International Journal of Psychophysiology 185 (2023) 27–49

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Heart and brain traumatic stress biomarker analysis with and without machine learning: A scoping review

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ARTICLE INFO

Keywords:
Electroencephalogram (EEG)
Electrocardiogram (ECG)
Heart rate variability (HRV)
Heartbeat evoked potential (HEP)
Machine learning (ML)
Biomarker

ABSTRACT

The enigma of post-traumatic stress disorder (PTSD) is embedded in a complex array of physiological responses to stressful situations that result in disruptions in arousal and cognitions that characterise the psychological disorder. Deciphering these physiological patterns is complex, which has seen the use of machine learning (ML) grow in popularity. However, it is unclear to what extent ML has been used with physiological data, specifically, the electroencephalogram (EEG) and electrocardiogram (ECG) to further understand the physiological responses associated with PTSD. To better understand the use of EEG and ECG biomarkers, with and without ML, a scoping review was undertaken. A total of 124 papers based on adult samples were identified comprising 19 ML studies involving EEG and ECG. A further 21 studies using EEG data, and 84 studies employing ECG meeting all other criteria but not employing ML were included for comparison. Identified studies indicate classical ML methodologies currently dominate EEG and ECG biomarkers research, with derived biomarkers holding clinically relevant diagnostic implications for PTSD. Discussion of the emerging trends, algorithms used and their success is provided, along with areas for future research.

1. Introduction

Post-traumatic stress disorder (PTSD) is a multi-causal and multimodal disorder (Galatzer-levy and Bryant, 2013; Schauer and Elbert, 2010) that has complex effects upon the central (Butt et al., 2019) and autonomic (Ge et al., 2020) nervous systems. Use of the electroencephalogram (EEG) and electrocardiograph (ECG) has helped to highlight potential biomarkers (Lobo et al., 2015; Pyne et al., 2016; Thome et al., 2017; Tursich et al., 2015) for PTSD such as increased alpha frequency in the right parietal lobe (Metzger et al., 2004; Wahbeh and Oken, 2013) and low heart-rate variability (Jin et al., 2018; Kim et al., 2018). Biomarker identification is important to the conceptualisation of mental health conditions and is a critical element in personalised psychiatry, allowing individualised treatment (Arns et al., 2022). Generation of both the EEG and ECG involves complex non-linear phenomena (Goldberger, 1991; Lehrer and Eddie, 2013; Yang and Tsai, 2013) that are difficult to characterise (Arns et al., 2009; McCraty and Tomasino, 2009) using conventional analytic techniques (Kim et al., 2020). Machine learning (ML) is a useful tool for detecting patterns in complex datasets and using these features to build predictive models for specific health conditions (Bzdok and Meyer-Lindenberg, 2018; Khondoker et al., 2016). The application of ML methodologies to identify biomarkers in complex psychophysiological data and to use these biomarkers to classify psychological disorders has had mixed success (Cho et al., 2019; Ramos-lima et al., 2020). However, using ML biomarker analysis to make reliable treatment decisions is promising; with examples including antidepressant response in major depression disorder (Wu et al., 2020) and transcranial magnetic stimulation prediction in PTSD (Zandvakili et al., 2020).

A recent review by Ramos-Lima et al. (2020) provides a good overview of applications of ML for PTSD (Ramos-lima et al., 2020). However, the articles they identified tended to use psychometrics and demographics as training data (e.g., Augsburger and Elbert, 2017; Conrad et al., 2017; He et al., 2017; Gradus et al., 2017; Leightley et al., 2019; Rosellini et al., 2018), with only eight neuroimaging biomarker studies identified (Cisler et al., 2015; C. Jin et al., 2017; Li et al., 2016; Nicholson et al., 2018; Posner et al., 2009; Wang et al., 2016; Yuan et al., 2018; Zandvakili et al., 2020), none of which used resting-state ECG or EEG data. A focus on EEG and ECG data is important for the characterization of mental health conditions as these modalities have the

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https://doi.org/10.1016/j.ijpsycho.2023.01.009
Received 14 June 2022; Received in revised form 22 January 2023; Accepted 25 January 2023
Available online 30 January 2023

highest temporal accuracy and consequentially are thought to better capture moment-to-moment processes characterising thought (Jain and Ramakrishnan, 2020; Meyer, 2015). Additionally, in excluding engineering journals that typically published ML research and only searching for limited types of ML algorithm terms they may have missed some important studies. This limitation is noteworthy given rapid developments in the ML arena (Dhall et al., 2019; Du et al., 2020; Vargas et al., 2017). Moreover, the more restrictive approach associated with a systematic review methodology may have excluded recently developed techniques and analysis trends. To address these issues, a scoping review of ML in PTSD is required. Given the limited number of biomarker studies identified in Ramos-Lima and colleagues' review (Ramos-lima et al., 2020), the current scoping review focuses on ML analysis of resting-state EEG and ECG in PTSD research, as prior research indicates both central and autonomic changes may differentiate individuals diagnosed with the disorder (Thome et al., 2017; Toll et al., 2020; Wahbeh and Oken, 2013).

The objective of this scoping review is to identify research gaps in current PTSD ML research conducted using resting-state EEG and ECG metrics. To assist in identifying research gaps in PTSD literature using ML, studies meeting all criteria except for using ML were also included. The inclusion of such statistically based research enabled a comparative evaluation of the ML literature to be undertaken. Additionally, there is no definitive definition of ML, with some analyses, such as regression considered ML by the European Union (European Commission, 2021), while some researchers consider regression as a statistical method (Sadeghi et al., 2020a, 2020b). Inclusion of these statistical studies accommodates this definitional uncertainty and provides a more comprehensive representation of current research. Two specific questions were addressed; 1) which EEG and ECG metrics have been used in conjunction with which ML approaches and to what success? 2) are there any specific ML methodologies and features emerging from this research that should inform future research? A scoping review is the most appropriate review methodology to answer the ML questions (Munn et al., 2018) as evidence in this area is still emerging and needs to be identified, key concepts and terms are diverse and unclearly defined, varying ML methodologies and input data have been used, and it is not clear where current gaps in the literature stand and what key factors have already emerged.

2. Methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension for scoping reviews (Arksey and O'Malley, 2005), was adopted in conjunction with additional scoping review recommendations (Munn et al., 2018; Pham et al., 2014) and recommended reported items from Ramos-lima et al. (2020) framework. Additional ML-specific reporting items were captured by drawing upon Roy et al. (2019) systematic review of deep learning methodologies. Duplicate articles were removed using reference management software. Screening assessment was based on title and abstract, without blinding the author and journal. For instances where an abstract was not available, the full article was included for later assessment. Conflicts and uncertainties were discussed and resolved between authors through the scoping review process. Articles that met all other criteria besides the use of ML were retained and tabulated separately from the main review.

The initial search was conducted on 28 August 2020 in seven electronic databases: Medline/PubMed, SciVerse Scopus/Elsevier, Current Contents Connect/Web of Science, Cochrane Library, Embase, Institute of Electrical and Electronic Engineers (IEEE) Xplore and Google Scholar. Search dates restricted articles to publication between 1960 and the date of the initial search. To ensure any recent research was included, a follow-up search for articles published between 2020 and 14 January 2022 was conducted. All search results identified were reviewed. The titles of eligible articles were subjected to additional searches and were entered into Google Scholar, connectedpapers.com and PubMed PubReMiner to explore related articles and articles citing the eligible paper, with all results assessed using the identification and screening step criteria used initially. For all articles identified for screening, a "snowball" technique was used, searching reference lists of the identified and any subsequent newly identified articles for further applicable references. The reference lists of review articles and articles from other sources identified through snowballing or additional search processes were also screened for relevant articles. Supplementary material and in-article keyword searches were conducted for instances of missing information. When these approaches failed to answer relevant questions, corresponding authors were contacted to provide clarification.

2.1. Search terms

Building upon the search terms used by Ramos-lima et al. (2020) three searches linked by common terms for PTSD and ML, with a varying third term relating to EEG, ECG or HEP metrics were conducted. The specific combination of terms used is summarised below.

(PTSD, OR Stress Disorder, OR Post Traumatic, OR Neuroses, Post-traumatic, OR Posttraumatic Neuroses, OR Posttraumatic Stress Disorder, OR Post-Traumatic Stress Disorder, OR Post Traumatic Stress Disorder, OR Stress Disorder, Post-Traumatic) AND (Machine learning, OR AI, OR Artificial Intelligence, OR ML, OR Deep learning, OR supervised machine learning, OR Semi-supervised Learning, OR Semi supervised Learning, OR Unsupervised Machine Learning, OR Algorithm, OR Support Vector Machine) AND (Electroencephalography, OR EEG, OR Electroencephalogram, OR Electroencephalograms, OR electroencephalograph, OR Brain waves, OR Electroencephalographic OR Quantitative Electroencephalograph, OR Electroencephalographic, OR Quantitative Electroencephalogram, OR QEEG) AND (Electrocardiography, OR ECG, OR EKG, OR Electrocardiogram, OR Electrocardiograms, OR Electrocardiograph, OR heart rate variability, OR HRV, OR Heart Variability OR Heart Period Variability OR Instantaneous Heart Rate OR RR interval OR RR Variability OR RR interval variability OR IBI OR Inter Beat Interval) AND (Heartbeat Evoked Potential, OR Heartbeat-Evoked Potential, OR Heart beat evoked potential, OR Neural responses to heartbeats, OR Heartbeat-evoked brain potential, OR Heartbeat evoked brain potential, OR Heartbeat related Potential).

2.2. Inclusion criteria

Primary eligibility criteria included publication in the English language. The target population were adults (over 18 years of age), who are experiencing PTSD and had been diagnosed with PTSD according to the Diagnostic and Statistical Manual of Mental Health Disorders (DSM) criteria from the fourth and fifth editions (American Psychiatric Association, 2000, 2013). Resting-state EEG research using empirical metrics such as frequency, power/amplitude, asymmetry, coherence and evaluative frameworks such as vigilance state (Arns et al., 2011) or endophenotype classification (Johnstone et al., 2005) were included. ECG resting-state metrics such as average heart rate, time, frequency and non-linear HRV metrics (Shaffer and Ginsberg, 2017) and evaluative terms such as vagal tone, sympathovagal balance (Porges, 1995, 2009) and autonomic regulation (Beauchaine and Thayer, 2015; Thayer and Lane, 2000) were included. The combined ECG-EEG metric heartbeat evoked potential (HEP), which is also called an evoked response was also included (Gentsch et al., 2019; Park et al., 2018).

2.3. Exclusion criteria

Developmental/paediatric trauma studies were excluded as the physiological underpinnings of the disorder are thought to differ based on the developmental stage impacted by trauma exposure (Teicher et al., 2014; Teicher et al., 2016). Additional exclusion criteria comprised studies that included a) epileptiform activity, b) participants with acquired health conditions such as traumatic brain injury, stroke,

myocardial infarct, myocarditis or similar conditions; c) non-human studies; and d) research identifying medication side effects were excluded. Task-dependent EEG and ECG metrics such as auditory oddball ERP studies (Shim et al., 2019) or emotional word or face reactivity and recovery metrics (Iffland et al., 2020) were excluded.

3. Results

The search identified 26,146 articles which were reduced to 24,462 articles after the removal of duplicates. Screening for publications in the English language and review of title and abstract against inclusion and exclusion criteria narrowed the focus to 656 articles selected for further screening. No articles were included for further screening because of a missing abstract. The PRISMA flowchart detailing the search process is presented in Fig. 1 and the final sample included 124 papers. The breakdown of these papers included 19 ML studies involving EEG and ECG and 21 EEG studies and 84 ECG studies that met all other criteria besides the use of ML.

3.1. Data items

Across the identified ML studies, missing information was most apparent for outcome measures, with positive and negative predictive values being the most underreported (Dean et al., 2020; Galatzer-levy et al., 2014; Galatzer-Levy et al., 2017; Grisanzio et al., 2018; Karstoft et al., 2015; Kim et al., 2020; Kleim et al., 2007; McDonald et al., 2019; Morris et al., 2020; Park et al., 2021; Sadeghi et al., 2020a, 2020b; Schultebraucks et al., 2020, 2021; Shim et al., 2021; Toll et al., 2020). Reporting of sensitivity and specificity values was also poor in ML studies (Cakmak et al., 2021; Galatzer-levy et al., 2014; Grisanzio et al., 2018; Karstoft et al., 2015; McDonald et al., 2019; Morris et al., 2020; Sadeghi et al., 2020a, 2020b; Schultebraucks et al., 2021). Sadeghi et al. (2020a, 2020b) did not report any outcome metrics at all. Missing data and performance metrics can serve as a proxy for the reliability of ML predictions. Studies that provide this information may achieve better performance and may be of higher quality.

All the ML studies relied upon unblinded outcome measures such as clinical interviews, self-reports or medical records. Most studies adequately described the demographics, trauma exposure and screening methodologies but these details were incomplete in three publications (Reinertsen et al., 2017; Sadeghi et al., 2020a, 2020b; Shim et al., 2021). Comparison to healthy control samples were documented in eight publications (Dean et al., 2020; Grisanzio et al., 2018; Kim et al., 2020; Park et al., 2021; Reinertsen et al., 2017; Shim et al., 2021; Toll et al., 2020; Zhang et al., 2021). Alternative control samples included comparisons with other psychiatric disorders (Park et al., 2021; Zhang et al., 2021) and sub-clinical PTSD (Toll et al., 2020) and comparison to a treatment group (Schultebraucks et al., 2021). Publications without controls longitudinally tracked patients to build models predictive of PTSD status from baseline biomarkers and psychometrics (Cakmak et al., 2021; Galatzer-levy et al., 2014; Galatzer-Levy et al., 2017; Karstoft et al., 2015; Kleim et al., 2007; McDonald et al., 2019; Morris et al., 2020; Papini et al., 2018; Sadeghi et al., 2020a, 2020b; Schultebraucks et al., 2020). A minority of the identified ML studies reported diverse and representative samples in terms of gender, age, ethnicity and sample size (Cakmak et al., 2021; Dean et al., 2020; Galatzer-levy et al., 2014; Grisanzio et al., 2018; Karstoft et al., 2015; Sadeghi et al., 2020a, 2020b; Shim et al., 2021; Zhang et al., 2021). In the remainder of the studies, there was some attempt to mitigate any sample imbalances with consideration and methodological accommodation of confounding variables, see Table 1 for more details. In three studies details of feature selection and class imbalance minimisation methods were not provided (Dean et al., 2020; Karstoft et al., 2015; Sadeghi et al., 2020a, 2020b). Inclusion of diverse participants and trauma presentations, with equal sampling or use of adequate covariates, improves the generalisability and robustness of results.

