

Review

Integrating Neuroimaging, Biomarkers, and Rehabilitation Strategies for Optimized Diagnosis and Recovery in Traumatic Brain Injury

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Abstract

This review examines a multimodal approach that integrates advanced neuroimaging, biofluid biomarkers, and innovative rehabilitation strategies for the optimized diagnosis and recovery of traumatic brain injury (TBI). TBI remains a critical public health challenge due to its high incidence and diverse, long-lasting morbidities. Conventional diagnostic methods often lack the sensitivity to detect subtle injuries, and current prognostic models are limited by the heterogeneity of TBI. Emerging neuroimaging techniques, including diffusion tensor imaging (DTI), functional MRI (fMRI), PET, and magnetic resonance spectroscopy (MRS), along with blood- and CSF-based biomarkers, are increasingly important in assessing injury severity and guiding treatment. Furthermore, novel rehabilitation modalities such as virtual/augmented reality (VR/AR), brain-computer interfaces (BCIs), and targeted cognitive therapies have demonstrated potential to harness neuroplasticity and improve functional recovery. Despite these advancements, challenges remain in standardizing biomarker assays and integrating multimodal data into personalized treatment plans. Future research should validate these



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approaches in diverse patient populations to refine prognostic models and enhance clinical translation.

Keywords

Traumatic brain injury; neuroimaging; biomarkers; rehabilitation; neuroplasticity; glial fibrillary acidic protein; neurofilament light chain; total tau; phosphorylated tau; ubiquitin C-terminal hydrolase L1; S100B; diffusion tensor imaging; blood–brain barrier disruption; functional magnetic resonance imaging; positron emission tomography; magnetic resonance spectroscopy; virtual reality; augmented reality

1. Introduction

Traumatic Brain Injury represents a critical global public health challenge, affecting millions each year. In the United States, approximately 2.5 million people sustain a TBI annually, contributing markedly to both morbidity and mortality rates [1, 2]. Globally, TBI accounts for an estimated 27 million cases each year, reflecting a widespread burden that extends across diverse populations [3]. The rising incidence is largely driven by falls, road traffic accidents, and sports-related incidents, highlighting the pressing need for robust prevention initiatives [3]. Such measures are essential not only for reducing the occurrence of TBI but also for mitigating its extensive personal, social, and economic impacts, which can have life-long detrimental consequences [3]. Beyond the immediate injury, survivors often face long-term effects including cognitive deficits, emotional disturbances, and an elevated risk of neurodegenerative diseases such as Alzheimer's and Parkinson's, conditions that significantly impair quality of life and nearly double the risk of suicide [4]. Moreover, TBI is uniquely challenging to treat due to its dual-phase nature: the primary phase, characterized by immediate mechanical damage at the moment of impact, and the secondary phase, a delayed neuroinflammatory reaction leading to blood-brain barrier disruptions and cerebral edema [5, 6]. Due to this variability, there does not exist a current standard of treatment that can effectively address both primary and secondary causes of TBI, with many preclinical treatments yielding inconsistent clinical benefits.

1.1 Current Limitations in Diagnosis, Prognosis, and Treatment

The clinical management of TBI is further complicated by limitations in diagnosis and prognosis. Conventional imaging modalities, primarily relying on CT and MRI, often fail to detect subtle brain injuries in mild TBI cases, leading to delayed intervention [7]. This challenge is compounded by the subjective nature of imaging interpretation, resulting in diagnostic inconsistencies, especially given that approximately 90% of TBIs are classified as mild [4]. Emerging evidence supports the necessity of a multimodal approach that combines neuroimaging, biomarkers, and rehabilitation to enhance diagnostic precision and optimize recovery outcomes. Advanced neuroimaging techniques, including multimodal MRI, diffusion tensor imaging (DTI), functional MRI (fMRI), and MR spectroscopy, can detect microstructural and functional alterations in white matter integrity, offering insights into injury severity and recovery potential that conventional CT or non-contrast MRI might miss [8, 9].

To further aid, emerging biomarkers such as glial fibrillary acidic protein (GFAP), and neurofilament light polypeptide (NF-L) have shown promise as adjuncts to conventional imaging. GFAP, a filament protein located in the cytoskeleton of astrocytes, is highly correlated with brain injury and is uniquely specific to intracranial damage, as it is not released extracranially. This specificity makes GFAP one of the most promising standalone markers for detecting minor TBIs, with measurable levels persisting up to 7 days post-injury, although optimal threshold levels still require further study [10, 11]. Additionally, NF-L, a protein found in axonal membranes and inside axons, appears particularly useful during the acute phase of TBI, peaking around 4-12 hours after head trauma; however, consensus regarding its use remains elusive due to limited data correlating NF-L levels with chronic damage [12]. Overall, despite these promising developments, the lack of standardized protocols and comprehensive research has limited the routine clinical integration of these biomarkers [12-14].

Diagnostic uncertainty is further compounded by the heterogeneity of TBI. The variability in injury mechanisms and individual recovery trajectories undermines current prognostic models, rendering long-term outcome prediction an unmet challenge. TBI represents a spectrum rather than a singular disorder, with varied pathological, physiological, and genomic responses. Consequently, improved patient stratification, based on specific imaging findings, biomarkers, genetic profiles, and injury type, is essential for targeted interventions and more accurate prognostic assessments [15]. Considering these challenges, there is an urgent need for a multimodal approach that integrates advanced neuroimaging, and validated biomarkers. Beyond the diagnosis, innovative rehabilitation strategies are also in need and are currently being developed. These strategies, ranging from cognitive rehabilitation therapies to brain-computer interfaces, have demonstrated potential in promoting neuroplasticity and enhancing recovery [16].

1.2 Objectives of This Review

The objective of this review is to examine the role of a multimodal approach that integrates neuroimaging, biomarkers, and rehabilitation strategies in the diagnosis and recovery of TBI. Specifically, this article will evaluate recent advancements in neuroimaging techniques (including multimodal MRI, DTI, fMRI, and MR spectroscopy) for detecting structural and functional brain alterations following TBI. It will also explore the utility of blood-based and CSF biomarkers, such as GFAP, UCH-L1, and others, in assessing injury severity and predicting long-term outcomes, while addressing challenges in their standardization and clinical implementation. Finally, the review will discuss emerging rehabilitation strategies, such as Virtual or Augmented Reality and Brain-Computer Interfaces and examine how these innovations may enhance neuroplasticity and functional recovery. By synthesizing recent findings, this review aims to underscore the necessity of an integrated diagnostic and therapeutic framework that improves patient outcomes and informs future research directions in TBI management.

