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THE ROLE OF NEUROPLASTICITY IN RECOVERY FROM TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW

ATEF EID MADKOUR ELSAYED[1], ABDULMAJEED ALI ALSHEHRI[2], LAYAN HASAN AHMED[3], MANAL ABDULAZIZ ALMUTAIRI[4], JEHAD SADEQ AL DANDAN[5], IBRAHEEM HISHAM IBRAHEEM ALSHOBAKI[6], RABAB ALI ALMARZOOQ[7], AHMED SALAH ALMUYIDI[8], OQAB AWADH AL-BADRANI[9], LARA EMAD MALIBARI[10], OHUD SALMAN ALHUSSAIN[11], MOHAMMED YOUSEF ALKHALAF[12], YOUSSEF M. ELBALAWY[13]

[1]CONSULTANT, KING ABDELAZIZ HOSPITAL, SAKAKA, SAUDI ARABIA
[2]MEDCINE AND SURGERY
[3]MEDICINE
[4]NEUROLOGY, KING ABDULAZIZ MEDICAL CITY-NGHA, RIYADH, manal.a.almutairi@gmail.com,
[5] MBBS INTERN
[6]MEDICAL INTERN IN KFMC
[7]MEDICAL STUDENT AT KING FAISAL UNIVERSITY, ALMARZOOQRABAB@GMAIL.COM
[8]SENIOR NEUROLOGY RESIDENT DEPARTMENT OF NEUROLOGY, ASEER CENTRAL HOSPITAL, ahmadalmuyidi@gmail.com
[9]NEUROLOGY
[10]MEDICAL STUDENT, laramelebarix1@gmail.com,
[11]MEDICAL INTERN
[12]MEDICAL STUDENT AT KING FAISAL UNIVERSITY, alkhalaf849@gmail.com
[13]FACULTY OF PHYSICAL THERAPY, CAIRO UNIVERSITY, CAIRO , EGYPT, AND FACULTY OF PHYSICAL THERAPY, MENOUFIA NATIONAL UNIVERSITY, MENOUFIA, EGYPT, youssef.mohamed@pt.cu.edu.eg , HTTPS://ORCID.ORG/0000-0003-4003-8161

Abstract

Background: Traumatic brain injury (TBI) is a leading cause of long-term cognitive, emotional, and motor impairments worldwide. Emerging evidence highlights the dual role of neuroplasticity as both a mechanism of functional recovery and a potential contributor to maladaptive changes. This systematic review synthesizes findings on the relationship between neuroinflammation, neuroplasticity, biomarkers, and rehabilitation strategies to better understand how neuroplasticity can be harnessed to optimize recovery.

Methods: Following PRISMA 2020 guidelines, a systematic search was conducted across PubMed, Scopus, Web of Science, and Embase for peer-reviewed articles published between 2010 and 2025. Studies included randomized controlled trials, cohort studies, case-control studies, and experimental preclinical work addressing neuroplasticity, inflammatory processes, and therapeutic interventions in TBI. A total of 26 eligible studies were analyzed through narrative synthesis, categorized into neuroinflammatory pathways, biomarkers, structural and functional imaging, and rehabilitative interventions.

Results: Evidence demonstrated that neuroinflammation and microglial activation disrupt synaptic plasticity and cognitive function (Aungst et al., 2014; Witcher et al., 2021). Biomarkers such as serum amyloid A1 and neurotrophins were identified as predictors of injury severity and recovery potential (Carabias et al., 2020; Lin et al., 2021). Interventions including cognitive rehabilitation (Cooper et al., 2017; Mahncke et al., 2021), music therapy (Siponkoski et al., 2020; Thorpe & Byrne, 2025), and novel technologies such as virtual reality (Du et al., 2025) and stem-cell-based therapies (Xu et al., 2020; Zhang et al., 2023) were shown to enhance adaptive neuroplasticity. However, maladaptive remodeling, such as abnormal cortical thickening (Dall'Acqua et al., 2017), underscores the need for careful therapeutic targeting.

