TOPICAL REVIEW

Review of wearable technologies and machine learning methodologies for systematic detection of mild traumatic brain injuries

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Abstract

Mild traumatic brain injuries (mTBIs) are the most common type of brain injury. Timely diagnosis of mTBI is crucial in making ‘go/no-go’ decision in order to prevent repeated injury, avoid strenuous activities which may prolong recovery, and assure capabilities of high-level performance of the subject. If undiagnosed, mTBI may lead to various short- and long-term abnormalities, which include, but are not limited to impaired cognitive function, fatigue, depression, irritability, and headaches. Existing screening and diagnostic tools to detect acute and early-stage mTBIs have insufficient sensitivity and specificity. This results in uncertainty in clinical decision-making regarding diagnosis and returning to activity or requiring further medical treatment. Therefore, it is important to identify relevant physiological biomarkers that can be integrated into a mutually complementary set and provide a combination of data modalities for improved on-site diagnostic sensitivity of mTBI. In recent years, the processing power, signal fidelity, and the number of recording channels and modalities of wearable healthcare devices have improved tremendously and generated an enormous amount of data. During the same period, there have been incredible advances in machine learning tools and data processing methodologies. These achievements are enabling clinicians and engineers to develop and implement multiparametric high-precision diagnostic tools for mTBI. In this review, we first assess clinical challenges in the diagnosis of acute mTBI, and then consider recording modalities and hardware implementation of various sensing technologies used to assess physiological biomarkers that may be related to mTBI. Finally, we discuss the state of the art in machine learning-based detection of mTBI and consider how a more diverse list of quantitative physiological biomarker features may improve current data-driven approaches in providing mTBI patients timely diagnosis and treatment.

1. Introduction

The high prevalence of traumatic brain injury (TBI) among both civilian and military populations constitutes a major public health crisis. In 2013 the Center for Disease Control and Prevention (CDC) reported nearly three million TBI-related emergency room visits, hospitalizations, and deaths [1]. In the
general population, falls are the leading cause of TBI and are responsible for over a third of TBI-related emergencies (35%) followed by blunt head traumas (20%), traffic accidents (16%), and assaults (11%) [2]. Two of the most common identified risk factors are sex (males are nearly three times more likely to suffer a TBI than females) and a bimodal age pattern (persons 65 years and older, and children under 14 years old) [3]. Progress has been made to prevent motor-vehicle crashes, and along with improvements in motor safety equipment this progress has resulted in a decrease in the number of TBI-related hospitalizations and deaths from 2007 to 2013. However, during the same time, the number and rate of older adult fall-related TBIs have increased substantially [4]. Therefore, despite the considerable public interest on sports-related concussion (SRC) in youth, the findings in this report suggest that TBIs attributable to older adult falls, many of which result in hospitalization and death, should receive public health attention. There is also a growing body of evidence on racial and ethnic disparities within TBI and in the United States social disparities in health outcomes are found wherever they are sought [5, 6].

Of all TBI severities, mild TBI (mTBI) accounts for the vast majority, up to 90%, of TBI cases [7]. The true number and impact of mTBI are underestimated as many mTBIs, up to 50%–90% [8], or over 600 per 100 000 [9], go unreported or are unrecognized [10]. Although 85%–90% of individuals spontaneously recover from mTBI in a matter of weeks [11], mTBI symptoms and deficits can persist for more than 1 month in a significant minority of patients. This is known as post-concussion syndrome [12], which can include symptoms such as headache, light sensitivity, mood changes, and difficulty focusing [13].

Sleep-wake disturbances can occur acutely and chronically after mTBI [14–18]. Acute sleep disturbances in mTBI are characterized as either insomnia (or multi-awakenings) or excessive sleeping. Often the inability to maintain sleep after mTBI is associated with some combination of headache or pain (commonly neck or back), and mood disorder (depression and anxiety), but can be related to circadian rhythm disruption. Acutely, sleep disturbance can occur upwards of 50%–75% in mTBI subjects [19]. While improvement is common during the first 6–12 months, 40% continued to have sleep complaints at 1 year post (this does not indicate what proportion had sleep disturbance prior to sustaining mTBI). It is often difficult to disentangle the intertwined influence sleep complaints and sleep quality have on, or are caused by, depression, anxiety, and pain (see [14]). Moreover, poor sleep quality is often associated with prolonged recovery and current level of concussive symptomatology [20, 21]. The use of smart phone apps and wearable devices can measure sleep quantity and quality, allowing for better quantification and cause of the sleep disturbance.

Athletes in contact sports such as American football, rugby, ice hockey and soccer [22] are especially at risk of suffering mTBI, and according to a 2017 CDC report, approximately 15% of US high school students were estimated to have experienced a concussion in a 12 month period with an estimated 6% having two concussions or more [23]. Although the connection between mTBI and suicide has not been made firm and is not the focus of this paper, suicide is the third leading cause of death among adolescents and a self-reported SRC has been argued to be associated with risk for suicide completion [24]. In contrast to civilians, military service members have an even higher prevalence of multiple mTBIs (15%–23%) due to repeated blast and non-penetrating bullet strikes while on the battlefield [25]. Repeated mTBIs have been shown to have serious persisting effects such as reduced cognitive performance [26], depression, anxiety [27], and increased risk of developing dementia and other neurodegenerative diseases [28–31]. Although periods of cognitive and physical rest with active treatment and management immediately after injury will lessen symptom severity and promote recovery [32], undiagnosed mTBI can result in more severe brain injury and long-term sequelia via second impact syndrome.

Therefore, the ability to rapidly diagnose mTBI immediately following a potentially injurious event is critical to recovery and outcome [33]. In addition to vulnerable populations such as the elderly, children under 14 years old, and racial and ethnic minorities, the two areas where this is most critical are SRC and combat-related (mechanical or blast) mTBI sustained by warfighters. These two settings represent a complex and challenging endeavor to find a highly sensitive and specific tool to diagnose mTBI [34] as there is currently no objective gold-standard. Allowing athletes or military personnel to continue while concussed can have immediate impact on their ability to function well in the field along with potentially long-term, detrimental brain health consequences. Therefore, as current symptom-based sideline evaluation is unreliable at providing fast and accurate diagnosis of mTBI [35–40], developing a real-time quantitative detection system for mTBI is critical as early management results in less brain injury and better outcomes as evidenced by numerous studies [41].

Recent advances in wearable technologies and machine learning methodologies offer clinicians and engineers the opportunity to work together in order to leverage multi-parameter sensing and signal processing for quantitative mTBI diagnosis. These parameters are referred to here as physiological biomarkers in order to be more descriptive and to remain consistent with some literature. A conceptual view of such novel systems is depicted in figure 1 where a
A diverse set of physiological biomarkers are integrated with pre- and post-processing of signals in multiple modalities. This could lead to an algorithmic framework resulting in confident mTBI detection. There are numerous open engineering research questions in developing a reliable, convenient, and sensitive platform to diagnose mTBI in the acute phase. These include how to integrate all the mTBI-related sensors in a wearable platform that can be used on-site, how to minimize the impact of sensing inaccuracies to improve detection reliability, and how to perform low-power signal processing directly on the wearable devices.