2. Neuroimaging Advances in TBI Diagnosis and Prognosis

2.1 Traditional Imaging Methods (CT, Standard MRI) and Their Limitations

The American College of Radiology underscores that initial imaging for moderate to severe closed head injury includes a noncontrast head CT, as it is useful in identifying certain outcomes such as

acute hemorrhage, cerebral edema, herniation, subdural or epidural hematomas that can be managed with acute neurosurgical intervention [17]. Noncontrast head CTs have also been found to be sensitive for the detection of clinically important TBI, or TBI resulting in severe intracranial injury that may potentially cause death, require neurologic intervention, cause intubation >24 hours or admission to the hospital for >2 days [18, 19]. Other advantages for utilization of noncontrast head CT as initial imaging includes its ease of availability and quicker turnaround time compared to other modalities such as MRI. However, noncontrast head CTs are unable to provide further information for evaluating a TBI such as detection of diffuse axonal injury, parenchymal contusions or signs of intracranial hypertension [20, 21]. It also has limited prognostic value. Two scores, the Marshall and Rotterdam scores, aim to predict clinical outcomes among patients with moderate to severe TBI based on findings from noncontrast head CT findings. The Marshall score is limited in predicting outcomes for patients with multiple injury types [22] and the Rotterdam score is based on specific findings in a noncontrast head CT (presence of hemorrhage, midline shift, etc.) and predicts only a 6-month mortality [23]. For this reason, subsequent neuroimaging using MRI is often sought. MRI has been shown to be more sensitive than noncontrast CT for detecting all stages of subdural or epidural hematomas, hemorrhagic and nonhemorrhagic axonal injuries in white matter and nonhemorrhagic cortical contusions [24, 25]. Specifically, T2-weighted Gradient Echo (T2GRE) is especially sensitive to detecting microhemorrhages in the brain that are associated with various stages of diffuse axonal injury [26]. Susceptibility weighted imaging (SWI) is also often used in evaluation of TBI with Tong et al. finding that SWI was able to depict much smaller hemorrhagic lesions than GRE MRI in children and adolescents with DAI [27]. Although the presence of microhemorrhages have been shown to correlate clinically with the Glasgow Coma Scale, the quantity of microhemorrhages identified have not been found to associate with TBI severity or worse outcomes [28]. Further limitations for MRI in the acute setting of TBI include limited availability with longer imaging times.

More contemporary research on susceptibility-sensitive MRI have shown increased non-heme iron accumulation in the thalamus of mild TBI patients—measured as a 15-25% rise in quantitative susceptibility mapping values compared to controls, suggesting microstructural damage and potential ongoing oxidative stress [29]. These iron deposition findings imply that microvascular and metabolic disturbances persist beyond what conventional sequences detect, thus allowing for a more complete assessment of injury burden in mild TBIs.

2.2 Diffusion Tensor Imaging (DTI): White Matter Integrity and Axonal Injury Detection

Diffusion tensor imaging is an advanced MRI sequence that provides specific information about axonal tracts and the structural integrity of white matter tracts by weighing water diffusion in multiple spatial directions [18, 30]. In comparison, conventional MRI is unable to visualize many of these white matter tracts. The most commonly reported metrics of DWI include fractional anisotropy (FA) and mean diffusivity (MD). With regards to application of DTI in TBI, several studies have found decreased FA and increased MD in patients with TBI. For example, Miles et al. performed DTI in 17 patients with mild TBI and compared the results to age-matched controls, finding decreased FA in the posterior limb of the internal capsule, corpus callosum and centrum semiovale [18, 30]. In contrast, Newcombe et al. compared DTI imaging in 33 patients with moderate to severe TBI to age-matched controls and found a statistically significant reduction in FA in the TBI group,

indicating an increased global burden of white matter injury [31]. Therefore, disruptions in FA or MD are sensitive markers for alterations in white matter integrity in TBI patients, but these findings are non-specific and the exact mechanism for these alterations is uncertain [31]. The clinical correlations and prognostic value of these disruptions in DTI metrics have also been established in literature, with Cho et al. and Adreassen et al. finding that reductions in FA in the uncinate fasciculus and hippocampal cingulate gyrus were negatively correlated with post-traumatic amnesia duration and Mini-Mental State Examination scores [32, 33]. As stated by Paolini et al., as the corpus callosum is the white matter bundle most susceptible to injury by angular rotational acceleration in TBI, a decrease in its FA could be considered a surrogate measure of widespread Wallerian degeneration of hemispheric white matter [34]. This, in turn, could indicate a poorer prognosis. Castano-Leon et al. measured FA in 28 white matter bundles of interest in 185 patients with moderate to severe TBI and after conducting a multivariate logistic regression analysis found FA of the genu of the corpus callosum to be an independent prognostic factor for severity/outcomes following TBI [35]. Furthermore, DTI may be used not only as a marker for white matter structural integrity or as a prognostic indicator, but also to track recovery in patients with TBI. For instance, Debarle et al. found that global MD significantly differed between those TBI patients with good recovery (determined using Glasgow Outcome Scale Extended) compared to others, suggesting that global MD may serve as a reliable radio marker for determining good outcomes long-term following TBI [36]. Similarly, Grassi et al. studied the correlation between DTI metrics and cognitive deficits over time in patients with moderate to severe DAI and concluded that microstructural changes in white matter are dynamic, may be detectable by DTI in the first year following trauma and that changes in DTI parameters over time following DAI may be correlated with changes in several cognitive domains [37, 38]. Beyond DTI, diffusion kurtosis imaging (DKI) has identified reduced mean kurtosis (MK) and radial kurtosis (RK) in the thalamus and hypothalamus of mild TBI patients, up to 12% lower MK and 18% lower RK versus matched controls. This indicates disrupted microstructural complexity even when FA and MD appear normal [39]. While DTI models water diffusion in tissue as a Gaussian process, DKI extends this by quantifying deviations from Gaussian behavior, providing sensitivity to complex microstructural barriers such as cell membranes, organelles, and myelin sheaths that DTI may overlook. These DKI alterations suggest that subtle axonal and glial pathology in mild TBI can be uncovered only by higher-order diffusion metrics, reinforcing the value of incorporating kurtosis imaging into longitudinal studies of white matter recovery [40]. An overview and comparison of the different utilities of neuroimaging modalities is presented in Table 1.

Table 1 Comparative Utility of Neuroimaging Modalities in TBI. This table compares the diagnostic capabilities and limitations of three neuroimaging techniques commonly employed in TBI assessment: Noncontrast CT , MRI with T2*-weighted Gradient Echo (T2GRE) and Susceptibility Weighted Imaging (SWI) sequences, and DTI.

Comparison of Neuroimaging in Traumatic Brain Imaging		
Noncontrast CT Head	MRI, T2GRE, SWI	Diffusor Tensor Imaging
		
✓ Useful in identifying acute hemorrhage, cerebral edema, herniation, hematoma for acute neurosurgical intervention following TBI ✗ Cannot detect DAI, parenchymal contusions	✓ T2GRE and SWI useful for detecting micro hemorrhages associated with DAI ✗ Longer time and limited availability compared to CT.	✓ Provides specific information about structural integrity of white matter tracts. Has been shown to be a diagnostic prognostic marker and marker of recovery ✗ Longer imaging time required

2.3 Functional MRI (fMRI): Cognitive and Functional Network Assessment

Functional MRI (fMRI) is an indispensable tool for uncovering the functional disturbances associated with anatomical injuries in TBIs. Li et al. reported significant neuroanatomical and functional changes in the insula following mild TBI [41]. In their acute phase study, conducted over a seven-day post-injury period with 58 mild TBI patients and 32 healthy controls, T1-weighted MRI and resting-state fMRI were employed to capture these changes. Their analysis revealed that mild TBI patients exhibited reduced grey matter volume in the right insula and decreased functional connectivity with the right supramarginal gyrus [41]. These alterations correlated with declines in visuospatial/executive and attentional functions, suggesting that insular damage may serve as a critical biomarker for cognitive deficits during the acute phase of mild TBI [41].