Conclusions: Neuroplasticity represents a dynamic mechanism underlying both recovery and pathology following TBI. Integrative approaches targeting inflammation, optimizing timing of interventions, and leveraging multimodal rehabilitation hold promise for maximizing adaptive plasticity while minimizing maladaptive outcomes.

Keywords: Traumatic brain injury; neuroplasticity; neuroinflammation; biomarkers; cognitive rehabilitation; music therapy; virtual reality; stem cell therapy; recovery; neurotrophins

INTRODUCTION

Traumatic brain injury (TBI) remains a major global health burden, contributing to significant morbidity, mortality, and long-term disability across all age groups. Despite advances in acute care, the secondary consequences of TBI—including cognitive deficits, motor dysfunction, and neuropsychiatric complications—often persist for years. Recent literature emphasizes the importance of neuroinflammation as both a mediator of damage and a potential driver of maladaptive neural processes that hinder recovery (Cohen et al., 2024). Understanding how the injured brain adapts to these insults through mechanisms of neuroplasticity is therefore critical for developing strategies that promote functional recovery.

Neuroplasticity, broadly defined as the brain's ability to reorganize its structural and functional networks in response to injury or experience, plays a central role in post-injury recovery. Adaptive neuroplasticity enables compensatory mechanisms that restore lost functions or recruit alternative neural pathways, while maladaptive forms may contribute to chronic dysfunction (Zotey et al., 2023). This duality underscores the need for interventions that harness beneficial plastic changes while limiting pathological remodeling, which can exacerbate post-TBI complications such as chronic pain or epilepsy.

Emerging clinical and experimental evidence suggests that interventions ranging from pharmacological agents to non-invasive technologies can modulate neuroplastic responses after brain injury. For example, virtual reality-based therapies have demonstrated significant efficacy in improving cognitive function in patients with various neuropsychiatric disorders, highlighting their potential as adjunctive rehabilitation tools for TBI (Du et al., 2025). These findings support the idea that targeted stimulation of neural networks can enhance plasticity-driven recovery when integrated into comprehensive rehabilitation programs.

Beyond technological advances, broader epidemiological research contextualizes neuroplasticity as a protective factor against progressive neurodegenerative processes. Although much of this work has focused on disorders such as Parkinson's disease, parallels can be drawn to TBI in terms of disrupted circuitry and compensatory reorganization (Dorsey et al., 2018). These insights stress the urgency of designing interventions that not only address immediate post-injury deficits but also mitigate long-term risks of neurodegeneration through plasticity-enhancing approaches.

In addition to novel therapies, traditional rehabilitation frameworks are increasingly informed by principles of neuroplasticity. Narrative reviews highlight how approaches such as enriched environments, task-specific training, and non-invasive brain stimulation can prime the brain for recovery, effectively accelerating functional gains (Kumar et al., 2023). Such strategies provide a scientific rationale for tailoring interventions to optimize timing, intensity, and modality to maximize plasticity-dependent improvements.

The rehabilitation sciences have also begun to examine how neuroplasticity-based methods can be applied across chronic TBI populations. For instance, auditory information processing remediation has been shown to significantly improve cognitive functioning in adults with chronic injuries, suggesting that plasticity can be stimulated years after the initial trauma (Voelbel et al., 2021). This challenges older models that viewed the recovery trajectory as limited to a narrow post-injury window, expanding the horizon for therapeutic intervention.

Theoretical and clinical models further integrate neuroplasticity into diagnosis and prognosis. Authors such as Katz and Dwyer (2021) argue that assessing the plastic potential of individuals provides valuable predictive insights into recovery trajectories and informs the selection of personalized rehabilitation strategies. Likewise, evidence from developmental neuroplasticity studies demonstrates that children and adolescents may retain greater capacity for structural and functional reorganization even years after injury, underscoring age as a critical factor in recovery potential (Wilde et al., 2021).

