International Journal of
Translational Medicine

MDPI

Review

Mild Traumatic Brain Injury Biomarkers: Current Status and Future Directions

Ezekiel Fink [1,2,*], Marlin Wayne Causey [3], Geoffrey Peitz [4] and Adrian Hamburger [2]

[1] Houston Methodist Hospital, Houston, TX 77030, USA
[2] Asterion AI, Dallas, TX 75230, USA
[3] San Antonio Military Medical Center, San Antonio, TX 78234, USA
[4] Brooke Army Medical Center, Fort Sam Houston, TX 78234, USA
* Correspondence: efink@hspmgroup.com

Abstract

Mild traumatic brain injury (mTBI) contributes substantially to years lived with disability (YLD), decreases health-related quality of life, and imposes significant costs on healthcare systems and society. Millions of people experience mTBI each year, and healthcare costs for mTBI in just the first year after injury exceed $44 billion USD. Despite the common occurrence of mTBI, estimates of incidence, prevalence, related disability, and costs vary widely. This variance is attributed to the underreporting of head impacts, inconsistent definitions of mTBI, and a lack of objective biomarkers. Currently available clinical blood biomarkers primarily assist in ruling out CT-detectable intracranial injury rather than definitively diagnosing mTBI itself, underscoring the continued need for objective, portable, and clinically specific biomarkers. Numerous imaging findings, blood proteins, and physiological measures are under investigation for these purposes, and some may have multiple uses. Specific biomarkers for acute diagnosis are needed urgently. Although many systematic reviews have been published, most focus on a single biomarker or class of biomarkers. Given the breadth of potential biomarker categories, conducting a comprehensive, systematic review across modalities is challenging. Here, we provide a narrative review summarizing the extant literature across major biomarker domains studied in adolescents and adults. We emphasize candidates supported by the most robust evidence to guide continued research and clinical translation.

Keywords: mild traumatic brain injury; concussion; biomarkers; diagnosis; EEG; functional brain imaging; structural brain imaging; blood biomarkers; traumatic brain injury

Academic Editor: Pier Paolo Claudio

Received: 12 February 2026
Revised: 3 April 2026
Accepted: 7 April 2026
Published: 11 April 2026

1. Introduction: Clinical Impact of Mild Traumatic Brain Injury

Head impacts generate physical forces on the brain that cause structural and functional changes, producing symptoms known as mild traumatic brain injury (mTBI). Blood vessels and brain cells—especially neuronal axons—can be stretched and torn. Microstructural damage disrupts the blood–brain barrier, neurotransmitter systems, and cellular and extracellular environments [1]. These disruptions cause symptoms that include altered mental status and cognitive problems, dizziness, balance and gait disturbances, headaches, mood changes, seizures, visual problems, and sleep difficulties [2,3].

Most of the 19 to 22 million people who experience mTBI each year [4,5] recover in one to three weeks. However, 16% to 31% of patients develop long-lasting symptoms known as *post-concussion syndrome* (PCS) [6–8], which is associated with increased healthcare

utilization, disability, morbidity, and mortality [6–11]. After a first mTBI, patients have an increased risk of another, which increases further after each subsequent occurrence [12]. Repeat mTBIs can cause cumulative, microscopic brain damage consistent with advanced brain aging and neurodegenerative disease (e.g., chronic traumatic encephalopathy or Alzheimer's disease) [13–15].

Social determinants of health are associated with mTBI epidemiology and outcomes. Incidence and prevalence increase with age [2,3,16–20], and outcomes are worse for the very young and the very old. Black/African American, Hispanic/Latin, and rural patients appear to experience diagnostic and treatment disparities [21–24]. mTBI occurs slightly more often in men than in women (ratio 4:3) [25,26].

Estimates of hospital and emergency department-related costs in the first year after injury range from $13,564 in 2016 dollars to $28,563 in 2017 dollars [5,23], suggesting that annual costs for new mTBIs are $44 to $92 billion. US military service members with mTBI had three times higher health-related costs compared with those without mTBI [24]. Indirect costs include lost productivity, disability, caregiving costs, diminished quality of life, and increased morbidity and mortality. Approximately 59% of people with mTBI miss at least two weeks of work after injury, 17% do not return to work at 12 months, and 21% have reductions in their annual income [27]. Costs borne by family members and loved ones who help care for people with mTBI are both intangible and difficult to overstate.

2. The Need for Objective mTBI Biomarkers and Scope of This Review

The large ranges in estimates of mTBI incidence, prevalence, prognosis, and outcomes reflect our still nascent understanding of mTBI as a serious injury. Many head impacts go unreported, and even when a head impact is reported, mTBI is underdiagnosed, in part because of the absence of an objective diagnostic test for mTBI [2,3]. These challenges also make it difficult to assess mTBI prognosis and outcomes. Biomarkers—objective, measurable characteristics of biological processes—are needed and in development for these endpoints. Biomarkers are also important for identifying patients for clinical trials and, eventually, matching the right treatment to the right patient.

Candidate biomarkers range from changes in RNA and protein levels to structural and physiological differences measured with biofluid transcriptomics and proteomics, myriad imaging modalities, and multiple neurophysiologic measures. Studied endpoints vary from acute diagnosis to long-term prognosis. In addition to head injuries among the general public, specific populations studied include high school or professional athletes, military trainees, active-duty service members, and veterans. Adding to this high variability, different definitions of mTBI and its outcomes have been used across studies.

A systematic review across this broad range of candidates, modalities, and populations with varied definitions and endpoints is impractical. Instead, we provide a narrative review presenting our assessment based on a comprehensive literature search of which biomarkers studied in adolescents and adults have the strongest evidence to support further development for clinical use. Limited research on potential mTBI biomarkers in pre-adolescent children suggests that ongoing neurodevelopment in this population makes potential brain biomarkers inappropriate, warranting a separate study and evaluation. As such, studies on subjects younger than 12 years are outside the scope of this review. We identified articles on mTBI biomarkers in the PubMed.gov and EMBASE literature databases published between 2016 and 2024 using the search terms "(mTBI OR concussion) AND biomarker(s)." We limited the search to English-language articles with findings in adolescent and adult humans and freely available abstracts. We excluded addresses, biographies, duplicate publications, editorials, festschrifts, interviews, news, patient education, personal narratives, protocols, retracted publications, and veterinary studies. We screened abstracts to

identify 269 articles presenting evidence related to mTBI biomarkers and reviewed those articles in full to assess which biomarkers had the strongest evidence to support continued development. As needed, we also read articles that were cited within those 269 articles to ensure accurate reporting of research results. Because this was a narrative review rather than a formal systematic review or meta-analysis, the selection and emphasis of biomarker domains necessarily involved author judgment, although we sought to minimize bias through a broad literature search and full-text review. The references cited include those found through our literature search or cited in the search results and verified.

3. Potential Structural Imaging Biomarkers for mTBI

Conventional CT and MRI typically do not show macroscopic changes in mTBI. Some diagnostic criteria even make the absence of MRI or CT findings a requirement to classify a traumatic brain injury (TBI) as mild. More advanced MRI techniques provide evidence of microstructural changes in mTBI and are being evaluated as potential mTBI biomarkers (Table 1).

Brain volume measurement with T1-weighted MRI shows post-mTBI atrophy that, in some cases, resembles patterns observed in aging [28,29]. Similar changes have been observed in some studies of post-traumatic stress disorder (PTSD) [30]. In T1-weighted studies that control for comorbid PTSD, specific mTBI-related differences include volume changes in areas related to cognition and memory (i.e., the hippocampus, medial orbitofrontal cortex, and entorhinal cortex). Emerging evidence, however, suggests that deficits in these functions are a long-term consequence of mTBI [31–33], which raises the possibility that prior mTBIs may confound the interpretation of acute mTBI. To make T1-weighted MRI useful as a clinically meaningful mTBI biomarker, the temporal evolution of these changes and their specificity relative to comorbid or overlapping conditions would need to be better defined.

Fluid-attenuated inversion recovery MRI (FLAIR) and susceptibility-weighted imaging (SWI) both show white-matter hyperintensities (WMHs) and microscopic bleeds in patients with mTBI, as early as the day of injury and for years later. However, WMHs are not specific to mTBI and so are not yet useful as a biomarker [29,34–38].

Diffusion-tensor imaging (DTI) provides information about axon tract integrity and connections between brain regions [39–43]. A systematic review reported that most reviewed studies demonstrated white matter changes after mTBI. However, variability in designs, methods, and specific findings made it difficult to draw conclusions [41]. More recent studies in military personnel and veterans show that white-matter abnormalities are present up to five years after an mTBI and may correlate with premature aging and executive function deficits [39,42]. Another study combining DTI and T1-weighted MRI volumetric measurements suggests military service members with a history of mTBI have differences at the border of white and gray matter [43]. Based on this evidence, DTI holds promise as a useful prognostic biomarker. Whether DTI is useful for diagnosis is unclear because most DTI studies have been conducted months after an mTBI occurred. Well-controlled longitudinal studies with consistent, standardized methods and analytic techniques are needed [41].