Electrophysiological recording parameters influence qualitative and quantitative aspects of the data being collected, which can alter signal quality and interpretability. Provision of these details is also critical for future research to replicate findings. Studies focusing on heart rate (Table 2) frequently lacked details concerning collection parameters such as the number of channels, placements, posture, recording

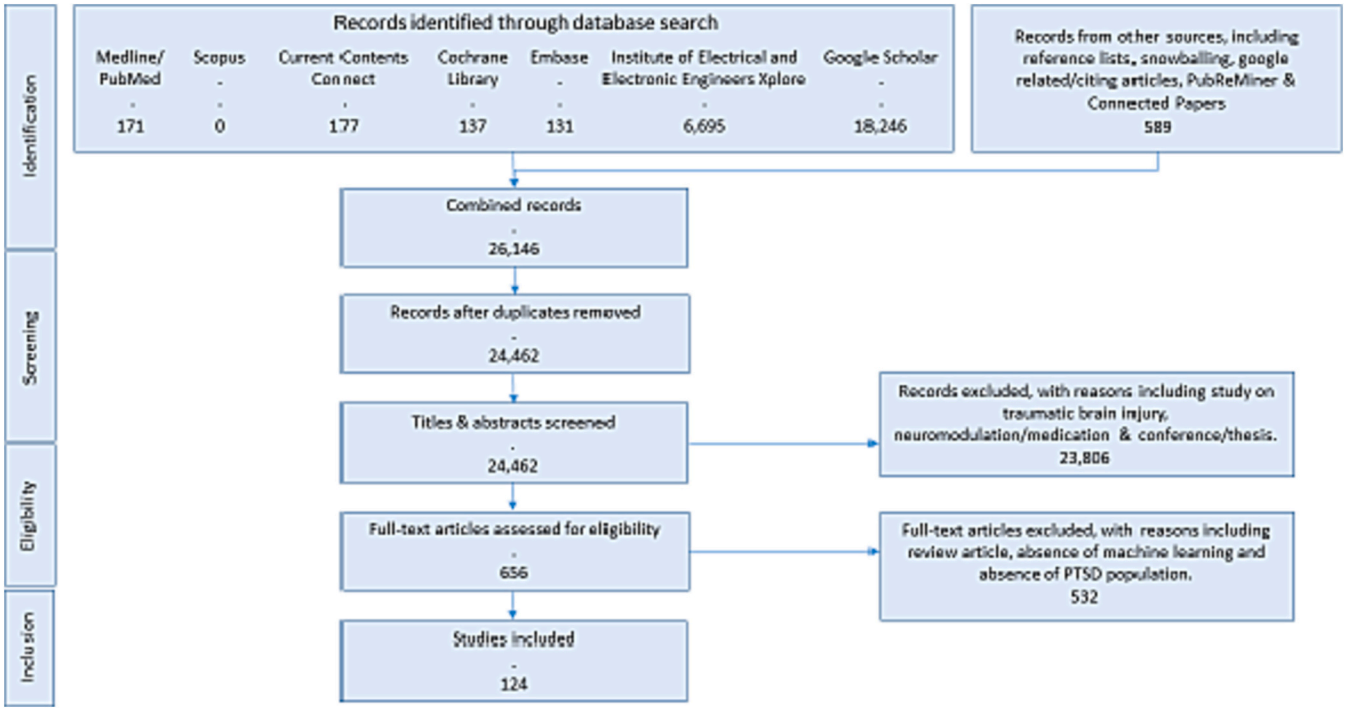

Fig. 1. PRISMA flow diagram
Note. Records from other sources were identified during full-text screening or eligibility levels.

Table 1
ML EEG and ECG study population characteristics.

Publication	Sample Size	Age	Gender Balance	Trauma exposure	Trauma severity assessment	Dissociative symptoms	Potential confounds and use of covariates.
Cakmak et al. (2021).	N = 1618	35 ± 13. PTSD = 30.7 ± 9.2.	Total = 1618, Female = 1037 (61.4 %). PTSD = 565, Female = 409 (25.3 %).	MVA, physical assault, sexual assault, fall, or mass casualty incidents	PCL-5, PDI, MCEPS & PSQIA-PanicSleep	No	Sample from hospital admissions, significant gender and age differences between groups.
Dean et al. (2020).	N = 281	Training data PTSD = 32.8 ± 7.4, HC = 32.6 ± 8.0. Cohort 3 Validation data PTSD = 36.6 ± 8.9, HC = 33.0 ± 8.2.	100 % male	Combat exposed veterans	SCID-IV & CAPS	No	Multiple diagnoses, substance (alcohol, tobacco) and medication use.
Galatzer-levy et al. (2014)	N = 957	36.29 ± 6.31	Male = 491 (51.1 %).	MVA 84.1 %, terrorist attack 9.4 %, work accidents 4.4 % and other 2.2 %.	PSS-I, ASDS, K6, CGI, PTCI & unvalidated coping efficiency screening instrument	No	Sample from hospital admissions, rural participants excluded, language fluency.
Galatzer-Levy et al. (2017)	N = 152	31.2 ± 10.9	59.12 % Male	MVA 125, terror attack 19, work accidents 11	SCID-IV, CAPS-V, GAF, IES-R, BDI, PDEQ & THQ	Yes	Prior childhood trauma in 19.4 % of PTSD and 30.6 % of no-PTSD groups. Traumatic events experienced by 38.7 % of PTSD and 15.3 % of no-PTSD groups.
Grisanzio et al. (2018).	N = 420 (PTSD 47, MDD 100, PD 53, HC 220)	39.8 ± 14.1	Female = 256 (61 %)	MVA 50 %, Assault 50 %.	MINI, HAM—D, CAPS, SCID-IV and CIDI, DASS-21 & IntegNeuro, BRRI	No	Comorbid MDD (14 %), GAD (9 %). No stratification by age or gender, or symptom-defined sub-groups. Average age post-exposure 65 ± 64 months
Karstoft et al. (2015)	N = 957	36.29 ± 6.31	Male = 491 (51 %)	MVA 84.1 %, terrorist attack 9.4 %, work accidents 4.4 % and other 2.2 %.	PSS-I, ASDS, K6, CGI, PTCI & unvalidated coping efficiency screening instrument	No	Sample from hospital admissions. Excluded rural participants & non-fluent.
Kim et al. (2020).	N = 81 (PTSD 42, HC 39)	PTSD 40.12 ± 11.07, HC 41.15 ± 12.31	PTSD, Male = 5, Females = 37. HC, Male = 8, Female = 31.	–	SCID-5, CAPS, PCL-5	No	Education level and medication effects.
Kleim et al. (2007).	N = 222, reducing to 205 at follow-up.	35 ± 11.5	68 % Male	Assault survivors	SCID-IV, ASDS, Family history, CSS, PLT, SDQ, PCI-Cognitive predictors, PCI-Negative Thoughts about the Self subscales, AMQ, MDS, & RIQ.	Yes	PTSD group reported less drug and alcohol consumption than the non-PTSD group.
McDonald et al. (2019).	N = 100	47.3 ± 11.0	100 % Male	combat veterans	Clinical diagnosis with symptoms in the last 30 days	No	Differences in battery life, device use and sensitivity and tolerance of PTSD triggers. Missing data due to exercise.
Morris et al. (2020).	N = 58	PTSD 25.0 ± 2, No PTSD 23.7 ± 3.4	100 % Female	Interpersonal violence	SCID-5, CTQ, PTCI & PDEQ	Yes	Time since traumatic event(s), contraceptive use and prior risk factors
Park et al. (2021).	N = 141 (PTSD 52, HC 95)	PTSD 42.72 ± 13.0, HC 25.72 ± 4.55	PTSD = 52, Female = 38 (73.1 %). HC = 95, Male = 60 (63.2 %)	–	MINI, DSM-4 or DSM-5 criteria	No	Sample from hospital admissions, significant gender and age differences between groups. Symptom stability over 8 weeks
Papini et al. (2018).	N = 505, reducing to 271 at follow-up. PTSD at 3 months n = 110.	Total 46.73 ± 17.35, PTSD 38.69 ± 13.66	Male = 173 (64 %). PTSD at follow-up male = 56 (67 %)	Fall = 76, MVA = 88, TBI 68, penetrating wound 31, orthopedic injury 149	PC-PTSD-IV, Yes/No responses to symptoms (Hanley & Brasel, 2013). PHQ-8, Veterans RAND 12-item Health Survey,	Numbing and detachment	Traumatic brain injury. Demographic, socioeconomic and other confounds addressed.

(*continued on next page*)

Table 1 (*continued*)

Publication	Sample Size	Age	Gender Balance	Trauma exposure	Trauma severity assessment	Dissociative symptoms	Potential confounds and use of covariates.
					SPS, CDRS, AUDIT-Consumption & Pain scales.		
Reinertsen et al. (2017).	N = 50 (PTSD 24, HC 26)	–	100 % Male	Combat exposure	SCID	No	Artifacting & cycle length dependence.
Sadeghi et al. (2020a, 2020b).	N = 99	–	–	Combat veterans	–	–	movement artifacts
Schultebraucks et al. (2020).	N = 377 (training), N = 221 (testing)	Training 36.05 ± 12.87, Testing 36.69 ± 13.46	47.1 % female (training), 37.1 % female (testing)	Gunshot 17, MVA 265, fall 14, sexual assault 23, non-sexual assault 26, other 32 (training). Gunshot 2, MVA 125, fall 41, sexual assault 0, non-sexual assault 16, other 36 (testing).	ISRC, PDEQ, PCL-5, Modified PTSD Symptom Scale (mPSS).	Yes	Only included participants with blood samples.
Schultebraucks et al. (2021).	N = 417, reducing to 273 at completion.	46.09 ± 15.88	62.8 % male	Road traffic accidents (62.4 %), falls (16.1 %), work-related accidents (12.0 %) and physical assault (4.2 %).	CAPS-5 & IES-R	No	Excluded rural & non-fluent participants. Differences in age, gender & education.
Shim et al. (2021).	N = 138 (PTSD 77, HC 58)	PTSD 40.92 ± 11.93, HC 39.98 ± 11.63	PTSD = 77, Female 49 (63.6 %). HC =58, Female 28 (48.3 %)	–	DSM-4, IES-R, BDI, BAI	No	Sample derived from hospital admissions.
Toll et al. (2020).	N = 210	30.4 ± 9.0	Male = 16 (44 %)	Combat exposed veterans	CAPS 5 diagnosed and sub-threshold PTSD	No	Collection site & psychometrics used as separate predictors.
Zhang et al. (2021).	N = 201 (PTSD 106, trauma-Exp HC 95). Independent data N = 314 (PTSD 72, MDD 63, No Med 228, Med 179).	PTSD samples 44.1 ± 13.1–47.2 ± 13.9	82.4 % - 84.1 % of PTSD were male	combat veterans	CAPS 4 & 5, PCL-4 & -5, BDI, DASS-21, WHOQOL, QIDS-SR, HAM—D, SHAPS, WASI & MASQ.	Yes	Medication use. Different amplifiers, channel count and montages.

Note. ASDS = Acute Stress Disorder Scale, AUDIT = Alcohol Use Disorder Identification Test, AMQ = Assault Memory Questionnaire, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, BRRI = Brief risk-resilience index, CAPS = Clinician Administered PTSD Scale, CTQ = Childhood Trauma Questionnaire, CGI = Clinical Global Impression, CAPS-V = Clinician-Administered PTSD Scale for DSM-IV, CIDI = composite international diagnostic interview, CDRS = Connor Davidson Resilience Scale, CSS = Crisis Support Scale, DASS-21 = Depression, Anxiety, Stress Scale - 21 item version, ED = Emergency Department, GAD = General Anxiety Disorder, GAF = Global Assessment of Functioning, Exp = exposed, HAM-D = Hamilton rating scale - depression, GAF = Global Assessment of Functioning, HC = healthy controls, ISRC = Immediate stress reaction checklist, IES-R = Impact of Events Scale-Revised, K6 = Kessler-6, MDD = Major Depressive Disorder, MDS = Mental Defeat Scale, MCEPS = Michigan Critical Events Perception Scale, MDD = Major Depression Disorder, MINI = Mini-international neuropsychiatric interview, MASQ = Mood and Anxiety Symptom Questionnaire, Med = Medication, MVA = Motor Vehicle Accident, PCL-5 = PTSD Checklist for DSM-V, PD = Panic Disorder, PDI = Peritraumatic Distress Inventory, PHQ-8 = Patient Health Questionnaire-8, PLT = Perceived life threat, PDEQ = Peritraumatic Dissociative Experience Questionnaire, PSQIA = Pittsburgh Sleep Quality Index Addendum, PC-PTSD-IV = Primary Care Posttraumatic Stress Disorder Screen for DSM-IV, PTCI = Post-traumatic Cognitions Inventory, PSS-I = PTSD Symptom Scale Interviewer, RIQ = Response to Intrusions Questionnaire, RR intervals = reflect the time between each heartbeat, SCID-IV/V = Structured Clinical Interview for DSM 4 = IV/V, SHAPS = Snaith-Hamilton Pleasure Scale, SPS = Social Provisions Scale, SDQ = State Dissociation Questionnaire, QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report, TBI = Traumatic Brain Injury, THQ = Trauma History Questionnaire, WASI = Wechsler Abbreviates Scale of Intelligence, WHOQOL = World Health Organisation Quality of Life, – = unknown information.

duration, sample rate and artifacting techniques (Dean et al., 2020; Galatzer-Levy et al., 2017; Galatzer-levy et al., 2014; Karstoft et al., 2015; Kleim et al., 2007; Papini et al., 2018; Sadeghi et al., 2020a, 2020b; Schultebraucks et al., 2020, 2021). In contrast, only two EEG studies (Table 3) did not report details of epochs used (Toll et al., 2020; Zhang et al., 2021). Details of physiological data recording including electrode numbers and placement, sampling rates and window characteristics, length of recording, recording conditions, signal filtering and artifacting practices were provided in every paper. Linked mastoids was the most common reference used for data analysis (Park et al., 2021; Shim et al., 2021; Zhang et al., 2021), with other references such as common (Kim et al., 2020) and regional averages (Grisanzio et al., 2018), nose (Toll et al., 2020) and linked-ear (Park et al., 2021) or all being used once. Analytic techniques, such as asymmetry (Grisanzio et al., 2018), source localisation (Kim et al., 2020; Toll et al., 2020), frequency ratios (Kim et al., 2020), cross-spectral matrices (Park et al., 2021), component analysis (Kim et al., 2020) and functional connectivity metrics such as coherence/phase locking value (Park et al., 2021; Shim et al., 2021; Toll et al., 2020), power-envelope connectivity (Toll et al., 2020; Zhang et al., 2021) and network strength, clustering coefficient and path length (Shim et al., 2021) were used. To understand data characteristics and ML input metrics, see Table 2 for ECG data and Table 3 for EEG data.

