2022-04-08

The Relationship Between Traumatic Brain Injury and Disruptions in Heart Rate Variability and Heart Rate Variability Biofeedback: A Systematic Review

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A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

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ABSTRACT

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Traumatic brain injury is a significant public health problem. Heart rate variability is a potential modality to measure physiological dysfunction following traumatic brain injury to assist in determining recovery time and the relationship between traumatic brain injury severity and recovery. To date, a summary of the evidence across injury severities and the possible role of heart rate variability biofeedback in traumatic brain injury treatment is lacking but needed to determine potential clinical utility. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Systematic literature searches on CINAHL, Embase, PsycINFO, SPORTDiscus, and MEDLINE were conducted in August of 2020. There were two parts to this systematic review. Part I reviewed the relationship between heart rate variability and injury severity, recovery, and cognitive and emotional functioning. Part II reviewed the relationship between heart rate variability biofeedback and traumatic brain injury. Regarding Part I, eighty-five papers met inclusion criteria. Overall, there appears to be a positive relationship between increased heart rate variability and recovery of clinical symptoms following traumatic brain injury. For Part II, seven papers met inclusion criteria. On average, participants completed 14 sessions of heart rate variability biofeedback (mean = 13.5, SD = 13.5, range = 1 to 40). Findings to date suggest a positive relationship between increased heart rate variability and recovery of clinical symptoms, including improvements in cognitive function and physical symptoms including headaches, dizziness, and sleep problems. Literature on traumatic brain injury and heart rate variability biofeedback treatment is in the early stages, and effectiveness is unclear due to poor-to-fair study quality, though early results are promising.

Keywords: traumatic brain injury, heart rate variability, biofeedback

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Dr. Larson for his invaluable mentorship, support, and sponsorship throughout my journey towards completing this thesis. His experience and knowledge have provided insight and encouragement throughout my training within the classroom, lab, and daily life. My gratitude extends to Dr. Darowski, Dr. Steffen, and Dr. Baldwin for their mentorship, which helped shape my scientific methodology and interpretation of this systematic review. I am also grateful for the mentorship of Dr. Hopkins, who gave her time to ensure that I had a foundation in scientific writing and ensure that I felt a part of a community of women in neuropsychology. I would like to thank my lab mates who dedicated their time to see this project through. I would also like to thank my husband for his unwavering support and patience during my study. Finally, I would like to express gratitude towards my family. Their encouragement and continuous support have made my journey possible.

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Traumatic brain injury is a significant public health problem. In 2014, the Center for Disease Control and Prevention reported that approximately 1.5 million people sustain a traumatic brain injury in North America each year, resulting in over 288,000 hospital stays and 56,800 deaths (Center for Disease Control and Prevention, 2014; Consensus Conference, 1999). The high prevalence of traumatic brain injury may be an underestimate due to many people with mild traumatic brain injury (i.e., concussion) that do not seek medical care and go unreported (Faul et al., 2010; Langlois et al., 2006). Current estimates of traumatic brain injury also tend to exclude those who received treatment within a federal facility (i.e., Veterans Affairs hospitals; Faul et al., 2010), suggesting that the high reported rates of traumatic brain injury each year may be even higher.

Traumatic brain injuries are typically divided into mild, moderate, and severe injuries, with worse outcomes following moderate-to-severe injuries. Moderate-to-severe traumatic brain injury is associated with long-term cognitive and neurological complications, often including impairments in processing speed, episodic memory, attention, and executive functioning (Goldstein & Levin, 1995; Vakil et al., 2019). Mild traumatic brain injury is generally associated with short-term cognitive difficulties that resolve within three-to-six months but can also be associated with long-term cognitive and affective difficulties in a subset of individuals (Arulsamy et al., 2019; Guskiewicz et al., 2005). Moderate-to-severe traumatic brain injury is frequently associated with long-term declines in quality of life and increased risk for persistent neurological difficulties, such as dementia, memory decline, impaired judgment, and poor impulse control (Arciniegas et al., 2002; Arulsamy et al., 2019; LoBue et al., 2019).

Given the cognitive difficulties and decreased quality of life often associated with traumatic brain injury (Dainter et al., 2019; Pettemeridou et al., 2020), it is essential to identify possible areas, including biomarkers, that can predict or enhance traumatic brain injury recovery. A potential biomarker of traumatic brain injury diagnosis and recovery is autonomic nervous system functioning (Clifton et al., 1983; Khalid et al., 2019; Purkayastha, Stokes et al., 2019). The autonomic nervous system involves a network between the brain stem, prefrontal cortex, amygdala, and hypothalamus, with the amygdala serving as a primary efferent source of cardiovascular and autonomic responses (Conder & Conder, 2014; Thayer et al., 2009) and the vagus nerve serving as a primary afferent source. The vagus nerve brings information to the brain from inner organs (i.e., heart, liver, gut, and lungs) and is modulated by the frontal cortex—an area often damaged following traumatic brain injury (Bishop et al., 2017).

Autonomic Nervous System Dysfunction Following Traumatic Brain Injury

The autonomic nervous system is divided into two major components: the sympathetic nervous system and the parasympathetic nervous system. The parasympathetic nervous system influences peripheral vasculature and decreases heart rate to conserve energy under quiet (i.e., resting) conditions. The sympathetic nervous system influences cardiac regulation and conditions of “fight or flight” (McCorry, 2007). More specifically, the sympathetic nervous system regulates sweating and vascular smooth muscle while innervating abdominal and pelvic cavities, thoracic viscera, and structures of the head. Widespread vasoconstriction of vascular smooth muscle in order to redistribute blood away from metabolically inactive tissues towards contracting muscles in the kidneys and gastrointestinal system results from sympathetic stimulation. The effects of the parasympathetic nervous system are more localized compared to the sympathetic nervous system. Specific tissues within the sacral region of the spinal cord and

nuclei of the brainstem are stimulated at any given time, unlike the diffuse discharge that is possible through the sympathetic nervous system (McCorry, 2007). Stimulation of neural sympathetic fibers increases vasodilation and heart rate along with norepinephrine and epinephrine release from the adrenal medulla (Esterov & Greenwald, 2017). Therefore, the autonomic nervous system is involved in the regulation of gastrointestinal responses, blood pressure, thermoregulation, pupil dilation and constriction, and contraction of the urinary bladder.

Autonomic nervous system dysfunction can occur following traumatic brain injury and has a widespread influence on injury-induced abnormalities in organ systems. Autonomic nervous system dysregulation is often associated with altered baroreflex sensitivity, sympathetic nervous system hyperactivity, and poor blood flow autoregulation (La Fountaine et al., 2019; Just, 2007; Khalid et al., 2019). Baroreceptors monitor blood pressure and transmit sensory impulses to the vasomotor center in the brainstem when there is a change in blood pressure. Consequently, autonomic nervous system activity to blood vessels and the heart is adjusted to cause changes in vascular resistance and heart rate (McCorry, 2007). Since baroreceptors relay information from blood pressure to the autonomic nervous system, baroreflex sensitivity is a measure of autonomic nervous system activity, which correlates with an increased risk of early mortality, morbidity, arterial hypertension, and cardiac complications (Armstrong et al., 2021; Hendén et al., 2014; Mikhailovich & Eduardovich, 2019). The alterations caused by autonomic imbalance can also be associated with altered homeostatic mechanisms and the regulatory function of the heart and kidneys (Blake et al., 2016; Dobson et al., 2017; Esterov & Greenwald, 2017; Khalid et al., 2019). Systemic abnormalities, including increased sympathetic nervous system activity causing immune system depression, may occur following injury (Esterov &

Greenwald, 2017).

Traumatic brain injury specifically can be associated with autonomic dysfunction, including neuroinflammation, oxidative stress, neurodegeneration, and blood-brain barrier disruption (mechanism described in detail below; Giza & Hovda, 2014; Jendoubi et al., 2017; Krishnamoorthy et al., 2017; McKeon et al., 2018; Purkayastha, Stokes et al., 2019; Toklu & Tumer, 2015). Furthermore, traumatic brain injury may cause hypothalamic-pituitary axis pathology and immune system depression by way of an increase in sympathetic activity (Kenney & Ganta, 2014). Yet the association between changes in autonomic nervous system functioning following traumatic brain injury and the role of traumatic brain injury severity in autonomic nervous system outcomes remains unclear. Thus, a growing area of research seeks to specifically understand the role of autonomic dysfunction in cognitive, quality of life, and physical symptoms, such as headaches, dizziness, nausea, and sleep problems, following traumatic brain injury (Purkayastha, Stokes et al., 2019). The current systematic review will provide a synthesis of the existing literature with a primary goal to elucidate the relationship between traumatic brain injury and autonomic nervous system functioning by way of heart rate variability as autonomic nervous system disruption may predict increased injury- related morbidity and mortality.

Assessing Autonomic Dysfunction Through Heart Rate Variability

There are multiple ways to measure physiological disruption, including autonomic nervous system changes, following traumatic brain injury. Potential measurement modalities include heart rate, cerebral blood flow, magnetic resonance spectroscopy, functional magnetic resonance imaging (MRI), transcranial magnetic stimulation, electrophysiology, diffusion tensor imaging, and fluid biomarkers. Heart rate variability is a specific and cost-effective measure of autonomic nervous system functioning that can be utilized following traumatic brain injury (Conder

& Conder, 2014; Khalid et al., 2019; King et al., 2009; Kox et al., 2012; Proctor et al., 2007).

Specifically, heart rate variability is the variation of heart rate and RR intervals (i.e., the time between heartbeats) measured between consecutive R waves (i.e., the peak ventricular polarization of an electrocardiography wave) that reflects the sympathetic and vagal activity of the autonomic nervous system on the sinus node of the heart as well as baroreceptor function, hormone levels, and circadian rhythms (Cygankiewicz & Zareba, 2013; Esterov & Greenwald, 2017; Task Force of The European Society of Cardiology, 1996). Although both the parasympathetic and sympathetic nervous systems influence the function of the heart, the activation of the parasympathetic nervous system slows the heart rate and increases heart rate variability, while activation of the sympathetic nervous system increases heart rate and decreases heart rate variability (Blake et al., 2016; Bishop et al., 2017; Purkayastha, Williams et al., 2019). Thus, heart rate variability is produced by the combined activity of the parasympathetic nervous system and the sympathetic nervous system (Blake et al., 2017; Keren et al., 2005).

Several studies have implicated the association between high heart rate variability (i.e., more variable intervals between heartbeats) and good physical and cognitive outcomes. High heart rate variability (more variability between beats) is associated with efficient modulation of heart rate by the autonomic nervous system (Abaji et al., 2016) and associated with increased performance on measures of executive skills, working memory, sustained attention, and recovery of clinical symptoms following traumatic brain injury, including improvements in cognitive function, headaches, dizziness, and sleep problems (Hansen et al., 2003; Krese et al., 2020; Murray & Russoniello, 2012). High heart rate variability is also a possible marker for mortality, with lower heart rate variability associated with increased mortality in patients with acute myocardial infarction as an example (Bigger et al., 1995). Heart rate variability has been negatively associated with injury severity following traumatic brain injury and risk of mortality

greater than age (Haji-Michael et al., 2000; Hendén et al., 2014; Lavinio et al., 2008; Melinosky et al., 2018; Olegovna et al., 2019; Petrucci, 1997; Winchell & Hoyt, 1997).

Furthermore, the associations between the limbic system and autonomic nervous system demonstrate the possibility that heart rate variability may also serve as a marker for psychological disorders, including post-traumatic stress disorder and anxiety disorders (Blechert et al., 2007; Brandt et al., 2020; Liao et al., 2016; Minassian et al., 2014; Sung, Chen et al., 2016). Generally, heart rate variability changes have been associated with a tendency to respond to external and internal stressors sympathetically. Additionally, autonomic nervous system dysregulation is an underlying characteristic of schizophrenia, panic disorders, and depression. Conversely, some studies indicate that high heart rate variability is associated with greater performance on tasks involving working memory, executive functioning, and attention (Hansen et al., 2003; Johnsen et al., 2003; Paniccia et al., 2018a; Paniccia et al., 2019; Skandsen et al., 2010). However, several have failed to support this finding (Jennings et al., 2015; Mann et al., 2015).

Heart Rate Variability Following Traumatic Brain Injury

Recent research suggests a strong relationship between prefrontal cortex functioning and heart rate variability (Thayer et al., 2009). Specifically, Thayer and colleagues (2009, 2012) indicate prefrontal brain areas tonically inhibit the amygdala, which has been associated with neural networks involving cognitive function, adaptability, and goal-directed behavior. Consequently, there is a net increase in sympathetic activity caused by deactivating inhibitory nuclei resulting in increased heart rate and decreased heart rate variability. Although the primary efferent source of modulation of cardiovascular, autonomic, and endocrine responses is considered to be the central nucleus of the amygdala, there are three postulated routes that cause an increase in heart rate, increase in sympathetic output, and decrease in heart rate variability.

The three routes include the disinhibition of sympathoexcitatory neurons that are tonically active within the rostral ventrolateral medulla, which causes an increase in sympathetic activity; inhibition of dorsal vagal motor nucleus and NA neurons that are tonically active through the inhibition of NTS neurons which causes a decrease in parasympathetic activity; and activation of RVLM neurons that are sympathoexcitatory which causes an increase in sympathetic activity. Lane and colleagues (2009) validated these pathways by measuring medial prefrontal activity and spectral heart rate variability. Throughout the studies, participants viewed films of emotional situations involving disgust, happiness, and sadness using positron emission tomography. Findings demonstrated a correlation between right prefrontal cortex activation and high-frequency heart rate variability.

Traumatic brain injury is associated with decreases in heart rate variability (Abaji et al., 2016; Campbell et al., 2019; Esterov & Greenwald, 2017; Goldstein et al., 1998; Lacquaniti et al., 1993; Lamb et al., 2017). Studies to date hypothesize that the decreases in heart rate variability observed following a moderate-to-severe traumatic brain injury may be due to the impact of the autonomic nervous system on cardiovascular regulation (Baguley et al., 2006; Gall et al., 2004b; Goldstein et al., 1998). More specifically, a reduction in heart rate variability is associated with changes in the autonomic nervous system: an increase in sympathetic activity, an increase in heart rate, and a decrease in parasympathetic activity (Thayer et al., 2009, 2012). These changes may reflect a disruption in critical white matter tracts between the heart and brain that cause impairment in emotion regulation and cognitive abilities (Williamson et al., 2013).