Table 1. Comparison of potential structural and functional imaging biomarkers for mild traumatic brain injury.

	Structural Imaging					Functional Imaging					
	T1-Weighted MRI [28,29]	**FLAIR or SWI [34–38]**	**DTI [39–42]**	**MRS [44–46]**	**T1-Weighted MRI/DTI [43]**	**fMRI or rs-fMRI [47–53]**	**SPECT [54–60]**	**fNIRS [61–68]**	**qEEG [69–74]**	**MEG [75]**	**qEEG/ MEG [75–78]**
Measures	Brain structure/ volume	WMHs	Axon tract integrity	Brain metabolites	Brain structure; axon integrity	Blood flow	Blood flow	Blood flow	Electrical activity	Magnetic fields	Electrical activity; magnetic fields
Spatial resolution	<1 mm	1 mm	<1 mm	5–10 mm	1–3 mm	1–3 mm	7–10 mm	1–3 cm	1–3 cm	2–5 mm	2–5 mm
Temporal resolution	Static	Minutes	Minutes	Seconds to minutes	Minutes	Seconds to minutes	Minutes	10–100 ms	1–5 ms	<1 ms	<1 ms
Timing of studies	<1 week to years	Day 1 to years	Weeks to years	Day 1 to months	Months	Months	Months	Months	Day 1 to years	Day 1 to years	Day 1 to years
Prehospital availability	No	No	No	No	No	No	No	Developing	Yes	No	No

Notes: These modalities differ substantially in their most studied clinical endpoints and should not be interpreted as interchangeable diagnostic tests. T1-weighted MRI is used primarily for evaluation of moderate-to-severe mTBI [28,29]. The WMHs observed with FLAIR or SWI are not specific to TBIs [29,34–38], and MEG findings are not specific to mTBI [75]. DTI, combined T1-weighted MRI and DTI, fMRI, and rs-fMRI have limited evidence at the time of injury but appear to be potential prognostic biomarkers for mTBI [39–43,47–60]. fNIRS and qEEG may have diagnostic and prognostic potential [61–74], although machine learning artifacts may confound qEEG findings [79–82]. Combined qEEG/MEG is potentially useful for both acute diagnosis and prognosis, but further validation is needed [75–78]. Abbreviations: DTI, diffusion-tensor imaging; FLAIR, fluid-attenuated inversion recovery; fMRI, functional MRI; fNIRS, functional near-infrared spectroscopy; MEG, magnetoencephalography; mTBI, mild traumatic brain injury; MRS, magnetic resonance spectroscopy; ms, millisecond; qEEG, quantitative electroencephalography; rs-fMRI, resting-state fMRI; SPECT, single-photon emission CT; SWI, susceptibility-weighted imaging; WMHs, white-matter hyperintensities.

MR spectroscopy (MRS) evaluates changes in brain metabolites thought to reflect brain cell injury. Metabolites evaluated as potential mTBI biomarkers include *N*-acetyl aspartate (NAA), creatine, choline, glutamate/glutamine, and *myo*-inositol. A small meta-analysis of six articles presenting results in 30 patients with mTBI compared with 31 age- and sex-matched healthy individuals suggested that decreased NAA and choline and increased glutamate correlated with cognitive changes in patients with mTBI [44]. A large meta-analysis of 138 studies found that changes were most frequently seen in the corpus callosum, reflecting axonal injuries. Decreases in NAA were most consistently observed and occurred at all endpoints, from acute injury and for weeks and months to come, and the amount of decrease correlated with time since injury, with the largest occurring immediately after injury. However, NAA changes occurred across all severities of brain injury, making NAA nonspecific for mTBI [45]. Ratios of these metabolites have also shown promise as a potential biomarker. A meta-analysis across TBI severities found overall decreased NAA/Cr compared with the controls. However, in pooled analyses, NAA/Cr reductions were more consistently detected in moderate-to-severe TBI rather than mTBI [46]. A better understanding of how these metabolites change over time after an mTBI is needed for any to be useful as biomarkers.

4. Potential Functional Neuroimaging Biomarkers for mTBI

4.1. Functional MRI

Functional MRI (fMRI) measures task-related changes in cerebral blood flow, which are commonly used as a proxy for neural activity during tasks. fMRI studies suggest that mTBI causes larger areas of the brain to be activated during tasks in comparison to people without mTBI [47–50]. The fMRI studies of TBI to date have been performed months after injury, however, and more research is needed to understand longitudinal changes in fMRI after mTBI to clarify whether it could become a clinically useful biomarker.

Resting-state fMRI (rs-fMRI) evaluates brain activity in the absence of a task, observing how activity shifts from one brain region to another over time to identify functional networks. In people with mTBI, rs-fMRI shows increases in functional connectivity that may correlate with working memory [51]. Some researchers postulate that this reflects brain recovery, with increased connections in one area compensating for damage in others. Of note, rs-fMRI findings may differ between mTBI and PTSD [52], making rs-fMRI a possible way of differentiating between these conditions, which often occur together. Once again, however, these studies have been conducted months after injury and technique is still highly variable [53], precluding clinical use. Accordingly, current fMRI and rs-fMRI findings are more suggestive of subacute or chronic network alteration than clinically deployable acute diagnostic biomarkers.

4.2. Single-Photon Emission CT

Single-photon emission CT (SPECT) also measures brain activity via blood flow. SPECT has lower spatial and temporal resolution compared with fMRI or rs-fMRI. Systematic reviews suggest that SPECT may detect perfusion abnormalities not evident on standard structural imaging in some TBI populations. However, the utility of SPECT for mTBI remains limited by heterogeneity of methodology, interpretation, and clinical reference standards. The most commonly reported SPECT finding was hypoperfusion (i.e., lower blood flow) of the frontal and temporal lobes of patients with mTBI [54,55]. Several studies have reported associations between hypoperfusion and clinical mTBI symptoms [56–60]. Evidence for SPECT studies in mTBI diagnosis is limited by variable image interpretation methods and a lack of sensitivity and specificity data [54]. Notably, SPECT is

the one imaging modality discussed in this review that requires an intravenous radioactive tracer, which may also decrease its clinical utility.

4.3. Functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy (fNIRS) uses a cap on the head that transmits light through the skull to measure blood flow. Although this technique measures blood flow only near the brain surface, a meta-analysis shows that it is useful in diagnosing and monitoring moderate-to-severe TBI [61]. fNIRS identifies alterations in patients with a history of mTBI that resemble changes reported in some neurodegenerative diseases [62–66]. Emerging evidence suggests that fNIRS may have the potential to detect day-of-injury changes and could eventually prove useful in the prehospital setting [67,68].

4.4. Electroencephalography

EEG directly measures electric pulses of brain activity with high temporal resolution if there is an adequate signal-to-noise ratio and appropriate artifact interpretation [69–72,83]. Like most other measures of brain activity, traditional EEG has low spatial resolution. Quantitative EEG (qEEG) uses mathematical calculations to analyze digitally recorded EEG and arrive at a more nuanced level of detail. The derived power spectrum characterizes functional interactions among brain region interactions and can be compared to normative data from age- and sex-matched healthy controls. Oscillation of brain activity in "frequency bands" can be evaluated independently or in aggregate as ratios between bands. Evaluation of these patterns over milliseconds to minutes can provide a functional interpretation of the recorded brain activity. Portable qEEG systems are being evaluated for use in prehospital settings with the same quality recording as in-hospital qEEG at the time of injury (e.g., in athletes on sidelines, in the ambulance, and upon presentation to an emergency department) [69,71–74].

In the 1930s, soon after EEG first became available, EEG changes after head trauma were reported [84]. Systematic reviews suggest that qEEG features can differentiate some mTBI cohorts from non-injured controls, although methods and findings remain variable. A systematic review showed that multiple studies identified P300 event-related potential differences in mTBI [85,86]. Recent studies suggest that both eye-blink-related and beta oscillations observed on qEEG could be mTBI biomarkers [76,87]. Multiple studies are exploring the use of machine learning to identify mTBI biomarkers within the wealth of data that EEG provides, alone or in combination with other biomarkers [79–82]. However, there is a risk of overfitting, in which signal noise is erroneously classified as a pathological pattern, producing apparently high accuracy in small training datasets that fails to generalize to independent cohorts. This failure of cross-validation accuracy may limit the usefulness of EEG features as mTBI biomarkers, and models using multiple, larger datasets with EEG from hundreds of patients and healthy individuals are needed. Additionally, the methodologies used in EEG and qEEG studies have been highly variable, and standardization of machinery, electrodes, and machine learning algorithms is needed [88].

