $F_{(1,1582)} = 4.03$, $p = 0.045$. The medical providers exhibited increased symptom severity as their levels of current autonomic reactivity increased. Although medical providers reported higher levels of hyperarousal and greater mindfulness difficulties, the effects were not influenced by their current autonomic reactivity.

In addition, binary logistic regression analyses indicated that both COVID-19 diagnosis (OR = 3.39, $p < 0.001$, 95% CI 2.55–4.52) and medical provider role (OR = 1.76, $p = 0.009$, 95% CI 1.15–2.68) significantly increased risk of scoring above the clinical cutoff for PTSD. Similarly, both having COVID-19 diagnosis (OR = 2.46, $p < 0.001$, 95% CI 1.90–3.18) and medical provider role (OR = 1.90, $p = 0.002$, 95% CI 1.26–2.85) significantly increased risk of scoring above the clinical cutoff for depression.

DISCUSSION

The current study investigates whether individuals infected with COVID-19 are experiencing higher levels of self-reported current autonomic reactivity and more MH difficulties, and whether their difficulties relate to their prior impact of MH and medical adversities. We also explored whether medical providers, who were caring for COVID-19 patients and had higher rates of COVID-19 infection, were having more MH difficulties than the general population. We found that participants infected with COVID-19 did report higher levels of current autonomic reactivity and more MH difficulties as well as being more impacted by prior MH and medical adversity. COVID-19 diagnosis moderated the effect of both prior MH and medical adversity on current autonomic reactivity and MH difficulties. Current autonomic reactivity also mediated the relationship between prior adversities and current MH difficulties. However, the effect was stronger in those also diagnosed with COVID-19. It was found that the medical provider role was associated with increased levels of current autonomic reactivity, especially for providers diagnosed with COVID-19.

Consistent with polyvagal theory, we conceptualized the current pandemic as a stressful event that may lead to increased

TABLE 2 | Results of stepwise linear regression analyses predicting autonomic reactivity from prior adversity and COVID-19 diagnosis.

Predictors	Step 1			Step 2		
	Beta	*t*	*p*	Beta	*t*	*p*
Model 1						
(Constant)		228.45	0.000		234.42	0.000
MH adversity	0.25	3.21	0.001	0.16	2.16	0.031
COVID-19 diagnosis	0.14	3.20	0.001	0.13	2.98	0.003
Interaction of MH adversity and COVID-19 diagnosis	0.30	3.03	0.002	0.24	2.44	0.015
Medical adversity				0.23	9.34	<0.001
	$F_{(3,1625)} = 350.47$, $p < 0.001$; $R^2 = 0.39$			$F_{(4,1624)} = 298.60$, $p < 0.001$; $R^2 = 0.42$		
Model 2						
(Constant)		223.49	0.000		234.86	0.000
Medical adversity	0.05	0.66	0.509	−0.02	−26	0.794
COVID-19 diagnosis	0.10	2.42	0.016	0.10	2.43	0.015
Interaction of medical adversity and COVID-19 DIAGNOSIS	0.48	4.70	<0.001	0.34	3.47	<0.001
MH adversity				0.33	13.05	<0.001
	$F_{(3,1625)} = 312.29$, $p < 0.001$; $R^2 = 0.37$			$F_{(4,1624)} = 301.23$, $p < 0.001$; $R^2 = 0.43$		

Beta coefficients are standardized and analyses were run with Z scores to facilitate comparisons among the variables.

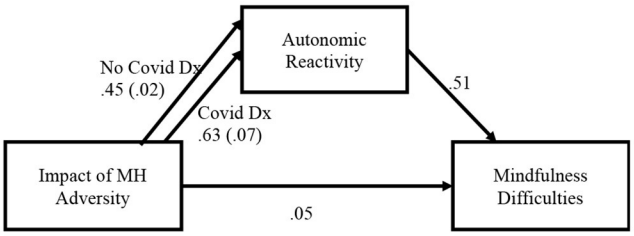
TABLE 3 | Current mental health by COVID diagnosis groups.

	COVID diagnosis	No diagnosis or symptoms	*F* or X^2	*η2*
	M (SD)	*M (SD)*		
Total scores			F	
Emotional distress	40.57 (12.13)	24.66 (10.06)	224.46***	0.12
Mindfulness difficulties	3.61 (0.91)	2.79 (0.91)	74.47***	0.04
Posttraumatic stress	57.29 (16.93)	33.53 (15.09)	222.91***	0.12
Re-experiencing	3.49 (1.89)	1.09 (1.70)	178.78***	0.10
Avoidance	5.27 (2.22)	1.96 (2.23)	201.89***	0.11
Hyperarousal	3.89 (1.65)	1.62 (1.75)	153.07***	0.09
Above clinical cutoff			X^2	
PTSD	75.3%	23.0%	129.31***	0.08
Depression symptoms	67.3%	25.5%	80.28***	0.05

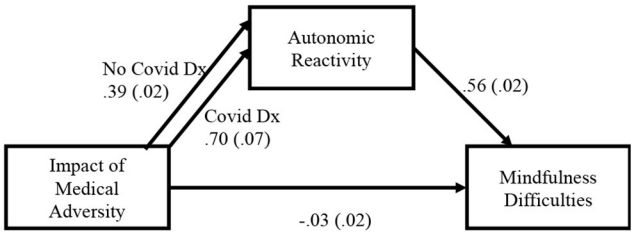
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

autonomic reactivity that relates to a retuning of the ANS. Stress leads to defense responses that increase sympathetic activation and bias neuroception toward the detection of threat cues, while becoming less sensitive to the detection of safety cues (2, 3). Consistent with the limited research investigating autonomic regulation difficulties in individuals diagnosed with COVID-19 (4, 5), we found that these individuals had significantly higher levels of self-reported current autonomic reactivity than individuals in the general populations and other US samples [e.g., (34)]. Since COVID-19 infection is both emotionally and medically traumatic, it leads one to speculate there may be some vulnerability to autonomic dysregulation. Considering prior research investigating the relation between the immune system and ANS particularly for MS disease activity (45), it is possible ANS dysregulation could influence immune response and accompany a COVID-19 infection in similar ways.

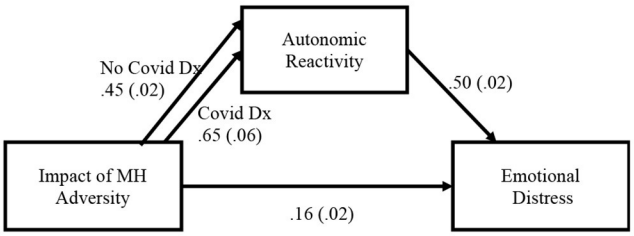
We also found that the levels of current autonomic reactivity were higher in those diagnosed with COVID-19 at the time of data collection than those previously diagnosed with COVID-19. Although it is encouraging that the rates appear to have dropped over time, it is concerning that the individuals



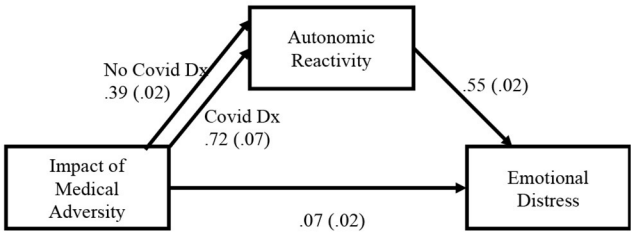
COVID Diagnosis moderates effect of MH Adversity on Mindfulness Difficulties, $B = .09$, $Bse = .03$, $t = 2.72$, p = .007
Greater autonomic reactivity was associated with more mindfulness difficulties, $B = .51$, $Bse = .03$, $t = 20.02$, p < .001
Index of moderated mediation = 0.09; 95% CI .003 to .183
COVID Group: effect = .32; SE = .05, 95 CI .230 to .414 No COVID Group: effect = .23, SE = .02; 95 CI .193 to .266



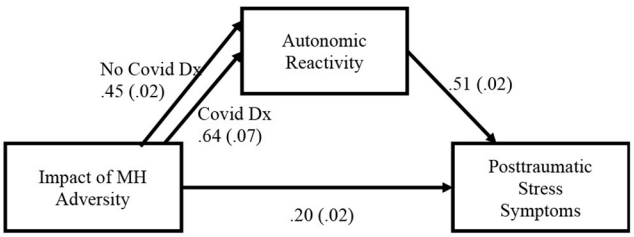
COVID Diagnosis moderates effect of Medical Adversity on Mindfulness Difficulties, $B = .16$, $Bse = .04$, $t = 4.22$, $p = <.001$
Greater autonomic reactivity was associated with more mindfulness difficulties, $B = .56$, $Bse = .03$, $t = 22.47$, $p < .001$
Index of moderated mediation = 0.17; 95% CI .077 to .269
COVID Group: effect = .39, SE = .05; 95 CI .298 to .487 No COVID Group : effect = 0.22, SE = .02; 95 CI .180 to .258



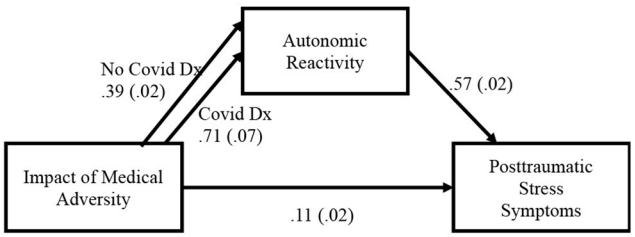
COVID Diagnosis moderates effect of MH Adversity on Emotional Distress, $B = .10$, $Bse = .03$, $t = 3.03$, $p = .002$
Greater autonomic reactivity was associated with more Emotional Distress, $B = .50$, $Bse = .02$, $t = 20.60$, $p < .001$
Index of moderated mediation = 0.10; 95% CI .012 to .185
COVID Group: effect = .32, SE = .04; 95 CI .236 to .409 No COVID Group : effect = 0.22, SE = .02; 95 CI .186 to .258



COVID Diagnosis moderates effect of Medical Adversity on Emotional Distress, $B = .16$, $Bse = .04$, $t = 4.56$, $p = <.001$
Greater autonomic reactivity was associated with more Emotional Distress, $B = .55$ $Bse = .02$, $t = 23.20$, $p < .001$
Index of moderated mediation = 0.18; 95% CI .089 to .264
COVID Group: effect = .39, SE = .04; 95 CI .307 to .479 No COVID Group: effect = 0.22, SE = .02; 95 CI .176 to .255



COVID Diagnosis moderates effect of MH Adversity on PTSD, $B = .10$, $Bse = .03$, $t = 2.94$, $p = .003$
Greater autonomic reactivity was associated with more PTSD, $B = .51$ $Bse = .02$, $t = 21.88$, $p < .001$
Index of moderated mediation = 0.10; 95% CI .011 to .186
COVID Group: effect = .32, SE = .04; 95 CI .241 to .412 No COVID Group : effect = 0.23, SE = .02; 95 CI .190 to .263



COVID Diagnosis moderates effect of Medical Adversity on PTSD, $B = .16$, $Bse = .04$, $t = 4.47$, $p = <.001$
Greater autonomic reactivity was associated with more PTSD, $B = .57$ $Bse = .02$, $t = 24.83$, $p < .001$
Index of moderated mediation = 0.18; 95% CI .089 to .269
COVID Group: effect = .40, SE = .05; 95 CI .314 to .488 No COVID Group : effect = 0.22, SE = .02; 95 CI .183 to .263

FIGURE 2 | Moderated mediation models testing relationship among prior adversity, current autonomic reactivity, and current mental health difficulties.

previously diagnosed had higher levels than those not diagnosed with COVID-19, which is consistent with prior findings that changes in the ANS may persist after the infection has dissipated (6).

Due to the stress of the risk of infection during the pandemic, the fear of significant morbidity due to becoming infected, and social isolation due to quarantining, we hypothesized that individuals diagnosed with COVID-19 would have more

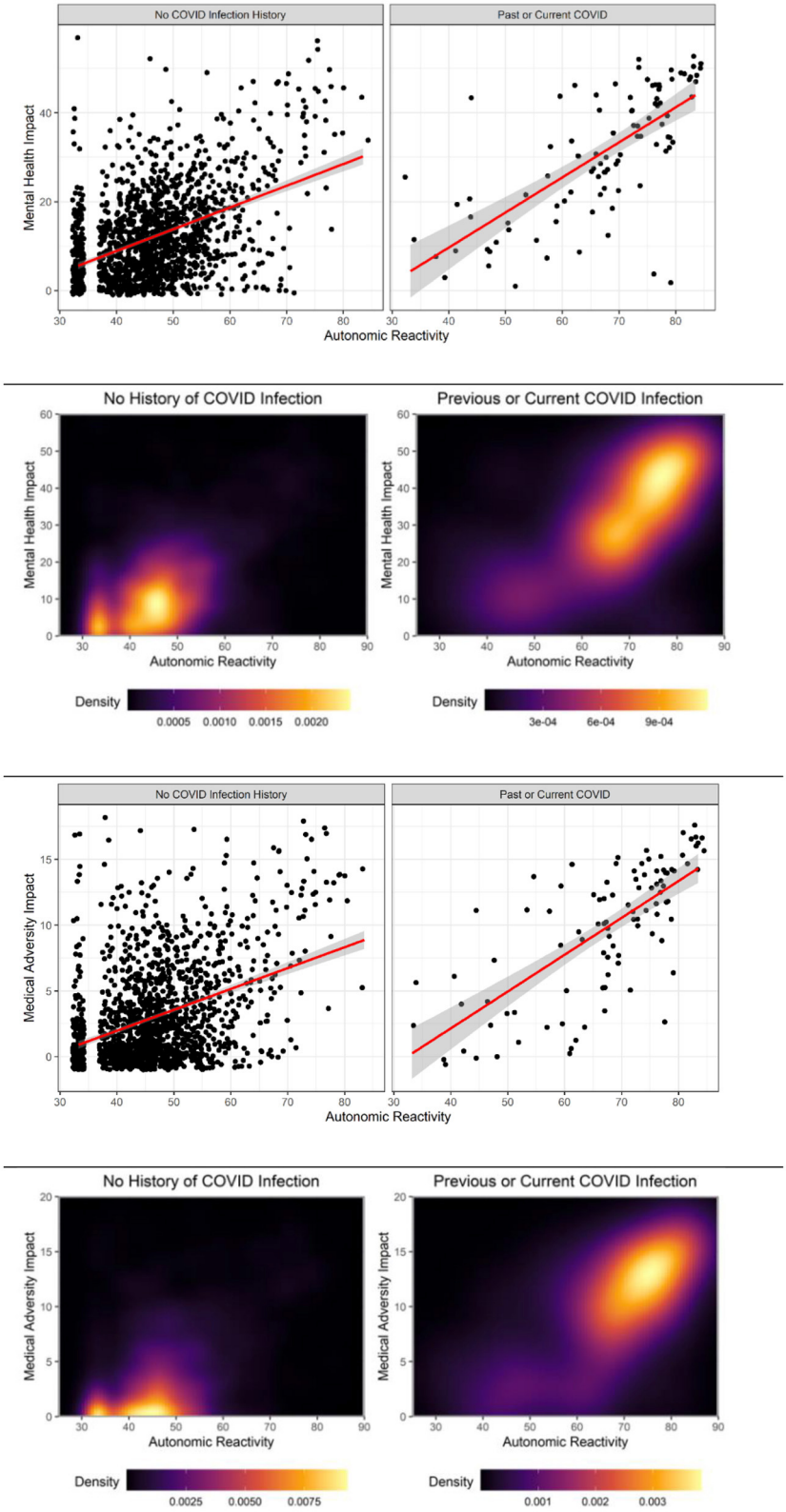


FIGURE 3 | COVID-19 diagnosis moderates relationship between adversity and autonomic reactivity.

MH difficulties. Consistent with the prior research (7–14) we found that individuals diagnosed with COVID-19 reported higher levels of current MH difficulties. Specifically, we found higher levels of emotional distress on a measure designed to tap the symptoms of distress identified by the CDC which includes items related to anxiety and depression. We also found that COVID-19 survivors were experiencing more mindfulness difficulties, which is consistent with the clinical impressions of brain fog (16) and prior research findings suggesting that changes in brain function may occur due to differences in gray matter (15). Lastly, we found that these individuals were experiencing more posttraumatic stress symptoms, including re-experiencing, avoidance, and hyperarousal. The latter symptoms relate directly to the reported high level of current autonomic reactivity, and accompanying difficulty of feeling safe as would be predicted by polyvagal theory.

Consistent with polyvagal theory, we also investigated whether individuals who were more impacted by prior MH and medical adversities may be more vulnerable to and impacted by the COVID-19 infection. Rather than asking about the occurrence of an adverse event, we focused on the individual's perception of how impacted they were by their prior MH and medical adversities. This was important as we believed that those more impacted are likely to have experienced more frequent/severe events that potentially alter their ANS and lead to vulnerability to developing disease and experiencing more significant effects.

As hypothesized, we found that individuals reporting they were more impacted by their prior MH and medical adversities reported higher levels of current autonomic reactivity. We also observed that these variables accounted for 58% of the variance in current autonomic reactivity in the individuals diagnosed with COVID-19. As would be expected, their autonomic reactivity was more affected by their medical adversity than their MH adversity—although both were important predictors. In contrast, prior MH adversity was more important than prior medical adversity in predicting current autonomic reactivity in individuals not diagnosed with COVID-19. Thus, our results suggested that both MH and medical adversity may impact current autonomic reactivity.

We were able to demonstrate that COVID-19 diagnosis may impact the relationship between prior MH and medical adversity and current autonomic reactivity through hierarchical regression and moderated mediation analyses. We also found that COVID-19 diagnosis may moderate the effect of MH and medical adversity on the current MH difficulties of increased emotional distress, mindfulness difficulties, and posttraumatic stress symptoms. Specifically, we found that individuals infected with COVID-19 had higher levels of current autonomic reactivity and were more likely to exhibit an increase in autonomic reactivity as their adversity impact scores increased. Additionally, we found that current autonomic reactivity mediated a large percentage (between 58.9 and 85.2%) of the relationship between prior MH and medical adversity and current MH difficulties, with the indirect effect being stronger for individuals diagnosed with COVID-19 than in those without a COVID-19 diagnosis. Although no definitive statements can be made because of the cross-sectional design, it is possible that the previously observed connection between prior adversity, current autonomic reactivity, and current MH difficulties (1) may be exacerbated in individuals diagnosed with COVID-19. It is not clear if this is because of the virus or the stress associated with the COVID-19 diagnosis.

Consistent with prior statistics (30), we found that 34% of the medical providers had been diagnosed with COVID-19, a rate which was considerably higher than the 4% found in our general population. We also found that both risk factors (i.e., COVID diagnosis and medical provider role) were significant predictors of current autonomic reactivity and that there was an incremental increase in levels of autonomic reactivity from the individuals with no risks to the individuals with both risk factors. Not only was there an interactive effect, the medical provider role moderated the relationship between current autonomic reactivity and levels of emotional distress and posttraumatic stress symptoms, with the medical providers exhibiting greater symptom severity as their levels of autonomic reactivity increased. In addition, we found that both COVID-19 diagnosis and medical provider role increased risk of scoring above the clinical cutoff for PTSD and depression. Thus, our findings suggest that the reported MH difficulties (e.g., anxiety, depression, and PTSD) in medical workers previously diagnosed with COVID-19 (31) may be related to increased autonomic reactivity.

LIMITATIONS AND FUTURE DIRECTIONS

The potential implications of the current study need to be considered in the context of the study's limitations. With the cross-sectional study design, it is not possible to make any definitive statements regarding causality and to determine how much of the COVID-19 group differences are related to the virus or the stress associated with the COVID-19 diagnosis. It is also unknown whether the participants were including their COVID-19 diagnosis when answering the question about a life-threatening illness that is part of the six items that made up the medical adversity scale.

Additionally, the sample included a higher percentage of females which research suggests are more likely to report mental health symptoms (46). Despite the large sample size (N = 1,638), only 98 individuals reported having COVID-19 and there was no confirmation of diagnosis. Although not a large group, those diagnosed with COVID-19 did not differ from the general population in terms of demographic characteristics, which could have impacted other factor assessed in our study.

Because many of the participants that had COVID-19 were medical providers, we addressed this limitation by exploring the combined impact of these factors. Future research should incorporate a confirmation of COVID-19 diagnosis and consider the timing and severity of illness as there were small differences in our sample between those who had COVID-19 at the time of data collection and those who had been previously diagnosed.

Due to a need to quickly understand how individuals are coping with the pandemic and the data collection limitations related to the COVID-19 pandemic, current autonomic reactivity could only be collected *via* self-report. Although the BPQ-SF appears to be an appropriate measure of autonomic reactivity as it has high convergent validity with similar measures and consistency across samples (34), it is unclear whether the self-reports reflect autonomic state reactivity prior to the pandemic or is a sensitive index of the individual autonomic reaction to the pandemic. Future research should explore objective measurements of autonomic reactivity prior to, during, and following COVID-19 infection.

It is also important to consider the limitations related to the ATES, which is a new measure with limited psychometric information. However, the negatives of this instrument are outweighed by its positives, as it asks about the perceived impact of a range of traumatic experiences. Rather than simply documenting whether traumatic experience occurred, the ATES indirectly assesses the frequency and severity of adversity/trauma. Lastly, the measure of emotional distress was created to tap symptoms of distress as identified by the CDC. Thus, it asked questions related to shock about the situations induced by the pandemic and primarily focused on symptoms of anxiety and depression. Although this measure was found to be internally consistent, it may have been better to use established measures of anxiety or depression. However, it is important to note that the CDC emotional distress measure directly relates to the overarching large-scale crisis of the pandemic, which may encourage more nuanced responses than a standardized measure.

CONCLUSION AND IMPLICATIONS

Our results suggest that individuals diagnosed with COVID-19, particularly medical providers, may have increased levels of current autonomic reactivity that is associated with their prior MH and medical adversities and current MH difficulties. Our findings are consistent with polyvagal theory and prior research suggesting autonomic dysregulation (5, 6) and poorer mental health outcomes in COVID-19 survivors (7–14), and are unique in indicating that the combination of the COVID-19 diagnosis and medical provider role could lead to more detrimental effects.

Our results suggest an important avenue for clinical treatment may lie in interventions that focus on both the body and mind and that COVID-19 survivors and their medical providers should be provided with somatic-focused interventions and cognitive strategies that will retune their potentially dysregulated ANS. Prior research suggests bottom-up approaches to therapy helps individuals to connect with their bodies and their feelings, thus teaching them to calm their physiology (47). Improvements in regulation documented in interventions focused on yoga (48) and mindfulness body scan mediation (49) suggest that body focused interventions have tremendous potential to be helpful to populations at risk for increased autonomic reactivity by way of COVID-19 diagnosis, medical provider status, or both. These body-focused interventions may benefit from addressing spirituality, which by encouraging transcendence, connection, wholeness, and compassion (50), fosters resilience (50) and is associated with reductions in stress (51) and improvements in physical and mental wellbeing (50, 51). Previous studies have found spirituality has been associated with more hopefulness and less fear, worry, and sadness in the midst of the COVID-19 pandemic (50).

Interventions should be implemented in the workplace to encourage resilience and psychological wellbeing through the employment-related services and social/emotional support (52). This is a promising avenue for individuals working in healthcare because prior research shows that healthcare providers who do not feel supported by their leadership in the workplace are more likely to experience exhaustion and disengagement (29). Thus, integrating interventions into their workplace environments may alleviate some of the stressors that contribute to dysregulation, which is essential when considering the vital role that healthcare providers play during this time.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Indiana University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LD developed study, analyzed data, and wrote all sections of manuscript. SC and SP developed study, reviewed analyses, and reviewed manuscript edits. JK developed study, collected and reviewed data, made figures, and reviewed analyses and versions of manuscript. KL and NB wrote sections of manuscript and edited final version. AB wrote sections of manuscript. EN collected and reviewed data. All authors contributed to the article and approved the submitted version.

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Childhood Maltreatment Influences Autonomic Regulation and Mental Health in College Students

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Childhood maltreatment history may influence autonomic reactivity and recovery to stressors. Hypothetically, the maltreatment history may contribute to a retuned autonomic nervous system that is reflected in a novel metric, vagal efficiency (VE), designed to assess the functional efficiency of vagal cardioinhibitory pathways on heart rate. We explored whether VE mediates the well-documented relationship between maltreatment history and psychiatric symptoms. We also investigated the relationship between measures of autonomic regulation in response to the physical and emotional challenges and psychiatric symptoms. Participants (n = 167) completed self-report measures of psychiatric symptoms and had continuous beat-to-beat heart rate monitored before, during, and after physical and emotional stressors. Participants with maltreatment histories exhibited lower VE, which mediated the association of maltreatment history and the psychiatric symptoms of anxiety and depression. Consistent with prior literature, there were significant associations between maltreatment history and autonomic reactivity (i.e., heart rate and respiratory sinus arrhythmia) during emotional and physical challenges; however, when VE was entered as a covariate these associations were no longer statistically significant. Blunted VE may reflect a neural pathway through which maltreatment retunes autonomic regulation and provides a neurophysiological platform that increases mental health risk.

Keywords: maltreatment, PTSD, heart rate variability, respiratory sinus arrhythmia, Polyvagal Theory, vagal efficiency

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INTRODUCTION

Exposure to traumatic events may have psychological and physiological consequences that may be a result of dysregulation of the autonomic nervous system. Survivors of maltreatment, even those who do not reach the diagnostic criteria for PTSD, may have psychiatric and physical health features that relate to an autonomic nervous system that has been retuned to have a lower threshold to react to cues of threat (1–4). Prior research has shown that female college students with maltreatment histories, who did not reach the diagnostic criterion for PTSD, experienced

more psychiatric symptoms, had lower levels of respiratory sinus arrythmia (RSA) and faster heart rates as demonstrated by their shorter heart periods (HP), and reacted differently to the physical stressor of riding a stationary bike and the emotional stressor of watching a video of a child being maltreated than women without maltreatment histories (5, 6). Additionally, meta-analyses found major depression and anxiety disorders such as panic disorder, PTSD, generalized anxiety disorder, and social anxiety are associated with lower heart rate variability (HRV) (7, 8). These patterns of autonomic reactivity and recovery to stressors might relate to atypical vagal regulation of the heart reflected in inefficient cardiohibitory vagal pathways (i.e., vagal brake) (6).

Polyvagal Theory (9, 10) proposes that these protective responses spontaneously emerge through neuroception, a reflexive adaptive process that triggers specific biobehavioral response patterns to cope with conditions of safety, danger, and life threat. If neuroception detects safety, the nervous system facilitates social communication and engagement. In contrast, if neuroception detects danger, the withdrawal of the parasympathetic system may be initiated, reducing the impact of cardioinhibitory vagal pathways on the heart to functionally diminish the influence of the vagal brake on the heart's pacemaker and increase access to greater metabolic resources in preparation for the challenge. Following a successful response to the challenge, the parasympathetic nervous system initiates recovery by re-engaging the vagal brake to slow heart rate by increasing the cardioinhibitory actions of the vagus, while simultaneously inhibiting the sympathetic control of the heart (11, 12). Since the early 1900s, it had been known that the cardioinhibitory function of the vagus was systematically influenced by respiration (13). This observation is the physiological basis for quantifying the amplitude of the oscillation in heart rate at the frequency of spontaneous breathing, as an index of cardiac vagal tone (14). Lower levels of RSA have been associated with a greater sensitivity to unpredictable threat (15), a finding that relates to neuroception and has implications for individuals with a history of maltreatment.

In this study, we explored this plausible explanation using vagal efficiency (VE), a metric proposed by Porges and colleagues (16) as a measure of the dynamic regulation of cardiac vagal tone on cardiac output represented in a single measure of slope between sequential measures of HP and RSA. We examined VE during the physical challenge of riding a stationary bike because it provided a physiological challenge with minimal potential psychological associations. In addition, the metabolic demands of biking require a systematic withdrawal of the vagal cardioinhibitory influence on the heart's pacemaker (i.e., vagal brake), while the post-biking recovery enables the vagal brake to re-engage to slow heart rate. If the heart rate is tightly coupled and efficiently driven by the vagal brake (i.e., measured by RSA), the linear regression between short (e.g., 15s) sequential estimates of RSA and heart rate will have a steep slope.

Although no published studies have examined how VE relates to maltreatment history and psychiatric symptoms, it is important to consider VE as it may be developmentally sensitive to environmental conditions. In preterm infants, VE has been found to increase with maturation and to be influenced by a psychosocial intervention (17). Furthermore, its sensitivity to environmental conditions was demonstrated as VE was reliably reduced following the administration of alcohol in adults (18). VE may also predict intervention response, with evidence showing that adolescents with low VE were more responsive to neurostimulation for their gastric pain than those whose VE was high (19).

Consistent with Polyvagal Theory (9–11, 20, 21), which emphasizes the mediational role of autonomic state as an intervening variable, it is important to investigate autonomic reactions to an emotional stressor because exposure to traumatic events may retune autonomic regulation and contribute to dysfunctional emotional processing (22, 23). These individuals may adaptably become hypervigilant for danger cues and have anticipatory or responsive physiological changes in their autonomic nervous system that promote defensive action and may influence psychological wellbeing. When confronted with emotional challenges, including emotional imagery and emotional scene viewing, individuals exposed to stressful events have consistently showed atypical physiological and neural responses (24–29). We also investigated autonomic responses during the emotional stressor of watching a video of a child being maltreated and contrasted it to the reaction during the physical stressor.