3.2. ML methodologies

All studies included used ML for the classification of PTSD status, supervised approaches were used nearly three times more frequently than unsupervised approaches. Testing was conducted with independent data sets in four studies (Dean et al., 2020; Grisanzio et al., 2018; Schultebraucks et al., 2020; Zhang et al., 2021), 70:30, 80:20 or 90:10 training to testing data splits were used by seven studies (Galatzer-levy et al., 2014; Karstoft et al., 2015; Kim et al., 2020; McDonald et al., 2019; Papini et al., 2018; Reinertsen et al., 2017; Schultebraucks et al.,

Table 2
ML-ECG data characteristics.

Publication	ECG measures	HRV metric	Channels	Site	Posture	Time	Sampling	Artifacting	Missing Data	Access
Cakmak et al., 2021	NN-Average, IQR-RR, Kurtosis-RR, Skewness-RR, Acceleration, Deceleration	SDNN, RMSSD, pNN50, LF, HF, Total power, LF/HF, Sample & Approx' Entropy	1	wrist	Ambulatory	30s/ 48 h	30 Hz	RR > 20 % Δ & RR outside set range removed	–	No
Dean et al., 2020	Average heart rate	–	–	–	–	–	–	–	–	Yes
Galatzer-Levy et al., 2017	Average heart rate	–	–	–	–	–	–	–	Removal if ≥30 % missing, 100-boot-strap replicated in ≥ 30 %	No
Galatzer-Levy et al., 2014	Average heart rate	–	–	–	–	–	–	–	Imputation with non-parametric nearest neighbour	No
Karstoft et al., 2015	Average heart rate	–	–	–	–	–	–	–	Imputation with non-parametric nearest neighbour	No
Kleim et al., 2007	Average heart rate	–	–	Wrist	Seated	3 min	–	–	Bootstrap resampling, with 1000 resamples.	No
McDonald et al., 2019	Average heart rate.	FFT and FFT coefficients, FFT aggregated skew, energy ratio, Change quantiles, Aggregated linear trend.	1	wrist	Ambulatory over 3 to 7 days.	1 min/ 14.58 ± 15 h	10 Hz	Windowing, window labelling, training/testing data	Kalman filter imputation. Excluded corruptions & windows >5 consecutive missing	No
Morris et al., 2020	Average heart rate	–	2	Chest	Ambulatory	20 min	1000 Hz	–	Winsorization, maximum-likelihood estimation, RF proximity imputation	No
Papini et al., 2018	Average heart rate	–	–	–	–	–	–	–	Gradient-boosted decision trees	No
Reinertsen et al., 2017	Phase-rectified signal averaging (quantifies acceleration/ deceleration)	ULF, VLF, LF, HF and total power, IQR, NNN, MNN, PNN, PNN50, RMSSD, SDNN, (RR: mean, median, mode, standard deviation in radians).	1	chest	Holter 24-h, restricted to light walking around campus.	5 or 10 min/ 24 h	512 Hz	0.33 < RR > 1.5 + RR ± 20 % Δ or overall average. RR re-sampled at 3.413 Hz. Parzen window, boxcar sampling. FFT.	Individuals with insufficient ECG data were removed from analyses. Linear spline interpolation for missing values.	No
Sadeghi et al., 2020a, 2020b	Non-linear measures	–	–	wrist	Bike riding	300 s	–	–	–	No
Schultebraucks et al., 2020	Average heart rate	–	–	–	–	–	–	–	> 45 % values missing excluded. Bootstrap aggregation (bagged) tree imputation	Yes
Schultebraucks et al., 2021	Average heart rate	–	–	–	–	–	–	–	Bagged imputation during 5 times 3-fold cross-validation.	No

Note. - = Unknown, Δ = change, ECG = Electrocardiogram, HF is High Frequency, Hz = Hertz, FFT = Fast Fourier Transformation, IQR = inter-quartile-range, LF = Low Frequency, LF/HF = the ratio of low frequency to high-frequency activity, MNN = mean of N-to-N intervals, NN = Normal to Normal heartbeat interval, NNN = Normal N-to-N interval a measure of heart periodicity, PNN = Percentage of N-to-N intervals, PNN50 = percentage of N-to-N intervals that differ from each other by >50 ms, RMSSD = Root Mean Square of Successive Differences between normal heartbeats, RR = QRS complex to QRS complex, SDNN = Standard Deviation between Normal N-to-N differences, ULF = Ultra Low Frequency & VLF = Very Low Frequency.

2021). The remainder of the studies used cross-fold methods (Cakmak et al., 2021; Park et al., 2021; Shim et al., 2021; Toll et al., 2020), bootstrap resampling (Kleim et al., 2007), split-half reliabilities (Galatzer-Levy et al., 2017), or optimism correction (Morris et al., 2020) methods, with no details available for one study (Sadeghi et al., 2020a, 2020b). Hyperparameter selection methods were not available for two studies (Karstoft et al., 2015; Sadeghi et al., 2020a, 2020b). Features based on current PTSD conceptualisations and research were pre-selected by researchers in eight studies (Galatzer-levy et al., 2014; Galatzer-Levy et al., 2017; Grisanzio et al., 2018; Karstoft et al., 2015; Kleim et al., 2007; Sadeghi et al., 2020a, 2020b; Toll et al., 2020; Zhang et al., 2021), with ML based feature identification used in the majority of studies (Cakmak et al., 2021; Dean et al., 2020; Kim et al., 2020; McDonald et al., 2019; Morris et al., 2020; Papini et al., 2018; Park et al., 2021; Reinertsen et al., 2017; Schultebraucks et al., 2020, 2021; Shim et al., 2021). Although, in studies using pre-selected features and those

Table 3
ML-EEG data characteristics.

Publication	EEG measures	Channels	Reference	Time	Epochs	Sampling	Artifacting Methods	Missing Data	Access
Grisanzio et al., (2018).	Averaged regional spectral power in alpha, beta, alpha/beta ratios and frontal asymmetries	32	Regional averages: posterior, frontal, etc.	2 EO, 2 EC	28 × 4 s (2 mins).	500 Hz	3 EOG channels. Activity 3 SD from channel mean power values were mean-replaced. Log transformed alpha power F3-F4 to norm asymmetry.	Individuals with incomplete symptom data were excluded	No
Kim et al. (2020)	4-8 Hz, 8-10 Hz, 10-12 Hz, 8-12 Hz, 12-18 Hz, 12-22 Hz. 18-30 Hz, 12-30 Hz, 30-50 Hz, θ/α/β1/β2/γ/θ + α/α + β1/β1 + β2/β2 + γ/θ + α + β1/α + β1 + β2/β1 + β2 + γ/θ + α + β1 + β2/α + β1 + β2 + γ/θ, θ + α + β1 + β2 + γ	62	Common Average	3 EC	30 × 2 s (> ± 75uV).	1000 Hz	0.1-100 Hz bandpass filter. Impedances under 5 kΩ, Eye movement artifacts removed, (CURRY 7, Semlitsch et al., 1986). 3rd order IIR bandpass filter, with forward-backward 0 phase filtering 1-50 Hz pandpass. Theta/alpha ratio over 1 resulted in epoch exclusion due to drowsiness.	None	No
Park et al. (2021)	Power spectral density and functional connectivity (coherence) in delta, θ, α, β1, β2 & γ	64 down to 19	Mastoids & Linked ear	5 mins EC	60 × 2 s clean epochs	500 Hz - 1000 Hz down to 128 Hz	Bandpass filter between 0.5 Hz −40 Hz,	–	No
Shim et al. (2021)	Frequency band, Phase Locking Value and network strength, clustering coefficient and path length	64	Mastoids	5 EO	4.096 s	1000 Hz	Bandpass filter between 1 and 55 Hz, voltage threshold ±100 uV, eye movements and muscle removed with ICA	–	No
Toll et al. (2020).	Theta-connectivity. Theta 4–7, alpha 8–12, beta 13–30, gamma 31–50 Hz. 74 ROI paired connectivity metrics	64	FCz	3 EO, 3 EC	–	500 Hz	High, low pass = 0, 1000 Hz. Connectivity metrics exceeding median ± 3 times the IQR were excluded.	Non-responses or timed-out responses in behavioral data were excluded.	No
Zhang et al., 2021	Eyes open weighted Beta band and source-space power envelope-based functional connectivity	64 down to 26	Mastoids	3 EO, 3 EC	–	5000 Hz down to 250 Hz	Notch & 0.01 Hz high-pass & voltage filters, correlation thresholding, >20 % bad channels discarded, interpolation, ICA rejection.	multiple imputations via Bayesian regression	No

Note. F3-F4 refers to the 10–20 EEG placement system, α = alpha activity, β1 and β2 = beta activity, γ = gamma activity. θ = theta activity, – = unknown information, EC = eyes closed, EO = eyes open, EOG = electrooculogram, Hz = Hertz, ICA = Independent Component Analysis, IIR = Infinite Impulse Response, ROI = Region of Interest, SD = Standard Deviation, uV = microvolts.

using ML to identify features, ML methodologies were used to reduce the number of features to those most predictive of PTSD status. Raw data was never used, with all ML studies pre-processing data to extract features before ML-based identification of those relevant to PTSD diagnosis. Support Vector Machines (SVM) were the most commonly employed approach appearing in eight studies (Cakmak et al., 2021; Dean et al., 2020; Galatzer-levy et al., 2014; Karstoft et al., 2015; Kim et al., 2020; McDonald et al., 2019; Park et al., 2021; Shim et al., 2021). Other commonly employed algorithms included Random Forrest (RF) (Dean et al., 2020; Kim et al., 2020; McDonald et al., 2019), regression methods (Cakmak et al., 2021; Dean et al., 2020; Galatzer-levy et al., 2014; Kim et al., 2020; Kleim et al., 2007; Park et al., 2021; Reinertsen et al., 2017), clustering algorithms (Grisanzio et al., 2018; Zhang et al., 2021) and latent growth mixture modelling (LGMM) (Galatzer-levy et al., 2014, 2017; Schultebraucks et al., 2020, 2021). Deep learning methods, such as neural networks (NN) were only used in one study (McDonald et al., 2019), while an uncommon approach relying upon a Riemannian geometry-based classifier was used in another (Kim et al., 2020). The performance of ML methodologies is not directly comparable given different assessment parameters, outputs and analysis techniques that make each solution unique. The use of ML is generally advantageous to identify relationships between complex psychophysiological data, without diminishing statistical power from multiple comparisons, which is a limitation of classical statistical methodologies. However, a disadvantage of some ML approaches, such as NN, is reduced interoperability of predictive associations between variables and PTSD status. The more restricted analyses used in statistical research may give greater certainty to ML findings and the identified associations. Full details of all ML approaches, identified biomarkers and their success in predicting PTSD are provided in Table 4 to inform future research.

3.3. ML EEG & ECG biomarkers

The main biomarker associated with PTSD via ML (see Table 4) was elevated average heart rate, which was included in 10 studies (Dean et al., 2020; Galatzer-Levy et al., 2017; Galatzer-levy et al., 2014; Kleim et al., 2007; McDonald et al., 2019; Morris et al., 2020; Papini et al., 2018; Sadeghi et al., 2020a, 2020b; Schultebraucks et al., 2020, 2021), with one study finding no association between HR and PTSD (Karstoft et al., 2015). RR-derived or HRV metrics were associated with PTSD in three studies (Cakmak et al., 2021; McDonald et al., 2019; Reinertsen et al., 2017). EEG studies employing ML largely utilised patterns associated with beta activity (Galatzer-levy et al., 2014; Grisanzio et al., 2018; Park et al., 2021; Zhang et al., 2021). Various functional connectivity changes associated with beta (Kim et al., 2020; Park et al., 2021; Shim et al., 2021; Zhang et al., 2021) and theta activity (Kim et al., 2020; Shim et al., 2021; Toll et al., 2020) were also common. No ML studies examined EEG and heart-derived metrics in conjunction and no studies examining HEPs in PTSD were identified, see Table 4 for full details of ML PTSD biomarkers.

3.4. Statistical EEG and ECG studies

There were 21 EEG and 84 ECG studies that met all criteria but did not utilise ML methodologies, despite using statistical analysis techniques such as regression, which is sometimes considered a form of ML (Dhall et al., 2019; European Commission, 2021; Maulud and Abdulazeez, 2020). The main analysis techniques used in this research were analysis of variance (ANOVA), covariance (ANCOVA) and various forms of regression analysis. In the EEG studies, the main features associated with PTSD were asymmetries (Cowdin et al., 2014; Gordon et al., 2010; Jokić-Begić and Begić, 2003; Kemp et al., 2010; Metzger et al., 2004;

Table 4
Machine learning outcome.