4.5. Magnetoencephalography

Magnetoencephalography (MEG) directly measures magnetic fields of electric brain activity with a helmet connected to a large device in a temperature-controlled room. Similar to EEG, MEG offers millisecond temporal resolution, but the two modalities differ in source sensitivity and spatial distortion, making them complementary rather than interchangeable. A systematic review suggested that MEG may be more sensitive than MRI or EEG for detecting changes associated with mTBI. After an mTBI, MEG findings most commonly involve atypical low-frequency magnetic activity. MEG differences in mTBI also correlate with clinical symptoms. However, the differences observed in mTBI with MEG are not

specific; similar changes occur in PTSD, brain tumors, WMHs/infarcts, epilepsy, and neurodegenerative diseases [75]. Until specificity is improved, MEG is likely to have the greatest clinical utility as part of a multimodal assessment strategy rather than as a stand-alone test. MEG measures activity only in one plane (tangential to the cortex), whereas EEG measures activity in three dimensions. Combined EEG-MEG approaches may improve source characterization by leveraging the complementary strengths of electrical and magnetic recordings [75–78].

5. Blood Biomarkers for mTBI

Blood levels of many proteins change immediately after an mTBI, and approximately 20 blood-based biomarker candidates have been evaluated [89,90]. Here, we focus on the two blood biomarkers that have been approved for clinical use and briefly summarize others that have the most accumulated evidence for eventual use.

Glial fibrillary acidic protein (GFAP) is also found primarily in astrocytes and released in the acute phase of brain injury. Ubiquitin C terminal hydrolase L1 (UCH-L1), also released in the acute phase of TBI, is highly expressed in neurons. GFAP shows high sensitivity and moderate specificity for detecting intracranial injury after mild head trauma, whereas UCH-L1 shows high sensitivity but lower specificity. When used together, sensitivity and specificity for the absence of acute intracranial lesions that could be visualized on CT increase [91–95]. In 2018, the U.S. Food and Drug Administration approved the GFAP/UCH-L1 assay to aid with the evaluation of potential TBI in adults with a Glasgow coma score of 13 to 15, noting that a negative assay result is associated with the absence of acute intracranial lesions visualized on a head CT [90,96]. Several factors affect the test results, including age [97–99], levels of other brain proteins (i.e., amyloid-β) [97], and physical activity level [100]. This consideration is particularly relevant in highly active populations, such as athletes and military personnel. Although GFAP and UCH-L1 are stable after collection, post-injury elevations are transient. A blood sample must be taken within 12 h of injury for the test to have utility [90]. A point-of-care assay for GFAP/UCH-L1 that uses a stabilized plasma sample has been approved [91], but preparation of such a sample may not always be feasible (e.g., in a setting remote from advanced healthcare facilities). A whole-blood assay is being developed [90]. Importantly, current clinical use of GFAP/UCH-L1 is best understood as aiding triage for CT-detectable intracranial injury rather than establishing a definitive diagnosis of clinical mTBI itself.

Protoplasmic astrocytes surround blood vessels and synapses in the brain to regulate the blood–brain barrier and maintain synapse structure. These astrocytes selectively express S-100 calcium-binding protein B (S-100B) in the brain, which is released in the acute phase of brain injury [101]. Blood levels of S-100B are highly sensitive for intracranial CT findings (e.g., contusion or hemorrhage) after adjusting for age [102–105]. Several European professional organizations recommend incorporating S-100B into the management of selected patients with potential TBIs to reduce unnecessary head CTs [90]. Considering the low incidence of intracranial lesions on CT in the population tested, the negative predictive value was 100% in one study (95% CI: 99–100%) [106]. However, S-100B has limited specificity for mTBI and may increase downstream imaging or referral in some patients. Additionally, the diagnostic utility of S-100B is optimized when samples are obtained within three hours of injury [107], which is not feasible in many cases of mTBI.

Other potential blood biomarkers include neurofilament light (NF-L), inflammatory cytokines (e.g., interleukins [ILs]), and tau, a protein implicated in neurodegenerative diseases. Elevated NF-L levels have been reported in some sports-related and military-associated mTBI cohorts, although the timing and magnitude of these elevations have varied across studies [108–110]. However, observed NF-L elevations last months to years,

which could confound the diagnosis of mTBI in those who have repeated events [108,109]. A meta-analysis suggests that NF-L may be better suited to prognostication than to acute diagnosis [111]. A systematic review of cytokines as potential mTBI biomarkers suggests high potential for IL-10, but varied methods across studies make it difficult to draw conclusions [112,113]. Elevated phosphorylated tau-181 levels have been correlated with mTBI in athletes and were significantly higher in those with MRI findings suggestive of mTBI [114]. Elevated tau has also been seen in military service members after exposure to sub-concussive blasts [115] with repeated mTBI, and with PCS [116,117].

6. Pupillometry

The pupillary light reflex (PLR) quantifies the speed and magnitude of pupil changes in response to light. mTBI alters PLR metrics [118–120], likely because attention affects PLR. However, because PLR metrics vary with age, gender, and race, multiple adjustments to normative values would be required in practice, which could complicate use. Fatigue, baseline vision, and other medical conditions also affect PLR, so pupillometry may not be specific enough to differentiate mTBI and other conditions [119–123]. Concerns have also been raised that PLR results in clinical trials differ from real-world implementation [120]. At present, pupillometry is best regarded as a potentially useful adjunctive physiologic marker rather than a stand-alone diagnostic or prognostic test.

7. Discussion

7.1. Current Barriers to Use and Development of mTBI Biomarkers

mTBI affects millions each year and causes adverse health, social, and economic outcomes. Objective biomarkers are needed to improve diagnostic certainty for improved clinical management and research to develop more effective treatments. Recent progress includes the development of blood biomarkers that can help rule out CT-detectable intracranial injuries, and these may reduce the use of head CTs. However, we still do not have an objective biomarker for mTBI diagnosis or prognosis with both sensitivity and specificity.

Although advanced structural and functional imaging measures show promise as potential mTBI biomarkers, only MEG and qEEG/MEG have sub-centimeter spatial resolution and sub-second temporal resolution (see Table 1). All but qEEG and MRS require large and costly equipment that is not always available, especially in the settings where mTBIs occur. Because many biomarker studies have been conducted months after injury, much of the current evidence is more relevant to prognosis than to acute diagnosis, with the notable exceptions of FLAIR, MRS, qEEG, and MEG. Currently available blood-based biomarkers primarily assist in ruling out CT-detectable intracranial injury rather than establishing a definitive diagnosis of clinical mTBI. However, these are not specific to mTBI, and the search for a blood biomarker that is both sensitive and specific for mTBI continues.

As noted throughout this review, populations and injury mechanisms (e.g., sports-related, blast injuries, falls, vehicle crashes) studied in the quest for mTBI biomarkers vary widely across studies. Biomarker research provides evidence that mTBI pathophysiology may differ with sex, age, race, and ethnicity, but few studies capture these demographics. Within biomarker domains (e.g., structural imaging, functional imaging, and blood or physiological tests), study methodology is also variable, including the timing of testing, the equipment used, and how the recorded data is analyzed. Small sample sizes and publication bias further limit generalizability and cross-study comparison.

7.2. Future Directions

Understanding prognosis and identifying reliable prognostic biomarkers depends on ensuring that the population evaluated has been correctly identified as having an mTBI,

making diagnostic biomarkers a priority. Ideally, large longitudinal studies would evaluate multiple biomarkers across modalities in a well-defined population with carefully recorded mechanisms of injury or the absence of head injury. Considering that such a study is likely infeasible, research into any potential diagnostic mTBI biomarker should carefully record and control demographic factors, injury mechanisms, and data collection methodologies. Potential biomarkers with high structural and temporal resolution warrant prioritization but typically have the drawback of not being available at the time of injury. Thus, research should also focus on evaluating potential mTBI biomarkers that could be available in remote or austere locations where mTBI is likely to occur (e.g., sports arenas, combat zones, worksites, and roads). Such candidates include blood biomarkers (if results can be available without large lab equipment), EEG, fNIRS, and pupillometry. Studies evaluating more than one potential biomarker in the same population might better optimize the trade-offs of resolution and portability. For example, a population could be evaluated at the time of injury in the field with a blood draw or an EEG, and then at the hospital within 72 h with MRS or MEG. The use of multiple biomarkers might also improve specificity and sensitivity that are still lacking. Immediate research priorities should include prospective, endpoint-specific studies that standardize case definitions, timing of collection, and analytic methods across sites. Acute field-deployable candidates such as EEG, fNIRS, and blood-based approaches merit priority for translational development, whereas advanced imaging modalities may be better positioned for prognostic enrichment and mechanistic studies. Ultimately, multimodal biomarker panels may prove more clinically useful than any single biomarker class alone.

Author Contributions: Conceptualization, E.F. and A.H.; methodology, E.F., M.W.C., G.P. and A.H., validation, E.F. and A.H.; formal analysis, E.F., M.W.C., G.P., and A.H.; investigation, E.F., M.W.C., G.P., and A.H.; data curation, E.F.; writing—original draft preparation, E.F.; writing—review and editing, M.W.C., G.P., and A.H.; visualization, E.F.; supervision, A.H.; project administration, E.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this review article.