The current study explored whether VE was reduced in those with a maltreatment history, and whether it mediated the relationship between maltreatment history and psychiatric symptoms (i.e., somatization, anxiety, depression, and PTSD). We also investigated whether VE mediated the relationship between measures of autonomic regulation in response to the physical and emotional challenges and psychiatric symptoms. We hypothesized that:

- Participants with a history of maltreatment would have lower VE and exhibit autonomic regulation difficulties in response to the physical and emotional stressor challenges.
- Measures of VE and autonomic reactivity and recovery would be correlated with psychiatric symptoms.
- VE would mediate the relationship between autonomic reactivity and psychiatric symptoms.

MATERIALS AND METHODS

Participants

Participants were 167 college students (65.9% identified as female), recruited from a university's participant pool for two separate studies, who had data for all the physiological measures. They were 18–25 years old (M = 19.18, SD = 1.33), predominantly first-year (45.5%) or second year (25.7%) students. The racially diverse sample identified themselves as White (43.7%), Black (16.8%), Hispanic (9.0%), Asian/Pacific Islander (6.0%), and mixed/other (24.6%). Those reporting a medical diagnosis (8.4%) did not report having a

cardiovascular disorder, which would have excluded them from participation in this study.

Participants with a prior psychiatric diagnosis (25.1%) most frequently reported having anxiety (15.6%), depression (14.4%), ADHD (8.4%), and PTSD (2.4%). There were no participants that did not endorse at least mild maltreatment for at least one of the items. Many reported experiencing moderate or severe childhood maltreatment (48.5%) including emotional neglect (31.1%), emotional abuse (28.1%), physical neglect (18.6%), physical abuse (16.8%), and sexual abuse (13.2%). Participants varied in their current symptomatology (non-windsorized values for somatization M = 3.27, SD = 4.01; depression M = 4.57, SD = 5.07; anxiety M = 4.93, SD = 5.14; and PTSD M = 30.33, SD = 10.49) and those reporting more of one symptom reported more of another (correlations ranged 0.52–0.75, $p < 0.001$).

Procedure

The university's Institutional Review Board approved all procedures. During the data collection sessions, the participant was provided with an informed consent form explaining the voluntary nature and purpose of the study, participation requirements, and confidentiality and privacy procedures. Each participant was informed there were no known physical or psychological risks from participating in this study and that the investigator should be notified if they were distressed. Once written consent was obtained, the participant completed self-report measures with the least sensitive/personal information being asked first and the most sensitive/personal information last. Then the participant was asked their height and weight and instructed on how to attach the electrodes for the heart rate monitoring. All participants were first exposed to the physical stressor of riding the stationary bike at a comfortable pace for half a mile (usually 2–4 min) and then the emotional stressor of watching a video in which a child is emotionally maltreated (3 min). Data were collected during a 3-min baseline prior to and after each stressor to enable the quantification of changes in heart rate and respiratory sinus arrhythmia to the experimental challenges.

As a precaution, the instruments assessing symptoms of depression and PTSD were scored immediately to determine if the participant reported having in the past 7 days any desire to end their life and being extremely hopeless about the future and endorsed a clinically significant level of traumatic stress (scored 44 or higher on the measure of PTSD symptomatology). This protocol identified about 30% of the participants that needed an immediate assessment to determine level of risk by the licensed clinical psychologist that was part of the research team. All participants were referred to the counseling center and provided with an information sheet that explained other relevant university services (e.g., academic support services). Because none of these participants required psychiatric hospitalization, they all remained in the study. After data collection, participants were provided with a debriefing form that had information about the study and resources on campus.

Constructs and Measures

Maltreatment history was assessed via the Childhood Trauma Questionnaire (30), which is a 28-item self-report questionnaire that asks adolescents and adults about how often they experienced emotional abuse, sexual abuse, physical abuse, emotional neglect, and physical neglect. This measure is internally consistent (α = 0.66–0.93), reliable (test-retest r = 0.86), and converges with corroborated clinician reports of maltreatment history (31, 32). A binary childhood maltreatment score was derived by determining if the individual reported moderate or severe maltreatment in any of the five domains.

Psychiatric symptoms were assessed via two measures. Depression, anxiety, and somatization symptoms were assessed via the 18-item version of the Brief Symptom Inventory (33), which asks participants to indicate via a 5-point Likert scale (*not at all* to *extremely*) how much they have been distressed or bothered in the past 7 days by each symptom. Reliability analyses indicated that the measure was internally consistent with the current sample (Cronbach's alpha scores somatization = 0.81; anxiety = 0.87, and depression = 0.88).

PTSD symptoms were assessed via the PTSD Checklist—Civilian Version (34), a 17-item self-report measure that corresponds to the criteria for PTSD and assesses via a 5-point Likert scale (*not at all* to *extremely*) level of distress related to stressful life experiences over the last month. This measure has good convergent and discriminant validity, internal consistency, and test–retest reliability (35) and was found to be internally consistent with the current sample (Cronbach's alpha = 0.92).

Physiological data were monitored with an EZ-IBI monitor (UFI, Morro Bay, CA). Two active electrodes were placed on the left side at the level of the heart and on the right lower abdomen. A ground electrode was placed above the right-side collarbone. ECG data was collected continuously while the participant went through the protocol. The EZ-IBI detected the peak of the R-wave with 1-ms accuracy (sampling rate = 1,000 Hz) and timed the interval ms between sequential R-R waves (i.e., heart period, HP), which were downloaded to a computer for off-line processing and analyses. Files of sequential HP were stored on a computer. HP was used as the metric of heart rate (i.e., HP is monotonically related to heart rate).

Quantification of heart rate variability requires the timing of intervals between successive heart beats synchronized with successive peaks of the R-wave in the ECG. In this paper, we label the R-R intervals defining interbeat intervals, as heart period. We elected to report the data using heart period instead of heart rate because heart period reflects a stronger linear relationship than heart rate with dynamic vagal influences (36).

RSA estimates calculated based on the methods developed by Porges (37) included the following procedures: (a) the R-R interval time series were converted to time-based data by resampling at successive 500-ms intervals; (b) a 21-point moving cubic polynomial filter was stepped through the time-sampled series to produce a smoothed template series; (c) the template series was subtracted from the original series to produce a residual time series; (d) the residual time series was processed by a digital bandpass filter with 25

TABLE 1 | Descriptive statistics for RSA and HP.

	RSA			HP		
Variable	***M***	**Min**	**Max**	***M***	**Min**	**Max**
Baseline	7.18 (1.14)	3.55	9.78	861.60 (143.52)	544.00	1320.68
Physical stressor						
Reactivity	−4.52 (1.63)	−8.78	0.02	−370.17 (130.09)	−873.67	−82.43
Recovery	3.48 (1.43)	0.40	6.99	222.55 (105.24)	47.46	561.59
Emotional stressor						
Reactivity	−0.02 (0.90)	−4.95	3.52	40.32 (60.06)	−271.83	245.03
Recovery	0.09 (0.63)	−1.55	3.11	−9.78 (58.54)	−180.16	480.88

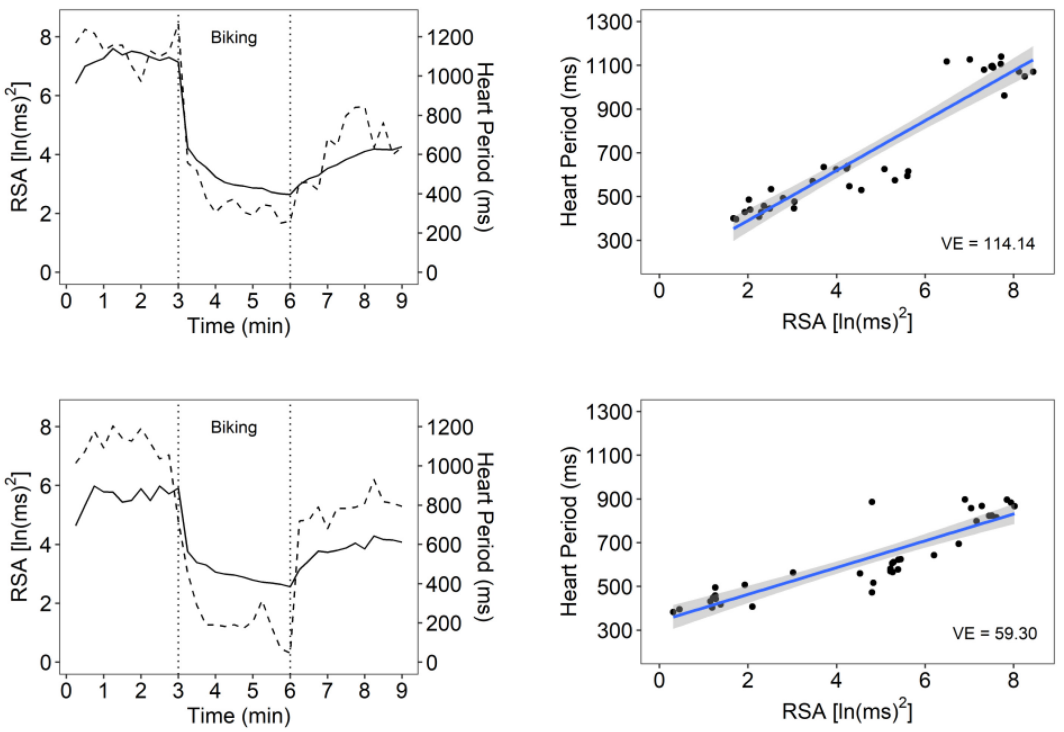


FIGURE 1 | An illustration of vagal efficiency (VE) during baseline, biking, and recovery. Data is displayed for 2 participants: one with high VE (top row) and one with low VE (bottom row). Figures in the left column show cardiac vagal tone [measured by respiratory sinus arrhythmia (RSA); dotted line] and HP (solid line) over the course of the protocol. The participant in the top row has strong coupling between RSA and HP, which can also be seen in the steep slope between synchronous observations in the top right figure (slope = 114.14). The top right plot reflects the participants' rapid shift from high RSA/high HP during baseline and recovery relative to low RSA/low HP states during physical exercise. These data suggest a rapid withdrawal and re-engagement of the vagal brake to regulate metabolic demands. The participant in the bottom panel had similar ranges of RSA values, but RSA was weakly associated with HP (slope = 59.30), suggesting that cardioinhibitory vagal influences were not efficient in slowing cardiac metabolic output.

coefficients to extract the variance in the frequency band of 0.12–0.40 Hz (i.e., frequency of spontaneous breathing for adults); and (e) bandpassed variance was transformed to its natural logarithm and used to quantify RSA. These procedures result in a sensitive, non-invasive marker of the influence of the myelinated vagal fibers on the heart (9, 11, 13, 38).

Data files were input into CardioEdit software (39) to visually display sequential R-R interval data and edit outliers. Edited data were processed with CardioBatch software (39) to generate measures of mean 30-s epochs for HP and RSA.

Baseline levels were based on the first segment collected. Autonomic metrics reflected the magnitude of change in RSA and HP from baseline to stressor (reactivity) and stressor to post-stressor (recovery) for the physical and emotional stressors. Reactivity change scores were calculated by subtracting the value during the pre-stressor baseline from the value during the stressor. Recovery change scores were calculated by subtracting the value during the stressor from the value during the post-stressor recovery period.

VE was used to measure cardiac autonomic regulation, specifically how vagal efferent pathways to the heart dynamically

TABLE 2 | Comparison of maltreatment and no maltreatment groups.

	Maltreatment group			No maltreatment group			$T_{1,165}$	*P*	*D*
	M (*SD*)	95% CI		*M* (*SD*)	95% CI				
		Lower	Upper		Lower	Upper			
Vagal efficiency	61.70 (19.48)	57.40	66.01	69.56 (25.54)	0.35	75.70	**−2.22**	**0.028**	0.37
Baseline RSA	6.97 (1.23)	6.69	7.24	7.38 (1.02)	0.37	7.60	**−2.35**	**0.020**	0.38
Baseline HP	831.70 (136.80)	801.45	861.95	888.79 (145.35)	0.40	920.14	**−2.60**	**0.010**	0.42
Physical stressor									
RSA reactivity	−4.71 (1.53)	−0.5.04	−4.37	−4.38 (1.68)	0.21	−4.01	−1.32	0.190	0.21
HP reactivity	−357.62 (129.28)	−386.20	−329.03	−382.68 (131.17)	−0.19	−354.22	1.24	0.218	−0.22
RSA recovery	3.47 (1.35)	3.18	3.77	3.51 (1.49)	0.03	3.84	−0.18	0.859	0.01
HP recovery	198.96 (96.70)	177.58	220.34	244.11 (108.96)	0.44	267.76	**−2.81**	**0.006**	0.45
Emotional stressor									
RSA reactivity	0.11 (0.90)	−0.09	0.31	−0.13 (0.90)	−0.27	0.06	1.72	0.087	−0.41
HP reactivity	32.78 (64.79)	18.45	47.11	49.06 (52.98)	0.28	60.56	−1.77	0.079	0.25
RSA recovery	0.01 (0.53)	−0.11	0.14	0.16 (0.70)	0.24	0.32	−1.50	0.136	0.19
HP recovery	−5.45 (40.00)	−14.41	3.51	−14.67 (71.80)	−0.29	1.01	1.00	0.318	−0.29
Symptoms									
Somatization	3.85 (4.13)	2.94	4.76	2.37 (2.62)	0.43	2.94	**2.75**	**0.007**	−0.43
Depression	5.77 (5.10)	4.64	6.89	3.16 (3.90)	0.57	4.02	**3.65**	**0.000**	−0.57
Anxiety	5.94 (4.97)	4.84	7.04	3.59 (4.05)	0.52	4.46	**3.30**	**0.001**	−0.53
PTSD	34.78 (13.28)	31.82	37.73	27.22 (9.40)	0.66	29.25	**4.20**	**0.000**	−0.53

D = Cohen's d. Bold values indicate significant group differences (p < 0.05).

influences heart rate, which is a process that is not captured in RSA alone (19). Following methods from prior studies (19, 40), VE was calculated for each participant as the slope of the regression line between RSA and HP using paired sequential epoch values (every 15 s) of HP and RSA during the physical challenge (i.e., 3-min baseline, riding the stationary bike, and post-biking recovery).

Statistical Analysis

Data analyses were conducted in SSPS and R. To retain participants and minimize the effects of symptomatology outliers, a 90% windsorization procedure was used. Correlational analyses explored the relationship among the autonomic measures (i.e., VE, baseline levels and changes in RSA and HP in response to physical and emotional stressors) and psychiatric symptomatology. Independent sample *t*-tests compared participant groups with and without self-reported history of maltreatment.

Mediation analyses, conducted using the Lavaan R package (41), assessed whether the association between the independent variable of maltreatment history (yes/no) and dependent variables of psychiatric symptoms could be attributed to the indirect effect of the third variable of VE. For this analysis, the indirect effect, which represents the strength of the mediation, is the product of the coefficient of the independent variable on the mediator and the mediator on the outcome variable and the direct effect is the effect of the independent variable on the dependent variable adjusting for the effect of the mediator. Mediation models were estimated using maximum likelihood. Indirect and total effect confidence intervals were calculated using bias-corrected adjusted bootstrap percentiles with 10,000 draws, which has superior power for detecting true effects with accurate Type I error rates compared to other methods (42). Mediation was supported if the indirect effect 95% confidence interval did not include zero.

TABLE 3 | Correlation among physiological measures and symptomatology.

	Somatization symptoms	Depression symptoms	Anxiety symptoms	PTSD symptoms
Vagal efficiency	−0.05	−0.16*	−0.17*	−0.10
Baseline				
Baseline RSA	0.01	0.05	−0.05	0.09
Baseline HP	−0.09	−0.15	−0.20**	−0.12
Physical stressor				
RSA reactivity	−0.02	−0.05	−0.03	−0.05
HP Reactivity	0.07	0.13	0.13	0.12
RSA recovery	−0.01	0.00	0.02	0.10
HP recovery	−0.18*	−0.17*	−0.21**	−0.11
Emotional stressor				
RSA reactivity	0.07	0.09	0.09	0.10
HP reactivity	−0.16*	−0.19**	−0.24**	−0.17*
RSA recovery	0.02	−0.11	−0.09	−0.08
HP recovery	0.01	0.05	0.03	−0.03

**p < 0.05, **p < 0.01.*

The final analyses did not focus on maltreatment history. Instead, the repeated measures analyses explored whether participants who scored above and below the clinical cutoff scores for somatization, depression, anxiety, and PTSD symptoms varied in their HP changes during the physical and emotional

stressor challenges. We also explored whether these effects remained when VE was entered as a covariate.

RESULTS

Distributions of the autonomic variables (i.e., VE, HP, and RSA) were explored for outliers. One extreme outlier on the VE measure (VE = 280.99, 6 *SD* above mean) was removed from the analysis. With this exclusion, VE scores ranged from 22.37 to 158.61 (M = 66.06, SD = 23.38). **Table 1** provides the descriptive statistics for the baseline and changes scores [natural log (ln) units for RSA and ms for HP].

Vagal Efficiency

Figure 1 illustrates VE for a participant with high VE and one with low VE. **Table 2** documents that participants with a maltreatment history exhibited dampened autonomic regulation reflected in lower RSA and HP baseline measures and lower VE. In addition, the participants with a maltreatment history reported more psychiatric symptoms.

Independent of maltreatment history, participants with lower VE reported more symptoms of depression and anxiety (**Table 3**). As illustrated in **Figure 2**, mediation analyses assessing whether the association between maltreatment history and the symptoms of depression and anxiety could be attributed to VE found evidence of partial mediation for both depression and anxiety. The indirect effect in both models was significant, with childhood maltreatment history being associated with lower VE, which—in turn—was associated with higher levels of anxiety and depression symptoms (**Figure 2** top panels). Plots of raw distributions showed that participants with childhood maltreatment had higher scores in adult depressive symptoms and adult anxiety that were associated with lower VE. This was in contrast to participants without childhood maltreatment history who had higher VE and concurrently lower levels of anxiety and depression symptoms (**Figure 2** bottom panels).

Maltreatment History, ANS Regulation, and Symptomatology

As reported in **Table 4**, VE was correlated with baseline levels, and HP reactivity and recovery to the physical stressor. The negative correlation between VE and HP reactivity indicates that participants with higher VE exhibited a greater reduction in HP in response to the physical stressor, which suggests greater increases in heart rate. Whereas, the positive correlation between VE and HP recovery indicates that participants with higher VE exhibited a greater increase in HP after the physical stressor, which suggests greater slowing of their heart rates.

As illustrated in **Figure 3**, the repeated measures were significantly different during the physical challenge for RSA and HP. During the emotional challenge, only HP systematically changed during the protocol. Note in the figure the significant between group differences with the maltreatment group having consistently lower levels of RSA and HP. In addition, a significant maltreatment group X repeated measures interaction documented that the HP reaction during the physical challenge significantly differed between the groups. As reported in **Table 2**, the participants with histories of maltreatment exhibited significantly less HP recovery in response to the physical stressor and less RSA reactivity in response to the emotional stressor.

As reported in **Table 3**, only measures of HP reactivity and recovery were associated with psychiatric symptoms. Participants with lower baseline HP levels reported more anxiety and PTSD symptoms; less HP recovery from the physical stressor reported more somatization, depression, and anxiety symptoms; and less HP reactivity in response to the emotional stressor reported more somatization, depression, anxiety, and PTSD symptoms. However, consistent with the mediation analyses, when VE was included as a covariate most correlations were no longer significant. The only remaining significant relationships were between HP recovery to the physical stressor and anxiety symptoms ($r = -0.25$, $p = 0.027$) and HP reactivity to the physical stressor and anxiety and PTSD symptoms ($r = 0.23$, $p = 0.042$ and $r = 0.35$, $p = 0.002$).

Exploring Pathways of Mediation

Table 5 displays the results of repeated measures analyses exploring whether participants who scored above and below the clinical cutoff scores for somatization, depression, anxiety, and PTSD symptoms varied in their HP changes during the physical and emotional stressor challenges. Specifically, we looked for main effects related to group status and interaction effects that considered the interaction of group status and HP levels. We also explored whether these effects remained when VE was entered as a covariate. As evident in **Table 5**, participants scoring above and below the clinical cutoffs for psychiatric symptomatology differed in the HP response to the physical and emotional stressor challenges. When VE was used as a covariate in analyses evaluating the autonomic responses to the physical stressor challenge for groups defined as above or below the clinical cutoffs for somatization, depression, anxiety, and PTSD the observed clinically related shorter HP was no longer statistically significant. In addition, for the groups defined by being below and above the clinical cutoffs for somatization, depression, anxiety, and PTSD there were significant group by repeated measures interactions. When VE was included as a covariate, the only significant interaction that remained was between the somatization groups. Similarly, with the emotional stressor challenge, the significant group differences related to depression, anxiety, and PTSD symptomatology were no longer present when VE was entered as a covariate. However, entering of VE as a covariate did not impact the HP by group interaction effects for the depression, anxiety, and PTSD groups (**Table 5**).

DISCUSSION

In this study, we expanded prior research (6) that documented that maltreatment history was associated with inefficient or atypical vagal regulation of the heart in response to physical and emotional stressors. In this study, we investigated whether

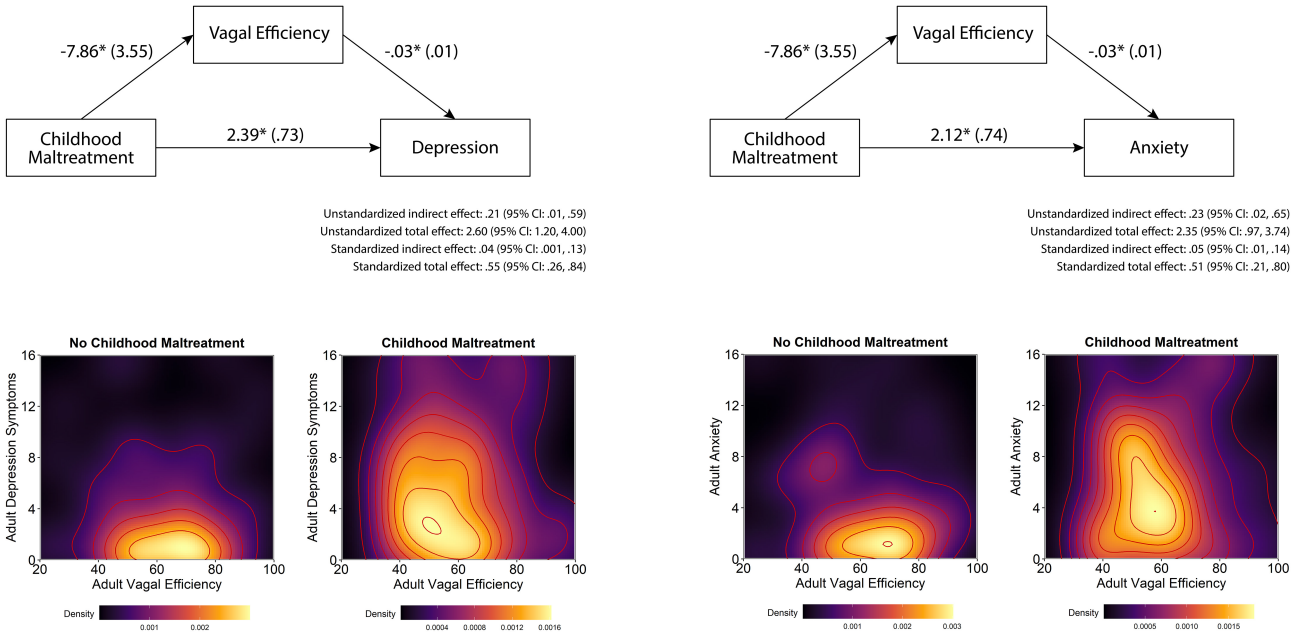


FIGURE 2 | Effects of childhood maltreatment on depression and anxiety as mediated by vagal efficiency. Note that in the top figures, first numbers represent path estimates and parentheses reflect standard errors, with significant paths marked with *. Partial mediation was supported by a non-zero indirect effects. In the bottom figures are density plots of VE and depression and anxiety symptoms, with lighter colors indicating higher density of observations and darker colors representing fewer observations. The modal tendency of the maltreatment sample skews left indicating poorer VE and upward indicating higher depression and anxiety symptomatology compared to the non-maltreated sample on the left.

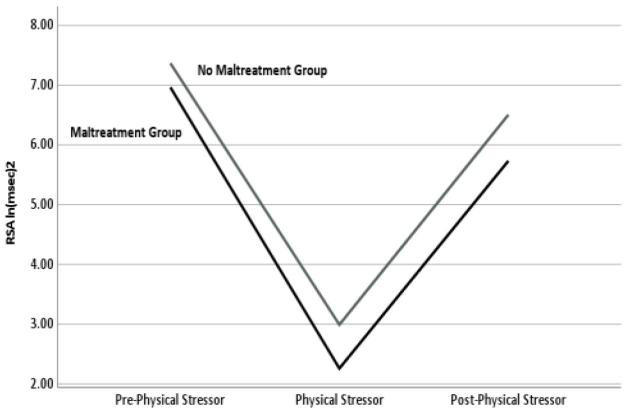
TABLE 4 | TableCorrelations among physiological variables.

	Physical stressor				Emotional stressor			
	Reactivity		Recovery		Reactivity		Recovery	
	RSA	HP	RSA	HP	RSA	HP	RSA	HP
Vagal efficiency	0.15	−0.51***	−0.10	0.48***	−0.03	0.07	0.04	0.04
Physical stressor								
RSA reactivity		0.45***	−0.45***	0.15	−0.26**	−0.14	0.16*	−0.03
HP reactivity			−0.35***	−0.45***	0.06	−0.21**	−0.16*	0.05
RSA recovery				0.48***	−0.09	0.04	−0.16*	−0.09
HP recovery					−0.34***	0.00	0.06	−0.14
Emotional stressor								
RSA reactivity						0.42***	−0.46***	−0.10
HP reactivity							−0.08	−0.41***
RSA recovery								0.40***

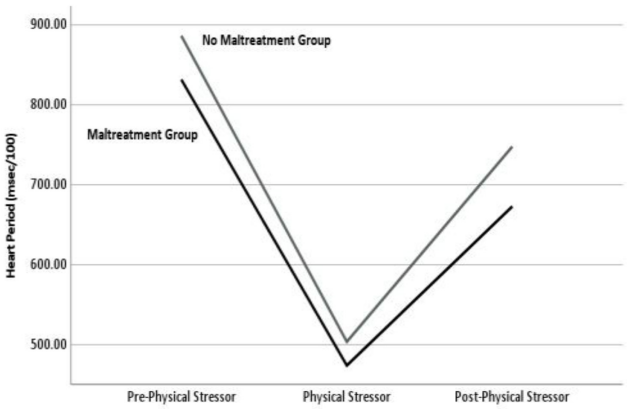
Vagal efficiency was calculated for the physical stressor.
**p < 0.05, **p < 0.01, ***p < 0.001.*

these findings relate to differences in VE. Consistent with our hypothesis, we documented that a history of maltreatment was related to lower levels of VE and that VE was related to dampened heart rate reactivity and recovery to the physical stressor.

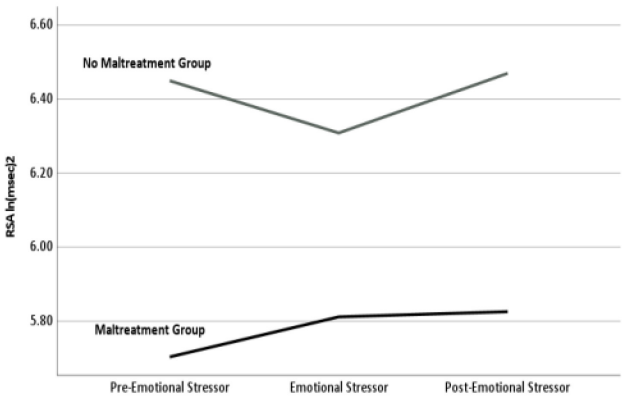
Further support comes from the finding that participants with lower VE levels reported more depression and anxiety symptoms, and that VE mediated the relationship between maltreatment history and depression and anxiety symptoms. These findings are consistent with Polyvagal Theory (9–11, 20, 21), which proposes that autonomic state functions as an intervening variable mediating reactivity to challenges. The findings are also consistent with prior research (43) that documented that a subjective measure of autonomic reactivity (i.e., Body Perception Questionnaire) (44, 45) mediated the relationship between maltreatment history and current worry, depression, and PTSD symptoms during the pandemic. Future research will need to address whether subjective experiences of autonomic symptoms positively correspond with sensor-based measures such as VE.



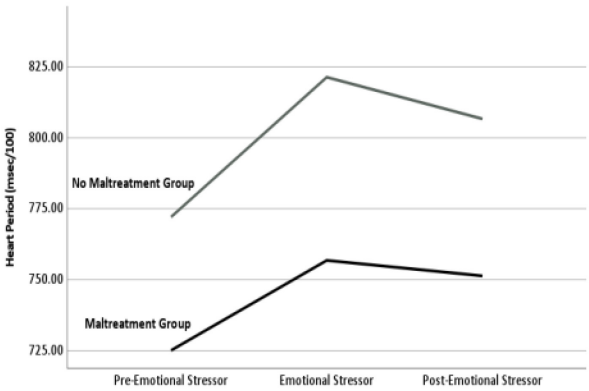
Time: $F(2, 162) = 801.28$, $p < .001$, partial $\eta = .91$
Time X Group: $F(2, 162) = 1.23$, $p = .297$, partial $\eta = .02$
Group: $F(1, 163) = 10.98$, $p = .001$, partial $\eta = .06$



Time: $F(2, 162) = 741.22$, $p < .001$, partial $\eta = .90$
Time X Group: $F(2, 162) = 3.93$, $p = .022$, partial $\eta = .05$
Group: $F(1, 163) = 9.46$, $p = .002$, partial $\eta = .06$



Time: $F(2, 162) = 1.79$, $p = .170$, partial $\eta = .02$
Time X Group: $F(2, 162) = 1.84$, $p = .162$, partial $\eta = .02$
Group: $F(1, 163) = 6.36$, $p = .013$, partial $\eta = .04$



Time: $F(2, 162) = 38.17$, $p < .001$, partial $\eta = .32$
Time X Group: $F(2, 162) = 1.80$, $p = .169$, partial $\eta = .02$
Group: $F(1, 163) = 6.10$, $p = .015$, partial $\eta = .04$

FIGURE 3 | Results of repeated measures analyses of variance documenting changes in respiratory sinus arrhythmia (RSA) and heart period (HP) in response to the physical stressor (i.e., riding a stationary bike) and the emotional stressor (i.e., viewing a video of a child being maltreated) as a function of maltreatment history.