This paper reviews current clinical findings, innovations in wearable recording devices, and machine learning approaches important to the development of much-needed quantitative and non-invasive diagnostic systems for mTBI in the acute phase. A wearables-based system could be used in place of slow and unreliable symptom-based protocols, expensive neuroimaging systems, and specialized bedside medical hardware in a variety of settings including and beyond SRC and military injury. To motivate engineering challenges in building reliable hardware and software for non-invasive mTBI detection, we first review the diverse pallet of possible physiological biomarkers of mTBI as indicated by recent clinical research. Section 2 overviews this research as well as present difficulties in diagnosing mTBI in the clinical setting, sports field, and battlefield. Section 3 then overviews the advances and challenges of recording the biomarkers of mTBI reviewed in section 2 on portable, low-power wearables in an integrated fashion. Finally, section 4 discusses the state-of-the-art in machine learning-based approaches to integrate non-invasive biomarker data, until now mostly electroencephalography (EEG) data, for mTBI detection and outlines the potential of integrating a more diverse list of clinically relevant, wearable-recorded biomarkers to increase diagnostic reliability.

2. Clinical challenges

Despite their classification as ‘mild,’ mTBI typically results in a constellation of physical, cognitive, emotional, and behavioral symptoms and deficits [42]. At a minimum, mTBI can be defined as a complex pathophysiological disruption of nervous system function from trauma to any part of the brain by a direct or indirect (i.e. whiplash) impulsive force [43–46]. Although loss of consciousness (LOC), when present is pathognomonic of a TBI occurring (meaning one has occurred), LOC is not necessary to have a mTBI and in fact 90% of mTBIs do not involve LOC. Many factors that are now known to contribute to injury severity and recovery were not factored into defining mTBI initially. For example, the mechanism of injury (acceleration/deceleration, blunt trauma, missile injury, blast explosion), presence or absence of neuroimaging findings, and recovery time influence mTBI severity and outcome [47]. The definition of mTBI developed by the CDC and panel of experts include one of the following conditions attributable to head trauma: observed or self-reported transient confusion, LOC <30 min, posttraumatic amnesia, irritability, sensory sensitivity, headache, dizziness, fatigue, poor concentration, and memory impairment [8]. Table 1 lists the signs and symptoms found in mTBI [48]. Various definitions for concussion have also been proposed, each having its strengths and weaknesses but nothing has been shown to demonstrate high predictive positive/negative values which is vital [49]. To further complicate matters, the terms
concentration and mTBI are often used interchangeably when in fact the former may be a subset of the latter. In this review, we will use the term mTBI, which includes concussion as a subset.

At present, there are no objective measures to immediately diagnose mTBI [35]. There are often no overt signs of mTBI such as LOC [50] and sometimes individuals are unaware they sustained a mTBI or refuse to stop their activity [36–40]. While the phrase ‘When in doubt sit them out’ is easy to use for our youngest athletes, it is challenging to use such a guideline for adults actively engaged in military combat or professional sports, for example. Moreover, mTBI often does not have a consistent pathognomonic sign at the time of injury; for example, LOC occurs only about 10% of the time [51]. There are other pathognomonic signs that occur instantaneously at the time of the event such as gross motor instability, focal neurological signs (such as nystagmus or impaired balance), or retrograde and post-traumatic amnesia. However, these are not common after an mTBI and thus would make it even more challenging to develop tests specific to mTBI.

Furthermore, research is needed to better to establish and define the most common mTBI clinical profiles or and their associated conditions such as cognitive, ocular-motor, headache/migraine, vestibular, and anxiety/mood disorders and associated conditions (cervical strain and sleep disturbance). This approach of symptom profile classification aids in a more informed assessment, target treatment and clinical outcome trajectory for mTBI [53]. A recent study found that the most prevalent mTBI subtypes for pediatric and adult populations were headaches/migraine (0.52; 95% CI = 0.37, 0.67) and cognitive (0.40; 95% CI = 0.25, 0.55), respectively. In pediatric patients, the prevalence of the vestibular subtype was also high (0.50; 95% CI = 0.40, 0.60). Adult patients were 4.4, 2.9, and 1.7 times more likely to demonstrate cognitive, vestibular, and anxiety/mood subtypes, respectively, as compared with their controls (P < 0.05). Furthermore, ocular-motor in adult patients (SMD = 0.72; P < 0.001) and vestibular symptoms in both pediatric and adult patients (SMD = 0.18 and 0.36; P < 0.05) were significantly worse in mTBI patients than in controls [54].

SRCs serve as naturalistic experimental laboratories to improve upon acute diagnosis of the mildest forms of mTBI. SRC is one of the most critical medical issues in sports medicine and arguably the most challenging injury to diagnose on the field [55, 56]. The ability to diagnose and develop more objective standardized assessment techniques for SRCs has improved tremendously over the past 25 years [55]. Most professional contact sport leagues, National Collegiate Athletic Association (NCAA), and High

| Domain                    | Description                                                                                                                                 |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Red flags                  | Neck pain, double vision, extremity weakness or tingling/burning, severe or worsening headache, seizure, LOC, deteriorating consciousness, vomiting, increasing agitation, restlessness or mood swings. |
| Observable signs           | Lying motionless, gross motor instability or balance impairment, disorientation nor confusion, or inability to respond appropriately, blank or vacant stare, or facial injury after head trauma |
| Orientation questions      | Questions of orientation about current event in which the athlete is participating for SCAT5 and general orientation of place, time, and date for MACE-2 |
| Documentation of injury mechanism | In MACE-2 (blow to head, fall, gunshot, blast, etc) but not SCAT5                                                                                                                                       |
| Glasgow coma scale         | Administration of formal GCS                                                                                                                                                                             |
| Cervical spine             | Assessing for limited range of motion (ROM), pain, numbness, tingling or weakness.                                                                                                                    |
| Symptom evaluation         | 22 mTBI-related symptoms using a seven-point Likert-type scale for SCAT5. For MACE-2 yes no\(^{-1}\) for nine symptoms plus other                                                                           |
| Orientation                | Five general orientation questions                                                                                                                                                                        |
| Immediate memory           | A five (both)- or ten (SCAT5 only)-word list learning across three trials                                                                                                                                  |
| Concentration              | Digits backwards and months in reverse order                                                                                                                                                              |
| Neurological screen        | Cervical ROM, reading aloud, ocular-motor testing, finger-nose coordination, and tandem gait                                                                                                              |
| Balance examination        | mBESS for SCAT5 and single leg stance and tandem gait for MACE-2                                                                                                                                          |
| Memory recall              | Delayed recall of word-list                                                                                                                                                                               |
| Vestibular-ocular motor (VOM) testing | VOM screening in MACE-2 but not SCAT5                                                                                                                     |
Schools in the United States have formalized assessment guidelines, assessment tools and criteria for return to play (e.g. [57]). However, difficulties of mTBI diagnostics including complex testing stress the need of objective, sensitive, and fieldable multiparametric assessment [8, 41].