Conflicts of Interest: Authors EF and AH were employed by the company Asterion. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

DTI	Diffusion-tensor imaging
EEG	Electroencephalography
FLAIR	Fluid-attenuated inversion recovery MRI
fMRI	Functional MRI
fNIRS	Functional near-infrared spectroscopy
GFAP	Glial fibrillary acidic protein
MEG	Magnetoencephalography
mTBI	Mild traumatic brain injury
NF-L	Neurofilament light
PCS	Post-concussive syndrome

PLR	Pupillary light reflex
PTSD	Post-traumatic stress disorder
SPECT	Single-photon emission CT
SWI	Susceptibility-weighted imaging
qEEG	Quantitative electroencephalography
rs-MRI	Resting-state MRI
S-100B	S-100 calcium-binding protein B
TBI	Traumatic brain injury
UCH-L1	Ubiquitin C terminal hydrolase L1
WHM	White-matter hyperintensities

References

1. Bauer, R.M.; Jaffee, M.S. Behavioral and Cognitive Aspects of Concussion. *Continuum* **2021**, *27*, 1646–1669. [CrossRef] [PubMed]
2. Patricios, J.S.; Schneider, K.J.; Dvorak, J.; Ahmed, O.H.; Blauwet, C.; Cantu, R.C.; Davis, G.A.; Echemendia, R.J.; Makdissi, M.; McNamee, M.; et al. Consensus statement on concussion in sport: The 6th International Conference on Concussion in Sport-Amsterdam, October 2022. *Br. J. Sports Med.* **2023**, *57*, 695–711. [CrossRef] [PubMed]
3. Silverberg, N.D.; Iverson, G.L.; ACRM Brain Injury Special Interest Group Mild TBI Task Force Members; Cogan, A.; Dams-O-Connor, K.; Delmonico, R.; Graf, M.J.P.; Iaccarino, M.A.; Kajankova, M.; Kamins, J.; et al. The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury. *Arch. Phys. Med. Rehabil.* **2023**, *104*, 1343–1355. [CrossRef]
4. Dewan, M.C.; Rattani, A.; Gupta, S.; Baticulon, R.E.; Hung, Y.C.; Punchak, M.; Agrawal, A.; Adeleye, A.O.; Shrime, M.G.; Rubiano, A.M.; et al. Estimating the global incidence of traumatic brain injury. *J. Neurosurg.* **2019**, *130*, 1080–1097. [CrossRef] [PubMed]
5. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **2019**, *18*, 459–480. [CrossRef]
6. van der Vlegel, M.; Polinder, S.; Toet, H.; Panneman, M.J.M.; Haagsma, J.A. Prevalence of Post-Concussion-Like Symptoms in the General Injury Population and the Association with Health-Related Quality of Life, Health Care Use, and Return to Work. *J. Clin. Med.* **2021**, *10*, 806. [CrossRef]
7. Levy, A.M.; Saling, M.M.; Anderson, J.F.I. Frequency and extent of cognitive complaint following adult civilian mild traumatic brain injury: A systematic review and meta-analysis. *Brain Impair.* **2023**, *24*, 309–332. [CrossRef] [PubMed]
8. Cancelliere, C.; Verville, L.; Stubbs, J.L.; Yu, H.; Hincapié, C.A.; Cassidy, J.D.; Wong, J.J.; Shearer, H.M.; Connell, G.; Southerst, D.; et al. Post-Concussion Symptoms and Disability in Adults with Mild Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *J. Neurotrauma* **2023**, *40*, 1045–1059. [CrossRef]
9. MacGregor, A.J.; Casachahua, J.D.; Walton, S.R.; Harbertson, J.; Jurick, S.M.; Dougherty, A.L.; McCabe, C.T.; Watrous, J.R.; Fraser, J.J. Deployment-related concussion and long-term health-related quality of life among US military personnel. *Qual. Life Res.* **2023**, *32*, 1971–1980. [CrossRef]
10. Agimi, Y.; Marion, D.; Schwab, K.; Stout, K. Estimates of Long-Term Disability Among US Service Members with Traumatic Brain Injuries. *J. Head Trauma Rehabil.* **2021**, *36*, 1–9. [CrossRef]
11. Fralick, M.; Sy, E.; Hassan, A.; Burke, M.J.; Mostofsky, E.; Karsies, T. Association of Concussion with the Risk of Suicide: A Systematic Review and Meta-analysis. *JAMA Neurol.* **2019**, *76*, 144–151. [CrossRef] [PubMed]
12. Zemper, E.D. Two-year prospective study of relative risk of a second cerebral concussion. *Am. J. Phys. Med. Rehabil.* **2003**, *82*, 653–659. [CrossRef] [PubMed]
13. Dennis, E.L.; Taylor, B.A.; Newsome, M.R.; Troyanskaya, M.; Abildskov, T.J.; Betts, A.M.; Bigler, E.D.; Cole, J.; Davenport, N.; Duncan, T.; et al. Advanced brain age in deployment-related traumatic brain injury: A LIMBIC-CENC neuroimaging study. *Brain Inj.* **2022**, *36*, 662–672. [CrossRef]
14. Nejtek, V.A.; James, R.N.; Salvatore, M.F.; Alphonso, H.M.; Boehm, G.W. Premature cognitive decline in specific domains found in young veterans with mTBI coincide with elder normative scores and advanced-age subjects with early-stage Parkinson's disease. *PLoS ONE* **2021**, *16*, e0258851. [CrossRef] [PubMed]
15. Gan, S.; Shi, W.; Wang, S.; Sun, Y.; Yin, B.; Bai, G.; Jia, X.; Sun, C.; Niu, X.; Wang, Z.; et al. Accelerated Brain Aging in Mild Traumatic Brain Injury: Longitudinal Pattern Recognition with White Matter Integrity. *J. Neurotrauma* **2021**, *38*, 2549–2559. [CrossRef]
16. Guan, B.; Anderson, D.B.; Chen, L.; Feng, S.; Zhou, H. Global, regional and national burden of traumatic brain injury and spinal cord injury, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *BMJ Open* **2023**, *13*, e075049. [CrossRef]
17. Peterson, A.B.; Waltzman, D.; Daugherty, J.; Chen, J.; Breiding, M. Sport and Recreation Related Concussion in Children: National Concussion Surveillance System. *Am. J. Prev. Med.* **2024**, *67*, 370–379. [CrossRef]