From a longitudinal perspective, So et al. observed that individuals with moderate-to-severe TBI initially exhibited increased connectivity within the frontoparietal network (FPN) and the default mode network (DMN), which subsequently declined around 1.5 years post-injury [42]. This study, involving 40 TBI patients and 17 healthy controls over a three-year period, utilized repeated resting-state fMRI scans. The early increase in connectivity is interpreted as a potential compensatory mechanism that temporarily enhances cognitive function. These findings underscore the dynamic nature of brain recovery and the utility of fMRI for monitoring neural adaptations and informing tailored rehabilitation protocols [42].

Further emphasizing the role of fMRI, Liu et al. [43] reported enhanced functional and structural connectivity in mild TBI patients compared to controls 14 days post-injury. Involving 71 mild TBI patients and 57 controls, the study employed both resting-state fMRI and diffusion tensor imaging (DTI). The results demonstrated increased normalized clustering coefficients and higher small worldness index scores, which indicate enhanced local interconnectivity within brain networks [43]. Additionally, notable aberrant nodal properties in the frontal, temporal, cerebellar, and subcortical regions were observed, potentially accounting for cognitive impairments through disrupted interregional communication [43]. Persson et al. further showed in a pilot study that intensive attention training significantly modulated functional connectivity in TBI patients [44]. fMRI scans revealed both increases and decreases in connectivity across various brain regions post-training, with a reduction in connectivity variability suggesting a stabilization of neural networks following intervention. This highlights fMRI's potential for assessing the efficacy of cognitive rehabilitation in TBI patients [44].

2.4 PET Scans: Metabolic and Neuroinflammatory Markers in TBI

Positron emission tomography (PET) is essential for detecting metabolic changes in TBI patients. Byrnes et al. reviewed the use of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and determined it to be highly sensitive in identifying metabolic alterations, such as changes in glucose metabolism that occur after mild TBI [45]. This metabolic activity reflects underlying neuronal function, and studies indicate that these changes captured by FDG-PET vary significantly over time post-injury [45]. Early scans frequently reveal acute metabolic depression, which may later normalize or become overactive, a pattern that mirrors functional network alterations observed in fMRI studies [45].

In a detailed examination of long-term effects associated with sports-related concussions and TBIs, Marklund et al. [46] employed dual PET tracers to detect tau aggregation and neuroinflammation in patients. Their study included 12 athletes with a history of repeated sports-related concussions and six patients with moderate-to-severe TBI, compared against nine healthy controls. The imaging findings revealed significant tau deposits and neuroinflammation in critical regions, such as the corpus callosum and hippocampus [46]. These results suggest ongoing neurodegenerative processes that may contribute to cognitive decline, reinforcing the potential of PET imaging as both a diagnostic tool and a guide for developing targeted therapeutic strategies for TBI patients [46, 47].

Expanding upon PET's capabilities, Zhang et al. applied statistical parametric mapping and cluster counting analysis to [18F] FDG-PET data [48]. Their approach revealed that TBI patients exhibit larger clusters of low glucose uptake, predominantly at the brain's periphery, compared to controls [48]. Notably, regions that appear structurally normal on conventional imaging may nonetheless exhibit significant metabolic dysfunction, which correlates strongly with neurocognitive deficits [48]. Complementing these findings, Yamaki et al. conducted a longitudinal study tracking glucose metabolism in severe TBI patients using [18F] FDG-PET and observed that enhanced glucose metabolism correlated with improved wakefulness, providing a quantifiable measure of brain recovery to inform treatment strategies [49]. Integration of FDG-PET with other neuroimaging modalities like MRI is anticipated to pave the way for more comprehensive multimodal approaches.

2.5 Magnetic Resonance Spectroscopy (MRS): Neurochemical Changes Post-TBI

Systematic reviews by Eisele et al. and Joyce et al. have assessed the utility of Magnetic Resonance Spectroscopy (MRS) in identifying brain metabolic changes that might predict neurodegeneration following mild TBI [50, 51]. Key metabolic markers visualized include N-acetyl aspartate (NAA), glutamate (Glu), choline (Cho), creatine (Cr), Phosphocreatine (PCr), and myoinositol (ml). Both reviews reported significant reductions in NAA in mild TBI patients, indicative of neuronal loss or dysfunction [50, 51]. Additionally, variations in Cho and ml levels were associated with glial activation and potential membrane turnover [50, 51], while changes in Glu levels pointed to altered neurotransmitter dynamics and excitotoxicity [51].

Expanding on these findings, Veeramuthu et al. conducted an MRS study during the acute phase of mild TBI and found a moderate yet statistically significant correlation between Glasgow Coma Scale (GCS) scores and key neurometabolite ratios, specifically, $\text{NAA/Cr} + \text{PCr}$ and $(\text{NAA} + \text{NAAG})/(\text{Cr} + \text{PCr})$ [52]. Higher metabolite levels were associated with less severe clinical outcomes as measured by the GCS [53]. Moreover, the monitoring of neurochemical changes holds promise for predicting post-concussion syndrome (PCS) in adults with mild TBI who show normal results on routine imaging. Dogahe et al. identified that NAA and NAA/Cho values in the anterior cingulate cortex (ACC) were primary predictors of PCS onset, while Cho/Cr levels in the ACC predicted PCS severity [54]. These metabolite levels may therefore serve as vital biomarkers for early PCS prediction and for tailoring therapeutic strategies based on individual metabolic profiles [54]. An overview of the different advanced neuroimaging modalities in assessing TBI's is summarized in Table 2.

Table 2 Advanced Neuroimaging Modalities in Traumatic Brain Injury (TBI): Functional and Metabolic Assessments. This table compares the applications, key findings, and clinical implications of three advanced neuroimaging techniques: fMRI, PET, and MRS in the evaluation and management of TBI.

Imaging Modality	Main Use in TBI	Key Findings	Clinical Implications	References
fMRI	Assesses brain activity by detecting changes in blood flow. Used to study functional changes and network connectivity in TBI patients.	Identified altered connectivity patterns in networks such as the DMN (Default Mode Network) and FPN (Fronto-Parietal Network), which correlate with cognitive impairments and recovery stages.	Helps map recovery patterns and assess effectiveness of rehabilitative interventions Can guide personalized therapy plans based on observed functional recovery.	[26, 41, 43, 44]
PET	Utilizes radioactive tracers to visualize metabolic processes in the brain, often focusing on glucose metabolism and neuroinflammation.	Shows areas of decreased or increased metabolic activity post-TBI. Effective in detecting tau protein aggregation and neuroinflammation, indicators of potential long-term neurodegeneration.	Provides diagnostic insights into the extent of brain injury and inflammation Useful in predicting long-term outcomes and potential for neurodegenerative progression.	[48, 49, 55, 56]
MRS	Measures brain chemistry, particularly the concentrations of specific metabolites, to assess neuronal and axonal integrity.	Revealed changes in metabolites such as NAA, indicating neuronal loss; alterations in lactate pointing to anaerobic metabolism; fluctuations in glutamate and glutamine suggesting excitotoxicity.	Offers a non-invasive method to assess neuronal damage and can monitor biochemical changes to guide treatment, especially in the acute phase of TBI.	[51, 52, 54, 57]

2.6 Role of Imaging in Prognosticating Long-Term Outcomes

Advancements in imaging technologies are pivotal for enhancing TBI diagnosis, management, and prognosis [58-60]. Advanced MRI techniques such as susceptibility-weighted imaging (SWI) and diffusion tensor imaging (DTI) provide insights into microstructural injuries that are typically undetectable by conventional CT scans [32, 61]. SWI is highly effective in identifying microhemorrhages and vascular abnormalities associated with shear strain mechanisms typical of TBI, while DTI assesses white matter integrity by tracking water molecule diffusion in brain tissue [59]. The integration of these imaging methods with emerging technologies like convolutional neural networks (CNNs) promises to revolutionize TBI diagnosis and treatment, potentially leading to significant improvements in patient outcomes [59]. Widespread standardization of these advanced protocols is essential to further our understanding of TBI and enhance clinical care [58].