Psychiatric symptoms were also related to metrics of autonomic regulation. Participants who exhibited less heart rate recovery in response to the physical stressor reported more somatization, depression, and anxiety symptoms, and those who exhibited less heart rate increases in response to the emotional stressor reported more somatization, depression, anxiety, and PTSD symptoms. Our findings provide a neurophysiological substrate for clinical observations that stress related disorders, such as anxiety, depression, and PTSD (46), are often marked by heightened reactivity and difficulty self-regulating while attempting to adaptively function (47) and adjust to environmental circumstances.

The results are consistent with prior research suggesting that major depression, anxiety disorders, and PTSD are associated with lower HRV (7, 8). Furthermore, the findings of an association between psychiatric symptoms and autonomic regulation builds on prior research that found those with lower vagal tone maintained consistently low HRV during a stress task and exhibited no post-stress recovery (48). Additionally, the results support previous research suggesting those with psychiatric disorders have less vagal activation and distinct, dysregulated autonomic profiles compared to healthy controls as demonstrated through measures of HRV and RSA (49). Thus, measures of heart rate regulation, particularly recovery from a physical stressor and reactivity to an emotional stressor, may be useful in assessing difficulties associated with the psychiatric components of PTSD. They may also be useful in measuring the autonomic dysregulation

TABLE 5 | Repeated measures ANOVA comparison of heart period regulation for the psychiatric symptom clinical cutoff groups.

Psychiatric symptom groups	Main effects for psychiatric groups and group × HP interaction effects	Without covariate			VE as Covariate		
		F	*p*	η^2	*F*	*p*	η^2
HP during physical stressor challenge							
Somatization	Group main effect	4.35	0.039	0.026	3.57	0.061	0.021
	Interaction effect	3.78	025	0.044	3.34	0.038	0.039
Depression	Group main effect	4.52	0.035	0.027	2.15	0.144	0.013
	Interaction effect	3.90	0.022	0.045	2.68	0.072	0.032
Anxiety	Group main effect	9.21	0.003	0.053	2.49	0.116	0.015
	Interaction effect	4.67	0.011	0.054	1.58	0.208	0.019
PTSD	Group main effect	5.06	0.026	0.030	1.96	0.163	0.012
	Interaction	3.40	0.036	0.040	1.83	0.165	0.022
HP during emotional stressor challenge							
Somatization	Group main effect	3.17	0.077	0.019	2.18	0.142	0.013
	Interaction effect	1.74	0.178	0.021	1.62	0.201	0.020
Depression	Group main effect	4.24	0.041	0.026	2.29	0.133	0.014
	Interaction effect	3.73	0.028	0.044	3.41	0.036	0.041
Anxiety	Group main effect	7.46	0.007	0.044	1.64	0.203	0.010
	Interaction effect	4.95	0.008	0.058	4.48	0.013	0.053
PTSD	Group main effect	5.31	0.022	0.032	2.66	0.105	0.016
	Interaction effect	3.81	0.024	0.046	3.53	0.032	0.043

that may precede cardiovascular, autoimmune, or stress-related disease (48).

Repeated measures analyses indicated participants above the clinical cutoff for the psychiatric symptoms exhibited faster heart rates (i.e., shorter HP). Changes related to heart rate reactivity and recovery were greater in the group below the clinical cutoff for PTSD, suggesting that the enhanced range of reactivity reflected more efficient neural control of heart rate through vagal mechanisms. Because many group-related differences in autonomic regulation were removed when VE was entered as a covariate, VE may influence accessibility to efficiently regulate metabolic resources to rapidly adjust to transitory demands and impact on psychiatric health by mediating the individual's ability to calm and socially engage.

Our findings are consistent with Polyvagal Theory (9–11), which proposes that following traumatic experiences the neural regulation of the "vagal brake" may become dysregulated (i.e., dampened) which may lead to less effective autonomic regulation and difficulties returning the body to a calm (i.e., ventral vagal regulated) baseline after experiencing a stressor. Several studies have reported an association between trauma history and atypical or disrupted autonomic functioning that leads to a heightened or potentially destabilized autonomic nervous system reflecting an inability to return to a more homeostatic state (50–52).

It is important to acknowledge that maltreatment history may also influence the sympathetic branch of the autonomic nervous system. Although no independent measure of sympathetic tone was monitored, a sympathetic contribution can be inferred from the heart rate data because neurophysiologically heart rate is determined by both sympathetic and vagal influences. If we assume that VE is effectively capturing the dynamic influence of vagal pathways on heart rate, then the use of VE as a covariate suggests that some of the remaining heart rate changes may be due to sympathetic influence. The results of covariate analyses support this speculation and document a relationship between clinical symptoms (anxiety and PTSD) and both HP reactivity and recovery to the physical challenge.

When interpreting these results, it is important to consider the limitations of this study. The use of a non-clinical sample of college students drawn from an introductory psychology participant pool at a private university necessitates the need for replication studies in non-college and clinical samples. In addition, maltreatment history and symptom data were obtained via self-report measures that may have been affected by social desirability and recall inaccuracies. Although the results are consistent with Polyvagal Theory, the cross-sectional design of this study does not allow us to determine whether VE is a causal determinant in the relationship between maltreatment history and symptomatology. Moreover, the lack of an independent measure of sympathetic activation limits interpretation of the dynamics between sympathetic and vagal influences. Thus, future research should be longitudinal, use larger and more diverse samples, conduct clinical interviews, obtain an independent measure of sympathetic tone, and use objective measures of symptomology.

Despite these limitations, the results highlight the importance of utilizing a biopsychosocial perspective when examining or predicting resilience, as both physiological and environmental factors relate to one's functioning and experience of symptoms (53, 54), and may impact or alter one's reactions to stress. The differences in autonomic regulation observed by those who experienced maltreatment suggest autonomic state regulation may be an important intervention target for trauma and PTSD, which could be supported by the inclusion of body-based, bottom-up methods as part of therapy (55, 56).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Hartford. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LD: oversee study planning, data collection and analyses, and write-up of manuscript. JK: data analyses, making figures, writing and editing of manuscript. JM: oversee data collection and data analyses. KL: editing of manuscript, fixing the references, and revising the manuscript after submission. KJ: writing of sections of manuscript. NB: creating of figures, editing of manuscript, and fixing of references. SP: conceptualization of manuscript, data analyses, and editing of manuscript. All authors contributed to the article and approved the submitted version.

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Resting Heart Rate Variability, Perceived Emotion Regulation, and Low-Risk Drug Use in College-Aged Adults: Gender as a Moderator

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Identification of individual differences in drug use is warranted, as a history of use is associated with future drug problems. Such drug use is thought to disrupt inhibitory and motivation networks involved in emotion regulation (ER). Higher resting heart rate variability (HRV), a biomarker of effective inhibitory abilities, is associated with less substance (e.g., alcohol, opioid) use. Higher HRV is associated with lower perceived ER difficulties, and this link is stronger in women relative to men. Evidence suggests women might engage in drug use primarily to reduce stress, and men primarily to induce feelings of elation. Research has yet to examine associations among individuals' difficulties in ER, resting HRV, and a recent history of drug use; the current study explored this, in addition to how these associations might differ as a function of gender. Young and healthy college students (N = 190; 88 women) completed a 5-min baseline to assess resting HRV, followed by the 36-item difficulties in ER Scale and 10-item Drug Abuse Screening Test. Higher difficulties in ER, but not resting HRV, were associated with a greater history of "low-risk" drug use in the full sample and moderation tests confirm this link was stronger in women. Moderated-mediation results confirmed an *indirect* association between resting HRV and drug use, mediated by self-reported difficulties among women only. A significant association between resting HRV and Difficulties in Emotion Regulation Scale (DERS) emerged only among women without a history of drug use. These results indicate that difficulties in ER are both associated with a low-risk history of drug use and underlie an indirect link between resting HRV and drug use history in women only. Among these women with a history of drug use relative to women without, there was no link between resting HRV and self-reported difficulties in ER, suggesting a disrupted inhibitory-motivational pathway. Additional work is needed to understand the psychophysiological correlates of a history of low-risk drug use in young men. These data are in line with research suggesting gender differences in the motivation to engage in recreational drug use and ER interventions might be important in women who engage in low-risk recreational drug use.

Keywords: history of drug use, emotion regulation, heart rate variability, motivation, vagal tone, health behaviors, gender, sex differences

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INTRODUCTION

The initial decision to engage in recreational drug use is typically voluntary, and with continued use, a person's ability to exert self-control can become seriously impaired (1, 2). In this regard, the Substance Abuse and Mental Health Services Administration (3) proposes that the earlier people begin to use drugs, the more likely they are to develop an addiction, known as a chronic, relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences (4, 5). Therefore, understanding the biological and motivational correlates of recreational drug use is both necessary and warranted for well-being and longevity.

Inhibition, Emotion Regulation, and Drug Usage

Drug use elicits powerful emotions that can range from remarkably high states, such as pronounced euphoria, to devastatingly low negative emotional states that in the extreme cause disruption and break with homeostasis (6). Repetitive drug use also produces an abnormal activation of incentive salience/reward systems, such as the release of dopamine and opioid peptides in the extended amygdala, which generally plays a crucial role in guiding behavior toward high-value incentives in the environment (6). Thus, it is clear that neurophysiological pathways underlying emotional-motivational states might be disrupted in individuals who engage in early recreational drug use. Such disruption is indicative of poorer emotion regulation (ER), defined as an individual's ability to modify their emotional experiences, expressions, and subsequent physiological responses to appropriately respond to ever-changing environmental demands (7). In other words, ER is a mechanism that enables better coping with environmental demands (8, 9). Therefore, it is possible that individuals with more difficulties in ER also have a history of recreational drug use, and vice versa.

Inhibitory control is a necessary component of ER as it involves controlling one's behaviors and thoughts, potentially overriding a strong internal predisposition or external temptation and choosing the most appropriate or needed response (10, 11). From a neurophysiological perspective, cortical brain regions, such as the prefrontal cortex, exert inhibitory control of subcortical structures, such as the amygdala, thereby allowing the organism to respond to environmental demands adaptively and effectively engaging in self-regulation such as ER (12). Therefore, in a resting state, active cortical brain regions may represent more flexibility in inhibitory control and thus self-regulation (12, 13). Importantly, converging evidence suggested that the reciprocal activity between the neural structures is reflected in autonomic nervous system activity (12). To elucidate the psychophysiological mechanisms connecting inhibition with overall health, Thayer and Lane (13) proposed that characteristic beat-to-beat variability in the heart rate time series – heart rate variability (HRV) – serves not only as an index of healthy heart function (14), but also as a readily available index and measure of inhibitory control, ER ability (11, 15), and overall self-regulatory (e.g., self-control) abilities (12).

Resting Heart Rate Variability as an Index of Emotion Regulation Abilities

Several neuroimaging and pharmacological studies have identified the link between inhibitory executive brain regions and cardiac parasympathetic activity as indexed by resting HRV (12, 16, 17). The Neurovisceral Integration Model (NIM) postulates that HRV is an index of parasympathetic activity, and thus *resting* HRV serves as a readily available biomarker of self-regulatory (e.g., emotional and cognitive control) abilities. For instance, individuals with higher resting HRV have been shown to exhibit effective behavioral responses (e.g., faster response times and better accuracy) on executive cognitive tasks (18) as well as more flexible and adaptive emotional responding relative to individuals with lower resting HRV (19, 20). In contrast, individuals with the latter pattern exhibit hypoactive prefrontal brain activation, which results in hyperactive subcortical structures that are believed to contribute to maladaptive cognitive and emotional self-regulation (12). Overall, a reciprocal cortico-subcortical inhibitory neural circuit may serve as the structural link between psychological processes such as ER and health-related physiological processes, and this circuit can be indexed by resting HRV (12).

As it relates to substance consequences, lower HRV is associated with greater alcohol problems (21, 22), cravings for alcohol and associated negative mood (23), and non-medical prescription opioid use (24). Furthermore, chronic drug use also tends to be associated with reduced HRV (25). Additionally, previous research showcased the possible feasibility of utilizing an HRV biofeedback intervention (added to a traditional 28-day substance disorder inpatient treatment program) and its efficacy for reducing alcohol and drug cravings (26). Specifically, lower resting HRV was related to increases in craving, whereas higher resting HRV was related to a greater decrease in craving from the start to the end of the treatment (26). This study highlighted the idea that lower resting HRV, marking poorer self-regulation, increases drug use. However, research has yet to link resting HRV with *self-reported* history of drug use. This is warranted as individual differences in resting HRV appear to be a useful index in identifying individuals' likelihood of engaging in recreational drug use – a gateway to drug problems.

Importantly and in line with the NIM, resting HRV has been linked with self-reported ER difficulties, such that higher resting HRV is linked with lesser perceived difficulties in ER (11, 15, 27). In young and apparently healthy individuals, it has been conceptualized that disruptions in the link between resting HRV and perceived ER difficulties might reflect a lack of consistency between ER capacity and ER motivations, respectively (27). As mentioned, disruptions in neurophysiological pathways underlying emotional-motivational states exist in drug users. Thus, the association between resting HRV and self-reported ER difficulties should be weaker in those with a history of drug use, as those individuals should be less accurate in their ER assessment thereby reflecting lesser disruption in emotional-motivational states. Yet, research has not considered how the association between resting HRV and self-reported ER difficulties might differ between those with and those without a history of drug use.

Gender Differences

While the gender gap has been decreasing over the past few decades (28), according to the (29) men are more likely than women to use almost all types of illicit drugs, including methamphetamines, cannabis, inhalants, tranquilizers, cocaine, narcotics, and hallucinogens (30). Recent research has found that the propensity for drug use has stayed consistent between genders in that men continued to display riskier behavioral patterns with regard to using illicit substances compared to women (31). Notably, the motivation to initiate drug use differs between men and women. One report proposed men typically engage in drug use to induce feelings of elation, energy, or focus, whereas women might engage in drug use to alleviate high-stress levels, feelings of alienation, depression, anxiety, or post-traumatic stress disorder (28). Additional research also supports a similar gender difference as it relates to the motivation to *initiate* drug use. It has been noted that men primarily misuse prescription opioids to "get high," whereas women misuse them to help with relaxation and sleep (32), and ER is a relevant factor here. Furthermore, men have been found to typically misuse psychostimulants (e.g., Ritalin, Dexedrine, and Adderall) for reasons related to partying, socializing, increasing sociability, and prolonging the effects of alcohol, while women are more likely to misuse psychostimulants for reasons related to schoolwork, particularly in regards to increased productivity (33). Previous research has also noted that men smoke cigarettes for the reinforcing drug effect of nicotine, whereas women smoke primarily for mood regulation and cue reactivity (34). Taken together, these reports suggest clear gender differences in the motivation to engage in drug use.

Moreover, a meta-analysis suggests that despite having greater heart rate, women also have higher resting HRV compared to men (35). Thus, gender differences in HRV might explain gender differences between men and women in drug use tendencies (i.e., women have greater inhibitory control thus less likely to have a history of drug use). Yet, higher psychopathology (i.e., depression and anxiety) is associated with greater substance issues (36, 37), and thus, ER difficulties may be particularly linked with a history of drug use in women. Relatedly, studies have shown that the negative association between resting HRV and both self-reported ER difficulties (27) and HR (38) is stronger in women than men; these data suggest basic psychophysiological differences between women and men which might extend to drug use tendencies.

Consequently, there is a possibility of gender differences in the relationships among resting HRV, self-reported difficulties in ER, and history of drug use. This is particularly important to consider in a young and apparently healthy population, as it would highlight how a history of drug use in early adulthood is related to psychophysiological processes differentially between men and women. Such results would potentially suggest a differential intervention between genders as it relates to decreasing the likelihood of drug use, supporting Cosgrove et al. (34) suggestion that more gender-sensitive treatments need to be taken into consideration. To this end, research on HRV and substance use has not often considered gender as a factor that may substantially alter such findings.

Present Study

Emotion regulation is implicated in substance use, including drug use; however, research has yet to consider the association among perceived ER difficulties (i.e., self-reported/subjective ER difficulties), resting HRV (i.e., objective ER abilities), and self-reported history of drug use. Such an investigation would work to understand psychophysiological processes related to drug use. Therefore, our study sought to evaluate the association between a history of drug use and both resting HRV and difficulties in ER. We were particularly interested in these direct associations, in addition to if the link between resting HRV and ER difficulties differed between those with and those without a history of drug use. Finally, we examined whether men and women differed in the above associations.

Considering converging evidence linking substance use with ER processes, we hypothesized a history of drug use to be correlated with lower resting HRV and higher perceptions of ER difficulties. Furthermore, as drug use might disrupt emotional-motivation systems (39), we hypothesized a weaker correlation between resting HRV and ER difficulties in those with relative to those without a history of drug use.

Given that the link between resting HRV and perceived ER difficulties (11, 15, 27), objective (35) and subjective ER (27), and the rationale for engaging in drug use (28, 32, 33) all differ between genders, it is likely that our hypotheses differ between men and women. We hypothesized that women would show both higher resting HRV and an unlikely history of drug use compared to men. In line with this, if women engage in early drug usage for feelings of stress in contrast to men who may engage in drug usage for feelings of elation, both resting HRV and self-reported ER difficulties should be more strongly associated with drug usage in women compared to men. In other words, we hypothesized that gender would moderate or alter the association between ER processes and a history of drug use (see **Figures 1A**-I,A-II for hypothesized conceptual model). Finally, the negative association between resting HRV and ER difficulties appears stronger in women (27), therefore we hypothesized that the correlation between resting HRV and ER difficulties should be particularly weaker in women with a history of drug use relative to women without.

As an exploratory analysis, we examined the potential mediated (i.e., three-way or indirect) association between resting HRV, ER difficulties, and a history of drug use (see **Figure 1B** for possible conceptual models) and if gender moderated this model (see **Figure 1C** for possible conceptual models).

MATERIALS AND METHODS

Participants

Archival data from two pooled studies conducted within the Emotions and Quantitative Psychophysiology Lab at The Ohio State University were combined for the current study. The primary focus of one study was to consider ethnic differences in the psychophysiological correlates of pain [see (40) for additional methods and procedure details], and the other study focused on false memory [see (41) for similar methods and procedure]. In

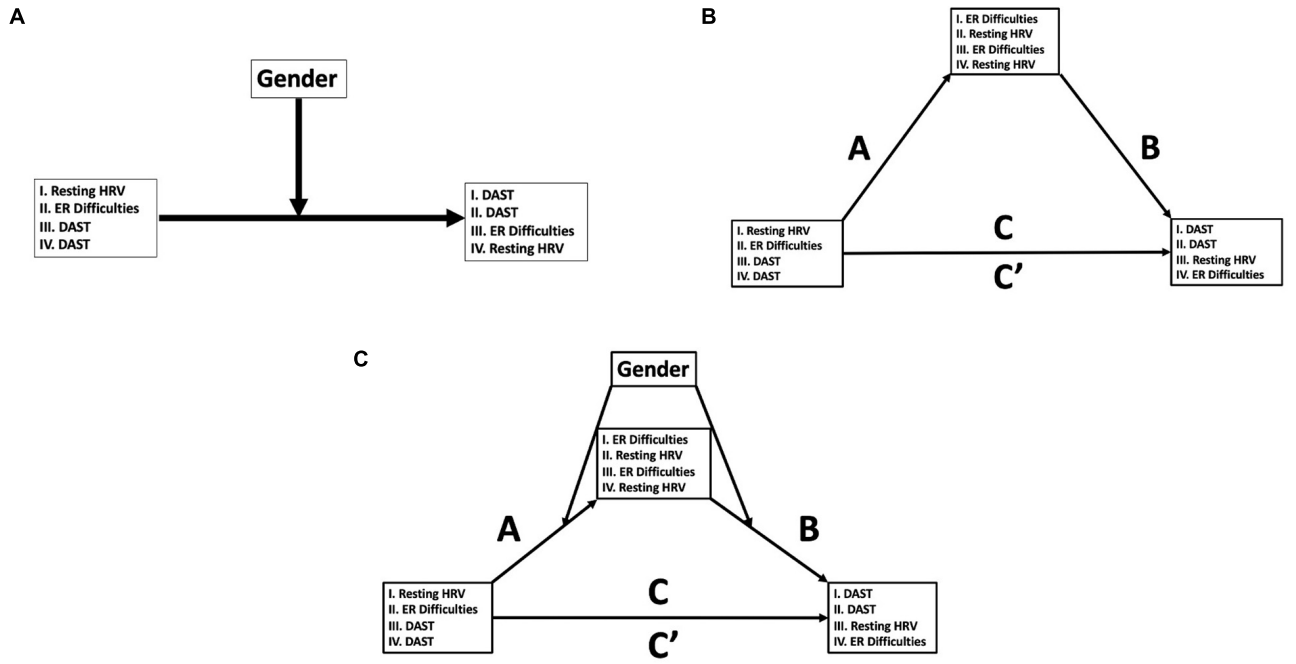

FIGURE 1 | Conceptual moderation, mediation, and moderated-mediation models. **(A)** PROCESS Model 1 (48): moderation models of variables of interest (HRV, heart rate variability; ER, emotion regulation; DAST, Drug Abuse Screening Test). Models 1A and 1B refers to hypothesized models, and Models 1C and 1D are alternative models that were examined (see section "Materials and Methods" for details). **(B)** PROCESS Model 4 (48): mediation models of variables of interest (HRV, heart rate variability; ER, emotion regulation; DAST, Drug Abuse Screening Test). Model 2A refers to the hypothesized model, and Models 2B and 2C are alternative models that were examined (see section "Materials and Methods" for details). **(C)** PROCESS Model 58 (48): moderated-mediation models of variables of interest (HRV, heart rate variability; ER, emotion regulation; DAST, Drug Abuse Screening Test). Model 3A refers to the hypothesized model, and Models 3B and 3C are alternative models that were examined (see section "Materials and Methods" for details).

both studies, participants were recruited *via* two methods: (1) a Research Experience Program (REP) pool at The Ohio State University, which allowed students to participate in research for partial class credit in an introductory level psychology course, and (2) cash compensation for individuals' participation outside of the research pool. A total of 190 participants (102 males, 88 females; 88 ethnic minorities; M_{age} = 20.07, SD = 2.87, age range: 18–38 years) were available for analysis. Of the 190 participants, 63 of the present study participants were included in Williams et al. (27). Participants younger than 18 years old and/or those who were allergic to adhesives were not able to participate in either study.

Procedure

In both studies, participants were asked not to smoke, undergo vigorous physical activity, or drink caffeine 6 h prior to the start of the experimental session. Each study was approved by the Institutional Review Board (IRB) at The Ohio State University, and all participants signed written informed consent. In both studies, participants were placed in a soundproof experimental room equipped with a camera and microphone for safety and instructional reasons and a high-definition TV for stimuli presentation. Participants were given a detailed explanation of the procedures that would occur without indicating the specific hypothesis under the study or manipulations applied. Electrocardiogram leads were attached to the subjects, and while in a separate control room, the experimenter led the subjects through the initial phases of the experiment. All participants first completed a 5-min baseline-resting period, which included viewing a blank, gray screen. They were told not to move or fall asleep and to simply relax and breathe normally. Participants then completed a set of self-report questionnaires; importantly, the questionnaires were administered prior to any experimental procedure in both studies.

Resting Heart Rate Variability

Cardiac activity data were recorded continuously throughout each experiment *via* a three-lead ECG at a 1000 Hz sampling rate using a Mindware^{TM} 2000D (MW2000D) Impedance Cardiograph package. Resting vmHRV was assessed during a 5-min baseline (spontaneous breathing and resting state) period prior to any experimental task. Electrodes were placed (1) below the right clavicle, (2) on the left side of the abdomen (below the heart), and (3) on the right side of the abdomen. The variability between successive R-spikes (or variability within inter-beat-intervals, IBIs) was obtained from ECG recordings to calculate HRV. Participants' successive IBIs, in milliseconds, were extracted using HRV 2.51 Analysis software. IBIs were written in a text file and analyzed using Kubios HRV analysis package 2.0 (42), allowing for the calculation of time-and frequency-domain indices of HRV. Artifacts within the R-to-R series were visually detected. An artifact correction level that would

differentiate and remove artifacts (differing abnormal IBIs from the mean IBI) using a piecewise cubic spline interpolation method was employed. The root mean square of successive differences (RMSSD), measured in milliseconds, was calculated and is considered to be a stable (43) and valid (44, 45) time-domain measure of HRV. Autoregressive estimates were also calculated, yielding high-frequency power HRV (HF-HRV, 0.15–0.4 Hz) (44, 45). In the present study, RMSSD correlated highly with HF power (r = 0.90, $p < 0.001$). For ease of interpretation, only HRV results using HF-HRV are reported, although results were virtually identical using RMSSD. HF-HRV values were natural log-transformed (ln) to fit assumptions of linear analyses (45).

Self-Report Questionnaires

Perceived difficulties in ER were assessed *via* self-report using the Difficulties in Emotion Regulation Scale (DERS; completed within 30 min of the baseline-resting period described above). The DERS is comprised of 36-items and 6 sub-scales designed to measure different facets of difficulties in ER (46). Participants are asked to respond on a scale from 1 (*almost never*) to 5 (*almost always*) regarding how much these statements are reflective of them (example item: "*When I'm upset, I believe that I will end up feeling very depressed*"). Subscales included (a) *difficulties in controlling impulsive behavior when experiencing negative emotions* (impulse); (b) *lack of strategies to regulate emotions* (strategies); (c) *lack of emotional awareness* (awareness); (d) *non-acceptance of emotional responses* (non-accept); (e) *lack of emotional clarity* (clarity); and (f) *difficulties engaging in goal-oriented behavior when experiencing negative emotions* (goals). The DERS total score is based on all 36-items, and subscales were calculated in accordance with prior psychometric studies.

Drug use history (over the prior 12 months) was assessed using the Short Form Drug Abuse Screening Test (DAST-10), a 10-item self-report scale adapted from the original 28-item DAST (47). Participants answer YES or NO on each of the 10 questions. A score of "1" is given for each YES response, and a score of "0" is given for each NO response. Higher scores are indicative of a higher risk of drug use. According to this scale, score labels are as follows: a score of zero – No problems reported; a score of 1–2 – Low level; a score of 3–5 – Harmful; a score of 6–8 – Substantial level; and a score of 9–10 – Severe level. All participants (n = 190) included in this study scored between 0 and 2, and thus, all individuals fell between "no risk" or those without a history of drug use, and "low-risk" or those with a history of drug use.

Statistical Analyses

Participants were stratified into groups based on their self-reported gender. In addition to keeping DAST scores as a "continuous" variable (scores 0–2), participants were also divided into two groups based on their DAST scores; those who scored a total score of zero were considered to be the "no risk" or no history of drug use group, and those who scored one or two points were grouped as the "low-risk" or history of drug use group.

Correlations were used to determine associations between variables of interest. Due to the non-normal distribution of DAST scores, all correlation coefficients between DAST scores and other variables are represented as Spearman's rank correlation coefficients (ρ), while all other correlation coefficients represent Pearson's r. These correlations were conducted in the entire sample as well as stratified by gender.

To test if gender moderated the relationship between resting HRV and DERS scores on DAST scores, the SPSS-macro PROCESS was used (48). In PROCESS, "Model 1" was used to test the moderating effect of the independent variables (IV; HF-HRV, DERS), a conditional effect of the moderator (M; gender), and an interaction effect of the two on the dependent variable (DV; DAST scores) (see **Figures 1A**-I for conceptual representation for HRV model; see **Figures 1A**-II for conceptual representation for DERS model). Conditional effects (48) were used to probe potential differential associations of the moderator (i.e., gender). In this regard, high and low values for the predictor variables are derived using ±1 SD from the mean, allowing the PROCESS program to yield predicted DV values at varying levels of the predictor variable *via* regions of significance and simple slope analyses. Models using DAST scores as IVs and both DERS (see **Figures 1A**-III for conceptual representation) and resting HRV (see **Figures 1A**-IV for conceptual representation) as DVs were also tested as alternatives.

In PROCESS (48), Model "4" was also used to explore potential mediation effects between resting HRV, DERS, and DAST scores. In this test, resting HRV was the IV with the mediating variable as DERS scores, with and DAST scores as the DV (see **Figures 1B**-I for conceptual representation). Alternative models were also considered, with DAST scores as the IV, DERS scores as the mediating variable, and resting HRV as the DV (see **Figures 1B**-III for conceptual representation), in addition DAST as the IV, M as resting HRV, and DERS scores as the DV (see **Figures 1B**-IV for conceptual representation). Finally, gender was considered the moderating variable in "Model 58" in PROCESS (48), which represents moderated mediation. That is, we tested if gender moderates a possible mediation model proposed among HRV, DERS, and DAST scores (see **Figure 1C** for all tested conceptual models). For both Models 4 and 58, statistics for Paths A (IV-M), B (M-DV), C (direct IV-DV), and C' (indirect IV-DV) are reported. Statistics include unstandardized beta (B) coefficients, standard errors (SEs; in brackets), 95% bootstrapping confidence intervals [95% boot CI in square brackets, 5000 samples; (48)], partial correlation coefficients (for main effects and interactions), and p-values.