Publication	Features	Clinical Significance	Test Data	Algorithms	Accuracy	Specificity	Sensitivity	PPV	NPV
Cakmak et al. (2021).	RR-IQR	Autonomic dysregulation is associated with PTSD.	5-Fold cross-validation	SVM, LogR, Multilayer perception	AUC = 0.56 ± 0.05 Log.R & SVM	–	–	0.55 ± 0.02	0.53 ± 0.06
Dean et al. (2020).	Average heart rate	Elevated autonomic arousal	2 independent data sets	SVM, SVM with recursive feature elimination, RF, LR, Tree-based boosting, Lasso	AUC = 0.81	0.77	0.85	–	–
Galatzer-levy et al. (2014)	Average heart rate	Elevated autonomic arousal	90 % training, 10 % testing, with 10 × 10 cross-validation	LGMM, Linear/ polynomial SVM, RF, AdaBoost, Kernel Ridge/ Bayesian-Binary Regression	AUC = 0.71	–	–	–	–
Galatzer-Levy et al. (2017)	Average heart rate	Elevated autonomic arousal	Split-half, 5 × 10 fold cross-validation	Nested LGMM algorithms, Linear SVM with recursive feature elimination	AUC = 0.93	0.75	0.70	–	–
Grisanzio et al. (2018).	Averaged frontal power values in resting Beta. Beta power in an emotion task.	Frontal beta power is particularly associated with anhedonia	2 independent data sets	F = 3.84, K-means++ Adjusted rand index 0.79, Seeded K-means 0.8.	–	–	–	–	–
Karstoft et al. (2015)	Average heart rate	No association between HR & PTSD.	90 % training, 10 % testing, with 10 × 10 cross-validation.	SVM	AUC = 0.75	–	–	–	–
Kim et al. (2020).	Full EEG-band source covariance.	Abnormal activity in most frequency bands linked to symptoms.	70 % training, 30 % testing.	Riemannian geometry-based classifier. SVM & RF, LDA	73.09 % ± 2.08 %, AUC = 0.797 ± 0.0141	77.14 ± 2.30	68.72 ± 3.78	–	–
Kleim et al. (2007).	Average heart rate 71.80 ± 12.35 (PTSD), 67.10 ± 10.8 (no PTSD).	Elevated autonomic arousal	Bootstrap resampling	Multivariate LR	$\chi^2 = 47.37$, $p = .000$	0.96	0.57	–	–
McDonald et al. (2019).	Average heart rate. FFT coefficient 0, 1st coefficient of FFT, coefficient 19, the 19th coefficient of the FFT, FFT 26, the 26th coefficient of the FFT, FFT 28, FFT aggregated skew, energy ratio. Change quantiles. Aggregated linear trend.	Elevated autonomic arousal related to triggering events	70 % training, 30 % testing.	DT, SVM, RF, NN and CNN.	SVM AUC, 0.67, RF AUC, 0.66, CNN AUC, 0.63, DT AUC, 0.61, NN AUC 0.60.	–	–	–	–
Morris et al. (2020).	Average heart rate	Elevated autonomic arousal	Optimism correction	Gradient boosting machine	AUC = 0.96	–	–	–	–
Papini et al. (2018).	Average heart rate 95.82 ± 20.59 (PTSD 3-months), 86.14 ± 15.85 (No PTSD 3-months).	Elevated autonomic arousal	10-fold cross-validation, repeated 5 times	Ensemble ML, gradient boosted DT	AUC = 0.85	0.83	0.69	0.65	0.86
Park et al. (2021).	Beta functional connectivity	Fragmented cortical processing & difficulties connecting thoughts	10-fold cross-validation,	SVM, RF, Penalized LR with Elastic Net Penalty	AUC = 95.38 ± 4.09 %	92 ± 10.32 %	95.88 ± 7.1 %	–	–
Reinertsen et al. (2017).	24 h SDrr, IQRrr, LF, SDNN. 5 min quiescent AC, DC, LF, SDNN	Lower vagal tone and deep sleep in PTSD. Low LF power in quiescent sleep may indicate baroreceptor insensitivity and disordered breathing	70 % training, 30 % testing.	L1L2 LR model.	AUC: 24Hrs = 0.67, Random (RDM) = 0.7, Quiescent (QST) = 0.86. Accuracy: 24Hr = 0.73, RDM = 0.73, QST = 0.80	24Hr = 0.94, RDM = 1, QST = 0.94	24Hr = 0.57, RDM = 0.43, QST = 0.71	24Hr = 0.92, RDM = 1.0, QST = 0.94	24Hr = 0.69, RDM = 0.67, QST = 0.79
Sadeghi et al. (2020a, 2020b).	Non-stationarity in heart rate (Average HR and	Alterations in autonomic arousal	–	Autoregressive Integrated	–	–	–	–	–

(*continued on next page*)

Table 4 (*continued*)

Publication	Features	Clinical Significance	Test Data	Algorithms	Accuracy	Specificity	Sensitivity	PPV	NPV
	HR variance is time-dependent)			Moving Average (ARIMA)					
Schultebraucks et al. (2020).	Average heart rate 84.51 ± 17.69 (training), 80.91 ± 15.80 (testing)	Elevated autonomic arousal.	2 Independent samples.	Ensemble ML, utilising 3–4 LGMM algorithms	AUC = 0.84, AUC = 0.83 in testing data.	0.86	–	27 of 164 (0.164)	–
Schultebraucks et al. (2021).	Average heart rate 82.37 ± 17.24 (resilient), 74.06 ± 2.25 (recovery), 91.88 ± (delayed onset), 74.29 ± 13.46 (non-remitting)	Alterations in autonomic arousal	80 % training, 20 % testing	Unconditional LGMM	AUC = 0.83	0.83	1	–	–
Shim et al. (2021).	Source theta and low-beta phase-locking values, nodal strength and clustering coefficients in theta and low-beta	Abnormal limbic-cortical interactions	leave-one-out cross-validation	SVM	70.37 %, AUC = 0.85	67.24 %	72.73 %	–	–
Toll et al. (2020).	74 brain region connections were significantly reduced in PTSD. Underconnectivity of the orbital and anterior middle frontal gyri were most prominent	Cognitive network disruptions (dorsal/ventral attention, frontoparietal control).	leave-one-out cross-validation	Linear mixed-effects	AUC = 0.898.	84.90	80.02	–	–
Zhang et al., 2021	Beta functional connectivity	Fragmented cortical processing & difficulties connecting thoughts	4 independent data sets	Sparse clustering algorithm	91.9 % PTSD, 80.1 % healthy control	–	89.20 %	92.8 % type 1. 89.2 % type 2	7.2 % type 1, 10.8 % type 2.

Note. - = Unknown, AC = alternating current, AUC = Area Under the Curve, CNN = convolutional neural networks, DC = Direct current, DT = decision tree, ER = Emergency Room, FFT = Fast Fourier Transformation, HR = Heart rate, IQR = inter-quartile-range, LF = Low frequency, LGMM = Latent Growth Mixture Modelling, LDA = Linear discriminant analysis, LR = linear regression, NN = neural network, NPV = negative predictive value, PPV = positive predictive value, PTSD = Post Traumatic Stress Disorder, RF = random forest, SDNN = Standard deviation of norm-to-norm intervals, SDrr = Standard deviation of R-R intervals & SVM = support vector machines.

Meyer et al., 2016; Rabe et al., 2006a, Rabe et al., 2006b; Shankman et al., 2008; Veltmeyer et al., 2006; Wahbeh and Oken, 2013), theta power (Chae et al., 2004; Cowdin et al., 2014; Imperatori et al., 2014; Todder et al., 2012; Veltmeyer et al., 2006), alpha power (Jokić-Begić and Begić, 2003; Kemp et al., 2010; Veltmeyer et al., 2006; Wahbeh and Oken, 2013), alterations in sleep-related activity (Cohen et al., 2013; Cowdin et al., 2014; Habukawa et al., 2007; Richards et al., 2013), beta power (Chae et al., 2004; Cohen et al., 2013; Jokić-Begić and Begić, 2003; Veltmeyer et al., 2006), entropy metrics (Begic et al., 2001; Chae et al., 2004; Lee et al., 2014), gamma power (Cohen et al., 2013; Ehlers et al., 2006), total power (Falconer et al., 2008) and coherence (Imperatori et al., 2014). Although, three of 11 asymmetry studies did not reach significance (Gordon et al., 2010; Meyer et al., 2016; Rabe et al., 2006a), nor did the only study looking at total power (Falconer et al., 2008). In the ECG studies, elevated average heart rate was associated with PTSD in 28 studies, uncorrelated in 19 studies and negatively correlated in seven studies. Low HRV was associated with PTSD in 18 studies, with six studies utilising this pattern during nocturnal recordings. Five studies showed PTSD symptom levels to be correlated with both elevated heart rate and low HRV. For one study, the full details could not be obtained of associations between autonomic function and PTSD (Bryant et al., 2008). The details of the associations of all other studies are presented in Tables 5 and 6 to give a more complete representation of current research and greater context to ML studies.

This scoping review explored the use of EEG and ECG biomarkers as predictors of PTSD with a focus on ML methods. A total of 19 studies were identified that met all criteria, six of which focused on EEG metrics, with the remaining 13 focusing on ECG metrics. An additional 21 EEG and 84 ECG studies were identified that met all criteria excluding the use of ML methodologies. Notably, no study was identified that explicitly examined PTSD via Heartbeat evoked potentials.

4. Discussion

One of the key objectives was to identify the types of ML algorithms used in predicting PTSD from biomarkers. The most common ML methods adopted were supervised approaches such as SVM (Cakmak et al., 2021; Dean et al., 2020; Galatzer-levy et al., 2014; Karstoft et al., 2015; McDonald et al., 2019; Shim et al., 2021; Zhang et al., 2021) and regression (Cakmak et al., 2021; Galatzer-levy et al., 2014; Kleim et al., 2007; Reinertsen et al., 2017; Zhang et al., 2021). Unsupervised approaches such as latent growth mixture modelling (Galatzer-levy et al., 2014, 2017; Schultebraucks et al., 2020, 2021), clustering algorithms (Grisanzio et al., 2018; Zhang et al., 2021) and neural networks (McDonald et al., 2019) were less common. Of note, Kim et al., 2020 employed an exotic solution involving a Riemannian geometry-based classifier based on fisher geodesic distance to the mean that might have some advantages in analysing non-linear EEG properties. Overall, supervised approaches were more commonly used than unsupervised methodologies; although there did not appear to be any performance advantage for either. The identification of 19 studies meeting inclusion criteria indicates a growing interest in this field. Consequentially, the current dominance of older ML methodologies and the absence of newer approaches, such as generative adversarial networks and deep neural networks (Dhall et al., 2019; Zhu et al., 2019) might be short-lived. Use of newer approaches is of critical importance because deep neural networks and related algorithms often outperform classical methodologies in a range of contexts, including neuroimaging (Zhu et al., 2019) and may be better suited to handling complex non-linear data due to their ability to detect and flexibly manipulate latent data structures and

Table 5
Statistical EEG studies.