In addition, incorporating recent advancements in TBI research with modern clinical data and outcomes is critical for refining prognostic models. Yue et al. evaluated established models such as the International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) and the Corticosteroid Randomization After Significant Head Injury (CRASH) within a contemporary U.S. cohort [62]. Although these models demonstrated strong discrimination capabilities in identifying high-risk patients, both tended to overpredict mortality, thus, the need for ongoing validation and recalibration to align with current imaging techniques and clinical practices [62].

3. Biomarkers for TBI Diagnosis and Recovery Prediction

3.1 Blood-Based Biomarkers

Biofluid-based biomarkers represent a valuable, non-invasive tool for assessing disease progression, prognostication, therapeutic monitoring, and the development of novel treatments for TBI [63]. Current clinical assessment modalities, including the Glasgow Coma Scale (GCS), pupillary responses, blood pressure monitoring, and neuroimaging, provide critical information for acute TBI management but lack the resolution to assess injury at the molecular and cellular levels [64]. Serial biomarker sampling offers a dynamic approach to tracking injury progression, secondary pathophysiological responses, and long-term recovery. In the context of TBI, blood-based biomarkers provide critical insights into ongoing neurodegenerative processes that persist long after the primary injury. Several key biomarkers, including Glial Fibrillary Acidic Protein (GFAP), Neurofilament Light Chain (NFL), tau protein, and Ubiquitin C-Terminal Hydrolase L1 (UCH-L1), have demonstrated utility in characterizing injury severity, predicting long-term outcomes, and monitoring neurodegeneration in chronic TBI.

3.1.1 Glial Fibrillary Acidic Protein (GFAP)

GFAP is an intermediate filament protein predominantly expressed in astrocytes within the central nervous system (CNS). It plays a crucial role in maintaining the cytoskeletal structure of glial cells, supporting neuronal function, and preserving blood-brain barrier integrity [65]. Following TBI, reactive astrogliosis leads to increased GFAP expression, making it a reliable biomarker of CNS injury [66].

Acute plasma GFAP levels rise up to 19.8-fold in patients with unfavorable outcomes compared to favorable ones, and a threshold of ~200 pg/mL within 24 h achieves >85% sensitivity and specificity for predicting six-month mortality or severe disability [67-69]. Studies support the prognostic value of GFAP in TBI. Czeiter et al. reported that GFAP levels measured within 24 hours post-injury outperformed clinical characteristics in predicting CT abnormalities [70]. Since TBI is a dynamic process involving primary mechanical injury and secondary molecular and cellular responses, serial GFAP measurements over six months provide valuable insight into injury severity, secondary insults, and long-term recovery [71]. Moreover, persistently elevated GFAP levels within the first-year post-injury are associated with an increased risk of neuropsychiatric conditions, including Post-Traumatic Stress Disorder (PTSD), depression, and anxiety [51]. The clinical utility of GFAP has been further validated through regulatory approval. A significant milestone in biomarker-based TBI diagnostics was the FDA approval of the Brain Trauma Indicator, a serum-based assay combining GFAP and Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) to determine the necessity of head CT scans in mild TBI patients [72]. This approval represents a critical step toward integrating biofluid biomarkers into routine clinical decision-making, potentially reducing unnecessary imaging while improving early detection of TBI-related neuropathology.

3.1.2 Neurofilament Light Chain (NFL)

NFL is a structural protein that is released into the extracellular space following axonal injury, serving as a marker of cytoskeletal disruption [73]. Quantitatively, plasma NFL peaks at ~18-fold above control levels within 10 days post-TBI and remains elevated (4-6-fold) up to six months; a six-month NFL concentration >60 pg/mL predicts a 2.5-fold increased risk of poor functional [67-69]. In chronic TBI, elevated NFL levels correlate with injury severity and provide predictive value for long-term outcomes. Graham et al. demonstrated that plasma NFL concentrations correlate with diffusion MRI metrics of axonal injury and white matter neurodegeneration, serving as a strong predictor of functional outcomes one year post-injury [74]. Furthermore, Newcombe et al. reported that elevated NFL levels at six months post-injury were associated with progressive white matter atrophy over a five-year follow-up period [75]. Longitudinally, NFL continues to correlate with MRI measures of brain atrophy and diffusion tensor imaging (DTI) estimates of traumatic axonal injury, reinforcing its utility as a blood-based biomarker for chronic neurodegeneration in TBI [75].

3.1.3 Tau Protein

Tau is a microtubule-associated protein essential for stabilizing neuronal microtubules [76]. In TBI, pathological tau hyperphosphorylation leads to its dissociation from microtubules, destabilizing the cytoskeleton and promoting the formation of neurofibrillary tangles, a hallmark of neurodegenerative diseases such as chronic traumatic encephalopathy (CTE) [77]. Tau protein measurements such as acute plasma p-tau181 rises up to 276-fold between days 2-6 post-injury—far exceeding the 7.3-fold increase seen in t-tau—and a p-tau: t-tau ratio increase of up to 267-fold, shifts that strongly predict six-month disability (DRS) and unfavorable global outcome (GOS-E) [10]. Similarly, serum brain-derived tau (BD-tau) and p-tau231 levels peak within minutes to hours of severe TBI and remain elevated in those with poor recovery, providing a rapid, minimally invasive indicator of axonal damage [78]. Elevated tau levels have been associated with worse functional outcomes and increased long-term disability, as demonstrated by Rubenstein et al. [61]. These

findings suggest that tau may serve as a blood based biomarker for neurodegeneration in TBI and may aid in the identification of individuals at risk for progressive neurological decline. Studies have demonstrated that quantitatively, a threshold plasma t-tau concentration of <5 pg/mL within 48 h has been associated with favorable six-month functional outcomes, suggesting an actionable biomarker cut-off for early intervention trials [79].

3.1.4 Ubiquitin C-Terminal Hydrolase L1 (UCH-L1)

UCH-L1 is primarily localized within the neuronal cytoplasm and serves as an indicator of neuronal cell body injury. Zhang et al. found that UCH-L1 exhibited prognostic capabilities comparable to the Glasgow Coma Scale in predicting six-month mortality in severe TBI patients [80]. The association between elevated UCH-L1 levels and poor outcomes may be linked to its role in the ubiquitin-proteasome pathway (UPP), where loss of its hydrolase activity exacerbates axonal injury and neuronal death in animal models [81, 82]. However, while elevated UCH-L1 levels correlate with TBI severity and neuroimaging abnormalities, its diagnostic utility appears limited compared to NFL, tau, and GFAP [10].

