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Neuron Regeneration and Biomaterials for Concussion Recovery

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Abstract

This paper presents a comprehensive review of using neuron regeneration to aid in recovery from concussions and other forms of mild traumatic brain injury (mTBI), focusing specifically on the use of biomaterials and cells. There are several studies regarding regenerative medicine, but few relate to using neural stem cells (NSCs) and bioengineering to improve recovery after mTBI. This paper evaluates recent studies that explore the use of cells and scaffolds and their impact on motor and cognitive functions after a concussion. Information from 35+ animal studies and clinical trials published between 2013 and 2025 on PubMed focusing on biomaterials, neuron regeneration, and concussions was analyzed. These studies were categorized by the type of scaffold used, primary objective, and outcome. Across the animal studies, evidence shows that extracellular matrix-based hydrogels and scaffolds with stem cells reduced glial scarring, inflammation, and lesion volume while also improving motor recovery. The clinical trials used mesenchymal stem cells (MSCs) and bone marrow mononuclear cells (BMMNCs) to aid in recovery, which proved to be safe and provided short-term motor recovery but had limited cognitive recovery. This review highlights the importance in the compatibility of the type of cell and scaffold. It also offers a

layout for future studies seeking to test multi-stage recovery processes that reduce inflammation paired with scaffold-guided regeneration, as this approach more accurately models the natural healing process. These insights can guide future research toward improved recovery methods, leading to lasting motor and cognitive improvement.

Keywords: traumatic brain injury, Neural Stem Cells, biomaterials, Regenerative Medicine

Introduction

Background information on concussions

Concussions are a type of mild TBI (mTBI) that occurs when the head is impacted by a sudden force, causing the brain to move in the skull. This damage often leads to a range of physical and cognitive symptoms. Since concussions are a form of non-penetrating TBI, they usually don't have any visible damage marks and can be hard to notice and diagnose. Most concussions only last for a few weeks; however, the length depends on the severity of the damage. After sustaining a concussion, it is recommended to rest for 1 - 2 days both physically and cognitively (Macnow et al., 2021). Rest is important since the brain is spending the majority of its energy to repair the damaged cells. Cognitive and physical activity can cause the demand for ATP to surpass the amount produced by the mitochondria in the brain, which can cause symptoms to worsen. Symptoms can range from physical ones like headache, dizziness, and nausea, to memory issues, to emotional symptoms like sadness and irritability (Mittenberg et al., 1992). Repeated concussions can often lead to long-term damage, along with chronic traumatic encephalopathy (CTE). This has become a major concern for athletes and people who work in environments where the risk for concussions is

high. Thus, there has been a growing concern around proper treatment and recovery from concussions.

The purpose of this literature review is to examine how bioengineering and neuron regeneration can be used to aid in recovery from TBI. First, I review key components of neurogenesis and the anatomy of a neuron. Then I explore multiple animal studies and categorize them based on the material used, and analyze the strengths and weaknesses of each one. After, I review multiple clinical trials and highlight recurring themes that occur throughout these studies. Finally, I identify major gaps and current limitations in this research and provide future directions for viable ECM-based treatments for TBI.

Prevalence

Each year, around 2.5 million people in the U.S. visit the emergency room for TBI. Studies show that individuals aged 10-19 have the highest concussion rates, with 15% of high school students reporting at least one concussion in 2017 (Macnow et al., 2021). An analysis of health records found that among 8.8 million patients, 1.37 of them were related to concussions out of 1000. However, this number increased to 6.79 out of 1000 for people who were under the age of 18. One of the major contributors to concussions is contact sports like soccer, football, and hockey. The CDC estimates that anywhere from 1.6 to 3.8 million people sustain concussions from sports annually (Daneshvar et al., 2011).