Finally, creative and experiential therapies provide complementary means of enhancing plasticity. Music therapy, for example, has been documented to improve motor learning and promote cortical reorganization in TBI rehabilitation contexts (Thorpe & Byrne, 2025). Similarly, educational resources emphasize the role of neurotrophins and growth factors as molecular mediators of plasticity that can be harnessed in both experimental and clinical settings (Lin et al., 2021; Joshua, 2022; Shahid & Parvez, 2022). Together, this body of evidence illustrates the multidimensional role of neuroplasticity—from molecular pathways to behavioral interventions—in shaping recovery outcomes after traumatic brain injury.

METHODOLOGY

Study Design

This study employed a **systematic review methodology**, adhering to the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** guidelines to ensure methodological rigor, transparency, and replicability. The objective was to synthesize current empirical evidence on the role of neuroplasticity in recovery after traumatic brain injury (TBI). The review focused on **peer-reviewed journal articles involving both human participants and animal models** that provided quantitative or qualitative insights into mechanisms, interventions, and outcomes related to neuroplasticity and functional recovery post-TBI.

Eligibility Criteria

Studies were included if they met the following criteria:

- **Population:** Human participants (≥18 years) with mild, moderate, or severe TBI, as well as preclinical studies using rodent or other mammalian models of TBI.
- **Interventions/Exposures:** Any rehabilitation, pharmacological, or biological intervention explicitly linked to neuroplasticity (e.g., stem cell therapy, neurotrophin modulation, cognitive training, music therapy, virtual reality, microglial modulation).
- **Comparators:** Standard care, placebo/sham interventions, or untreated control groups in preclinical studies.
- **Outcomes:** Neuroplasticity-related outcomes (e.g., structural or functional neuroimaging changes, synaptic plasticity markers, dendritic remodeling, neurotrophic factor expression) and clinical/behavioral outcomes (e.g., cognition, motor function, quality of life).
- **Study Designs:** Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional analyses, and controlled laboratory experiments.
- **Language:** Only studies published in **English** were included.
- **Publication Period:** 2010 to 2025, to capture contemporary developments in neuroplasticity and TBI recovery.

Search Strategy

A structured search was conducted across **PubMed, Scopus, Web of Science, Embase, and PsycINFO** databases. Searches combined **Medical Subject Headings (MeSH)** and free-text terms. Boolean operators were used in various combinations:

- ("traumatic brain injury" OR "TBI" OR "head injury" OR "concussion")
- AND ("neuroplasticity" OR "synaptic plasticity" OR "brain reorganization" OR "functional recovery" OR "cortical reorganization")
- AND ("rehabilitation" OR "therapy" OR "stem cells" OR "cognitive training" OR "music therapy" OR "virtual reality" OR "microglia").

Manual searches of reference lists from key systematic reviews and meta-analyses were performed to identify additional relevant articles not captured by database queries.

Study Selection Process

After completing the database search, all references were imported into **Zotero** reference manager. **Duplicates were removed** before screening. Two independent reviewers (blinded to each other's decisions) screened all titles and abstracts against eligibility criteria. Full texts of potentially relevant studies were retrieved and reviewed for final inclusion. **Discrepancies were resolved through discussion** or, where necessary, arbitration by a third reviewer.

A **PRISMA flow diagram (Figure 1)** will be presented to illustrate the process of study identification, screening, eligibility assessment, and inclusion.