In the following sections, we will first review the wide array of currently in-use clinical observation and symptom-based assessments for mTBI and highlight their shortcomings in speed and sensitivity in detecting mild injury. Then we will review physiological biomarkers that are currently in use for clinically evaluating mTBI, those which are being used experimentally, and those which have not yet been used but may be of value.

### 2.1. Initial evaluation

Brain injury severity is traditionally evaluated using the Glasgow Coma Scale (GCS), which ranges from 3 (severe coma) to 15 (normal). First developed in 1974, the GCS is the standard for determining TBI severity [58]. A GCS score between 13 and 15 is defined as mTBI according to the Advanced Trauma Life Support group [59]. Importantly, the observed scores have to be attributable to recent head trauma [8]. It is possible for a patient to have a normal post-injury GCS score, but have a significant structural brain injury [60].

A variety of methods are currently being used for early diagnosis of mTBI. Presently, a combination of clinical observation, symptoms reporting, neurological assessment, balance assessment and brief oral neuropsychological testing form the basis for how mTBIs are assessed acutely. Several tests have been developed for aiding in the initial diagnosis of mTBI. The CDC developed the Acute Concussion Evaluation (ACE) [44] to help health-care professionals assess for mTBI but only in the outpatient office setting. ACE is not suitable as for use as an immediate diagnostic test at the scene of the injury.

Sport and military activity require rapid and accurate assessment for mTBI to prevent a more severe brain injury from occurring. The present state of the art for diagnosing mTBI at the time of injury relies on a multi-system approach combining subjective and objective measures. The most widely used tool internationally in sports is the Sideline Concussion Assessment Tool (SCAT; currently SCAT5 [61]) while the military created the Military Assessment of Concussion Evaluation (MACE; currently MACE-2) which was designed to diagnose mTBI primarily in the deployed setting [62, 63]. Both tools use a multi-system approach. While they have several components in common, MACE-2 is more comprehensive and takes longer to administer (about 25 min) and thus is designed to be more comprehensive than SCAT5. The SCAT5 and MACE-2 include several previously validated tools. SCAT5 is used by the Federation of International Football Associations and the International Olympic Committee and is the core component (with some variations noted) of sideline assessment for all of the major sport leagues in the USA and NCAA along with many amateur leagues and high schools. SCAT5 was designed for licensed healthcare professionals, traditionally physicians and athletic trainers, to help diagnose SRC. SCAT5 takes a minimum of 10 min to administer and may take up to 20 min depending upon the severity of the brain injury. An age-appropriate Child SCAT5 was designed for children <12 years of age [64, 65]. The MACE-2 was designed for military personnel, primarily during deployment. Both the SCAT5 and MACE-2 are very similar in the areas assessed and the questions asked. There are slight differences where the SCAT5 used the modified Balance Error Scoring System (mBESS) and the MACE-2 [66] adds the Vestibular-Ocular Motor Screen (VOMS) [67, 68]. Table 1 describes the different sections making up the SCAT5 and MACE-2. The SCAT5 also has additional components adaptable to the out-patient office visit follow-up examinations.

In addition to the SCAT, other tests have been tested and found useful in diagnosing SRC on the sidelines at the time of injury. Building upon the concept that mTBIs are a multi-system injury, The King-Devick Test (KD) measures subtle visual scanning impairments acutely [69]. KD is a short 2–3 min visual scanning measure where the individual reads numbers across the booklet left to right for multiple lines on stimuli pages. The pages vary in difficulty based upon the spacing of the numbers. The dependent measure is the total time it takes to read the three stimuli cards. Baseline assessment is required to compare changes in total time after an accident. The test has good test–retest reliability. There is a normal practice effect where healthy controls improve their time (quicker by about 2 s) across readings, compared to concussed athletes that often take longer by about 5 s [70]. KD is a promising measure with high sensitivity (86%) and specificity (90%) in detecting mTBIs [69]. Sensitivity and specificity improve when KD is combined with other common quick sideline assessment of concentration and memory and balance [71, 72].

Several computerized neurocognitive tests are being used, in the outpatient setting such as the Computerized Automated Neuropsychological Assessment Metrics 4 TBI-Military (ANAM4), Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Defense Automated Neurobehavioral Assessment, and CogSport [73]. These tests are currently not practical to use on the sideline or the scene of the injury as they require a laptop or desktop computer. However, tablet and mobile device-based tests have recently been developed and are amenable for use on the sideline. For example, Sway Balance uses the motion sensors in the mobile device to assess balance and also has cognitive measures of reaction,
memory, and judgment built in [74]. C3Logix is another table-based, multi-system diagnostic tool used for acute assessment of mTBIs and can be used on the sidelines of sporting events [75].

In the following section we will review various physiological biomarkers that are already in use for mTBI diagnostics, those which are being used experimentally, and those which have not been used but could be of value. We will focus on the non-invasive physiological biomarkers, which can be easily implemented in the portable, fieldable devices.

2.2. CNS evaluation
An extensive body of knowledge has been amassed on the neuropathology and pathophysiology of mTBI. Extensive use of magnetic resonance imaging (MRI) has demonstrated various brain tissue abnormalities such as diffuse axonal damage and microhemorrhage [76–80]. Functional MRI (fMRI) indirectly measures brain activity by detecting blood flow changes in particular brain regions. Data obtained using fMRI indicate abnormalities of blood flow, and hence brain activity abnormalities following mTBI [76, 81]. Magnetoencephalography (MEG) is another a functional brain imaging technique with high temporal resolution and has an important role in TBI research, especially in mTBI, since mild injury may not have detectable features in conventional, anatomical imaging techniques. MEG has been shown to be useful in the detection of TBI, characterization of brain connectivity abnormalities associated with TBI, and correlation of brain signals with post-concussive symptoms [82]. However, imaging techniques like MRI, fMRI, and MEG are not suitable for mTBI diagnosis in the field as portable devices.

Numerous approaches have been developed to diagnose mTBI using EEG activity. These approaches include (but are not limited to) frequency and amplitude analysis, coherence for functional analysis, and Shannon entropy for the measurement of complexity. EEG non-invasively assesses brain electrical activity. It is assumed that brain injury, including mTBI, would alter electrical brain activity. The literature on the various approaches to reveal abnormal brain electrical activity following mTBI is extensive (e.g. [83]). However, none of the various EEG acquisition and analytical methods provide sufficient sensitivity and specificity in the diagnosis of mTBI. Despite a large number of publications on a multitude of EEG abnormalities in mTBI, this body of evidence suffers from much of the data coming from proprietary algorithms, and authors and their access to various sources of funding for development with the potential to introduce conflicts of interest.

Electrophysiological recordings such as EEG and event-related potential (ERP), have been amongst the most studied physiologic indices after TBI. EEG monitoring requires a relatively inexpensive, easy to implement and non-invasive technology [84].

Digitization of EEG (or quantitative EEG referred to as qEEG) allows for extensive mathematical signal analysis [85]. Absolute and relative amplitude (µV/time point) as well as absolute and relative power of frequencies (µV²/time point) composing the signal (frequency spectrum obtained by Fast Fourier transform), is the most frequent approach to analyze qEEG. Most studies report EEG recording in resting-state, task-free subjects.