In all PROCESS (48) analyses, several covariates were considered. Ethnicity has a non-trivial association with resting HRV (49, 50) and thus, was included as a covariate in applicable analyses (ethnicity coded as 1 = White, 2 = Black, 3 = Asian, 4 = Hispanic, 5 = Middle Eastern, 6 = Other). Higher body mass index (BMI) is also associated with decreased resting HRV [e.g., (51, 52)]; in the current sample, men showed greater BMI compared to with women (see section "Results" for details) and thus, BMI was also used as a covariate in applicable analyses. Gender was also included as a covariate for PROCESS models that did not include gender as a predictor variable.

All statistical tests were conducted using SPSS (ver. 27, IBM, Chicago, IL, United States). All tests were two-tailed, and significance levels were evaluated using an alpha of 0.05.

RESULTS

Participant Demographics

Means and standard deviations for all variables of interest, in addition to gender differences, are presented in **Table 1**. Women had marginally higher DERS (M = 84.47, SD = 20.15); [$t(188) = -1.716$, $p = 0.044$, $\eta = 0.124$] and strategies subscale (M = 16.32, SD = 6.29); [$t(188) = -1.87$, $p = 0.032$, $\eta = 0.135$] scores compared to men (DERS: M = 80.00, SD = 15.69; M = 14.83, SD = 4.64). There were no significant differences between men and women on resting HRV [$t(188) = 0.50$, $p = 0.309$, $\eta = 0.037$] or DAST scores; [$t(188) = -0.47$, $p = 0.318$, $\eta = 0.035$].

Zero-Order Correlations Among Variables of Interest

Correlations among the variables of interest in the entire sample are presented in **Table 2A**. In the full sample, higher DAST scores were related to higher DERS ($\rho = 0.196$, $p = 0.007$) and impulse subscale ($\rho = 0.202$, $p = 0.005$) scores. Resting HRV was not significantly correlated with any variables of interest at a bivariate level. Stratified by men and women (**Table 2B**), resting HRV was negatively correlated with DERS ($r = -0.238$, $p = 0.026$) and DERS-strategies subscale scores ($r = -0.288$, $p = 0.007$) for women. Drug use scores were positively correlated with DERS ($\rho = 0.336$, $p = 0.001$), DERS-impulse subscale ($\rho = 0.346$, $p < 0.001$), and DERS-strategies subscale ($\rho = 0.222$, $p = 0.037$) scores for women. No significant or notable associations were found among men. Stratified by drug group (**Table 2C**), resting HRV was negatively correlated with BMI ($r = -0.217$, $p = 0.016$) for the no-risk group. There were no significant or notable associations amongst the low-risk group.

The association between resting HRV and DERS was significant in no-risk women ($r = -0.304$, $p = 0.025$), but not in low-risk women ($r = -0.120$, $p = 0.500$), no-risk men ($r = 0.076$, $p = 0.533$), or low-risk men ($r = -0.072$, $p = 0.692$). See **Figure 2** for scatterplots of these associations by group; results remain the same considering covariates.

Moderation, Mediation, and Moderated-Mediation Analyses

Moderation analyses showed that gender significantly moderated the association between DAST and DERS scores [B = 12.67 (5.35), 95% boot CI [2.11, 23.24], $r_{partial} = 0.30$, $p < 0.05$]. Conditional analyses showed that women [B = 12.74 (3.82), 95% boot CI [5.21, 20.27], $p < 0.01$] compared with men [B = 0.07 (3.72), 95% boot CI [−7.28, 7.41], $p = 0.99$] showed a stronger association between DAST and DERS scores (see **Figure 3**). A similar moderation effect of gender was also found on the association between DAST and the DERS-impulse subscale [B = 2.75 (1.2), 95% boot CI [0.39, 5.11], $r_{partial} = 0.30$, $p < 0.05$]. Conditional analyses showed that women [B = 3.05 (0.85), 95% boot CI [1.36, 4.73], $p < 0.001$] compared with men [B = 0.29 (0.83), 95% boot CI [−1.35, 1.94], $p = 0.72$] showed a stronger association between DAST and DERS-impulse (not graphically represented).

Gender did not significantly moderate the association between drug use and HRV [$B = -0.15$ (0.22), 95% boot CI [−0.57, 0.28], $p = 0.493$]. Similarly, moderation analyses showed that gender did not significantly moderate the association between drug use and difficulties in ER [B = 6.463 (3.74), 95% boot CI [−0.92, 13.84], $p = 0.086$].

In the full sample, DERS mediated an *indirect* association between resting HRV and DAST scores [B = 0.007 (0.003), 95% boot CI [0.0014, 0.0123], $p < 0.05$], such that lower resting HRV was associated with higher DERS scores, but not statistically significant [Path A: $B = -1.88$ (1.30), 95% boot CI [−4.44, 0.68], $p = 0.149$]. Higher DERS scores were associated with higher DAST scores [Path B: B = 0.007 (0.003), 95% boot CI [0.001, 0.012], $p < 0.05$], and the indirect effect was significant [$B = -0.01$ (0.01), 95% boot CI [−0.03, 0.00]] (see **Figure 4A** for graphical representation). It is important to note that, and as expected given the correlation analyses, the direct effect was not significant [B = 0.007 (0.05), 95% boot CI [−0.091,

TABLE 1 | Mean differences between men and women on variables of interest.

	Total	Men	Women	*F*	*r*	*p*
N	190	102	88			
BMI	24.78 (6.13)	25.14 (4.96)	24.36 (7.27)	0.77	0.063	0.383
Mean HR	75.50 (11.45)	75.04 (11.79)	76.03 (11.45)	0.35	0.044	0.554
Resting HRV	6.74 (1.01)	6.720 (1.03)	6.760 (0.97)	0.09	0	0.764
Drug use	0.46 (0.69)	0.440 (0.70)	0.490 (0.68)	0.22	0.032	0.636
Total DERS	82.07 (17.98)	80.00 (15.69)	84.47 (20.15)	2.94	0.122	0.088
Impulse	11.03 (4.02)	10.75 (3.14)	11.35 (4.85)	1.04	0.077	0.308
Strategies	15.52 (5.50)	14.83 (4.64)	16.32 (6.29)	3.48	0.134	0.064
Awareness	18.85 (4.02)	18.98 (4.83)	18.70 (4.84)	0.15	0.032	0.695
Non-accept	11.58 (5.39)	10.80 (4.86)	12.48 (5.84)	4.65	0.155	**0.032***
Clarity	11.99 (3.09)	11.70 (2.96)	12.34 (3.23)	2.06	0.104	0.152
Goals	13.09 (3.69)	12.93 (3.33)	13.27 (4.09)	0.4	0.044	0.527

*This table presents the means and standard deviations (in brackets) on variables of interest both in the full sample and stratified by women and men. MANOVA statistics include F- and p-values along with effect size represented by eta (r). Significant differences bolded. HRV, heart rate variability; HR, heart rate; DERS, difficulties in emotion regulation (subscales italicized); BMI, body mass index. *p < 0.05.*

TABLE 2 | Correlation coefficients for full sample and stratified by gender and drug group.

A		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1	Drug use	–									
2	Resting HRV	−0.019	–								
3	Total DERS	**0.196****	−0.105	–							
4	*Impulse*	**0.202****	−0.080	**0.822****	–						
5	*Strategies*	0.126	−0.128	**0.870****	**0.729****	–					
6	*Awareness*	0.021	−0.069	**0.292****	0.091	−0.015	–				
7	*Non-accept*	0.084	−0.133	**0.746****	**0.549****	**0.663****	−0.067	–			
8	*Clarity*	0.107	0.054	**0.631****	**0.490****	**0.445****	**0.313****	**0.215****	–		
9	*Goals*	**0.202****	0.004	**0.680****	**0.497****	**0.630****	−0.123	**0.496****	**0.317****	–	
10	BMI	0.034	**−0.147***	0.104	0.121	0.084	0.080	0.050	0.101	−0.010	–
B		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1	Drug use	–	−0.071	**0.336****	**0.346****	**0.222***	0.052	0.174	0.158	**0.408****	−0.065
2	Resting HRV	0.023	–	**−0.238***	−0.140	**−0.288****	0.020	**−0.305****	0.017	−0.168	**−0.274****
3	Total DERS	0.052	0.022	–	**0.853****	**0.898****	0.172	**0.817****	**0.656****	**0.648****	0.118
4	*Impulse*	0.067	−0.015	**0.776****	–	**0.767****	−0.017	**0.654****	**0.567****	**0.479****	0.072
5	*Strategies*	0.030	0.033	**0.822****	**0.661****	–	−0.116	**0.759****	**0.531****	**0.615****	0.183
6	*Awareness*	−0.006	−0.140	**0.443****	**0.245***	0.112	–	−0.060	**0.223***	**−0.227***	0.043
7	*Non-accept*	−0.013	0.021	**0.643****	**0.385****	**0.515****	−0.069	–	**0.279****	**0.505****	0.147
8	*Clarity*	0.064	0.082	**0.596****	**0.385****	**0.324****	**0.407****	0.118	–	**0.292****	0.060
9	*Goals*	−0.007	0.171	**0.723****	**0.531****	**0.655****	−0.011	**0.484****	**0.341****	–	−0.095
10	BMI	0.145	−0.002	0.108	**0.232***	−0.058	0.126	−0.070	0.179	0.129	–
C		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
1	Resting HRV	–	−0.112	−0.100	−0.114	−0.076	−0.161	0.136	−0.023	−0.034	
2	Total DERS	−0.104	–	**0.866****	**0.917****	0.088	**0.734****	**0.576****	**0.704****	−0.026	
3	*Impulse*	−0.065	**0.780****	–	**0.777****	−0.025	**0.581****	**0.500****	**0.534****	0.058	
4	*Strategies*	−0.143	**0.830****	**0.667****	–	−0.101	**0.644****	**0.487****	**0.704****	−0.041	
5	*Awareness*	−0.064	**0.422****	0.177	0.040	–	−0.227	−0.066	−0.240	0.091	
6	*Non-accept*	−0.114	**0.758****	**0.531****	**0.681****	0.023	–	**0.255***	**0.471****	−0.218	
7	*Clarity*	−0.002	**0.656****	**0.469****	**0.399****	**0.534****	**0.181***	–	**0.311***	0.052	
8	*Goals*	0.023	**0.641****	**0.425****	**0.551****	−0.060	**0.510****	**0.294****	–	0.027	
9	BMI	**−0.217***	0.175	0.164	0.163	0.073	**0.193***	0.124	−0.044	–	

*Table A represents correlations between variables of interest for the full sample (n = 190). Table B represents correlations between variables of interest stratified by gender with men on the left side of the diagonal and women on the right. Finally, Table C represents correlations between variables of interest stratified by drug group with no risk individuals on the left of the diagonal and low risk individuals on the right. Significant correlations bolded. HRV, heart rate variability; DERS, difficulties in emotion regulation (subscales italicized); BMI, body mass index. *p < 0.05, **p < 0.01.*

0.104], $p = 0.89$]. Gender also moderated this mediation analysis [$B = 40.08$ (17.60), 95% boot CI [5.35, 74.81], $p < 0.05$] such that this indirect effect was present only in women [$B = -4.93$ (1.95), 95% boot CI [−8.78, −1.09], $p < 0.05$] but not men [$B = 0.34$ (1.69), 95% boot CI [−3.01, 3.68], $p = 0.84$] (see **Figure 4B**).

In the full sample, DERS did not significantly mediate a link between DAST scores and resting HRV [$B = -0.006$ (0.004), 95% boot CI [−0.014, 0.002], $p = 0.149$; see **Figures 1B**-III for conceptual model]. It is also important to note that the direct effect was not significant [$B = 0.015$ (0.108), 95% boot CI [−0.199, 0.229], $p = 0.890$]. Gender also did not moderate this mediation analysis [$B = 1.228$ (3.097), 95% boot CI [−4.883, 7.338], $p = 0.692$; see **Figures 1C**-III for conceptual model].

Furthermore, in the full sample, resting HRV did not significantly mediate the association between DAST scores and DERS [$B = -1.852$ (1.279), 95% boot CI [−4.374, 0.670], $p = 0.149$; see **Figures 1B**-IV for conceptual model], however, the direct effect was significant [$B = 4.670$ 1.872, 95% boot CI [0.977, 8.364], $p = 0.014$]. Gender did not moderate this mediation analysis [$B = 0.114$ (0.179), 95% boot CI [−0.238, 0.466], $p = 0.524$; see **Figures 1C**-IV for conceptual model].

DISCUSSION

The primary goals of the present study were: (1) to examine the association between a history of drug use and both resting HRV and ER difficulties; (2) to explore if a history of drug use impacts the link between resting HRV and difficulties in ER; and (3) investigate gender differences in these associations.

Correlation and moderation tests partially supported our hypotheses in that there was a direct association between a

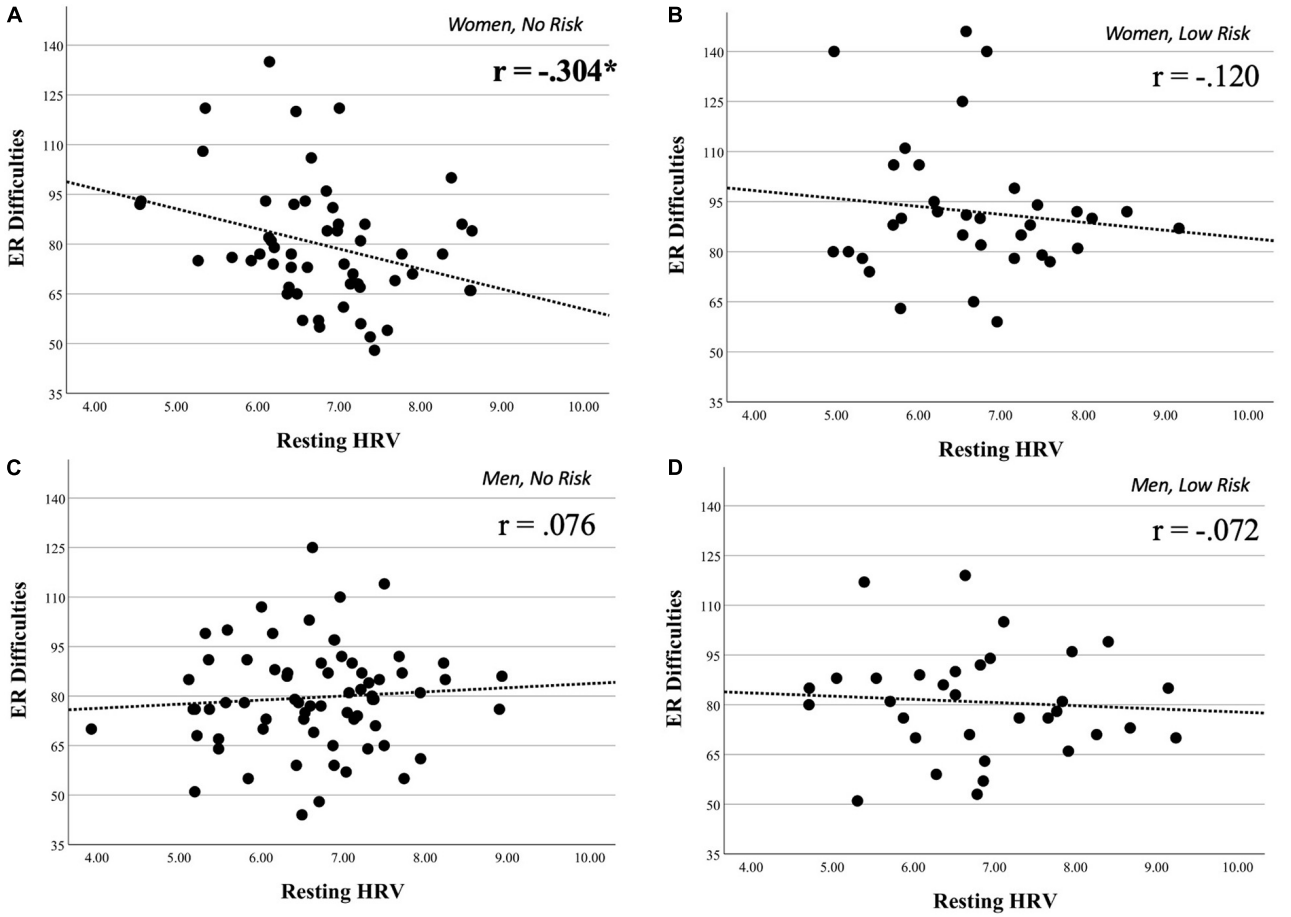

FIGURE 2 | Scatterplots on the association between resting HRV and ER difficulties on groups of interest. Scatterplots illustrating the associations between resting heart rate variability (HRV) and Difficulties in Emotion Regulation Scale (DERS) scores on four major groups of interest. These groups were obtained through the stratification of our full sample by gender and drug group. Panel **(A)**, which represents women **with no history of drug use**, shows the only significant association between HRV and DERS. Panel **(B)** (**women with a history of drug use**), panel **(C)** (**men with no history of drug use**), and panel **(D)** (**men with a history of drug use**) all show non-significant associations between HRV and DERS (see section "Materials and Methods" for details). $^{*}p < 0.05$.

history of drug use and ER difficulties, and this link was primarily evident in women. No link between resting HRV and drug use was found in men or women. Furthermore, showing a stronger link between resting HRV and difficulties in ER in women compared to men as in Williams et al. (27); importantly, novel data suggested no link between resting HRV and self-reported ER difficulties in women with a history of drug use. This finding potentially characterizes a disruption between ER capacities, marked by resting HRV, and ER difficulties, marked by self-reported ER difficulties, in women with a low-risk history of drug use. Among the six different facets of ER difficulties, only those related to difficulties with impulse control and ER strategies were most related to low-risk drug use in women but not men. Finally, while correlational analyses confirm resting HRV was not *directly* associated with DAST in the full sample or stratified by gender, our explorative mediation results suggested an *indirect* association between resting HRV and drug use mediated by self-reported difficulties in ER. However, this mediated association was also moderated by gender, such that this model was statistically reliable in women but not men.

Overall, this is the first study to explore how both resting HRV and difficulties in ER are related to drug usage and how these associations may differ as a function of gender. Women initiate drug use primarily for stress regulation (28), and our data are in line with this idea, as in women only, perceived ER difficulties were associated with drug use, self-reported difficulties in ER mediated the resting HRV and drug use link, and a history of drug use was associated with a weaker link between resting HRV and self-reported ER difficulties. Substantial research remains needed to understand appropriate mechanisms to decrease the likelihood of drug use in men, especially from an ER standpoint. Indeed, men tend to underreport symptomology, and thus, it is possible that with more data, the associations within men might be highlighted. As mentioned, research suggests men initiate drug use for the thrill, drive, and fun of the experience, and our study was not able to determine such motivations. Therefore, and alternatively, other self-regulatory scales need to be considered,

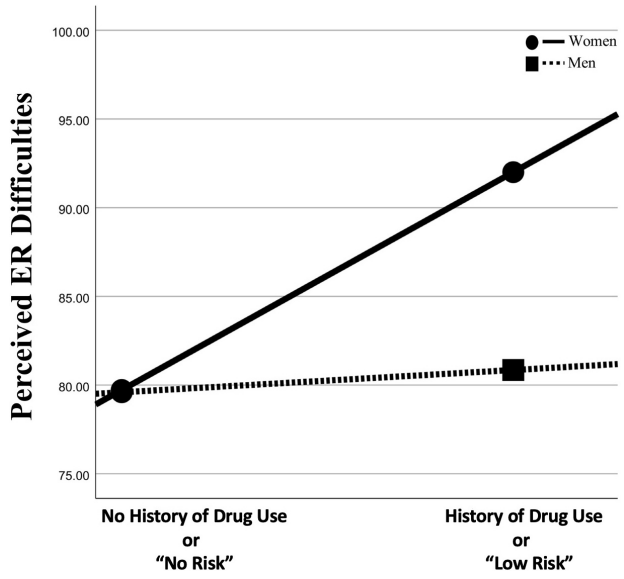

FIGURE 3 | Conditional effects of moderation test. This figure depicts the association between drug use and emotion regulation (ER) difficulties moderated by gender (see section "Materials and Methods" for details).

such as impulsiveness and drive-seeking behaviors, to understand the biological-motivational factors that drive drug behavior in men. In sum, these findings suggest that differences between men and women exist as it relates to the potential ER-related catalyst of drug use; perceived ER difficulties may drive low-risk drug behavior for women more than men, and that resting HRV and ER difficulties are only linked in low-risk women. These findings are in line with prior studies showing a disruption in the inhibitory pathway in those who engage in heavy alcohol use (53).

Another finding that was unexpected, yet unsurprising, was that among those without a history of drug use (both men and women), higher resting HRV was associated with lower BMI. Obesity is considered an inflammatory process (54), and resting HRV represents the physiological pathway underlying inflammatory processes (55). Thus, higher vagal activity, as indexed by higher resting HRV, should be associated with lower measures of adiposity (e.g., BMI) *via* proper regulation of the anti-inflammatory cholinergic pathway. As such, the link between resting HRV and BMI among those without a history of drug use appears intuitive and further supports the idea of a disrupted inhibitory pathway among those with a history of drug use. However, and importantly, this finding should be interpreted with extreme caution, especially given that our sample fell within the normal BMI range and no-to-low risk of drug use. Therefore, future research is needed to directly address how and if a history of drug use impacts the associations between resting HRV and indices of adiposity (i.e., BMI).

Overall, our data suggest that even for those considered low-risk, ER difficulties and resting HRV (indirectly) can be used to predict a history of drug use which potentially serves as a gateway to drug problems. Importantly, a lack of association between resting HRV and ER difficulties may signal a history and/or likelihood of drug use in women, and vice versa.

Implications

Our data suggest that a history of drug use, even at a low risk, is associated with a weaker link between resting HRV and ER difficulties among women. An alternative interpretation is that being accurate in one's assessment of ER capacities and subsequent ER difficulties may be key in decreasing the likelihood of young women to ever engage in low-risk drug use. It is interesting to consider that the stronger association between resting HRV and ER difficulties in women relative to men (27) might be a contributing factor underlying lesser drug use in women relative to men (although not supported in the current study). Thus, given that this association appears important in low-risk women in our sample, it is likely very impactful in those struggling with addiction more generally, and future research should investigate this possibility directly. Regarding men, it is not surprising the link between resting HRV and ER difficulties did not reach statistical significance as a similar effect size was found for men in our prior report (11).

Furthermore, and from a clinical standpoint, the target of decreasing the likelihood of recreational drug use in women is likely ER-based, whereas for men, it may be based on motivational factors unrelated to ER (i.e., thrill-seeking) and more research is needed in this regard. Given the indirect association of resting HRV and drug use among women, one promising intervention may be HRV biofeedback, which has been shown to reduce cravings among inpatient young men (26). In women, this feedback might be promising in that it may strengthen the understanding of one's own ER capabilities. An accurate assessment here allows the individuals to be more motivated in ER processes (i.e., lesser perceived ER difficulties), or on the other hand, motivated to change the capacity *via* additional HRV biofeedback sessions, which over time, may increase motivation to engage in ER and thus avoid drug use. Future studies are needed to explore these possibilities.

The present data also suggest that a history of drug use might impair an important psychophysiological compensatory mechanism in young adult women, marked by a disrupted link between resting HRV and ER (27). On the other hand, men appear to engage in drug use irrespective of ER processes which is particularly problematic from clinical, psychotherapeutic, and behavioral change perspective. Research is thus needed to understand psychological and physiological predictors and correlates of drug use in young adult men. Overall, perceived ER difficulties, as a primary factor, and resting HRV, potentially as a secondary factor – should be considered when targeting behavior change related to drug use, especially in young adult women.

Limitations and Future Directions

One limitation of the current study is that it was cross-sectional by nature and causation cannot be determined. It is certainly plausible that due to the nature of our scale (drug use over the past 12 months), history of drug use could impact resting HRV and ER difficulties, as opposed to resting HRV and ER predicting a history of drug use. Statistically, our results support the latter,

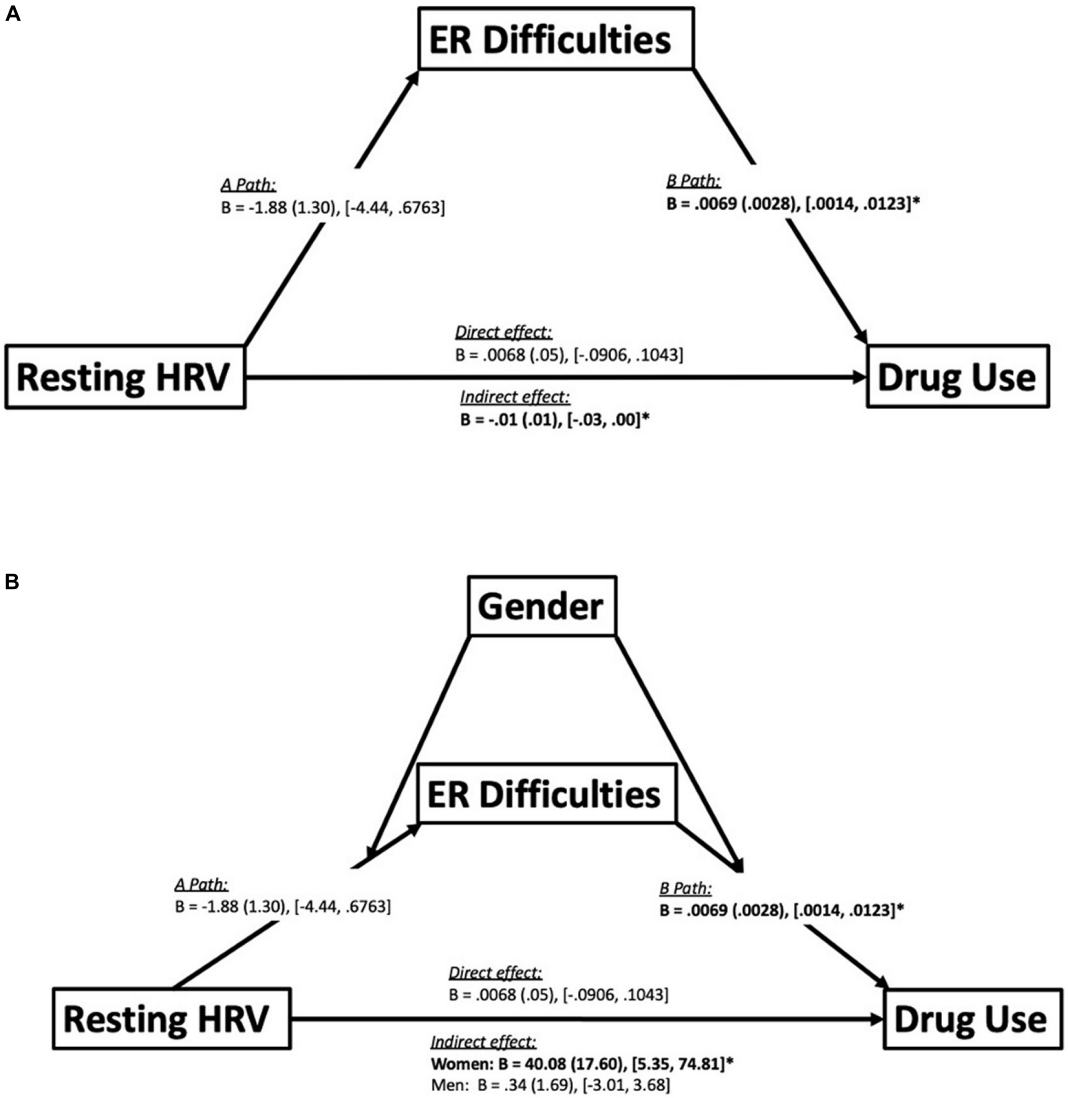

FIGURE 4 | Mediation and moderated-mediation model. Panel **(A)** depicts a mediation model illustrating emotion regulation (ER) difficulties mediating an indirect association between resting HRV and drug use. Statistics reported include unstandardized betas (B), standard error (in brackets) and the bootstrapping CI's (lower limit, upper limit) for each path of the model. Path A represents the association between the independent variable (resting HRV) and ER difficulties. Path B represents the association between ER difficulties and drug use. Furthermore, there were also direct and indirect paths between resting HRV and drug use. The direct path represents the direct effect between resting HRV and drug use. The indirect path represents the indirect effect of resting HRV on drug use through ER difficulties. Significant effects bolded. *$p < 0.05$ (see section "Materials and Methods" for details). Panel **(B)** depicts a moderated-mediation model illustrating the effects of utilizing gender as a moderator on the mediation analysis seen in **(A)**. Statistics reported include unstandardized betas (B), standard error (in brackets) and the bootstrapping CI's (lower limit, upper limit) for each path of the model. The moderation of gender revealed that the indirect effect between resting heart rate variability (HRV) and drug use mediated by difficulties in emotion regulation (ER), was only significant amongst women but not men. Significant effects bolded. *$p < 0.05$ (see section "Materials and Methods" for details).

as models involving history of drug use as an independent variable and resting HRV and ER difficulties as DVs were not significant. These data suggest ER processes as the predictor of drug use history. Likewise, in mediation models, ER difficulties did not predict resting HRV. From a theoretical standpoint, this makes sense as resting HRV is considered an endophenotype (56) and thus more stable over time relative to both perceived ER difficulties and recreational drug use (especially between no-risk and low-risk levels). Nonetheless, we propose, and prior research suggests (6, 21), substance use is detrimental for psychophysiological function. Therefore, it is important that future studies track changes in HRV, ER difficulties, and drug use over time to understand causal (and likely bidirectional) links.