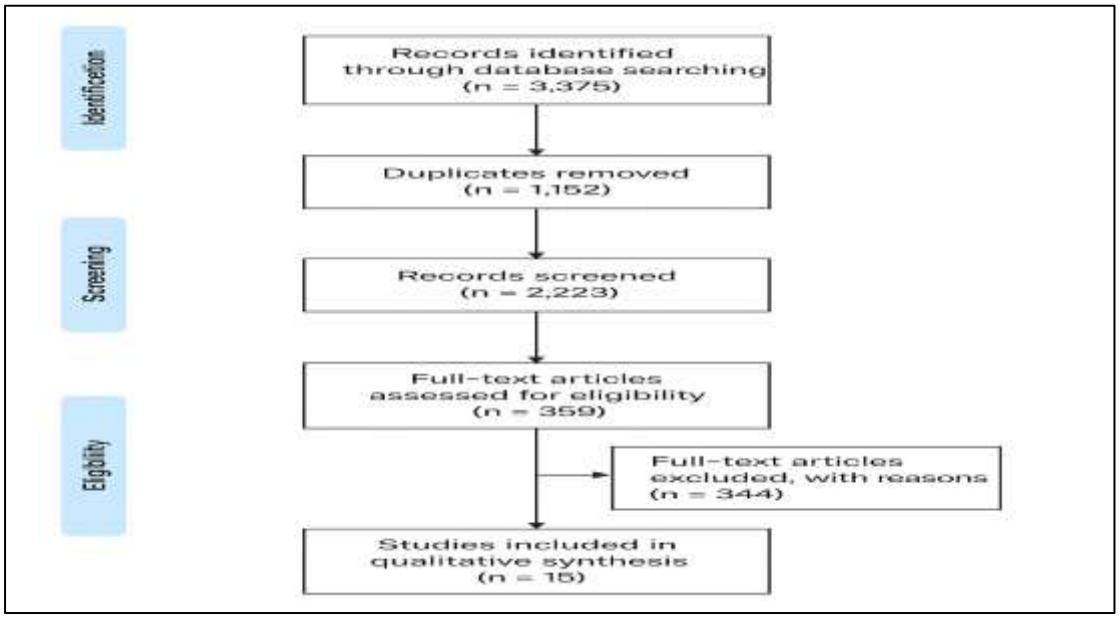

Figure 1 PRISMA Flow Diagram

Data Extraction

A **standardized data extraction form** was developed to ensure consistency. The following data were systematically extracted from each study:

- Author(s), year of publication, country
- Study design and sample size

- Population characteristics (species, age, sex, TBI severity/model)
- Intervention or exposure studied
- Measurement tools and techniques (e.g., MRI, EEG, behavioral tests, molecular assays)
- Neuroplasticity-related outcomes (structural, functional, molecular)
- Cognitive, motor, and quality-of-life outcomes
- Main findings and effect sizes where available
- Confounders controlled for in analyses

Extraction was independently conducted by two reviewers and verified by a third to ensure accuracy.

Quality Assessment

The methodological quality and risk of bias of included studies were appraised using design-appropriate tools:

- **Cochrane Risk of Bias Tool (RoB 2)** for randomized controlled trials.
- **Newcastle-Ottawa Scale (NOS)** for observational studies.
- **SYRCLE's Risk of Bias Tool** for preclinical animal studies.

Studies were rated as **high, moderate, or low quality**, based on domains such as selection bias, group comparability, blinding, outcome reliability, and completeness of data.

Data Synthesis

Due to heterogeneity in study designs, populations, interventions, and outcome measures, a **narrative synthesis** was conducted rather than a meta-analysis. Findings were thematically categorized into:

1. **Molecular and cellular mechanisms of neuroplasticity in TBI**
2. **Intervention-based approaches enhancing neuroplasticity**
3. **Cognitive and motor rehabilitation outcomes**
4. **Biomarkers and imaging correlates of plasticity**

Where available, **quantitative results (e.g., % improvement in cognition, effect sizes, odds ratios)** were extracted and reported.

Ethical Considerations

As this research involved the **secondary analysis of published data**, no ethical approval or informed consent was required. All included studies were peer-reviewed and were assumed to have adhered to ethical standards appropriate to their respective institutions and jurisdictions.