18. DePadilla, L.; Miller, G.F.; Jones, S.E.; Peterson, A.B.; Breiding, M.J. Self-Reported Concussions from Playing a Sport or Being Physically Active Among High School Students—United States, 2017. *MMWR Morb. Mortal. Wkly. Rep.* **2018**, *67*, 682–685. [CrossRef]
19. Wågberg, S.; Stålnacke, B.M.; Magnusson, B.M. Gender and Age Differences in Outcomes after Mild Traumatic Brain Injury. *J. Clin. Med.* **2023**, *12*, 4883. [CrossRef]
20. Richey, L.N.; Rao, V.; Roy, D.; Narapareddy, B.R.; Wigh, S.; Bechtold, K.T.; Sair, H.I.; Van Meter, T.E.; Falk, H.; Leoutsakos, J.M.; et al. Age differences in outcome after mild traumatic brain injury: Results from the HeadSMART study. *Int. Rev. Psychiatry* **2020**, *32*, 22–30. [CrossRef]
21. Daugherty, J.; Waltzman, D.; Sarmiento, K.; Xu, L. Traumatic Brain Injury-Related Deaths by Race/Ethnicity, Sex, Intent, and Mechanism of Injury—United States, 2000–2017. *MMWR Morb. Mortal. Wkly. Rep.* **2019**, *68*, 1050–1056. [CrossRef] [PubMed]
22. Bahraini, N.; Adams, R.S.; Caban, J.; Kinney, A.R.; Forster, J.E.; Hoffmire, C.A.; Monteith, L.L.; Brenner, L.A. Racial and Ethnic Differences in Deaths by Suicide, Drug Overdose, and Opioid-Related Overdose in a National Sample of Military Members with Mild Traumatic Brain Injury, 1999–2019. *J. Head Trauma Rehabil.* **2023**, *38*, 114–124. [CrossRef]
23. Pavlov, V.; Thompson-Leduc, P.; Zimmer, L.; Wen, J.; Shea, J.; Beyhaghi, H.; Toback, S.; Kirson, N.; Miller, M. Mild traumatic brain injury in the United States: Demographics, brain imaging procedures, health-care utilization and costs. *Brain Inj.* **2019**, *33*, 1151–1157. [CrossRef]
24. Dismuke-Greer, C.; Hirsch, S.; Carlson, K.; Pogoda, T.; Nakase-Richardson, R.; Bhatnagar, S.; Eapen, B.; Troyanskaya, M.; Miles, S.; Nolen, T.; et al. Health Services Utilization, Health Care Costs, and Diagnoses by Mild Traumatic Brain Injury Exposure: A Chronic Effects of Neurotrauma Consortium Study. *Arch. Phys. Med. Rehabil.* **2020**, *101*, 1720–1730. [CrossRef] [PubMed]
25. D'Alonzo, B.A.; Bretzin, A.C.; Schneider, A.L.; Morse, R.B.; Canelón, S.P.; Wiebe, D.J.; Boland, M.R. Comparison of different definitions of traumatic brain injury: Implications for cohort characteristics and survival in women, Philadelphia, USA. *Inj. Prev.* **2024**, *31*, 198–204. [CrossRef] [PubMed]
26. Levin, H.S.; Temkin, N.R.; Barber, J.; Nelson, L.D.; Robertson, C.; Brennan, J.; Stein, M.B.; Yue, J.K.; Giacino, J.T.; McCrea, M.A.; et al. Association of Sex and Age with Mild Traumatic Brain Injury-Related Symptoms: A TRACK-TBI Study. *JAMA Netw. Open* **2021**, *4*, e213046. [CrossRef] [PubMed]
27. Gaudette, É.; Seabury, S.A.; Temkin, N.; Barber, J.; DiGiorgio, A.M.; Markowitz, A.J.; Manley, G.T.; TRACK-TBI Investigators. Employment and Economic Outcomes of Participants with Mild Traumatic Brain Injury in the TRACK-TBI Study. *JAMA Netw. Open* **2022**, *5*, e2219444. [CrossRef]
28. Bigler, E.D. Volumetric MRI Findings in Mild Traumatic Brain Injury (mTBI) and Neuropsychological Outcome. *Neuropsychol. Rev.* **2023**, *33*, 5–41. [CrossRef]
29. Patel, J.B.; Wilson, S.H.; Oakes, T.R.; Santhanam, P.; Weaver, L.K. Structural and Volumetric Brain MRI Findings in Mild Traumatic Brain Injury. *AJNR Am. J. Neuroradiol.* **2020**, *41*, 92–99. [CrossRef]
30. Santhanam, P.; Wilson, S.H.; Mulatya, C.; Oakes, T.R.; Weaver, L.K. Age-Accelerated Reduction in Cortical Surface Area in United States Service Members and Veterans with Mild Traumatic Brain Injury and Post-Traumatic Stress Disorder. *J. Neurotrauma* **2019**, *36*, 2922–2929. [CrossRef]
31. Martindale, S.L.; Rostami, R.; Shura, R.D.; Taber, K.H.; Rowland, J.A. Brain Volume in Veterans: Relationship to Posttraumatic Stress Disorder and Mild Traumatic Brain Injury. *J. Head Trauma Rehabil.* **2020**, *35*, E330–E341. [CrossRef]
32. Eierud, C.; Nathan, D.E.; Bonavia, G.H.; Ollinger, J.; Riedy, G. Cortical thinning in military blast compared to non-blast persistent mild traumatic brain injuries. *Neuroimage Clin.* **2019**, *22*, 101793. [CrossRef]
33. Lopez, K.C.; Leary, J.B.; Pham, D.L.; Chou, Y.Y.; Dsurney, J.; Chan, L. Brain Volume, Connectivity, and Neuropsychological Performance in Mild Traumatic Brain Injury: The Impact of Post-Traumatic Stress Disorder Symptoms. *J. Neurotrauma* **2017**, *34*, 16–22. [CrossRef]
34. Tate, D.F.; Gusman, M.; Kini, J.; Reid, M.; Velez, C.S.; Drennon, A.M.; Cooper, D.B.; Kennedy, J.E.; Bowles, A.O.; Bigler, E.D.; et al. Susceptibility Weighted Imaging and White Matter Abnormality Findings in Service Members with Persistent Cognitive Symptoms Following Mild Traumatic Brain Injury. *Mil. Med.* **2017**, *182*, e1651–e1658. [CrossRef]
35. Hageman, G.; Hof, J.; Nihom, J. Susceptibility-Weighted MRI and Microbleeds in Mild Traumatic Brain Injury: Prediction of Posttraumatic Complaints? *Eur. Neurol.* **2022**, *85*, 177–185. [CrossRef] [PubMed]
36. Clark, A.L.; Sorg, S.F.; Schiehser, D.M.; Luc, N.; Bondi, M.W.; Sanderson, M.; Werhane, M.L.; Delano-Wood, L. Deep white matter hyperintensities affect verbal memory independent of PTSD symptoms in veterans with mild traumatic brain injury. *Brain Inj.* **2016**, *30*, 864–871. [CrossRef] [PubMed]
37. Berginström, N.; Nordström, P.; Nyberg, L.; Nordström, A. White matter hyperintensities increases with traumatic brain injury severity: Associations to neuropsychological performance and fatigue. *Brain Inj.* **2020**, *34*, 415–420. [CrossRef] [PubMed]
38. Lippa, S.M.; Kenney, K.; Riedy, G.; Ollinger, J. White Matter Hyperintensities Are Not Related to Symptomatology or Cognitive Functioning in Service Members with a Remote History of Traumatic Brain Injury. *Neurotrauma Rep.* **2021**, *2*, 245–254. [CrossRef]