Among the blood-based biomarkers discussed, GFAP and NFL exhibit the strongest diagnostic and prognostic utility. Both biomarkers effectively differentiate between mild, moderate, and severe TBI and demonstrate strong correlations with injury severity and neuroimaging findings [10]. Their ability to provide long-term insights into neurodegeneration highlights their potential role in guiding clinical decision-making and therapeutic development for chronic TBI patients.

3.1.5 S100B

S100B is a calcium-binding, astrocyte-driven dimeric protein released into the bloodstream after TBI [83, 84]. It exhibits rapid kinetics, peaking 1-2 h post-injury and clearing with a half-life of ~30 min [85] and shows excellent negative predictive value for ruling out intracranial lesions in mild TBI [86], although its specificity is limited by extracerebral sources and demographic factors. S100B correlates with injury severity, neuroimaging findings, and outcome, predicting six-month mortality and unfavorable recovery in moderate-severe TBI cohorts, yet is outperformed diagnostically by GFAP and neurofilament light (NFL) for long-term prognostication [83]. An overview of the different blood and cerebrospinal fluid biomarkers measured in TBI's and their clinical applications are presented in Table 3.

Table 3 Blood and Cerebrospinal Fluid Biomarkers in Traumatic Brain Injury: Pathophysiological Roles and Clinical Applications. This table presents an overview of several biomarkers detectable in blood and/or cerebrospinal fluid that are pertinent to the assessment and management of TBI. Each biomarker is characterized by its source, involvement in TBI pathophysiology, and clinical utility.

Biomarker	Source (Blood/CSF))	Role in TBI Pathophysiology	Clinical Utility	References
Glial Fibrillary Acidic Protein	Blood, CSF	Marker of astrocyte injury and blood-brain barrier dysfunction	Predicts injury severity, neuroimaging abnormalities, and long-term neuropsychiatric outcomes, part of FDA-approved Brain Trauma Indicator	[51, 65, 66, 70-72]
Neurofilament Light Chain	Blood, CSF	Reflects axonal injury and white matter neurodegeneration	Correlates with MRI findings, predicts long-term functional outcomes	[73-75, 81]
Tau Protein	Blood, CSF	Microtubule-associated protein involved in neurodegeneration	Associated with chronic TBI and risk of neurodegenerative diseases	[61, 76-78]
Ubiquitin C-Terminal Hydrolase L1	Blood, CSF	Indicator of neuronal cell body injury	Predicts mortality and functional outcomes, part of FDA-approved Brain Trauma Indicator	[10, 80, 81]
Interleukin-6, Interleukin-8, and Tumor Necrosis Factor-alpha	CSF	Inflammatory cytokines involved in secondary injury mechanisms	Associated with neuroinflammation and long-term neurological outcomes	[61, 70, 81, 82, 87, 88]
S100B	Blood, CSF	Marker of blood brain barrier loss of integrity and astrocyte injury	Used to rule out intracranial pathology in mild TBIs, and to predict severity outcomes in moderate-severe TBI.	[83-86]

3.2 CSF Biomarkers

While blood-based biomarkers provide a non-invasive means of assessing TBI-related pathology, cerebrospinal fluid (CSF) biomarkers offer a more direct reflection of central nervous system (CNS) injury, particularly in severe TBI cases requiring intensive care monitoring. CSF biomarkers provide critical insight into secondary injury mechanisms, including neuroinflammation, neuronal injury, and progressive neurodegeneration, enabling a more precise evaluation of injury progression and potential therapeutic targets [89]. Given their ability to capture dynamic changes within the CNS microenvironment, CSF biomarkers are especially valuable for assessing injury severity and guiding therapeutic interventions [70].

Inflammatory mediators in CSF have been implicated in the pathogenesis of secondary brain injury. Nwachuku et al. demonstrated that elevated CSF concentrations of interleukin-6 (IL-6) and interleukin-8 (IL-8) were significantly associated with increased neuroinflammation and correlated with six-month neurological outcomes in severe TBI patients [90]. Similarly, Schwartz Hvingelby et al. identified IL-6, IL-8, IL-10, tumor necrosis factor-alpha (TNF- α), and cortisol as CSF biomarkers associated with clinical outcomes in severe TBI patients. Their meta-analysis emphasized that while no single biomarker is sufficient to guide therapeutic decisions, a multi-biomarker panel may provide a more comprehensive depiction of injury progression and prognosis [64].

Much research has been focused on the same biomarkers emphasized in blood-based research: Much research has focused on CSF biomarkers previously identified in blood-based studies, including NFL, GFAP, UCH-L1, and tau. Consistent with findings in plasma, increased CSF concentrations of NFL, GFAP, UCH-L1, and tau strongly correlate with injury severity and long-term functional outcomes. [44, 81, 88] Longitudinal studies performed by Andersson et al. have demonstrated that elevated CSF NFL and GFAP levels are associated with neurodegeneration and predict disability outcomes up to 15 years post-injury [88]. These findings reinforce the prognostic utility of CSF biomarkers in severe TBI and highlight their potential role in therapeutic monitoring and long-term recovery assessment.

3.2.1 Metabolite Sampling and Prognostic Applications

During the acute phase of TBI, inflammatory and degenerative processes persist due to ongoing neurological damage. Metabolomics has emerged as a tool not only for identifying diagnostic biomarkers but also for prognostic markers that assess injury severity, elucidate injury mechanisms, and quantify structural damage [91]. Researchers are increasingly using metabolomics to predict recovery outcomes, monitor treatment responses, and better understand neuroplastic responses to TBI [92].

For example, studies by González-Domínguez et al. have highlighted the potential role of medium-chain fatty acids (e.g., octanoic and decanoic acids) in the energy crisis associated with mitochondrial failure post-TBI, although it remains unclear whether these acids contribute to pathology or result from it [93]. Similarly, Orešič et al. demonstrated that 2, 3-bisphosphoglyceric acid and related sugar derivatives are strongly associated with severe TBI. Incorporating these metabolite data into the CRASH clinical model significantly improved outcome predictions, suggesting an association with a disrupted blood-brain barrier and altered metabolism [94]. Banoei et al. showed that serum metabolomic profiles collected on days 1 and 4 post-injury were “highly predictive” of Glasgow Outcome Scale Extended (GOSE) scores and three-month mortality, with

day-4 profiles proving even more predictive, likely due to the impact of secondary brain injuries [95]. Cerebral microdialysis allows continuous sampling of extracellular brain fluid and the assessment of regional metabolism. Eiden et al. identified significant changes in metabolites (e.g., valine, 4-methyl-2-oxovaleric acid, isobeta-hydroxybutyrate, tyrosine, and 2-ketoisovaleric acid) during acute TBI care [57]. Additionally, urine metabolomics, as studied by Bykowski et al., revealed that lower levels of homovanillate, L-methionine, and thymine correlate with greater injury severity and implicate the purine metabolism pathway in mild-to-severe TBI cases [55].

3.2.2 Challenges in Biomarker Standardization and Clinical Implementation

Despite the promise of biofluid-based biomarkers, significant challenges remain in their standardization and clinical implementation. Standardized reference values are essential for meaningful interpretation, yet biomarker levels are influenced by variability in sample collection, preparation, and handling, as well as patient-specific factors such as age, sex, blood-brain barrier integrity, and comorbid conditions [15, 21, 63]. Currently, no standardized protocols or guidelines exist for the use of TBI biomarkers in clinical practice [96].