RESULTS

Summary and Interpretation of Included Studies on Neuroplasticity and Recovery After TBI

1. Study Designs and Populations

The included studies span a range of experimental animal models (e.g., lateral fluid percussion injury, repeated mild TBI) and randomized controlled trials in human TBI populations. Preclinical models (e.g., Corser-Jensen et al., 2014; Aungst et al., 2014; Witcher et al., 2021) provided mechanistic insights into microglial activity, synaptic plasticity, and neuroinflammation. Clinical studies (e.g., Siponkoski et al., 2020; Cooper et al., 2017; Mahncke et al., 2021) evaluated rehabilitation modalities such as cognitive training, music therapy, and constraint-induced movement therapy (CIMT) in TBI survivors. Sample sizes varied considerably—from small-scale rodent groups (n = 10–30) to large RCTs in human cohorts (n = 126 military personnel; Cooper et al., 2017; n = 83 participants; Mahncke et al., 2021).

2. Neuroplasticity Mechanisms Investigated

Mechanistic studies highlighted multiple neuroplasticity-related pathways:

- **Synaptic plasticity & dendritic remodeling:** Aungst et al. (2014) showed that repeated mild TBI increased hippocampal long-term potentiation but reduced functional plasticity with associated neuronal loss.
- **Microglial modulation:** Bray et al. (2022) and Witcher et al. (2021) demonstrated that CSF1R antagonism-induced microglial turnover reversed ~90% of cortical gene expression changes and improved cognitive outcomes.
- **Stress and sleep-related neuroplasticity:** Tapp et al. (2022) found sleep fragmentation post-TBI impaired hippocampal function and enhanced inflammation, suggesting HPA-axis driven maladaptive plasticity.
- **Neurotrophic and regenerative effects:** Xu et al. (2020) and Zhang et al. (2023) showed mesenchymal stem cell (MSC)-derived secretome and extracellular vesicles enhanced microglial M2 polarization, reduced edema, and improved cognition.

3. Cognitive and Functional Outcomes

- **Animal studies:** Corser-Jensen et al. (2014) reported MK-886 (a FLAP inhibitor) prevented trauma-induced synaptic dysfunction, with rats showing significantly fewer memory deficits in the radial arms water maze. Aungst et al. (2014) found repeated mTBI impaired memory in Morris water maze and novel object recognition tasks.
- **Human rehabilitation trials:**
  - Cooper et al. (2017) found all rehabilitation groups improved cognition, but therapist-directed CR showed superior performance on executive tasks compared to psychoeducation.

○ Siponkoski et al. (2020) showed neurological music therapy improved executive functions (Frontal Assessment Battery scores ↑ significantly, $p < 0.05$) and increased gray matter volume in right inferior frontal gyrus.
○ Mahncke et al. (2021) found plasticity-based computerized training improved composite cognitive scores by +6.9 points vs active control post-treatment ($p = 0.025$, d = 0.555).

4. Biomarker and Imaging Evidence

- **Neuroinflammatory biomarkers:** Serum Amyloid A1 (Carabias et al., 2020; Farré-Alins et al., 2021) correlated strongly with TBI severity and outcomes (AUC = 0.90 for predicting hospital mortality).
- **MRI markers:** Dall'Acqua et al. (2017) found prefrontal cortical thickening in mTBI patients—beneficial in good outcome patients but maladaptive (linked with cognitive decline) in poor outcome cases.

5. Summary of Effect Estimates

Across preclinical and clinical studies, interventions targeting neuroplasticity (microglial turnover, stem cell-derived EVs, and cognitive/music-based therapies) consistently improved recovery outcomes. Effect sizes ranged from **~90% reversal of neuropathology-related gene expression changes** (Bray et al., 2022) to **+6–7 point gains in neuropsychological composite scores** (Mahncke et al., 2021). Biomarker studies reinforced the role of neuroinflammation as both a maladaptive driver and therapeutic target for neuroplasticity-based recovery.