Neuron Anatomy and Function

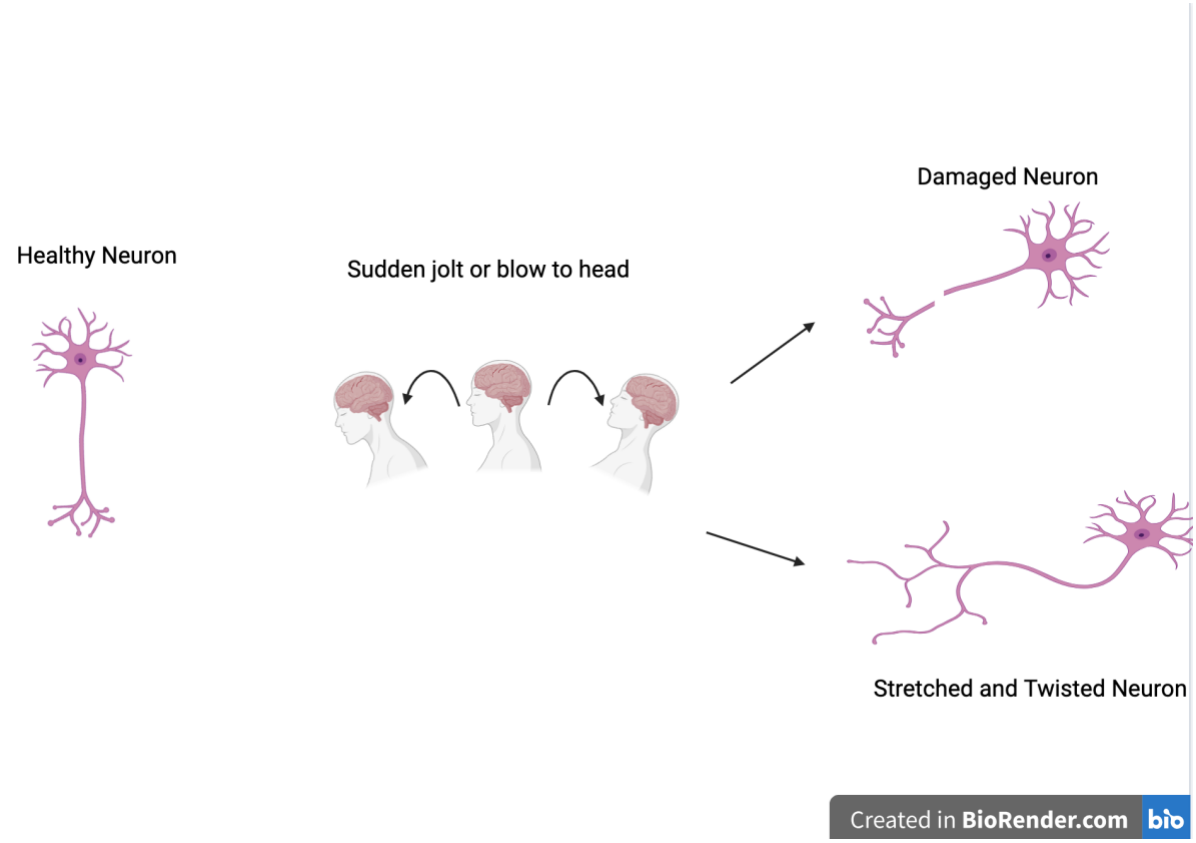
Neurons are the main cell type in the nervous system. Their main function is to transmit electrical and chemical signals throughout the body. The basic structure of a neuron has three main parts: the soma, dendrites, and axon. The soma is the cell body of the neuron

and consists of the organelles. It receives electrical signals from dendrites and sends depolarizing signals to the axon. Dendrites are extensions of the neuron that receive signals from neighboring neurons and transmit them to the soma. The axon is a long extension that sends action potentials from the soma to target cells. During a concussion or some form of TBI, these components of the neuron can be easily damaged, which impairs their ability to send and receive signals. The neurons in the brain become stretched and twisted from the shockwaves of the impact, which damage and kill the axons that connect these neurons (Figure 1). The membrane and cytoskeleton of axons are easily damaged, which inhibits the transport of essential neurotransmitters and electrical signals. The resulting damage can lead to diffuse axonal injury (DAI), which disrupts the nervous system and impairs communication between brain regions (Song et al., 2022). Although sometimes the neurons can naturally regenerate, other times the damage is too severe, leading to a permanent loss of function. This is where neurogenesis is emerging as a new solution, as it can grow new neurons to replace the ones that are severely damaged.

