Review Article:

Synaptic Plasticity and Circuit Rewiring After CNS Injury: Mechanisms of Reorganization and Functional Recovery

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Abstract:

Central nervous system (CNS) injuries, long regarded as irreversible, are now understood to trigger extensive synaptic plasticity and circuit reorganization that underlie functional recovery. This review synthesizes evidence from molecular, imaging, and transcriptomic studies to elucidate the mechanisms of adaptive and maladaptive neuroplasticity. Activity-dependent NMDA-CaMKII-CREB signaling and neurotrophic support drive synaptic remodeling, while growth-associated proteins (GAP-43) and glial modulation facilitate axonal sprouting. Advances in optogenetics, single-cell transcriptomics, and in vivo imaging reveal dynamic rewiring across scales, reshaping our understanding of CNS repair. Emerging therapeutic strategies; ranging from neuromodulation to gene-based and cell-based interventions, highlight translational opportunities for precision neurorehabilitation. This synthesis uniquely integrates recent molecular, glial, and network-level insights with cutting-edge neurotechnological methods to propose a unified translational framework for adaptive CNS repair.

Keywords:

Synaptic plasticity; CNS injury; axonal sprouting; network reorganization; neuromodulation; transcriptomics.

Introduction:

Key Points:

- CNS injury induces multi-level plasticity: Neural circuits exhibit adaptive and maladaptive rewiring driven by molecular, cellular, and network-scale processes.
- Synaptic remodeling underpins recovery: NMDA–CaMKII–CREB signaling, dendritic spine turnover and glial-derived neurotrophic support orchestrate synaptic strengthening and reorganization.
- Glial–neuronal interactions are pivotal in synaptic plasticity and circuit rewiring: Astrocytes and microglia balance synaptogenesis and inflammatory signaling, determining recovery versus pathology.
- Emerging technologies enable systems-level insights: Optogenetics, in vivo imaging, and spatial transcriptomics reveal dynamic rewiring mechanisms with translational relevance.
- Therapeutic convergence for precision rehabilitation: Integrating molecular modulation, neuromodulation, and regenerative approaches offers a framework for individualized neurorehabilitation.

Central nervous system (CNS) injuries (such as traumatic brain injury (TBI), spinal cord injury (SCI), and ischemic stroke) represent major causes of long-term disability globally, affecting millions of individuals annually [1,2]. These injuries severely disrupt neuronal networks, leading to persistent deficits in cognition, mobility, and sensorimotor integration. Traditionally, the CNS has been viewed as a non-regenerative system, owing to intrinsic neuronal limitations and the presence of extrinsic inhibitors such as Nogo-A, chondroitin sulfate proteoglycans, and the glial scar [3,4].

However, recent discoveries challenge this longstanding notion, demonstrating that the adult CNS retains latent plasticity. Surviving neurons can undergo axonal sprouting, synaptic remodeling, and circuit reorganization, particularly when supported by targeted interventions [5,6]. Among the most critical processes enabling functional recovery are those occurring at the synaptic and network levels, such as dendritic spine remodeling, functional remapping, and compensatory synaptogenesis, which have emerged as central mediators of post-injury adaptation [7].

The adult CNS is increasingly conceptualized as a dynamic and adaptive system capable of reorganization following injury. This plasticity operates on a

continuum from adaptive to maladaptive responses. Adaptive plasticity involves re-establishment of lost functions via functional rerouting, while maladaptive plasticity can contribute to neuropathologies such as spasticity, chronic pain, or epilepsy[8,9].

The coordination of synaptic and circuit-level plasticity relies on multiple interacting mechanisms, including activity-dependent gene expression, receptor trafficking, dendritic remodeling, and glial–neuronal interactions. These processes are shaped by extrinsic cues such as neurotrophic factors and inflammatory mediators, as well as intrinsic transcriptional and epigenetic programs. Thus, a multiscale systems-level approach is essential to fully capture the complexity of CNS rewiring after injury. However, existing reviews have rarely linked these multiscale findings into a cohesive mechanistic narrative bridging molecular and systems-level recovery.

Despite decades of research on neuroplasticity, most studies have investigated synaptic remodeling and circuit reorganization in isolation (either at the molecular, cellular, or systems level) without integrating how these processes interact to produce functional recovery after CNS injury. Furthermore, translational frameworks that link mechanistic discoveries to clinical rehabilitation remain fragmented. This review addresses these gaps by synthesizing recent multi-scale evidence (from molecular signaling pathways and glial–neuronal crosstalk to connectomic and transcriptomic analyses) to provide a unified perspective on how synaptic and network plasticity collectively drive adaptive and maladaptive outcomes.