Table (1): General Characteristics and Results of Included Studies

Study	Country/ Model	Design	Sample Size	Intervention/Exposure	Neuroplasticity Outcomes	Cognitive/Functional Results	Key Findings
Corser-Jensen et al. (2014)	Rat LFP	Preclinical	n = 30 rats	MK-886 (FLAP inhibitor)	Prevented trauma-induced synaptic dysfunction	Improved RAWM performance, fewer memory deficits	Leukotriene blockade reduced secondary injury and improved cognition
Aungst et al. (2014)	Rat LFP	Preclinical	n = 20 rats	Single vs repeated mTBI	Altered hippocampal synaptic plasticity	Repeated mTBI impaired MWM & NOR	Chronic neuroinflammation drove cognitive decline
Witcher et al. (2021)	Mouse mFPI	Preclinical	n = 25 mice	PLX5622 (CSF1R antagonist)	Restored dendritic complexity, synaptic plasticity	Prevented 30 dpi cognitive impairment	Microglia promoted persistent neuropathology
Bray et al. (2022)	Mouse mFPI	Preclinical	n = 30 mice	Forced microglia turnover	90% of cortical gene changes reversed	Improved depressive-like behavior and memory	Microglial turnover mitigated chronic inflammation
Tapp et al. (2022)	Mouse TBI	Preclinical	n = 24 mice	Sleep fragmentation	Reduced hippocampal neuroplasticity	Cognitive impairment under stress	Stress-induced sleep disruption worsened recovery
Xu et al. (2020)	Rat TBI	Preclinical	n = 36 rats	ASC-secretome infusion	M2 polarization, reduced glial activation	Improved neurological scores, ↓ edema	MSC-secretome enhanced recovery
Zhang et al. (2023)	Rat TBI	Preclinical	n = 20 rats	MSC-derived EVs	Promoted neuroregeneration	Improved cognition, ↓ neuronal damage	EVs as promising therapy
Dall'Acqua et al. (2017)	Switzerland	MRI cohort study	n = 49 mTBI patients	Longitudinal MRI	Prefrontal cortical thickening	GO: recovery; PO: cognitive worsening	Cortical thickness reflects adaptive vs

							maladaptive plasticity
Carabias et al. (2020)	Spain	Clinical cohort	n = 115	Biomarkers (SAA1, YKL-40, PCT, S100β)	Linked with inflammatory neuroplasticity	AUC = 0.90 (mortality prediction)	SAA1 robust biomarker of injury severity
Farré-Alins et al. (2021)	Spain	Clinical	n = 60	SAA1–TLR4 axis	Inflammatory loop affecting plasticity	TAK242 improved outcomes	TLR4 antagonism reduced damage
Cooper et al. (2017)	USA (Military)	RCT	n = 126	Cognitive rehab (4 arms)	Enhanced cognitive recovery	Therapist-led CR > psychoeducation	Structured CR improves outcomes
Siponkoski et al. (2020)	Finland	RCT	n = 40	Music therapy	GMV ↑ in right IFG	FAB & set-shifting improved	Music therapy promoted executive neuroplasticity
Voelbel et al. (2021)	USA	RCT	n = 48	Auditory info processing program	↑ processing efficiency	Improved WJ-III & TMT-A	Cognitive remediation improved chronic deficits
Mahncke et al. (2021)	Multisite (Veteran cohort)	RCT	n = 83 ITT	Plasticity-based cognitive training	Targeted speed/accuracy of processing	+6.9 cognitive composite points (p = 0.025)	Self-administered training improved cognition
Taub & Uswatte (2018)	USA	Pilot study	Not specified	CIMT + fitness training	White matter changes hypothesized	Improved motor ability	Harnessing neuroplasticity via CIMT

DISCUSSION

Traumatic brain injury (TBI) triggers a complex cascade of pathophysiological events, among which neuroinflammation and disrupted neural networks play a critical role in determining recovery outcomes. The findings from Corser-Jensen et al. (2014) and Aungst et al. (2014) highlight how leukotriene synthesis and repeated mild injuries induce persistent neuroinflammation, which subsequently alters synaptic plasticity and memory performance. These results align with broader trends noted by Cohen et al. (2024), who emphasized the centrality of neuroinflammatory cascades in neurodegenerative processes, underscoring the importance of anti-inflammatory targets in post-TBI therapy.

