Towards a Taxonomy for Analyzing Heart Rate as a Physiological Indicator of Post-Traumatic Stress Disorder (PTSD)

Mahnoosh Sadeghi, Farzan Sasangohar, Anthony McDonald

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Abstract

Background: Post Traumatic Stress Disorder (PTSD) is a prevalent psychiatric condition that is associated with symptoms such as hyperarousal and overreactions. Treatments for PTSD are limited to medications and in-session therapies. Assessing heart responses to PTSD has shown promise in detecting and understanding the onset of symptoms.

Objective: To extract statistical and mathematical approaches that researchers can use to analyze heart rate data in terms of PTSD.

Methods: A scoping literature review was conducted to extract heart rate models. Five databases including Medline OVID, Medline EBSCO, CINAHL EBSCO, Embase Ovid, and Google Scholar were searched. Non-English studies, as well as the studies that did not analyze human data, were excluded. 45 articles were chosen to be in the review based on their relevance.

Results: We identified four categories of models: descriptive time-independent output, descriptive/time-dependent output, predictive/time-independent output, and predictive/time-dependent output. Descriptive/time-independent output models include Analysis of Variance (ANOVA) and first-order exponential; descriptive time-dependent output includes classical time series analysis and mixed regression. Predictive time-independent output models include machine learning methods and analyzing heart rate-based fluctuation-dissipation theory. Finally, predictive time-dependent output includes time variant method and nonlinear dynamic modeling.

Conclusions: All of the identified modeling categories have relevance for PTSD, although modeling selection is dependent on the specific goals of the study. Descriptive models are well-founded for inference about PTSD. However, there is a need for additional studies in this area that explore a broader set of predictive models, and other factors (e.g., activity level) that have not been analyzed with descriptive models.

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Keywords: Heart Rate; Models; Statistics; PTSD; Analysis, Physiology

Introduction

Post-Traumatic Stress Disorder (PTSD) is a psychiatric condition that develops as a result of experiencing injury, severe psychological shocks, and other trauma [1]. Individuals with PTSD suffer from the recall of traumatic experience and often develop depression, anxiety, emotional instabilities, and suicidal thoughts [2]. Recent reports suggest that individuals with PTSD are about 5
times more likely to commit suicide than individuals without PTSD [3]. Approximately 10% of American women and 4% of men experience PTSD in their lifetime [4]. PTSD is an endemic disorder among veterans as well—affecting between 17% to 24% of veterans from recent conflicts [5].

While an alarming number of individuals are afflicted with PTSD, there are significant barriers to care delivery [6,7]. These barriers include shortage of qualified clinicians and understaffed mental health clinics, geographical constraints to access mental health facilities, financial obstacles, and cultural factors such as the social stigma and limited capabilities in objective diagnosis (currently limited to self-reported measures such as the PTSD Checklist [PCL-5]) [8]. Studies have shown that self-management and factors such as positivity directly affect PTSD symptoms and ease in dealing with them [9]. Mobile health apps (mHealth) have shown promise to facilitate self-management (e.g., education, mindfulness, and self-assessment) and have the potential to facilitate direct communication between people who have PTSD and their health care providers [10]. mHealth apps deployed on wearable devices (e.g., smartwatches) that are equipped with an array of physiological sensors (e.g., heart rate) may also enable remote continuous monitoring of signs and symptoms of PTSD. Indeed, recent efforts have shown promising application of watch-based heart rate sensors to detect the onsets of PTSD hyperarousal events [11].

Despite the recent work, the extent of knowledge on the physiological reactions to PTSD and, in particular, Heart Rate (HR) is limited and work is needed to better understand changes to HR associated with PTSD. Few models (e.g., Analysis of Variance, regression analysis) have been developed to relate changes in heart activity to disorder states. In particular, given the opportunity to collect HR data non-intrusively, it is important to use appropriate mathematical and statistical methods to ensure the accumulation of convergent knowledge in this field and to characterize and understand heart rate in terms of PTSD. In this article, we document the findings from a review of the current literature on measures and models used in various domains to analyze HR data. In addition to summarizing and synthesizing the HR analysis methods, we provide an evaluation of methods for applications relevant to PTSD detection and diagnosis.

Methods

Search Strategy

A scoping review was conducted using the strategies outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology [12]. The scoping review approach was selected because it is effective for knowledge evaluation and gap identification [13]. The review spanned five main databases: (1) Medline OVID, (2) Medline EBSCO, (3) CINAHL EBSCO, (4) Embase Ovid and (5) Google Scholar. Search terms included: “heart*”, “pulse*”, “Heart Rate*”, “model*”, “heart beat*”, and “analysis*”. All studies published in or after the year 2000 were included. This search was supplemented by secondary search of cited articles in the results. The search was completed on January 15th, 2020.

Study Selection, Inclusion, and Exclusion Criteria

Abstracts were reviewed for relevance and articles that did not discuss heart rate related measures in detail and did not provide/use quantitative methods for analysis were excluded. Other exclusion criteria were non-English articles and articles that assessed non-heart-based physiology measures such as skin conductance and blood pressure. Further, studies that did not analyze human physiology were excluded. The inclusion criteria were all articles that discussed human heart rate analysis. Our initial search yielded 1,905 results. After removing duplicate articles and checking for eligibility using Rayyan (a web application for assisting literature reviews), 270 articles were further reviewed.
Out of the 270, 138 were exclusively about non-heart-based measures reactions, 67 did not focus on human physiology, and 11 had duplicated content. 54 articles from the search were included in this review based on their relevance to the topic.