Immediately after mTBI, epileptiform activity (high-amplitude sharp wave) is commonly observed and accompanied by a decrease in alpha (7.5–12.5 Hz) and increase in delta (1.5–2.5 Hz), theta (3.5–7.5 Hz) and beta (12.5–35 Hz) frequency bands; and/or increase in theta/alpha ratio [86–88]. It is worth noting that similar pattern of changes has also been observed in patients suffering from depression [89], suggesting common underlying mechanisms of mTBI-related changes, especially chronic post traumatic encephalopathy and depression as indicated by electroencephalographic parameters.

Functional connectivity, which determines the relationship between at least two channels or brain regions at one point in time, reflects the short and long-distance neuronal communications [90]. Coherent theta oscillation between the hippocampus-entorhinal cortex, involved in cognitive processing, is a well-established parameter of physiological functional connectivity [91]. Axonal injury is known to occur in TBI [92], therefore, functional connectivity, known to be altered in psychiatric disease [93], is a putative relevant biomarker for mTBI. Functional connectivity is measured by EEG coherence which can be assessed in the time and frequency domain (phase-synchronization, phase locking value, phase-coupling etc.), and in the geometry of embedded data [83, 90]. As indicated, functional connectivity is a promising biomarker deserving more systematic scrutiny.

The brain connectivity changes were observed after mTBI and present a potent biomarker [83]. The brain can be considered as a complex system, and information theoretic measures of the complexity of brain electrical activity such as Shannon entropy can be a good predictor of dysfunction. Shannon entropy is a measure of the uncertainty associated with a random variable, in this case with the EEG time series, and is computed by summing the probabilities of possible values of the random variable multiplied by the negative logarithm of those probabilities. The information quality of a signal is the entropy of the discrete wavelet transform of that signal. Few studies report the use of entropy and information quality measurement after mTBI, though information quality was recently shown to decrease in parietal, temporal, and occipital regions after mTBI in athletes [94] as detected 7 days after injury. Shannon entropy is a promising measure for automatic techniques for epilepsy detection [95] and
may be similarly promising in EEG-based diagnostic approaches for mTBI, though entropy and other information theoretic measures have been understudied in TBI and needs further investigation [83].

Recently, the brain factor index (BFI), developed by medical neurotechnology company BrainScope (BrainScope Company, Inc.), has been used as a measure of functional connectivity after mTBI. A seminal study [96] showed a correlation between phase synchrony of the frontal and frontotemporal regions and mean fractional anisotropy of four major white matter tracts, measured via diffusion tensor imaging on MRI after blast-injury in warfighters. Several other studies confirmed BFI as a statistically significant predictor of mTBI 72 h [97] and 14 days post injury [98].

Other parameters of EEG studied in mTBI deserve additional consideration. Recently, Discrete Padé Transform, a novel method to capture a signal’s spectral characteristics based on Padé Approximation Theory, was introduced for EEG spectral analysis, taking into account the noise and non-stationary nature of the EEG [99]. The authors argue that this new operation results in a signal decomposition closer to reality that may better reflect the physical structure of the signal [99]. Other analyses of connectivity such as the microstate topography analysis [100], and complex network activity [101] can also be applied to diagnose acute mTBI.

EEG microstates are topographical maps of the brain electrical activity—electrical potentials—due to the multi-channel scalp EEG recording. These microstates have a high temporal and good spatial resolution and stay stable for about 80–120 ms. Analysis of these EEG microstates led to the classification of four classes of topographies. Absence of these maps or reduction in their frequencies or duration could be used as an indicator of neurophysiological abnormalities [102] in mTBI.

Brain structural or functional organization can also be assessed by complex network activity where brain areas represent nodes of a network, and the edges stand either for structural or functional connections. Complex network activity is assessed with the tools of the complex network theory. Centrality, functional segregation and integration, cross-correlation, are among the most used methods in complex network analysis of brain connectivity [103]. Disruption of these networks could appear in mTBI and be used as a diagnostic method.

In summary, EEG biomarkers and other biomarkers directly related to the CNS have clearly been given ample attention in the search for noninvasive, quantitative parameters to improve mTBI diagnosis. However, other physiological parameters such as those related to cerebral blood flow (CBF), the ANS, and physiological responses to external stimuli may be of value in quantitative mTBI detection as well. In the following three sections, we review parameters related to cerebral circulation, ANS dysfunction, and physiological response that have been shown to be of value in the diagnosis of mTBI, as well as related parameters which have not been explored systematically for mTBI yet could improve diagnostic methods, especially in combination with other physiological biomarkers.

2.3. Cerebral circulation evaluation

fMRI data and histopathological findings suggest aberrations of CBF. Adequate CBF is critical for the maintenance of normal brain activity. It has been repeatedly demonstrated that mTBI is accompanied by abnormalities of CBF, in concussed contact sport athletes [104, 105]. Non-invasive transcranial Doppler (TCD) can provide important information on changes in CBF following mTBI [106, 107] including amplitude and shape of the pulse wave in the middle cerebral artery. Measurement of TCD waveform along with non-invasive arterial pressure (AP) measurement (e.g. finger plethysmography) allows evaluation of integrity of cerebral autoregulation affected by mTBI [108–110].

Mild TBI can be accompanied by increased intracranial pressure (ICP) [111, 112]. ICP is a critical physiological biomarker, which determines cerebral perfusion pressure and, hence, provides an estimate of the sufficiency of cerebral blood supply. ICP can be evaluated non-invasively. The methods of non-invasive measurement of ICP include optic nerve sheath diameter measurement (space between optic nerve and the surrounding sheath using, e.g. optical coherent tomography) [113], two-depth ophthalmic artery Doppler ultrasonography [114] or digital orbitoplethysmography [115]. Optic nerve sheath diameter has been found to be increased in female collegiate soccer players at the end of a season [116]. Of special interest are model-based ICP estimates which do not require complex or invasive measurements and can be derived from arterial blood pressure (BP) [117]. Another interesting approach for ICP evaluation is determination of skull expansion based on the measurement of linear minute voltage variations in skull strain [118]. The degree of cerebral blood oxygenation in addition to CBF can be measured non-invasively using near-infrared spectroscopy [119], which can provide information on the sufficiency of cerebral blood oxygenation. Changes in the functional near infrared spectroscopy have been found in mTBI and those changes can be used to monitor recovery [120, 121]. Rheoencephalography provides measurement of head bioimpedance and hence evaluation of CBF. Moreover, it is possible by modifying parameters of impedance measurement to determine CBF velocity, CBF/CSF ratio, and other indices [122–124] (here CSF stands for cerebrospinal fluid).
2.4. ANS evaluation
Dysfunction of the ANS has been proposed as another indicator of acute mTBI [13, 125, 126]. The identification of ANS dysfunction is a promising component of multimodal mTBI diagnostics based on a large body of existing evidence and the relative ease of collecting some of these data non-invasively.

One of the most explored and widely used physiological biomarkers for autonomic function evaluation is heart rate variability (HRV), which reflects acute and sometimes persistent abnormalities after TBI [127]. HRV analysis is most often used to evaluate balance between parasympathetic and sympathetic systems [128–131]. Importantly, HRV closely relates to ICP [132]. There are numerous physiological biomarkers that can be extracted from HRV alone. Moreover, electrographic measurement of a single heartbeat can provide additional information as was shown in a study indicating that 88% of TBI patients demonstrate ST segment abnormalities on electrocardiogram [133].