Synaptic Plasticity Mechanisms Post-CNS Injury:

Synaptic plasticity following CNS injury is heavily influenced by activity-dependent mechanisms. Activation of NMDA receptors leads to Ca^{2+} influx, which in turn activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). CaMKII autophosphorylates at T286, a key step in maintaining long-term potentiation (LTP) and facilitating synaptic strength [12]. Concurrently, Ca^{2+}-stimulated phosphorylation of CREB regulates gene transcription essential for synaptic remodeling and functional recovery, with one study demonstrating that enhanced CREB expression in peri-infarct cortex promotes motor recovery following stroke in mice [13]. Together, these pathways drive both LTP and long-term depression (LTD) adaptations in neurons near injured regions, reinforcing circuit rewiring.

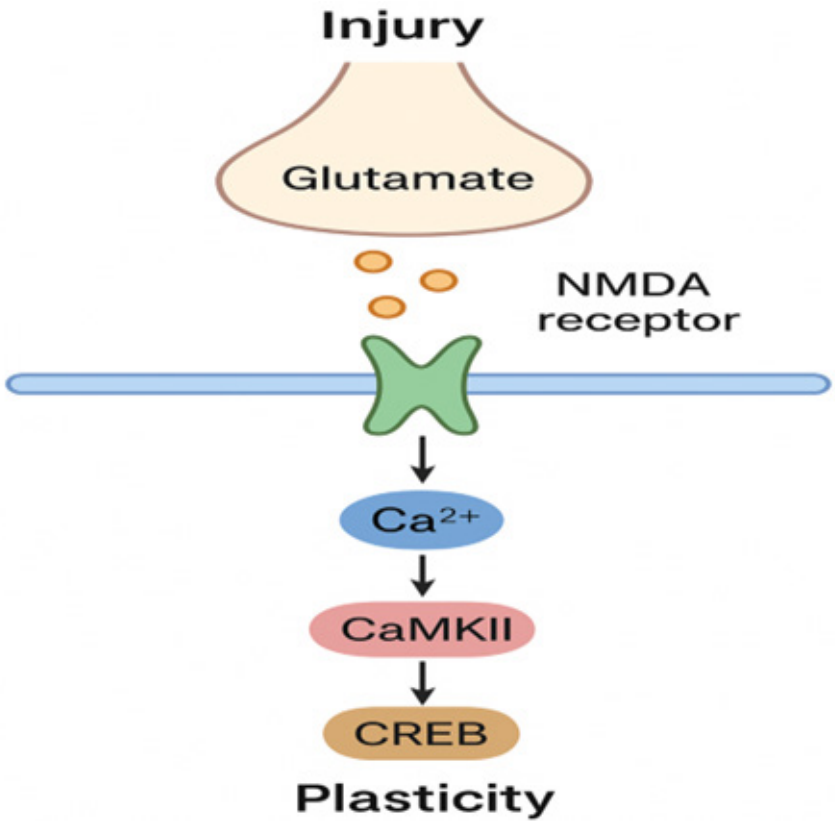


Figure 1: NMDA–CaMKII–CREB Signaling Pathway in Synaptic Plasticity.

Figure 1: NMDA–CaMKII–CREB Signaling Pathway in Synaptic Plasticity: Schematic representation of the molecular cascade underlying synaptic plasticity after CNS injury. Glutamate released from presynaptic terminals activates NMDA receptors, resulting in calcium (Ca^{2+}) influx into the postsynaptic neuron. Elevated intracellular Ca^{2+} activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which undergoes autophosphorylation and subsequently phosphorylates the transcription factor CREB (cAMP response element-binding protein). Activated CREB drives gene expression required for dendritic spine remodeling, long-term potentiation (LTP), and activity-dependent synaptic strengthening—key processes contributing to adaptive neural circuit reorganization after injury.

Structural plasticity in peri-lesional cortex is marked by dynamic changes in dendritic spines. In vivo two-photon imaging in a middle cerebral artery occlusion (MCAO) model revealed a 20 % acute spine loss in layer V pyramidal neurons, followed by gradual recovery or even overcompensation of spine density over several weeks—dependent on local perfusion [14]. Photothrombotic stroke models using Golgi-Cox staining also highlighted rapid spine loss and elongation within

minutes post-injury [15]. These findings underscore a time-dependent cycle of spine pruning and regrowth that supports synaptic reorganization.