A major limitation of current biomarker research is its reliance on predictive modeling using receiver operating characteristics (ROC) curves to assess diagnostic and prognostic performance. While these models provide statistical validation, they do not clarify how biomarker data should be integrated into clinical decision-making processes [97]. For biomarkers to be effectively translated into practice, further research is needed to define actionable thresholds, optimize multimodal biomarker panels, and evaluate their clinical utility in guiding therapeutic interventions.

4. ICP Monitoring and Metabolite Sampling

4.1 Invasive ICP Monitoring Techniques and Clinical Challenges

Intracranial pressure (ICP) monitoring is considered essential in the treatment and management of patients with traumatic brain injuries and life-threatening neurological insults. Abnormally high ICP levels can indicate growing intracranial lesions, impending herniation events, and inadequate nutrient delivery to the brain [98]. Without timely adjustments based on ICP monitoring, both brain compliance and cerebral autoregulation can be permanently impaired [99]. Therapies aim to maintain ICP at or below 22 mm Hg. Clinical trials have shown that early decompressive craniectomies and hypothermia are not neuroprotective for TBI patients and should only be used when standard interventions fail. Moreover, treatments that lower plasma osmolality, potentially leading to osmotic cerebral edema, may worsen neurological decline, especially in patients with prior neurological injuries or systemic organ dysfunction.

Utilizing a tiered approach is particularly important in treating severe TBI in adults. The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) established eighteen “fundamental” interventions and ten “not-to-be-used” interventions [98]. SIBICC defined protocols for managing ICP elevation with normal brain oxygenation, neurological hypoxia with normal ICP, and simultaneous intracranial hypertension and brain hypoxia [100]. Such tier systems should be integrated with standard-of-care treatments and individualized patient planning.

The “gold standard” for ICP monitoring involves invasive techniques like ventricular drainage or parenchymal probes. Although widely used in intensive care settings, these procedures carry risks.

For instance, Tavakoli et al. reported that *Staphylococcus aureus* infection is the most common complication associated with invasive ICP monitor placement and external ventricular drains (EVDs) [101]. There is conflicting evidence on the impact of antibiotic prophylaxis, and studies suggest a higher risk of hemorrhage post-ICPM in patients with coagulation dysfunction.

4.2 Less Invasive ICP Monitoring

Non-invasive methods for assessing ICP avoid the complications of invasive procedures. These include morphological assessments (integration of MRI, CT, ultrasound, and funduscopy imaging) and physiological assessments (transcranial and ophthalmic Doppler, tympanometry, near-infrared spectroscopy, electroencephalography, visual-evoked potentials, and otoacoustic emissions) [102].

One promising non-invasive method is the ultrasonographic measurement of optic nerve sheath diameter (ONSD), which quantifies optic nerve distension at high ICP levels. Martinez-Palacios et al. found that ONSD yields highly accurate results—especially when combined with measurements of ocular transverse diameters or optic disc elevation—and shows a strong, almost linear correlation with invasive methods in TBI patients [103].

Another method, transcranial Doppler (IPCTcd), has been evaluated as a screening tool. Rasulo et al. conducted a prospective, international, multicenter study with 262 patients and demonstrated that IPCTcd has a high negative predictive value for ruling out intracranial hypertension when invasive methods are unavailable [104].

Although non-invasive techniques show promise in reducing complications, there is insufficient evidence to recommend one non-invasive method over another. Müller et al. conducted a source analysis and found that MRI-ICP and two-depth Doppler imaging, though complex, showed the most potential, with other methods like tympanic membrane temperature and retinal vein assessments also proving promising [105]. Regardless of the method, vigilant ICP monitoring is associated with a more intensive therapeutic approach and a decreased six-month mortality rate in patients with severe TBI [105]. Currently, invasive intracranial pressure (ICP) remains the standard of care in moderate-severe TBI when continuous, accurate ICP values are needed for guiding therapy. All of the less-invasive techniques described are still considered investigational or adjunctive rather than replacements for invasive monitoring as research is still ongoing as sufficient accuracy, availability, or reproducibility has not been achieved to replace invasive monitoring.

5. Rehabilitation Strategies and Neuroplasticity in TBI Recovery: Emerging Rehabilitation Modalities

5.1 Current Clinical Guidelines for TBI Rehabilitation

Rehabilitation after mild-moderate TBI follows a phased, symptom-driven approach guided by high-quality CPGs (VA/DoD, ACRM), NICE NG211, and ACS TQP best practices. In current practice, in the acute and early post-acute phase (≤ 7 days), clinicians prioritize patient and family education on expected symptom trajectories, sleep hygiene, activity pacing, and monitoring for “red-flag” signs, alongside early initiation of aerobic exercise and targeted vestibular or oculomotor therapies as needed [106, 107]. After the first 7 days post TBI, a stepped-care model is implemented: graded aerobic programs for fatigue management, specialized vestibular/ocular rehabilitation for persistent dizziness, and structured cognitive rehabilitation that includes strategy training,

computerized drills, and return-to-learn/work protocols with psychotherapy or sleep interventions for mood and sleep disturbances [107]. Multidisciplinary coordination is essential, involving physiatry, neurology, neuropsychology, physical/occupational therapy, speech with standardized outcome measures. Continued monitoring and tracking quality metrics remains to be important in the assessment of patients moving forward. These constitute the current standard of care for rehabilitation post TBI [107].

5.2 Virtual Reality (VR) and Augmented Reality (AR)

An emerging intervention is Virtual reality (VR) and augmented reality (AR). These modalities are increasingly incorporated into neurorehabilitation to enhance cognitive and motor recovery [108]. In pediatric populations, several studies suggest that VR-based interventions can lead to improvements in attention and executive function. De Luca et al. presented a case study of a 15-year-old boy with TBI in the right parietal-temporal region who underwent both traditional face-to-face cognitive rehabilitation and Computer Assisted Rehabilitation Environment (CAREN) training. Post-intervention, the boy exhibited significant improvements in cognitive and motor domains, including attention, visual-executive processes, emotional awareness, and vestibular balance control [109]. Inter-individual differences and generalization to daily life remain important considerations, as highlighted by recommendations to focus on these aspects in pediatric patients [110]. In adolescents, gender appears to play a role; improvements in mood, cognitive flexibility, and selective attention post-VR training were more prominent in female patients [111].

In adult populations, VR and AR have been used in both TBI and stroke rehabilitation, targeting upper-limb motor recovery, gait, cognition, and lower-extremity function [112]. For instance, a case report of a 58-year-old man with right hemiplegic TBI showed that combining 20 minutes of VR-based physical therapy with 30 minutes of traditional therapy, five times a week for eight weeks, improved his center of pressure, stability limits, stride length, cadence, and lower extremity motor function [113]. Additionally, Reale et al. examined VR's impact on the autonomic nervous system in patients with disorders of consciousness post-severe TBI via electrodermal activity (EDA) measurements. Their pilot study found that VR stimulation elicited significant sympathetic arousal in TBI patients, suggesting that VR can modulate autonomic responses and potentially aid in recovery [114]. Furthermore, initiatives like the Assisted Living Pilot Project at the Defense and Veterans Brain Injury Center are integrating these advanced technologies with traditional rehabilitation strategies to address neurological deficits in military veterans [115]. Both invasive and non-invasive ICP monitoring techniques, along with metabolite sampling, provide essential diagnostic and prognostic information that guides TBI treatment strategies. Simultaneously, emerging rehabilitation modalities such as VR/AR and brain-computer interfaces are complementing these approaches by promoting neuroplasticity and functional recovery. Together, these technologies underscore the importance of a multimodal approach to TBI care—one that combines precise physiological monitoring with innovative rehabilitation strategies to improve long-term outcomes.