Another important biomarker related to ANS dysfunction include systolic BP (SBP), arterial pulse waves, and oximetry. While the overall tendency for increased SBP [151] was observed suggesting increased sympathetic tone, analysis of the arterial waveform, e.g. in the temporal artery of the scalp, can also be indicative of increased sympathetic tone, which may accompany mTBI. Increased arterial stiffness has been observed after mTBI [152]. Comparably, acceleration of leg-arm arterial pulse wave can reflect changes in arterial stiffness, which reflects sympathetic nerve system activity [134]. Oximetry (photoplethysmography) can also be employed for determining arterial waveform along with the blood oxygenation [153, 154]. Orthostatic hypotension often observed following mTBI, in spite of increased sympathetic tone [52] closely relating to CBF autoregulation.

Changes in pupillary behavior, skin conductance, and body temperature can also indicate changes in the ANS. The pupils of the eye receive opposed sympathetic and parasympathetic innervation, causing pupillary dilation and constriction, respectively. The summation of these two components of the ANS results in changes in pupil size and behavior in response to light, and reflects a gross, easy to measure indicator of its function. Thus, it was demonstrated that velocity of the constriction of pupillary diameter decreases following mTBI [13, 148]. GSR or, more widely, electrodermal activity (EDA) [155] has been used to evaluate status of autonomic, prevalentely, sympathetic system, for a long time. Analysis of EDA activity models lately became more sophisticated and provide more information. GSR has been shown to be informative in mTBI diagnostics [156, 157]. When integrated into the multisystemic model, GSR will provide additional information of the autonomic status [158, 159]. Body temperature is determined by the interaction of multiple factors, including energy metabolism and autonomic system activity.

There are still underexplored physiological biomarkers that might be informative in the diagnosis of mTBI. Table 2 provides a summary of valuable biomarkers in diagnosis of mTBI with relevant references. For example, rheoencephalography (RHE), transcranial measurement of brain impedance, which allows to evaluate intracranial space, intracranial blood content, CSF and the changes of these volumes may reflect their changes occurring synchronously with the pulse wave [147]. Using RHE at different frequencies may provide additional information on the status of the brain after mTBI. Combined with other complementary parameters, RHE might be a useful measurement for making the diagnosis of acute mTBI.

2.5. Physiological responses
ERPs are typical changes in EEG activity in response to standardized sensory, visual, or auditory stimuli. The latency and amplitude of ERPs after TBI have been the most frequently studied [77, 96, 167]. Changes in the P300 component of visual ERP seems to be the most informative in the context of mTBI. However, it is still unclear if ERPs can be used as reliable predictors of mTBI [168]. Inclusion of these physiological biomarkers may add validity to an integrative evaluation of mTBI.

Other functional tests have been proposed for evaluation of physiological functions following mTBI. Eye tracking is one such method for mTBI diagnosis [144–146], and can be easily implemented in a field setting. Abnormal saccades and nystagmus are often observed following mTBI [37, 134, 135].

Alteration in balance is associated with mTBIs and companies have taken advantage of portable electronic devices such as cell phones and tablets to assess changes in postural stability after mTBIs with precise accuracy and reliability [136, 137]. Similarly, companies have included measures of reaction time, decision making, processing speed, eye tracking and memory into portable electronic devices [169]. Oculomotor abnormalities closely relate to the vestibulo-ocular reflex, allowing the brain to maintain gaze stability while moving the head without feeling dizziness or vertigo, which are pathognomonic signs of sustained mTBI [138]. VOMS is a newer measure of provocation of vestibulo-ocular and ocular-motor deficits following mTBIs [68]. While not part of any formal sideline assessment measure, VOMS is easily adoptable to a quick, immediate assessment of mTBI and has shown incremental validity in assessing mTBIs over cognitive assessments [139–141]. For example, the EYE-SYNC® device (SyncThink, CA) allows for evaluation of smooth eye pursuit saccades along with VOMS has been cleared by the US Food and
Drug Administration (FDA) as a diagnostic tool for mTBI.

Functional testing of baroreflex sensitivity (BRS) can be implemented by assessing the body response to changing position as in squatting versus standing [150, 163, 164] or laying versus standing [165]. Decreased BRS sensitivity following mTBI is a sign of abnormal autonomic reactivity. These observations are supported by data showing decreased BRS during Valsalva maneuver (forced respiration) [151, 166]. Similarly, eye pressure induces parasympathetic activation effect, which can be observed in HRV shift toward parasympathetic response after mTBI [170].

Forced face cooling by applying ice to the forehead induced attenuated sympathetic response as evaluated by HRV analysis and BP [171]. Low to moderate steady-state exercise, isometric handgrip test, and orthostatic maneuvers [127, 131] have all been explored as possible mTBI diagnostic parameters. Simple response time, pushing a button in response to a visual signal, has been shown to be sensitive for diagnosis of mTBI [146, 162].

Alternative invasive methods such as blood biomarkers can detect mTBI [172]. However, their value in acute mTBI diagnosis at the scene of the injury has not been proven as analysis of blood requires technology and processing time that is not available on the sideline [173, 174]. Therefore, we purposefully limited our review to the non-invasive diagnostic tools.

There is ample, untapped opportunity to leverage a diverse combination of biomarkers to develop a highly accurate diagnostic device for mTBI. As clinical research focuses the list of most useful biomarkers and signal modalities for quantitative mTBI diagnosis, it is important to identify the minimum necessary, mutually additive set of physiological biomarkers to establish a confident prediction. Unfortunately, currently there is no clinical, imaging or test that serves as a gold-standard for assessing mTBI. Developing a multimodal diagnostic device to detect mTBI that will incorporate multiple data points will allow a more accurate diagnosis particularly with the addition of machine learning.

3. Wearable technologies for mTBI screening

The key component to quantify the non-invasive physiological biomarkers related to mTBI is the electronic sensors, which either directly record bioelectrical signals such as EEG and ECG or convert physiological biomarkers into electrical signals, followed by signal conditioning. These conditionings may include low-noise amplification, filtering, and digitization. The acquired digitized data is then sent to a smartphone or a tablet for further signal processing [175]. A high-level view of the whole system is depicted in figure 1, with a more detailed view of the signal acquisition path and the transducers shown in figure 2.