Heart rate variability may also serve as a predictor of outcome following traumatic brain injury (Cooke et al., 2006). Specifically, evidence suggests an association between cognitive and physical outcomes following traumatic brain injury, low-frequency power within heart rate variability, and autonomic dysfunction (Paniccia et al., 2018a; Rapenne et al., 2001).

Significantly lower parasympathetic tone and decreased global heart rate variability predict a poor neurological state. Furthermore, there are associations between reductions in the low-frequency/high-frequency ratio (i.e., the heart rate variability power spectral analysis), an increased risk of brain death, and low Glasgow Coma Scale scores (Biswas et al., 2000; Freitas et al., 1996; Hildebrandt et al., 1998). The increase in brain death is due to a reduction in heart rate variability and distinct heart rate variability (i.e., loss of control of the heart; Riordan et al., 2009). Interestingly, normalization of heart rate variability may also predict recovery of autonomic dysfunction following traumatic brain injury (Keren et al., 2005). Keren and colleagues (2005) assessed heart rate variability following traumatic brain injury in the sub-acute period and found that heart rate variability changes towards normalization occurred within the first three months post-injury, indicating autonomic nervous system recovery.

Rehabilitation with Heart Rate Variability Biofeedback

Given that evidence suggests prefrontal activity modulates cardiac output (Thayer & Lane, 2009), it is no surprise that there is an association between heart rate variability and frontal-lobe mediated cognitive abilities following traumatic brain injury (McCorry, 2007; Murray & Russoniello, 2012; Thayer & Lane, 2009). Indeed, heart rate variability training and heart rate variability biofeedback may improve post-concussive symptoms and increase cognitive performance in patients who have experienced any level of traumatic brain injury using diaphragmatic breathing techniques (Bazanova et al., 2013; Hansen et al., 2003; Lagos et al., 2012; Murray & Russoniello, 2012). Heart rate variability biofeedback treatment may, therefore, be a potential treatment target to improve autonomic nervous system functioning following traumatic brain injury. For example, in a case study by Lagos and colleagues (2012), heart rate variability biofeedback was associated with reductions in depressive symptoms, headaches, and post-concussive symptoms following ten weeks of treatment in a patient with post-concussion

syndrome.

The current consensus on post-traumatic brain injury recovery suggests heart rate variability may be useful clinically as a modality to measure physiological function or dysfunction (Esterov & Greenwald, 2017; Katz-Leurer et al., 2016; Sorek et al., 2020). Heart rate variability may also assist in determining recovery time following head injury by elucidating the relationship between traumatic brain injury severity and physiological and clinical recovery (McCrory et al., 2018; Riganello et al., 2010). However, an evidence-based understanding of heart rate variability and recovery of clinical symptoms following traumatic brain injury, as well as how injury severity moderates the relationship between heart rate variability and clinical recovery, is necessary before such a modality may be reliably invoked as an evidence-based practice. Therefore, a systematic review of the literature is needed to understand the current state of the evidence as to whether heart rate variability may be a useful measure for clinical recovery following traumatic brain injury and how injury severity impacts the relationship between heart rate variability and recovery of clinical symptoms.

Additionally, heart rate variability biofeedback has been implicated in potentially enhancing cognitive functioning following traumatic brain injury (Francis et al., 2016; Hansen et al., 2003; Lagos et al., 2012; Murray & Russoniello, 2012). Yet without a systematic evidence-based understanding of how heart rate variability biofeedback training is associated with traumatic brain injury outcome improvement, there are limitations as to whether heart rate variability biofeedback has sufficient evidence to be implemented as an early intervention post-traumatic brain injury. A systematic review of the literature is necessary to evaluate heart rate variability biofeedback as a form of rehabilitation following traumatic brain injury and the role of injury severity.

Specific Aims and Hypotheses

The current thesis is a two-part systematic review of the literature on autonomic nervous system function measured using heart rate variability following traumatic brain injury. The first part of this systematic review methodically reports on the relationship between traumatic brain injury and autonomic nervous system functioning through heart rate variability measurement. Specifically, part one has two aims: (1) review the literature to determine if evidence to date supports a positive relationship between heart rate variability and recovery of clinical symptoms following traumatic brain injury, including improvements in cognitive function, headaches, dizziness, and sleep problems; and (2) evaluate whether the severity of traumatic brain injury moderates the relationship between heart rate variability and recovery of clinical symptoms.

Part two has three aims: (1) determine the evidence available for the use of heart rate variability biofeedback in treating traumatic brain injury; (2) understand the strength of the literature on the connection between cognitive rehabilitation with heart rate variability biofeedback and neurocognitive functioning following traumatic brain injury; and (3) examine whether the assessment and training of heart rate variability are associated with a decrease in clinical symptoms such as cognitive and social functioning impairment following traumatic brain injury. We chose a systematic review over a meta-analysis as a preliminary literature search showed too few total papers to date for aggregation, as well as considerable heterogeneity in papers and methods that are present that will not allow for aggregate effect sizes to be compiled. That said, an overarching aim of the current systematic review is to test the quality of the literature on heart rate variability biofeedback for the treatment of traumatic brain injury.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; Moher et al., 2015; Page et al., 2021). Systematic

literature searches were conducted using PsycINFO, MEDLINE, Embase, CINAHL, and SPORTDiscus and a compilation of relevant keywords (see below) for articles published on the topic of heart rate variability and traumatic brain injury. A psychology research librarian with expertise in systematic review design aided in the development of search strategies and terms. The database searches were completed in December of 2020.

The following keywords were used for part one of the systematic review: ("heart rate variability" or ANS or HRV or "autonomic nervous system" or "baroreceptor sensitivity" or "baroreceptor" or "Cardiovascular autonomic nervous system" or "CV-ANS" or "Respiratory Sinus Arrhythmia" or RSA) AND (Concussion or "mild tbi" or "Mild traumatic brain injury" or "brain injury" or mTBI or "head injury" or "post-concussive syndrome" or "post-traumatic headache" or "post-concussion syndrome" or "post-concussion" or "post-concussion" or "moderate or severe TBI" or "severe TBI" or "moderate TBI" or "severe head injury" or "moderate or severe traumatic brain injury" or "moderate traumatic brain injury" or "severe traumatic brain injury").

The following keywords were used for part two of the systematic review: (Biofeedback or neurofeedback or "neuro feedback" or "heart rate variability biofeedback" or "HRV-BF" or "HRV BFB") AND (Concussion or "mild tbi" or "Mild traumatic brain injury" or "brain injury" or mTBI or "head injury" or "post-concussive syndrome" or "post-traumatic headache" or "post- concussion syndrome" or "post-concussion" or "post-concussion" or "moderate or severe TBI" or "severe TBI" or "moderate TBI" or "severe head injury" or "moderate or severe traumatic brain injury" or "moderate traumatic brain injury" or "severe traumatic brain injury"). Only studies that were peer-reviewed and in English were included in the systematic review.

Study Selection Criteria

Articles were included within part one of this systematic review if they included participants who experienced a mild, moderate, or severe traumatic brain injury; provided data on heart rate or heart rate variability; were published in a peer-reviewed journal; and were available in English. Articles were included in part two of this systematic review if they included individuals who experienced a mild, moderate, or severe traumatic brain injury; provided data on heart rate or heart rate variability; used heart rate variability biofeedback as a primary form of treatment; were published within a peer-reviewed publication; and were available in English.

Articles were excluded from part one of this systematic review if the studies only included participants with acquired brain injury (i.e., were heterogeneous and not specific to traumatic brain injury), review articles, opinion-based publications (e.g., editorials), studies with subjective descriptions of autonomic dysfunction in the absence of quantitative assessments of heart rate variability, and non-English-language studies. Additionally, abstracts without data on heart rate variability parameters and traumatic brain injury were excluded. Articles were excluded from part two of this systematic review using the same criteria as part one with the addition of studies not including a clear heart rate variability biofeedback intervention or description of the intervention and case studies without pre-and post-injury data.

Study Screening and Data Coding

Studies were initially screened by titles and abstracts by two coders. Any discrepancies were settled by consensus and a third coder following consultation of the original papers. During the screening process, duplicate titles were removed. The numbers of articles included and excluded for part one (85 articles included; 72 articles excluded) and part two (7 articles included; 8 articles excluded) according to PRISMA criteria are presented in Figures 1 and 2, respectively. A team

of four coders participated in subsequent study coding based on the variables in the codebook (see Appendix A for codebook). Each article was randomly assigned and coded by two of the coders. Any discrepancies between coders were resolved by consensus and consultation from a third independent coder (MJL).

Data Synthesis

Coding variables included study characteristics, eligibility, methods, participants, outcomes, results, key conclusions, and quality assessment (see Appendix A for full coding manual). The coding results for each article were synthesized by themes that structured the narrative of the systematic review. The first process for developing themes across studies included the development of topics based on study titles and abstracts. Each study was then coded as a "yes" or "no" for each theme and integrated into the results with additional themes determined if articles did not fit into existing themes.

Quality Assessment

As part of data coding, each article was rated for quality assessment independently by two coders using the Research Triangle Institute International and National Heart, Lung, and Blood Institute (NHLBI) quality assessment questionnaires for observational cohort/cross-sectional, case-control studies, pre-post studies, and controlled intervention studies (NHLBI, 2013). The quality assessment aimed to critically appraise the internal validity of the included studies. Each quality assessment questionnaire includes items that assess for study power, causality strength, confounding, and sources of bias (i.e., detection, patient selection, and performance), including attrition (see Appendix B). Inter-rater reliability was assessed for the primary variables of interest between coders for each variable and the quality assessment.

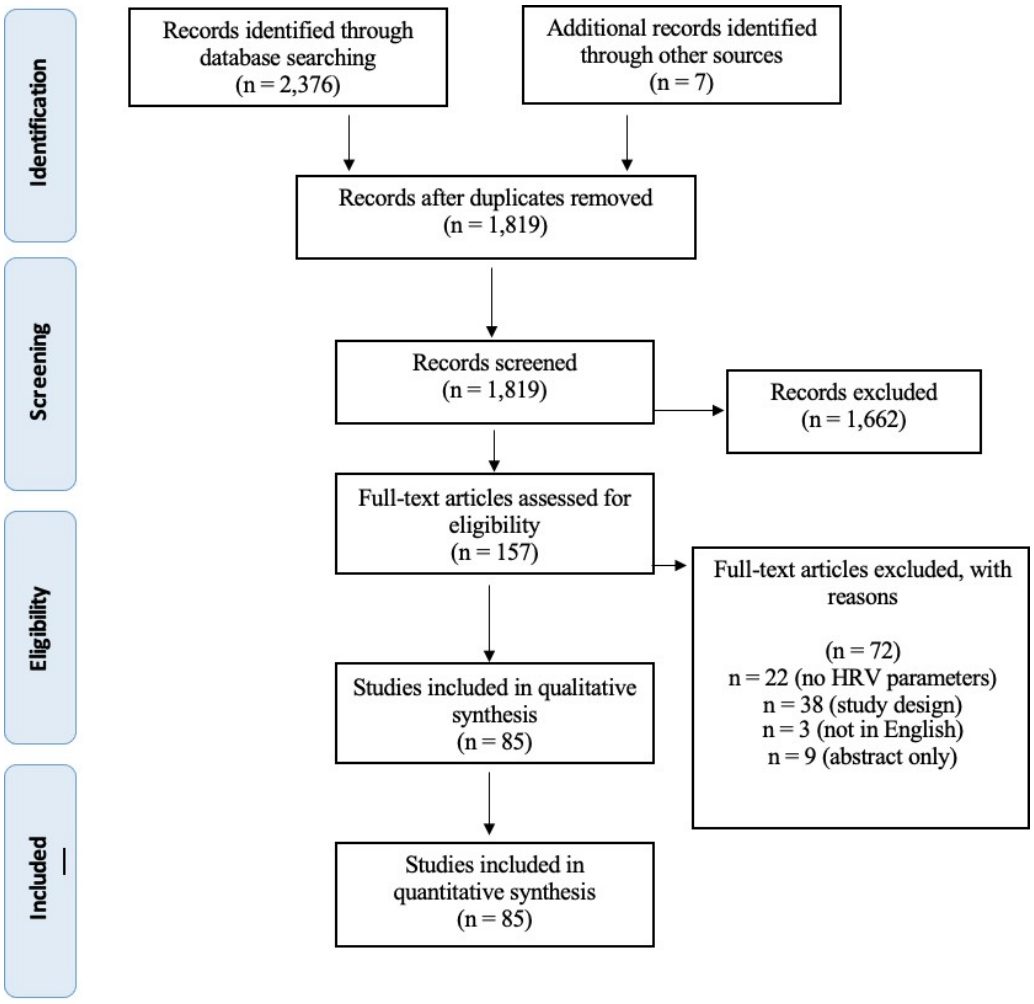

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection processes.