Figure 1

Impact of Concussions on Neurons. A sudden impact to the head causes the brain to move within the skull, generating shear and tensile forces on neurons. These forces can

stretch/twist axons, leading to diffuse axonal injury and impairing function.



Note. This figure is created using Biorender by Eric Li.

Neuronal Stem Cells

Neuronal stem cells (NSCs) are multipotent cells that can self-renew and differentiate into various other cells, like neurons, oligodendrocytes, and astrocytes (Ladran et al., 2013). NSCs are controlled tightly by a combination of intrinsic factors and epigenetic modifiers. Intrinsic factors include transcription factors and cell cycle regulators, while epigenetic modifiers include histone modifications and DNA methylation (Niklison-Chirou et al., 2020).

Mechanisms and advancements behind Neurogenesis

Neurogenesis is the growth and development of new neurons from neural stem cells

during embryonic development and adulthood. It takes place in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and the subventricular zone (SVZ), which lines the walls of the lateral ventricles (Niklison-Chirou et al., 2020). The process of neurogenesis takes many weeks and includes activating neural stem cells, proliferation and differentiation into neuroblasts, and migration and integration into existing neural circuits.

Neurogenesis is regulated by both intrinsic and extrinsic factors. Transcription factors like Sox2 and NeuroD1 are examples of intrinsic regulators that regulate stem cell maintenance and neuron differentiation (Hsieh & Eisch, 2010). External activity-dependent signals like GABA and glutamate influence the transition of inactive cells to differentiation and integration of new neurons into the existing networks (Ge et al. 2006). Not only is neurogenesis regulated by intrinsic influences, but also by external conditions. Recent advancements have shown that stem cell proliferation is increased from exercise and learning, while factors like aging and stress cause neurogenesis to diminish (Kuhn et al., 2018). Additionally, a study by Shin J et al. shows how advancements in single-cell RNA sequencing map the transcription states of adult neural progenitors and provide information about how NSCs transition from dormant to active (Shin et al. 2015). Recently, tissue engineering has become a new strategy to hopefully treat TBI by creating scaffolds that can mimic the extracellular matrix to provide structural and biochemical signals to help with regeneration. Although scaffolds were developed for applications in bone and skin repair, they can also be adapted to help with neural applications to help recreate an environment to support axon growth and synapse formation after TBI (Zhu et al. 2024). By combining scaffolds with neuron regeneration, researchers can strengthen the success rate of the survival and differentiation of neural stem cells.

Discussion

The majority of existing animal studies focus on recovery from TBI using rodent models. These models use extracellular matrix (ECM) models and biochemical cues to help the microenvironment recover post-injury, pairing scaffolds with cells to improve survival and integration into existing circuits.

ECM Models

A hyaluronan (HA) hydrogel designed to mimic the brain ECM treated with adhesion ligands (poly-L-ornithine, laminin, and fibronectin) was tested for niche repair after controlled cortical impact (CCI) in mice. The study aimed to determine whether an HA matrix could support cellular and structural regeneration after TBI. The hydrogel was implanted either immediately after CCI or one week later, became vascularized in vivo, and reduced glial-scar thickness. It also supported the presence of new oligodendrocytes and neurons within the scaffold (Lainé et al. 2022).

Another study evaluated whether brain ECM hydrogel implantation improved tissue strength and modulated immune responsiveness. Researchers filled a lesion cavity in TBI-induced mice with a decellularized brain-derived ECM hydrogel and found reduced neurodegeneration and white matter injury in the hippocampal region. ECM implantation also reduced TBI-induced gliosis—glial proliferation that can form a scar and obstruct neuronal regeneration when present in excess amounts (Wu et al. 2017).