Post-injury elevations in neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) are pivotal for synaptogenesis. Astrocytes and microglia release BDNF and IGF-1, respectively, promoting synaptic and neural connectivity[16]. Additionally, astrocyte-derived growth factors like FGF-2 and D-serine regulate synaptic formation and NMDA receptor activity, facilitating glutamate transmission critical for new synapse stabilization [17]. Glial participation thus balances synapse formation and pruning in the injured brain.

Circuit Rewiring and Network Reorganization:

Following CNS injury, spared axonal pathways initiate sprouting to compensate for lost connections. Classic studies in spinal cord lesion models revealed that collateral sprouting, marked by upregulation of GAP-43, enables damaged tracts to reinnervate adjacent regions and partially restore function [18]. However, the presence of inhibitors such as Nogo-A in myelin significantly hampers this process. Genetic or antibody-mediated inhibition of Nogo-A enhances corticospinal tract (CST) sprouting and improves motor function post-injury [19], especially when combined with intrinsic growth-promoting interventions like PTEN deletion [20].

Functional MRI studies in stroke patients consistently show early disruptions in interhemispheric connectivity, followed by compensatory activation in ipsilesional and contralesional motor cortices [21,22]. Longitudinal analyses reveal that increased task-related BOLD signals in both hemispheres correlate with improved motor recovery, suggesting restorative plasticity alongside compensatory reorganization. Moreover, advanced network metrics (such as distance-dependent functional connectivity density) highlight how spatial integration and segregation of brain networks predict motor outcomes in non-acute stroke patients [23].

Post-injury, cortical oscillatory patterns shift markedly. Acute ischemic strokes often trigger increased delta power and decreased beta and gamma rhythms over affected regions; higher delta-band synchrony parallels greater functional impairment [24], while preserved beta activity is linked to better neurological recovery[25]. Theta–gamma coupling emerges as a strong biomarker for improvement in motor performance in chronic stroke, guiding interventions like brain-computer interface training and non-invasive neuromodulation[25].

Molecular and Cellular Drivers of Post-Injury Plasticity:

CNS injury triggers complex transcriptional reprogramming in excitatory and inhibitory neurons. A study on RNA sequencing of peri-infarct tissue in mice 3 days post-ischemic stroke revealed altered expression of over 1,200 genes—including upregulation of axon-growth–associated factors and synaptic remodeling proteins—illustrating the injury-induced activation of intrinsic plasticity pathways [26]. Meanwhile, epigenetic mechanisms fine-tune this response: class I and II histone deacetylases (HDACs) upregulate in injured neurons, and HDAC inhibition enhances axonal sprouting and functional recovery in rodent spinal cord injury models [27]. MicroRNAs such as miR-124 and miR-9 also modulate synaptic gene networks—miR-124 suppression leads to dendritic spine abnormalities, while miR-9 promotes axonal regeneration via REST complex targeting [28,29].

Microglial activation plays a dual role: it can support synaptogenesis via phagocytic pruning of defunct synapses or hinder plasticity through excessive cytokine release. Post-TBI, IL-1β blockade (a neutralizing antibody administered within 30 minutes) attenuated microglial activation and preserved parvalbumin interneurons in mice, highlighting IL-1β's detrimental role in synaptic integrity [30]. Likewise, TNF-α contributes to synaptic homeostasis: glial TNF-α promotes excitatory transmission initially yet chronic elevation disrupts LTP in hippocampus through TNFR1-mediated AMPA receptor trafficking [31,32].