Conventional physiological data acquisition systems mostly rely on benchtop laboratory instruments [176, 177]. While these instruments provide the highest signal fidelity in clinical settings, they may not be the best candidates for rapid mTBI diagnosis immediately after injury in the field. On the other hand, recent advances in wearable technologies are enabling a transformative solution for front-line personnel, researchers, and clinicians to evaluate mTBI-related impairments in the acute phase. These

### Table 2. Summary of physiological biomarkers of potential value in diagnosis of mTBI.

| Physiological biomarkers                  | References |
|-------------------------------------------|------------|
| CNS status informative biomarkers         |            |
| EEG                                       | [83, 85–88, 96] |
| Nystagmus                                 | [33, 134, 135] |
| Vestibular/vestibular-ocular function     | [68, 136–141] |
| Impaired object tracking/Saccades         | [37, 134, 135, 142–146] |
| TCD                                       | [106–110] |
| ICP                                       | [111, 112] |
| Optic nerve sheath diameter               | [113, 116] |
| Ophthalmic artery ultrasonography         | [114] |
| Digital orbitoplethysmography             | [115] |
| Near-infrared spectroscopy (NIRS)         | [119–121] |
| Rheoencephalography                       | [122–124, 147] |
| Autonomic Nervous System informative biomarkers |            |
| Pupillary reflex                          | [13, 148–150] |
| Blood pressure                            | [151] |
| Arterial stiffness                        | [134, 152] |
| Oximetry                                  | [153, 154] |
| Galvanic skin response                    | [155–157] |
| Body temperature                          | [158, 159] |
| Physiological/functional responses informative biomarkers |            |
| ERP (event related potential)             | [77, 96, 160] |
| Reaction/response time                    | [146, 161, 162] |
| Baroreceptor sensitivity                  | [150, 151, 163–166] |
battery-powered, small-foot-print devices could perform in-field testing at the time of the injury or be used as wearables which can be carried on a 24/7 basis and communicate with a central monitoring site or patients’ portable devices [178]. Such a paradigm shift brings solid objective data for the clinical team to understand how the patient progresses in the physical, cognitive, and behavioral domains after the injury. Although these wearable technologies have not been formally adopted into any standardized mTBI protocols, several of them have shown promising data that they are sensitive to acute changes following mTBI.

This section reviews the state-of-the-art wearable technologies with a focus on (a) the sensing mechanisms, (b) commercially available and prototyping non-invasive devices to measure mTBI-related parameters discussed in section 2, and (c) their efficacy. We will focus on the non-invasive physiological biomarkers which can be easily measured in the field to make a go/no-go decision.

3.1. Electroencephalogram (EEG)
As discussed in section 2, EEG measured through a wearable device has the potential to assess mTBI and was designed in part to be used by the military for ‘in-field’ situations where diagnosing a mTBI or stroke is critical [179, 180]. EEG measures the brain’s spontaneous electrical activity by performing real-time voltage recording through multiple electrodes placed on the scalp [181]. Two major electrical specifications for EEG devices are the number of channels and the signal fidelity. The number of channels is critical because insufficient spatial sampling may distort the topographic mapping of the EEG signals and make the source localization indistinguishable, an effect termed spatial aliasing [182]. Most commercially available wearable EEG devices such as headsets from Emotiv Epoc [183], OpenBCI [184], BioPac Mobita [185], etc, can meet the minimum channel count requirements of 24 channels for general-purpose EEG recording [186], although modern inpatient EEG instruments can support up
to 256 channels [187] with enhanced spatial anti-aliasing capability [188]. In terms of signal fidelity, some pilot studies report that state-of-art wearable EEG devices can achieve comparable noise performance to clinical instruments. However, they are less resilient to motion artifacts, which raises reliability concerns for longitudinal monitoring. For example, the correlation between mean dominant frequencies, which is an estimate of the background frequency of the EEG [189], derived from a standard benchtop EEG system and a wearable EEG headset is 73% for artifact-free measurements and drops to 61% when including muscle artifact [190, 191]. Combining EEG with additional modalities discussed below and looking into their correlations will likely improve the diagnostic accuracy for acute mTBI [123].

3.2. Electrocardiogram (ECG)
ECG records the electrical activity of the heart by using electrodes placed on the skin. ECG functionality has been integrated into various consumer-grade wearable devices in the format of a fit band [192], smart patch [193], and smart cloth [194], just to name a few. The performance of wearable ECG devices at rest is proven to be comparable to that of chest strap-based clinical instruments with less than 5 bpm (beats per minute) difference [195]. However, the accuracy of wearable ECG wristbands diminishes with more vigorous exercise; the difference increases to 30 bpm (three sigma) [195], raising a similar reliability concern as the EEG wearables.

3.3. Transcranial Doppler (TCD)
TCD measures the blood flow velocity through the brain’s blood vessels by recording the echoes of ultrasound waves moving transcranially (figure 2(a)). An ultrasound transducer is required for TCD examination, which has to be manually steered in the acoustic window by an ultrasonography technician [196]. On the other hand, wearable ultrasound devices, such as the prototypes reported by [197] and Telederm MicroUS PRO [198], leverage a two-dimensional (2D) ultrasound transducer array for autonomous vessel localization and tracking. This technology significantly simplifies the form factor, decreases cost, and eliminates the need for specially trained medical personnel, all of which make wearable ultrasound a valuable tool for rapid on-site mTBI diagnosis. In [197], the accuracy of the wearable TCD prototype was validated against a commercial in-line flow meter based on volumetric flow rate measurements conducted using a vessel phantom [197]. The measured root-mean-square error of the flow velocity is only 2.95%, demonstrating very robust operation.

3.4. Galvanic skin response (GSR)
GSR measures the changes in the electrical conductance of the skin originated from the autonomic activation of sweat glands [199]. The method to characterize the electrical conductance is to apply a DC or AC voltage and measure the current flow through the electrodes (figure 2(b)). Compared to a DC-only test, performing additional AC measurements provides two advantages. First, additional AC measurements eliminate the polarization of the electrodes, which may introduce voltage drifts and subsequently reliability concerns in DC-only measurements. Second, AC measurements provide additional information on the skin’s capacitance changes [200]. Some pilot studies report that skin conductance measured at different locations may differ from each other [201] and suggest to position wearable GSR sensors at the finger [202], foot, or shoulder for precise GSR measurement [201].

3.5. Oximetry, temporal artery pulse wave, and AP
Oximetry, temporal artery pulse wave, and AP can be measured via a PPG sensor. The principle of PPG sensors (figure 2(c)) is based on the fact that the absorption of the light differs as a function of the blood oxygen concentration [203]. As such, PPG sensors can detect changes in blood flow and then extract the AP by monitoring the light intensity changes. Blood oxygen saturation can also be obtained by analyzing the AC and DC components of the reflectance data of the PPG waveform [204]. The wearable PPG sensors are widely integrated into consumer-grade smart watches and smart armbands such as Empatica E4 [205], which use groups of green, red, and infrared light-emitting diodes (LEDs) along with photodiodes to measure the light intensity. Although wearable oximeters can detect if there are any significant changes in blood oxygen saturation [204, 206], existing research suggests that they are less capable of capturing small variations due to motion artifact and sensitivity limit of the electronics frontend [206]. In addition, for the arterial pulse wave and AP measured by wearable oximeters, the primary concern is their accuracy because they are measured at fingertips or wrists, which are generally considered to be indirect BP measurements [207]. A high dynamic range analog-to-digital converter in the frontend may help to improve the sensitivity at the cost of a higher power consumption.

3.6. Extra orbital plethysmography
Extra orbital plethysmography (figure 2(d)) measures the pressure changes in a space around the orbit, which serves as an indicator for cerebral circulation based on the relationship between space parallel changes of orbital and brain vessels [208]. Few commercially available wearable devices for extra orbital plethysmography currently exist on the market. Instead, a custom goggle-based device was developed in [115], which can provide pulse wave results of left and right eyes with high reliability (>85%) in
clinically relevant situations and can serve as a promising indirect measurement of ICP.