A key study investigated a systemically infusible ECM (iECM) to assess if it could restore vascular integrity by reducing blood–brain barrier (BBB) permeability. The iECM was produced from decellularized ECM that was milled and processed into a formulation suitable for intravenous infusion. It significantly reduced BBB leakage, limiting toxicity by maintaining

homeostasis and keeping harmful substances out of the brain, and reducing secondary injury like swelling and inflammation. (Diaz et al. 2023).

A decellularized porcine urinary bladder matrix (UBM) hydrogel was also tested for biocompatibility and therapeutic potential after TBI. The UBM was injected into the cerebral cortex of rats 24 hours after CCI, resulting in decreased lesion volume and reduced white matter injury, alongside improvements in early motor recovery. However, spatial learning showed no significant improvement (Zhang et al. 2013).

Collectively, these ECM models reduce glial scarring, white matter injury, and BBB leakage, which allows for vascular growth and cell differentiation without the need for added cells or growth factors. However, this lack of improvement in spatial learning suggests that ECMs aid instructional repair but remain limited in promoting circuit-level recovery. Many ECM models are described as “brain-like” without providing sufficient physical or chemical specifications, making replication difficult. Additionally, the placement of the ECM influences outcomes. Implants are assumed to behave similarly regardless of their proximity to blood vessels and perivascular flow paths, even though differences can significantly alter nutrient and waste transport. Finally, decellularized ECMs contain glycans and peptides that are unaccounted for, which can potentially alter microglial and astrocyte behavior (Downs et al. 2023).

Stem Cells-Laden Scaffolds

A study using a GelMA/alginate hybrid scaffold aimed to address the low retention rate of transplanted neural stem cells (NSCs) in the brain after TBI, which is often caused by cerebrospinal fluid flow through the injured area. The hybrid hydrogel, composed of GelMA

and sodium alginate, was selected for its ability to support NSC adhesion, growth, and differentiation. Researchers found that NSCs pre-differentiated for seven days achieved the highest retention rate compared to undifferentiated or fully differentiated cells. The scaffold reduced acute microglial activation and neuronal death, and chronically improved tissue preservation, motor function, and neurogenesis in mice (Chen et al., 2023).

Similarly, a study used a urinary bladder matrix (UBM) as a carrier for NSCs to enhance their survival and therapeutic efficacy after TBI. When the UBM scaffold carrying NSCs was transplanted into the peri-lesional cortex of mice after controlled cortical impact (CCI), the mice exhibited reduced neuronal and tissue loss, along with improved motor, memory, and cognitive outcomes (Wang et al., 2013).

Additional work investigated collagen/heparan sulfate porous scaffolds filled with NSCs for functional repair after TBI. These scaffolds were freeze-dried and implanted into lesion sites in mice post-CCI. After two months, the treated mice showed increased neuronal and synaptic density, reduced apoptosis, and improved motor and cognitive function (Zhang et al., 2021).

Another study explored whether 3D-printed scaffolds loaded with NSC-derived exosomes could promote neural regeneration. Collagen and chitosan scaffolds were printed and infused with exosomes before being implanted in mouse lesions. The constructs enhanced motor and cognitive recovery, increased angiogenesis and neurogenesis, and reduced inflammation and apoptosis (Liu et al., 2023).

Finally, Tork et al. (2025) tested an SDF-1–functionalized RADA16 self-assembling peptide nanoscaffold designed to enhance NSC behavior and synaptogenesis—the formation

of new synapses between neurons. The RADA16 scaffold, injected into mice after TBI, significantly promoted NSC proliferation, migration, and differentiation, while also improving behavioral performance.