Further, the bibliography of references in each research paper was investigated thoroughly (backward search) to identify pertinent articles, and then Google Scholar searches (forward search) were conducted to find the full text. Figure 1 shows the PRISMA flow chart for the article selection process.

Results and Discussion

We listed the articles identified by the search process into two categories based on our synthesis:
studies of the effects of PTSD on heart physiology and quantitative modeling techniques for heart data. We further partitioned studies of PTSD effects into two types: (1) studies that investigate the effect of PTSD on heart rate variability and (2) studies that explore the effect of PTSD on heart rate. The literature on models can be further classified by the model’s focus on describing versus predicting data, and the model output. These categories and sub-divisions are discussed in the following sections.

Effects of PTSD on heart rate variability

Heart rate variability (HRV) measures variations in heartbeats and is related to the electrical activity of the heart [14]. Common frequency domain analysis metrics for HRV include: High Frequency (HF), Low Frequency (LF), the ratio of LF to HF (LF/HF), Coherence Score (COH), the Root Mean Square of Successive Differences between normal heart beats (RMSSD), and the Standard Deviation of the interbeat interval of Normal sinus beats (SDNN) [15–18]. LF and HF are frequency bands of HRV that tend to correlate with parasympathetic nervous system activity. LF is the frequency activity in the range of 0.04–0.15Hz and HF is the activity in the range of 0.15–0.4Hz. The quantified relative intensity of these measures is referred to as power [1] and such power is obtained by applying power spectral and frequency domain analyses [19].

The reviewed articles found that PTSD causes sustained changes in Autonomic Nervous System (ANS) (part of the nervous system that is responsible for regulating automated functions in the body such as heart activity) [20]. The ANS consists of Parasympathetic Nervous System (PNS)—which regulates blood pressure and breathing rate during rest, and the Sympathetic Nervous System (SNS)—which adjusts blood pressure and heart rate during activity. Heart activity is representative of the performance of these systems [21]. Various effects of PTSD on ANS have also been documented. Higher heart rate levels indicate lower heart rate variability and are linked to increased rates of mental stress and physical activity [22,23]. PTSD as a particular type of anxiety disorder also disturbs HR and HRV. Heart rate variability has been studied widely in the literature to assess PTSD (e.g., [18,24–26]). Evidence suggest that individuals with PTSD have lower resting HRV than individuals without PTSD when other factors (age, gender, and health level) are controlled [27]. According to Nagpal et al.’s [1] metareview, HF, a measure for the parasympathetic activity of ANS, is significantly lower in individuals with PTSD than individuals without PTSD (~0.6ms²). However, LF which assesses both sympathetic and parasympathetic activity of the ANS is slightly reduced in individuals with PTSD (~0.2 ms²). This results in a significant increase in LF/HF individuals with PTSD [1,28–30].

RMSSD and SDNN are time domain measures of HRV. SDNN is an index for SNS activity [24]. SDNN is decreased in individuals with PTSD compared to healthy individuals (~6.7ms) showing an increase in sympathetic activity [1,31]. In addition, decreased levels of RMSSD was observed among individuals with PTSD (~7.5ms) that suggests lower vagal activity in this population [1,31].

Although HRV analysis is common among studies of anxiety [32], some factors need to be considered when HRV measures are used. First, studies show that HRV is dependent upon heart rate and cannot be analyzed independently to represent the ANS activity [32,33]. In addition, prior research has linked high HRV to pathological conditions related to heart deficiencies [32]. For instance, diseases such as atrial fibrillation increase HRV and HR, and are associated with higher mortality rates [34]. Hence, higher rates of HRV do not always indicate abnormal mental state. Ideally, measurements should take into account patient’s comorbidities such as heart deficiencies in addition to subjective (e.g., self-reported scales) and objective (e.g., HRV, ECG) methods [35].
Gender, health, age, and heart rate also affect HRV, and they need to be considered as covariates when HRV measures are used [24]. Aging decreases HRV time domain features such as SDNN [36,37]. HRV time domain features increase by improved health conditions [38,39]. LF and SDNN are also lower in females than in males; however, HF parameter of HRV is greater in women than in men [40]. Higher heart rate levels are also associated with decreased HRV [41], because when the heart beats faster, beat to beat intervals are smaller. Other factors such as climate, job satisfaction, lifestyle, and medications can also affect HRV and should be considered as an influential factor when HRV is analyzed [42].

**Effect of PTSD on heart rate**

Heart Rate (HR) is the count of heartbeats per 60 seconds. Normal heart rate differs among individuals based on age and gender, health level, and respiratory activity [43]. Both HR and HRV are modulated by ANS [44]. As the SNS activates, PNS activity decays; therefore HR increases and HRV decreases [45]. As a result, there is an inverse relationship between HR and HRV [33].