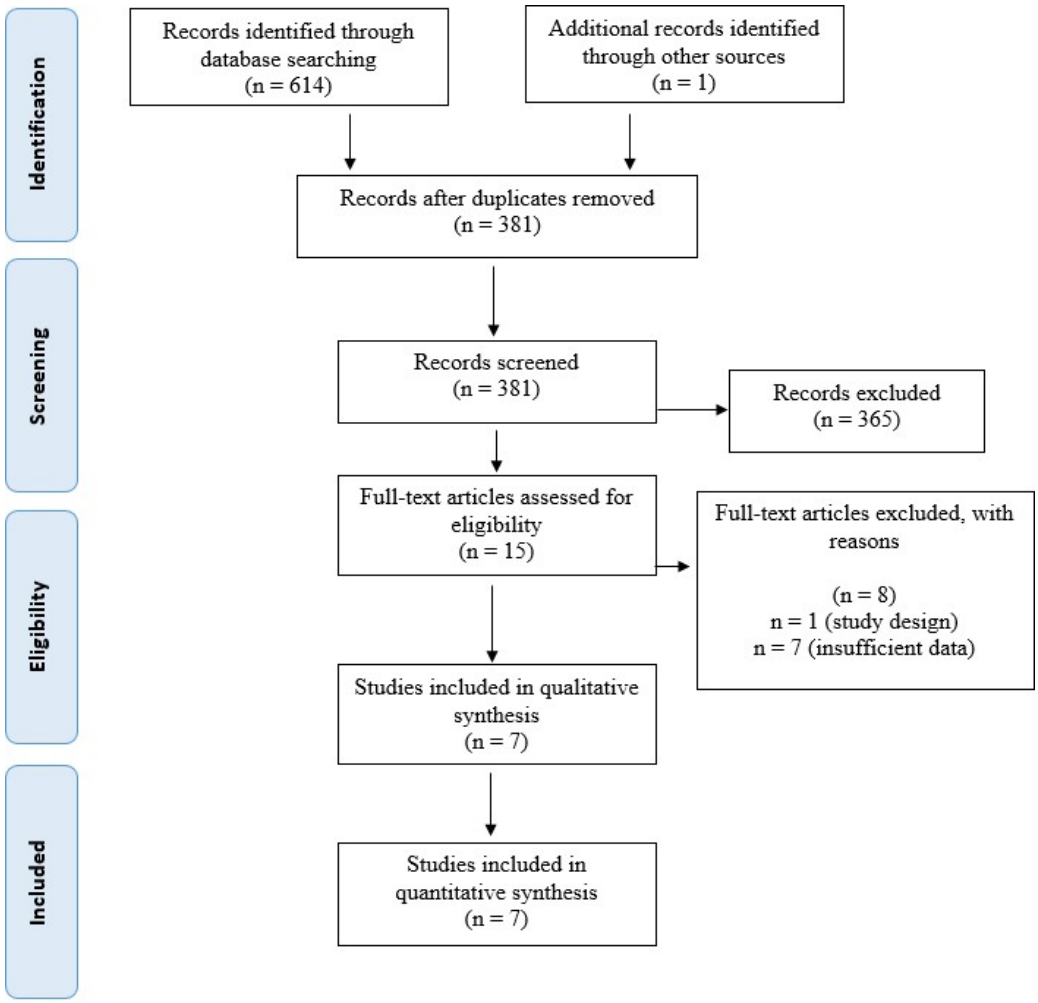

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection processes.

Results

Inter-rater Reliability

The NHLBI criteria for inter-rater agreement ranged from good, fair, or poor. Each coder had the option to code "yes," "no," or "not reported/not applicable," coded as a 1, 2, or 3, respectively, for each item. All discrepancies between the two coders for each article were resolved by a third coder.

Part I: Heart Rate Variability Following Traumatic Brain Injury

Eighty-five papers met inclusion criteria, including 1 randomized controlled trial, 1 pre-

post intervention design, 31 case-control studies, 11 cohort studies, 5 case series, 7 cross-sectional designs, 7 retrospective designs, 11 observational designs, and 11 studies with unclear designs. The relative absence of randomized-controlled intervention studies (only one thus far) and pre/post-intervention designs (only one thus far) shows the literature data is primarily observational in nature, and few studies rigorously test HRV-related interventions. Forty-seven studies (55%) used a control group or sham intervention. Sample sizes ranged from 1 to 11,977 (mean sample size = 232.1, median = 30, 25th percentile = 20, 75th percentile = 62, SD = 1317.5). Thirty-one (36%) studies included participants with mild traumatic brain injury, twenty-nine studies (34%) included participants with moderate-to-severe traumatic brain injury, twenty-one (25%) studies included multiple severity levels of traumatic brain injury, and three studies (4%) did not report severity level.

For outcome measures, 10 of 85 studies (18%) focused on HRV as a predictor of mortality following moderate-to-severe traumatic brain injury; 9 studies (10%) included a measure of post-concussive symptom improvement; 7 studies (8%) included a measure of mood disturbance/change; and 3 studies (3%) assessed the relationship between HRV and return to consciousness. Regarding the rigor of the studies, on average, studies had 8 of 12 indicators of bias (SD = 1.9), suggesting overall poor-to-fair study quality. The primary methodological biases were a lack of sample size justification, lack of multiple exposure assessments, and lack of blinding of assessors to the participants' exposures/interventions.

Based on the systematic analysis for Part I, the following primary themes were present: whether heart rate variability changes following traumatic brain injury; the correlation between heart rate variability alterations and severity of traumatic brain injury; whether heart rate variability predicts mortality and morbidity following moderate-to-severe traumatic brain injury;

and heart rate variability as an aid to facilitate safe return-to-play following mild traumatic brain injury. Summaries of the results by theme are presented in Tables 1 to 4.

Does heart rate variability change following traumatic brain injury?

In patients with a history of traumatic brain injury, 47 studies (47 of 85; 55%; see Table 1 for the summary) reported changes in autonomic nervous system functioning following traumatic brain injury indicated by heart rate variability measures (Hilz et al., 2011; Katz-Leurer et al., 2014; Mirow et al., 2016; Reid-Chung et al., 2015). Sample sizes ranged from 1 to 264 (mean = 57.3, SD = 61.5). There are 19 studies (19 of 47; 40%) that included mild traumatic brain injury, 19 studies (19 of 47; 40%) that included severe traumatic brain injury, 8 studies (8 of 47; 17%) that included multiple severity levels of traumatic brain injury, and 1 study (1 of 47; 2%) did not report severity level.

Overall, there are decreases in heart rate variability following injury for all levels of traumatic brain injury, from mild traumatic brain injury (Hilz et al., 2016; LaFountaine et al., 2011) to severe traumatic brain injury (Goldstein et al., 1996; Winchell & Hoyt, 1997; Zahn & Mirsky, 1999). However, Gall and colleagues (2004a) found no significant difference in heart rate variability two- or seven days post-injury between individuals with a history of mild traumatic brain injury compared to matched controls at rest. During an exercise task, individuals with a history of mild traumatic brain injury demonstrated a significantly lower LF and HF power and RR interval compared to matched controls. The difference in findings between conditions suggests mild traumatic brain injury may be less likely to lead to autonomic dysregulation and cardiac dysfunction during rest.

In studies that used HRV to predict symptom recovery following traumatic brain injury, all reported a positive relationship between heart rate variability and recovery of clinical

symptoms following traumatic brain injury. Specifically, higher HRV was associated with improved outcomes, including improvements in cognitive function (Reid-Chung et al., 2015) and physical symptoms including headaches (Lagos et al., 2013), dizziness (Senthinathan et al., 2017), and sleep problems (Bhandari et al., 2013). Overall, the clear consensus is that heart rate variability is reduced following injury compared to healthy individuals and that increases in HRV are associated with improvement in clinical symptoms during traumatic brain injury recovery.

Table 1

Part I: Does heart rate variability change following traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Pyndiura et al., 2020)	113 (Injury: 41, Control: 72)	Mild	Mean RR, SDNN, VLF power, LF power, HF power, total power, LF/HF ratio	Participants in the autonomically aroused group experienced, on average, significantly poorer outcomes, more severe injuries and larger costs. Within this group, dysautonomic participants also experienced significantly higher costs and poorer outcomes, including a longer period of hospitalization when participants who had early deaths were excluded.
(Tegeler et al., 2016)	15	Mild	SDNN, RMSSD, LF, HF	Athletes in the acoustic stimulation were correlated with a significantly higher rate of return to play, as well as return to exercise, recreational, and academic activities; reduced clinical symptoms; and improvements in autonomic cardiovascular regulation.
Winchell & Hoyt, 1997)	80	Severe	Total power, HF power, LF power, HF/LF ratio	Decreased HRV is associated with altered cerebral perfusion and poorer outcome.
(Tan et al., 2009)	28	Mild	SDNN	There is a possible synergistic effect of pain, PTSD, and mTBI on decreased HRV.
(LaFountaine et al., 2019)	20 (Injury: 10, Control: 10)	Mild	HF, LF, R-R intervals	HF-HRV, LF-HRV, and LF-SBP outcomes were not statistically different between groups at either of the two study visits.
(Zahn & Mirsky, 1999)	83 (Injury: 20, Control: 63)	Severe	Mean HR	During the instructions, the CHI group had a small increase in SCR/min. There were no group differences in spontaneous SCR frequency, SCL, or HR base levels.

(Fathizadeh et al., 2004)	14	NR	HR, LF, HF	During the period immediately following emergency department admission, there was an increase in autonomic activity for trauma patients. This was associated with reduced tissue oxygenation, as well as increased cardiac index, mean arterial pressure, and heart rate.
(Goldstein et al., 1996)	37	Severe	Very-low frequency HR total power, mid-low frequency HR total power, low frequency HR total power, high-frequency HR total power	For children after acute brain injury, the degree of neurologic insult is proportional to the disruption in autonomic nervous system control of heart rate.
(Balestrini et al., 2021)	119 (Injury: 65, Control: 54)	Mild	RMSSD, HR	During two study visits, there were no statistical differences between groups for HF-HRV, LF-HRV, and LF-SBP outcomes.
(Sykora et al., 2016)	262	Severe	LF, HF, total power, LF/HF ratio	After traumatic brain injury, autonomic impairment is significantly associated with increased mortality when measured by heart rate variability and baroreflex sensitivity.
(Estevez et al., 2019)	80 (Injury: 47, Control: 33)	Moderate/Severe	MRRi, SDRR, RMSSD	For patients in coma, HRV is a reliable measure to assess patient mortality and neural control of the caudal brainstem centers.
(Wijnen et al., 2006)	16	Severe	Mid frequency, high frequency, MF/HF	During sensory stimulation, recovery to consciousness during the post-acute phase is associated with changes in SCL and HRV when determined by clinical observation in sTBI.
(Henden et al., 2014)	19	Mild, Moderate/Severe	LF, HF, total power, LF/HF	BRS and HRV are acceptable variables for predicting GOSE < 5 at a 1 year follow-up.
(Mowery et al., 2008)	145	Severe	SDNN	Increased heart rate variability and IHC are associated with increased mortality.
(Lavinio et al., 2008)	18	Severe	HF, LF, spectral power	Following TBI, HRV is a tool for screening patients at risk for cerebral autoregulation derangement.
(Pattoneri et al., 2005)	20 (Injury: 10, Control: 10)	Severe	HR	Compared to healthy subjects, patients in a persistent vegetative state after traumatic brain injury had altered circadian BP and HR pattern, and higher SBP, DBP, and HR values and lower variability.
(Olegovna et al., 2019)	134 (Injury: 102, Control: 32)	Mild	SDNN, RMSSD	In the acute period, patients with combined trauma have psycho-emotional disorders of different degrees, have cognitive deficits, and vegetative dysfunction.

(Rapenne et al., 2001)	20	Severe	rMSSD, pNN50, index of variability (IV), LF, HF, and LF/HF analysis, total power (TP), LnHF	Worsened clinical cerebral impairments were associated with decreased HRV while imminent brain death was associated with preserved HRV, especially its vagal component.
(Baguley, Nott et al., 2009)	27 (Injury: 16, Control: 11)	Moderate/Severe	Total power, LF, HF, LF normalized, HF normalized, LF/HF ratio, mean HR (bpm)	Afferent stimuli elicit over responsiveness in dysautonomic participants.
(Baguley, Heriseanu et al., 2009)	26 (Injury: 7, Control: 19)	Severe	nLF, nHF, LF/HF, HR	Compared to non-Ds groups, participants five years post-injury had higher stimulus-related LF/HF ratios.
(Baguley et al., 2006)	32 (Injury: 16, Control: 16)	Severe	VLF, LF, HF, LF/HF, SDNN	Compared to non-dysautonomic subjects and controls, dysautonomic subjects had prolonged uncoupling of heart rate and HRV parameters.
(Sung, Lee et al., 2016)	264 (Injury: 181, Control: 83)	Mild	R-R interval values, total power, VLF, LF, HF, LF/HF	Compared to healthy controls, reduced ANS activity in female mTBI patients was associated with late depression accompanied by reduced ANS activity.
(Piantino et al., 2019)	23 (Injury: 6, Control: 17)	Severe	Heart rate, rMSSD, SDNN, LF, LF/HF, HF	Heart rate variability was significantly lower for frequency and time domains in patients who progressed to brain death.
(Hilz et al., 2020)	34 (Injury: 17, Control: 17)	Mild	RRI	For months or years after initial trauma, patients with a history of mTBI show slightly altered responses to unpleasant and pleasant olfactory stimuli.
(Hilz et al., 2015)	51 (Injury: 24, Control: 27)	Mild	RR intervals, LF, HF, RRI-LF/HF ratio	Patients with a history of mTBI had significantly lower LF-powers of BPsys and LF-powers of BPdia.
(Johnson et al., 2018)	21 (Injury: 11, Control: 10)	Mild	RMSSD (msec), High frequency (msec2)	College athletes with recent mild traumatic brain injuries displayed impaired autonomic nervous system activation, including the parasympathetic and sympathetic branches.
(Hilz et al., 2011)	40 (Injury: 20, Control: 20)	Mild	RMSSD, HF, LF, LF-BP oscillations, RRI-LF/HF-ratio	Post-mTBI, impaired autonomic modulation seems to be related to cardiovascular irregularities.
(Katz-Leurer et al., 2010)	30 (Injury: 12, Control: 19)	Severe	Standard deviation of the R-R interval, square root of the mean squared differences of successive R-R differences	The TBI group displayed significantly lower time domain measures of HRV at rest while TD children had decreased mean time domain values during exercise. Children had higher mean HR both at rest and during exercise post-TBI.