Relatedly, another limitation is that all participants fell between the "no-risk" or "low-risk" category based on the Short Form DAST-10 (i.e., individuals who scored less than 3 on the DAST). A more direct effect of resting HRV on DAST may exist with a larger and more diverse sample. Future studies should also

examine how the link between resting HRV and ER difficulties might diminish *over time* in those who engage in recreational drug use. It will be imperative for future work to understand how interventions might impact both difficulties in ER and resting HRV over time to avoid initial drug use and/or relapse into a drug use disorder. Future research should also work to examine the association between resting HRV and drug use in individuals of different age and ethnic groups.

Another limitation of the study is that we did not assess the duration, frequency, recency, or reasons/motivations of recreational drug use, and therefore it is difficult to determine how these play a role in the current results. Future studies should replicate this work and be understood within the context of these variables to gain a clearer picture of these associations. Finally, we did not assess other substance use, such as alcohol, which is a limitation considering our college sample. High-risk drinking that may be present in this sample may contribute directly to the history of drug use and the disruption between psychophysiological measure. Therefore, future studies must explore these results in the context of other substances, in addition to the frequency and duration of such substances.

However, our study is not without strengths; this is the first study to show associations between ER processes and a history of drug use even in those considered low-risk. Second, this is one of the few studies to consider gender differences in psychophysiological data, especially as it relates to drug use. Finally, we utilized mediation and moderation analyses as a means to understand how these variables are intercorrelated, which we hope will provide fruitful avenues for future research.

CONCLUSION

This was the first study, in a young and apparently healthy population within a non-pathological range of drug use scores, to link perceived ER difficulties with a history of low-risk drug use. Higher ER difficulties are associated with a history of drug use, and such a history of drug use disrupts the link between resting HRV and ER difficulties, particularly among young adult women. These findings are in line with studies suggesting women engage in drug use for stress regulation (28, 32, 33). Moreover, more perceived ER difficulties carried the indirect association between lower resting HRV and low-risk drug use history in women. In conclusion, lesser perceived ER difficulties, higher resting HRV, and a stronger link between the two is particularly important in decreasing the likelihood of recreational drug use in college-aged women relative to college-aged men.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ohio State University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EK wrote the initial draft of the manuscript. DW contributed to writing some elements of the manuscript. EK and DW performed the statistical analyses. AK, GG, and JK collected and processed the data. JT, JK, GG, and DW oversaw the study. All authors contributed to the theorizing and conceptualization of the study. All authors contributed to the revision, read, and approval of the final manuscript.

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Use and perceived usefulness of a just-in-time resonance breathing intervention adjunct for substance use disorder: Contextual and physiological predictors

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Craving for alcohol and other drugs is often described as a momentary hyperarousal state that interferes with one's ability to use top-down strategies. As such, it may be best interrupted 'in the moment' through bottom-up modulation. We recently reported that episodic resonance paced breathing (eRPB) delivered via mobile phone app as an add-on to outpatient treatment for substance use disorder (SUD) was effective at dampening craving over the course of an 8-week intervention (NCT#02579317). However, not all participants engaged with the eRPB app and there was high intra- and inter-individual variability in weekly ratings of usefulness. Here we examined baseline demographic, physiological, and psychiatric measures as well as time-varying exposure to positive, negative, and temptation craving triggers as predictors of frequency of eRPB app use and ratings of usefulness. Seventy-seven outpatient women were randomized to an eRPB (0.1 Hz) or a faster paced breathing sham (0.23 Hz) condition. Baseline measures were assessed within the first 3 weeks of treatment entry prior to randomization. App use frequency, ratings of usefulness, and trigger exposure were measured weekly throughout the intervention. Variables were entered into marginal means models with forward stepwise model selection and examined as predictors of use and usefulness. Frequent app use was associated with a lifetime alcohol use disorder (AUD) diagnosis ($p = 0.026$), higher ratings of usefulness ($p < 0.001$), and fewer exposures to positive triggers (e.g., celebration, socialization; $p < 0.001$). There was a trend-level association between frequency of app use and greater cardiovascular capacity at baseline ($p = 0.088$). Higher ratings of usefulness were associated with greater exposure to negative triggers (e.g,. loneliness, frustration; $p < 0.001$) and parasympathetic dysregulation at baseline ($p = 0.05$). A positive relationship between app use frequency and ratings of usefulness was present

only in the eRPB group ($p = 0.045$). Matching ideal candidates and moments to an arousal modulation anti-craving intervention can help streamline screening and implementation of eRPB in the treatment of SUD.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT02579317, identifier NCT02579317.

KEYWORDS

heart rate variability, baroreflex, resonance breathing, substance use disorder, clinical trial, cardiovascular, craving, just-in-time intervention

Introduction

Craving for alcohol and other drugs is a core feature of substance use disorder (SUD) and a primary interrupter of recovery (1, 2). The experience of craving is complex and involves intense emotionality, behavioral activation, and autonomic physiological experiences that can block higher order cognitive processes (3–7). Physiologically, craving is marked by a shift toward sympathetic control, including increased heart rate (HR) (8, 9) and blood pressure (9, 10), decreased heart rate variability (HRV) (11, 12), and rapid respiration (13, 14). Bottom-up communication of these physiological correlates of craving can persist for hours (15–17), disengage top-down processes (18–20), and promote unintended substance use (7, 21, 22). A number of pharmacological and psychological anti-craving interventions have received empirical support (23–27). Supplementation by a just-in-time, bio-behavioral intervention that interrupts the relay of visceral craving signals from the body to the brain theoretically could create a temporal window for an individual to recruit top-down processes in risky contexts and thereby enhance existing approaches to support recovery in everyday life (20, 28–32).

HRV biofeedback, a bottom-up intervention used to dampen arousal, slows and paces respiration to drive vagally-mediated HR oscillations (∼0.2–0.33 Hz) to match the periodicity of the HR baroreflex (∼0.1 Hz) (33–35). In doing so, immediate increases in HRV and baroreflex sensitivity as well as decreases in BP and sometimes HR are observed (34, 36). All of these changes are indicators of parasympathetic control and likely underlie the beneficial effects of HRV biofeedback on stress/arousal (37, 38) and reactivity to appetitive cues (39–41). In addition, HRV biofeedback activates central-autonomic neural pathways that convey cardiovascular information to multiple cortical centers (42); this feedforward path has been proposed to underlie decreased craving for alcohol and other drugs (30, 43–47).

Standard HRV biofeedback is a clinician-guided intervention that requires a trained practitioner to lead a series of breath-based exercises to identify one's unique resonance frequency (i.e., the precise frequency of the periodicity of an individual's HR baroreflex; range: 0.075–0.12 Hz). Individuals are then instructed to practice breathing at their resonance frequency on their own time, usually with the aid of photoplethysmography (PPG) to visually synchronize respiration and HR oscillations; they return weekly for in-person practitioner-guided sessions. The duration of HRV biofeedback involvement, number of in-person sessions, and frequency of self-practice vary, but generally individuals complete weekly in-person visits for 2–10 weeks paired with 5–30 minutes of daily self-practice (45, 48). Self-guided episodic resonance-paced breathing (eRPB) is a parallel, but less intensive intervention strategy that leverages the respiratory strategies of HRV biofeedback. This intervention requires individuals to pace their breath to 0.1 Hz to approximate the resonance frequency of the HR baroreflex (36, 49). Without the assistance of a practitioner, eRPB can be used in the real world through mobile health platforms, allowing the active ingredient of HRV biofeedback to be implemented in daily life.

The utility of a just-in-time intervention like eRPB relies on self-administration of the application. Individual-level factors such as age, general health, mood, and baseline physiological traits have been associated with level of engagement with just-in-time interventions (39, 48, 50); and while racial and ethnic minority individuals find personalized interventions promising (51, 52), societal barriers continue to limit access and decrease enthusiasm for their implementation (53, 54). These studies suggest a need for more research aimed not only at whether a just-in-time intervention is efficacious, but also at quality of implementation, including who uses it, when it is used, and whether it is found to be useful.

The current analyses used data from a randomized clinical trial (RCT) of an adjunctive eRPB intervention for women attending an outpatient behavioral treatment program for SUD. Our initial report on clinical outcomes found improvements in craving that varied with the frequency of eRPB use during intervention weeks in this sample, compared to a breathing sham control group (55). Here, we focused on a complimentary aim of the RCT that addressed when and for whom the eRPB intervention was most useful. We examined a series of *a priori* baseline demographic, substance use, and physiological characteristics as well as time-varying exposure to triggers for substance craving to predict two metrics of utility: frequency of use and self-reported usefulness of eRPB. Based on previous reports that relate age, health, and baseline physiology with

use of technology-based interventions, we hypothesized that younger age, greater basal cardiovascular dysregulation, and metrics of poor health would be associated with more frequent use and higher ratings of app usefulness. We further evaluated time-varying predictors of app utility in line with its intended use in daily life. Given that negative emotionality is commonly cited as a trigger to relapse (56, 57), particularly in women (58), it was hypothesized that increased exposure to negative craving triggers (e.g., loneliness, experiencing conflict, feeling shaky) would be associated with greater use and usefulness of an arousal modulating intervention compared to positive affect triggers (e.g., celebration, socialization).

Materials and methods

Trial design

The Project IMPACT (In-the-moment Protection Against Craving Triggers; NCT#02579317) design used a parallel-assignment RCT to test whether self-administered, in-the-moment, resonance breathing episodes would improve outcomes for women receiving SUD treatment. Urn randomization was used to assign participants to either the eRPB or sham breathing intervention to maximize the probability of balanced groups with regard to important prognostic characteristics [age 18–30, >30 years; alcohol use disorder (AUD) or other substance use disorder (SUD) diagnosis] and to preserve unpredictability/allocation concealment. The protocol was approved by and conducted in accordance with the Institutional Review Board for the Protection of Human Subjects Involved in Research.

Recruitment and sample characteristics

Participants were recruited between November 2015 and March 2020 from a community outpatient substance use treatment facility that offered a continuum of care for women. This client-centered facility used evidence-based treatment approaches that optimize clinical care for women and their children including seeking safety (59), motivational interviewing (60), and child parent psychotherapy (61). Consecutive admissions to the program were invited to take part in an 8-week paced breathing study with two arms: 6 breaths per min (eRPB) or 14 breaths per minute (sham breathing control). Inclusion criteria included age between 18 and 65 years, the ability to provide informed consent and complete breathing tasks, and not pregnant. Women who qualified as having a current or lifetime SUD (alcohol included) were included in the study. Six women had achieved more than 30 days of abstinence at the time of enrollment. Women who exhibited severe mental health symptoms did not qualify for the intensive outpatient program; no further psychiatric criteria were applied.

A timeline of study involvement and relevant measures can be seen in Figure 1. As part of the intake evaluation, clinicians administered the New Jersey Substance Abuse Monitoring System (NJSAMS), a clinical interview conducted by all NJ state-funded treatment facilities that collects demographic information, substance use history, financial status, medical history, and clinical information to help treatment providers identify the appropriate treatment level for clients. At initial research contact, all participants provided written informed consent ($n = 107$). Participants then completed demographic and health screening information (week 1). During week 2, a trained, graduate-level clinical researcher administered the alcohol and substance use disorder sections of the Structured Clinical Interview for DSM-5 [SCID-5 (62)] to verify diagnoses, the Mini International Neuropsychiatric Interview (MINI) 7.0 (63) to assess psychiatric comorbidities, and the Inventory of Drug Taking Situations [IDTS (64)], which identifies positive, negative, and temptation-related triggers for substance use. The following week, the researcher returned to administer a 90-day TimeLine Follow Back in-person interview [TLFB (65)] that assessed alcohol and other drug use (opiate, stimulant, nicotine, cannabis, hallucinogens); craving scale [Penn Alcohol Craving Scale (PACS) (66)], and depressive and anxiety symptoms inventories [Beck Depressive Inventory, BDI (67) and Beck Anxiety Inventory, BAI (68)]. An in-laboratory session was then scheduled.

Of the 107 consented participants, 4 did not meet criteria and were excluded from the study, 17 dropped out of treatment and study procedures prior to the baseline in-lab assessment, and 6 withdrew from study procedures, but remained in treatment. Due to the pandemic-related suspension of non-essential human subjects research in March 2020, three participants were discontinued prior to data collection and study enrollment was terminated before the full target sample could be recruited. Seventy-seven participants completed the baseline in-lab cardiovascular assessment and were randomized. Seven discontinued treatment and study involvement after randomization but before app use data collection. Four participants had unusable baseline cardiovascular data. Time-varying covariate data were missing for four participants. The final sample for the current analyses included 62 participants. Thirteen women reported on the weekly usefulness measure but failed to provide their phone for data uploads and thus are missing app use frequency data. The CONSORT flow diagram is presented in Figure 2.

Pre-intervention laboratory phase

During the laboratory session, participants were given a light lunch and completed questionnaires and cognitive tasks [Not

	Baseline (WK 1-2)	Laboratory Assessment (WK 3/4)	Intervention Phase									Laboratory Assessment (WK 12)
			WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 12	
NJSAMS	X											
Demographics	X											
SCID	X											
BDI/BAI		X										X
Physiologic Assessment		X										X
Intervention (App Use)			X	X	X	X	X	X	X	X	X	
VAS (Triggers, Usefulness)			X	X	X	X	X	X	X	X	X	

FIGURE 1
Timeline of study involvement and relevant measures. NJSAMS, New Jersey Substance Abuse Monitoring System; Structured Clinical Interview for DSM-5; BDI, Beck Depressive Inventory; BAI, Beck Anxiety Inventory; VAS, Visual Analog Scale.

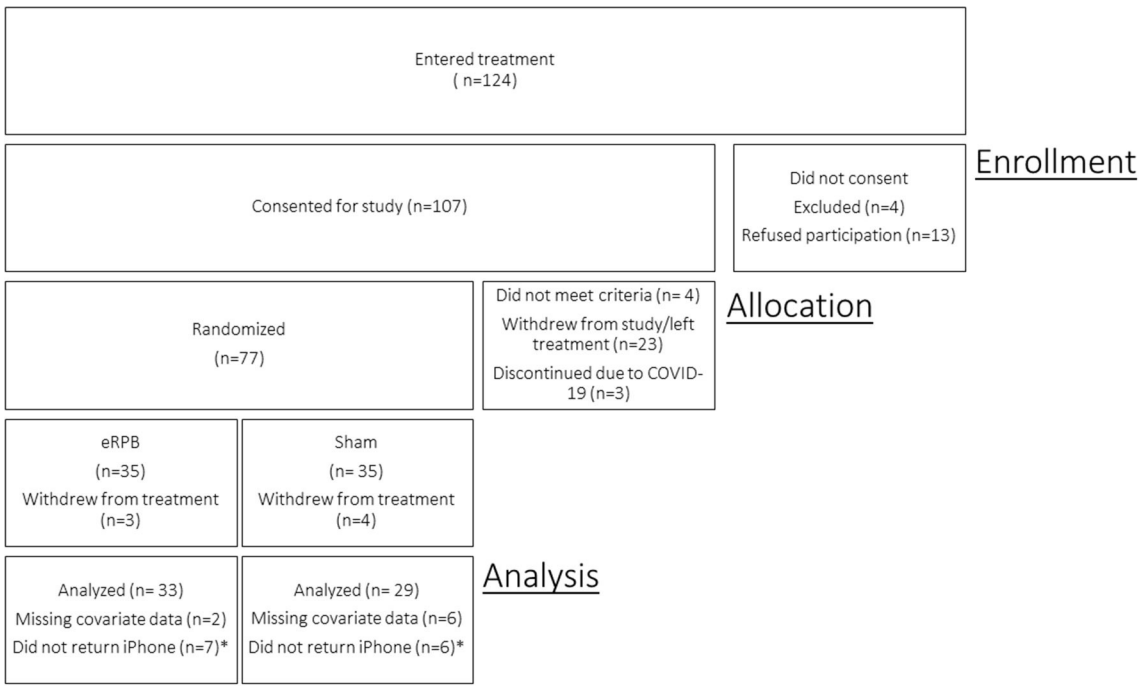

FIGURE 2
CONSORT enrollment diagram. *Participants remained in the study and reported on usefulness of the intervention but did not return iPhone for app usage data download. Participants are included in model of Usefulness but not Use Frequency.

reported here; see Supplementary material in Price et al. (55)]. Participants then were seated comfortably in front of an LCD TV screen. A standard lead II configuration (arm & ankle) was used for electrocardiogram (ECG) measurement. A cuff sensor for beat-to-beat blood pressure measurement was placed around the second phalange of the right middle finger. A stretch belt with piezoelectric sensors for respiratory measurement was set around the chest. ECG, respiration, and blood pressure were continuously acquired at a 2,000 Hz sampling rate using PowerLab Acquisition System (ADInstruments,

Colorado Springs, CO) and Finometer MIDI (Finapres Medical Systems, Enschede, Netherlands). Data were post-processed prior to analysis using WinCPRS software (Absolut Aliens Oy, Turku, Finland) to manually modify artifacts and missed or irregular beats by interpolation from other physiological signals. Frequency domain indices were computed from spectral analysis after cubic interpolation of the equidistant waveform and 4 Hz resampling.

Participants were asked to take 5 breaths into a calibration tube (completely filling and then emptying the bag of air) to calibrate respiratory volume. ECG, blood pressure, and respiration data were then recorded during three 5-min tasks. Baseline: A rectangle presented in the center of the TV screen changed color every 10 seconds and participants silently counted the number of blue rectangles (69). Sham Breathing: Participants breathed at a rate of ∼14 breaths/min following a visual pacer (E-Z Air, Biofeedback Foundation of Europe, Montreal, Canada). They inhaled as the pacer moved vertically up and exhaled as it moved down. Resonance Breathing: Participants breathed at a rate of 6 breaths/min following the visual pacer to inhale as the pacer moved up and exhale as it moved down.

After completion of the physiological recording, participants were randomized into the eRPB or sham breathing group. Participants were given an iPhone programmed with CameraHRV [© Marco Altini, Amsterdam, Netherlands], an app that uses PPG in combination with a breathing pacer. Participants in both groups were instructed on how to open the app, enter the reason that prompted their app use, place their index finger over the camera lens to capture pulse data, and follow the app's pacer (inhaling as the vertical breathing bar moved up and exhaling as it moved down). The pacer was preset at 6 breaths per minutes for the eRPB group and 14 breaths per minute for the sham group. Randomization was double blind; iPhone app programming (eRPB vs. sham) was conducted by one unblinded researcher. Participants were asked to use their app for 5 min any time they anticipated or experienced a trigger and/or any other reason that might encourage them to drink or use drugs. In the event no such situations were encountered, participants were asked to use the app at the end of the day for 5 min. Preliminary observations of the PPG data suggested that participants breathed at the frequencies assigned to them during their self-initiated episodes of app use.

Intervention

Participants were engaged in the intervention phase of the study for 8 weeks. The primary variables for the current analyses were collected during this phase. Research personnel met with participants weekly to upload app use data and collect self-report measures. Participants completed four Visual Analog Scale (VAS) questions to assess how much they were triggered by positive, negative, and temptation cues (per the IDTS cue categorization), and their perceived usefulness of the app. Participants also completed the Positive And Negative Affect Scale (PANAS) (70), PACS, and TLFB since last visit.

Statistical approach

Analyses were conducted using SAS 9.4 (Cary, NC: SAS Institute Inc). Demographic and substance use comparisons of the eRPB and sham groups were conducted using ANOVA and chi-square.

Two measures of eRPB utility served as dependent variables in marginal means models: number of app uses per week as recorded from the iPhone app and weekly VAS ratings of usefulness. Traditional Intent-to-Treat analyses were not performed due to the seven participants with no outcome data points. Instead, maximum likelihood estimation was used to retain participants who were missing some, but not all, outcome data. Figure 3 depicts the week-to-week changes in both dependent variables, demonstrating a high degree of within- and between-subjects variability to be explained. Fixed predictors were extracted from the screening session [age, race (1 = Black, 0 = not Black), and frequency of exercise (weekly, monthly, or not at all)], the NJSAMS interview (existence of a current chronic medical condition), the SCID (lifetime AUD and SUD diagnoses), and the pre-intervention assessment [depressive and anxiety symptoms (BDI, BAI), cardiovascular parameters]. Cardiovascular predictors included mean power of high frequency (HF) HRV (0.15–0.40 Hz) during the baseline task, an index of resting parasympathetic activity, κ and peak power achieved at 0.1 Hz during resonance breathing, a proxy for baroreflex activity. Weekly VAS assessment of positive, negative, and temptation triggers during the intervention phase were included as time-varying predictors.

VAS questionnaires were scaled 0–100. Arcsin square root transformation $2^* \left(\sqrt{p}\right)$), was applied to all four VAS scales (Positive, Negative, and Temptation Triggers, Usefulness); this transform is a variance standardizing procedure for percentage (p) data (71). The natural log was taken of all physiological variables as is standard practice. Multicollinearity was assessed by first examining the bivariate correlation matrix and flagging correlations $r \approx > 0.70$ (72). Second, the specified dependent and independent variables, including interactions with condition randomization, were initially run in an ordinary least squares (OLS) regression model to examine the tolerances and variance inflation factors (VIF) for each entry in the regression equation.

Marginal means models were fit with a forward stepwise model selection procedure informed by fit indices (−2 log likelihood). Predictors that did not significantly improve model fit (non-significant X^2) were dropped from the model. Model fit comparisons can be seen in the Table 1 noting which predictors were retained and which predictors were

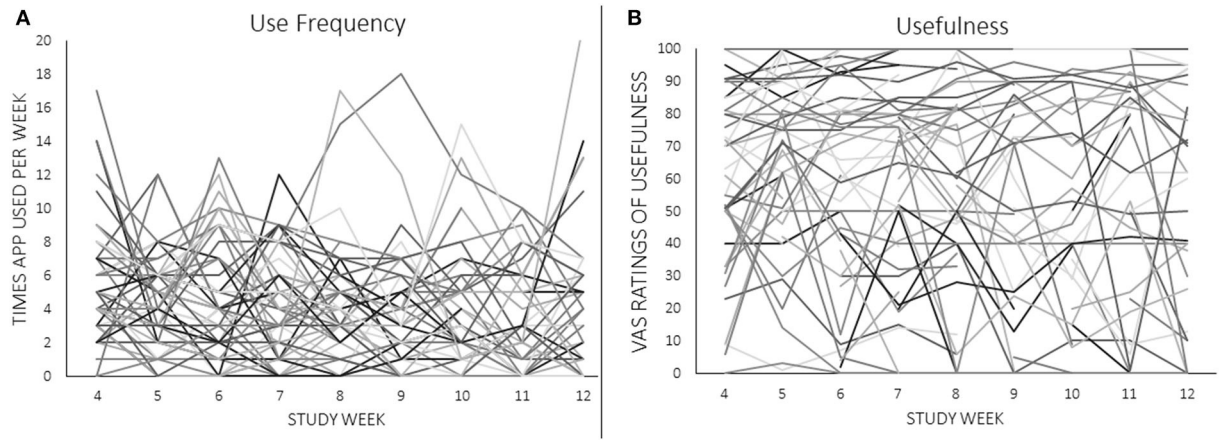

FIGURE 3
(A,B) Individual trajectories of app use frequency and ratings of usefulness across the 8-week intervention. Raw values of VAS ratings are shown.

dropped from each model. All predictors were entered individually. Fixed demographic and health variables were entered first (age, race, exercise, medical condition), followed by substance use and affect variables (AUD/SUD, BDI, BAI), physiological indices (resting HF HRV, peak 0.1 Hz during resonance breathing), and then time-varying covariates (weekly negative, positive, and temptation triggers). The two dependent variables were hypothesized to be highly related and predictive of each other (i.e., frequency of use would be influenced by perceived usefulness; perceived usefulness would be influenced by the frequency of use). Thus, each dependent variable was entered into the opposing model as a time-varying predictor. Condition (eRPB vs. sham) and its interaction with all variables that remained in the model were then entered in the same manner. Robust standard errors were specified. Statistically significant effects ($\alpha = 0.05$) are reported in-text with raw regression coefficients, *t*-statistics, and *p*-values.

Results

Multicollinearity

The bivariate correlation matrix can be seen in Table 2. A number of predictors were modestly associated with one another ($r < 0.5$). Scores on the BDI and BAI were correlated ($r = 0.69$) as were mean VAS trigger scales (Negative, Positive, Temptation, $r = 0.32$–0.58). VIF of main and interactive effects were well-below 10 and ranged from 1.55 to 8.71 [with the exception of condition, which was included in the calculation of interaction terms and thus had high collinearity with each interaction predictor (VIF$\leq$ 16.63)]. All planned predictors were maintained in the analyses.

Frequency of app use

A summary of significant findings can be seen in Table 3. Two baseline characteristics were associated with app use frequency. More frequent use was significantly associated with having an AUD diagnosis (ß = 2.41, t35 = 2.32, $p = 0.026$) and associated at a trend level with a higher peak 0.1 Hz index during resonance breathing (ß = 0.568, t35 = 1.75, $p = 0.088$). Of the time-varying covariates, more frequent use was associated with fewer weekly exposures to positive triggers (ß= −1.11, t238 = −3.46, $p < 0.001$) but high weekly ratings of app usefulness (ß = 1.35, t238 = 3.46, $p < 0.001$). The residual r^2 determined that the final model accounted for 41% of the within-subject variance.

Ratings of app usefulness

High ratings of usefulness were associated with both lower basal high frequency HRV at intake (ß = −0.150, t33 = −2.01, $p = 0.05$) and greater weekly exposure to negative triggers (ß = 0.508, $t(241) = 4.48$, $p < 0.001$). There was a significant interaction between frequency of use and condition; more frequent use was predictive of higher ratings of usefulness only in the eRPB group (Figure 4, ß = 0.830, $t(241) = 2.01$, $p = 0.045$). The residual r^2 suggested that the final model accounted for 50% of the within-subject variance.

TABLE 1A Model fit statistics (compared to previous row): App use frequency.

	-2LL	X^2	df	*p*-value	Residual	R^2 within	Dropped/Retained
Null	2236.58	–	–	–	12.03	–	
Age	2230.26	6.32	1	0.012	11.85	0.015	R
Exercise	2213.75	16.51	1	<.001	11.39	0.0532	R
Medical condition	2210.75	3	1	0.083	11.31	0.0599	D
Race	2213.73	0.02	1	0.888	11.39	0.0532	D
BDI	2212.68	1.07	1	0.301	11.36	0.0557	D
BAI	2212.48	1.27	1	0.259	11.36	0.0557	D
AUD/SUD	2200.19	13.56	1	<0.001	11.03	0.0831	R
Resting HF HRV	2199.79	0.4	1	0.527	11.02	0.0840	D
Peak 0.1 Hz HRV	1991.8	207.99	1	<.001	8.3	0.3101	R
Negative Triggers	1634.95	356.85	1	<.001	8.69	0.2776	R
Positive Triggers	1515.58	119.37	1	<.001	8.29	0.3109	R
Temptation Triggers	1470.63	44.95	1	<.001	8.42	0.3001	R
App Usefulness	1388.6	82.03	1	<.001	7.27	0.3957	R
Condition X Age	1388.19	0.41	2	0.815	7.27	0.3957	D
Condition X Exercise	1388.37	0.23	2	0.891	7.26	0.3965	D
****Condition X AUD/SUD**	**1379.89**	**8.71**	**2**	**0.013**	**7.05**	**0.4140**	**R**

Predictors with poor model fit ($p > 0.05$) were excluded from the model. Shaded rows indicate predictors retained in the final model.
**Final model (Use = Age, Exercise, AUD/SUD, peak 0.01 Hz HRV, Negative, Positive, Temptation, Usefulness, Condition, Condition*AUD/SUD).

TABLE 1B Model fit statistics (compared to previous row): Usefulness.

	-2LL	X^2	df	*p*-value	Residual	R^2 within	Dropped/Retained
Null	1007.01	–	–	–	0.683		
Age	1006.35	0.66	1	0.41	0.682	0.0015	D
Exercise	1000.61	6.4	1	0.011	0.672	0.0161	R
Medical Condition	997.15	3.46	1	0.063	0.666	0.0249	D
Race	992.49	4.66	1	0.031	0.659	0.0351	R
BDI	992.42	0.07	1	0.791	0.659	0.0351	D
BAI	992.45	0.04	1	0.841	0.659	0.0351	D
AUD/SUD	974.89	17.6	1	<0.001	0.631	0.0761	R
Resting HF HRV	957.72	17.17	1	<0.001	0.605	0.1142	R
Peak 0.1 HZ HRV	891.78	65.94	1	<0.001	0.576	0.1567	R
Negative Triggers	810.52	81.26	1	<0.001	0.491	0.2811	R
Positive Triggers	752.12	58.4	1	<0.001	0.484	0.2914	R
Temptation Triggers	719.22	32.9	1	<0.001	0.477	0.3016	R
App Use Frequency	556.6	162.6	1	<0.001	0.405	0.4070	R
Condition X Exercise	544.93	11.67	2	0.003	0.388	0.4319	R
Condition X Race	541.8	3.13	1	0.077	0.383	0.4392	D
Condition X AUD/SUD	527.36	14.44	1	<0.001	0.365	0.4656	R
Condition XHF HRV	524.76	2.6	1	0.11	0.362	0.4700	D
Condition X Peak 0.1 Hz HRV	526.16	1.2	1	0.273	0.364	0.4671	D
Condition X Negative Triggers	519.97	7.39	1	0.007	0.356	0.4788	R
Condition X Positive Triggers	515.6	4.37	1	0.037	0.351	0.4861	R
Condition X Temptation Triggers	515.23	0.37	1	0.543	0.35	0.4876	D
****Condition X App Use Freq.**	**505.5**	**10.1**	**1**	**<0.001**	**0.339**	**0.5037**	**R**

Predictors with poor model fit ($p > 0.05$) are removed from the model. Shaded rows indicate predictors retained in the final model.
** Final Model (Usefulness= Exercise, Race, HF HRV, Peak 0.01 Hz HRV, Negative, Positive, Temptation, Use Frequency, Condition, Condition*Exercise, Condition*AUD/SUD, Condition*Negative, Condition*Positive, Condition*Use Frequency).