Across these studies, retention of NSCs or exosomes within the lesion proved critical for reducing microglial activation and tissue loss during the acute phase. However, long-term repair requires additional trophic cues such as chemotactic and synaptogenic signaling to promote axonal and synaptic network formation. A major determinant of outcomes across these experiments is the compatibility between the scaffold's material properties and the cellular state of the NSCs. The GelMA/alginate scaffold's adhesive and viscoelastic characteristics enabled pre-differentiated NSCs to adhere, survive, and spread effectively, explaining both their high retention and the reduction in inflammation (Yue et al., 2015). In contrast, collagen/heparan sulfate scaffolds bind and protect growth factors, which likely contributed to the enhanced neurological function observed in Zhang et al.(Sarrazin et al., 2011). Exosome-loaded collagen/chitosan scaffolds improved angiogenesis and neurogenesis, demonstrating that pre-conditioning the microenvironment is achievable even without transplanting live cells (Liu et al., 2023). Meanwhile, the RADA16 nanoscaffold assembles ECM-like nanofibers that, when combined with SDF-1, stimulate vascular and neurological recovery—a mechanism consistent with previous evidence that SDF-1 enhances neurovascular repair after TBI (Sankar et al., 2021). These material-specific characteristics clarify why NSCs in the same developmental state yield distinct outcomes depending on the scaffold composition.

Reducing neuroinflammation

Another study investigated whether a self-assembling peptide nanoscaffold (R-GSIK) combined with mesenchymal stem cells (MSCs) could enhance motor recovery and reduce inflammation after TBI. Rats were divided into four groups: MSCs alone, R-GSIK alone, MSC + R-GSIK, and a control. The MSC + R-GSIK group exhibited the most significant motor function improvement, along with lower pro-inflammatory cytokine levels and reduced numbers of reactive astrocytes and microglia (Negah et al., 2020). A separate study tested whether delivering dexamethasone—a corticosteroid that suppresses immune activity and inflammation—via degradable hydrogels could reduce neuroinflammation and improve recovery after TBI.

In a rat model of mild controlled cortical impact (CCI), researchers applied a degradable PEG-bis-AA hydrogel conjugated with dexamethasone-bound hyaluronic acid at the lesion site. After 7–14 days, treated rats showed improved motor and cognitive performance, reduced inflammation and apoptosis, and smaller lesion volumes compared to controls (Macks et al., 2022).

Another study evaluated whether a crosslinked hyaluronic acid (HA) hydrogel delivering bone marrow–derived MSCs and nerve growth factor (NGF) could promote neural repair after TBI. The loaded HA hydrogel was injected into lesion sites of mice post-CCI. The treatment improved neurological performance, reduced inflammatory and apoptotic markers, and decreased lesion volume relative to control animals (Wang et al., 2021).

Collectively, these studies demonstrate that combining a cell-permeable scaffold with temporally coordinated biochemical signals yields better outcomes than delivering cells or

scaffolds alone. The R-GSIK nanoscaffold achieved the greatest behavioral improvement and reduction in glial activity, suggesting that MSCs paired with a cell-adhesive matrix and bioactive signaling promote effective regeneration. The PEG-bis-AA hydrogel delivering dexamethasone provided rapid anti-inflammatory action, reducing lesion size and enhancing functional recovery. Meanwhile, the HA hydrogel incorporating NGF offered sustained trophic support, lowering inflammation and apoptosis while improving long-term outcomes. Together, these findings highlight that brain-mimetic, viscoelastic scaffolds capable of retaining MSCs—when paired with short-term local immunomodulation (e.g., dexamethasone) and trophic cues—can provide both acute neuroprotection and long-term guidance for neural reconnection and tissue repair.

Clinical Trials

In a sham-surgery–controlled Phase 2 randomized clinical trial of adults with chronic TBI, allogeneic modified mesenchymal stem cells (MSCs; SB623) were stereotactically implanted directly into brain tissue. The patient cohort (n = 61, mean age = 34) was assessed using the Fugl-Meyer Motor Score (FMMS) to evaluate motor recovery. At 24 weeks, the SB623 group demonstrated an average improvement of 8.3 points, compared to only 2.3 points in the sham group. By 48 weeks, both groups showed continued improvement, but the between-group difference was no longer statistically significant (Okonkwo et al., 2024).