(Riganello et al., 2008)	42 (Injury: 16, Control: 26)	Severe	Mean RR, STD RR, Mean HR, STD HR, RMSSD, NN50, pNN50, VLF, LF, HF), and normalized unit (nu)	HRV is a measure of brain function, individual differences in regulating the emotional conditions or responses, and is an autonomic index.
(Keren et al., 2005)	40 (Injury: 20, Control: 20)	Moderate/Severe	SD-RR, LF, HF, total power	The control group and patients with TBI differed in HRV. During the first 3 months after the injury, tendency to HRV normalization was detected.
(Biswas et al., 2000)	19 (Injury: 15, Control: 4)	Moderate/Severe	LF/HF, RR intervals, HF HRV, LF HRV	Patients with significantly higher LF/HF ratios tended to have more favorable outcomes. A markedly lower LF/HF ratio, with a significant decrease after the first 4 hrs of hospitalization, was associated with progression to brain death.
(Lai et al., 2017)	1	Mild	mean RR interval, SDRR, LF, HF, LF/HF, TP, ApEn	Compared to rest, mean RR interval, SDRR, LF power, HF power, and total power were lower after exertion at two weeks post-injury.
(Ryan et al., 2011)	216	Mild, Moderate/Severe	VLF, LF, wideband frequency, HF, low to HF index ratio, SDNN, RMSSD, VLF, LF, HF, WF, LF/HF	Multiple HRV measurements were significantly associated with increased morbidity, overall mortality, brain injury, and prolonged requirements for treatment, with VLF being the most robust predictor of outcome.
(Gall et al., 2004b)	28 (Injury: 14, Control: 14)	Mild	RR (ms), SDRR (ms), LF (ms2), HF (ms2), LF norm (nu), HF norm (nu) LF/HF ratio, Total power (ms2)	In concussed athletes, neuroautonomic cardiovascular dysfunction is elicited by low-moderate steady-state exercise that is not present in a rested state.
(King et al., 1997)	14 (Injury: 7, Control: 7)	Severe	SDNN, RMSSD, HF, LF, total power	During the post-acute recovery phase, patients with TBI displayed decreased HRV.
(LaFountaine et al., 2011)	6 (Injury: 3, Control: 3)	Mild	QTVI	Compared to uninjured, matched control participants, recently concussed athletes demonstrate a higher QTVI within 48 hours of injury presentation.
(Mirow et al.,. 2016)	61	Mild	RR intervals, total power, HF, LF, LF/HF, SDNN, AVNN, SDANN, RMSDD, pNN50, SD1, SD3	Across all segments, participants had sympathetic nervous system dominance.
(Katz-Leurer et al., 2014)	25	Severe	SDNN, RMSSD, LF, HF, LF/HF	During PTS, HR increased significantly during different activities and varied positions among patients post-brain injury.

(Deepika et al., 2018)	109 (Injury: 89, Control: 20)	Severe	RR intervals, SDNN, RMSSD, pNN50	Excluding low-frequency normalized units (LFnu) and LF/HF, time domain and frequency domain parameters were significantly lower than that of healthy controls.
(Bishop et al., 2017)	101 (Injury: 12, Control: 89)	Mild	RRmean, RRSD, HRmean, SDHR, NN50, pNN50, VLFpower, LFpower, HFpower, Total Power, %LF, %HF, LF:HFratio, SampEn, ApEn, PETCO2	Following mTBI, autonomic function is dysregulated within the first 72 hours of injury.
(Abaji et al., 2016)	24 (Injury: 12, Control: 12)	Mild	LF/HF, RR intervals, mean NN intervals, SDNN, RMSSD	For weeks to months following injury, concussed athletes have modified cardiac autonomic modulation.
(Levine et al., 1987)	59 (Injury: 30, Control: 29)	Severe	mean heart rate, HRV, heart rate deceleration, heart rate acceleration	During the performance of recall tasks, there were differences in heart rate adjustments between the CHI and NC groups.
(Hilz et al., 2017)	60 (Injury: 40, Control: 20)	Mild, Moderate/Severe	RR intervals, HF, LF, LF/HF-RRI ratios, LF/HF RRI powers	At rest, patients with histories of moderate-severe and mild TBI had increased sympathetic and decreased parasympathetic cardiovascular autonomic modulation.
(LaFountaine et al., 2009)	6 (Injury: 3, Control: 3)	Mild	HRV, heart rate complexity (HRC)	Compared to a matched control group during an IHGT, HRC was passed 48-hours after mild traumatic brain injury. Compared to the lower values observed at 48 hours, HRC returned to control group levels two weeks after injury, a difference that was significant.
(Amorapanth et al., 2018)	26 (Injury: 16, Control: 10)	Severe	RFA, RSA, LFA, LFA/RFA ratio, cvLFA and cvRFA	Compared to controls, participants with TBI displayed decreased sympathetic activity in response to positively valenced stimuli and increased sympathetic activity to negatively valenced stimuli.
(Hilz et al., 2016)	54 (Injury: 25, Control: 29)	Mild	HR, RRI, HF, LF, total power, LF/HF	Patients with a mTBI history had slightly decreased autonomic modulation of HR and BP.
(Haji-Michael et al., 2000)	29	Moderate/Severe	LF, HF, TF, VLF, RRI, total power	After neurosurgical illness, poor quality recovery and death were associated with reduced total power variability of RRI and a decreased LF/HF ratio of the RRI.

Is heart rate variability change related to the severity of traumatic brain injury?

A growing consensus suggests that traumatic brain injury of any severity is associated with decreased (i.e., worse) heart rate variability (see above). The current review of the literature further suggests that the severity of traumatic brain injury is directly associated with the degree of uncoupling between the autonomic and cardiovascular systems (Baguley et al., 2006; Deepika et al., 2018; Gall et al., 2004b; Mowery et al., 2008). Such autonomic changes are believed to reflect injury severity and correlate with increased mortality and morbidity (Baillard et al., 2002; Ryan et al., 2011). Seven studies (7 of 85; 8%; see Table 2 for the summary) reported autonomic changes due to traumatic brain injury and investigated the association between severity and heart rate variability change through the assessment of baroreflex sensitivity and heart rate variability (Fathizadeh et al., 2004; Hilz et al., 2017; Ley et al., 2010; Sykora et al., 2016). Sample sizes ranged from 14 to 11,977 (mean = 1769.9, SD = 4501.8).

More prominent autonomic dysregulation and cardiac dysfunction have been found in patients with moderate or severe traumatic brain injury (Evans, 1979; Goldstein, 1996; Goldstein, 1998; Hilz et al., 2017; Lowensohn et al., 1977; Papaioannou et al., 2008). At rest, individuals with a history of moderate or severe traumatic brain injury demonstrate lower LF/HF ratio and HFnu-RRI power mediated parasympathetically while higher LFnu-RRI power when compared to healthy controls (Hilz et al., 2017). Multiple studies report a correlation between brain injury severity, heart rate variability parameters, functional outcome, and survival (Goldstein et al., 1996; Papaioannou et al., 2008; Biswas et al., 2000). Specifically, there is a negative correlation between high-frequency HRV power and the severity of traumatic brain injury, while low-frequency power positively correlates with neurological outcome measures and the presence of brain death. Overall, the severity of traumatic brain injury appears to moderate

the relationship between heart rate variability and recovery, with lower (i.e., worse) HRV, the more severe the traumatic brain injury and increased HRV parameters as individuals recover from injury.

Table 2

Part I: Does reduction in heart rate variability change by the severity of traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Fathizadeh et al., 2004)	14	NR	HR, LF, HF	During the period immediately following emergency department admission, there was an increase in autonomic activity for trauma patients. This was associated with reduced tissue oxygenation, as well as increased cardiac index, mean arterial pressure, and heart rate.
(Goldstein et al., 1996)	37	Severe	Very-low frequency HR total power, mid-low frequency HR total power, low frequency HR total power, high-frequency HR total power	For children after acute brain injury, the degree of neurologic insult is proportional to the disruption in autonomic nervous system control of heart rate.
(Sykora et al., 2016)	262	Severe	LF, HF, total power, LF/HF ratio	After traumatic brain injury, autonomic impairment is significantly associated with increased mortality when measured by heart rate variability and baroreflex sensitivity.
(Biswas et al., 2000)	19 (Injury: 15, Control: 4)	Moderate/Severe	LF/HF, RR intervals, HF HRV, LF HRV	Patients with significantly higher LF/HF ratios tended to have more favorable outcomes. A markedly lower LF/HF ratio, with a significant decrease after the first 4 hrs of hospitalization, was associated with progression to brain death.
(Papaioannou et al., 2008)	20	Severe	HF, LF, LF/HF, HR variance	High mortality rates were associated with low variability, low baroreflex sensitivity, and sustained decrease in LF/HF of HR signals in acute brain injury patients.
(Ley et al., 2010)	11977	Moderate/Severe	HR	HR was an independent predictor of increased mortality after isolated moderate to severe TBI.
(Hilz et al., 2017)	60 (Injury: 40, Control: 20)	Mild, Moderate/Severe	RR intervals, HF, LF, LF/HF-RRI ratios, LF/HF RRI powers	At rest, patients with histories of moderate-severe and mild TBI had increased sympathetic and decreased parasympathetic cardiovascular autonomic modulation.

Does heart rate variability predict mortality and morbidity following a traumatic brain injury?

There are 8 studies (8 of 85; 9%; see Table 3 for the summary) demonstrating decreased

HRV following traumatic brain injury predicts mortality beyond age (Haji-Michael et al., 2000; Hendén et al., 2014; Lavinio et al., 2008; Melinosky et al., 2018; Olegovna et al., 2019; Winchell & Hoyt, 1997). Sample sizes ranged from 20 to 11,977 (mean = 1601.9, median = 112.5, 25th percentile = 59.25, 75th percentile = 227.5, SD = 4193). However, the predictive power of heart rate variability appears to be limited to the first twelve hours of admission into the ICU (Mowery et al., 2008). One study with a sample size of 145 demonstrated an association between heart rate variability and increased mortality in patients with severe traumatic brain injury (Mowery et al., 2008). Decreased heart rate variability within the first 24 hours of ICU admission reflects an increased risk for mortality in patients with severe traumatic brain injury (Riordan et al., 2006).

Heart rate variability power spectral analysis is useful in determining the prognosis for recovery and injury severity in patients following traumatic brain injury (Biswas et al., 2000). While the LF/HF ratio may be helpful in predicting patients who will have favorable outcomes, it may also be helpful in predicting progression to brain death as there appears to be an association between autonomic impairment, measured through baroreflex sensitivity and heart rate variability, and increased mortality following brain injury (Rapenne et al., 2001; Sykora et al., 2016). This association was found independent of injury severity, age, and intracranial pressure in sedated patients with severe traumatic brain injury. Consistent among these findings is a significant relationship between decreased heart rate variability, low baroreceptor sensitivity, poor outcome, and higher mortality. Thus, heart rate variability predicts mortality.

Table 3

Part I: Does heart rate variability predict mortality and morbidity following a traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Sykora et al., 2016)	262	Severe	LF, HF, total power, LF/HF ratio	After traumatic brain injury, autonomic impairment is significantly associated with increased mortality when measured by heart rate variability and baroreflex sensitivity.

(Estevez et al., 2019)	80 (Injury: 47, Control: 33)	Moderate/Severe	MRRi, SDRR, RMSSD	For patients in coma, HRV is a reliable measure to assess patient mortality and neural control of the caudal brainstem centers.
(Mowery et al., 2008)	145	Severe	SDNN	Increased heart rate variability and IHC are associated with increased mortality.
(Ryan et al., 2011)	216	Mild, Moderate/Severe	VLF, LF, wideband frequency, HF, low to HF index ratio, SDNN, RMSSD, VLF, LF, HF, WF, LF/HF	Multiple HRV measurements were significantly associated with increased morbidity, overall mortality, brain injury, and prolonged requirements for treatment, with VLF being the most robust predictor of outcome.
(Papaioannou et al., 2008)	20	Severe	HF, LF, LF/HF, HR variance	High mortality rates were associated with low variability, low baroreflex sensitivity, and sustained decrease in LF/HF of HR signals in acute brain injury patients.
(Ley et al., 2010)	11977	Moderate/Severe	HR	HR was an independent predictor of increased mortality after isolated moderate to severe TBI.
(Hilz et al., 2016)	54 (Injury: 25, Control: 29)	Mild	HR, RRI, HF, LF, total power, LF/HF	Patients with a mTBI history had slightly decreased autonomic modulation of HR and BP. Cardiovascular dysregulation contributed to increased mortality risk in post-mTBI-patients.
(Mirow et al.,. 2016)	61	Mild	RR intervals, total power, HF, LF, LF/HF, SDNN, AVNN, SDANN, RMSDD, pNN50, SD1, SD3	Across all segments, participants had sympathetic nervous system dominance though there was insufficient evidence for cardiovascular death.

Can heart rate variability help clinicians facilitate safe return-to-play following mild traumatic brain injury?

There are 3 studies that report heart rate variability disturbances may persist beyond return-to-play and symptom resolution following traumatic brain injury (see Table 4 for the summary). Sample sizes ranged from 1 to 46 (mean = 20.7, SD = 23.0). These studies specifically show that, following a mild traumatic brain injury, physiological dysfunction can persist for two weeks or more when asymptomatic (Abaji et al., 2016; La Fountaine et al., 2009; La Fountaine et al., 2011). In a study with 11 athletes, Senthinatha and colleagues (2017) found that concussed athletes demonstrated decreased HF norm and increased LF

norm while sitting in the acute phase of mild traumatic brain injury. On the other hand, concussed athletes showed a reduced change in LF and HF norm measures between standing and sitting. The dysfunction captured by these measures of heart rate variability persisted beyond return-to-play and medical clearance for exercise progression, demonstrating an association with a history of mild traumatic brain injury. Therefore, it is possible that return-to-play protocols for concussed athletes could be modified to address psychological and physiological stressors with respect to a history of mild traumatic brain injuries, and HRV may be a useful indicator of when return to play is feasible, though more studies are needed in this regard as only three are present to date.

Table 4

Part I: Can heart rate variability help clinicians facilitate safe return-to-play following mild traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Tegeler et al., 2016)	15	Mild	SDNN, RMSSD, LF, HF	Athletes in the acoustic stimulation were correlated with a significantly higher rate of return to play, as well as return to exercise, recreational, and academic activities; reduced clinical symptoms; and improvements in autonomic cardiovascular regulation.
(Lai et al., 2017)	1	Mild	mean RR interval, SDRR, LF, HF, LF/HF, TP, ApEn	Compared to rest, mean RR interval, SDRR, LF power, HF power, and total power were lower after exertion at two weeks post-injury.
(Huang et al., 2019)	46 (Injury: 23, Control: 23)	Mild	HF power	Following mild traumatic brain injury, lower HRV was displayed at rest.