Authors	Statistics	Performance	Measures	Implication
Begic et al., 2001	ANOVA	$p < .05$	Psychometrics and EEG including reduced non-linear dimensional complexity in PTSD patients (Fp1, F8, C4, P4, T3, T4, T5, T6 and O1).	Theta activity may relate to changes in hippocampal volume and beta may relate to hyperexcitability, prolonged wakefulness and attention disturbances.
Chae et al., 2004	ANOVA	$F = 24.6$, d.f. $= 1$, $P < .001$	Lower dimensional complexity at Fp1, F8, C4, P4, T3, T4, T5, T6 & O1	Disturbed information processing
Cowdin et al., 2014	Mixed ANOVA, Fisher's exact test, *t*-Test	$F(1,28) = 4.90$; $p = .035$	Psychometrics and EEG data including increased right hemisphere prefrontal theta power in REM sleep in trauma-resilient but not individuals diagnosed with PTSD	Right prefrontal theta power during REM sleep may be adaptive for memory integration
Ehlers et al., 2006	ANOVA	$F = 8.7$, $P < .004$	Psychometrics and EEG spectral power including elevated gamma (20 Hz - 40 Hz at frontal locations) in PTSD.	Elevated arousal levels and alterations in cortical processing.
Falconer et al., 2008	ANOVA & ANCOVA	$p > .05$	Psychometrics and EEG power.	No association between resting-state EEG power and PTSD
Imperatori et al., 2014	T-Level thresholds	$p < .05$	Psychometrics and EEG including increased theta power (sLORETA bilateral BA7, BA4, BA5, BA40 & BA6) and increased phase lagged synchronisation (Pz-P4).	PTSD is associated with alterations in emotional-memory processing.
Lee et al., 2014	*t*-Test & Pearson correlation	$p < .0006$	Psychometrics and EEG metrics including reduced Dnodal centrality in beta activity (FCz) and gamma (AF4, FC1, FC2, FC4, C1) and Enodal centrality in beta (FC4, C1) and gamma (FC6, C1). Dnodal beta and gamma activity was correlated with depressive symptoms and increased arousal respectively. Enodal beta and gamma activity was correlated with re-experiencing symptoms, increased arousal and severity and frequency of PTSD symptoms.	PTSD symptoms are associated with alterations in functional connectivity.
Metzger et al., 2004	Pearson correlations and hierarchical linear regression	$R^2 = 0.25$, $F(3, 38) = 4.31$, $p = .01$	Psychometrics and EEG metrics including increased right parietal power asymmetry	PTSD arousal and depression symptoms are associated with right parietal power asymmetry.
Meyer et al., 2016	ANOVA	$F(2, 51) = 10.91$, $p < .001$, $\eta_p^2 = 0.30$	Psychometrics and EEG metrics including no correlation of resting frontal asymmetry to PTSD symptoms	No association between resting frontal asymmetry and PTSD
Rabe et al., 2006a	MANOVA & One-Way ANOVA	$F(1, 79) = 7.39$, $p < .01$, $\eta^2 = 0.086$	Psychometrics and EEG metrics including increased right frontal resting frontal power asymmetry, but no association with PTSD	No association between increased resting right frontal asymmetry and PTSD
Rabe et al., 2006b	Pearson product-moment correlations	$r = 0.34$, $p < .001$	Psychometrics and EEG metrics including increased left frontal resting frontal power asymmetry associated with post-traumatic growth	Post-traumatic growth is associated with greater left frontal asymmetry.
Shankman et al., 2008	ANOVA	$F(1, 72) = 5.86$, $p < .05$	Psychometrics and EEG metrics including theta/beta ratio-right hemispheric asymmetry in PTSD. No association between PTSD and frontal alpha asymmetry.	PTSD is not associated with frontal alpha asymmetry but is associated with right elevated frontal theta/beta suggesting different other processes than approach/avoidance are involved
Todder et al., 2012.	Paired *t*-Test	$p < .05$	Psychometrics and EEG metrics including reduced low theta power in the right temporal lobe and lower high theta power over the right and left frontal lobes	PTSD is associated with emotion processing and regulation deficits
Veltmeyer et al., 2006.	ANOVA	$F(1, 167) > 1.28$, $P < .05$	Psychometrics and EEG metrics including lower theta, alpha 1 power, beta power and theta/beta ratios in PTSD. Hemispheric decreases in alpha 2 power and theta/beta ratio in PTSD and increased theta/alpha ratio at frontal/posterior locations in PTSD.	PTSD is associated with alterations in brain activity, with global and regional
Wahbeh and Oken, 2013.	ANOVA, ANCOVA	$F(1, 84) > 4.1$, $p < .05$	Psychometrics and EEG metrics including greater global alpha peak in PTSD. PTSD was associated with greater left and right frontal asymmetry and frontal and posterior asymmetries.	PTSD is associated with increased arousal levels and asymmetries in brain activity.
Gordon et al., 2010	ANOVA	$p > .05$	Psychometrics and EEG frontal asymmetry	No association between resting-state EEG frontal asymmetry and PTSD
Habukawa et al., 2007	Mann-Whitney *U* Test	$p < .05$	Psychometrics and EEG metrics including increased REM interruption, increased wake time after sleep onset, reduced sleep efficiency and slow-wave sleep.	PTSD is associated with impaired memory integration during REM sleep and elevated nocturnal arousal levels.
Jokić-Begić and Begić, 2003	ANOVA	$p < .06$	Psychometrics and EEG metrics including suppressed alpha 1 power over frontal, central and occipital regions (F3, F7, C3, C4, T3, T4, T5, T6, O1, O2) especially in the left hemisphere and increased beta 1 power at frontal and central locations (Fp1, Fp2, F3, F7, F8, T3, T4) with a slight left hemispheric asymmetry.	PTSD is associated with alterations in arousal and emotional-memory processing.
Kemp et al., 2010.	ANOVA & Tukey's pair-wise comparisons	$r = -0.62$, $p = .02$	Psychometrics and EEG metrics including increased right-lateralised frontal alpha power	PTSD is associated with symptom severity and may be related to withdrawal behaviours
Cohen et al., 2013	Independent *t*-Tests, Cohen's d and Spearman's correlations	$p > .05$, $d > 0.37$	Psychometrics and EEG metrics including reduced REM beta and sigma power and increased non-REM gamma power.	PTSD patients have altered information processing during REM sleep.
Richards et al., 2013	ANOVA	$F(3, 821) = 6.79$, $P = .011$	Psychometrics and EEG metrics including reduced delta power during non-REM sleep, especially in males with PTSD	PTSD is associated with impairments in homeostatic sleep processes

Note: ANCOVA = Analysis of Covariance, ANOVA = Analysis of variance, BA = Brodmann Area, Dnodal = Connection strength, Enodal = Communication efficiency, EEG = Electroencephalogram, Hz = Hertz, MANOVA = Multivariate Analysis of Variance, PTSD = Post Traumatic Stress Disorder, REM = Rapid Eye Movement & sLORETA = standardised Low-Resolution Electric Tomography Software.

associations (Emmert-Streib et al., 2020). Whether the use of complex algorithms such as Riemannian geometry-based classification (Kim et al., 2020) and neural networks may more reliably decipher complex physiological patterns than older ML methodologies is an open question for future research.

A further aim of the current review was to determine the accuracy of biomarker-based ML prediction of PTSD. Despite differences in methodology, population characteristics and other aspects of study design that prevent direct comparisons from being made, good performance was seen in most cases, with a surprising degree of commonality in utilised biomarkers. The best-performing EEG study achieved an AUC of 95.38 ± 4.09 % employing a combination of SVM, RF, and penalized linear regression algorithms that found beta coherence as being predictive of PTSD (Park et al., 2021). A similar finding was reported based on four independent, larger and more representative datasets, which were examined with sparse clustering algorithms achieving a 91.9 % accurate prediction of PTSD status from beta power-envelope connectivity (Zhang et al., 2021). The utilisation of two beta connectivity metrics and the validation of one with independent data sets, suggests such metrics might have some generalisability but further research is required here. Within the ECG studies, Morris et al. (2020) found that elevated average heart rate and gradient boosting machines, with multilevel hierarchical linear models, had an accuracy of 96 % in predicting PTSD. Although, some caution may be required as these researchers did not use separate training/testing data and relied upon a small female-only sample (Morris et al., 2020). The combination of nested LGMM algorithms and average heart rate had the second-best performance (AUC = 93 %) of the ECG studies (Galatzer-Levy et al., 2017). Again, the absence of testing and training data (use of split-half and 5 × 10-fold cross-validation) and a male-only Israeli military cohort, may suggest the Galatzer-Levy et al. (2017) study also lacks generalisability. Of the remaining ECG studies that used training and testing data, the best performance (AUC = 0.84) was derived from an ensemble of LGMM algorithms and average heart rate (Schultebraucks et al., 2020). These results show promise for the use of EEG and ECG metrics for the prediction of PTSD status, but highlight the need for large and representative samples to optimise bias-variance trade-offs (Belkin et al., 2019; Sharma et al., 2014). As noted, by Ramos-Lima et al. (2020), unrepresentative trauma sample populations are a persistent issue across ML research into PTSD, which perpetuates misconceptions of the construct.

Understanding what biomarkers had been associated with PTSD was a further objective for this review. In EEG research using ML and statistical methods, PTSD diagnosis was most frequently predicted by local average power and various connectivity metrics. Notably, beta power irregularities were found in four ML studies (Grisanzio et al., 2018; Park et al., 2021; Shim et al., 2021; Zhang et al., 2021) and five statistical studies (Chae et al., 2004; Cohen et al., 2013; Jokić-Begić and Begić, 2003; Shankman et al., 2008; Veltmeyer et al., 2006). Similarly, theta power abnormalities were documented in two ML studies (Shim et al., 2021; Toll et al., 2020) and six statistical studies (Chae et al., 2004; Cowdin et al., 2014; Imperatori et al., 2014; Shankman et al., 2008; Todder et al., 2012; Veltmeyer et al., 2006). EEG connectivity metrics appeared to be more commonly associated with PTSD via ML methods (Kim et al., 2020; Park et al., 2021; Shim et al., 2021; Toll et al., 2020; Zhang et al., 2021) than statistical methods, where there was only one applicable study (Imperatori et al., 2014). A disparity between ML and statistical studies is present regarding EEG asymmetry, which was the most common biomarker associated with PTSD in statistical research but was not relevant in ML studies. Although, four of the 11 statistical EEG asymmetry studies found no associations with PTSD (Gordon et al., 2010; Meyer et al., 2016; Rabe et al., 2006a; Shankman et al., 2008). Reviews into frontal asymmetry and PTSD indicate the relationship between them is inconsistent or state-dependent (Lobo et al., 2015; Meyer et al., 2015), with the measure often impacted by artefactual issues (Allen et al., 2018) and generally of questionable prognostic value (Olbrich and Arns, 2013; Meyer et al., 2015). These issues could potentially explain why only one ML study using resting-state asymmetry was identified (Grisanzio et al., 2018), with ML studies using task-based asymmetry metrics being rejected based on the exclusion criteria used, or not including asymmetry metrics at all. From these results, it appears that power and connectivity metrics have been most successful in predicting PTSD with ML methods. As beta is typically considered a cortical rhythm (Chang et al., 2011) and theta a septohippocampal rhythm (McNaughton and Gray, 2000) despite some cortical theta generators (Cantero et al., 2003), these findings are consistent with research showing local cortical and subcortical and network-level disruptions in PTSD (Terpou et al., 2018, 2019). Focusing on theta, PTSD-related impacts on the hippocampus (Henigsberg et al., 2019) have been linked with contextual orientation difficulties and impaired goal-conflict resolution leading to anxiety and defensive behaviours (McNaughton, 2017; McNaughton and Gray, 2000; Sainsbury et al., 1987). Increased theta is also associated with attention (Cassaday, 2014) and working memory difficulties (Klimesch, 1999, 2012; Kleim et al., 2007), low cognitive control and anxiety (Cavanagh and Shackman, 2015) and neuroticism and avoidance (Neo and Mcnaughton, 2011). In healthy individuals, memory, attention and contextual orientation are associated with limbic theta and thalamocortical alpha rhythms (Klimesch, 1999, 2012; Klimesch et al., 2007), which act as carrier waves through cross-frequency coupling (Canolty and Knight, 2012; Sarnthein et al., 2005) to transmit information to frontal reward evaluation networks (Schultz, 2000). These networks, in conjunction with other large-scale brain networks (McTeague et al., 2017; Menon, 2011), use past experience (Aru et al., 2016; Roux and Uhlhaas, 2014) to underpin sensory processing, self-referential processing and planning (Menon, 2011), which give rise to prediction-confirmations, novelty-detection or prediction-errors encoded in beta 1, beta 2 and gamma activity respectively (Hajihosseini et al., 2012; Ruiz et al., 2011). Thus the beta power irregularities in ML and statistical studies might reflect persistent network issues underpinning a wide array of sensory, self-referential and cognitive issues observed in individuals with PTSD due to underlying issues in hippocampal functioning. Although, it is odd that alpha abnormalities were mainly observed in statistical studies (Jokić-Begić and Begić, 2003; Kemp et al., 2010; Veltmeyer et al., 2006; Wahbeh and Oken, 2013) given their importance in networks (Klimesch, 1999, 2012; Klimesch et al., 2007) and relevant PTSD related fMRI findings (Kim et al., 2006; Nicholson et al., 2018). Importantly, during sleep, impaired hippocampal functioning has been linked to nightmares (McNaughton and Gray, 2000), which may be a factor in spindling excessive beta endophenotype associated with sleep maintenance and impulse control issues (Arns et al., 2015; Johnstone et al., 2005; Krepel et al., 2021). This may suggest that impaired hippocampal functioning could impact emotional memory integration in networks during sleep (Nishida et al., 2009). This may perpetuate forms of abnormal beta connectivity within these networks and consequentially the poor contextual orientation, goal-conflict resolution, alterations in mood and defensive behaviours seen in PTSD. These theta and beta irregularities, in combination with changes in various connectivity metrics (Kim et al., 2020; Park et al., 2021; Shim et al., 2021; Toll et al., 2020; Zhang et al., 2021) and the numerous studies linking elevated heart rate and low HRV suggest nervous systems impacted by PTSD have disruptions in arousal and associated networks issues that limit behavioral flexibility (Porges, 2009; Thome et al., 2017). These findings provide a promising basis for EEG and ECG biomarkers to be used diagnostically and as symptom

Table 6
Statistical ECG studies.