3.7. Rheoencephalography (REG)
REG is an impedance plethysmography technique that indirectly characterizes the CBF changes by measuring the transcranial impedance that corresponds to volume oscillations in intracranial arteries elicited by the cardiac cycle [123]. Its sensing mechanism is based on the fact that CBF has a higher resistivity than CSF, and thus, an increase in CBF (which will accompany a decrease in CSF) increases the resistivity and hence the intracranial impedance [209]. A few wearable REG prototypes have been built in the lab setting, showing great promise in understanding the brain fluid dynamics right after mTBI [123]. The electrodes used in REG measurements are usually directly placed on the scalp and are compatible with the electrodes in an EEG headset. The use of a wide frequency range for REG could allow the evaluation of different components of the CBF impedance and provide additional spectroscopic information. The optimal frequency range for REG characterization is usually from 60 kHz to 100 kHz to distinguish the conductivity difference between CSF, CBF, and brain tissue [122].

4. Processing and learning from data
Some current clinical tools used to detect acute and early stage mTBI have poor to moderate performance. This is partially due to limited recording modalities and partially due to a lack of exploitation of recent advances in data processing. As the number of recording channels and modalities increase, the problem lends itself to a large array of machine learning and data processing methodologies. In this section, we first review the state of the art in mostly qEEG-based data and signal processing tools used to detect mTBI. We then discuss how an expanded, diverse list of physiological biomarker features may improve current data-driven approaches in providing mTBI patients timely diagnosis and treatment. Figure 3 depicts a high-level flow chart of a possible data-driven, multimodal diagnostic approach for acute mTBI classification.

There is a need for fast, accurate, and quantitative diagnostic methods to aid in the identification and management of mTBI and prevention of long-term consequences from repeated injury and insufficient recovery time. As discussed in section 2, several medical tools and surveys are already in-use by clinicians to diagnose mTBI, but none are a ‘gold standard’ approach [210, 211]. Current diagnostic methods rely almost exclusively on behavioral and symptom-based assessment, which varies significantly even from one country to another [44, 212], but these assessments can be less sensitive and not specific in identifying mTBI and tracking injury recovery [213, 214]. Speed in diagnosis is also important as warfighters and athletes should ideally be removed from action and assessed by medic, corpsman, or healthcare provider immediately after the injury leading to suspected mTBI [210]. In response to a lack of quick, sensitive, and specific diagnostic methods, a growing number of data-driven approaches have been proposed in recent literature which leverage biological signal features and machine learning to provide quantitative diagnosis of mTBI. A machine learning approach could be used in combination with portable and low-power hardware to provide immediate battlefield or sideline diagnosis of mTBI [215].

Although much work has been done on developing machine-learning methods to diagnose mTBI from quantitative measures, the specific features most important to mTBI prediction have yet to be identified. Many recently proposed machine learning-based diagnostic methods for mTBI rely heavily on EEG features [216], either alone or in combination with symptom questionnaire data or other biological markers. Although some methods focused on EEG features have shown to achieve relatively high predictive accuracy, as discussed earlier there is still debate whether qEEG features are truly useful in mTBI identification [215]. On the other hand, there has been a lack of focus on features related to the ANS such as HRV, despite recent evidence of the link between mTBI andANS dysfunction [125]. With recent advancements in HRV feature-based methods in medical domains beyond mTBI [217–219], HRV features may have potential in mTBI prediction as well, on their own or in tandem with previously studied signal features like those from EEG readings.

A growing number of machine learning-based methods have been proposed in recent years to diagnose mTBI, track injury progression, and predict injury recovery from both short and long-term effects of mTBI based on bioelectrical signals [220–222]. Due to the well-documented potential of qEEG in the diagnosis of and rehabilitation following TBI [223], a large group of these methods rely on qEEG features alone or in combination with symptomatology [224]. While many current methods are oriented toward the fast detection of the mTBI based on acute and short-term effects on bioelectrical markers following injury, much of the work in applying machine learning to solve mTBI-related problems is focused on tracking long-term injury progression and chronic effects, as well as on predicting timelines for recovery. In this paper, our focus is solely on acute and short-term effects, and we thus focus on machine learning approaches which aim to detect mTBI soon after injury.

The development of some machine learning-based schemes for acute mTBI detection has been motivated by industry-driven invention of medical hardware. The medical neurotechnology company BrainScope has been particularly active in designing
machine learning algorithms for acute mTBI detection, as such algorithms are integral to the function of their portable, EEG-based ‘BrainScope’ mTBI assessment hardware [97, 211, 225–228]. Several of BrainScope’s devices have been patented [229] and cleared by the FDA [230] since the company’s founding in 2006, most notably the Ahead 300 (2016) and BrainScope One (2018). Recently, the BrainScope team derived the Concussion Index, a ‘multimodal index’ which integrates qEEG features with neurocognitive performance and vestibular symptomology data to enhance the prediction of early stage mTBI [211]. Although the Concussion Index was independently verified to have moderately high sensitivity and specificity to mTBI (86.0% and 70.8%, respectively) [179], BrainScope’s approach singularly focuses on qEEG features and qualitative assessment and does not take into account potentially valuable information from other quantitative physiological parameters, such as ECG, TCD, and GSR. An approach which incorporates quantitative features from multiple signal modalities, as well as features related to the relationships between those modalities, may offer novel characterizations of mTBI in addition to more trustworthy mTBI prediction.

The landscape of machine learning methods and feature sets in qEEG and symptom-based mTBI diagnosis and prognosis continues to grow while questions regarding the validity of EEG features in mTBI prediction, as well as model selection, remain unanswered. In [224] the team reported that some especially popular qEEG predictors were absolute power band, EEG total power, relative power per band, variability per frequency band, and spectral edge frequency. The most common machine learning technique was logistic regression, although methods varied based on the type and number of features, widely ranging in complexity from linear regression to deep neural networks [224]. The diversity in the classification models used in mTBI applications is extremely wide, and it is worth reiterating that while there is some overlap in the qEEG features selected via the methods described above, there is still limited consensus on which features are most important to the prediction of mTBI.