Part II: Heart Rate Variability Biofeedback Treatment Following Traumatic Brain Injury

There were 7 papers that met inclusion criteria, including 2 case studies, 3 pre-post intervention designs, 1 retrospective study, and 1 case-control study. Notably, there were no randomized controlled trials, and only 1 study (1 of 7; 14%) utilized a control group or

sham intervention. Thus, it is difficult to make clear conclusions from this literature, and more studies with rigorous designs are necessary. Sample sizes were modest, ranging from 1 to 60 participants (mean = 14.7, median = 13, 25th percentile = 1.5, 75th percentile = 13, SD = 20.8). The small sample sizes limit the generalizability and utility of the literature to date. All seven studies included a measure of mood; 5 studies (5 of 7; 71%) included neuropsychological functioning as an outcome measure; 1 study (1 of 7; 14%) included a measure of life satisfaction. On average, participants completed 14 sessions of heart rate variability biofeedback (mean = 13.5, median = 10, 25th percentile = 10, 75th percentile = 10, SD = 13.5, range = 1 to 40).

Regarding the rigor of the studies, the primary methodological biases were a lack of control or sham comparison, lack of randomization, and lack of blinding of assessors to the participants' exposures/interventions. On average, studies had 5 of 12 indicators of bias (SD = 2.1), suggesting overall poor-to-fair study quality. Based on the systematic analysis for Part II, the following themes emerged: increased autonomic control following heart rate variability biofeedback; physical symptoms improvement following heart rate variability biofeedback; cognition following heart rate variability biofeedback; and social and emotional functioning following heart rate variability biofeedback.

Were there improvements in heart rate variability after biofeedback?

Regarding outcomes, all 7 studies that met inclusion criteria showed significant increases from pre-treatment to post-treatment in heart rate variability measures, including frequency- (i.e., LF, HF, LF:HF ratio) and time-domain measures (i.e., SDNN, pNN50, rMSSD; see Table 5 for a summary). There were 4 studies (4 of 7; 57%) that showed heart rate variability biofeedback training enhances coherence between the sympathetic and parasympathetic nervous systems after moderate to severe traumatic brain injury (Bhandari et al., 2013; Kim et al., 2013; Kim et al., 2015; Lagos et al., 2013). Sample sizes ranged from 1 to 13 (mean = 7, SD = 6.9). Kim and

colleagues (2015) demonstrate significant increases in both the coherence ratio and LF/HF ratio from pre-treatment to post-treatment. Patients with severe traumatic brain injury were trained to increase heart rate variability using biofeedback. In a case study by Lagos and colleagues (2012), heart rate variability biofeedback was associated with decreases in sympathetic activation, increases in parasympathetic activation, and improved cerebral blood flow following ten weeks of treatment in a patient with post-concussion syndrome. Overall, heart rate variability biofeedback was associated with improved heart rate variability following traumatic brain injury, though the methodological quality is questionable, and more controlled studies and randomized controlled trials are needed.

Table 5

Part II: Heart Rate Variability Biofeedback Treatment Following Traumatic Brain Injury

Study	Sample	TBI Severity	HRV Measures	Biofeedback Sessions	Instrument	Key conclusions
(Kim et al., 2015)	13	Moderate/Severe	LF, HF, coherence ratio	10	HeartMath emWave PC	From pretreatment to post-treatment testing, participants' HRV measures, including LF/HF and the coherence ratio, increased.
(Kim et al., 2018)	13	Severe	Coherence ratio	10	HeartMath emWave PC	When positive affect was high, there was a large effect on problem solving from HRV biofeedback.
(O'Neill & Findlay., 2014)	2	Severe	VLF, LF, HF, coherence ratio	NR	HeartMath emWave PC	There were reduced aggressive outbursts, an increased sense of self-efficacy and behavioral control, and an increased ability to recognize frustration.

(Bhandari et al., 2013)	1	Severe	NN50, total power	40	NR	There were improvements in mood, memory, sleep and energy, as well as regaining mental sharpness, and completion of revisions to his thesis.
(Kim et. al., 2018)	13	Severe	RR intervals, peak power, total power	10	HeartMath emWave PC	The most gains and best post-treatment performance on problem-solving ability was seen in participants who had the most positive emotions.
(Lagos et al., 2013)	1	Mild	LF, HR STD DEV	10	ProComp Infiniti	Among longer term effects, improved autonomic control, decreased mood disturbances, and improved headaches occurred, as well as large short-term effects.
(Francis et al., 2016)	60 (30 TBI; 30 Controls)	Severe	SDNN, rMSSD, LF, HF, LF/HF ratio	1	BioGraph Infiniti Software 6.0	Compared to baseline, both control and TBI groups displayed significantly increased HRV on SDNN, rMSSD, LF, HF, LF:HF ratio during biofeedback.

Were there improvements in physical symptoms (including headaches)?

All 7 studies showed improvements in mood and physical symptoms (e.g., headaches, sleep) following HRV biofeedback in people with traumatic brain injury, which positively correlated with improved heart rate variability measures. These studies were primarily in people with moderate-to-severe traumatic brain injury (7 of 7 included moderate-to-severe participants). Only 1 study (1 of 7; 14%) was conducted on patients with a history of mild traumatic brain injury. While it is unclear whether outcomes differ by severity, it is clear that positive emotions were correlated with the most gains following heart rate variability biofeedback (Kim et al., 2018). A preliminary study (Lagos et al., 2013) demonstrated the impact of a 10-week protocol of heart rate variability biofeedback following mild traumatic brain injury in an athlete suffering from post-concussion syndrome. Results indicated a significant decrease in the severity of

headaches, mood, and post-concussion symptoms. Following a severe traumatic brain injury, heart rate variability biofeedback training showed improvement on three heart rate variability measures, headaches, irritability, mood, and cognitive performance (Bhandari, 2013). Overall, there is a positive relationship between increased heart rate variability and recovery of physical symptoms, including headaches, dizziness, and sleep problems.

Were there improvements in cognition?

There are 5 studies (5 of 7; 71%) that included a measure of executive functioning, and all 5 studies showed improved executive functioning (i.e., problem-solving, attention, cognitive flexibility) and improved life satisfaction (see Table 5 for the summary) following HRV biofeedback. Sample sizes ranged from 1 to 13 (mean = 10.6, median = 13, 25th percentile = 1, 75th percentile = 13, SD = 5.4). 4 studies (4 of 8; 50%) show that heart rate variability biofeedback was associated with improvements in working memory and executive functioning in patients who have experienced any level of traumatic brain injury (Bhandari et al., 2013; Kim et al., 2013; Kim et al., 2015; Kim et al., 2018). One study, with a sample size of 13, demonstrated positive linear associations between higher heart rate variability coherence and higher attention scores following heart rate variability biofeedback training in patients with severe traumatic brain injury (Kim et al., 2015).

One case study (1 of 7; 14%) of executive functioning demonstrated that multimodal approaches, including more than forty sessions of biofeedback and neurofeedback, was associated with improvements in decision-making, planning, and memory following severe traumatic brain injury. Specifically, Bhandari et al. (2013) conducted this case study on a man who experienced a severe traumatic brain injury following a motor vehicle accident. Following heart rate variability biofeedback training and neurofeedback, the patient demonstrated

improvements on continuous performance tests of attention, academics, mental sharpness, and visual and auditory performance tests, though the treatment was very intensive and included more than HRV biofeedback.

Were there improvements in emotional functioning?

All 7 studies included a measure of mood and showed improvements in mood, which positively correlated with improved heart rate variability measures. A decrease in heart rate variability is associated with changes in the autonomic nervous system: increase in sympathetic activity, increase in heart rate, and decrease in parasympathetic activity. These changes reflect a disruption in key white matter tracts between the heart and brain, which cause impairment in emotion regulation and cognitive abilities. Increased coherence between the sympathetic and parasympathetic nervous systems has been associated with improved regulations of behavior and emotions (Bhandari et al., 2013; Francis et al., 2016; Kim et al., 2015; O'Neill & Findlay, 2014).

Francis and colleagues (2016) investigated the association between heart rate variability biofeedback and social functioning following severe traumatic brain injury. Their findings indicated that heart rate variability was lower in participants with a history of traumatic brain injury. This decreased heart rate variability was associated with social and emotional functioning. Following a heart rate variability biofeedback session, heart rate variability increased among participants who had a history of traumatic brain injury and those who did not have a history of traumatic brain injury.

In studying individuals with severe traumatic brain injury, Kim et al. (2015) demonstrated that coherence ratio, LF/HF, and heart rate variability measures increased from pretreatment to posttreatment assessment. Additionally, this study has shown that improvements in the LF/HF index were associated with improvements in emotional control, self-esteem, and

satisfaction with life. Kim et al. (2018) examined how positive affect moderated the relationship between heart rate variability coherence and cognitive performance in individuals with severe traumatic brain injury following heart rate variability biofeedback treatment. Positive affect improved mental flexibility, problem-solving ability, and cognition. Overall, there is a positive relationship between increased heart rate variability and recovery of emotional control and life satisfaction.

Discussion

Summary of Evidence

Part I: Heart Rate Variability Following Traumatic Brain Injury

Eighty-five papers met inclusion criteria for the first part of our systematic review. The following primary themes were present: whether heart rate variability changes following traumatic brain injury; the correlation between heart rate variability alterations and severity of traumatic brain injury; whether heart rate variability predicts mortality and morbidity following moderate-to-severe traumatic brain injury; and heart rate variability as an aid to facilitate safe return-to-play following mild traumatic brain injury. The literature demonstrates an association between heart rate variability and the presence of a traumatic brain injury, particularly early in the injury. Subsequent recovery is also related to heart rate variability measures. Heart rate variability may be used as a potential indicator of physiological change following traumatic brain injury as well as potential predictor of recovery. There are also associations between decreased heart rate variability, greater severity in symptoms following traumatic brain injury, and increased mortality. Thus, poor heart rate variability may be useful in the assessment and monitoring of patients, particularly following moderate or severe traumatic brain injury.

What is the mechanism for heart rate variability changes following injury? Traumatic brain injury often involves subsequent autonomic nervous system dysregulation, which leads to

an altered baroreflex sensitivity, sympathetic hyperactivity, and impaired blood flow autoregulation (Ding et al., 2020). Furthermore, the alterations caused by autonomic hyperactivity and imbalance causes altered regulatory function of the heart and kidneys through hemodynamic changes such as an imbalance in electrolytes, disturbances in regional blood flow, change in renal clearance and cardiac output. Traumatic brain injury also causes an imbalance in homeostatic mechanisms; however, more translational research is necessary to understand how treatment may improve patient prognosis. Improving patient prognosis is important because research has found a 40% mortality rate for patients who have a history of traumatic brain injury and acute kidney injury (Khalid et al., 2019).

Most of the literature was case-control studies with a notable absence of randomized controlled trials. Such observational research is generally appropriate as most of the studies are examining changes in heart rate variability following a head injury, so randomization is generally not possible. Furthermore, when someone has a moderate-or-severe traumatic brain injury intervention that may alter heart rate variability, treatment such as biofeedback is not available until further into rehabilitation and recovery. Thus, observational studies suggesting heart rate variability may be a useful measure in testing injury severity and outcomes is useful.

In more mild injuries, the evidence to date suggests that mild traumatic brain injury can cause observable increases in resting systolic blood pressure, heart rate, systolic blood pressure, and diastolic blood pressure perturbations within 48 hours post-mild traumatic brain injury (Dobson et al., 2017). During standing, mild traumatic brain injury caused observable increases in resting systolic blood pressure, heart rate, systolic blood pressure, and diastolic blood pressure perturbations within 48 hours post-mild traumatic brain injury. Yet still, heart rate variability may recover within three weeks of a mild traumatic brain injury (Purkayastha, Stokes et al., 2019).

Mild traumatic brain injury negatively impacts cardiovascular autonomic nervous system functioning, including the functioning of the arterial baroreflex (Fountaine et al., 2019; Haji-Michael et al., 2000; Hilz et al., 2011; Hilz et al., 2016; King et al., 1997; Lagos et al., 2013; Papaioannou et al., 2008; Sykora et al., 2016). More specifically, there are reductions in resting baroreceptor sensitivity following a mild traumatic brain injury which inhibits the ability to buffer arterial blood pressure up to one-week post-injury. Reduced baroreceptor sensitivity is associated with increased mortality risk, congestive heart failure, hypertension, obesity, and other abnormal outcomes (Fountaine et al., 2019). Yet still, heart rate variability following mild traumatic brain injury demonstrates conflicting evidence for statistically significant differences in heart rate variability between concussed participants and control groups during rest (Paniccia et al., 2018b). There is evidence for decreased heart rate variability during low-intensity exercise in concussed participants up to ten days post-injury. There is no evidence for differences in heart rate variability during high-intensity exercise 5-10 days post-injury between concussed participants and the control group.

Although autonomic nervous system dysregulation has been reported following sports-related mild traumatic brain injury, the relationship between heart rate variability and cerebral blood flow following mild traumatic brain injury remains uncertain. Although heart rate variability appears to be lower in athletes with a history of mild traumatic brain injury compared to controls during the acute phase of recovery, heart rate variability after mild traumatic brain injury was comparable to the control group during the sub-acute phase of recovery (Purkayastha, Stokes et al., 2019). Furthermore, although middle cerebral artery blood velocity does not seem to differ across groups, during the acute phase, middle cerebral artery blood velocity has been associated with greater cognitive scores on the standardized assessment of mild traumatic brain injury and Trails making tests A & B (Purkayastha, Williams et al., 2019). These findings

indicate that heart rate variability recovers within three weeks of a mild traumatic brain injury; a relationship between higher heart rate variability and higher middle cerebral artery blood velocity; an association between higher heart rate variability and greater cerebral blood flow; and a correlation between reduced cerebral blood flow during the acute phase of recovery and cognitive deficits.

Findings also show that mild traumatic brain injury negatively impacts cardiovascular autonomic nervous system functioning, including the functioning of the arterial baroreflex (Haji-Michael et al., 2000; Hilz et al., 2011; Hilz et al., 2016; King et al., 1997; Lagos et al., 2013; Papaioannou et al., 2008; Sykora et al., 2016). Based on the research of abnormal arterial blood pressure following mild traumatic brain injury within several weeks post-injury, there appear to be reductions in resting baroreceptor sensitivity following a mild traumatic brain injury which inhibits the ability to buffer arterial blood pressure up to one-week post-injury (Fountaine et al., 2019). Although few studies have investigated clinical symptoms associated with reduced baroreceptor sensitivity, reduced baroreceptor sensitivity appears to be associated with increased mortality risk, congestive heart failure, hypertension, obesity, and other abnormal outcomes (Armstrong et al., 2021; Hendén et al., 2014). Overall, the clear consensus is that there are reduced heart rate variability parameters during the sub-acute stage post-traumatic brain injury when compared to healthy controls.