A randomized, double-blind, placebo-controlled pediatric trial investigated the use of autologous bone marrow mononuclear cells (BMMNCs) in patients with acute severe TBI. Forty-seven participants aged 5–17 were randomized, and 37 completed a 1-year follow-up (23 BMMNC, 14 placebo). The BMMNC-treated group exhibited a 23% reduction in ventilator

days and a 14% reduction in intensive care unit stay, along with greater preservation of white matter volume after one year (Cox et al., 2024).

In a separate adult Phase 1 trial, researchers evaluated the safety of escalating doses of autologous BMMNCs in patients aged 18–55 with severe TBI but no irreversible brain injury. Twenty-five participants were divided into control and treatment groups receiving 6, 9, or 12 $\times 10^6$ cells/kg body weight. Bone marrow was harvested, the mononuclear fraction isolated, and cells were reinfused within 48 hours of injury. No serious adverse events occurred, confirming that intravenous BMMNC infusion is safe and well tolerated (Cox et al., 2017).

Another pediatric Phase 1 clinical trial assessed whether autologous BMMNC infusion could reduce the therapeutic intensity required to manage intracranial pressure (ICP) following severe TBI. Participants aged 5–14 were divided into a treatment group (n = 10) receiving 6 $\times$ 10^6 BMMNCs/kg body weight intravenously 48 hours post-injury, and a control group (n = 19). Treatment intensity was measured using the Pediatric Intensity Level of Therapy (PILOT) scale. Within 24 hours of infusion, the treatment group showed a reduction in PILOT scores, indicating decreased ICP management requirements (Liao et al., 2015).

Across these clinical studies, distinct trends emerge between chronic and acute TBI interventions. In chronic TBI, intracerebral delivery of modified allogeneic MSCs (SB623) produced significant short-term motor improvements, but the effects diminished over time, suggesting that trophic signaling benefits may be transient and require reinforcement through repeated or sustained dosing. In contrast, autologous BMMNC therapy for acute severe TBI demonstrated safety across escalating doses and measurable physiological benefits, including reduced inflammation, preserved white matter, and decreased ICP treatment burden. Together, these findings suggest that acute TBI interventions should prioritize neuroprotection and tissue

preservation, while chronic TBI therapies may require localized cell delivery and repeated reinforcement to sustain functional recovery.

Table 1

Animal Trials

Study (Year)	Objective	Animal Model & Approach	Key Outcomes	Scaffold Type
Laine et al. 2022	To evaluate the therapeutic effect of an HA hydrogel on host tissue after cortical trauma.	Mouse (C57BL/6), TBI via controlled cortical impact. Hydrogel was implanted immediately or with a one-week delay.	Hydrogel became vascularized, reduced glial scar thickness, and supported new oligodendrocytes and neurons.	Hyaluronan-based hydrogel (intermediate MW, ~300 Pa stiffness) enhanced with poly-L-ornithine, laminin, and fibronectin.
Chen et al. 2023	To improve the low retention rate of transplanted Neural Stem	Mouse TBI model. NSCs loaded onto GelMA/Alg hydrogel and transplanted.	High NSC retention; reduced microglia activation and neuronal death (acute); reduced tissue	Hybrid hydrogel of Gelatin Methacrylate (GelMA) and

	Cells (NSCs) in the injured brain.		loss, improved motor behavior, enhanced neurogenesis (chronic).	Sodium Alginate (Alg).
Wu et al. 2017	To investigate whether a brain-derived ECM hydrogel improves the brain microenvironment and recovery post-TBI.	Mouse TBI model. Brain-derived ECM hydrogel is implanted into the lesion site.	Less neurodegeneration and white matter injury; reduced gliosis and pro-inflammatory microglial activation.	Brain-derived extracellular matrix (ECM) hydrogel.
Diaz et al. 2023	To determine if an infusible ECM biomaterial can target TBI, restore BBB integrity, and modulate inflammation.	Mouse TBI model. Intravenous infusion of a soluble, ECM-derived biomaterial (iECM).	Reduced blood-brain barrier (BBB) leakage; enhanced endothelial integrity.	Infusible extracellular matrix-derived biomaterial (iECM).