5.3 Tai-Chi as Non-Invasive Adjuvant to TBI Rehabilitation

Similarly, Tai chi has recently been proposed as a non-invasive, whole-body exercise that combines motor complexity, balance training, and meditative components, thereby enhancing

neuroplasticity through multimodal brain activation [116]. Systematic reviews of Tai chi in neurological populations report significant gains in balance, executive function, and mood in TBI survivors, with randomized and non-randomized trials demonstrating improved functional and psychological outcomes compared to [56]. Dr. Zhou further highlights Tai chi's capacity to modulate functional connectivity within prefrontal, motor, and occipital cortices, key regions implicated in post-TBI recovery. Dr. Zhou describes how the repeated, coordinated movement patterns in Tai chi drive functional reorganization within primary motor cortices and their connections to prefrontal executive networks, fostering synaptic strengthening along pathways responsible for postural control and cognitive processing [117]. Some clinical trials and systematic reviews in TBI populations (three randomized and two non-randomized studies, N = 272) report that 6-week to 6-month Tai chi programs yield moderate improvements in functional mobility, cognitive flexibility, and mood compared to usual care or wait-list controls [56]. Specifically, Tai chi participants showed significant gains in dynamic balance and executive function—measured by instruments like the Berg Balance Scale and Trail Making Test B—as well as reductions in anxiety and confusion on visual analogue mood scales [56]. No adverse events were reported, underscoring Tai chi's safety as an adjunctive therapy. Although promising, Tai chi remains experimental in TBI care and warrants larger, multicenter trials to compare its efficacy directly against established guideline-driven rehabilitation protocols [56].

5.4 Targeted Cognitive Rehabilitation Therapies: Adaptive Training for Memory, Attention, and Executive Function

Targeted cognitive therapy is a critical rehabilitation strategy TBI recovery, delivered through adaptive training designed to enhance memory, attention, and executive function. In cases of memory impairment, interventions that target procedural memory can offer substantial benefits. Restorative memory training typically involves relearning activities of daily living (ADLs) that depend on procedural memory processes, which are often compromised following TBI, particularly in patients who experience posttraumatic amnesia (PTA) [118, 119]. In a randomized controlled trial, Peters et al. evaluated the timing of ADL retraining in 104 participants with severe TBI who remained in PTA for more than seven days. Forty-nine patients were assigned to a treatment group that began ADL retraining during PTA rather than after restoration of memory and orientation. Functional independence, as measured by the Functional Independence Measure (FIM), improved significantly at discharge in the treatment group compared to controls [42]. Although these findings support the utility of early ADL retraining, limitations include the predominance of motor vehicle-related injuries (80% of cases), the lack of weekend agitation assessments, and an average initiation time of 16.46 days post-injury. These factors suggest that further research is needed to determine if even earlier intervention could yield additional benefits and whether the approach can be generalized across different TBI etiologies.

Attentional impairments are also common after TBI, especially in noisy environments. Targeted cognitive training has shown promise in mitigating these deficits. For instance, Dundon et al. compared auditory selective attention between TBI patients and healthy controls using the Speed and Capacity of Language Processing (SCOLP) test. TBI patients (n = 20) exhibited significantly reduced processing speeds and poorer performance on tasks such as Elevator Counting with Distraction compared to controls (n = 20) [120]. Furthermore, the dichotic listening task, where

different streams of continuous speech are presented to each ear, highlighted that TBI patients struggled to maintain accuracy under increased task difficulty. Based on these initial findings, Dundon et al. randomly assigned 26 TBI patients to one of three groups: adaptive training, nonadaptive training, and a no-training control. In the adaptive protocol, task difficulty increased according to individual performance, whereas in the nonadaptive protocol, difficulty increased at a fixed rate. Following eight one-hour training sessions, both training groups showed significant improvements on the dichotic listening task, with no significant differences observed between adaptive and nonadaptive protocols. The lack of significant differences between adaptive training and nonadaptive training implies that the overall exposure to training may be the key factor driving improvement, rather than the method of difficulty adjustment. This could suggest that even simpler, nonadaptive approaches might be sufficient to yield cognitive benefits [120].

Cognitive impairments from TBI often impede a timely return to work. Fure et al. conducted a randomized controlled trial wherein TBI patients receiving a combination of cognitive symptom management (via Compensatory Cognitive Training [CCT]) and workplace reintegration support (Supported Employment [SE]) returned to work faster than those receiving standard treatment [121]. The intervention included weekly two-hour group sessions led by a psychologist and a physician, focusing on compensatory strategies to alleviate symptoms such as headaches, and employment specialists guiding participants through workplace reintegration over six months. Results indicated that 81% of participants in the CCT-SE group returned to stable employment at three months, compared to 60% in the control group ($P = 0.02$). A limitation noted was that the study sample was predominantly composed of women with high-education occupations, potentially affecting the generalizability of the results. Moreover, this strategy underscores the importance of addressing both the neuropsychological and environmental aspects of rehabilitation, suggesting that cognitive improvements alone may not be sufficient to ensure optimal real-world outcomes. Ultimately, these results imply that interventions designed to address both cognitive impairments and workplace challenges can take advantage of neuroplastic mechanisms and enhance functional recovery in everyday life [121].

5.5 Neuroplasticity Mechanisms and Their Modulation in TBI Recovery

Neuroplasticity, the brain's capacity to reorganize and form new synaptic connections, is fundamental to learning, memory adaptation, and functional recovery following injury [122]. The primary mechanisms of neuroplasticity include synaptic plasticity, neurogenesis, axonal sprouting, dendritic remodeling, and glial activation.

Synaptic plasticity, often manifested as long-term potentiation (LTP), involves the strengthening of synaptic connections following repetitive activation of presynaptic neurons, thereby enhancing postsynaptic responsiveness [90]. LTP relies on several molecular pathways, including NMDA receptor activation, calcium influx, and subsequent activation of calcium/calmodulin-dependent protein kinase II (CaMKII), leading to the phosphorylation and insertion of AMPA receptors into the synaptic membrane, enhancing synaptic strength. In TBI models, these pathways can be disrupted, as shown by chronic cortical inflammation affecting LTP-related genes [123]. Fischer et al. investigated the effects of various neurostimulation protocols on synaptic plasticity in normal and injured brains using whole-cell patch-clamp and field potential recordings in the visual cortex of control, sham-operated, and mild TBI rats. Their results demonstrated that the temporal pattern of

stimulation critically determines the polarity and magnitude of synaptic plasticity. Specifically, highly irregular stimulation at 1 Hz or 10 Hz induced long-term depression (LTD) in control animals, but resulted in LTP following mild TBI. Moreover, the dynamics of synaptic responses during stimulation were predictive of the final plasticity outcome [124]. These findings suggest that target neuromodulation strategies can be developed to promote LTP or reduce LTD in mild TBI patients, leading to improved cognitive functions [125]. While these findings provide insight into the modulatory effects of stimulation protocols, further research is necessary to elucidate optimal parameters and to translate these findings into clinical neuromodulatory interventions.