39. O'Brien, M.C.; Disner, S.G.; Davenport, N.D.; Sponheim, S.R. The relationship between blast-related mild traumatic brain injury and executive function is moderated by white matter integrity. *Brain Imaging Behav.* **2024**, *18*, 764–772. [CrossRef]
40. Vakhtin, A.A.; Zhang, Y.; Wintermark, M.; Massaband, P.; Robinson, M.T.; Ashford, J.W.; Furst, A.J. White Matter Asymmetry: A Reflection of Pathology in Traumatic Brain Injury. *J. Neurotrauma* **2020**, *37*, 373–381. [CrossRef]
41. Asken, B.M.; DeKosky, S.T.; Clugston, J.R.; Jaffee, M.S.; Bauer, R.M. Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): A systematic critical review. *Brain Imaging Behav.* **2018**, *12*, 585–612. [CrossRef] [PubMed]
42. Yeh, P.H.; Lippa, S.M.; Brickell, T.A.; Ollinger, J.; French, L.M.; Lange, R.T. Longitudinal changes of white matter microstructure following traumatic brain injury in U.S. military service members. *Brain Commun.* **2022**, *4*, fcac132. [CrossRef]
43. Pankatz, L.; Rojczyk, P.; Seitz-Holland, J.; Bouix, S.; Jung, L.B.; Wiegand, T.L.T.; Bonke, E.M.; Sollmann, N.; Kaufmann, E.; Carrington, H.; et al. Adverse Outcome Following Mild Traumatic Brain Injury Is Associated with Microstructure Alterations at the Gray and White Matter Boundary. *J. Clin. Med.* **2023**, *12*, 5415. [CrossRef] [PubMed]
44. Eisele, A.; Hill-Strathy, M.; Michels, L.; Rauen, K. Magnetic Resonance Spectroscopy following Mild Traumatic Brain Injury: A Systematic Review and Meta-Analysis on the Potential to Detect Posttraumatic Neurodegeneration. *Neurodegener. Dis.* **2020**, *20*, 2–11. [CrossRef]
45. Joyce, J.M.; La, P.L.; Walker, R.; Harris, A.D. Magnetic Resonance Spectroscopy of Traumatic Brain Injury and Subconcussive Hits: A Systematic Review and Meta-Analysis. *J. Neurotrauma* **2022**, *39*, 1455–1476. [CrossRef]
46. Brown, M.; Baradaran, H.; Christos, P.J.; Wright, D.; Gupta, A.; Tsiouris, A.J. Magnetic resonance spectroscopy abnormalities in traumatic brain injury: A meta-analysis. *J. Neuroradiol.* **2018**, *45*, 123–129. [CrossRef]
47. Dretsch, M.N.; Daniel, T.A.; Goodman, A.M.; Katz, J.S.; Denney, T.; Deshpande, G.; Robinson, J.L. Differential neural activation when voluntarily regulating emotions in service members with chronic mild traumatic brain injury. *Appl. Neuropsychol. Adult* **2019**, *26*, 76–88. [CrossRef]
48. Dretsch, M.N.; Rangaprakash, D.; Katz, J.S.; Daniel, T.A.; Goodman, A.M.; Denney, T.S.; Deshpande, G. Strength and Temporal Variance of the Default Mode Network to Investigate Chronic Mild Traumatic Brain Injury in Service Members with Psychological Trauma. *J. Exp. Neurosci.* **2019**, *13*, 1179069519833966. [CrossRef]
49. Scheibel, R.S.; Newsome, M.R.; Troyanskaya, M.; Lin, X.; Steinberg, J.L.; Radaideh, M.; Levin, H.S. Altered brain activation in military personnel with one or more traumatic brain injuries following blast. *J. Int. Neuropsychol. Soc.* **2012**, *18*, 89–100. [CrossRef] [PubMed]
50. Fischer, B.L.; Parsons, M.; Durgerian, S.; Reece, C.; Mourany, L.; Lowe, M.J.; Beall, E.B.; Koenig, K.A.; Jones, S.E.; Newsome, M.R.; et al. Neural activation during response inhibition differentiates blast from mechanical causes of mild to moderate traumatic brain injury. *J. Neurotrauma* **2014**, *31*, 169–179. [CrossRef]
51. Sheth, C.; Rogowska, J.; Legarreta, M.; McGlade, E.; Yurgelun-Todd, D. Functional connectivity of the anterior cingulate cortex in Veterans with mild traumatic brain injury. *Behav. Brain Res.* **2021**, *396*, 112882. [CrossRef] [PubMed]
52. Philippi, C.L.; Velez, C.S.; Wade, B.S.C.; Drennon, A.M.; Cooper, D.B.; Kennedy, J.E.; Bowles, A.O.; Lewis, J.D.; Reid, M.W.; York, G.E.; et al. Distinct patterns of resting-state connectivity in U.S. service members with mild traumatic brain injury versus posttraumatic stress disorder. *Brain Imaging Behav.* **2021**, *15*, 2616–2626. [CrossRef] [PubMed]
53. Dogra, S.; Arabshahi, S.; Wei, J.; Saidenberg, L.; Kang, S.K.; Chung, S.; Laine, A.; Lui, Y.W. Functional Connectivity Changes on Resting-State fMRI after Mild Traumatic Brain Injury: A Systematic Review. *AJNR Am. J. Neuroradiol.* **2024**, *45*, 795–801. [CrossRef]
54. Koziarz, A.; Koziarz, F.; Shen, R.; Gopee-Ramanan, P.; Black, S.E.; Worsley, D.; Chan, I.Y.M.; Streiner, D.L.; Zukotynski, K.A. Diagnostic Accuracy of SPECT for Mild Traumatic Brain Injury: A Systematic Review and Meta-analysis. *Clin. Nucl. Med.* **2024**, *49*, 938–947. [CrossRef]
55. Raji, C.A.; Tarzwell, R.; Pavel, D.; Schneider, H.; Uszler, M.; Thornton, J.; van Lierop, M.; Cohen, P.; Amen, D.G.; Henderson, T. Clinical utility of SPECT neuroimaging in the diagnosis and treatment of traumatic brain injury: A systematic review. *PLoS ONE* **2014**, *9*, e91088. [CrossRef]
56. Jacobs, A.; Put, E.; Ingels, M.; Put, T.; Bossuyt, A. One-year follow-up of technetium-99m-HMPAO SPECT in mild head injury. *J. Nucl. Med.* **1996**, *37*, 1605–1609. [PubMed]
57. Abu-Judeh, H.H.; Parker, R.; Aleksic, S.; Singh, M.L.; Naddaf, S.; Atay, S.; Kumar, M.; Omar, W.; El-Zeftawy, H.; Luo, J.Q.; et al. SPECT brain perfusion findings in mild or moderate traumatic brain injury. *Nucl. Med. Rev. Cent. East Eur.* **2000**, *3*, 5–11. [PubMed]
58. Hofman, P.A.; Stapert, S.Z.; van Kroonenburgh, M.J.; Jolles, J.; de Kruijk, J.; Wilmink, J.T. MR imaging, single-photon emission CT, and neurocognitive performance after mild traumatic brain injury. *AJNR Am. J. Neuroradiol.* **2001**, *22*, 441–449. [PubMed] [PubMed Central]
59. Lorberboym, M.; Lampl, Y.; Gerzon, I.; Sadeh, M. Brain SPECT evaluation of amnestic ED patients after mild head trauma. *Am. J. Emerg. Med.* **2002**, *20*, 310–313. [CrossRef] [PubMed]

60. Umile, E.M.; Sandel, M.E.; Alavi, A.; Terry, C.M.; Plotkin, R.C. Dynamic imaging in mild traumatic brain injury: Support for the theory of medial temporal vulnerability. *Arch. Phys. Med. Rehabil.* **2002**, *83*, 1506–1513. [CrossRef] [PubMed]
61. Roldán, M.; Kyriacou, P.A. Near-Infrared Spectroscopy (NIRS) in Traumatic Brain Injury (TBI). *Sensors* **2021**, *21*, 1586. [CrossRef] [PubMed] [PubMed Central]
62. Chang, F.; Li, H.; Li, N.; Zhang, S.; Liu, C.; Zhang, Q.; Cai, W. Functional near-infrared spectroscopy as a potential objective evaluation technique in neurocognitive disorders after traumatic brain injury. *Front. Psychiatry* **2022**, *13*, 903756. [CrossRef] [PubMed]
63. Sirant, L.W.; Singh, J.; Martin, S.; Gaul, C.A.; Stuart-Hill, L.; Candow, D.G.; Mang, C.; Neary, J.P. Long-term effects of multiple concussions on prefrontal cortex oxygenation during neurovascular coupling activation in retired male contact sport athletes. *Curr. Res. Physiol.* **2022**, *5*, 421–428. [CrossRef]
64. Sirant, L.W.; Singh, J.; Martin, S.; Gaul, C.A.; Stuart-Hill, L.; Candow, D.G.; Mang, C.; Neary, J.P. Long-term effects of multiple concussions on prefrontal cortex oxygenation during repeated squat-stands in retired contact sport athletes. *Brain Inj.* **2022**, *36*, 931–938. [CrossRef]
65. Tiberini, P.; D'Antona, G.; Cicchella, A. Brain Oxygenation in Post-concussion Combat Sport Athletes. *Front. Sports Act. Living* **2021**, *3*, 725096. [CrossRef] [PubMed]
66. Sharma, A.; Hind, K.; Hume, P.; Singh, J.; Neary, J.P. Neurovascular Coupling by Functional Near Infra-Red Spectroscopy and Sport-Related Concussion in Retired Rugby Players: The UK Rugby Health Project. *Front. Hum. Neurosci.* **2020**, *14*, 42. [CrossRef]
67. Smith, C.M.; Ugale, C.B.; Segovia, M.D.; Salmon, O.F.; Lee, K.M.; Gallucci, A.R. Identifying Traumatic Brain Injuries Using a Morlet Wavelet fNIRS Analysis in Role of Care 1 and 2 Environments: A Feasibility Study. *Mil. Med.* **2025**, *190*, 13–19. [CrossRef] [PubMed]
68. Jones, B.; Jamalifard, M.; Waterworth, S.; Rogerson, M.; Andreu-Perez, J.; Perrett, J.; Hope, E.; Moran, J.; Adams, T.; Singh, J.; et al. Cerebral Haemodynamic Assessment Following Sport-related Concussion (Mild Traumatic Brain Injury) in Youth and Amateur Rugby Union Players. *Sports Med. Open* **2025**, *11*, 47, Erratum in *Sports Med. Open* **2025**, *11*, 51. https://doi.org/10.1186/s40798-025-00866-1. [CrossRef]
69. O'Neil, B.; Prichep, L.S.; Naunheim, R.; Chabot, R. Quantitative brain electrical activity in the initial screening of mild traumatic brain injuries. *West. J. Emerg. Med.* **2012**, *13*, 394–400. [CrossRef]
70. Haneef, Z.; Levin, H.S.; Frost, J.D.; Mizrahi, E.M. Electroencephalography and quantitative electroencephalography in mild traumatic brain injury. *J. Neurotrauma* **2013**, *30*, 653–656. [CrossRef]
71. Hanley, D.; Prichep, L.S.; Badjatia, N.; Bazarian, J.; Chiacchierini, R.; Curley, K.C.; Garrett, J.; Jones, E.; Naunheim, R.; O'Neil, B.; et al. A Brain Electrical Activity Electroencephalographic-Based Biomarker of Functional Impairment in Traumatic Brain Injury: A Multi-Site Validation Trial. *J. Neurotrauma* **2018**, *35*, 41–47. [CrossRef] [PubMed]
72. Barr, W.B.; Prichep, L.S.; Chabot, R.; Powell, M.R.; McCrea, M. Measuring brain electrical activity to track recovery from sport-related concussion. *Brain Inj.* **2012**, *26*, 58–66. [CrossRef] [PubMed]
73. Vivaldi, N.; Caiola, M.; Solarana, K.; Ye, M. Evaluating Performance of EEG Data-Driven Machine Learning for Traumatic Brain Injury Classification. *IEEE Trans. Biomed. Eng.* **2021**, *68*, 3205–3216. [CrossRef] [PubMed]
74. Franke, L.M.; Perera, R.A.; Sponheim, S.R. Long-term resting EEG correlates of repetitive mild traumatic brain injury and loss of consciousness: Alterations in alpha-beta power. *Front. Neurol.* **2023**, *14*, 1241481. [CrossRef]
75. Peitz, G.W.; Wilde, E.A.; Grandhi, R. Magnetoencephalography in the Detection and Characterization of Brain Abnormalities Associated with Traumatic Brain Injury: A Comprehensive Review. *Med. Sci.* **2021**, *9*, 7. [CrossRef]
76. Sattari, S.; Kenny, R.; Liu, C.C.; Hajra, S.G.; Dumont, G.A.; Virji-Babul, N. Blink-related EEG oscillations are neurophysiological indicators of subconcussive head impacts in female soccer players: A preliminary study. *Front. Hum. Neurosci.* **2023**, *17*, 1208498. [CrossRef]
77. Desjardins, M.; Drisdelle, B.L.; Lefebvre, C.; Gagnon, J.F.; De Beaumont, L.; Jolicoeur, P. Interhemispheric differences in P1 and N1 amplitude in EEG and MEG differ across older individuals with a concussion compared with age-matched controls. *Psychophysiology* **2021**, *58*, e13751. [CrossRef]
78. Li, L.; Pagnotta, M.F.; Arakaki, X.; Tran, T.; Strickland, D.; Harrington, M.; Zouridakis, G. Brain activation profiles in mTBI: Evidence from combined resting-state EEG and MEG activity. In *Proceedings of the 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*; IEEE: New York, NY, USA, 2015; pp. 6963–6966. [CrossRef]
79. Itälinna, V.; Kaltiainen, H.; Forss, N.; Liljeström, M.; Parkkonen, L. Using normative modeling and machine learning for detecting mild traumatic brain injury from magnetoencephalography data. *PLoS Comput. Biol.* **2023**, *19*, e1011613. [CrossRef]
80. Jacob, D.; Unnsteinsdóttir Kristensen, I.S.; Aubonnet, R.; Recenti, M.; Donisi, L.; Ricciardi, C.; Svansson, H.Á.R.; Agnarsdóttir, S.; Colacino, A.; Jónsdóttir, M.K.; et al. Towards defining biomarkers to evaluate concussions using virtual reality and a moving platform (BioVRSea). *Sci. Rep.* **2022**, *12*, 8996. [CrossRef]