TABLE 2 Demographics and bivariate correlation matrix.

	Mean/N	Var	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Condition			1	0.17	−0.21	−0.02	0.10	0.02	0.03	−0.24	0.10	0.01	0.13	−0.13	0.06
2. Age	33.5	8.51		1.00	0.01	−0.27 *	0.13	−0.05	−0.24	−0.21	−0.19	−0.33	−0.31*	−0.33*	−0.31*
3. Race (Black)	12	—			1.00	−0.18	−0.07	−0.12	−0.15	−0.03	−0.32*	−0.32*	−0.35*	0.05	0.08
4. Exercise frequency (none/monthly/weekly)	19/13/25	—				1.00	−0.20	−0.01	−0.03	0.05	−0.10	0.15	0.12	0.09	0.25
5. Existing Medical condition	12	—					1.00	−0.01	0.14	−0.02	−0.14	0.30*	−0.14	−0.12	−0.13
6. BDI	14.97	10.37						1.00	0.69*	0.29*	0.44*	0.33*	0.40*	0.04	−0.16
7. BAI	16.92	12.63							1.00	0.12	0.29*	0.36*	0.29*	0.01	−0.16
8. AUD/SUD/ASUD	11/18/28	–								1.00	0.18	0.19	0.14	0.18	0.02
9. Negative Triggers	1.29	0.689									1.00	0.32*	0.58*	0.00	0.01
10. Positive Triggers	0.848	0.618										1.00	0.53*	0.02	−0.01
11. Temptation Triggers (Arcsin sqrt)	0.99	0.636											1.00	0.09	0.12
12. High frequency HRV	5.78	1.52												1.00	0.59*
13. Peak 0.1 Hz HRV	12.75	1.12													1.00

*$p < 0.05$.

BDI, Beck Depressive Inventory; BAI, Beck Anxiety Inventory; AUD, Alcohol Use Disorder; SUD, Substance Use Disorder; ASUD, comorbid Alcohol and Substance Use Disorder; Arcsin squareroot transformation was applied to Negative, Positive, and Temptation Trigger values; High frequency and Peak 0.1 HZ HRV measures are log transformed.

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TABLE 3 Standardized beta weights of significant predictors.

Baseline characteristic predictors	Frequency of use		Usefulness	
	ß	*p*-value	ß	*p*-value
AUD diagnosis	+2.41	0.026		
Peak 0.1 Hz during resonance	+0.568	0.088		
High frequency HRV			−0.15	0.05
Time-varying predictors				
Positive trigger exposure	−1.11	<0.001		
Negative trigger exposure			+0.508	<0.001
*Frequency of use X condition interaction			+0.830	0.045
Usefulness	+1.35	<0.001		

ß = Standardized beta weights.
*Frequency of use was only a significant predictor of Usefulness in the eRPB group.

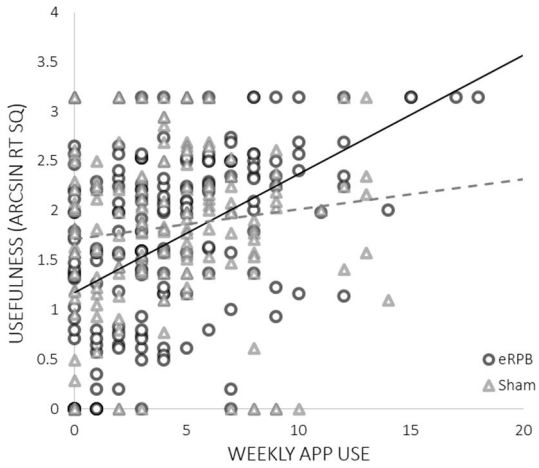

FIGURE 4
Relationship between app use and ratings of usefulness by condition.

Discussion

The accessibility of eHealth platforms is a powerful advancement for the delivery of just-in-time interventions to potentially reduce the influence of daily life triggers on substance use behavior. This study sought to identify factors that affect compliance with the use of an app-based breathing intervention as well as its perceived usefulness in dampening alcohol and drug craving in-the-moment in women receiving outpatient treatment for SUD. Identifying individuals who may be most likely to use app-based interventions can contribute to efficient screening (i.e., person-intervention matching) and support aftercare planning that best promotes long term recovery. Further, triangulation of app use with its perceived usefulness can provide information about internal and contextual moderators of eRBP's effectiveness for craving blockade.

The results of the current analyses supplement our prior demonstration of the efficacy of eRPB as an anti-craving, just-in-time, bottom-up intervention. They provide several notable observations about who engaged in the study paradigm and for whom it was most useful. Perhaps most compelling was the observation that participants in the eRPB group, but not the sham breathing group, who used the app more frequently rated the app as most useful for countering triggers of substance craving. The sham control condition had high face validity and paced respiration within the lower range of normal respiration rates. That the association between use and usefulness was limited to the eRPB group supports the study's hypothesis that it is the activation of the HR baroreflex system, as opposed to a general calming or distraction effect of paced breathing, that dampens arousal and stabilizes craving.

Beyond this support for eRPB's ability to activate putative physiologic mechanisms of behavior change, the present results suggest that a number of state-level physiologic factors influence acceptability and usefulness of the app in the sample as a whole. Women who entered the intervention with lower resting parasympathetic activity found the app to be more useful. This makes intuitive sense from a physiological perspective as women with signs of autonomic dysregulation would be most likely to benefit from an intervention aimed at modulating autonomic arousal, and is also consistent with our previous study that showed lower basal HRV was a predictor of HRV biofeedback efficacy (39). There was also a trend for women who generated larger responses to eRPB during their initial laboratory visit to use the app more frequently; again, this makes intuitive physiological sense in that when an app accomplishes what it sets out to do (in this case, maximizing heart rate oscillations), it is more likely to be used. Several factors, however, can influence the 0.1 Hz HRV peak obtained during eRPB (45, 73); thus, more research with larger samples is needed to discern the

effects of sex, race, and ethnicity. Larger samples may further identify momentary factors related to the intervention's efficacy. Nonetheless, this study found evidence of pre-intervention physiological predictors of app utility, suggesting that simple, brief cardiovascular assessments at intake could help identify those who are mostly likely to benefit from an eRPB add-on to treatment to mitigate craving and support long-term recovery.

Importantly, the strongest predictors in both models were contextual in nature. Weeks of high exposure to negative triggers were associated with high ratings of usefulness. In contrast, weeks with high exposure to positive triggers were associated with less frequent use. eRPB is designed as a just-in-time intervention that is non-invasive and easy to perform in the context of daily life, without expensive equipment or the need for clinical supervision. The identification of time-varying predictors of frequency of app use and self-reported ratings of app utility supports eRPB as such an intervention. Furthermore, considered in the context of our prior studies linking eRPB and HRV biofeedback to craving modulation (39, 48, 55, 74) and the widely held perspective of craving as a highly contextual state (as opposed to trait) factor (75, 76), it is perhaps unsurprising that the greatest predictors of app use and usefulness are the equally dynamic daily life triggers that a person navigates during recovery.

A previous study of a traditional, clinician-led course of HRV biofeedback in a college recovery sample found that within-person variations in depression symptoms (i.e., weeks when symptoms were higher than the person's average level) significantly contributed to the prediction of craving during an 8-week intervention (74). We thus hypothesized that mood would influence how useful the app would be in the face of craving, or how frequently participants would use it. However, we found no relationship between depression symptoms and participants' frequency of use or reported usefulness of the resonance breathing app. A likely explanation for the difference is that mood is a similarly dynamic state that fluctuates in tandem with craving. Alayan and colleagues found a significant effect of within-person variability in weekly BDI, but not mean-level between-subjects BDI, on craving. The current study assessed BDI at the initial assessment, and not continuously throughout the intervention. Regular monitoring of mood states in conjunction with craving may therefore be necessary to clarify times when the resonance breathing app may be most beneficial.

Control of craving is an important but complex intervention target. Biobehavioral interventions such as eRPB may be valuable as components of a comprehensive treatment regimen along with pharmacological and other behavioral interventions. Currently approved anti-craving medications, primarily naltrexone and acamprosate, have demonstrated therapeutic benefit (77, 78). Off-label use of anticonvulsants (topiramate, gabapentin) and atypical antipsychotics (aripiprazole) also appear to decrease craving (25, 26, 79). Although anti-craving medications remain under-prescribed, evidence suggests that they are mostly like to be effective when used in combination with psychological treatments (80); eRPB can be seamlessly integrated with pharmacological treatment to augment craving control.

Limitations and future directions

One *a priori* predictor was not included in analyses or reported here. Upon launching the resonance breathing app, participants were prompted to enter the reason for use. Our intention was to code and categorize entries; however, women had difficulty naming their reasons for app use in the moment and the open text format of the prompts was not successful. It may be that the craving hyperarousal state sufficiently blocked cognitive processes and impeded participants' capacity to generate a free-response answer.

During the weekly in-person assessments, clinical researchers probed whether participants had difficulty using the breathing app, but responses were not recorded because this information primarily was used to solve technical issues. However, such qualitative data about the app's utility could help identify barriers to using the eHealth intervention. Such information is integral to dissemination and implementation and should be considered in future large scale trials.

The just-in-time self-administration aspect of the breathing app was a key component of the clinical trial. While women in the eRPB group who used the app more frequently found the app to be more useful, the mean number of uses per week was 4 (range 0–21), despite study instructions of at least daily use. There were possibly times when participants experienced craving and did not use the app, as well as days when craving triggers were not encountered. Recent computational modeling approaches using in-the-field autonomic signals, GPS indicators of trigger-heavy environments, and ecological momentary assessment (EMA) of subjective stress successfully predicted substance craving with a high degree of accuracy (16, 17, 81). Development of a neurocardiac intervention that is able to "ping" an individual to launch the resonance breathing app based on EMA and continuous physiological and location data may improve upon the self-administration model. This is a fertile area for future research.

Conclusion

eRPB, as a just-in-time, body-focused, anti-craving intervention has been shown effective in dampening craving. The ability to match patient phenotypes and momentary craving triggers with its utility optimizes use of continuously evolving intervention technology. These data provide implementation information to help identify treatment-seekers most suited for bottom-up arousal modulation. Brief assessment of

baseline cardiovascular function and identification of momentary exposure to negative triggers may help target ideal candidates, and instances, of need to supplement treatment with resonance breathing.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Rutgers University Arts and Science Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JP performed formal data analysis and drafted the current manuscript. MB was responsible for funding acquisition, conceptualization, study design, review and editing the current manuscript, and supervision. AP performed formal data analysis and contributed to writing of the manuscript. SU, ST, and JM were responsible for conducting the study procedures, data management, preliminary analyses, and drafting an earlier version of this work. JB was responsible for funding acquisition, conceptualization, study design, review and editing the current manuscript, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Pilot examination of stress, heart rate variability, and alcohol craving and use among female veterans

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Rates of alcohol use disorder (AUD) are increasing among civilian and veteran populations of women in the United States, and stress pathophysiology (i.e., abnormal acute and long-term change in physiological responses to stress) is central to the maintenance of alcohol misuse within this population. Heart rate variability (HRV) is one measure of stress regulation that may help to explain the association of stress with alcohol misuse among women. In the current analysis of pilot data, 20 women veterans attended an in-person laboratory session and completed 35 daily assessments of their alcohol use and craving. During the lab session, the effects of a stress induction procedure on self-reported alcohol craving and HRV were assessed. HRV was continuously measured and indexed in the time domain, using the root mean square of successive differences between normal heartbeats (RMSSD). Alcohol craving and use during the longitudinal 35-day study period were measured *via* self-report questionnaires sent to participants' phones. Results indicated that resting HRV in the lab was positively associated with odds of daily craving. Moreover, HRV during the stressor, as measured in lab, was positively associated with (1) overall alcohol craving in the lab (i.e., with resting and post-stress craving), and (2) number of daily drinks during the 35-day study period. This pilot study suggests the potential role of HRV in response to stressors in predicting alcohol craving and use among female veterans. It provides pilot data for research on stress-reactive HRV as a biomarker for alcohol misuse among women, and discusses directions for future research.

KEYWORDS

heart rate variability, alcohol use, craving, female, veteran

Introduction

Between 2000 and 2016, there was a substantial increase in alcohol use and binge drinking among civilian and veteran populations of women in the United States (1), a trend that continued up to and during the COVID-19 pandemic in 2020 (2). Lifetime Alcohol Use Disorders (AUD) among women veterans are estimated at 27% (3), with up to 32% reporting binge drinking (4). Women veterans are at greater risk of chronic and acute stress exposure (5) and alcohol misuse (3) compared to civilian women. Research on the roles of stress and negative affect in alcohol use and relapse demonstrates greater salience of these processes in women's alcohol misuse than men's (6). Women with AUD have higher rates of all mood and anxiety disorders (7, 8) and greater likelihood of drinking in response to stress and negative affect compared to men (9, 10). Furthermore, alcohol-induced alterations in emotional and biophysiological markers of adaptive stress response are more common in female participants with heavy drinking and/or AUD than male participants (6). Given these findings, there is a need for more research on mechanisms that explain the associations of stress and alcohol use among women. This study considers the role of stress regulation as indexed by heart rate variability (HRV) in explaining stress-related alcohol craving and use among female veterans.

Heart rate variability (HRV) and alcohol use

Heart rate variability (HRV) is a measure of changes in the timing between consecutive heart beats in response to a variety of internal and external demands or to maintain homeostasis. These changes can be driven by sympathetic, parasympathetic, and other influences (11). People vary in their "resting" or "tonic" HRV levels. Among healthy individuals, higher resting HRV is viewed as a trait-like marker of individual differences in the capacity to respond effectively to situational challenges, including psychological stressors (12–14). Some scholars are also interested in studying "phasic" HRV, or changes in HRV in response to a specific stressor or other (e.g., alcohol) cue. In healthy samples, HRV tends to decrease in the immediate aftermath of a stressor. However, some studies have observed phasic increases in HRV that appear to reflect efforts to regulate the stress response (15), regardless of whether that effort is adaptive (e.g., cognitive reappraisal) or maladaptive (e.g., emotional suppression) (16). In the current paper, we will use the following terms: "resting" HRV to refer to baseline/quiet sitting and "stress-reactive" HRV to refer to the phasic change in HRV from a resting state to an induced stressed state.

Resting and stress-reactive HRV have been studied among individuals with heavy drinking and AUD. One meta-analysis of 15 studies found that patients with AUD had significantly lower resting HRV than healthy controls ($g = -0.43, p = 0.01$) and that this difference seemed to be mostly mediated by HRV measures with strong parasympathetic nervous system influence (17). In terms of phasic changes in HRV, pronounced restriction in HRV after an emotion or stress induction is typically associated with psychopathology (18). However, elevated HRV in reaction to emotional or stressful stimuli may reflect irregularities in parasympathetic responding, in which a more robust response occurs (19). Research on emotion regulation and HRV has found increased HRV when participants are instructed to use emotion regulation strategies (either adaptive and maladaptive strategies) to cope with an emotional or stressful situation (16, 20). Among a sample of individuals recovering from AUD, those with better self-control over alcohol craving had increased HRV in response to a drinking task, compared to those with poorer self-control over cravings (14). These findings are consistent with theory that increased phasic HRV reflects engagement of self-regulatory efforts (15).

Regarding HRV response to an appetitive stimulus (e.g., an alcohol or other substance-related cue), self-regulatory efforts in responding to the appetitive cue may similarly be associated with increased HRV (21). In the substance use literature, results on the directionality of association between phasic HRV and substance related behavior, in response to stress or not, are mixed. Results vary based on cue type (e.g., stress vs. alcohol cues), HRV measure used, and whether the participants are actively using substances or have varying times of abstinence. However, studies have found increased HRV in response to alcohol-related stimuli or stress to be associated with negative outcomes. For example, among recently abstinent participants with AUD, phasic HRV was found to increase upon exposure to negatively valanced emotion pictures cues compared to control/healthy participants, and this higher HRV after the cues was associated with higher craving (22). Another study found that patients with AUD who had higher increases in HRV in response to stress-primed alcohol cues had a greater likelihood of relapse at a 6-month follow-up, compared to patients with lower HRV cue-reactivity to stress-primed alcohol cues (23). Higher HRV in response to stress and appetitive stimuli, such as alcohol cues, may reflect greater regulatory effort required to cope with reactions. Continued research on the association of HRV with self-regulatory behaviors, including the association of resting and stress-modulated HRV with alcohol use over a longitudinal data collection period, is needed.

In sum, research suggests that individuals with heavy drinking or AUD demonstrate differential HRV responses to stress compared to healthy control participants, and this stress response is associated with alcohol craving and use. Stress-reactive, phasic changes in HRV may impact momentary and daily alcohol craving and use among women. Given that women have historically been under-represented in AUD research (24), that HRV has been identified as a potential biomarker of

addiction and risk for relapse (18, 25), and that stress is closely related to alcohol misuse and relapse among women (6), these questions have important research and clinical implications. Furthermore, given the heightened chronic stress and trauma exposure among women veterans (5), stress responding n may be especially salient for understanding this population's risk for AUD and alcohol misuse more generally.

Aims and hypotheses

The first study aim was to test the associations of stress-reactive, phasic HRV with stress-reactive, phasic alcohol craving among female veterans in the lab. It was hypothesized there would be positive associations of stress-reactive HRV and craving, given research cited above showing that, although phasic HRV is inversely associated with emotional responding, this association may differ among individuals with AUD and in association with alcohol craving. The second aim was to examine the association of stress-reactive HRV in the lab to longitudinal measures of alcohol craving and use across a 35-day period. This aim examines whether the HRV assessed in the lab in aim 1 are also associated with craving and drinking during daily life.

Methods

Participants

Data for these pilot analyses were drawn from a larger, ongoing clinical trial. In that study, half of the participants are taught an emotion regulation strategy (cognitive reappraisal, compared to a psychoeducation control group) during a single 50-min session. This single intervention focuses on teaching participants in that condition how to down-regulate negative affect and does not address alcohol use or cravings or encourage or teach skills for participants to change their drinking. The intervention was delivered at the start of the 35-day study period. Preliminary analyses revealed no condition-related effects on craving or drinking in this pilot sample and there was a lack of power to demonstrate such an effect of condition with the current pilot sample. Participants were 20 women veterans recruited from US Veteran Affairs Medical Centers in New England. Recruitment was conducted *via* flyers, provider referrals, and medical record reviews with letters sent to potentially eligible participants. Inclusion criteria were: (1) age 18 and older; (2) current unhealthy alcohol use, defined as scoring 3 or higher on the Alcohol Use Disorder Identification Test, Concise [AUDIT-C; see below for measure details; note: women veterans with AUDIT-C scores of 3+ have been found to have increased rates of alcohol-related consequences and blackouts, tolerance, and self-reported need to cut down on use (26)]; the average full AUDIT score for this sample was 8 ($SD = 4$); (3) if using other illicit substances, alcohol is their primary substance of use; (4) alcohol use in the past 45 days; (5) able to write and speak in English; (6) served in the U.S. military; (7) willing to provide blood samples at laboratory sessions to assay hormone levels and take urine ovulation tests at home. All inclusion criteria were established *via* participant self-report during the phone screen and confirmed at session 1. Exclusion criteria were: (1) psychotic symptoms or uncontrolled bipolar disorder; (2) brain damage or were in an accident that affects ability to complete the computerized task; (3) current (past 3 months) active suicidal ideation or intent; (4) current pregnancy; (5) currently receiving treatment for alcohol use.

Procedures

Procedures were approved by the Institutional Review Board. Participants attended a total of 5 sessions, with data for current analyses being collected in the first 3 of those sessions. Participants also completed 35 days of questionnaires, with the start of the 35 days coinciding with their session 2. After an initial phone screen, session 1 (intake session) including study consent, baseline self-report measures, and a clinical intake.

In session 2, study staff used a manualized procedure (27) to develop a personal stress script that was used as a stress induction in the experimental session. That procedure required participants to verbally describe an event which they found "most stressful," as staff recorded the details provided. This event was one that the participant rated as an 8 or higher on a 1–10 scale, where 10 was defined as the most stressful thing that they experienced in the past year; however, participants were encouraged to use an event that is "common in today's world, such as an argument with a loved one." Events that were traumatic were avoided to maintain consistency between participants who did and did not have posttraumatic stress disorder, as well as to avoid a trauma response as opposed to a non-traumatic stress response. Events concerning substance use were also avoided, so as not to directly influence alcohol cravings which were evaluated before and after each stress induction. If participants provided a trauma or substance-related event, the interviewer re-directed them and reminded them to choose a stressful event that is a common event and/or did not occur in the context of substance use. Participants were asked to briefly describe the event in mind, and study staff guided them to an appropriate stressful event. The participants were asked to describe the event in detail with special attention given to their thoughts and actions. The staff then followed manualized procedures to generate the personalized stress induction scripts during the experimental (third) session.

In relation to a parent study aim that is focused on ovarian hormones, and based in hypotheses that these hormones influence stress reactivity among female participants, each

participant with regular menses was then urn randomized to start their 35-day study period and have their experimental laboratory session in either the early follicular phase or mid-luteal phase of their menstrual cycle. Women who did not menstruate (i.e., due to medications, medical conditions, or menopause) were scheduled independent of any menstrual cycle status. This ensured that, for women who do experience expected hormonal fluctuations and elevated levels of progesterone (the hormones expected to be associated with HRV and stress response), those levels would be randomly distributed at the time of the experimental session.

Across the 35-day period, participants completed daily questionnaires *via* REDCap (Research Electronic Data Capture) electronic data capture tools (28, 29). REDCap is a secure, web-based software platform designed to support data capture for research studies. Questionnaire links were sent to participants' phone *via* text at 9 am each day. Participants provided information about their alcohol consumption and cravings pertaining to the past 24 h.

In the experimental session, a continuous recording of each participant's electrocardiogram (ECG) was made following procedures that are described in greater detail in the Measures section below. Participants completed outcome measures of alcohol craving and affect after a 5-min ("resting") baseline period, during which they were asked to sit quietly. They then completed a stress induction (3.5 min) focused on their selected stressful scenario. HRV during this stress induction is used as the independent variable in analyses ("HRV during the stressor"; when controlling for resting HRV in both statistical models, this represents phasic "stress-reactive HRV" in association with alcohol craving and use). Participants were instructed to close their eyes and imagine that the situation was "happening right now." They were told to "become completely involved in the situation, by involving your mind and body and actually doing what is being described." After the stress induction, they once again completed the measures of alcohol craving and affect ("post-stress"). At the end of study participation, participants were compensated up to $300 gift cards for their time, the exact amount based on their session attendance and completion of daily questionnaires.

Measures

Clinical interview at session 1

Structured clinical interview for the diagnostic and statistical manual—5 (SCID-5)

During session 1, all participants completed the SCID-5 (30) with a study assessor. Specifically, all participants were interviewed using modules that assess mood disorders, psychotic disorders, substance use disorders, and posttraumatic stress disorder.

Timeline follow-back (TLFB)

The TLFB (31) uses a calendar and other memory aids to determine an individual's drinking over a specified time. At baseline, participants were interviewed about their alcohol use on each of the 45 days prior session. The TLFB has excellent reliability and validity for alcohol use (32). TLFB data were used to calculate the baseline percentage of days drinking (PDD).

Self-report measures, session 1 and experimental session

Alcohol use disorders identification test (AUDIT)

The 10-item AUDIT (33) assesses alcohol consumption, drinking behaviors, and alcohol-related problems. Items are scored on a scale of 0–4, for a total possible score of 0–40. A total of 8 or more indicates hazardous or harmful alcohol use. The AUDIT-C (concise) was assessed at phone screen, and full AUDIT was administered at intake session 1.

Alcohol craving questionnaire short-form revised (ACQ-SF R)

The 12-item ACQ-SF (34) assesses alcohol cravings in the current moment (e.g., "If I used alcohol, I would feel less tense"). Each item is scored on a 7-point scale from "strongly disagree" to "strongly agree," and items are averaged to generate a total score. Two ACQ total scores were used in analyses: (1) at baseline/the start of experimental session ("resting" or tonic ACQ), and (2) after the stress induction ("post-stress" ACQ). These 2 administration time points allows for the examination of change in craving in response to stress.

Positive affect negative affect schedule (PANAS)

The 20-item PANAS (35) assesses positive and negative affect in the moment. Each emotion (e.g., enthusiastic, irritable, nervous) is rated on a 5-point scale from "very slightly or not at all" to "extremely." Answers are summed to create positive affect and negative affect scores, each comprising 10 items and ranging from 10 to 50. The PANAS was administered at baseline and after the stress induction during the experimental session, as outlined above for the ACQ.

Biological measures, experimental sessions

Heart rate variability (HRV)

After appropriate skin preparation, three BIOPAC EL503 series disposable electrocardiogram (ECG) electrodes were attached below the left and right clavicles and the reference electrode was placed on the lower left side of the ribs. Lead 100 series leads were attached to these electrodes and taped down to minimize movement artifact. Participants were seated and instructed to keep movement to a minimum while ECG data were collected. A BIOPAC MP160 data acquisition system (Biopac Systems, Inc., Goleta, CA, USA), with an ECG100C amplifier, continuously sampled ECG at 1,000 Hz.

The raw ECG waveforms were visualized and analyzed using BIOPAC *AcqKnowledge* software version 5.05. Waveforms were visually inspected for artifact prior to data collection, to ensure proper electrode placement, and then examined again offline afterwards. Event markers were added to the file to indicate the timeframes during the resting baseline and during the stress induction, which were the only heart beats included in the HRV analyses. No significant artifact was observed in these time windows. Among possible HRV measures, we selected the root mean square of successive (inter-beat interval) differences (RMSSD), a time-domain measure that is calculated by determining and squaring the difference between each heartbeat in milliseconds, which are then averaged together before the square root is applied. RMSSD is one of the most widely reported measures of HRV because of its good reliability over relatively short durations (such as those used in this study) and because it is considered the primary time-domain measure to estimate parasympathetic influences on cardiac activity in a way that is relatively unaffected by breathing artifact (11).

Daily alcohol use and craving questionnaires

Via REDCap, as described above, participants were prompted *via* text over the course of 35 days to provide information about their alcohol use and alcohol craving over the past 24 h. Specifically, participants were asked "Did you have cravings for alcohol in the past 24 h?" and "Did you drink alcohol in the past 24 h?" If participants responded "yes," follow-up questions about frequency and intensity were asked. Exact number of drinks were collected *via* TLFB on a weekly basis. For the current analyses, we used dichotomous yes/no to indicate whether participants reported alcohol cravings over the prior 24 h and used the reported number of drinks per day as the outcome variables for aim 2.

Data analysis plan

Distributions of the variables of interest were examined and independent variables were grand mean-centered prior to running analyses. Bivariate correlations of baseline AUDIT score, HRV during the stress induction, and subjective negative affect and alcohol craving at baseline and after the stress induction ("post-stress") were calculated.

Aim 1 was to examine the association of stress-reactive HRV (i.e., resting RMSSD as a covariate, with RMSSD during the stressor as the independent variable) as the independent variable with stress-reactive alcohol craving (i.e., baseline craving as a covariate, with post-stress craving as the dependent variable) among female veterans in the lab. A repeated measure general linear model was conducted. Menstrual cycle status [i.e., women with regular cycles (n= 11) compared to without regular cycles (n= 7)], post-stress negative affect, and resting levels of RMSSD were entered as covariates, and RMSSD during the stressor was entered as the main independent variable of interest. Resting RMSSD was added as a covariate to statistically model phasic change in HRV. Post-stress negative affect was included as a covariate, given the well-established association of negative affect with craving and expected individual variability in intensity of the stress response to the induction. Baseline alcohol craving and post-stress alcohol craving in the lab were entered as the two measures of the repeated outcome. Within- (change between the two timepoints of craving—baseline and post-stress) and between- (collapsed across time) subject effects of our predictors on craving were examined. Aim 1 analyses were conducted utilizing Statistical Package for the Social Sciences (SPSS) Version 22.

Aim 2 was to again examine the association of stress-reactive HRV with alcohol craving, but using craving data from participants' 35 daily assessment logs as the dependent variable in the first model and number of drinks per day as the dependent variable in the second model. Two mixed level models (MLMs) were run using R software, one for daily report of alcohol craving (yes/no, whether craving was experienced that day) and one for daily number of standard drinks of alcohol. For the first model, predicting daily craving, the *glmer* package was used with model fit by maximum likelihood and Laplace approximation, and binomial fit given the dichotomous outcome. These models provide the estimated probability of craving on a given day, based on the predictors included in the model. The second model, testing the HRV-daily drinks association, used the *lmer* package and a linear mixed model was fit by restricted maximum likelihood (REML), with t-tests for significance using Satterthwaite's method. Both models included as predictors the intercept, menstrual cycle status (having regular menses or not, as in aim 1), resting RMSSD, then RMSSD during the stressor. All continuous variables were grand-mean centered, as such the intercept can be interpreted as adjusting for all included predictors at an average point in the 35-day study period. First, null models were fit to examine variation in the outcome (i.e., cravings, drinks) across individuals. Next, models were fitted in a forward stepping procedure, adding each predictor of interest with relevant covariates into the model one at a time. To illustrate, the full equation for cravings is as follows:

$$\eta_{ti} = \beta_{00} + \beta_{01}\left(menstrual\ cycle\ status\right) + \beta_{02}\left(HRV_{resting}\right) + \beta_{03}\left(HRV_{stress}\right) + r_{0i}$$

In this model, $\eta_{ti} = \log(\frac{\varnothing_{ti}}{1-\varnothing_{ti}})$ reflects the log-odds of reporting cravings, β_{00} = the average log-odds of reporting cravings across individuals, and β_{01} through β_{03} reflect the effects of the covariates and HRV during the stress induction ("HRV stress") on the log-odds of reporting cravings. An identical, albeit linear,

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TABLE 1 Participant demographics and descriptive statistics ($n = 20$).