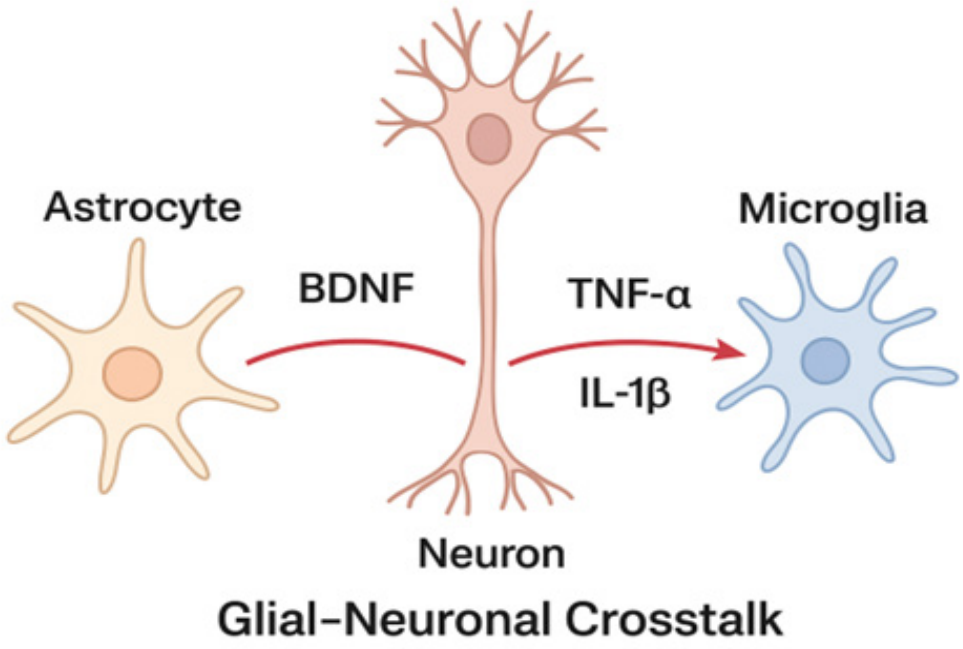


Figure 2: Glial–Neuronal Crosstalk in Synaptic Plasticity and Neuroregulation

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Illustration of bidirectional communication between glial cells and neurons following central nervous system (CNS) injury. Astrocytes release neurotrophic and modulatory factors such as brain-derived neurotrophic factor (BDNF) and D-serine, which support synaptic formation, NMDA receptor activity, and neuronal survival. In contrast, activated microglia secrete pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-**α**) and interleukin-1 beta (IL-1**β**), which can either facilitate synaptic scaling and repair in the acute phase or contribute to excitotoxicity and maladaptive remodeling during chronic inflammation. This balance between supportive astrocytic signaling and microglial activation determines whether post-injury plasticity promotes functional recovery or pathological outcomes such as chronic pain or spasticity.

Guidance molecules such as netrins and semaphorins also play reparative roles. After spinal cord hemisection, viral overexpression of FGF22 (a key presynaptic organizer) enhanced corticospinal-bypass synapse formation and motor recovery in mice, underlining time-sensitive circuit reorganization[33]. Additionally, class 3 semaphorins (e.g., Sema3A) are upregulated post-injury and inhibit neural regeneration. Blocking semaphorin signaling improved axonal regrowth and remyelination in CNS injury models [34].

Technological Advances Redefining Plasticity Research:

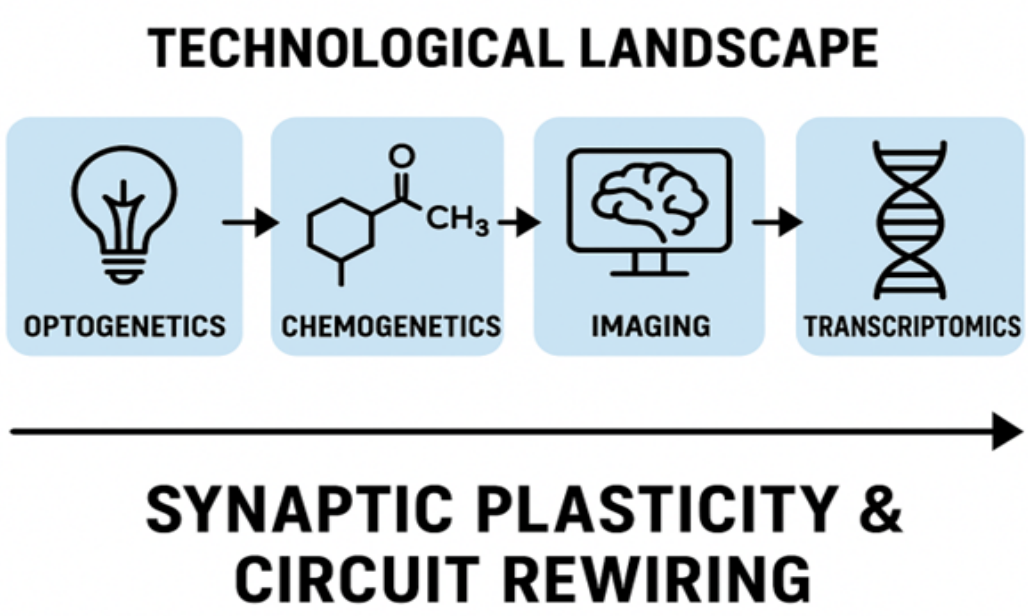


Figure 3: Technological Landscape for Studying Neural Plasticity after CNS Injury.