The negative impact on cardiovascular autonomic nervous system functioning appears to occur due to a lack of neurotransmission between organs such as the heart and vasculature. The outcome measurement of functioning for the arterial baroreflex is baroreceptor sensitivity. However, there is a lack of generalizability and internal validity found in the literature due to unreported confounding variables associated with the cardiac autonomic function (e.g., body position during testing, sex, age, and pre-existence of neck pain or headaches). There is clinical

utility in heart rate variability as a measure of traumatic brain injury recovery as a significant association was found between heart rate variability and clinical measures administered in mild traumatic brain injury assessment and management.

Decreased heart rate variability has been demonstrated to be a component of autonomic nervous system dysfunction during acute and subacute phases of traumatic brain injury. Furthermore, individuals with recent head injuries demonstrate dysfunction in both the parasympathetic and sympathetic branches of the autonomic nervous system. Although the return to academic activity may be expedited by cognitive training four days following the injury, heart rate variability disturbances appear to persist beyond return to play and symptom resolution. Therefore, future research should aim to discern whether prolonged heart rate variability disturbances are due to the physiological components of head injury or psychological stressors of recovery.

Part II: Heart Rate Variability Biofeedback Treatment Following Traumatic Brain Injury

Seven papers met inclusion criteria for the second part of our systematic review. Overall, biofeedback was associated with improved heart rate variability following mild traumatic brain injury. All studies found heart rate variability biofeedback to be effective at enhancing cognition (including working memory and executive function), emotional and social functioning, and physical symptoms following traumatic brain injury. More specifically, heart rate variability biofeedback is associated with decreases in sympathetic activation, increases in parasympathetic activation, and improved cerebral blood flow following ten weeks of treatment in a patient with post-mild traumatic brain injury syndrome (Bhandari, 2013; Lagos et al., 2012).

Preliminary studies have also demonstrated significant decreases in the severity of

headaches, mood, and post-mild traumatic brain injury symptoms following a 10-week protocol of heart rate variability biofeedback (Lagos et al., 2013). However, few studies have explored the influence of multimodal approaches in enhancing cognitive functioning following traumatic brain injury. One case study demonstrated improvements on continuous performance tests of attention, academics, mental sharpness, and visual and auditory performance tests following multiple sessions of heart rate variability biofeedback training and neurofeedback.

On average, participants completed 14 sessions of heart rate variability biofeedback; however, the number of sessions varied from 1 to 40 sessions. Furthermore, studies applied a variety of heart rate variability biofeedback protocols. Four studies utilized ten sessions of 45-60 minutes (Kim et al., 2013; Kim et al., 2015; Kim et al., 2018; Lagos et al., 2013). One study used a combination of neurofeedback and heart rate variability training across forty sessions (Bhandari et al., 2013). Other studies utilized one formal session of heart rate variability biofeedback treatment or did not report the number of sessions. The variability in the number of sessions indicates that the research on the effectiveness of heart rate variability biofeedback is in its early stages; however, ten sessions of 30-45 minutes has demonstrated to increase heart variability (Lehrer et al., 2000).

While findings of this systematic review suggest that heart rate variability biofeedback may be a useful measure for clinical recovery following traumatic brain injury, future studies with control groups and randomization are needed to determine effectiveness. A decrease in heart rate variability is associated with changes in the autonomic nervous system: increase in sympathetic activity, increase in heart rate, and decrease in parasympathetic activity. These changes reflect a disruption in key white matter tracts between the heart and brain, which cause impairment in emotion regulation and cognitive abilities. Heart rate variability biofeedback has led to improvements in working memory and executive functioning in

patients who have experienced any level of traumatic brain injury. These findings further the research that implicates prefrontal brain areas in the inhibition of a key brain area, the amygdala, thought to serve an important role in autonomic and cardiovascular responses.

Limitations & Future Directions

Part I: Heart Rate Variability Following Traumatic Brain Injury

While there were large sample sizes, many studies relied on self-report measures to establish traumatic brain injury, which is less accurate than an objective, comprehensive clinical history and failed to provide sufficient statistical data. Additionally, male athletes with a history of traumatic brain injury show decreased mean RR in comparison to female athletes in the months-to-years post-injury. Future studies would benefit from testing the influence of confounding variables such as age and sex.

While there has been considerable research investigating the association between heart rate variability and post-concussive symptoms, the association has been largely based on the perspective that heart rate variability can be used to measure the influences of the parasympathetic and sympathetic nervous systems. However, Bishop and colleagues (2018) establish that heart rate variability also consists of baroreceptor reflex activity, breathing rate, hormones, and external factors. Furthermore, Bishop and colleagues (2018) demonstrate the importance of reporting confounding variables such as circadian rhythm and hours of sleep.

Circadian rhythm is an important variable because research has shown that cortisol changes throughout the day, and circadian rhythm changes occur with injury. Therefore, it is important that concussed participants are tested at the same time of follow-up testing and at the same time as matched controls. While the review emphasizes the cost-effectiveness and accessibility of using heart rate variability during concussion recovery, multimodal assessment of blood pressure and cerebral blood flow facilitates a greater understanding

of the influence of heart rate variability on autonomic control.

Studies within the first part of the systematic review were limited in comparisons of heart rate variability and participants with a history of traumatic brain injury, without a history of traumatic brain injury, and multiple previous head injuries. Many studies used homogenous and small sample sizes, limiting the generalizability of the results. Additionally, there are several approaches to measuring heart rate variability though most studies reported only three. Studies also contained high levels of bias due to a lack of control or sham comparison, lack of randomization, lack of blinding of assessors to the participants' exposures/interventions, lack of sample size justification, and lack of multiple exposure assessments.

Part II: Heart Rate Variability Biofeedback Treatment Following Traumatic Brain Injury

The literature on heart rate variability biofeedback and traumatic brain injury remains in the early stages, and conclusions on effectiveness are unclear and may be biased. That said, findings to date suggest heart rate variability biofeedback may be a valuable measure for clinical recovery following traumatic brain injury. Study results were positive, with gains in autonomic control, mood, executive functioning, and quality of life.

More extensive controlled trials are warranted to more clearly determine the effectiveness of heart rate variability biofeedback following traumatic brain injury. An important factor of this review is the lack of generalizability and internal validity found in the literature due to unreported confounding variables associated with cardiac autonomic function (e.g., body position during testing, sex, age, and pre-existence of neck pain or headaches). Notably, there were no randomized controlled trials within the second part of the systematic review, while one study utilized a control group or sham intervention. Thus, it is difficult to make clear conclusions from this literature. Sample sizes were modest and thus limited the generalizability and utility of the literature to date.

Current Review

There are also several limitations to this systematic review that should be discussed. The primary limitation is reflected by the publication bias, which depicts the ease of finding studies with "positive" results resulting in a bias towards reporting predominantly positive outcomes. Another limitation is the limited number of databases reviewed for the identification of eligible studies. Despite these limitations, the current systematic review provides an understanding of the association between heart rate variability biofeedback training and traumatic brain injury outcome improvement, an understanding of whether heart rate variability biofeedback has sufficient evidence to be implemented as an early intervention post-traumatic brain injury, and an evaluation of the role of injury severity in rehabilitation following traumatic brain injury.

Conclusions

Heart rate variability is an essential component to understanding the interactive connection between neurocognitive and cardiac systems. The impact of decreased heart rate variability has been associated with quality of life, cardiopathology, mortality, and morbidity. Conversely, increased heart rate variability has been associated with good physical and cognitive outcomes, including increased performance on measures of executive skills, working memory, sustained attention, and recovery of clinical symptoms following traumatic brain injury, including improvements in cognitive function, headaches, dizziness, and sleep problems (Murray & Russoniello, 2012). Building on this knowledge, traumatic brain injury has been associated with decreases in heart rate variability potentially due to the impact of the autonomic nervous system on cardiovascular regulation (Gall et al., 2004b; Goldstein et al., 1998).

Given the evidence that supports heart rate variability as a predictor of outcome following traumatic brain injury, including cognitive and physical outcomes, it is no surprise that

heart rate variability biofeedback appears to improve post-concussive symptoms and increase cognitive performance in patients who have experienced any level of traumatic brain injury (Hansen et al., 2003; Lagos et al., 2012). Heart rate variability biofeedback treatment may be a potential treatment target to improve autonomic nervous system functioning following traumatic brain injury.

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Appendix A

Coding Manual

Section	Sub-section	Variable	Data/Code	Instructions/Comments
Study Characteristics	**Study Identifiers**	Study Number	1- (Study Part I) 2- (Study Part II)	This is the number that uniquely identifies a study that is being coded. We will use the database ID#
		Reviewer ID		Identifier for the coder
		Source of Information	1 = Journal 2 = unpublished report 3 = dissertation 4 = book/chapter 5 = other	
		Study Purpose		This section should include the aims of the study.
		Year of publication	YYYY	Year the report appears in print.
		Funding	1 = Federal Agency 2 = State Agency 3 = Local Agency 4 = Foundation 5 = University supported 6 = Other (Specify) 0 = No source listed	Code source of funding and support for the study
	Study Setting	Country	0= Not reported 1 = US 2 = Canada 3 = Europe 4 = Australia 5 = New Zealand 6 = Taiwan 7 = Multi-country 8 = Other (Specify)	Code the country where the study was conducted

	Other	Analyzed measures of HRV		This section may include: -SDNN (the standard deviation of R-R intervals) -RMSSD (the root mean square of successive heartbeat interval differences) -HF HRV (high frequency heart rate variability): frequency activity in the 0.15 - 0.40Hz range -LF HRV (low frequency heart rate variability): frequency activity in the 0.04 - 0.15Hz range -RSA (respiratory sinus arrhythmia)
		Type of biofeedback employed		This section may include: -HRV biofeedback -GSR (Galvanic skin response) -Skin temperature
		Biofeedback treatment number of sessions		
Eligibility	**Inclusion**	Required TBI Characteristics		
		Additional TBI Information		
		Mechanism of Injury		
		How was the injury assessed?	1 = Physician Diagnosis 2 = Self-report 3 = Neuropsychologist/Psychologist 4 = Other (specify)	
	Exclusion	Reason for Exclusion	1 = insufficient data onresults 2 = no intervention 3 = concerns about bias 4 = language 5 = other (specify)	

Methods	Study Design	1 = Randomized Control Trial (RCT) 2 = Controlled Clinical Trial 3 = Time-series 4 = Pre-post 5 = Case-control 6 = Cohort 7 = Case-series 8 = Cohort study with historical control 9 = Cross-sectional 10 = Retrospective 11 = Observational 12 = Survey 13= Other (Specify)	
	No. of sites		No. of practices where study was tested
	Data Collection Year	YYYY	If not available, respond "N/A"
	Data Collection (Time period)	___in years ___In months ___In weeks ___In days	
	IRB reported	0 = no 1 = yes	
	Inter-rater reliability reported	0 = no 1 = yes	
	Inter-rater reliability value reported	0 = no 1 = yes	
	Operational definitions	0 = no 1 = yes	
Participants	Total no. of participants		
	No. of women		
	No. of men		
	Percent of women	999 – not reported	
	Percent Black		
	Percent White		
	Percent Hispanic/Latino		
	Percent Other		
	Age groups	1 = young adult 2 = older adult 3= children	-young adult (18 - 39) -older adult (40 & over) -children (17 & under)
	Mean age in years	999 – Not reported	
	Mean Education of sample	999 – Not reported	
	Language		
	Injury Group - Total no. of participants		
	Injury Group - No. of women		
	Injury Group - No. of men		

	Injury Group - Percent of women	999 – not reported
	Injury Group - Percent Black	
	Injury Group - Percent White	
	Injury Group - Percent Hispanic/Latino	
	Injury Group - Percent Other	
	Injury Group - Age groups	1 = young adult 2 = older adult 3= children
	Injury Group - Mean age in years	999 – Not reported
	Injury Group - Mean Education of sample	999 – Not reported
	Injury Group - Language	
	Injury Group - Age at injury (mean)	
	Injury Group - Interval between injury and diagnosis (mean)	
	Injury Group - Time since injury (mean)	
	Control Group - Total no. of participants	
	Control Group - No. of women	
	Control Group - No. of men	
	Control Group - Percent of women	999 – not reported
	Control Group - Percent Black	
	Control Group - Percent White	
	Control Group - Percent Hispanic/Latino	
	Control Group - Percent Other	
	Control Group - Age groups	1 = young adult 2 = older adult 3= children

		Control Group - Mean age in years	999 – Not reported	For studies with a single Tx and control group, code the overall mean of the sample. If the study reports mean age separately for Tx and Control group. Calculate a mean from these separate means.
		Control Group - Mean Education of sample	999 – Not reported	
		Control Group - Language		
Outcomes	**Instrumentation**	Measurement used	0 = no 1 = yes	
		Standardized instrument	0 = no 1 = yes	
		Name the instrument used to measure HRV		
		Name the instrument used to measure biofeedback		
	Other	List specific outcomes being measured		
Results	**Overview**	What is being compared		
		Tx group baseline mean		
		Tx group baseline SD		
		Tx group baseline SE		
		Tx group outcome mean		
		Tx group outcome SD		
		Tx group outcome SE		
		Control/Comparison Group		
		Co group baseline mean		
		Co group baseline SD		
		Co group baseline SE		
		Co group outcome mean		
		Co group outcome SD		
		Co group outcome SE		

	Statistic	P-value in the hypothesized direction for Tx vs. Co	
		P-value in the hypothesized direction for Tx-outcome vs. Tx-baseline	
		P-value in the hypothesized direction for Co-outcome vs. Co-baseline	
		Effect Size in the hypothesized direction for Tx vs. Co	1 = Tx group outcome score better than control group outcome scores 0 = Tx and Co group outcome scores are the same -1 = Co group outcome score better than Tx group outcome score 999 = single group study that did not compare independent Tx and Co groups
		Effect Size in the hypothesized direction for Tx-outcome vs. Tx-baseline	1 = Tx group outcome score better than Tx group baseline score 0 = Tx outcome and baseline scores are the same -1 = Tx group baseline outcome score better than Tx group outcome score 999 = if no baseline and outcome data to compare for the Tx group
		Effect Size in the hypothesized direction for Co-outcome vs. Co-baseline	1 = Co group outcome score better than Co group baseline score 0 = Co outcome and baseline scores are the same -1 = Co group baseline outcome score better than Co group outcome score 999 = if no baseline and outcome data to compare for the Tx group
Miscellaneous	**Miscellaneous**	Key conclusions of the study authors	
		Comments and/or observations of the coders	

Appendix B

Controlled Intervention Studies

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
4. Were study participants and providers blinded to treatment group assignment?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
5. Were the people assessing the outcomes blinded to the participants' group assignments?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

9. Was there high adherence to the intervention protocols for each treatment group?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

Note. Provided by the Research Triangle Institute International and National Heart, Lung, and Blood Institute (NHLBI) quality assessment questionnaires.