PTSD can affect heart rate (HR) in two modalities: resting, and fluctuation tone [1,46–48]. Studies suggest that resting heart rate can be between 5 to 6.6 beats higher in individuals with PTSD than individuals without PTSD depending on the type of population (e.g., veteran, civilian) [49–51]. For example, resting HR is roughly 5 beats per minute higher in civilians with PTSD than civilians with no PTSD, and this number increases to 6.6 beats per minute difference in the veterans population [51,52]. In the non-resting state, evidence suggests that heart rate increases in the exposure of PTSD stressors [1].

Another heart rate measure that has been investigated in terms of PTSD is heart rate fluctuations (changes in heart rate levels) in the presence of stimuli [53]. There are conflicting findings on the comparison of this measure between individuals with and without PTSD. While the study by [54] show that heart rate changes are higher in people with PTSD than people without PTSD, [55] claims the opposite.

**Heart rate models**

Based on our synthesis of the existing literature, we categorized mathematical models of heart rate into descriptive and predictive models, both of which could provide insight relevant to understanding the psychophysiological responses to PTSD. Descriptive methods can be used to describe and make inferences about a dataset, while predictive ones can be applied to forecast trends and patterns in the data. Predictive and descriptive models can be further characterized by their type of output—time-independent or time-dependent (Figure 2). Time-dependent outputs use time as one of the descriptive variables to analyze the dependent variable(s) or output(s). Time-independent output, however, does not depend on time and does not change over time. While the models reviewed below are summarized and synthesized for relevance to PTSD-related analysis, these methods are not limited to PTSD and anxiety disorder domains.
Descriptive Models

Time-independent output

Analysis of Variance (ANOVA)

Linear regression, and in particular ANOVA, is a statistical model used for analysis of HR in several articles (Table 1). ANOVA can be used to compare HR trends, and group means in experimental studies [56,57]. Studies used ANOVA to account for the effectiveness of treatments in individuals with PTSD as measured by HR [58]. Some studies chose ANOVA as their method of analysis to show that resting heart rate is higher in individuals with PTSD than individuals without PTSD [57]. For example, the study by Gelpin et al. [59] compared the resting HR in individuals pre- and post-treatment to measure the success of therapy sessions. Buckley et al. [52] used ANOVA to compare resting HR in PTSD patients with that of healthy controls, finding that PTSD patients, in general, have significantly higher resting HR levels (~6 beats per minute difference). While using ANOVA for the analysis of time-independent HR data, it is limited in several respects. ANOVA has strong assumptions and is ill-suited to model-dependent measures with strong temporal correlations. For instance, independency of observations is one of the main assumptions of ANOVA; however, consecutive heart rate real time-based data is a highly correlative type of data. Thus ANOVA should not be used to make time-based HR predictions [60].

First-order exponential model

A first-order exponential model provides a function with a sustained growth or decay rate [61]. In terms of heart rate analysis, first order exponential models have been used to generate a nonlinear regression model for HR based on Heart Rate Recovery (HRR) [62]. Heart Rate Recovery (HRR) is an indicator of vagal reactivation and SNS deactivation [63].

Bartels-Ferreira et al. [63] used first order exponential method to measure postexercise time-independent HRR based on heart rate decay curves. Recovering from the onset of PTSD symptoms is associated with activation of vagal tone and withdrawal of SNS activity, both of which are correlated
with HRR [64]. While this method shows promise in assessment of heart rate fluctuations associated with PTSD, the reviewed literature (Table 1) examined ANS in the context of physical activity and HR decay after activity was curve fitted by a first order exponential function ([63]). In this case the goodness of fit was moderate (R^2 ~0.65), which warrants additional research. Another limitation associated with this method is that the exponential functions show erroneous patterns for very small (30-second) and very large (600-second) time windows [61]. For instance, Bartels-Ferreira et al. [63] found that the least goodness of fit was for the smallest time window which was 30 seconds (r^2 =0.42 ). Conversely, when the length of the window of time is a moderate number (~360 seconds) a relatively better goodness of fit was obtained (~0.69). This shows that HRR curve fitted by first order exponential models performs better (higher R^2) when windows of times are neither too big nor too small. Table 1 shows a summary of articles that studied descriptive models with time-independent output. In this table, domain is the field of the study. Independent variables are factors that are controlled by researchers, and dependent variable are dependent on them. “Independent Variables” are used to describe/classify dependent variable.

### Table 1: Results studies that used descriptive models with time-independent output

| Method                | Authors                      | Domain                  | Independent Variables                                      | Dependent Variable |
|-----------------------|------------------------------|-------------------------|------------------------------------------------------------|--------------------|
| ANOVA                 | Shalev et al. (1998) [57]    | PTSD                    | Gender, age, heart rate, trauma history, event security    | HR                 |
|                       | Strath et al. (2000) [65]    | Physical Activity       | Heart rate, Oxygen intake, age, fitness                    | HR                 |
|                       | Romero-Ugalde et al. (2017) [66] | Physical Activity | Accelerometer, energy expenditure, heart rate               | HR                 |
|                       | Khoueiry et al. (2012) [67]  | Medical                 | Heart rate, hospitalization duration, age                  | HR                 |
|                       | Tonhajzerova et al. (2012) [68] | Physiology           | Resting HR, Major depressive disorder                      | HR                 |
| First order exponential | Bartels et al. (2015) [63]   | Physical activity       | Heart rate peak, resting heart rate, heart rate recovery    | HR Variation       |

### Time-dependent output

**Classical time series analysis**

Classical time series analysis is a common statistical method that can analyze time-dependent data trends by looking into linear relationships. Classical time series analysis is also a promising method for analyzing HR and HR fluctuations since these measures are time-based [69,70].