81. Vishwanath, M.; Jafarlou, S.; Shin, I.; Dutt, N.; Rahmani, A.M.; Jones, C.E.; Lim, M.M.; Cao, H. Investigation of Machine Learning and Deep Learning Approaches for Detection of Mild Traumatic Brain Injury from Human Sleep Electroencephalogram. In *Proceedings of the 2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society*; IEEE: New York, NY, USA, 2021; pp. 6134–6137. [CrossRef]
82. Gozt, A.K.; Hellewell, S.C.; Thorne, J.; Thomas, E.; Buhagiar, F.; Markovic, S.; Van Houselt, A.; Ring, A.; Arendts, G.; Smedley, B.; et al. Predicting outcome following mild traumatic brain injury: Protocol for the longitudinal, prospective, observational Concussion Recovery. *BMJ Open* **2021**, *11*, e046460. [CrossRef]
83. Thatcher, R.W.; Walker, R.A.; Gerson, I.; Geisler, F.H. EEG discriminant analyses of mild head trauma. *Electroencephalogr. Clin. Neurophysiol.* **1989**, *73*, 94–106. [CrossRef]
84. Alouani, A.T.; Elfouly, T. Traumatic Brain Injury (TBI) Detection: Past, Present, and Future. *Biomedicines* **2022**, *10*, 2472. [CrossRef]
85. Corbin-Berrigan, L.A.; Teel, E.; Vinet, S.A.; PDe Koninck, B.; Guay, S.; Beaulieu, C.; De Beaumont, L. The Use of Electroencephalography as an Informative Tool in Assisting Early Clinical Management after Sport-Related Concussion: A Systematic Review. *Neuropsychol. Rev.* **2023**, *33*, 144–159. [CrossRef] [PubMed]
86. Zhang, J.; Safar, K.; Emami, Z.; Ibrahim, G.M.; Scratch, S.E.; da Costa, L.; Dunkley, B.T. Local and large-scale beta oscillatory dysfunction in males with mild traumatic brain injury. *J. Neurophysiol.* **2020**, *124*, 1948–1958. [CrossRef]
87. Varoquaux, G. Cross-validation failure: Small sample sizes lead to large error bars. *Neuroimage* **2018**, *180*, 68–77. [CrossRef]
88. Conley, A.C.; Cooper, P.S.; Karayanidis, F.; Gardner, A.J.; Levi, C.R.; Stanwell, P.; Gaetz, M.B.; Iverson, G.L. Resting State Electroencephalography and Sports-Related Concussion: A Systematic Review. *J. Neurotrauma* **2018**, *36*, 1–13. [CrossRef]
89. Kim, H.J.; Tsao, J.W.; Stanfill, A.G. The current state of biomarkers of mild traumatic brain injury. *JCI Insight* **2018**, *3*, e97105. [CrossRef]
90. Oris, C.; Kahouadji, S.; Bouvier, D.; Sapin, V. Blood Biomarkers for the Management of Mild Traumatic Brain Injury in Clinical Practice. *Clin. Chem.* **2024**, *70*, 1023–1036. [CrossRef]
91. Papa, L.; McKinley, W.I.; Valadka, A.B.; Newman, Z.C.; Nordgren, R.K.; Pramuka, P.E.; Barbosa, C.E.; Brito, A.M.P.; Loss, L.J.; Tinoco-Garcia, L.; et al. Diagnostic Performance of GFAP, UCH-L1, and MAP-2 within 30 and 60 Minutes of Traumatic Brain Injury. *JAMA Netw. Open* **2024**, *7*, e2431115. [CrossRef] [PubMed]
92. Korley, F.K.; Jain, S.; Sun, X.; Puccio, A.M.; Yue, J.K.; Gardner, R.C.; Wang, K.K.W.; Okonkwo, D.O.; Yuh, E.L.; Mukherjee, P.; et al. Prognostic value of day-of-injury plasma GFAP and UCH-L1 concentrations for predicting functional recovery after traumatic brain injury in patients from the US TRACK-TBI cohort: An observational cohort study. *Lancet Neurol.* **2022**, *21*, 803–813. [CrossRef] [PubMed]
93. Puccio, A.M.; Yue, J.K.; Korley, F.K.; Okonkwo, D.O.; Diaz-Arrastia, R.; Yuh, E.L.; Ferguson, A.R.; Mukherjee, P.; Wang, K.K.W.; Taylor, S.R.; et al. Diagnostic Utility of Glial Fibrillary Acidic Protein Beyond 12 Hours After Traumatic Brain Injury: A TRACK-TBI Study. *J. Neurotrauma* **2024**, *41*, 1353–1363. [CrossRef] [PubMed]
94. Bazarian, J.J.; Welch, R.D.; Caudle, K.; Jeffrey, C.A.; Chen, J.Y.; Chandran, R.; McCaw, T.; Datwyler, S.A.; Zhang, H.; McQuiston, B. Accuracy of a rapid glial fibrillary acidic protein/ubiquitin carboxyl-terminal hydrolase L1 test for the prediction of intracranial injuries on head computed tomography after mild traumatic brain injury. *Acad. Emerg. Med.* **2021**, *28*, 1308–1317. [CrossRef]
95. Bazarian, J.J.; Biberthaler, P.; Welch, R.D.; Lewis, L.M.; Barzo, P.; Bogner-Flatz, V.; Gunnar Brolinson, P.; Büki, A.; Chen, J.Y.; Christenson, R.H.; et al. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): A multicentre observational study. *Lancet Neurol.* **2018**, *17*, 782–789. [CrossRef]
96. U.S. Food & Drug Administration. *FDA Authorizes Marketing of First Blood Test to Aid in the Evaluation of Concussion in Adults [Press Release]*; U.S. Food and Drug Administration: Silver Spring, MD, USA, 2018.
97. Tybirk, L.; Hviid, C.V.B.; Knudsen, C.S.; Parkner, T. Serum GFAP—Reference interval and preanalytical properties in Danish adults. *Clin. Chem. Lab. Med.* **2022**, *60*, 1830–1838. [CrossRef]
98. Mondello, S.; Kobeissy, F.; Vestri, A.; Hayes, R.L.; Kochanek, P.M.; Berger, R.P. Serum Concentrations of Ubiquitin C-Terminal Hydrolase-L1 and Glial Fibrillary Acidic Protein after Pediatric Traumatic Brain Injury. *Sci. Rep.* **2016**, *6*, 28203. [CrossRef] [PubMed]
99. Calluy, E.; Beaudart, C.; Alokail, M.S.; Al-Daghri, N.M.; Bruyère, O.; Reginster, J.Y.; Cavalier, E.; Ladang, A. Confounding factors of the expression of mTBI biomarkers, S100B, GFAP and UCH-L1 in an aging population. *Clin. Chem. Lab. Med.* **2024**, *62*, 2062–2069. [CrossRef]
100. Bazarian, J.J.; Abar, B.; Merchant-Borna, K.; Pham, D.L.; Rozen, E.; Mannix, R.; Kawata, K.; Chou, Y.; Stephen, S.; Gill, J.M. Effects of Physical Exertion on Early Changes in Blood-Based Brain Biomarkers: Implications for the Acute Point of Care Diagnosis of Concussion. *J. Neurotrauma* **2023**, *40*, 693–705. [CrossRef]
101. Michetti, F.; Clementi, M.E.; Di Liddo, R.; Valeriani, F.; Ria, F.; Rende, M.; Di Sante, G.; Romano Spica, V. The S100B Protein: A Multifaceted Pathogenic Factor More Than a Biomarker. *Int. J. Mol. Sci.* **2023**, *24*, 9605. [CrossRef]