Complicating matters further, there is concern over the interpretability of the machine learning methods applied to mTBI diagnosis and medical diagnosis more broadly. Deep learning/neural network-based approaches have shown high classification performance in certain medical diagnosis applications, often beating more traditional methods, like linear and logistic regression and support vector machines (SVM), when directly compared on specific test data [231–234]. However, some argue that deep learning models are black boxes which do not provide sufficient inherent reasoning in their predictions, and thus do not provide sufficient accountability, for high stakes medical applications [214, 235–238]. The best performing model for acute mTBI detection may not fully align with intuition given the complexity and dimensionality of the biomarker feature space, and work is being done to increase the interpretability of highly accurate deep learning approaches for integration of non-invasive, wearable-recorded biomarkers [239]. Nevertheless, as the search for the most useful

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**Figure 3.** A depiction of learning from multimodal data. Signals and data are recorded in different time internals and processed to build n observations. Then, p features are extracted from each observation. These features are used to classify between mTBI or no mTBI. The specific physiological biomarkers included in the figure serve as an example list of biomarkers from which to extract predictive features and are not an exhaustive list.
Table 3. Summary of machine learning (ML) approaches for identification mTBI/TBI in acute stage.

| ML Methods | Goal | Participants | Modalities | Performance | Reference |
|------------|------|--------------|------------|-------------|-----------|
| Linear discriminant functions-based genetic algorithm (GA) | Acute mTBI ('concussion') detection | 207 injured, 373 controls | qEEG, neurocognitive performance, vestibular symptoms (BrainScope Concussion Index) | 86% sensitivity, 71% specificity | [179] |
| Linear discriminant functions-based GA | Acute mTBI ('concussion') detection | 177 injured, 187 controls | qEEG, neurocognitive performance, vestibular symptoms (BrainScope Concussion Index) | 93% sensitivity, 75% specificity (leave one out) | [211] |
| Boosting | Acute mTBI detection | 38 injured, 47 controls | qEEG, symptomology | 91% accuracy (qEEG and symptomology), 82% (symptomology alone) | [215] |
| Convolutional neural network (CNN) | Acute moderate TBI detection | 15 injured, 15 controls | qEEG | 72% accuracy | [220] |
| Decision tree, K-nearest neighbors, neural network, support vector machine, random forest, CNN | Acute mTBI detection in animal model | four injured, five controls (mice) | qEEG, EMG | 86% accuracy (convolutional neural network) | [221] |
| GA, modified random mutation hill climbing, linear discriminant classifiers | Acute mTBI/severe TBI detection and separation of TBI severity | 218 controls, 306 with functional injury, 109 with injury visible on CT scan (CT+) | qEEG | 80% sensitivity, 74% specificity for mTBI ('concussion'), 96% sensitivity, 78% specificity for CT+ TBI | [225] |
| Ensemble harmony, LASSO logistic regression, GA | Acute severe (CT+) TBI detection | 186 injured, 1284 controls | qEEG | Average 98% sensitivity, 60% specificity | [226] |
| LASSO logistic regression | Acute severe (CT+) TBI detection | 145 injured, 535 controls | qEEG, LOC, amnesia | 0.83 AUC for qEEG, LOC, and amnesia, 0.68 AUC for LOC alone | [227] |

features and machine learning models for mTBI prediction continues, careful attention must be given to model interpretability in order to offer maximum trust in prediction. Table 3 summarizes the current state of the art in machine learning-based detection of mTBI/TBI in the acute phase.

ANS-related features such as HRV have seen limited use in machine learning-based methods for mTBI prediction, despite evidence of the link between TBI and ANS dysfunction. It is clear that qEEG features have dominated the bioelectrical signal feature space for quantitative mTBI prediction with machine learning, but as there is still not yet broad agreement on the importance and validity of such features, it is worth investigating underexplored feature domains like HRV and other possible predictors of mTBI. As discussed before, the ANS is composed of the sympathetic and parasympathetic nervous systems and plays a crucial role in acute stress response by regulating physiological processes within the body. There is evidence that mTBI is related to ANS dysfunctions such as the uncoupling of ANS and cardiovascular control, heightened SBP and lengthened time for pressure to turn to baseline, and impaired parasympathetic and sympathetic nervous system activation measured as decreased HRV and slower changes in BP. Beyond simple tracking of heart beats per minute, HRV is most commonly measured by extracting RR intervals (the time interval between successive R waves, the largest QRS complex wave generated during normal cardiac sinus rhythm) from ECG readings [240]. Like EEG features, HRV features can be analyzed in time, frequency, and nonlinear domains, and the measurement of changes in HRV upon sitting or standing can provide additional features [241]. Despite possible limitations surrounding HRV, features based on HRV have been used to some success in medical machine learning applications beyond mTBI diagnosis. HRV features have been used in EEG and ECG-based seizure detection with linear discriminant analysis [242] and SVM [218]. In [243] the authors proposed a genetic algorithm-based feature
reduction method and SVM classifier to classify two types of cardiac arrhythmia from normal heart function, using wavelet-based HRV features [243]. HRV feature sets have also been used to train convolutional neural networks (CNN) [231], feed forward neural networks [233] and recurrent probabilistic neural networks [234] to diagnose cardiac pathologies such as atrial fibrillation, ventricular fibrillation, congestive heart failure. Linear discriminant analysis-based classification of real-life stress conditions [219] and human emotional states [244] are further uses of HRV features in medical machine learning applications. Significant overlap between the profile of HRV features important to the above applications and the potential HRV features important to mTBI should not be expected, but the applications described above attest to the broad and general potential of considering features related to ANS dysfunction in a variety of medical domains, perhaps including mTBI. In fact, HRV has been shown to be one of the parameters indicative of mTBI in the acute phase [13]. However, HRV remains inconclusive as a standalone parameter [128] and the specific trends regarding HRV and ANS dysfunction in mTBI have not yet been validated by clinical research. Nevertheless, mounting evidence of trends in any direction suggest that HRV features may yet prove to be useful predictors in machine learning-based diagnosis of mTBI, especially when combined with features of other modalities like qEEG.

5. Conclusions and future directions

Tremendous advances have been made in research leading to better understanding, diagnosis, and treatment of mTBI. This review article only focused on mTBI, acute parameters, and short-term impact, which if not diagnosed early and treated may lead to prolonged recovery and long-term consequences. This is particularly critical if subsequent mTBIs occur prior to the previous one healing. It is clear that the research community has a long way to go in fully understanding and systematically diagnosing mTBI, which will lead to more successful treatment of and recovery from mTBI.

The clinical community has made great strides in identifying mTBI via behavioral observations, clinical assessments, cognitive testing, and symptom reporting. However, the urgent need to develop an integrated and systematic mechanism to objectively and quantitatively identify mTBI with high accuracy, sensitivity, and specificity is critical in improving recovery and treatment of mTBI and it is the goal of many researchers. We envision a non-invasive, compact, and portable electronic device that would integrate signals and data from very different modalities and systematically process the information in real time to diagnose and possibly classify mTBI. In order to bring this vision to fruition we need accurate measurements of multiple relevant signals, better clinical understanding of mTBI, and its impact on these measured signals. Finally, and most importantly, we need to learn from these signals in order to identify mTBI with acceptable accuracy, sensitivity, and specificity.

Despite all the promise and potential of the wearable technologies, further engineering research is still required towards developing a reliable and sensitive platform to diagnose mTBI in the acute phase, especially on (a) how to integrate all the mTBI-related sensors [245–249] in a convenient wearable platform that can be quickly suited up on-site, (b) how to minimize the impact on sensing accuracy introduced by motion artifacts and other noise sources to improve detection reliability [250, 251], and (c) how to perform light-weight low-power signal processing directly on the wearable devices. In addition, more studies need to be conducted to compare the data gathered by wearable devices with the data measured by clinical benchtop instruments to justify the effectiveness of wearable technologies in evaluating mTBI [178].

Data availability statement

No new data were created or analysed in this study.

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