Negah et al. (2020)	To test if a self-assembling peptide scaffold with MSCs enhances motor recovery and reduces neuroinflammation.	Rat TBI model. Comparison of MSC-only, scaffold-only, and MSCs+scaffold groups.	Improved motor function; reduced reactive astrocytes and microglia; lowered pro-inflammatory cytokines.	R-GSIK self-assembling peptide nano-scaffold.
Zhang et al. 2013	To test the biocompatibility and therapeutic effect of a porcine urinary bladder matrix (UBM) hydrogel.	Mouse TBI model. Intracortical injection of UBM hydrogel.	Reduced lesion volume and white matter injury; improved early motor recovery.	Decellularized porcine urinary bladder matrix (UBM) hydrogel.
Wang et al. 2013	To evaluate whether UBM improves the survival and effectiveness of	Mouse TBI model. UBM scaffold carrying NSCs transplanted into the peri-lesional cortex.	Reduced neuron/tissue loss and white matter injury; improved motor, memory, and cognitive outcomes.	Porcine urinary bladder matrix (UBM) bioactive scaffold.

	transplanted NSCs.			
Zhang et al. 2021	To assess collagen/heparan sulfate scaffolds loaded with NSCs for functional repair.	Mouse TBI model. Freeze-dried scaffold seeded with NSCs implanted into lesions.	Increased neurons, synapses, and myelin; reduced edema and apoptosis; improved motor & cognitive function.	Porous collagen/heparan sulfate scaffold.
Liu et al. 2023	To enhance neural regeneration using exosome-laden 3D-printed scaffolds.	Mouse TBI model. 3D-printed scaffold loaded with NSC-derived exosomes implanted in the lesion.	Improved motor and cognitive recovery; increased angiogenesis & neurogenesis; reduced inflammation & apoptosis.	3D-printed collagen/chitosan porous scaffold.
Tork et al. 2025	To determine if an SDF-1 functionalized self-assembling peptide enhances NSC	Mouse TBI model. Injection of RADA16-based scaffold functionalized with SDF-1 motif.	Increased NSC proliferation/migration/differentiation; enhanced synaptic markers; behavioral improvements.	Self-assembling peptide (RADA16) nano-scaffold with SDF-1

	behavior and synaptogenesis.			functional motif.
Macks et al. 2022	To test local hydrogel delivery of dexamethasone for neuroinflammation and recovery.	Mouse TBI model. Application of a hydrolytically degradable PEG hydrogel containing dexamethasone.	Improved motor & cognitive function; reduced inflammation, apoptosis, and lesion volume.	PEG-bis-AA hydrogel with hyaluronic acid-dexamethasone conjugate (drug-releasing).
Wang et al. 2021	To evaluate a dual-crosslinked HA hydrogel co-delivering BMSCs and NGF for TBI.	Mouse TBI model. Injection of tyramine-modified HA hydrogel loaded with BMSCs and NGF.	Improved functional scores; increased neurotrophic factors; reduced inflammation; decreased lesion volume.	Injectable tyramine-modified hyaluronic acid hydrogel (dual-enzymatically crosslinked).

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Table 2

Clinical Trials

Study (Year)	Patient Cohort (Age, #)	Type of Scaffold/Cell	Time/Status of Trial	Outcome
Okonkwo et al. 2024	Adults; mean age ~34; n=61	Allogeneic modified MSCs (SB623)	Chronic TBI (≥12 mo); Phase 2 RCT; 48-wk follow-up; completed	FMMS change at 24 wk: +8.3 vs +2.3 (sham), p=0.04; benefit persisted to 48 wk; safety comparable.
Cox et al. 2024	Children 5–17; n=47 randomized	Autologous bone-marrow mononuclear cells (BMMNC), IV	Acute severe TBI (≤48 h); randomized, double-blind; 12-mo follow-up; completed	Decreased ICU intensity/duration; reduced white-matter volume loss at 1 yr; feasible/safe.
Cox et al. 2017	Adults with severe TBI (GCS 5–8); n=25	Autologous BMMNC, IV (6–12×10^6 cells/kg)	Acute (≤48 h); phase 1/2, dose-escalation; 6-mo follow-up; completed	Safe/feasible; signals of structural preservation on MRI and downregulated inflammatory cytokines.