Peng et al. [70] applied time series analysis to look into longterm correlation within heart rate data and its relation to heart diseases such as cogestive heart failure. Using this method, the authors showed that there is some independency between beat to beat HR fluctuations in healthy people that does not exist in cardiovascular disease patients. The findings further suggest that classical time series analysis is a promising direction for PTSD hyperarousal analysis because similar HR changes have been documented in PTSD patients compared to healthy people in the presence of stimuli [71].

Beyond the analogous use case, classical time series has several benefits compared to ANOVA. Since the model explicitly considers autocorrelation, it does not require the assumption of independence of
observations [72]. The models also have predictive capability and are well validated for illustrating trends and forecasting [73]. However, one drawback of this method is the stationary assumption (constant mean value of the series), which is not always reasonable in HR data (e.g., when data is collected before and during exercise).

**Mixed regression model**

Mixed regression analysis has been used in the literature to evaluate physiological responses to energy expenditure [74]. This type of modeling can be applied with correlated observations. Thus, it is beneficial for psychophysiology analyses that need to account for individual similarities in responses that make these responses correlated [60]. Multiple regression typically proceeds in a stepwise process with a focus on identifying two main effects: the population-fixed effect and the random effect. The population effect explains similarities in the dataset (for instance HR), while random effect represents the differences among observations (the error term). For instance, Gee et al. [75] used respiration as a random effect to estimate heart rate and ultimately predict episodes of bradycardia in infants. Using mixed regression method and accounting for respiration as a covariate in this case has increased accuracy of the measured heart rate by 11%.

The ability of mixed regression models to account for individual differences makes them an advantageous choice for modeling PTSD. Several studies have identified significant individual differences in people with PTSD [1,57,76,77]. Specifically, HR and heart rate variability levels are significantly affected by individual differences such as age, general health, and gender [24].

This type of modeling might produce similar results to ANOVA in many cases. However, in comparison with ANOVA, mixed regression models are more effective for datasets with missing values and multiple random effects [78]. This is important since in real world and naturalistic studies, datasets with high rates of missing values are common and can be challenging to deal with [79]. For comparison of time-dependent output methods, see Table 2.

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**Table 2: Results from studies that used descriptive models with time-dependent output**

| Method              | Authors                  | Domain                        | Independent Variables                                      | Dependent Variable |
|---------------------|--------------------------|-------------------------------|------------------------------------------------------------|--------------------|
| **Classical time series** |                          |                               |                                                            |                    |
| Classical time series | Chen et al. (2016) [69]  | Healthcare (patient data)     | HR, resting heart rate                                     | Heartbeat          |
| Classical time series | Kazmi et al. (2016) [33] | Physiology                    | HR, HRV, time                                              | Heart rate         |
| Classical time series | Zakeri et al. (2012) [80]| Physical activity             | Heart rate, energy expenditure, accelerometer, age         | Energy expenditure |
| Classical time series | Peng et al. (1995) [70]  | Medical                       | Heart rate, heartbeat, time                                | Heart rate         |
| **Mixed regression** |                          |                               |                                                            |                    |
| Mixed regression     | Gee et al. (2017) [75]   | Biomedical                    | Heart rate, heartbeat, respiration, time                   | Heart rate         |
| Mixed regression     | Bonomi et al. (2015) [81]| Physical activity             | Heart rate, energy expenditure, photoplethysmography, accelerometer | Heart rate         |
| Mixed regression     | Xu et al. (2015) [82]    | Physical activity             | Heart rate, energy expenditure, different training paradigms, age, | Energy expenditure |

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**Predictive Models**

**Time-independent output**

*Machine learning methods*

Machine learning methods refer to a set of training and predictive algorithms that use data to learn complex trends associated with labels (e.g., symptom presence) in a dataset. Machine learning analysis is a multiple step process consisting of dividing a dataset into training and testing data (or leveraging re-sampling techniques such as cross-validation), developing a model from the training data, and evaluating the model on the testing data. This approach is advantageous relative to approaches that use all of the data for training a model (e.g., ANOVA) and approximate metrics to evaluate generalizability (e.g., Adjusted R\(^2\)). Furthermore, the ability of machine learning algorithms to identify complex patterns in datasets make them a promising approach for analyzing physiological data that is often noisy[cite the review paper on HRV etc. for stress].

The success of applying machine learning methods depends on the data used to train and evaluate the algorithm. Machine learning algorithms typically require large training sets—several thousand observations—and they implicitly assume that the data and associated labels are of equal quality. In cases where the data is noisy or labels are unreliable, machine learning training algorithms may fail to converge to a generalizable solution. Further, if the training data examples are biased (e.g., non-representative population samples) the machine learning algorithms trained on the data may also be similarly biased. It is often difficult to identify these issues through standard training and testing processes of machine learning algorithms, thus machine learning analyses should be accompanied by descriptive analyses to obtain better understanding of the data and potential errors or bias [83].