Authors	Statistics	Performance	measures	implication
Agorastos et al., 2013	ANCOVA	Average HR, $F = 8.488$, $p = .017$	Psychometric and ECG recording including average heart rate (64.1 ± 4.2 PTSD, 56.8 ± 6.8 No-PTSD), nocturnal HR (61.3.1 ± 6.5 PTSD, 51.8 ± 7.5 No-PTSD), NN_{24h} (942.4 ± 59.0 PTSD, 1076.7 ± 131.9 No-PTSD), and LF/HF ratio at night (1.73 ± 0.97 PTSD, 0.76 ± 0.35 No-PTSD).	Elevated arousal and nocturnal autonomic dysregulation are associated with PTSD
Alarcon et al., 2011	*t*-test	$p = .58$	Psychometric and hospital medical records including average heart rate (PTSD 93 ± 18 bpm, No PTSD 93 ± 19 bpm).	Elevated arousal is associated with PTSD
Arditi-Babchuk et al., 2009	Correlation	$r(40) = 0.33$, $p < .05$	Psychometrics and electrocardiogram records including heart rate.	Elevated arousal is associated with PTSD
Blanchard et al., 2002	Chi Square, correlation	$\chi 2 = 8.08$, $p < .01$	Psychometric and hospital medical records including average heart rate (PTSD <87.7 ± 20.9 bpm, No PTSD >86.3 ± 18.2 bpm).	Elevated arousal is negatively associated with PTSD
Blechert et al., 2007	MANOVA	$F = 4.95$, $p = .01$	Psychometric and electrocardiogram records including heart interval (PTSD 762 ms ± 92.5 ms. No PTSD 868 ms ± 125 ms) and RSA (PTSD 5.36 nu ±0.88 nu. No PTSD 6.16 nu ±4.84 nu).	Elevated arousal is associated with PTSD
Bryant et al., 2011	Hierarchical logistic regression	$p = .001$, Sensitivity = 0.59, Specificity = 0.80	Psychometric and hospital medical records including average heart rate (PTSD >96 bpm, No PTSD <96 bpm).	Elevated arousal is positively associated with PTSD
Bryant et al., 2008	–	$p < .01$	Psychometric and hospital medical records including average heart rate (PTSD >90.16 ± 18.66, No PTSD <84.84 ± 17.41) at 3 months follow up HR > 96 more likely to have PTSD.	Elevated arousal is associated with PTSD
Bryant et al., 2003	One-way ANOVA and Pearson Correlation Coefficients	Sensitivity (74 %) specificity (91 %)	Psychometric and hospital medical records including average heart rate (82.9 ± 13.2 PTSD, 76.3 ± 9.8 No-PTSD).	Elevated arousal is associated with PTSD
Bryant et al., 2000	Forward stepwise multiple regression	β = 0.2, Sensitivity 88 %, specificity 85 %	Psychometric and hospital medical records including average heart rate (HR > 90 bpm).	Elevated arousal is negatively associated with PTSD
Bryant et al., 2013	Hierarchical linear regression	$p = .95$	Psychometric and hospital medical records including average heart rate (PTSD 10 bpm > no PTSD).	No correlation between HR and PTSD.
Buckley et al., 2004a	Hierarchical linear modelling	$P > .10$	Psychometric and hospital medical records including average heart rate (94.1 ± 17.9 PTSD, 94.0 ± 17.0 No-PTSD).	No correlation between HR and PTSD.
Buckley et al., 2004b	Hierarchical linear modelling	t Ratio 30.73, $p < .001$	Psychometric and hospital medical records including average heart rate (PTSD 6.63 bpm < No-PTSD).	Elevated arousal is associated with PTSD
Carson et al., 2007	One way ANOVA	$F(2, 87) = 3.98$, $p < .05$	Psychometric and ECG recording including average heart rate (75.0 ± 11.7 PTSD, 78.6 ± 9.2 Past PTSD, 73.8 ± 11.2 No-PTSD).	Elevated arousal is associated with PTSD
Carson et al., 2000	Discriminant function and two-factor ANCOVA	HR $F(1,35) = 6.3$, $p = .02$. Discriminant function classification 76 % sensitivity, 81 % specificity, $p = .001$	Psychometric and ECG recording including LF/HF (5.68 ± 5.88 PTSD, 2.50 ± 1.86 No-PTSD).	Elevated arousal is associated with PTSD
Chang et al., 2013	*t*-Test, Mann-Whitney U	$p < .05$	Psychometric and electrocardiogram records including heart interval (PTSD 848.16 ms ± 124.95 ms. No PTSD 893.48 ms ± 144.34 ms, Past PTSD 853.47 ms ± 130.48 ms), LF (PTSD 5.34 ± 1.17, No PTSD 5.9 ± 1.07, Past PTSD 6.09 ± 0.92), HF (PTSD 5.07 ± 1.13, No PTSD 5.75 ± 1.1, Past PTSD 5.9 ± 0.92) and LF/HF (PTSD 0.26 ± 0.72, No PTSD 0.15 ± 0.81, Past PTSD 0.19 ± 0.64).	Low HRV is associated with PTSD
Cohen et al., 2000	ANCOVA	$p < .05$	Psychometric and electrocardiogram records including Average HR (PTSD 82.4 ± 1.7 s. No PTSD 62.0 ± 3.25 s), HRV (PTSD 0.0732 ± 0.016 nu. No PTSD 0.95 ± 0.04 nu), LF% (PTSD 89.4 ± 1.1 nu. No PTSD 48.6 ± 1.1 nu), HF% (PTSD 10.6 ± 1.1 nu. No PTSD 51.4 ± 1.1 nu) and LF/HF (PTSD 10.025 ± 1.5 nu. No PTSD 0.95 ± 0.044 nu).	Elevated arousal & autonomic dysregulation is associated with PTSD
Cohen et al., 1997	Linear regression and one-way ANCOVA	$F = 7.0$, p - = 0.019	Psychometric and ECG recording including average heart rate (71.32 ± 3.53 PTSD, 61.9 ± 2.14 No-PTSD).	Elevated arousal is associated with PTSD
Cohen et al., 1998	ANCOVA	$F = 52.16$, $p = .0000$	Psychometric and electrocardiogram records including average heart rate (PTSD 71.32 ± 2.14 bpm. No PTSD 61.9 ± 3.5 bpm) and HRV (0.12 ± 0.02 nu PTSD, 0.18 ± 0.04 nu No-PTSD).	Elevated arousal is negatively associated with PTSD
Coronas et al., 2011	Multivariate logistic regression models	Sensitivity (62.5 %) specificity (75.0 %)	Psychometric and hospital medical records including average heart rate (PTSD >84 bpm).	Elevated arousal is associated with PTSD
Cremeans-Smith et al., 2012	Pearson product-moment correlations and *t*-Tests	$r = 0.245$, $p < .05$	Psychometric and hospital medical records including average heart rate (PTSD >79.752 ± 11.848 bpm).	Elevated arousal is associated with PTS

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Table 6 (*continued*)

Authors	Statistics	Performance	measures	implication
				symptoms (intrusive thoughts)
Delahanty et al., 2003	One-way ANOVAs and Pearson product correlations	$p < .05$	Psychometric and hospital medical records including average heart rate (95.36 ± 16.25 bpm).	No correlation between HR and PTSD.
Dennis et al., 2014	t-tests & latent variable modelling	$t(223)$, $p < .05$	Psychometric and ECG recording including standard deviation of norm-to-norm intervals (135.40 ± 41.97 PTSD, 150.10 ± 49.51 No-PTSD), triangular index (37.10 ± 12.95 PTSD, 41.26 ± 13.17 No-PTSD), log high frequency (5.72 ± 1.12 PTSD, 6.22 ± 1.31 No-PTSD) and log low frequency (6.76 ± 0.85 PTSD, 7.11 ± 0.91 No-PTSD).	Elevated arousal and autonomic dysregulation are associated with PTSD
Dennis et al., 2014	Multilevel modelling, Pearson correlations,	$t(1257) = 2.76$, $p = .006$	Psychometrics and electrocardiogram, including average heart rate (87.24 ± 11.78 bpm PTSD, 82.93 ± 12.56 bpm No PTSD).	Elevated arousal is associated with PTSD
Ehring et al., 2008	Two-tailed ANOVAs, Pearson product-moment correlation coefficients	r = −0.15 to −0.22, $p > .5$	Psychometric and hospital medical records including average heart rate (74.97 ± 11.16 bpm).	No correlation between HR and PTSD.
Elsesser et al., 2004	ANOVA	$F(2, 75) = 3.2$, $p < .05$	Psychometric and electrocardiogram records including average heart rate (PTSD 65.41 bpm ± 8.89 bpm. No PTSD 71.6 bpm ± 8.86 bpm).	Elevated arousal is negatively associated with PTSD
Forneris et al., 2004	X^2 & ANOVA	$p = .03$	Psychometric and hospital medical records including average heart rate (PTSD = 83.9 ± 12.6 bpm, No PTSD = 77.5 ± 11.2 bpm).	Elevated arousal is positively associated with PTSD
Gandubert et al., 2016	Logistic and multivariate regression	$p > .05$	Psychometric and electrocardiograph recordings to access median heart rate (76 [67–80] bpm)	No correlation between HR and PTSD.
Ginsberg et al., 2010	Mann-Whitney *U* test	$p < .05$	Psychometrics and photoplethysmography, including total power (813 ms^2/Hz PTSD, 1142 ms2/Hz No PTSD).	Low HRV is associated with PTSD
Ginsberg et al., 2008	Correlation, factor analysis and hierarchical linear regression	r = −0.14382	Psychometrics and electrocardiogram, including average HRV (10.6 PTSD).	Low HRV is associated with PTSD
Gould et al., 2011	Multivariate logistic regression models	$R^2_{adj} = 0.55$	Psychometric and hospital medical records including average heart rate (74.97 ± 11.16 bpm).	Elevated arousal is associated with PTSD
Green et al., 2016	Multilevel modelling and correlations	PTSD & LF amplitude r = −0.25, $p < .05$	Psychometric and ECG recording including LF (PTSD 35.12 ± 15.13 nu) and HF (PTSD 22.33 ± 15.13 nu).	Low HRV is associated with PTSD
Griffin, 2008	Repeated measures ANOVA	$p > .05$	Psychometric and electrocardiogram records including average heart rate (PTSD 69.5 ± 11.2 bpm. No PTSD 72.7 ± 8.4).	No correlation between HR and PTSD.
Hamanaka et al., 2006	Multiple logistic analysis	$p = .085$	Psychometric and hospital medical records including average heart rate (HR =84.67 ± 14.92)	No correlation between HR and PTSD.
Hauschildt et al., 2011	MANCOVA	$F(2, 67) = 0.91$, $p > .4$	Psychometric and electrocardiograph recordings to access average heart rate (PTSD 69.92 ± 14.15 bpm, No PTSD 66.85 ± 9.01 bpm, No trauma 65.50 ± 9.59 bpm) and heart rate variability (RMSSD & HF-HRV lower in PTSD than no PTSD or trauma).	No correlation between average HR and PTSD, but low HRV values associated with PTSD.
Hinton et al., 2004	Pearson correlation	r = 0.4, $p < .05$	Psychometrics and electrocardiogram, including average heart rate (Approximately 78 bpm PTSD, & 70 bpm No PTSD).	Elevated arousal is associated with PTSD
Hopper et al., 2006	ANCOVA	$p = .76$	Psychometric and ECG recording including average heart rate (71.5 ± 11.27 PTSD), LF HRV (6.68 ± 1.01 ln(ms)2) and RSA (7.0 ± 1.5 ln(ms)2 PTSD).	No correlation between HR and PTSD.
Jovanovic et al., 2009	Mixed ANOVA	$F(1,76) = 11.2$, $p = .001$	Psychometric and hospital medical records including average heart rate (≥ 95 PTSD, ≤95 No-PTSD).	Elevated arousal & low HRV in PTSD
Keary et al., 2009	Independent samples *t*-test	$p > .05$	Psychometric and ECG recording including average heart rate (116.6 ± 20.3 PTSD, 106.4 ± 11.7 No-PTSD).	No correlation between HR and PTSD.
Kinzie et al., 1998	one way ANOVA	$F = 2.2$, $p < .075$	Psychometric and photoplethysmography records including average heart rate (PTSD 83.2 ± 17.42 bpm & 80.0 ± 16.23 bpm. No PTSD 76.5 ± 9.36 bpm & 70.3 ± 10.56 bpm).	Elevated arousal is associated with PTSD
Kleim et al., 2007	Multivariate logistic regression models	$R^2 = 4.90$	Psychometric and hospital medical records including average heart rate (PTSD >71.80 ± 12.35 bpm, No PTSD <67.10 ± 10.80 bpm).	Elevated arousal is associated with PTSD
Kobayashi et al., 2014	Hierarchical linear regression	$R^2 = 0.2$	Psychometric and electrocardiograph recordings to access heart rate variability (PTSD associated with lower HF during sleep)	Low HRV in sleep is associated with PTSD
Kraemer et al., 2008	Sequential multiple regression	$R^2 = 0.126$	Psychometric and hospital medical records including average heart rate (88.3 ± 20.4 PTSD, 81.7 ± 16.7 No-PTSD).	Elevated arousal is associated with PTSD
Kuhn et al., 2006	Spearman correlation	r = 0.31, $p < .5$ HR & SDQ. r = 0.27, $p < .01$ HR & PDI.	Psychometric and hospital medical records including average heart rate (85.9 ± 16.4 bpm).	Elevated arousal is associated with PTSD
Lee et al., 2018	MANCOVA & Binary logistic regression	PTSD & HRV metrics $F(2, 44) = 3.90$, $p = .028$. LF/HF ratio and PTSD metrics r = 0.34, $p = .015$.	Psychometrics and electrocardiogram, including LF, HF and LF/HF ratio (LF/HF ratio, PTSD 0.12 ± 0.88, No PTSD -0.16 ± 0.91 No PTSD).	Low HRV is associated with PTSD

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Table 6 (*continued*)