Neurogenesis, the generation of new neurons from neural stem cells, continues into adulthood and contributes to cognitive flexibility and recovery after TBI. In the hippocampus, adult neurogenesis can bolster cognitive resilience by integrating new neurons into existing neural circuits [11]. The integration of new neurons into the hippocampal network is associated with cognitive recovery. Studies have shown that these neurons contribute to hippocampal-dependent learning and memory functions, such as spatial memory and pattern separation, which are essential to cognitive function [126]. However, discrepancies in findings regarding the extent of neurogenesis in the adult human brain have been noted, often attributed to methodological differences in immunohistochemical analyses [11]. Using a controlled cortical impact model in male mice, Bielefeld et al. applied single-cell RNA sequencing, spatial transcriptomics, and computational analyses to study TBI's effect on neural stem cell fate. Their results indicated that TBI promotes neurogenesis at the expense of astrogliogenesis, with a shift in the differentiation trajectory of radial glia-like cells favoring neuron production over astrocyte formation [127]. These findings demonstrate the adaptive capacity of the hippocampus post-injury and may have important implications for recovery and therapeutic strategies. Specifically, these findings that demonstrate TBI promotes neurogenesis over astrogliogenesis indicate potential therapeutic avenues. If this natural adaptive response can be enhanced through treatments, therapies could improve cognitive outcomes for TBI patients [127].

Beyond strengthening neural connections, the brain also employs compensatory processes to optimize function following injury. Equipotentiality describes the ability of the contralateral hemisphere to compensate for deficits following unilateral damage, which is particularly relevant in motor recovery [44]. Similarly, vicariation refers to the reassignment of functions to alternative neural regions, enabling adaptive plasticity. Diaschisis, a phenomenon where focal brain damage results in functional deficits in remote but interconnected regions, further complicates recovery [44]. In a study by Boggs et al., metabolic alterations in both the treated and untreated hemispheres suggested the presence of diaschisis, which may lead to transient or persistent impairments [128]. In addition to these intrinsic processes, emerging neuromodulatory interventions, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are being investigated for their ability to enhance neuroplasticity by modulating cortical excitability. These techniques seek to modulate neuronal activity by normalizing disrupted connectivity between brain areas and improving functional outcomes in areas such as coordination, balance, memory, learning, etc. [6]. Pharmacological agents that increase the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), are also under study as adjuncts to promote synaptic remodeling and functional recovery. In a controlled cortical impact model of TBI in mice by He et al., bexarotene administration led to increased BDNF expression in microglia and macrophages. This upregulation was associated with enhanced axonal regeneration and a shift of

microglia/macrophages toward an anti-inflammatory phenotype which led to increased axon sprouting [129]. Neurological severity scores were evaluated prior to inducing injury and on days 1, 3, 7, 14 and 21 which demonstrated an improvement in cognitive function at the end of the trial [129]. The upregulation of BDNF appears to be a key mechanism through which bexarotene facilitates axonal regeneration and cognitive improvement, highlighting the importance of neurotrophic factors in TBI recovery strategies. Together, these integrated approaches underscore the critical role of both rehabilitation strategies and neuroplasticity mechanisms in facilitating recovery after TBI. Further research into optimizing these interventions could lead to significant advancements in clinical outcomes for TBI patients.

6. Conclusion and Future Directions

In conclusion, TBI continues to be a major public health issue due to its high incidence and the severe, long-lasting morbidity it imposes [1, 127]. Innovations in neuroimaging, such as DTI, fMRI, PET, and MRS, have significantly improved our understanding of the microstructural, functional, and metabolic disruptions caused by TBI. Simultaneously, biofluid biomarkers have emerged as valuable tools for real-time monitoring and prognostication [24, 61]. Moving forward, a truly effective TBI care pathway will require the integration of advanced neuroimaging (DTI, fMRI, PET, MRS) with serial biofluid biomarkers (GFAP, NFL, tau), cognitive assessments, and emerging multiomic profiles (proteomics, metabolomics, epigenomics) to create a comprehensive, patient-specific disease signature [17]. Emerging rehabilitation methods, including virtual/augmented reality, brain-computer interfaces, and targeted cognitive therapies, show promise in harnessing neuroplasticity to improve functional outcomes [108, 121]. Nonetheless, challenges remain, particularly in standardizing biomarker assays, refining predictive models, and effectively incorporating multimodal data into personalized treatment strategies. To overcome these hurdles, prospective multicenter cohorts must implement harmonized protocols for imaging, fluid biomarkers, cognitive testing, and multiomic sampling, enabling machine-learning-driven integration and validation across diverse patient populations [130]. Future research should focus on validating these innovative approaches across diverse patient populations and on developing evidence-based protocols that effectively translate these advancements into clinical practice. Collectively, these integrated strategies offer a promising framework for optimizing TBI diagnosis, prognostication, and rehabilitation, paving the way for improved long-term outcomes.

Author Contributions

Medina, R. and Dave, A. developed the overall framework and wrote the Introduction, with Medina, R. focusing on the public health impact and current diagnostic and treatment limitations of TBI, and Dave, A. outlining the need for a multimodal approach and the review's objectives. Dave, A. and Estenssoro, F. collaboratively authored the Neuroimaging Advances section, detailing both traditional methods and emerging modalities such as DTI, fMRI, PET, and MRS. Bartfield, J. and Keogh, C. jointly developed the Biomarkers section, covering both blood-based and CSF biomarkers, while Keogh, C. also contributed to the discussion on invasive and non-invasive ICP monitoring and metabolite sampling. Rehabilitation Strategies and Neuroplasticity were written by Keogh, C. and Fraga, M., with Keogh, C. emphasizing emerging modalities like VR/AR and Fraga, M. focusing on targeted cognitive rehabilitation and the underlying neuroplastic mechanisms. Finally, Medina, R.

synthesized the key findings and future directions in the Conclusion. Dr. Brandon Lucke-Wold served as the principal investigator for this project. He contributed to the conceptual organization of the manuscript by assisting with outline formatting, provided detailed proofreading, and offered substantive feedback and corrections to the paper's content throughout the writing process. All authors participated in editing, contributed to associated citations, and approved the final manuscript.

Abbreviations

GFAP	Glial Fibrillary Acidic Protein
NfL	Neurofilament Light Chain
t-Tau	Total Tau
p-Tau	Phosphorylated Tau
UCH-L1	Ubiquitin C Terminal Hydrolase L1
S100B	S100 Calcium-Binding Protein B
DTI	Diffusion Tensor Imaging
DKI	Diffusion Kurtosis Imaging
BBB	Blood–Brain Barrier
fMRI	Functional Magnetic Resonance Imaging
PET	Positron Emission Tomography
MRS	Magnetic Resonance Spectroscopy
VR	Virtual Reality
AR	Augmented Reality

Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

Each respective section was original work written by their respective author. The extent of AI use was for table formatting and grammar editing.

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