Most of the reviewed studies used heart rate variability along with machine learning algorithms to predict the stress level in individuals [84–86]. Machine learning studies evaluating HR primarily have focused on energy expenditure[87,88]. One exception is McDonald et al. [11] who evaluated several machine learning algorithms—neural networks, decision trees, support vector machines, convolutional neural networks, and random forests—to predict the onset of PTSD symptoms for the veteran population. This study used heart rate data with 1HZ frequency (1 observation per second) as the input of these algorithms. While the raw 1Hz data was used to train the neural network-based models, additional feature generation and selection was performed before training the decision tree, support vector machine, and random forest algorithms. This feature generation identified linear trends, Fourier Transforms, and change quantiles as relevant features for PTSD symptom onset detection. Among all machine learning methods, support vector machines and random forest algorithms performed best (i.e., had the highest area under the Receiver Operating Characteristic (ROC) curve: 0.67). While machine learning shows promise for inferential analysis of HR data for PTSD research, explaining the purpose of machine learning components may be difficult, and often predictive results have limited rational explanation [89].

*Fluctuation-dissipation theory*

Fluctuation-dissipation Theory (FDT) is a common approach in thermodynamics that is used to predict system behavior by breaking the system responses into small forces [90]. This theorem that follows thermodynamic rules can model heart rate response after stress moments.

Chen et al. [91] used FDT to predict patients’ HR reactions to pre- and post- spontaneous breathing trial treatment. They used this method to divide the system (in this case, treatment process) into different phases, including pre-treatment, mid-treatment, and post-treatment. After breaking the
entire treatment process to these small phases, each phase was modeled separately. The reactions to
treatments in each phase were modeled with HRR measures. All models were then combined to
make the final comprehensive model. Chen et al. [91] found that thermodynamic rules can also
model HR response after stress moments. This is because of the similar effect of stress and
spontaneous breathing trials on organs (common clinical procedure used to assess ventilation
performance of patients). These researchers suggest dividing the system into pre and post stress
moments, modeling each phase and finally assembling a model for final prediction. They further
suggest that the HRR extracted from this type of modeling can be used to personalize care as HR can
be remotely monitored through noninvasive hospital devices.

In terms of mathematical concepts, this type of modeling has a powerful predictive capability by
grouping individuals and therefore minimizing error rate [91]. This approach requires significantly
less data than other methods such as time-variant modeling of heart rate. Hence, it enables
researchers to include more variables in their model. Moreover, Chen et al. [91] claim that while
models that use Gaussian functions have around 65% error rate to predict patients’ response to
spontaneous breathing trial, implementing FDT decreases this error rate by over 10%. Therefore, this
approach provides more accurate results than methods that use Gaussian function such as some
machine learning algorithms (e.g., ANFIS). A potential reason for this could be that by using FDT
the system is broken down into smaller pieces where each part has its own specific and defining
features. However, in ANFIS the system was considered as a whole, and a set of features was defined
for the entire system overlooking dissimilarities within the system. Also, unlike most of the statistical
approaches that make assumptions about the data, this method is assumption-free and is considered
more robust to assumptions (e.g., normality of residuals, independency of measurements). Despite its
promising application to analysis of HR and the lack of restrictive assumptions, FDT is
computationally intense. This means that the model needs a high levels of proficiency in
understanding mathematics and statistics behind FDT. Especially in comparison to approaches such
as ANOVA, classical time series and mixed regression using this approach requires higher levels of
domain knowledge. For example studies in machine learning and FDT methods, see Table 3

| Method               | Authors          | Domain                  | Independent Variables                                                                 | Dependent Variable   |
|----------------------|------------------|-------------------------|---------------------------------------------------------------------------------------|----------------------|
| Machine learning     |                  |                         |                                                                                        |                      |
| Kolus et al. (2016)  | (Biomedical       | Heart rate, oxygen      | Work Rate                                                                             |                      |
| [87]                 | (Energy consumption, work rate) |                       |                                                                                        |                      |
|                      |                  |                         |                                                                                        |                      |
| McDonald et al.      | (PTSD)           | Heart rate, subjective stress moments | Stress moment                                                                         |                      |
| (2019) [11]          |                  |                         |                                                                                        |                      |
|                      |                  |                         |                                                                                        |                      |
| Healey et al. (2005) | (Driving)        | Heart rate, HRV, skin conductance, muscle activity, Muscle tension, breathing rate | To detect stress                                                      |                      |
| [86]                 |                  |                         |                                                                                        |                      |
|                      |                  |                         |                                                                                        |                      |
| Kolus et al. (2016)  | (Physical activity) | Heart rate, Max heart rate, oxygen consumption, body type, work rate | Work rate                                                                           |                      |
| [88]                 |                  |                         |                                                                                        |                      |
|                      |                  |                         |                                                                                        |                      |
| Zhang et al. (2012)  | (Physical activity) | Heart rate, body attitude information, body movement | HR                                                                                |                      |
| [92]                 |                  |                         |                                                                                        |                      |
Fluctuation-dissipation Theory

| Chen et al. (2013) | Healthcare | Hear rate recovery, blood pressure, instantaneous heart rate | HR |

Time-dependent output

Time-variant modeling

Time-variant modeling is a mathematical approach used to analyze time-dependent datasets, and provides time-dependent output. Time-variant models of HR can generate heart rate recovery measures in real time. Some studies suggest that measuring heart rate recovery in real time can especially help assess arousals and arousability in different individuals in response to mental stressors [93]. This shows promise for PTSD research given its potential to enable the comparison between the effect of internal stimuli (stressors generated through memory) to external stimuli (stressors generated from the environment) on PTSD patients’ arousability.