	M/N	(SD)/%
Age (years)	44	(13)
Education (years)	17	(2)
Annual household income	$78,922	($57,756)
Percent days drinking (45 days prior to session 1)	60%	(31%)
Total baseline AUDIT score	8	4
Lifetime AUD diagnosis	12	60%
Race	—	—
White	18	90%
Mixed race	1	5%
Asian	1	5%
Hispanic ethnicity	1	5%
Sexual orientation	—	—
Heterosexual/straight	17	85%
Bisexual	3	15%
Employment	—	—
Full-time	13	65%
Part-time	2	10%
Student, retired, disability, homemaker	4	20%
Unemployed	1	5%
Marital status	—	—
Single	8	40%
Married	3	15%
Living as married	1	5%
Separated	1	5%
Committed relationship	5	25%
Widowed	2	10%

model was built as illustrated for alcohol drinks per day as the outcome variable.

Results

Descriptive statistics

See Table 1 for descriptive statistics and Table 2 for Pearson correlation coefficients. Significant, positive correlations were found for HRV during the stressor with baseline ($p = 0.02$) and post-stress alcohol craving ($p = 0.04$). Near-significant positive associations were found for resting HRV with post-stress craving ($p = 0.07$) and HRV during the stressor with AUDIT total score ($p = 0.055$).

Aim 1

Repeated measure general linear models tested HRV as statistical predictor of alcohol craving, as measured in the lab. Multivariate tests showed a non-significant association of time-by-RMSSD during the stressor with alcohol craving at baseline and post-stress, $F = 0.09$, $p = 0.77$. The time-by-resting RMSSD was also non-significant, $F = 2.48$, $p = 0.14$. Tests of between-subject effects, however, showed a significant association of RMSSD during the stressor with alcohol craving across time points, $F = 7.15$, $p = 0.02$, Cohen's $f = 0.64$, such that higher HRV during the stress induction was associated with higher overall alcohol craving reported in the lab. The between-subjects association of resting RMSSD with alcohol craving across timepoints was non-significant, $F = 2.41$, $p = 0.15$, Cohen's $f = 0.31$. Other covariates were non-significant, all $p < 0.05$.

Aim 2

Aim 2 examined the association of HRV, measured in the lab, with daily alcohol craving and alcohol use across the 35-day study period. For both aim 2 models, the null models showed that the random effects varied significantly (ps < 0.05). Two metrics of clustering in the data were calculated from the null models, specifically the interclass correlation coefficient (ICC) and design effects (DEFF). Greater values on these metrics indicate greater impact of clustering on the data, with ICC values about 0.20 and DEFFs >2 suggesting clustering should not be ignored in the data. For both outcomes, ICC and DEFFS were above recommended cut offs (ICC = 0.83, 0.55; DEFF = 25.38, 17.32 for craving and drinks models, respectively), suggesting that MLM is an appropriate statistical approach. Further, multicollinearity was explored for predictors in the models; variance inflation factors ranged from 1.18 to 1.35, suggesting that there was not significant multicollinearity between the predictors included in the models.

See Table 3 for results of aim 2 models. The model predicting daily alcohol cravings showed that for every unit increase in resting HRV there was a 0.07 increase in the log-odds of reporting craving on daily assessments ($z = 1.96$, $p = 0.049$, OR = 1.07). HRV during the stressor was not significantly associated with odds of reporting craving on daily logs ($p = 0.40$). The model predicting daily number of drinks consumed indicated the opposite, with HRV during the stressor significantly associated with number of drinks consumed (B = 0.015, $t = 2.38$, $p = 0.032$). Again, higher HRV during a stress induction in the lab was associated with more drinks during the study period. Resting HRV (RMSSD; $p = 0.91$) and status of menstrual cycle ($p = 0.49$) were not associated with the number of drinks during the study phase.

TABLE 2 Correlation (Pearson's *r*) of variables of interest.

		RMSSD		ACQ		PANAS negative affect	
	Resting	**During stressor**	**Resting**	**Post-stress**	**Resting**	**Post-stress**	
ACQ	Resting	0.37	0.54*	—	—	—	—
	Post-stress	0.43†	0.49*	—	—	—	—
PANAS negative affect	Resting	0.12	0.16	0.25	0.12	—	—
	Post-stress	0.06	−0.01	0.27	0.24	—	—
Baseline AUDIT	0.14	0.46†	0.72**	0.71**	0.29	0.25	

**Correlation is significant at 0.01.
*Correlation is significant at 0.05.
†Correlation p <0.1 (2-tailed).
ACQ, Alcohol Craving Questionnaire (total score); PANAS, Positive Affect Negative Affect Scale; AUDIT, Alcohol Use Disorder Identification Test.
"Resting" refers to baseline, while participant sits quietly, "During Stressor" refers to the time frame during which participants listen to the stress induction script, and "Post-Stress" refers to ratings after a personalized stress induction procedure. Correlations reflect associations among the full sample, including women without regular menstrual cycles.

TABLE 3 Aim 2 model results.

	Cravings (binomial)					Number of drinks (linear)				
Predictors	**Estimates**	**SE**	***z***	***p***	**OR**	**Estimate**	**SE**	**df**	***t***	***p***
(Intercept)	−3.04	1.27	−2.39	0.017	-	1.55	0.47	14	3.27	>0.001
Cycle	0.50	2.08	0.24	0.811	1.65	0.59	0.83	14.07	0.71	0.492
Resting RMSSD	0.07	0.04	1.96	0.049	1.07	−0.001	0.013	14.11	−0.11	0.914
RMSSD during stressor	0.01	0.02	0.83	0.405	1.01	0.01	0.01	14.06	2.38	0.032

Cycle is coded 1 = regular menstrual cycle, 0 = without regular cycle.
OR, Odds ratio.

Discussion

The current study examined the associations of heart rate variability (HRV) in response to a personalized stress induction with alcohol craving and use among a sample of female veterans. A growing body of research suggests the important role of psychological and physiological stress reactivity in alcohol use disorder (AUD) among women, and women veterans are at heightened risk of chronic stress and trauma exposure. In the current study, higher stress-reactive HRV (i.e., HRV during the stressor, while controlling for resting HRV) was associated with higher alcohol craving and use among female veterans, in the lab and in daily life. In the lab, higher HRV in response to the stress induction was associated with higher overall craving (i.e., craving reported at baseline and after the stressor). When examined in relation to "real life" alcohol use, this higher HRV as measured in the lab was associated more drinks per day. While these pilot data indicate the important role of stress-reactive HRV in alcohol use among women—in the lab and in "real life"—the results need to be replicated with the larger sample. Although not the focus of these pilot analyses, results also demonstrated a positive association of *resting* HRV with odds of daily craving. The effect of these findings, however, was small, particularly in comparison to the findings regarding HRV during the stressor with craving and use. Collectively, however, these results suggest the relevance of HRV as a factor in women's alcohol use and highlight changes in HRV in response to stressful life events as a potential biomarker of the intensity of women's drinking, even among non-treatment seeking individuals.

The results demonstrating a positive association of stress-reactive HRV with alcohol craving are consistent with previous research (22, 23); this study extends that work to demonstrate the associations of HRV during the stressor with drinking over the 35 study days, within a sample of female veterans. As suggested in the introduction, such findings initially seem contradictory to general findings on HRV and psychopathology, which broadly support an association of higher HRV with better physical and mental health states. However, they are supportive of findings and hypotheses, outlined above, that increased HRV in this population may reflect heightened efforts at self-regulation (whether or not those efforts are adaptive). It is feasible that the positive association of HRV with craving in the lab, in this sample, reflects increased stress or emotion regulatory efforts, and/or attempts at down-regulating, or suppressing, cravings in response to stress. It is notable, however, that this was not a treatment seeking sample and therefore the participants may not have been actively regulating alcohol

cravings. In this case, increased HRV may be more reflective of increased stress (not necessarily craving) regulation efforts. Alternatively, increased craving in response to stress may reflect participant's habitual use of alcohol as a maladaptive regulation strategy itself (i.e., participants have learned that alcohol use is a strategy used for reducing stress or negative emotion and craving reflects a regulatory effort in the moment). In this case, increased HRV correlated with increased craving and drinking may reflect a classically conditioned response to stress in which alcohol follows stress and directly impacts HRV among regular alcohol users (23). These, along with the other findings, require continued research among women. In particular, research that experimentally manipulates emotion and craving regulation in this population can help elucidate these findings.

Limitations

A primary limitation of this pilot study is its small sample size. The findings are intended to inform future research questions and should be interpreted cautiously until they can be replicated in a larger sample. The small sample size also limited our statistical power to detect small effects and prevented us from conducting some statistical tests that we might otherwise have run. Concern about making Type I errors prevented the addition of other cardiac measures to our analyses (e.g., heart rate, low-frequency HRV), which may, in the future, help us to better interpret the biological mechanisms driving our findings.

Conclusion and future directions

Data collection for the current study is ongoing. While preliminary, these findings and relatively large effect sizes warrant continued research that will allow us to address the limitations raised above. The findings from this study extend past research, using longitudinal data collection on alcohol craving and use among a non-treatment seeking population of female veterans. There is a deficit of prospective research with female veterans, who are at increased risk for stress-related disorders including AUD. Future analyses will include clinical diagnoses of posttraumatic stress disorder and lifetime trauma exposure, as these conditions—in addition to chronic alcohol use—have been shown to directly impact stress reactivity and regulation (36) and may serve to further our understanding of the stress-alcohol association in this population.

Given the focus on women, the larger study will also examine the potential moderating role of the ovarian hormone progesterone in the association of HRV with alcohol craving and use. HRV appears to vary across women's menstrual cycle in accordance with fluctuations of progesterone (37–39), and progesterone has been shown to influence women's physiological stress responses (40, 41), as well as alcohol craving and use among women with heavy alcohol use and/or AUD (42). While menstrual cycle status (has regular menstrual cycles/does not) was entered as a covariate in these analyses, examining HRV response to stress and its associations with alcohol use among those women with fluctuating hormone levels is an important next step. The potential implications of hormones for women's self-regulatory behavior and HRV responding has not been explored.

HRV predicted substantive variance in craving among this sample of women veterans, even with a small sample size, providing additional support for HRV as a proximate measure of stress and alcohol craving and use. Collectively, understanding and targeting the biological mechanisms which contribute to stress-induced alcohol use has the potential for enhancing treatments, predicting use, and providing care tailored to the needs of women.

Data availability statement

Datasets are available in accordance with local and national guidelines regarding data sharing. Requests to access the datasets should be directed to cathryn.holzhauer@va.gov.

Ethics statement

The studies involving human participants were reviewed and approved by VA Connecticut Healthcare System Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CH: study conceptualization, data curation, statistical analysis, funding acquisition, methodology, project administration, supervision, and writing and editing the manuscript. EE, MS, DS, and KM: assisted with study conceptualization, planning of methodology, supervision, funding acquisition, and editing the manuscript. NP assisted with planning the psychophysiological methodology and contributed to the writing about heart rate variability. LB coordinated the study, assisted with data curation, project administration, and editing of the manuscript. RE assisted with data curation, project administration, statistical analyses, and writing and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Heart rate variability may index emotion dysregulation in alcohol-related intimate partner violence

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Introduction: Intimate partner violence is a serious public health problem that costs the United States more than $4.1 billion in direct medical and mental health costs alone. Furthermore, alcohol use contributes to more frequent and more severe intimate partner violence incidents. Compounding this problem is treatments for intimate partner violence have largely been socially informed and demonstrate poor efficacy. We argue that improvements in intimate partner treatment will be gained through systematic scientific study of mechanisms through which alcohol is related to intimate partner violence. We hypothesize that poor emotional and behavioral regulation as indexed by the respiratory sinus arrythymia measure of heart rate variability is a key mechanism between alcohol use and intimate partner violence.

Method: The present study is a placebo-controlled alcohol administration study with an emotion-regulation task that investigated heart rate variability in distressed violent and distressed nonviolent partners.

Results: We found a main effect for alcohol on heart rate variability. We also found a four-way interaction whereby distressed violent partners exhibited significant reductions in heart rate variability when acutely intoxicated and attempting to not respond to their partners evocative stimuli.

Discussion: These findings suggest that distressed violent partners may adopt maladaptive emotion regulation strategies such as rumination and suppression when intoxicated and attempting to not respond to partner conflict. Such strategies of emotion regulation have been shown to have many deleterious emotional, cognitive and social consequences for individuals who adopt them, possibly including intimate partner violence. These findings also highlight an important novel treatment target for intimate partner violence and suggest that novel treatments should focus on teaching effective conflict resolution and emotion-regulation strategies that may be augmented by biobehavioral treatments such as heart rate variability biofeedback.

KEYWORDS

intimate partner violence, alcohol, heart rate variability, emotion regulation, couple conflict

Introduction

Intimate partner violence (IPV) is a significant public health problem costing more than $5.8 billion annually with more than $4.1 billion in direct medical and mental health services alone. There are approximately 22.4 million physical assaults committed by a current or former intimate partner per year against an estimated 10 million Americans (1, 2) and an increasing number of homicides by intimate partners (3). National surveys reveal that nearly one third of couples will experience physical aggression

at some point in their relationship and 35% of couples will experience IPV in any given year (4). Compounding the issue of IPV is alcohol use. Alcohol use has been found to be present in most instances of IPV (57 to 70% of IPV incidents), and more severe IPV incidents occur during heavier drinking episodes [e.g., binge drinking; (5–10)]. Although the association between alcohol use and intimate partner violence is well established, the mechanisms of this association are poorly understood, which has stymied the development of treatments that effectively engage these mechanisms to produce appreciable decreases in IPV (11–16).

Distressed violent couples' behavior and physiological over-arousal

Distressed violent couples engage in several unique dyadic behavioral and affective patterns that escalate conflict and physiological arousal more than distressed nonviolent couples. Distressed violent couples are more likely to engage in *negative reciprocity,* which is the tendency to continue or escalate negative and evocative behavior once it begins (17). They also display abnormal *demand-withdraw patterns* (18–20). Individuals exhibiting demanding behavior generally want more intimacy or closeness in an interaction and individuals displaying withdrawing behavior generally want greater autonomy or separateness. If this demand-withdraw pattern is present in a couple interaction, one partner typically exhibits demanding behavior while the other partner exhibits withdrawing behavior. In distressed violent couples, however, partners alternate these behavioral patterns. For example, expressions of desires for assistance, closeness or intimacy by each partner are met by withdrawal by the other partner; a dynamic that lays the foundation for high conflict, power struggles, clinging, and hypervigilant responses; all experiences reported by distressed violent couples (21, 22).

Distressed violent couples are further distinguished from distressed nonviolent couples in both partners' propensity to express blends and higher levels of negative affect, such as contempt and belligerence, which escalate conflict beyond that seen in distressed nonviolent couples (23). In fact, distressed violent couples become more psychologically abusive, emotionally aggressive, and increasingly physiologically aroused as their conflict continues because of these patterns (18, 24–26). Distressed violent couples also have difficulty disengaging from conflict once it begins without escalating to physical aggression due to their inability to regulate affect and behavior when in a highly aroused state (24–28). Furthermore, partners in relationships whose conflict chronically generate such arousal become hypervigilant to potentially threatening and escalating interactions and are more likely to misattribute threat potential to relatively neutral or positive acts (29) suggesting a sensitization process whereby repeated exposures to aversive dyadic interactions result in a progressive amplification of the arousal response to the partner's behavior.

Sympathetic dominance

Research suggests that the unique dyadic patterns seen in distressed violent couples may be moderated by low heart rate variability and a shift to dominance of the sympathetic branch of the autonomic nervous system. For example, low heart rate variability has been associated with suppressed anger and social isolation (30), aversive reactions to harmless, nonthreatening stimuli (31), and more extreme evaluations of blame in anger-inducing situations (32). Seminal research on marital interactions of nonviolent couples (33) found that blends of high levels of negative affect (contempt, belligerence, criticism, defensiveness and stonewalling) increased activation of the sympathetic branch of the autonomic nervous system and that this shift to sympathetic dominance was associated with a loss of affect and behavioral regulation in these marital interactions.

Alcohol's effect on affect regulation and aggression

In addition to the physiological changes caused by conflict and emotional stress, low to moderate alcohol exposure also leads to decreases in heart rate variability measures of parasympathetically mediated cardiac activity (34–37) and a shift toward sympathetic dominance (38). Although alcohol is classified as a pharmacological depressant, during the absorption phase (ascending limb of intoxication), and at peak Blood Alcohol Concentration (BAC), alcohol is actually neuropsychophysiologically arousing (39–41). Like experimental studies of arousal and aggression, experimental studies of alcohol and aggression find that alcohol is associated with aggressive behavior only under conditions of provocation and frustration [see Exum (42) for review]. Furthermore, experimental manipulation of alcohol limb effects (i.e., ascending vs. descending limb) have provided evidence of increased aggressive tendencies on the ascending limb compared to the descending limb, thus providing further evidence of the physiological influence of alcohol playing a facilitative role in IPV due to the disruption in normal physiological functioning (43).

Present study

The present study integrates and extends the findings of previous research examining the physiological changes in distressed nonviolent couples and alcohol-related aggression to understanding a potential mechanism of alcohol-related intimate partner violence. In the present study distressed violent and distressed nonviolent partners were matched on sex, age and relationship distress and participated in a placebo-controlled alcohol administration study with an emotion-regulation task during which electrocardiogram measures of heart rate variability (HRV) were recorded. The HRV measure of interest in the present study is respiratory sinus arrythmia (RSA) as it is an index parasympathetic activation and partners' abilities to respond adaptively to interoceptive (strong affect blends) and exteroceptive (evocative partner behavior) stimuli. We made four hypotheses in this study. First, we hypothesized that alcohol would reduce respiratory sinus arrythmia in in partners consistent with previous literature. Second, we hypothesized that distressed violent partners would exhibit lower respiratory sinus arrythmia when intoxicated than distressed nonviolent partners. Third, distressed violent partners would exhibit lower respiratory sinus arrythmia when intoxicated and attempting to regulate emotion than distressed nonviolent partners. Lastly, we hypothesized, compared to distressed nonviolent partners, acute alcohol intoxication would produce lower respiratory sinus arrythmia, in distressed violent partners when in a highly arousing condition of being asked to view evocative partner stimuli while being asked to feel the emotions associated with those evocative stimuli.

Methods

Participants

Data from partners in the present study were drawn from a parent study investigating over-arousal as a mechanism between alcohol use and partner violence (AA022367). Participants were recruited from the

community through radio, television and newspaper advertisements seeking opposite sex couples who were experiencing conflict in their relationships and who drank alcohol to participate in a research study examining emotions and cognitions in conflict. Eligibility screening occurred at the couple level. Eligible couples were (1) English speaking, (2) heterosexual, (3) age 21–45-years-old, (4) in a distressed relationship, (5) had two binge drinking episodes in the previous 30 days (to qualify for an alcohol-administration study), (6) were married or cohabitating at least 6 months, (7) showed no signs of physical aggression outside of the intimate partner relationship, and (8) provided a breath alcohol level of 0.0 g% at all visits. Distressed violent partners exhibited at least mild physical aggression (e.g., pushed or shoved partner, twisted partner's arm or hair) in the previous 6 months, whereas distressed nonviolent partners exhibited only relationship distress. The age range of participants reflects the legal drinking age and a range that reduces heterogeneity due to age-related changes in the physiological measures collected. Participants were excluded if they (1) were currently separated, (2) had an order of protection in place, (3) were facing violence-related criminal charges, (4) were currently in a domestic violence shelter, (5) presented with evidence of psychosis or severe personality disturbance, (6) were pregnant (female participants were pregnancy tested at all experimental sessions), (7) were taking a medication contraindicated for use with alcohol, (8) were currently taking insulin or oral hypoglycemic medication, (9) had an alcohol use disorder identification test score > 19 and/or indicating alcohol dependence symptoms, (10) reported illicit drug use (except marijuana) and (11) provided a positive urinalysis for opioid or illicit drug use at the stimuli acquisition session.

Participants in the present analyses were 26 distressed violent (18 female, 8 males) and 16 distressed nonviolent partners (7 females, 9 males). The mean age of the sample was 32 (SD 4.8 years, range 23–40 years). Fifty-one percent of participants were Hispanic, 27% White, Non-Hispanic, 10% African American, 7% Native American, and 5% self-identified as other race/ethnicity (e.g., Asian/Pacific Islander, Mexican-American).

Ethical considerations

The study was approved and overseen by the Human Research Review Committee of the academic health center in the southwest United States where the study was conducted. There were protections in place both for IPV and for alcohol consumption. Protections for IPV: both partners completed a mood survey at the conclusion of the stimuli acquisition session, and at the conclusion of the experimental session by the participating partner. Participants could not rate feeling worse than 'slightly negative' on a scale ranging from 'very negative' to 'very positive' and be dismissed from the study session. If one or both partners rated feeling worse than 'slightly negative,' they were interviewed by the PI, a licensed clinical psychologist, who used interviewing techniques to de-escalate the partner(s). Each partner was also phoned 24 h after each study session, and 1 week after completion of the experimental sessions to ensure that study procedures did not contribute to a violent argument between partners. Assurance was sought from each partner that he/she was alone when responding to these questions. Each partner was also individually provided with referral materials to therapy and legal resources.

Protections for the consumption of alcohol included participants being required to have reported at least two binge drinking episodes in the previous month (>4 drinks for males, >3 drinks for females) to ensure that participants were not dosed at a level of alcohol that they were unaccustomed to achieving on their own. Pregnancy testing was completed for all female participants before the placebo and the alcohol conditions. During detoxification, participants were breathalyzed every 15 min and required to remain in the laboratory until two consecutive breath alcohol concentration (BAC) readings of 0.03% or below were achieved, as recommended by the NIH National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines for the safe release of participants.[1]

Materials

Psychosis and severe personality disturbance

To exclude potential participants with psychosis or anti-social personality disorder, both partners of each couple completed the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (44). Because this study was investigating alcohol-related intimate partner violence in family-only violent couples, participants were also screened and excluded if they reported facing violence-related criminal charges as this is indicative of individuals who are violent outside of their intimate relationships.

Alcohol use

For the purposes of assessing alcohol use for meeting exclusion criteria at screening, both partners completed an Alcohol Use Disorders Identification Test [AUDIT; (45)]. Participants who scored a 10 or above (indicating hazardous drinking) were provided with a brief intervention for alcohol use, provided with an active referral to treatment and excluded from the study.

To ensure that participants consumed sufficient amounts of alcohol to ensure that alcohol administration procedures would not result in alcohol levels higher than what participants routinely achieved on their own, a Timeline Follow-Back (46) was completed. Partners who were selected for the experimental conditions reported two binge (per sitting, three or more standard drinks for females, or four or more standard drinks for males) alcohol drinking episodes in the previous 30-days. Secondly, consistent with assessing violence in the past 6 months in couples, drinking was assessed. There were no significant differences between distressed violent (M = 185.56, SD = 221.27) and distressed nonviolent partners (M = 222.57, SD = 308.65) in standard drinks consumed in the previous 6 months ($t = -0.439$, $p = 0.133$).

Relationship distress

Relationship distress was determined using the total score of Dyadic Adjustment Scale [DAS; (47)]. The DAS is a 32-item measure of relationship quality that is divided into four subscales: dyadic consensus, dyadic satisfaction, dyadic cohesion and dyadic affection. Total scores of 97 or less reflect relationship distress. For partners of a couple who did not both have DAS scores less than 97, the couple was considered distressed if their averaged DAS score was 97 or less. The mean total score in the current study was 94.27 (SD = 20.26, range 52.00–124.00). There were no significant differences in relationship distress between distressed violent and distressed nonviolent partners ($t = -1.567$, $p = 0.126$). In the current study, Cronbach alpha for the total scale was 0.92.

Intimate partner violence

For the purposes of partner classification, IPV was determined using the revised conflict tactics scale [CTS2; (48)]. The CTS2 is 39-item

1 https://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm

paired self-report and partner report scale developed to assess the use of tactics by partners in resolving conflict. The CTS2 is comprised of five subscales that include: negotiation, psychological aggression, physical assault, sexual coercion and injury. In using the CTS2 to classify distressed violent and distressed nonviolent partners, the physical assault subscale was consulted, and a couple was classified as distressed if a partner self-reported the use of physical aggression toward his or her intimate partner. The Cronbach alpha for the total scale in this sample was 0.90, and 0.63 for the physical assault subscale.

Partner stimuli for emotion-regulation task

Video clips of partner stimuli selected for use in the emotion-regulation task were obtained from a researcher facilitated discussion of a disagreement that occurred in the initial couple session of the study. Using the Couple Problem Inventory [CPI; (49)], partners identified areas of disagreement that were most significant for them. The couple was then asked to discuss the area of disagreement for 15 min and attempt to research a resolution. A video camera was trained on the head and shoulders of each partner and videos were later coded using the Specific Affect Coding System (50). Twenty-five video clips that were approximately four to 8 s in length and of displays of contempt, belligerence, criticism, defensiveness and stonewalling were selected for presentation during the evocative condition of the emotion-regulation task. Twenty-five video clips of neutral behavior were selected for presentation during the neutral control condition of the emotion-regulation task.

Anger expression

Anger expression was measured using the STAXI-2 (51). The STAXI-2 is a self-report questionnaire that measures the experience, expression, and control of anger in both research and clinical samples. The STAXI-2 is comprised of six scales (state anger, trait anger, anger expression-out, anger expression-in, anger control-out and anger control-in). Responses are made on a likert-type scale ranging from 1 (almost never) to 4 (almost always). Trait anger indexes frequent angry feelings and feeling of being treated unfairly. Anger expression-out indexes anger expressed in verbally or physically aggressive behavior directed at others or objects. Anger expression-in indexes the suppression of frequent intense angry feelings. Anger control-out is an index of effort expended in the monitoring and prevention of outward experiences and expressions of anger. Anger control-in indexes effort expended in calming down, and reducing angry feelings immediately, which reduces awareness of when assertive behavior is needed in facilitating constructive resolutions to conflict situations. Mean scale responses from the trait anger, anger expression-out, anger expression-in, anger control-out and anger control-in were used for analysis. In the current study, the Cronbach alpha for the trait anger scale was 0.85, anger expression-out was 0.63, anger expression-in was 0.81, anger control-out was 0.82 and anger control-in was 0.86. As reported in our previous work (52), there were no significant differences in anger experiences between partner types.

Procedure

The present study was a counter-balanced placebo-controlled alcohol administration study that consisted of three sessions; an initial stimuli acquisition session that involved both partners, and two experimental sessions that involved only one partner. Data presented here were drawn from the experimental sessions. Distressed violent partners were pseudo-randomly selected for participation in the experimental sessions. If gender symmetry in the use of physical aggression was reported by a couple, a partner was randomly selected for participation. If the couple was asymmetrical in their self-reported use of physical aggression, the partner self-reporting the greatest use of physical aggression was invited to participate. Distressed nonviolent participants were matched on sex, relationship distress and age to distressed violent participants and reported only relationship distress and no physical aggression by either partner.

We also collapsed across gender in our experimental sessions. There are several studies that supported this decision. For example, over 200 studies have demonstrated at least gender symmetry in family-only IPV (53). Also, distressed violent females are as verbally aggressive as distressed violent males (25), and verbal aggression and physical aggression are highly correlated (54). Also, drinking alcohol within 3 h of an argument with a partner is a strong predictor of female IPV (55), and there are no gender differences in aggressive tendencies once males and females are drinking (56). There are also no gender differences among adults in the use of physical aggression once emotional arousal is present (57), nor gender differences in aggression under conditions of high provocation (58). Furthermore, follow-up analyses confirmed our assertion that there are no gender differences in physiological responding to the beverage condition ($F = 0.710$, $p = 0.410$) or stimuli ($F = 1.278$, $p = 0.269$) among distressed violent partners.

The partners selected for the experimental sessions returned to the laboratory on two separate occasions for counter-balanced alcohol and placebo beverage emotion-regulation sessions. For each session, participants were seated in a chair a comfortable distance from a TV monitor displaying stimuli, prepared for electrocardiogram recording, and then administered either an alcohol beverage or a placebo beverage. Participants engaged in a 5-min baseline Vanilla Task (59) while the recording of electrocardiogram (ECG) activity was collected. The Vanilla Task is a minimally demanding color detection task (viewing blocks as they change color and counting number of blue boxes) that has been shown to be superior to a resting baseline task in between- and within-baseline stability, amplitude and responsivity (60).