Neuroplasticity emerges as both a protective and maladaptive response to injury. Studies on structural remodeling, such as Dall'Acqua et al. (2017), demonstrated prefrontal cortical thickening in mild TBI patients, which correlated with cognitive recovery in some individuals but maladaptive outcomes in others. This duality resonates with Shahid and Parvez (2022), who described neuroplasticity as a double-edged sword: while it enables functional reorganization, excessive or aberrant remodeling may exacerbate deficits.

The role of microglia in sustaining or mitigating neuropathology has gained significant attention. Witcher et al. (2021) and Bray et al. (2022) demonstrated that microglial activity contributes to chronic cortical inflammation, neuronal dysfunction, and cognitive decline, but that microglial turnover can restore homeostasis and improve behavioral outcomes. These findings are consistent with Kumar et al. (2023), who reviewed how cellular and molecular interventions targeting neuroplasticity mechanisms could rebalance immune responses and promote recovery.

Biomarker research has added a translational dimension to TBI studies. Carabias et al. (2020) identified serum amyloid A1 as a potential biomarker for both intracranial and extracranial severity, while Farré-Alins et al. (2021) linked SAA1-TLR4 signaling to inflammation and prognosis. Together, these biomarkers not only reflect secondary injury severity but also provide potential therapeutic targets. Lin et al. (2021) emphasized that neurotrophins such as BDNF are equally critical molecular indicators, influencing both neuroinflammatory processes and neuronal survival after TBI.

Beyond molecular markers, functional rehabilitation strategies demonstrate how neuroplasticity can be harnessed therapeutically. Cooper et al. (2017) reported significant cognitive improvements in military service members with mild TBI following structured cognitive rehabilitation, with therapist-directed approaches outperforming psychoeducation alone. Similarly, Mahncke et al. (2021) showed that plasticity-based computerized cognitive training led to superior improvements in cognitive composites compared to active controls. These findings support Katz and Dwyer (2021), who argued that rehabilitation grounded in neuroplasticity principles enables more tailored and effective treatment planning.

Adjunctive therapies such as music-based interventions also show promise. Siponkoski et al. (2020) demonstrated that music therapy not only enhanced executive functions but also increased prefrontal gray matter volume, a structural correlate of neuroplastic recovery. Case-based evidence from Thorpe and Byrne (2025) further suggests that music therapy can enhance motor learning and rehabilitation in severe TBI cases. These results align with Joshua (2022), who noted that experiential and sensory interventions drive cortical reorganization and support recovery trajectories.

The interaction between sleep, stress, and recovery represents another critical axis. Tapp et al. (2022) revealed that sleep fragmentation post-injury exacerbates inflammation, impairs hippocampal function, and worsens outcomes. This is supported by Wilde et al. (2021), who showed developmental neuroplastic changes persisting up to 15 years after early childhood TBI, suggesting that external stressors and environmental contexts significantly shape long-term outcomes.

Emerging biotechnological therapies also play a role. Xu et al. (2020) showed that the secretome of adipose-derived mesenchymal stem cells reduces neuroinflammation and enhances neurological functioning after TBI. Zhang et al. (2023) extended this work by demonstrating that microRNAs from extracellular vesicles derived from human mesenchymal stem cells improved motor and cognitive recovery. Together, these studies highlight the translational potential of cell-based therapies to modulate neuroplasticity pathways and mitigate secondary injury cascades.

The growing integration of digital and immersive technologies in rehabilitation further illustrates the adaptability of neuroplastic systems. Du et al. (2025) found that virtual reality–based interventions enhanced cognitive function in neuropsychiatric disorders, a finding that extrapolates to TBI populations where immersive environments can stimulate sensory and cognitive pathways. This resonates with Zotey et al. (2023), who emphasized adaptive neuroplasticity strategies that leverage novel technological tools to accelerate functional recovery.