Although time-variant modeling has been replicated in the literature and has showed promise in analyzing heart rate data [33,94], it is computationally intense. The process of solving the equations within the model includes defining multiplex matrices for each variable, which is time- and space-consuming. Moreover, time-variant modeling requires large datasets of high frequency (e.g., 100 Hz) HR data which is often not feasible for real-time data collection instruments such as wearable devices which record continuous data for large windows of time (e.g., more than 30 minutes).

Nonlinear dynamic modeling

Nonlinear dynamic modeling of HR consists of depicting HR as the output of a non-linear dynamic system [95].

Nonlinear dynamic modeling of HR can be a promising method to assess arousal patterns by measuring SNS activity [96]. Hence, this approach may be useful for analyzing PTSD hyperarousal patterns since they are associated with SNS activity. Despite the advantages of this model, it requires high-frequency HR data (e.g., 100 Hz) or even instantaneous HR [96]. Instantaneous HR is an HR measure derived from HRV, which is different from raw HR measured by wearable devices. Instantaneous HR can be extracted from multiplying RR intervals by the number 60 and needs to be measured with high frequency (>250HZ), whereas smart watches collect heart rate data with much lower frequency (<5HZ) [96].

This model accounts for the natural nonlinearity and time-dependent features of heart rate data. Also, the learnability and predictability of this method can help detect the onset of symptoms in PTSD patients. A limitation of this method to characterize PTSD aspects is the assumption of invertibility [97]. This assumption indicates that all the variable matrices used in equations are required to be invertible. In many cases, and mainly in non-laboratory settings, this assumption cannot be met [97]. Moreover, these methods are relatively slow and more intense computationally compared to other methods like machine learning (for both training and testing the model) because they involve solving multiple complex mathematical equations [66]. For examples of predictive models with time-dependent output, see Table 4.

Table 4: Results from studies that used predictive models with time-dependent output

| Method | Authors | Domain | Independent Variables | Dependent Variable |
|--------|---------|--------|-----------------------|--------------------|
Descriptive framework based on the summary of findings

We categorized methods used to analyze heart rate data into two categories: descriptive and predictive. In the context of PTSD, descriptive models may be used to characterize PTSD triggers and the factors that affect their occurrence, whereas predictive models may be useful to predict PTSD onset to facilitate timely intervention. The extracted models provide methods of evaluating, describing, comparing, interpreting, and understanding patterns in the HR data. However, interpreting the data in a meaningful way depends on the specific objectives of the study. The data at hand can be analyzed with one or multiple of the reviewed models based on the goal of the study and the assumptions of models. Each model corresponds to the distinct type of output and different interpretations of the data with different assumptions. Based on the process of data collection, number of observations, and variables in the data, researchers might choose one or a combination of models provided. Table 5 provides a framework for choosing a model based on the limitations, assumptions, and features of each model and the data at hand. Further, Table 5 represents the articles that used a specific method.

Table 5: Descriptive framework for the HR-related analysis methods extracted from the literature

| Model                        | Assumptions                                                                 | Features                                                                 | Limitations                                                                              | Cases                                                                 |
|------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Analysis of Variance (ANOVA) | • Normal distribution of residuals • Constant variance of populations • Independence and identically distributed observations | • Capable of comparing groups and looking at trends • Computationally simple | • Restrictive assumptions • Type 1 error • Just applicable to linear analysis          | [65], [66], [67], [47], [57], [52], [58], [59], [53], [68], [54],   |
| Method                        | Continuous observations | Observations should be identical (e.g., no age, gender difference) | Easy to apply and learn | Gives higher weights to recent observations | Not repeated in studies | Higher error rates than classical time series and mixed regression | Does not show trends | Not accurate for very small and very large windows of time |
|-------------------------------|-------------------------|---------------------------------------------------------------|------------------------|-----------------------------------------------|-------------------------|---------------------------------------------------------------|---------------------|-------------------------------------------------------------|
| A first-order exponential model |                         |                                                              |                        |                                               |                         |                                                               |                     |                                                             |

### Descriptive, time-dependent output

| Method                        | Stationary observations (constant mean values of series) | Advantageous for analyzing time-based trends | Does not require independence of data points | Used in the literature to analyze cardiovascular disease | Includes linear and nonlinear analysis | Requires stationary datasets |                         |                                               |
|-------------------------------|----------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------------------------------|----------------------------------------|----------------------------|-------------------------|------------------------|
| Classical time series analysis |                                                           |                                               |                                               |                                                         |                                       | [69], [33], [80], [70] |                         |                                               |