Authors	Statistics	Performance	measures	implication
Liddell et al., 2016	ANOVA & Bivariate Correlation	HRV $t(72) = -2.07$, $p = .021$, $d = 0.19$. HR $t(72) = -0.91$, $p = .37$, $d = 0.5$	Psychometric and ECG recording including HR (PTSD 75.18 ± 12.68 bpm, No PTSD 77.84 ± 11.47 bpm) and RMSSD (PTSD 1.46 ± 0.26 nu, No PTSD 1.58 ± 0.22 nu).	Low HRV is associated with PTSD
Litz et al., 2000	Repeated measures ANOVA	$p < .05$	Psychometric and electrocardiogram records including average heart rate (PTSD 68.9 ± 10.1 bpm. No PTSD 67.6 ± 15.1).	No correlation between HR and PTSD.
MacGregor et al., 2009	Logistic regression	$p = .51$	Psychometric and hospital medical records including average heart rate (PTSD >83.4 ± 12.8 bpm, No PTSD <89.5 ± 12.5 bpm).	Elevated arousal is associated with PTSD
Matsuoka et al., 2008	Multivariate logistic regression	OR, 1.6; 95 % CI, 1.2–2.2; $p < .01$	Psychometric and hospital medical records including average heart rate (84.4 ± 17.7 bpm).	Elevated arousal is associated with PTSD
Matsuoka et al., 2009	None descriptives only.	None, descriptives only	Psychometric and hospital medical records including average heart rate (HR = 84.9 ± 16.5)	Elevated arousal is associated with PTSD
Mellman et al., 2004	Repeated ANOVA	Higher LF/HF ratio in REM $F(1, 17) = 10.67$, $p < .01$	Psychometric and ECG recording including average heart rate (66.6 ± 9.2 PTSD, 61.2 ± 7.7 No-PTSD) and RSA (0.25 ± 0.8 PTSD, 0.21 ± 1.0 No-PTSD).	Nocturnal autonomic dysregulation and elevated arousal are associated with PTSD
Meyer et al., 2016	Kruskal-Wallis one-way ANOVA & Pairwise Mann-Whitney *U* tests	$p < .05$	Psychometric and electrocardiogram records including RMSSD (PTSD 48.6 ms ± 23.5 ms. No PTSD 84.11 ms ± 41.7 ms), SDNN (PTSD 48.9 ± 20.0, No PTSD 74.27 ± 30.5), NN50 (PTSD 73.3 ± 58.2, No PTSD 120.1 ± 70.5), total power (PTSD 2338.38 ± 1925, No PTSD 5745 ± 4333) and HF power (PTSD 896 ± 796, No PTSD 2509 ± 29,903).	Low HRV is associated with PTSD
Minassian et al., 2014	Multinominial logistic regression and ordinal regression	$\chi2 = 77.7$, $p < .01$. $\chi2 = 65.5$, $p < .01$	Psychometrics and electrocardiogram, including average heart rate (67.1 ± 10.2 bpm), SDNN (64.1 ± 26.9 ms), RMSSD (58.9 ± 34.5 ms), VLF (2380.2 ± 2470.9 ms^2/Hz) LF (5144.1 ± 5467.4 ms2/Hz), HF (4153.8 ± 5074.4 ms2/Hz) and LFnorm, HFnorm, and LF/HF ratio.	Elevated arousal is associated with PTSD
Minassian et al., 2015	Multivariate logistic regression	OR, 1.57; 95 % CI, 1.04–2.37; $P = .03$	Psychometrics and photoplethysmography, including LF/HF ratio (PTSD <1.47 > No PTSD).	Low HRV is associated with PTSD
Mitani et al., 2006	*t*-test	$p = .001$	Psychometrics and electrocardiogram, including LF/HF (4.25 ± 1.85 PTSD, 1.70 ± 0.56 No PTSD) and HF/total power (0.21 ± 0.07 PTSD, 0.39 ± 0.008 No PTSD).	Low HRV is associated with PTSD
Moon et al., 2013	Multivariate ANOVA	$F < 0.05$	Psychometric and electrocardiogram records including SDNN (PTSD 31.21 ms ± 1.96 ms. No PTSD 38.57 ms ± 2.22 ms), RMSSD (PTSD 22.36 ± 2.09, No PTSD 30.27 ± 2.35), LF (PTSD 7178.86 ± 39.65, No PTSD 335.48 ± 44.70), HF (PTSD 157.56 ± 31.99, No PTSD 332.83 ± 36.07) and total power (PTSD 737.71 ± 105.03, No PTSD 1174.69 ± 118.41).	Low HRV is associated with PTSD
Nishi et al., 2013	Multivariate and univariate logistic regression model	Univariate OR (95 % CI) = 0.91 (0.78, 1.05), Multivariate OR (95 % CI) = 0.87 (0.70, 1.09)	Psychometric and hospital medical records including average heart rate (84.1 ± 16.8 bpm).	No correlation between HR and PTSD.
Norte et al., 2013	Mann-Whitney U test	$p = .02$	Psychometrics and electrocardiogram, including average heart rate and HRV.	Elevated arousal & autonomic dysregulation is associated with PTSD
O'Donnell et al., 2007	Logistic regression	$F = 0.76$	Psychometric and hospital medical records including average heart rate (83.5 ± 12.82 PTSD, 88.55 ± 17.94 No-PTSD, 90.22 ± 11.93 Subsyndromal PTSD).	Elevated arousal is negatively associated with PTSD
Orr et al., 2003	Mixed model t	$t = 1.7$, $p = .09$	Psychometrics and electrocardiogram, including average heart rate (77.5 ± 15.8 bpm PTSD,73.6 ± 11.3 bpm No PTSD).	Elevated arousal is associated with PTSD
Orr et al., 2000	t-test	$t(31) = 3.3$, $p = .002$	Psychometrics and electrocardiogram, including average heart rate (77.9 ± 12.9 bpm PTSD, 66.2 ± 7.3 bpm No PTSD).	Elevated arousal is associated with PTSD
Park et al., 2017	*t*-test and ANCOVA	$p < .01$	Psychometrics and electrocardiogram, including average heart rate (70.5 ± 1.2 PTSD, 65.4 ± 1.2 No PTSD) SDNN (21.9 ± 1.4 PTSD, 28.6 ± 1.3 No PTSD) RMSSD (15.6 ± 1.6 PTSD, 23.1 ± 1.5 No PTSD) and log HF (3.7 ± 0.1 PTSD, 4.3 ± 0.1 No PTSD).	Elevated arousal & autonomic dysregulation is associated with PTSD
Pitman et al., 2001	MANOVA	$p > .05$	Psychometrics and electrocardiogram, including average heart rate (82.5 ± 6.9 PTSD, 71.1 ± 12.8 No PTSD, 72.7 ± 7.0 Past PTSD).	No correlation between HR and PTSD.
Pole et al., 2006	Mixed ANOVA and MANOVAS	$p > .05$	Psychometrics and electrocardiogram, including average heart rate (84.3 ± 21.0 Peritraumatic dissociation, 76.8 ± 13.8 Low PD).	No correlation between HR and Peritraumatic dissociation.
Price et al., 2014	Mixed effects modelling	AUC = 0.68, sensitivity (0.91), specificity (0.57)	Psychometric and hospital medical records including average heart rate (84.73 ± 19.20).	No correlation between HR and PTSD.

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Table 6 (*continued*)

Authors	Statistics	Performance	measures	implication
Pyne et al., 2016	t-Test, chi-square and generalized linear mixed models	$p < .05$	Psychometric and electrocardiogram records including log HF (PTSD 4.64 ± 1.23) and SDNN (PTSD 47.25 ms ± 21.29 ms).	Low HRV is associated with PTSD
Ray et al., 2017	Hierarchical regression	$R^2 < 0.05$	Psychometric and electrocardiogram records including log HF (PTSD 4.98 ± 1.27, No PTSD -4.76 ± 1.78) and SDNN (PTSD 29.75 ms ± 12.07 ms, No PTSD 50.00 ms ± 16.00 ms), RMSSD (PTSD 23.82 ms ± 14.11 ms, No PTSD 42.00 ms ± 15.00 ms) and HF power (315.89 ± 509.96, No PTSD 657.00 ± 777.00).	Low HRV is associated with PTSD
Rissling et al., 2016	Multilevel modelling, Pearson correlations,	Resting $t(10883) = 1.34$, $p = .180$, $d = 0.09$. Nocturnal $t(1083) = 2.20$, $p = .28$, d = 0.12	Psychometric and electrocardiogram records including resting LF power (PTSD 44.52 ± 17.00, No PTSD 37.81 ± 15.07).	Nocturnal autonomic dysregulation is associated with PTSD
Sahar et al., 2001	Mann-Whitney *U* test	$p > .05$	Psychometric and electrocardiogram records including heart interval (PTSD 840.4 ms ± 173 ms. No PTSD 843.7 ms ± 161 ms).	No correlation between HR interval and PTSD.
Shah et al., 2013	Generalized estimating equations	$p < .01$	Psychometric and electrocardiograph recordings to access heart rate variability (PTSD associated with lower HRV)	Low HRV is associated with PTSD
Shaikh al Arab et al., 2012	Mann-Whitney *U* test, Fisher exact test, spearman coefficient correlations	$p < .05$	Psychometric and electrocardiogram records including pNN50 (PTSD IQR 1.59 [0.68; 5.67] No PTSD IQR 9.95 [2.67; 42.52]) RMSSD (PTSD IQR 17.7 [16.94; 27.35], No PTSD IQR 49.50 [22.72; 93.46]), variability index (PTSD IQR 1.91 [1.49; 2.61], No PTSD IQR 2.84[1.98; 7.04]) SDANN (PTSD IQR 75.92 [43.08; 88.64], No PTSD IQR 93.57 [77.33; 112.43]), SDNN (PTSD IQR 86.14 [67.99; 102.67], No PTSD IQR 118.32 [92.89; 154.60]) and average HR (PTSD IQR 93.50 [77.70; 97.70], No PTSD IQR 72.90 [66.33; 80.80])	Low HRV is associated with PTSD
Shalev and Freedman, 2005	Hierarchical logistic regression	$\chi 2 = 6.63$, df = 1, $p = .01$. OR = 1.29, 95 % CI = 0.92–1.80	Psychometric and hospital medical records including average heart rate (86.96–93.41 PTSD, 81.87–94.90 No-PTSD).	Elevated arousal is negatively associated with PTSD
Slewa-Younan et al., 2012	Linear regression	$p < .001$	Psychometric and hospital medical records including average heart rate (PTSD 78.74 ± 2.19 bpm, No PTSD 60.08 ± 2.25 bpm).	Elevated arousal is associated with PTSD
Song et al., 2011	Mann-Whitney U and regression	$R^2 = 0.138$, F = 4.695, $p = .041$	Psychometric and electrocardiogram records including LF/HF (PTSD 2.5 ± 1.9, No PTSD 1.5 ± 1.5).	Low HRV is associated with PTSD
Tan et al., 2011	*t*-Test	$p < .001$	Psychometric and electrocardiogram records including SDNN (PTSD 48.10 ms ± 47.84 ms. No PTSD 138.70 ms ± 47.87 ms).	Low HRV is associated with PTSD
Thome et al., 2017	*t*-Test	$p < .05$	Psychometric and pulse oximeter lnRMMSD (PTSD 3.76 ± 0.09 ms, No PTSD 4.06 ± 0.11 ms), lnLF (PTSD 6.05 ± 0.20, No PTSD 6.91 ± 0.23) and lnHF (PTSD 6.35 ± 0.19, No PTSD 6.93 ± 0.25).	Low HRV is associated with PTSD
Tucker et al., 2012	Wilcoxon rank test and chi-square	$p < .05$	Psychometric and electrocardiogram records including average HR (PTSD 80.82 bpm ± 13.60 bpm, No PTSD 74.85 bpm ± 10.67), HF (PTSD 40.14 nu ± 23.81 nu, No PTSD 50.67 nu ± 19.93 nu) and LF/HF ratio (PTSD 2.83 ± 3.08, No PTSD 1.35 ± 1.08).	Low HRV is associated with PTSD
van Liempt et al., 2013	ANOVA, MANCOVA,	$F(2, 34) = 3.66$, $p = .036$ PTSD HR in sleep	Psychometric and ECG recording including average heart rate (64.66 ± 5.63 bpm PTSD, 58.01 ± 7.25 bpm No-PTSD, 57.44 ± 6.04 bpm Trauma Control).	Nocturnal autonomic dysregulation is associated with PTSD
Veazey et al., 2004	ANOVA	$F(2,131) = 1.78$, $p = .173$	Psychometric and electrocardiogram records including average HR (PTSD 77.0 bpm, No PTSD 77.0 bpm, 70.0 bpm Trauma Control).	No correlation between HR and PTSD.
Vaiva et al., 2003	Wilcoxon rank test and Fisher exact test	$U = 85$, $p = .037$	Psychometric and hospital medical records including average heart rate (≥79.4 ± 9.3 bpm PTSD).	Elevated arousal is associated with PTSD
Videlock et al., 2008	Pearson product-moment correlations and ANOVA	None, uses *p* values	Psychometric and hospital medical records including average heart rate (86.9 ± 14.0 PTSD, 83.4 ± 13.2 No-PTSD).	No correlation between HR and PTSD.
Wahbeh and Oken, 2013	ANOVA	$F(2, 78) = 26.5$, $p < .000005$	Psychometric and ECG recording including HF peak frequency (PTSD 0.21 ± 0.07 Hz, No PTSD 0.23 ± 0.06 Hz).	Elevated arousal is associated with PTSD
Woodward et al., 2009	Univariate ANOVA and Fisher's least significant difference and simple and partial correlation and multiple regression	$F(3, 51) = 2.89$, $p < .05$ PTSD HR in sleep > control, $r(56) = 0.332$, $p < .05$ with PSQI. $F(3, 51) = 3.55$, $p < .05$ PTSD RSA in sleep < control, $r(56) = -0.333$, $p < .05$ with PSQI.	Psychometric and ECG recording including average heart rate (75.2 ± 7.9 PTSD, 67.7 ± 9.5 No-PTSD).	Nocturnal autonomic dysregulation is associated with PTSD
Wu and Cheung, 2006	Latent growth modelling	$p > .05$	Psychometric and hospital medical records including average heart rate (HR = 97.1 ± 18.1)	No correlation between HR and PTSD.

(*continued on next page*)

Table 6 (*continued*)

Authors	Statistics	Performance	measures	implication
Zatzick et al., 2005	Mixed effects random-coefficient regression modelling	F = 14.4, F = 3.8 for 6 months and 12 months respectively	Psychometric and hospital medical records including average heart rate (PTSD 90.16 ± 18.66 bpm, No PTSD 84.84 ± 17.41).	Elevated arousal is negatively associated with PTSD

Note: - = Unknown, ANCOVA = Analysis of Covariance, ANOVA = Analysis of variance, bpm = beats per minute, ECG = Electrocardiogram, HF = High Frequency, HFnorm = Normalised High Frequency, IQR = Inter Quartile Range, LF = Low Frequency, LF/HF = Ratio of Low-Frequency to High-Frequency power, LFnorm = Normalised Low Frequency, Ln = Natural Logarithm, MANOVA = Multivariate Analysis of Variance, ms = millisecond, NN = Normal to Normal (RR) intervals, NN50 = Normal-to-Normal heartbeats that differ by >50 ms, nu = normal units, PNN50 = NN50 divided by the total number of NN intervals, PTSD = Post Traumatic Stress Disorder, PDI = Peritraumatic Distress Inventory, PSQI = Pittsburgh Sleep Quality Index, PTSD = Post Traumatic Stress Disorder, REM = Rapid Eye Movement., RMSSD = Root Mean Square of Successive Differences, RSA = Respiratory Sinus Arrhythmia, RR = the time between consecutive heartbeats, SDQ = State Dissociation Questionnaire & VLF = Very Low Frequency.

prognostics. However, it is important to note the methodological decisions might have preferenced the utilisation of certain biomarkers. For instance, the eyes-open/closed assessment durations of under three (Grisanzio et al., 2018; Kim et al., 2020; Toll et al., 2020; Zhang et al., 2021) or five minutes (Park et al., 2021; Shim et al., 2021) used in the EEG research may be insufficiently long to detect changes in vigilance (Arns et al., 2011; Jawinski et al., 2018) that might be associated with PTSD. Using 10-min EC assessments, distinct vigilance patterns have been detected for other disorders such as attention deficit hyperactivity disorder (Arns et al., 2015), mania (Hegerl et al., 2010) depression (Hegerl et al., 2012), obsessive-compulsive disorder (Dohrmann et al., 2017) and borderline personality disorder (Hegerl et al., 2008). Given this wide array of disorders associated with distinct vigilance patterns, it is likely, that they may also exist in PTSD, although, this appears to have not been researched.