The clinical translation of these findings requires careful consideration of variability in patient trajectories. Dorsey et al. (2018) highlighted the importance of viewing TBI within the broader context of neurodegenerative disorders such as Parkinson's disease, where maladaptive neuroplasticity contributes to long-term decline. This perspective urges clinicians to differentiate between recovery-promoting neuroplasticity and processes that predispose to chronic neuropathology.

Across interventions, one consistent theme is the role of timing in influencing recovery. Early interventions targeting neuroinflammatory cascades, such as leukotriene inhibition (Corser-Jensen et al., 2014), and microglial modulation (Bray et al., 2022; Witcher et al., 2021), appear most effective in preventing maladaptive plasticity. Later-phase strategies, including music therapy (Siponkoski et al., 2020) and VR training (Du et al., 2025), can then reinforce adaptive neuroplasticity and support reintegration into functional life roles.

Nonetheless, challenges remain in ensuring equitable access to therapies. As Katz and Dwyer (2021) noted, individualized rehabilitation demands substantial resources, and not all patients may benefit equally due to heterogeneity in injury severity, age, and comorbidities. Future research must therefore refine biomarkers (Carabias et al., 2020; Farré-Alins et al., 2021) to stratify patients and match interventions with recovery potential.

The interplay of neuroinflammation and neuroplasticity after TBI suggests a continuum between pathophysiology and recovery. Cohen et al. (2024) underscored that neuroinflammation is not merely a secondary injury but also a regulator of plasticity processes. This dual role underscores why integrative approaches that combine pharmacological, rehabilitative, and technological interventions are necessary for optimal outcomes.

Finally, theoretical contributions by Joshua (2022), Shahid and Parvez (2022), and Kumar et al. (2023) emphasize that neuroplasticity should not be considered in isolation but as part of a systems-level recovery model involving immune, endocrine, and cognitive networks. By synthesizing structural imaging findings (Dall'Acqua et al., 2017), molecular biomarkers (Lin et al., 2021), and rehabilitation strategies (Cooper et al., 2017; Mahncke et al., 2021), this review illustrates how converging evidence can inform a more holistic, personalized framework for recovery.

CONCLUSION

This systematic review highlights the central role of neuroplasticity in shaping recovery trajectories after traumatic brain injury. While inflammation-driven maladaptive plasticity contributes to chronic impairments, targeted therapeutic strategies—ranging from pharmacological modulation of microglia to immersive rehabilitation interventions—have shown potential in promoting adaptive reorganization. Cognitive rehabilitation, music therapy, virtual reality, and stem-cell-based approaches collectively illustrate how diverse therapies can stimulate plastic changes to support cognitive and motor recovery.

At the same time, the findings underscore the complexity of balancing beneficial and harmful forms of plasticity. Biomarkers such as serum amyloid A1 and neurotrophins may help clinicians identify patients most likely to benefit from specific interventions, supporting a more personalized approach. Ultimately, advancing TBI care requires integrated frameworks that combine molecular, structural, and functional perspectives to guide therapeutic timing and selection, ensuring that neuroplasticity is harnessed to improve long-term outcomes.

Limitations

This review has several limitations. First, heterogeneity across included studies—in terms of populations, injury severity, outcome measures, and interventions—limits the comparability of findings and precludes meta-analysis. The majority of included preclinical studies, while offering mechanistic insights, may not fully translate to human recovery trajectories.

Second, the review was restricted to studies published in English between 2010 and 2025, which may have excluded relevant non-English or earlier foundational work. Publication bias may also be present, as studies reporting positive outcomes of rehabilitation or therapeutic interventions are more likely to be published. Finally, while narrative synthesis highlights important trends, more standardized measures of neuroplasticity and larger multicenter trials are needed to confirm the efficacy and generalizability of interventions.

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