### Predictive, time-independent output

| Method                        | Limited dependencies of the observations (each machine learning algorithm has its assumptions that need to be checked) | Proactive algorithm (can be used for action-reaction type of datasets) | Powerful predictive method | Rapid analysis prediction, and processing, Simplifies time-intensive | Can over fit-under fit data | Cannot be applied to datasets with highly dependent variables | The process has little rational explanation |                                               |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|---------------------------|-------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------|---------------------------------------------|------------------------|
| Machine learning methods      |                                                                                                                             |                                                                        |                           |                                                                   |                             |                                                              |                                                             |                                               |

![Preprint](https://preprints.jmir.org/preprint/16654) [unpublished, non-peer-reviewed preprint]
| Fluctuation-dissipation theory | Computations | Predictive, time-dependent output |
|-------------------------------|--------------|---------------------------------|
| • Equilibrium system (the system and observations are not changing) | • Powerful predictive capability, • Does not have restrictive assumptions such as normality of residuals • Significantly less data needed compared to general data fitting approach | • Computationally intense • Time-consuming |
| [91], [70], [111] |

| Time-variant modeling | Computations | Predictive, time-dependent output |
|-----------------------|--------------|---------------------------------|
| • Requires big datasets with high-frequency data points (more than 60 HZ) | • Can be used to describe data as well as forecasting the future | • Computationally intense • Slow process |
| [33], [112], [94], [113], [98], [114], [96], [115], [116], [93] |

| Nonlinear dynamic modeling | Computations | Predictive, time-dependent output |
|---------------------------|--------------|---------------------------------|
| • Invertible matrices | • Very accurate • Replicated multiple times in studies | • Computationally intense • Slow process • Requires invertible matrices that is not always feasible in naturalistic settings |
| [66], [33], [113], [117], [98], [96], [112], [118], [116], [104], [119], [120], [121] |

**Fit assessment**

Fit assessment can be conducted to examine the efficiency of each method in modeling a specific dataset. Fit assessment is especially promising for comparing different methods if they are applied to the same dataset. However, considering the wide range of applicable fit indices, researchers might
struggle comparing them. In the category of descriptive models, $R^2$ and adjusted $R^2$ are the main indices of fit assessment. $R^2$ indicates the degree of variation in the dependent variable caused by the independent variable(s). Adjusted $R^2$ is a revised version of $R^2$ that accounts for the number of independent variables in a model [122]. Generally, adjusted $R^2$ is more promising than $R^2$ as it is more robust to overfitting [122]. In the prediction methods category, a variety of measures other than $R^2$ and adjusted $R^2$ were used to assess quality of fit. Some of these measures include sensitivity, specificity, accuracy, and Area Under the Receiver Operating Characteristics Curve (AUC)-ROC. Sensitivity is the number of true positives divided by the total number of observations and specificity is the number of true negatives divided by the total number of observations [123]. Accuracy is the number of true predictions divided by total number of predictions. Error rate is 1 minus accuracy or the number of wrong detections divided by the total number of observations [124]. Finally, AUC-ROC is a curve that plots true positive rate (Y axis) vs false positive rate (X axis) to measure the performance of the model. It is important to bear in mind that fit indices are data dependent; therefore, comparisons are best made by fitting multiple models to the same dataset.

In statistical analysis of data in the PTSD domain, fit assessments have been used to show the efficiency of results. For instance, McDonald et al. [11] used ROC curves along with accuracy to show that random forest works better than other machine learning methods to predict hyperarousal moments in people with PTSD. Shalev et al. [125] used sensitivity and specificity to predict development of PTSD based on their instant responses to trauma. Bartels et al. [63] applied adjusted $R^2$ to assess the goodness of fit for their proposed exponential model. Examples of fit adjustments are summarized in Table 6.

Table 6: Examples of fit assessment for different methods used in studies

| Study                      | Method                  | Variables                                                                 | Fit measure                                      |
|----------------------------|-------------------------|---------------------------------------------------------------------------|--------------------------------------------------|
| Strath et al. (2000) [65]  | ANOVA                   | Heart rate, oxygen intake, age, fitness                                    | $R^2=0.87$                                       |
| Zakeri et al. (2012) [80]  | Classical time series   | Heart rate, energy expenditure, accelerometer, age                        | $R^2=0.84$                                       |
| McDonald et al. (2019) [11]| Machine learning        | Heart rate, subjective stress moments                                      | AUC (area under receiver operating characteristics curve) = 0.67 |
| Healey et al. (2005) [86]  | Machine learning        | Heart rate, HRV, skin conductance, muscle activity, muscle tension, breathing rate | Accuracy=97%                                       |
| Chen et al. (2013) [91]    | Fluctuation dissipation theory | Hear rate recovery, blood pressure, instantaneous heart rate            | Error rate= 25%                                |
| Chen et al. (2016) [66]    | Nonlinear dynamic       | Resting HR, ABP (Arterial Blood Pressure), heart rate, heart rate variability | Sensitivity: 0.941 Predictability: 0.988          |

Methodological considerations for heart rate assessments

The models identified in this review represent several promising directions for future exploration, but they also illustrate a hidden complexity in the use of HR data as model input. HR is impacted by individual characteristics including age, sex, health, resting HR, respiration, and lifestyle [24]. Maximum HR typically decreases with age. Females have higher HR levels than men [126]. Athletes have lower HRs levels than sedentary people [127]. Resting HR is lower in more active
people, and lower resting heart rates result in lower HR levels [128]. Since the respiratory system affects heart activity, studies suggest that incorporating respiration as a factor in HR models improves HR estimation significantly [78]. Lifestyle such as smoking habits affect heart rate as well; people who smoke have higher heart rate than non-smokers [129].