Observational Cohort/Cross-Sectional Studies

1. Was the research question or objective in this paper clearly stated?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
2. Was the study population clearly specified and defined?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
3. Was the participation rate of eligible persons at least 50%?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
5. Was a sample size justification, power description, or variance and effect estimates provided?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
10. Was the exposure(s) assessed more than once over time?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
12. Were the outcome assessors blinded to the exposure status of participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
13. Was loss to follow-up after baseline 20% or less?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

Note. Provided by the Research Triangle Institute International and National Heart, Lung, and Blood Institute (NHLBI) quality assessment questionnaires.

Case-Control Studies

1. Was the research question or objective in this paper clearly stated and appropriate?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
2. Was the study population clearly specified and defined?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
3. Did the authors include a sample size justification?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
6. Were the cases clearly defined and differentiated from controls?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
8. Was there use of concurrent controls?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

Note. Provided by the Research Triangle Institute International and National Heart, Lung, and Blood Institute (NHLBI) quality assessment questionnaires.

Pre-Post Studies (no control group)

1. Was the study question or objective clearly stated?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
4. Were all eligible participants that met the prespecified entry criteria enrolled?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
5. Was the sample size sufficiently large to provide confidence in the findings?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	1 = Yes 2 = No 3 = Other (Specify: CD, cannot determine; NA, not applicable; NR, not reported)

Note. Provided by the Research Triangle Institute International and National Heart, Lung, and Blood Institute (NHLBI) quality assessment questionnaires.

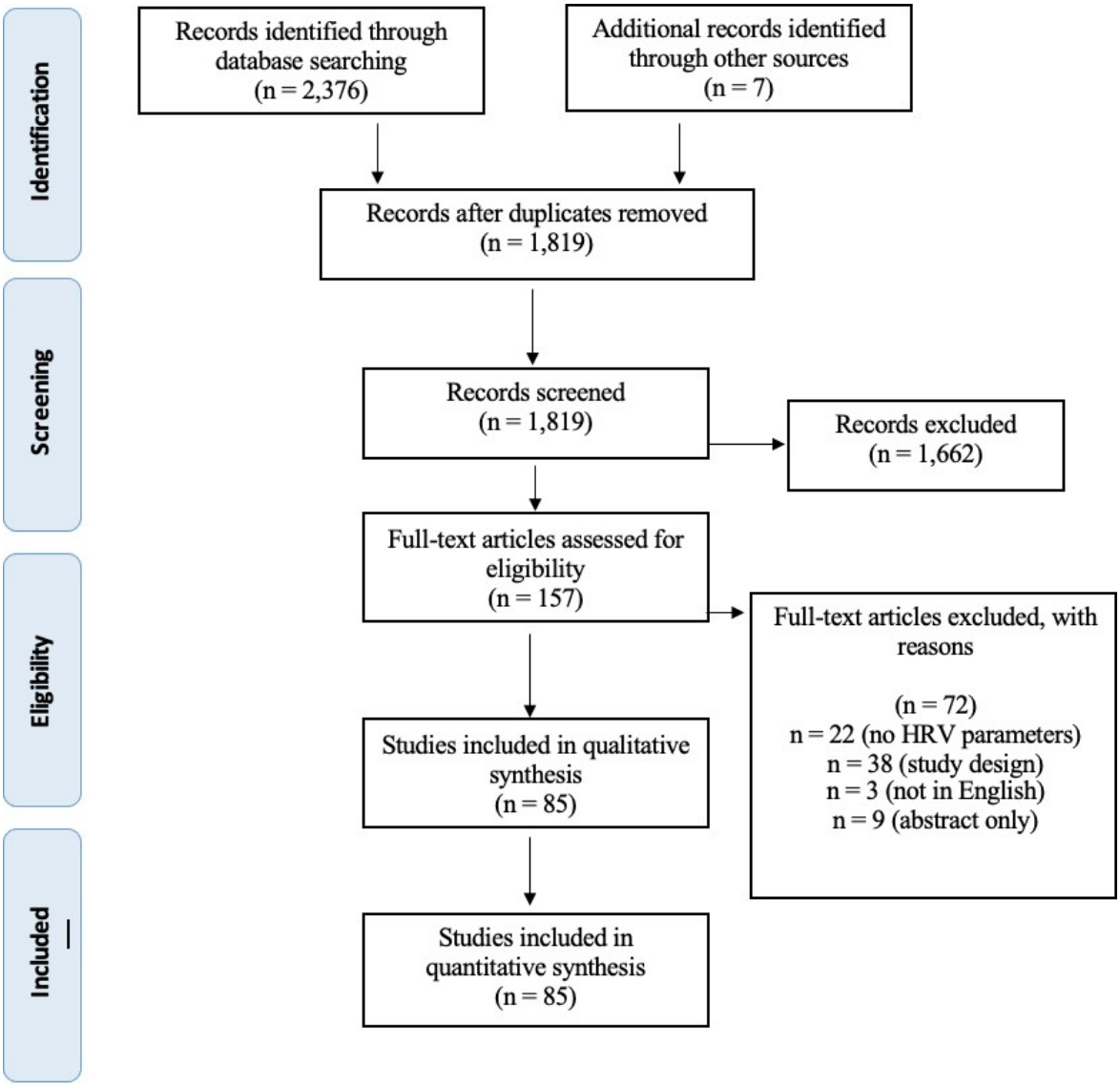

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection processes.

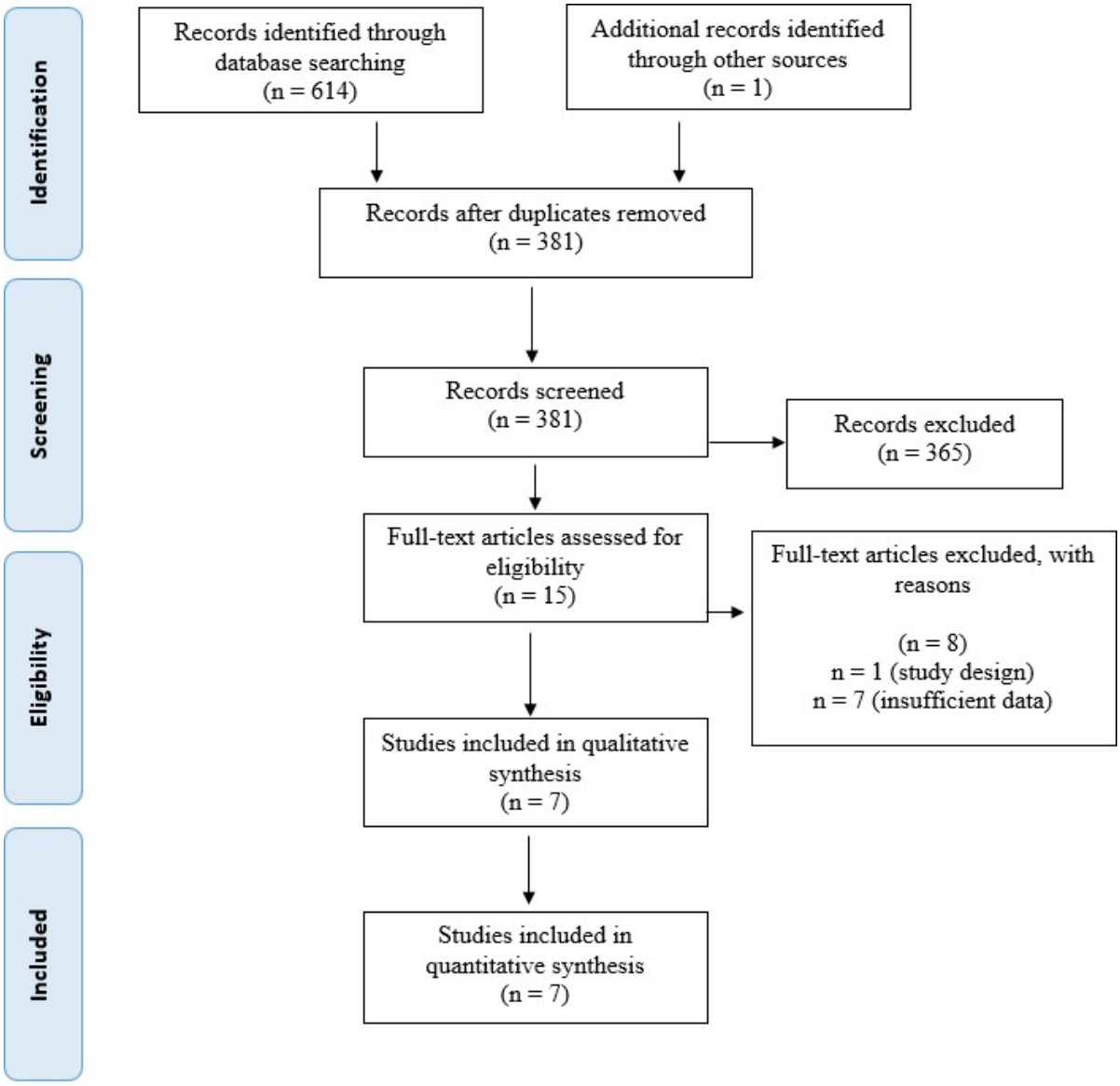

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection processes.

Table 1

Part I: Does heart rate variability change following traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Pyndiura et al., 2020)	113 (Injury: 41, Control: 72)	Mild	Mean RR, SDNN, VLF power, LF power, HF power, total power, LF/HF ratio	Participants in the autonomically aroused group experienced, on average, significantly poorer outcomes, more severe injuries and larger costs. Within this group, dysautonomic participants also experienced significantly higher costs and poorer outcomes, including a longer period of hospitalization when participants who had early deaths were excluded.
(Tegeler et al., 2016)	15	Mild	SDNN, RMSSD, LF, HF	Athletes in the acoustic stimulation were correlated with a significantly higher rate of return to play, as well as return to exercise, recreational, and academic activities; reduced clinical symptoms; and improvements in autonomic cardiovascular regulation.
(Winchell & Hoyt, 1997)	80	Severe	Total power, HF power, LF power, HF/LF ratio	Decreased HRV is associated with altered cerebral perfusion and poorer outcome.
(Tan et al., 2009)	28	Mild	SDNN	There is a possible synergistic effect of pain, PTSD, and mTBI on decreased HRV.
(LaFountaine et al., 2019)	20 (Injury: 10, Control: 10)	Mild	HF, LF, R-R intervals	HF-HRV, LF-HRV, and LF-SBP outcomes were not statistically different between groups at either of the two study visits.
(Zahn & Mirsky, 1999)	83 (Injury: 20, Control: 63)	Severe	Mean HR	During the instructions, the CHI group had a small increase in SCR/min. There were no group differences in spontaneous SCR frequency, SCL, or HR base levels.
(Fathizadeh et al., 2004)	14	NR	HR, LF, HF	During the period immediately following emergency department admission, there was an increase in autonomic activity for trauma patients. This was associated with reduced tissue oxygenation, as well as increased cardiac index, mean arterial pressure, and heart rate.
(Goldstein et al., 1996)	37	Severe	Very-low frequency HR total power, mid-low frequency HR total power, low frequency HR total power, high-frequency HR total power	For children after acute brain injury, the degree of neurologic insult is proportional to the disruption in autonomic nervous system control of heart rate.
(Balestrini et al., 2021)	119 (Injury: 65, Control: 54)	Mild	RMSSD, HR	During two study visits, there were no statistical differences between groups for HF-HRV, LF-HRV, and LF-SBP outcomes.

(Sykora et al., 2016)	262	Severe	LF, HF, total power, LF/HF ratio	After traumatic brain injury, autonomic impairment is significantly associated with increased mortality when measured by heart rate variability and baroreflex sensitivity.
(Estevez et al., 2019)	80 (Injury: 47, Control: 33)	Moderate/Severe	MRRi, SDRR, RMSSD	For patients in coma, HRV is a reliable measure to assess patient mortality and neural control of the caudal brainstem centers.
(Wijnen et al., 2006)	16	Severe	Mid frequency, high frequency, MF/HF	During sensory stimulation, recovery to consciousness during the post-acute phase is associated with changes in SCL and HRV when determined by clinical observation in sTBI.
(Henden et al., 2014)	19	Mild, Moderate/Severe	LF, HF, total power, LF/HF	BRS and HRV are acceptable variables for predicting GOSE < 5 at a 1 year follow-up.
(Mowery et al., 2008)	145	Severe	SDNN	Increased heart rate variability and IHC are associated with increased mortality.
(Lavinio et al., 2008)	18	Severe	HF, LF, spectral power	Following TBI, HRV is a tool for screening patients at risk for cerebral autoregulation derangement.
(Pattoneri et al., 2005)	20 (Injury: 10, Control: 10)	Severe	HR	Compared to healthy subjects, patients in a persistent vegetative state after traumatic brain injury had altered circadian BP and HR pattern, and higher SBP, DBP, and HR values and lower variability.
(Olegovna et al., 2019)	134 (Injury: 102, Control: 32)	Mild	SDNN, RMSSD	In the acute period, patients with combined trauma have psycho-emotional disorders of different degrees, have cognitive deficits, and vegetative dysfunction.
(Rapenne et al., 2001)	20	Severe	rMSSD, pNN50, index of variability (IV), LF, HF, and LF/HF analysis, total power (TP), LnHF	Worsened clinical cerebral impairments were associated with decreased HRV while imminent brain death was associated with preserved HRV, especially its vagal component.
(Baguley, Nott et al., 2009)	27 (Injury: 16, Control: 11)	Moderate/Severe	Total power, LF, HF, LF normalized, HF normalized, LF/HF ratio, mean HR (bpm)	Afferent stimuli elicit over responsiveness in dysautonomic participants.
(Baguley, Heriseanu et al., 2009)	26 (Injury: 7, Control: 19)	Severe	nLF, nHF, LF/HF, HR	Compared to non-Ds groups, participants five years post-injury had higher stimulus-related LF/HF ratios.
(Baguley et al., 2006)	32 (Injury: 16, Control: 16)	Severe	VLF, LF, HF, LF/HF, SDNN	Compared to non-dysautonomic subjects and controls, dysautonomic subjects had prolonged uncoupling of heart rate and HRV parameters.
(Sung, Lee et al., 2016)	264 (Injury: 181, Control: 83)	Mild	R-R interval values, total power, VLF, LF, HF, LF/HF	Compared to healthy controls, reduced ANS activity in female mTBI patients was associated with late depression accompanied by reduced ANS activity.