Emotion regulation task

The approach for studying emotion regulation in the present study has been used in several previous studies (61), but we utilized participant-tailored stimuli (video clips of respective partner's evocative behavior) to enhance the emotional arousal, valence and salience the stimuli in the emotion regulation task. In the WATCH condition, participants were instructed to let their emotional experience occur naturally, and to pay attention to how they felt during the clip. In the DO NOT REACT condition, participants were instructed to attempt to suppress any feelings of emotion so as to prevent an observer from knowing that an emotional response had occurred. A total of 50 unique video clips between four and 8 s in length were used in the task; 25 evocative and 25 neutral. Each stimulus was presented twice: once in the WATCH condition and once in the DO NOT REACT condition. On each block of trials (WATCH or DO NOT REACT), participants viewed the instruction (WATCH or DO NOT REACT; 1.5 s), a blank screen (1 s), fixation cross (1.5 s), blank screen (0.5 s), video clip (4–8 s) and a blank screen (up to 2.5 s). The total amount of time required for the task was approximately 25 min.

Beverage protocol

Alcohol condition protocol

Participants received a mixed drink (cranberry juice and 100-proof vodka) intended to raise their blood alcohol concentration (BAC) to a

target dose of 0.08 g% using a standard formula for calibrating alcohol doses to achieve target BACs. Specifically: Alcohol dose (g) = [(10 * BAC * TBW)/0.8] + [10 * MR * (DDP + TPB)] * [TBW/0.8; BAC = blood alcohol concentration, TBW = total body water, MR = alcohol metabolism rate, DDP = duration of drinking period, TPB = time to peak BAC; (57)]. Participants were asked to drink the beverage within 9 mins to ensure they remained on the ascending limb or reached peak BAC during the experimental task. Baseline recording began when participants reached a BAC of 0.06 g%.

Placebo condition protocol

Procedures were identical to the alcohol condition, except participants consumed a volume of juice equivalent to the volume of beverage consumed in the alcohol condition. To maintain blindness to the condition, the cup was misted with vodka and 3 milliliters of vodka was floated on top of the cranberry juice to produce the smell and taste of an alcohol beverage.

Heart rate variability recording and processing

Electrocardiogram (ECG) data were collected using the BrainVision actiCHamp 64-channel, DC amplifier, 24-bit resolution, biopotential system. Respiration and ECG were measured using an integrated BrainVision respiration belt, and an ECG in Lead II position. Baseline measures were collected, and ECG data were time locked to stimuli presentation during the emotion-regulation task. ECG data were quantified and measures of respiratory sinus arrythmia (RSA), a measure of parasympathic activity and cardiac vagal control (62), using the integrated QRSTool and CMetX to extract the inter-beat-interval (IBI) from the ECG data and calculate RSA from the IBI series (63).

Results

Statistical Package for the Social Sciences 28 (SPSS 28) was used to perform the statistical analyses of the data for this study. Preliminary analyses were conducted to assure no violations of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Because predictions for all analyses were directional, derived from theory and specified in advance, they were evaluated using a one-tailed criterion of significance (64). Assuming a two-tailed test, Type I error = 0.05, and $r = 0.32$ we conservatively projected that we would require 40 (20 DV, 20 DNV) participants to have sufficient statistical power (0.801) to reject the null interaction hypothesis. The study design is repeated measures within-subjects design with a between-subjects factor and the data analysis strategy utilized was a repeated measures analysis of variance with a between subjects factor (e.g., partner type) that follows directly from the study design. Significant main effects and interactions are reported below. A Bonferroni correction was used to correct for multiple comparisons. SPSS utilizes a mathematically equivalent adjustment and multiplies the observed (uncorrected) value of p by the number of comparisons made to obtain a corrected value of p. Please note that the corrected p-values are reported below.

Effect of alcohol on respiratory sinus arrhythmia

To examine the effect of alcohol on the respiratory sinus arrhythmia (RSA) measure of heart rate variability we conducted a repeated-measures analysis of variance (RMANOVA) and examined the main effect of beverage (Alcohol vs. Placebo) as the within-subjects factor collapsed across partner type. A Bonferroni correction was used to correct for multiple comparisons. The effect of alcohol on RSA was marginally significant ($F = 4.077$, $p = 0.051$, partial eta squared = 0.102). Although only marginally significant, alcohol produced lower RSA values than the placebo beverage. The effect size was large, however, suggesting an effect of alcohol on reducing RSA and thereby suggesting the capacity for effective emotion and behavior regulation is impaired by acute alcohol intoxication. See Figure 1.

Distressed violent partners exhibited lower respiratory sinus arrhythmia when acutely intoxicated

There was a significant interaction between partner type (Distressed Violent vs. Distressed Nonviolent) and beverage type (Alcohol vs. Placebo; $F = 6.300$, $p = 0.017$, partial eta squared = 0.149) indicating that alcohol affected RSA differently in distressed violent and distressed nonviolent partners. To understand this interaction, contrasts compared alcohol to placebo beverage across distressed violent and distressed nonviolent partners. A Bonferroni correction was used to adjust for multiple comparisons. These contrasts reveal that compared to the placebo beverage, alcohol significantly reduced RSA in distressed violent partners, but not distressed nonviolent partners (M difference = −0.424, $p = 0.017$). See Figure 2.

Distressed violent partners exhibit lower respiratory sinus arrhythmia when acutely intoxicated and attempting to regulate emotion

To test our hypothesis that distressed violent partners exhibit worse emotion regulation than distressed nonviolent partners as indexed by RSA, we conducted a repeated-measures analysis of variance (RMANOVA) and examined the interaction between emotion-regulation condition (Watch and Do Not React), beverage condition (Alcohol and Placebo), and partner type (Distressed Violent vs. Distressed Nonviolent). Results reveal a significant interaction ($F = 5.092$, $p = 0.030$, partial eta squared = 0.124). Follow-up contrasts were conducted to understand this interaction. A Bonferroni correction was used to adjust for multiple comparisons. Contrasts reveal that when intoxicated distressed violent partners exhibited significantly lower RSA when watching their partners' stimuli (Watch; M difference = −0.395, $p = 0.030$) compared to intoxicated distressed nonviolent partners. Distressed violent partners also exhibited even lower RSA when intoxicated and trying not to react to their partners' stimuli (Do Not React; M difference = − 450, $p = 0.014$). Distressed nonviolent partners did not exhibit significant differences in RSA in either emotion regulation condition while intoxicated. These findings suggest that not only do distressed violent partners exhibit worse capacity for emotion regulation, but this capacity is further worsened when attempting to not respond to their partners' stimuli. See Figure 3.

Distressed violent partners exhibit lower respiratory sinus Arrythmia when intoxicated and attempting to regulate emotion to evocative stimuli

To test our hypothesis that distressed violent partners would exhibit reduced respiratory sinus arrythmia, thereby impaired emotional and behavioral control, compared to distressed nonviolent partners

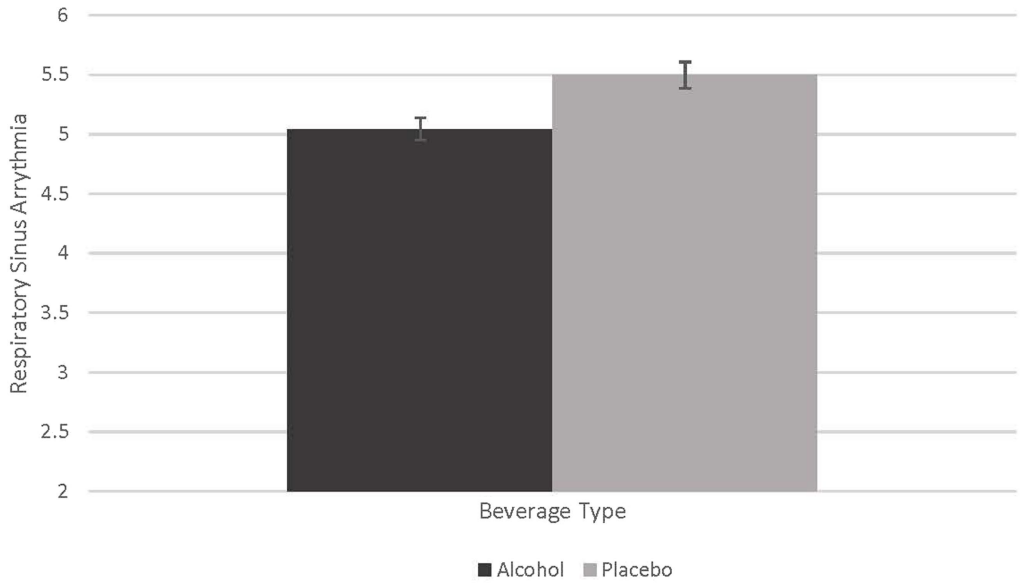

FIGURE 1
Effect of alcohol on respiratory sinus arrythmia. This figure demonstrates the marginally significant difference in beverage type on respiratory sinus arrythmia (RSA; $F=4.077$, $p=0.51$, partial eta squared=0.102).

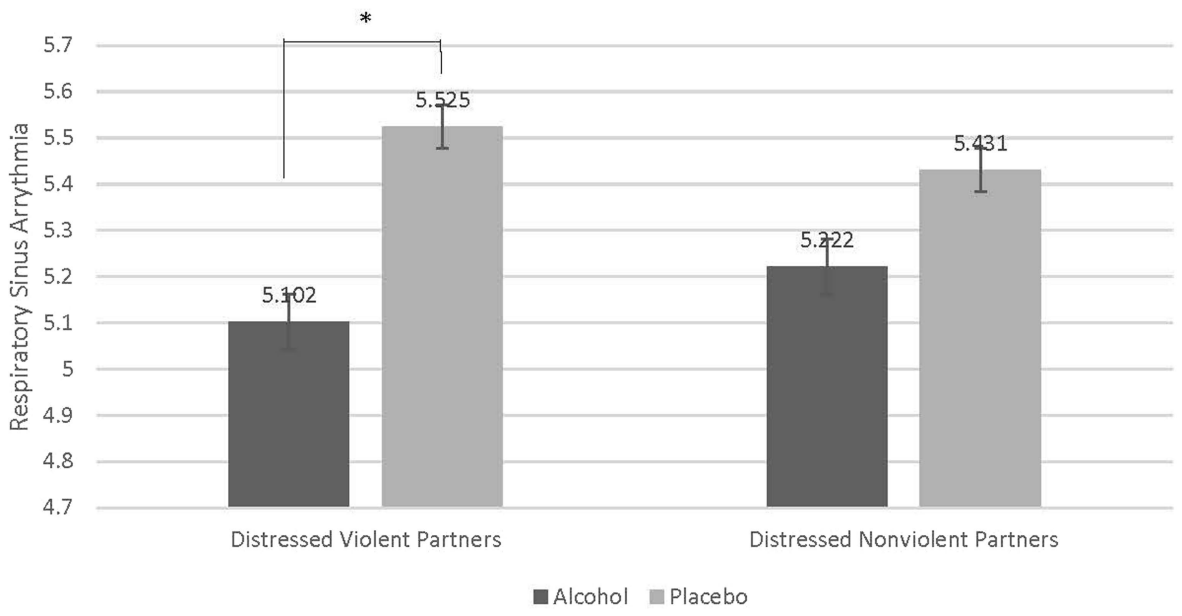

FIGURE 2
Contrast comparing decrease in respiratory sinus arrythmia in distressed violent partners when intoxicated. Compared to distressed nonviolent partners there was a statistically significant difference of the effect of alcohol on respiratory sinus arrythmia (RSA) in distressed violent partners (M difference=−0.424, $p=0.017$). Acute alcohol intoxication reduced RSA in distressed violent partners to a greater degree than in distressed nonviolent partners.

we conducted a repeated-measures analysis of variance (RMANOVA) and examined the interaction of beverage condition (Alcohol vs. Placebo), emotion-regulation condition [(Watch vs. Do Not React), stimuli type (Evocative vs. Neutral) within-subjects factors], and partner type (Distressed Violent vs. Distressed Nonviolent) as the between-subjects factor (See Figure 1). A Bonferroni correction was used to adjust for multiple comparisons. The expected beverage type by emotion-regulation condition by stimuli type by partner type interaction was statistically significant ($F=4.890$, $p=0.033$, partial eta squared = 0.120). To understand this interaction, we conducted follow-up contrasts which revealed counter-intuitive results. For distressed violent partners, there were no significant differences in RSA when Watching evocative partner stimuli in either beverage condition. Compared to distressed nonviolent partners there were, however, significant and large reductions in RSA when distressed violent partners were intoxicated and attempting to Not React to their partners' evocative stimuli (M difference = − 0.555, $p=0.009$), and even when intoxicated and attempting to Not React to Neutral partner stimuli (M

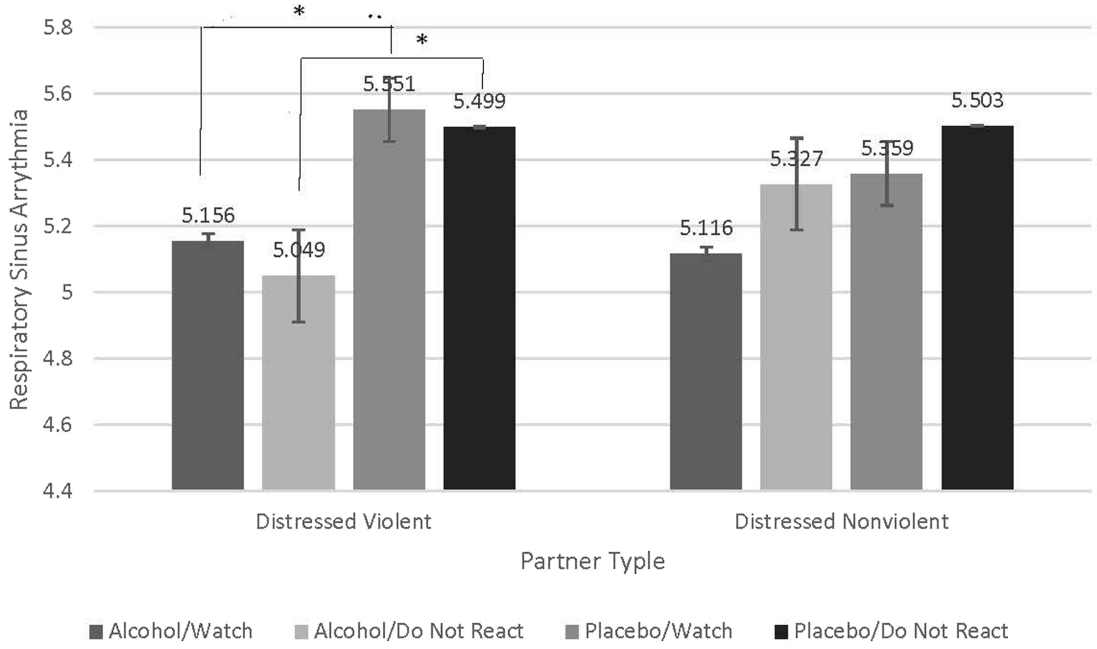

FIGURE 3
Contrasts examining significant interaction indicate greater decreases in respiratory sinus arrythmia in distressed violent partners compared to distressed nonviolent partners when intoxicated and attempting to not react to partner stimuli. Contrasts reveal that compared to distressed nonviolent partners, distressed violent partners, when intoxicated, exhibited significantly lower RSA when watching their partners' stimuli (Watch; *M* difference=−0.395, p=0.030). Distressed violent partners also exhibited even lower RSA when intoxicated and trying not to react to their partners' stimuli (Do Not React; *M* difference=−0.450, p=0.014). Distressed nonviolent partners did not exhibit significant differences in RSA in either emotion regulation condition under any beverage condition.

difference = − 0.345, p=0.037). Distressed violent partners also experienced a significant reduction in RSA when intoxicated and Watching neutral partner stimuli (*M* difference = − 0.425, p=0.019) which may have been an artifact of the pharmacological effects of alcohol. None of the follow-up contrasts were significant for distressed nonviolent partners. These findings suggest that the method of emotion regulation that distressed violent partners adopt when attempting to not respond to their partners' stimuli is maladaptive and worse when they are intoxicated, and their partners are behaving evocatively. See Figure 4.

Discussion

The present study was an examination of the effects of acute alcohol intoxication on biobehavioral emotion regulation capabilities of distressed violent partners with our hypotheses being partially supported. We hypothesized that compared to distressed nonviolent partners, distressed violent partners experienced reduced respiratory sinus arrythmia, thereby reducing emotion regulation capabilities, under conditions of acute alcohol intoxication, viewing evocative partner stimuli and being asked to feel the emotions they associated with the evocative stimuli. While our hypotheses were supported with respect to partner type and the effects of acute alcohol intoxication, we found that distressed violent partners experienced reduced respiratory sinus arrythmia when acutely intoxicated and attempting to not respond to their partners' evocative stimuli. This stands in contrast to distressed nonviolent partners who in this condition experienced increased respiratory sinus arrythmia. These findings suggest in the context of their severe relationship distress and acute alcohol intoxication, distressed violent partners may adopt strategies for emotion regulation that further impair their ability to respond adaptively. This finding stands in contrast to the distressed nonviolent partners who appeared to adopt a more adaptive emotion regulation strategy in this condition.

Rumination and suppression strategies are two emotion regulation strategies with particular relevance to partner violence. Watkins et al. (65) demonstrated that individuals produced more aggressive responses to provocation when asked to adopt a ruminative emotion regulation strategy when acutely intoxicated and believed to be in a competition with their partners. Rumination is thought to impel aggressive actions because it maintains a high level of physiological arousal, maintains focus on anger-inducing memories, and thoughts of retaliation (66). Similarly, experimental suppression techniques have been associated with reduced behavioral expressions of negative affect, but an increased experience of the negative affect and physiological activation (67), much like the responses of the distressed violent couples in our study. Suppression strategies have been shown to have many deleterious affective, cognitive and social consequences. Cognitively, these same techniques have also been shown to impair memory for details of conversations of interpersonal conflict (68). Socially, suppression techniques have been shown to cause greater stress in the partner of the individual exhibiting the suppression technique (69). Our previous research (52) demonstrated a very similar process in the partners in distressed violent participants. The partners of the distressed violent participants reported significantly greater effort in monitoring and preventing outward manifestations of anger, but that those attempts eventually failed and their own anger expressions took the form of contemptuous, critical and insulting comments and physically aggressive behavior. Further research is needed to fully elucidate this process, however.

We have also extended the findings from the physiological work with nonviolent couples in conflict (33) to distressed violent partners who, compared to distressed nonviolent partners, exhibited both overall

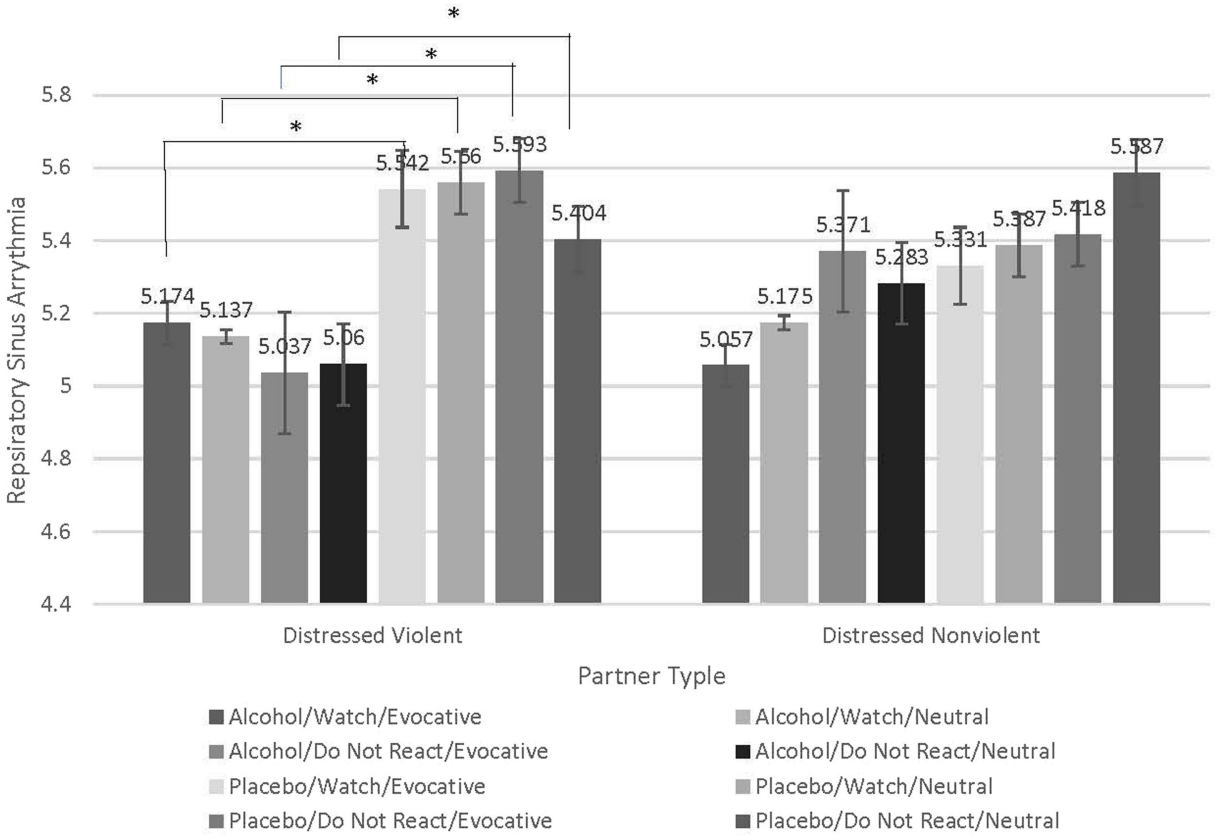

FIGURE 4
Contrasts examining significant interaction indicate greater respiratory sinus arrythmia decreases when distressed violent partners are intoxicated, attempting to regulate emotion in response to evocative partner stimuli. Contrasts conducted to understand the significant interaction between beverage condition (Alcohol vs. Placebo), emotion-regulation condition (Watch vs. Do Not React), stimuli type (Evocative vs. Neutral), and the between-subjects factor of partner type (Distressed Violent vs Distressed Nonviolent). Compared to distressed nonviolent partners, there were significant and large reductions in RSA when distressed violent partners were intoxicated and attempting to Not React to their partners' evocative stimuli (*M* difference = −0.555, $p = 0.009$), and even when intoxicated and attempting to Not React to their partner's Neutral stimuli (*M* difference = −0.345, $p = 0.037$). Although statistically significant, this effect to Neutral stimuli was not to the magnitude of that of the Evocative stimuli. Distressed violent partners also experienced a significant reduction in RSA when intoxicated and Watching neutral partner stimuli (*M* difference = −0.425, $p = 0.019$) which may have been an artifact of the pharmacological effects of alcohol. Distressed nonviolent partners did not exhibit significant differences in RSA in either emotion regulation condition under any beverage condition.

sympathetic dominance as evidenced by the low respiratory sinus arrhythmia (RSA) measure of HRV, and even stronger sympathetic dominance when intoxicated, viewing evocative stimuli and attempting to regulate their emotional response. Such sympathetic dominance causes a loss of capacity to respond adaptively to introceptive (strong affective blends) and extroceptive (evocative partner behavior) stressors. Previous studies have shown low respiratory sinus arrythmia is associated with the loss of capacity to respond adaptively to introceptive and extroceptive stressors, as well as a tendency to respond to stressors with increased dysregulated affect (70–75).

Lastly, our choice of conducting a placebo-controlled alcohol administration study warrants further discussion. While some argue that alcohol administration studies should include a no-alcohol control conditions to control for compensatory behaviors often witnessed in placebo conditions (76), there were several factors that drove our decision to include only a placebo control condition in the present design. Our primary consideration was including a second control condition may cause participants to habituate to the effect of viewing the same evocative partner stimuli numerous times. This was an important consideration given that we employed a within-subjects design. With a no-alcohol control condition, participants would have been exposed to the same partner stimuli a total of six times, potentially reducing the stimuli's evocative and physiologically arousing ability. In addition, such a procedure in the present study would have been unwieldy, a significant burden on participants (sessions were each 2 to 5 h long) and would have complicated the interpretation of an already complex set of findings. We also argue that a placebo condition versus a no-alcohol condition was the appropriate control condition in the present study. The effect of the substances often cannot be explained solely by their pharmacological properties, and expectations are partly responsible for how one responds to the effects of substances (77). This is particularly true for alcohol consumption where expectations may be learned through experiences and socialization, especially in the case of couple conflict. As such, placebo alcohol control conditions have been almost exclusively used to disentangle the effects of pharmacological and expectations on a range of behaviors, including aggression (78, 79). With the inclusion of a placebo beverage control condition, we felt we were best able to control for the expectancies surrounding alcohol use in couple conflict.

Clinical implications

The present study is an analogue of costs to society from hazardous or harmful drinking that include putting individuals at a risk for

violence. In addition, the largest proportion of individuals who report alcohol-related IPV do not report alcohol dependence symptoms. As such, this present study is representative of most alcohol-related IPV. Understanding the factors involved in alcohol-related IPV in this population is important for the development of treatments as current substance use treatment and conflict-focused couples treatments have proven to be insufficient to meaningfully influence the occurrence of alcohol-related IPV. This work has also identified novel targets for treating alcohol-related intimate partner violence. For example, in addition to behavioral treatments focused on improved emotion and behavior regulation, and conflict resolution in distressed violent couples (both partners), heart rate variability biofeedback (HRV-BFB) may enhance this learning and mitigate the loss of capacity to respond adaptively to interoceptive and exteroceptive stressors. HRV-BFB is an intervention delivered for disorders associated with affect dysregulation, including substance use disorders, PTSD, major depression, and anxiety disorders (70–75, 80). This biobehavioral intervention takes advantage of the respiratory sinus arrhythmia, that is, the innate entrainment of heart rate (HR) to the breath. Maximal increases in the amplitude of heart rate oscillation (i.e., higher levels of HRV) are produced when the cardiovascular system is rhythmically stimulated by paced breathing at a frequency of about 0.1 Hz [i.e., six breaths per minute; (81, 82)]. By instructing individuals in this specialized paced breathing technique using biofeedback visualization of their real-time respiratory and cardiac parameters, one can increase HRV (83), and at the same time increase sensitivity of the baroreflex, the body's regulatory mechanism for dynamic control of HR and blood pressure (84). As a result, HRV-BFB can enhance parasympathetic nervous system functioning, autonomic stability and affect regulation (72, 84). It is important to note that a biofeedback procedure is necessary to accomplish this as one needs to learn to breathe at the resonant frequency of the cardiovascular system of each individual (85). This cannot be accomplished simply by relaxation or other deep breathing techniques.

Additionally, a key feature of the drinking rates of the participants in the present study was that we excluded individuals who showed signs of alcohol dependence. As such, participants exhibited, at worst, hazardous or harmful drinking levels. Decades of research has demonstrated that brief interventions for hazardous or harmful drinking are highly effective at reducing drinking to low risk levels (86–89). Recent reviews of IPV treatment also suggest promise for treatments that address substances (90). Given that the distressed violent couples in our study reported significantly more heavy drinking days than distressed nonviolent couples, providing a brief intervention to reduce their drinking to a low risk level, including not engaging in conflict with their partners when drinking, should also be a key feature of treatment.

Limitations and future directions

There are several limitations of the present study which may limit the generalizability of our findings. First, we had unequal sample sizes in our two groups of partners. Recruitment of couples with conflict in their relationships yielded a largely distressed violent sample. In addition, most potential distressed nonviolent couples did not consume enough alcohol to qualify for an alcohol administration study. Future studies should attempt to over-recruit distressed nonviolent couples. Relatedly, these findings do not generalize to partners or couples with severe alcohol use disorders who would require treatment beyond a brief intervention to address the alcohol use disorder. Also, in an attempt to control for relationship stability, we recruited couples who were married or living together at least 6 months. This inclusion criteria may have been overly strict and not representative of couples who experience physical aggression in their relationships. Future studies should broaden the inclusion criteria to include couples who are also in dating relationships. Similarly, since this was the first of its kind investigation of heart rate variability in alcohol-related intimate partner violence our inclusion criteria were restricted to heterosexual couples. Future studies should extend these findings to same-sex couples to determine if similar processes are present.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research Review Committee, The University of New Mexico Health Sciences. The patients/participants provided their written informed consent to participate in this study.

Author contributions

BF, EC, JC, and DH contributed to the design, the conduct of the study, and interpretation of study results. BF drafted the manuscript. EC, JC, DH, and JB provided critical feedback on the manuscript draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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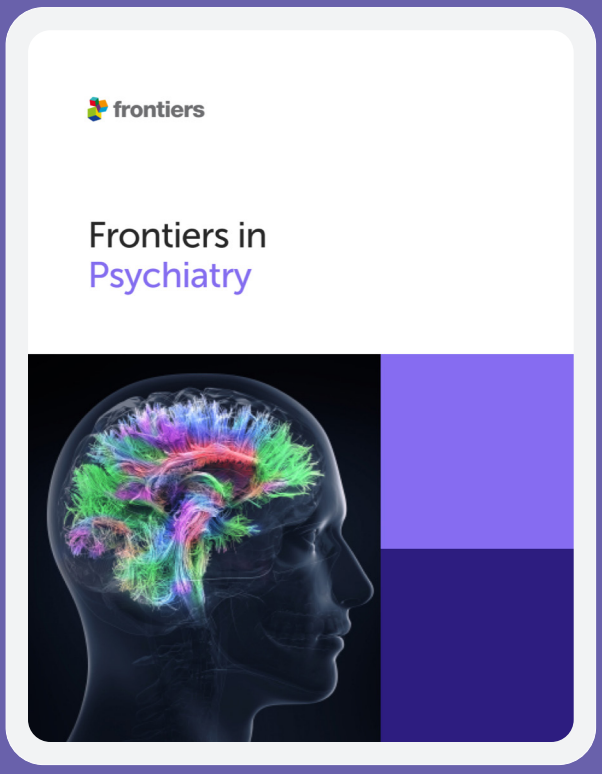

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