A further consideration in ML biomarker detection is the use of 32 (Grisanzio et al., 2018) or >62 EEG sensors (Kim et al., 2020; Park et al., 2021; Shim et al., 2021; Zhang et al., 2021). Higher electrode densities are typically associated with increased connectivity measure accuracy (Allouch et al., 2022; Liu et al., 2018), which may increase the likelihood of connectivity metrics emerging as features. These high sensor counts may not be as applicable for clinics that typically employ 19 channels (Tatum et al., 2016) and would exclude comparison to most normative EEG databases used for qEEG assessment (Johnstone et al., 2005) including the Brain Resource International Database used by two studies identified in this review (Gordon et al., 2010; Veltmeyer et al., 2006). Consequentially, the method of data collection may have implications for the types of biomarkers detected and their predictive power. Considering differences between the methodologies and the variation in ML used in each study identified, the trends for power and various connectivity differences in resting-state EEG suggest continued attention to and standardisation (Miljevic et al., 2022; Pernet et al., 2020) of these metrics, with ample scope to continue testing all classes of ML for PTSD symptom.

In ECG research, average heart rate was the most ubiquitous measure; successfully predicting PTSD in eight ML studies and failing in one (Karstoft et al., 2015) and being positively correlated in 28 statistical studies, negatively correlated in seven and uncorrelated in 19 (see Table 6). These discrepancies between elevated HR and PTSD, especially in the statistical studies may derive from differences in assessment, such as self-assessment versus clinician diagnosis for PTSD, the sequence of assessments, the timing of HR recordings after traumatic event/s, injury or event severity and differences in patient samples, such as age. Regardless of this variability, several meta-analyses have shown a correlation between average HR and PTSD (Buckley and Kaloupek, 2001; Morris et al., 2016; Nagpal et al., 2013). HRV metrics being predictive of PTSD status in four ML studies (Cakmak et al., 2021; McDonald et al., 2019; Reinertsen et al., 2017; Sadeghi et al., 2020a, 2020b) and associated with PTSD in all but one (Hopper et al., 2006) of the 30 statistically-based studies (see Table 6) is consistent with PTSD research. Indeed, in two large studies based on US marine samples assessed before and after combat, initially low HRV was a predictor of the subsequent development of PTSD (Minassian et al., 2014; Shah and Vaccarino, 2015), which suggests individuals with reduced autonomic regulation are predisposed to develop PTSD. Unfortunately, due to large variations in recording duration in the identified ML studies, no conclusions about specific metrics can be garnered as values arising from different record lengths aren't comparable due to their cycle-length-dependence (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). Although, some interesting trends were identified in this pool of studies including, utilisation of predictive biomarkers during sleep (Mellman et al., 2004; Rissling et al., 2016; Van Liempt et al., 2013; Woodward et al., 2009), recording HRV values in the five minutes following the slowest heart-rate during sleep (Reinertsen et al., 2017) and using heart rate acceleration to predict PSTD and flashbacks (McDonald et al., 2019), which were more accurate than other HRV metrics in these studies. These findings suggest further ML approaches should explore the acceleration and deceleration changes in heart rate as events from which to extract potential biomarkers, such as the Fourier coefficients used by McDonald et al. (2019) and the HRV metrics used by Reinertsen et al. (2017). The large number of identified studies examining elevated HR via regression and the strong support for an association with PTSD supports the use of ML to further elucidate this relationship.

The biomarkers successful in predicting PTSD status are revealing of underlying physiological processes occurring within the multi-modal PTSD classification. Consistent with wider research (Henigsberg et al., 2019), biomarkers suggesting frontal lobe dysregulation were a key emerging trend in the ML EEG studies. Specifically, frontal beta power was linked to symptoms of anhedonia (Grisanzio et al., 2018), beta coherence/phase locking values (Shim et al., 2021) and beta power-envelope connectivity (Zhang et al., 2021) both predicted PTSD status, while divergent dorsal attention, visual attention, frontoparietal control and default mode network activity in beta separated PTSD subtypes (Zhang et al., 2021) and irregular theta connectivity between frontal regions and broader attention networks associated with PTSD, attention and working memory difficulties (Toll et al., 2020). Poor frontal lobe and control network function are indicative of failures in attention and arousal regulation that are critical for goal-directed behavior, or the ability to adaptively respond to a stressor (Thayer and Lane, 2000), which may contribute to the disorganised orientation in time and place seen in PTSD (Liberzon & Abelson, 2016). The broad EEG spectral differences to controls used by Kim et al. (2020) to detect PTSD are compatible with the arousal regulation deficit argument, as brain activity in controls typically follows a log-linear and hierarchical stratification depending upon frequency (Buzsáki, 2009; Klimesch, 2014; Penttonen and Buzsáki, 2003). In contrast, the loss of this proportionality is associated with dysregulated arousal (Arns et al., 2011; Canolty and Knight, 2012; Herrmann et al., 2016; Schwartz and Roth, 2008). Similarly, arousal regulation difficulties are suggested by divergent beta and theta power (Cavanagh and Shackman, 2015; Enoch et al., 2008; Johnstone et al., 2005; Niedermeyer, 1990; Pizzagalli, 2010), elevated HR and low HRV metrics (Porges, 2001; Shaffer et al., 2014; Shaffer and Ginsberg, 2017; Thayer and Lane, 2000, 2009) described in both the ML

and statistically based research. As discussed earlier, abnormal theta and beta patterns have also been linked to sleep issues (Arns et al., 2013, 2015; Monastra et al., 1999; Nishida et al., 2009), which is in keeping with the suggested trend for abnormal autonomic functioning in sleep (Mellman et al., 2004; Reinertsen et al., 2017; Rissling et al., 2016; Van Liempt et al., 2013; Woodward et al., 2009) and supports arousal dysregulation being a consistent feature of PTSD. The consistency of PTSD biomarkers between ML and statistically based research is suggestive that arousal regulation and alterations in arousal are defining features of PTSD that can be identified through both EEG and ECG biomarker analysis.

The 19 ML studies identified all sought to solve classification problems pertaining to PTSD diagnosis and in two instances, ongoing symptom monitoring (McDonald et al., 2019; Sadeghi et al., 2020a, 2020b). Either EEG or ECG biometrics were combined with psychometrics derived through an un-blinded clinical interview and self-reporting scale. In most instances short (2–5 min) recordings were sufficient to distinguish PTSD participants from controls, with varying degrees of success. Although, the trend for improved predictive power during sleep observed in some studies suggests longer recording periods could lead to the use of EEG vigilance-related markers (Jawinski et al., 2018). There was very little commonality in data acquisition, artifacting or rationale for feature selection, with the relatively high commonality of biomarkers utilised speaking to their ubiquity. Participants were predominately male, who had largely experienced combat or motor-vehicle accidents and only a minority of samples were considered ethnically diverse and demographically representative populations (Cakmak et al., 2021; Dean et al., 2020; Galatzer-levy et al., 2014; Grisanzio et al., 2018; Karstoft et al., 2015; Papini et al., 2018; Shim et al., 2021; Zhang et al., 2021). Other studies were unrepresentative due to smaller samples (Kim et al., 2020; Morris et al., 2020), low ethnic/cultural diversity (Galatzer-Levy et al., 2017; Park et al., 2021; Schultebraucks et al., 2020, 2021; Zhang et al., 2021), low education levels (Toll et al., 2020) and individuals willing and able to participate a bike-riding program (McDonald et al., 2019; Sadeghi et al., 2020a, 2020b). Dataset class imbalances, where variables have uneaven cases of targets to non-targets (Kumar et al., 2021), when present, were accounted for in all studies and confounds were explored for unique sample characteristics in each study. As noted, by Ramos-Lima et al. (2020), unrepresentative trauma sample populations are a persistent issue across ML research into PTSD, which perpetuates misconceptions of the construct. This is of particular importance as only six of the ML studies measured dissociative features (Galatzer-Levy et al., 2017; Kleim et al., 2007; Morris et al., 2020; Papini et al., 2018; Schultebraucks et al., 2020; Zhang et al., 2021), which may have limited the detection of biomarkers associated with PTSD subtypes and perpetuated a misconception of PTSD as a uniform construct.

In most studies, the biomarkers used to classify PTSD status and symptoms were linked to dysregulated arousal, which can also be linked to abnormal defensive responding (Porges, 1995; Williamson et al., 2015). Given the increased appreciation for the embodiment of trauma (Harricharan et al., 2017; Terpou et al., 2019; Thome et al., 2017), it is logical that biomarkers for PTSD symptoms were often associated with frontal sites and cardiac periodicity, as the frontal lobe is considered to mediate autonomic regulation and neurovisceral integration via the central autonomic network (Smith et al., 2017; Thayer and Lane, 2000; Thome et al., 2017). Hence, the need to consider the embodied impact of PTSD and neurovisceral dysregulation is apparent from the studies identified in this review including the absence of research combining EEG and ECG metrics, such as HEP. Future research should also explore if arousal dysregulation in PTSD is associated with vigilance pattern differences that appear likely, but also appear not to have been researched. Returning to the two questions posed in the introduction, the majority of ML research into PTSD has used classical supervised and unsupervised algorithms, focusing on HR, EEG power and various connectivity metrics that performed well. Although, the diversity of methodologies and samples prevents definitive associations between these biomarkers and PTSD symptoms from being drawn, leaving ample scope for future ML research into these associations.

5. Limitations

This review's focus on electrophysiological biomarkers intentionally overlooks other potential PTSD biomarkers that appear in the identified research, such as cortisol (Galatzer-Levy et al., 2017). Variations in data collection methods, such as varying assessment times and sensor counts, smaller size and poor representativeness of samples, along with resampling techniques rather than split or independent data sets for training and testing may limit the generalisability of these predictions and the further advancement in understanding the PTSD construct. Such variation could also impact the emergent biomarkers and their predictive power. This lack of standardisation, validation with independent data and replication highlights the need for shared data and analytic pipelines. Broader adoption of the Research Domain Criteria (RDoC) framework (Cuthbert and Insel, 2013), open EEG databases (van Dijk et al., 2022) and area-specific guidelines, such as those proposed for HRV (Laborde et al., 2017), EEG (Pernet et al., 2020) and connectivity measure research (Miljevic et al., 2022) are recommended to begin addressing these issues. Emphasis was placed upon the diagnosis of PTSD in this review, largely leaving prognostic and status monitoring-related biomarkers unaddressed. This may be of particular importance given the transdiagnostic nature of some biomarkers, such as beta dysregulation, which is also seen in alcoholism and anxiety (Enoch et al., 2008), impulse control issues (Krepel et al., 2021), developmental trauma and affective lability (Jin et al., 2018) and obsessive-compulsive disorder (Dohrmann et al., 2017). Such transdiagnostic markers could be considered endophenotypes (Johnstone et al., 2005), which have important prognostic implications for dysregulated beta activity (Swatzyna et al., 2014). Further work should seek to integrate such transdiagnostic associations and further elucidate the largely unexplained underlying causes and physiological mechanisms underpinning transdiagnostic endophenotype biomarkers, such as beta dysregulation.

6. Conclusion

This scoping review sought to understand which EEG and ECG metrics are associated with PTSD and have been used in conjunction with statistical and ML approaches and to what success. Were there any specific ML methodologies and features emerging from this research that should inform future research? From 24,462 potential references, 124 studies were identified, with only 19 of these meeting all criteria, with the remaining 84 ECG and 21 EEG studies respectively using statistical methodologies. Of the ML studies, six used EEG and 13 ECG. There was a slight trend towards supervised over unsupervised learning methods, with SVM and regression approaches used more commonly. The predictive capabilities of ML with EEG and ECG data were high. Although, newer ML methodologies, such as deep learning algorithms were notably absent, with neural networks only employed in one study. The superiority of such newer algorithms to detect patterns in complex non-linear data (Emmert-Streib et al., 2020) including neuroimaging data (Zhu et al., 2019) is a promising area for future research. Despite methodological variation between studies there appeared to be some commonality in utilised biomarkers, with beta and theta power and various connectivity metrics appearing most predictive in the EEG research, while ECG research focused on elevated HR and low HRV values. No ML studies analysed EEG and ECG metrics concurrently and only one study sought to classify PTSD subtypes. Importantly, this scoping review builds upon the recent findings from Ramos-Lima et al.'s (2020) recent review by explicitly focusing on identifying studies using resting-state ECG and EEG data that were excluded from this previous review. The current findings highlight how statistical and ML research has been conducted using resting-state biomarkers to classify PTSD

status and symptoms and argues the need to explore transdiagnostic endophenotypes biomarkers (Johnstone et al., 2005), specifically, biomarkers of neurovisceral integration (Thayer and Lane, 2000) and vigilance state changes (Arns et al., 2011) to better understand the multimodal nature of PTSD. Future research should consider using naturalistic resting-state events such as sleep-sub-stage transitions (Roth, 1961) that have been associated with changes in HRV (Boudreau et al., 2013) and HEP amplitudes (Lechinger et al., 2015) that are considered to relate to autonomic disturbances in PTSD (Clancy et al., 2017). This builds upon the research identified in this review documenting the importance of heart rate changes to refine predictive biomarkers for PTSD while associating it with HEP potentials related to frontal lobe regulatory structures that are potential source structures to many of the EEG biomarkers utilised in research highlighted by this review.

Declaration of competing interest

Financial support from the NSW Service for the Rehabilitation and Treatment of Torture and Trauma Survivors (STARTTS). The authors have no financial interests or conflicts of interest to disclose.

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