(Piantino et al., 2019)	23 (Injury: 6, Control: 17)	Severe	Heart rate, rMSSD, SDNN, LF, LF/HF, HF	Heart rate variability was significantly lower for frequency and time domains in patients who progressed to brain death.
(Hilz et al., 2020)	34 (Injury: 17, Control: 17)	Mild	RRI	For months or years after initial trauma, patients with a history of mTBI show slightly altered responses to unpleasant and pleasant olfactory stimuli.
(Hilz et al., 2015)	51 (Injury: 24, Control: 27)	Mild	RR intervals, LF, HF, RRI-LF/HF ratio	Patients with a history of mTBI had significantly lower LF-powers of BPsys and LF-powers of BPdia.
(Johnson et al., 2018)	21 (Injury: 11, Control: 10)	Mild	RMSSD (msec), High frequency (msec2)	College athletes with recent mild traumatic brain injuries displayed impaired autonomic nervous system activation, including the parasympathetic and sympathetic branches.
(Hilz et al., 2011)	40 (Injury: 20, Control: 20)	Mild	RMSSD, HF, LF, LF-BP oscillations, RRI-LF/HF-ratio	Post-mTBI, impaired autonomic modulation seems to be related to cardiovascular irregularities.
(Katz-Leurer et al., 2010)	30 (Injury: 12, Control: 19)	Severe	Standard deviation of the R-R interval, square root of the mean squared differences of successive R-R differences	The TBI group displayed significantly lower time domain measures of HRV at rest while TD children had decreased mean time domain values during exercise. Children had higher mean HR both at rest and during exercise post-TBI.
(Riganello et al., 2008)	42 (Injury: 16, Control: 26)	Severe	Mean RR, STD RR, Mean HR, STD HR, RMSSD, NN50, pNN50, VLF, LF, HF), and normalized unit (nu)	HRV is a measure of brain function, individual differences in regulating the emotional conditions or responses, and is an autonomic index.
(Keren et al., 2005)	40 (Injury: 20, Control: 20)	Moderate/Severe	SD-RR, LF, HF, total power	The control group and patients with TBI differed in HRV. During the first 3 months after the injury, tendency to HRV normalization was detected.
(Biswas et al., 2000)	19 (Injury: 15, Control: 4)	Moderate/Severe	LF/HF, RR intervals, HF HRV, LF HRV	Patients with significantly higher LF/HF ratios tended to have more favorable outcomes. A markedly lower LF/HF ratio, with a significant decrease after the first 4 hrs of hospitalization, was associated with progression to brain death.
(Lai et al., 2017)	1	Mild	mean RR interval, SDRR, LF, HF, LF/HF, TP, ApEn	Compared to rest, mean RR interval, SDRR, LF power, HF power, and total power were lower after exertion at two weeks post-injury.
(Ryan et al., 2011)	216	Mild, Moderate/Severe	VLF, LF, wideband frequency, HF, low to HF index ratio, SDNN, RMSSD, VLF, LF, HF, WF, LF/HF	Multiple HRV measurements were significantly associated with increased morbidity, overall mortality, brain injury, and prolonged requirements for treatment, with VLF being the most robust predictor of outcome.
(Gall et al., 2004b)	28 (Injury: 14, Control: 14)	Mild	RR (ms), SDRR (ms), LF (ms2), HF (ms2), LF norm (nu), HF norm (nu) LF/HF ratio, Total power (ms2)	In concussed athletes, neuroautonomic cardiovascular dysfunction is elicited by low-moderate steady-state exercise that is not present in a rested state.

(King et al., 1997)	14 (Injury: 7, Control: 7)	Severe	SDNN, RMSSD, HF, LF, total power	During the post-acute recovery phase, patients with TBI displayed decreased HRV.
(LaFountaine et al., 2011)	6 (Injury: 3, Control: 3)	Mild	QTVI	Compared to uninjured, matched control participants, recently concussed athletes demonstrate a higher QTVI within 48 hours of injury presentation.
(Mirow et al., 2016)	61	Mild	RR intervals, total power, HF, LF, LF/HF, SDNN, AVNN, SDANN, RMSDD, pNN50, SD1, SD3	Across all segments, participants had sympathetic nervous system dominance.
(Katz-Leurer et al., 2014)	25	Severe	SDNN, RMSSD, LF, HF, LF/HF	During PTS, HR increased significantly during different activities and varied positions among patients post-brain injury.
(Deepika et al., 2018)	109 (Injury: 89, Control: 20)	Severe	RR intervals, SDNN, RMSSD, pNN50	Excluding low-frequency normalized units (LFnu) and LF/HF, time domain and frequency domain parameters were significantly lower than that of healthy controls.
(Bishop et al., 2017)	101 (Injury: 12, Control: 89)	Mild	RRmean, RRSD, HR mean, SDHR, NN50, pNN50, VLFpower, LFpower, HFpower, Total Power, %LF, %HF, LF:HFratio, SampEn, ApEn, PETCO2	Following mTBI, autonomic function is dysregulated within the first 72 hours of injury.
(Abaji et al., 2016)	24 (Injury: 12, Control: 12)	Mild	LF/HF, RR intervals, mean NN intervals, SDNN, RMSSD	For weeks to months following injury, concussed athletes have modified cardiac autonomic modulation.
(Levine et al., 1987)	59 (Injury: 30, Control: 29)	Severe	mean heart rate, HRV, heart rate deceleration, heart rate acceleration	During the performance of recall tasks, there were differences in heart rate adjustments between the CHI and NC groups.
(Hilz et al., 2017)	60 (Injury: 40, Control: 20)	Mild, Moderate/Severe	RR intervals, HF, LF, LF/HF-RRI ratios, LF/HF RRI powers	At rest, patients with histories of moderate-severe and mild TBI had increased sympathetic and decreased parasympathetic cardiovascular autonomic modulation.
(LaFountaine et al., 2009)	6 (Injury: 3, Control: 3)	Mild	HRV, heart rate complexity (HRC)	Compared to a matched control group during an IHGT, HRC was passed 48-hours after mild traumatic brain injury. Compared to the lower values observed at 48 hours, HRC returned to control group levels two weeks after injury, a difference that was significant.
(Amorapanth et al., 2018)	26 (Injury: 16, Control: 10)	Severe	RFA, RSA, LFA, LFA/RFA ratio, cvLFA and cvRFA	Compared to controls, participants with TBI displayed decreased sympathetic activity in response to positively valenced stimuli and increased sympathetic activity to negatively valenced stimuli.

(Hilz et al., 2016)	54 (Injury: 25, Control: 29)	Mild	HR, RRI, HF, LF, total power, LF/HF	Patients with a mTBI history had slightly decreased autonomic modulation of HR and BP.
(Haji-Michael et al., 2000)	29	Moderate/Severe	LF, HF, TF, VLF, RRI, total power	After neurosurgical illness, poor quality recovery and death were associated with reduced total power variability of RRI and a decreased LF/HF ratio of the RRI.

Table 2

Part I: Does reduction in heart rate variability change by the severity of traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Fathizadeh et al., 2004)	14	NR	HR, LF, HF	During the period immediately following emergency department admission, there was an increase in autonomic activity for trauma patients. This was associated with reduced tissue oxygenation, as well as increased cardiac index, mean arterial pressure, and heart rate.
(Goldstein et al., 1996)	37	Severe	Very-low frequency HR total power, mid-low frequency HR total power, low frequency HR total power, high-frequency HR total power	For children after acute brain injury, the degree of neurologic insult is proportional to the disruption in autonomic nervous system control of heart rate.
(Sykora et al., 2016)	262	Severe	LF, HF, total power, LF/HF ratio	After traumatic brain injury, autonomic impairment is significantly associated with increased mortality when measured by heart rate variability and baroreflex sensitivity.
(Biswas et al., 2000)	19 (Injury: 15, Control: 4)	Moderate/Severe	LF/HF, RR intervals, HF HRV, LF HRV	Patients with significantly higher LF/HF ratios tended to have more favorable outcomes. A markedly lower LF/HF ratio, with a significant decrease after the first 4 hrs of hospitalization, was associated with progression to brain death.

(Papaioannou et al., 2008)	20	Severe	HF, LF, LF/HF, HR variance	High mortality rates were associated with low variability, low baroreflex sensitivity, and sustained decrease in LF/HF of HR signals in acute brain injury patients.
(Ley et al., 2010)	11977	Moderate/Severe	HR	HR was an independent predictor of increased mortality after isolated moderate to severe TBI.
(Hilz et al., 2017)	60 (Injury: 40, Control: 20)	Mild, Moderate/Severe	RR intervals, HF, LF, LF/HF-RRI ratios, LF/HF RRI powers	At rest, patients with histories of moderate-severe and mild TBI had increased sympathetic and decreased parasympathetic cardiovascular autonomic modulation.

Table 3

Part I: Does heart rate variability predict mortality and morbidity following a traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Sykora et al., 2016)	262	Severe	LF, HF, total power, LF/HF ratio	After traumatic brain injury, autonomic impairment is significantly associated with increased mortality when measured by heart rate variability and baroreflex sensitivity.
(Estevez et al., 2019)	80 (Injury: 47, Control: 33)	Moderate/Severe	MRRi, SDRR, RMSSD	For patients in coma, HRV is a reliable measure to assess patient mortality and neural control of the caudal brainstem centers.
(Mowery et al., 2008)	145	Severe	SDNN	Increased heart rate variability and IHC are associated with increased mortality.
(Ryan et al., 2011)	216	Mild, Moderate/Severe	VLF, LF, wideband frequency, HF, low to HF index ratio, SDNN, RMSSD, VLF, LF, HF, WF, LF/HF	Multiple HRV measurements were significantly associated with increased morbidity, overall mortality, brain injury, and prolonged requirements for treatment, with VLF being the most robust predictor of outcome.
(Papaioannou et al., 2008)	20	Severe	HF, LF, LF/HF, HR variance	High mortality rates were associated with low variability, low baroreflex sensitivity, and sustained decrease in LF/HF of HR signals in acute brain injury patients.
(Ley et al., 2010)	11977	Moderate/Severe	HR	HR was an independent predictor of increased mortality after isolated moderate to severe TBI.
(Hilz et al., 2016)	54 (Injury: 25, Control: 29)	Mild	HR, RRI, HF, LF, total power, LF/HF	Patients with a mTBI history had slightly decreased autonomic modulation of HR and BP. Cardiovascular dysregulation contributed to increased mortality risk in post-mTBI-patients.
(Mirow et al., 2016)	61	Mild	RR intervals, total power, HF, LF, LF/HF, SDNN, AVNN, SDANN, RMSDD, pNN50, SD1, SD3	Across all segments, participants had sympathetic nervous system dominance though there was insufficient evidence for cardiovascular death.

Table 4

Part I: Can heart rate variability help clinicians facilitate safe return-to-play following mild traumatic brain injury?

Study	Sample	TBI Severity	HRV Measures	Key conclusions
(Tegeler et al., 2016)	15	Mild	SDNN, RMSSD, LF, HF	Athletes in the acoustic stimulation were correlated with a significantly higher rate of return to play, as well as return to exercise, recreational, and academic activities; reduced clinical symptoms; and improvements in autonomic cardiovascular regulation.
(Lai et al., 2017)	1	Mild	mean RR interval, SDRR, LF, HF, LF/HF, TP, ApEn	Compared to rest, mean RR interval, SDRR, LF power, HF power, and total power were lower after exertion at two weeks post-injury.
(Huang et al., 2019)	46 (Injury: 23, Control: 23)	Mild	HF power	Following mild traumatic brain injury, lower HRV was displayed at rest.

Table 5

Part II: Heart Rate Variability Biofeedback Treatment Following Traumatic Brain Injury

Study	Sample	TBI Severity	HRV Measures	Biofeedback Sessions	Instrument	Key conclusions
(Kim et al., 2015)	13	Moderate/Severe	LF, HF, coherence ratio	10	HeartMath emWave PC	From pretreatment to post-treatment testing, participants' HRV measures, including LF/HF and the coherence ratio, increased.
(Kim et al., 2018)	13	Severe	Coherence ratio	10	HeartMath emWave PC	When positive affect was high, there was a large effect on problem solving from HRV biofeedback.
(O'Neill & Findlay, 2014)	2	Severe	VLF, LF, HF, coherence ratio	NR	HeartMath emWave PC	There were reduced aggressive outbursts, an increased sense of self-efficacy and behavioral control, and an increased ability to recognize frustration.
(Bhandari et al., 2013)	1	Severe	NN50, total power	40	NR	There were improvements in mood, memory, sleep and energy, as well as regaining mental sharpness, and completion of revisions to his thesis.
(Kim et. al., 2018)	13	Severe	RR intervals, peak power, total power	10	HeartMath emWave PC	The most gains and best post-treatment performance on problem-solving ability was seen in participants who had the most positive emotions.
(Lagos et al., 2013)	1	Mild	LF, HR STD DEV	10	ProComp Infiniti	Among longer term effects, improved autonomic control, decreased mood disturbances, and improved headaches occurred, as well as large short-term effects.
(Francis et al., 2016)	60 (30 TBI; 30 Controls)	Severe	SDNN, rMSSD, LF, HF, LF/HF ratio	1	BioGraph Infiniti Software 6.0	Compared to baseline, both control and TBI groups displayed significantly increased HRV on SDNN, rMSSD, LF, HF, LF:HF ratio during biofeedback.