Beyond these general characteristics, it is important to consider the type of physical activity in the analysis. Physical activity significantly affects HR [130], where high-intensity activities such as running and cycling affect HR differently from low intense activities such as sitting and lying down [99]. Concerns regarding activity were common in the reviewed studies, particularly in energy expenditure domain [131]. Green et al. [131] suggest that body acceleration is a reliable indicator of physical activity and should be included in all analyses as a covariate or constraint. While activity is directly related to energy expenditure outcomes, it is also relevant for studies investigating stress. While some of the reviewed studies on stress included body acceleration in their analysis [100], many neglected this factor [46,132].

Heart rate assessments in anxiety domains

Heart rate data has been widely investigated in the domain of physical activity and energy expenditure. Although there are some differences between the effects of mental stress on HR and the effects of physical activity on HR, there are many similarities that make these domains connected. Physical activity affects SNS performance in the short term and PNS performance in the long term [133]. As a result, heart rate elevates during physical activities (due to SNS activation), and resting heart rate is lower in athletes who have higher rates of physical activity (because of PNS performance) [133].

Similarly, in terms of mental stress, while acute stress or immediate response to stressors activates SNS, chronic stress increases the vagal and parasympathetic activity [134]. These similarities enable researchers in mental stress domains to employ models and pathways that are extracted in physical activity domains. For instance, one main measure that is used broadly to examine energy expenditure is heart rate recovery (HRR). This measure is an accepted indicator of SNS deactivations and PNS activation. Recovering from acute stress and arousability is also associated with withdrawal of SNS and activation of PNS. As a result, HRR can be a proper measure to be considered in studies that examine acute stress.

Limitations

This scoping review attempted to include all articles that analyzed heart rate; however, it is still likely that some were overlooked. Further, the authors categorized the heart rate models based on their own synthesis of literature and relevance to PTSD. These models can be listed and categorized in a variety of ways such as deterministic vs. stochastic.

Another limitation in this review is that while the identified models have been applied across various domains (e.g., energy expenditure, general stress prediction), to our knowledge only two papers [11,57] directly applied these methods to data from patients diagnosed with PTSD. In particular, only one study [11] used a predictive approach in the PTSD domain. Other studies were primarily limited to linear descriptive statistics such as the t-test or ANOVA [60,65–67]. These methods are valid for making inferences about PTSD and comparing its effects on HR among different groups. However, there is a need for additional studies in this area that explore a broader set of predictive models and other factors (e.g., activity level) that have not been analyzed with descriptive models.

Beyond the specific application of these models to PTSD, there are several more general challenges.
The reviewed research often proceeded independently with few links between the various studies. This diversity makes comparison across studies difficult. Studies have used different datasets with different variables based on individual goals. Further, the reviewed work often focused on testing one specific model rather than a broad comparison. Often critical details, such as the model and parameter selection process, were not reported in the articles. Another critical detail often not addressed in the reviewed studies was the mismatch between the model requirements and the sampling rates, which may result in conditions such as overfitting [135].

Collectively these limits suggest a need for substantial additional work in modeling the relationship between HR and PTSD. Future studies should consider comparisons between several models, analyze or explicitly discuss decisions made throughout the modeling process, and comprehensively document their HR data collection. As future studies are conducted that enact these criteria, the utility of the modeling approaches identified here will become clearer, and the path to more effective PTSD treatments will become more attainable.

Conclusions

The goals of this review were to identify and characterize quantitative heart rate models for relevant applications in PTSD. One of the gaps in this area is the absence of a framework that researchers can use before, during, and after their data collection to choose a method to analyze heart rate data. In this regard, we developed a descriptive framework that can be used to determine the method to apply to heart rate data in order to achieve more efficient results. We identified four broad categories of methods: descriptive time-independent output, descriptive time-dependent output, predictive time-independent output, and predictive time-dependent output. Descriptive time-independent output models include ANOVA and first-order exponential while descriptive time-dependent output includes classical time series analysis and mixed regression. Predictive time-independent output includes machine learning methods and analyzing heart rate-based fluctuation-dissipation theory. Finally, predictive time-independent output includes time variant method and nonlinear dynamic modeling.

All of the identified modeling categories have relevance for PTSD, although modeling selection is highly dependent on the specific goals of the modeler. For instance, one might use ANOVA to look at the differences in resting heart rate in individuals with PTSD vs without PTSD [54].

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Conflicts of Interest

None declared.

Abbreviations

ANOVA: Analysis of Variance
ANS: Autonomic Nervous System
(AUC)-ROC: Area Under the Receiver Operating Characteristics Curve
COH: Coherence Score
FDT: Fluctuation-dissipation Theory
HF: High Frequency
HR: Heart Rate
HRV: Heart Rate Variability
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