Liao et al. 2015	Children 5–14 years; n=10 treated (vs n=19 controls)	Autologous bone-marrow–derived mononuclear cells (BMMNC), IV	Acute severe TBI (≤48 h); Phase I vs matched controls; completed	Significant reduction in PILOT score from 24 hours through week one (P<0.05).

Challenges and Future Directions

From these animal studies and clinical trials, many challenges still exist preventing consistent recovery after TBI. First, scaffold and cell-based strategies that increase cell retention reduce acute inflammation and tissue loss, but don't seem to provide any benefit towards cognition or neural circuits without axon guidance or synaptogenesis cues. Second, the outcomes of these trials heavily depend on the scaffold and cell matching. The pre-differentiated NSCs perform better on stress-relaxing scaffolds like the GelMA/alginate, while the UBM scaffolds work best with concentrated trophic factors. The ECM models must also accurately account for perivascular flows, ECM porosity, and the diffusion and convection in the living brain. Otherwise, the model wouldn't accurately represent those in the brain, and the scaffold may release cues that release too quickly or too slowly. This variety of possible combinations and scaffolds, and complex mechanics of such matrices, limits the reproducibility for future studies. Similarly, for clinical trials, consistent categorization of patients also affects the outcome. Current cohorts of patients are a mix of injury type (DAI, focal contusion), severity, and phase (acute, chronic). Currently, these

studies focus mainly on the impact of neurons; however, axon insulation recovery and repair of the neurovascular unit, which maintains the BBB and regulates energy delivery, is underresearched despite slower cognitive function from concussions being linked with white-matter and vascular dysfunction (Bai 2020). Finally, some concussion models fail to replicate real concussion physics, like the rotational shear forces that twist axons. This leads to cells and scaffolds producing positive results in simpler scenarios, but underperforming in more complex real-life issues.

Future studies could test out a design with a GelMA center, to help NSCs stick and survive, combined with a Heparan Sulfate exterior would provide growth factors that would theoretically keep NSCs alive and signal them to move the right way. This design could potentially lead to better cell survival and accurate migration of NSCs compared to just the GelMA or Heparan Sulfate scaffolds on their own. Also, testing out future studies on timing could provide positive benefits. Using an acute phase anti-inflammatory drug to calm inflammation and stabilize the BBB, then a delayed phase with a scaffold to promote neuron growth and wiring to mimic the natural healing process. Another possible improvement is using multi-site implants to reach broader tissue. Since concussions often lead to DAI, a single implant may not cover the lesion. Thus, using multiple micro-implants would cover more area. Additionally, pairing this strategy with a mechanism that provides scheduled booster shots would be more realistic since different phases of recovery have different requirements, and a single dose rarely provides for all the phases. Finally, expanding the animal test subjects to larger animals like pigs would allow for a better comparison for humans. Pigs would be a more accurate representation of human brains since their brains are gyrencephalic and have human-like white matter proportions and brain biomechanics.

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Conclusion

Concussions remain a prominent topic in public health due to their prevalence and lasting damage. While current professionals recommend rest before returning to activity, new research highlights the possibility of using regenerative medicine like NSCs, scaffolds, and biomaterials to hopefully treat lasting impacts left from concussions. Current animal studies have shown that regenerative medicine can reduce tissue loss, improve motor recovery, and reduce inflammation; however, higher-level cognition improvement is still unclear. Clinical trials have suggested that MSCs and BMMNCs can be used safely to produce short-term improvements in motor function in patients with TBI. Moreover, regenerative medicine shows promise in improving concussion recovery despite significant challenges. With more studies, especially clinical trials, these methods could eventually lead to safer and faster recoveries and fewer long-term effects of concussions.

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