102. Mastandrea, P.; Mengozzi, S.; Bernardini, S. Systematic review and meta-analysis of observational studies evaluating glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCHL1) as blood biomarkers of mild acute traumatic brain injury (mTBI) or sport-related concussion (SRC) in adult subjects. *Diagnosis* **2024**, *12*, 1–16. [CrossRef] [PubMed]
103. Oris, C.; Bouillon-Minois, J.B.; Pinguet, J.; Kahouadji, S.; Durif, J.; Meslé, V.; Pereira, B.; Schmidt, J.; Sapin, V.; Bouvier, D. Predictive Performance of Blood S100B in the Management of Patients Over 65 Years Old with Mild Traumatic Brain Injury. *J. Gerontol. A Biol. Sci. Med. Sci.* **2021**, *76*, 1471–1479. [CrossRef] [PubMed]
104. Undén, J.; Romner, B. Can low serum levels of S100B predict normal CT findings after minor head injury in adults? An evidence-based review and meta-analysis. *J. Head Trauma Rehabil.* **2010**, *25*, 228–240. [CrossRef]
105. Allouchery, G.; Moustafa, F.; Roubin, J.; Pereira, B.; Schmidt, J.; Raconnat, J.; Pic, D.; Sapin, V.; Bouvier, D. Clinical validation of S100B in the management of a mild traumatic brain injury: Issues from an interventional cohort of 1449 adult patients. *Clin. Chem. Lab. Med.* **2018**, *56*, 1897–1904. [CrossRef]
106. Biberthaler, P.; Linsenmeier, U.; Pfeifer, K.J.; Kroetz, M.; Mussack, T.; Kanz, K.G.; Hoecherl, E.F.; Jonas, F.; Marzi, I.; Leucht, P.; et al. Serum S-100B concentration provides additional information fot the indication of computed tomography in patients after minor head injury: A prospective multicenter study. *Shock* **2006**, *25*, 446–453. [CrossRef] [PubMed]
107. Townend, W.; Dibble, C.; Abid, K.; Vail, A.; Sherwood, R.; Lecky, F. Rapid elimination of protein S-100B from serum after minor head trauma. *J. Neurotrauma* **2006**, *23*, 149–155. [CrossRef] [PubMed]
108. Shahim, P.; Politis, A.; van der Merwe, A.; Moore, B.; Chou, Y.Y.; Pham, D.L.; Butman, J.A.; Diaz-Arrastia, R.; Gill, J.M.; Brody, D.L.; et al. Neurofilament light as a biomarker in traumatic brain injury. *Neurology* **2020**, *95*, e610–e622, Erratum in *Neurology* **2021**, *96*, 593. [CrossRef]
109. Shahim, P.; Politis, A.; van der Merwe, A.; Moore, B.; Ekanayake, V.; Lippa, S.M.; Chou, Y.Y.; Pham, D.L.; Butman, J.A.; Diaz-Arrastia, R.; et al. Time course and diagnostic utility of NfL, tau, GFAP, and UCH-L1 in subacute and chronic TBI. *Neurology* **2020**, *95*, e623–e636, Erratum in *Neurology* **2021**, *96*, 593. [CrossRef]
110. Guedes, V.A.; Lange, R.T.; Lippa, S.M.; Lai, C.; Greer, K.; Mithani, S.; Devoto, C.A.; Edwards, K.; Wagner, C.L.; Martin, C.A.; et al. Extracellular vesicle neurofilament light is elevated within the first 12-months following traumatic brain injury in a U.S military population. *Sci. Rep.* **2022**, *12*, 4002. [CrossRef] [PubMed]
111. Karantali, E.; Kazis, D.; McKenna, J.; Chatzikonstantinou, S.; Petridis, F.; Mavroudis, I. Neurofilament light chain in patients with a concussion or head impacts: A systematic review and meta-analysis. *Eur. J. Trauma Emerg. Surg.* **2022**, *48*, 1555–1567. [CrossRef]
112. Farragher, C.D.; Ku, Y.; Powers, J.E. The Potential Role of Neurofilament Light in Mild Traumatic Brain Injury Diagnosis: A Systematic Review. *Cureus* **2022**, *14*, e31301. [CrossRef]
113. Visser, K.; Koggel, M.; Blaauw, J.; van der Horn, H.J.; Jacobs, B.; van der Naalt, J. Blood-based biomarkers of inflammation in mild traumatic brain injury: A systematic review. *Neurosci. Biobehav. Rev.* **2022**, *132*, 154–168. [CrossRef]
114. Devoto, C.; Vorn, R.; Mithani, S.; Meier, T.B.; Lai, C.; Broglio, S.P.; McAllister, T.; Giza, C.C.; Huber, D.; Harezlak, J.; et al. Plasma phosphorylated tau181 as a biomarker of mild traumatic brain injury: Findings from THINC and NCAA-DoD CARE Consortium prospective cohorts. *Front. Neurol.* **2023**, *14*, 1202967. [CrossRef]
115. Vorn, R.; Mithani, S.; Devoto, C.; Meier, T.B.; Lai, C.; Yun, S.; Broglio, S.P.; McAllister, T.W.; Giza, C.C.; Kim, H.S.; et al. Proteomic Profiling of Plasma Biomarkers Associated with Return to Sport Following Concussion: Findings from the NCAA and Department of Defense CARE Consortium. *Front. Neurol.* **2022**, *13*, 901238. [CrossRef] [PubMed]
116. Kenney, K.; Qu, B.X.; Lai, C.; Devoto, C.; Motamedi, V.; Walker, W.C.; Levin, H.S.; Nolen, T.; Wilde, E.A.; Diaz-Arrastia, R.; et al. Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury. *Brain Inj.* **2018**, *32*, 1276–1284. [CrossRef] [PubMed]
117. Pattinson, C.L.; Shahim, P.; Taylor, P.; Dunbar, K.; Guedes, V.A.; Motamedi, V.; Lai, C.; Devoto, C.; Peyer, J.; Roy, M.J.; et al. Elevated Tau in Military Personnel Relates to Chronic Symptoms Following Traumatic Brain Injury. *J. Head Trauma Rehabil.* **2020**, *35*, 66–73. [CrossRef]
118. Ciuffreda, K.J.; Joshi, N.R.; Truong, J.Q. Understanding the effects of mild traumatic brain injury on the pupillary light reflex. *Concussion* **2017**, *2*, CNC36. [CrossRef] [PubMed] [PubMed Central]
119. Dengler, B.A.; Meister, M.; Aderman, M.; Malvasi, S.R.; Ross, J.D.; Fu, A.; Haight, T.; Bartanusz, V.; Boulter, J.H.; Rudolph, J.; et al. Quantitative pupillometry as a biomarker for prediction of return to play in mild traumatic brain injury: A Military Traumatic Brain Injury Initiative study. *Neurosurg. Focus* **2024**, *57*, E12. [CrossRef]
120. Carrick, F.R.; Azzolino, S.F.; Hunfalvay, M.; Pagnacco, G.; Oggero, E.; D'Arcy, R.C.N.; Abdulrahman, M.; Sugaya, K. The Pupillary Light Reflex as a Biomarker of Concussion. *Life* **2021**, *11*, 1104. [CrossRef]
121. Huyghe, T.; Calleja-González, J.; Bird, S.P.; Alcaraz, P.E. Pupillometry as a new window to player fatigue? A glimpse inside the eyes of a Euro Cup Women's Basketball team. *Biol. Sport* **2024**, *41*, 3–15. [CrossRef]

122. Rach, H.; Reynaud, E.; Kilic-Huck, U.; Ruppert, E.; Comtet, H.; Roy de Belleplaine, V.; Fuchs, F.; Van Someren, E.J.W.; Geoffroy, P.A.; Bourgin, P. Pupillometry to differentiate idiopathic hypersomnia from narcolepsy type 1. *J. Sleep Res.* **2023**, *32*, e13885. [CrossRef]
123. Truong, J.Q.; Joshi, N.R.; Ciuffreda, K.J. Influence of refractive error on pupillary dynamics in the normal and mild traumatic brain injury (mTBI) populations. *J. Optom.* **2018**, *11*, 93–102. [CrossRef]