Figure 3: Technological Landscape for Studying Neural Plasticity after CNS Injury:

Flowchart summarizing the integration of emerging neurotechnological tools used to investigate synaptic plasticity and circuit rewiring following central nervous system (CNS) injury. Optogenetics enables cell-type–specific modulation of neuronal activity with light-sensitive ion channels; chemogenetics employs designer receptors exclusively activated by designer drugs (DREADDs) for reversible control of neuronal excitability; in vivo imaging techniques such as two-photon microscopy and functional MRI allow visualization of structural and functional reorganization across time; and single-cell or spatial transcriptomics provide molecular resolution of cell-specific gene expression during repair. Together, these technologies bridge functional, structural, and transcriptional domains, offering a comprehensive systems-level framework for understanding and enhancing adaptive neuroplasticity.

Optogenetics and Chemogenetics:

Optogenetic tools have transformed the study of neural circuits in CNS injury models by enabling precise, cell-type-specific modulation of neuronal activity. In one landmark experiment, optogenetic stimulation of parvalbumin-positive neurons in the ipsilesional motor cortex of stroke-afflicted rats restored excitatory/inhibitory balance, reduced neurological deficits, and improved motor function [35]. Similarly, optogenetic activation of the contralesional lateral cerebellar nucleus enhanced neurovascular coupling and hastened functional recovery in mice, with concurrent reductions in neuronal nitric oxide synthase expression [36]. These targeted stimulation protocols can guide adaptive circuit rewiring and synaptogenesis, supporting rehabilitation efficacy. Meanwhile, emerging chemogenetic strategies using DREADDs provide a non-invasive alternative to optogenetics by enabling reversible modulation of circuit excitability with designer ligands, suitable for long-term studies [37].

In Vivo Imaging and Connectomics:

High-resolution imaging of spine dynamics in the injured brain has been revolutionized by two-photon microscopy. Longitudinal imaging reveals acute dendritic spine loss within minutes of stroke onset, followed by gradual peri-infarct spine remodeling over days to weeks[38]. This enables direct visualization of how local perfusion and synaptic turnover predict recovery potential. Complementing this, CLARITY-based whole-brain clearing and viral tract tracing now allow

researchers to map axonal sprouting and rewiring across entire neural circuits post-injury [39]. Integrating these anatomical maps with functional imaging highlights circuit-level changes underlying behavioral improvements.

Single-Cell and Spatial Transcriptomics:

Advanced single-cell RNA sequencing (scRNA-seq) combined with spatial transcriptomics (ST) offer unprecedented insight into cellular heterogeneity and microenvironmental gradients following CNS injury. In mouse stroke models, scRNA-seq and ST uncovered previously unrecognized microglial subpopulations localized within the infarct boundary, each with distinct functional roles. Manipulation of these specific microglia subclusters altered lesion size and neuronal apoptosis [38]. Similarly, spatial multi-omics has identified astrocyte subtypes with unique spatial gene expression patterns, including differential lipid-handling functions proximal to injury sites [40]. Together, these multimodal approaches enable unprecedented integration of functional, structural, and molecular data streams.

Therapeutic Strategies to Enhance Adaptive Rewiring:

Rehabilitation and Activity-Dependent Plasticity:

Constraint-Induced Movement Therapy (CIMT) remains a cornerstone of rehabilitative neuroplasticity. A 2020 randomized clinical trial applying CIMT to lower extremity function after stroke demonstrated improved mobility and balance when administered intensively (3.5 h/day for 10 days) [41]. Another 2021 pilot RCT of modified CIMT protocols in chronic stroke survivors supported its practicality and potential efficacy in community settings [42].

Electrical and non-invasive brain stimulation, including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), have been shown to enhance cortical excitability and accelerate rehabilitation outcomes[43]. A double-blind RCT combining early bihemispheric tDCS with modified CIMT in hospitalized stroke patients yielded improvements in upper-limb motor function and strengthened descending corticospinal pathways, evidenced by enhanced event-related desynchronization on EEG [42].

Pharmacological and Molecular Interventions:

Ampakines, AMPA receptor positive allosteric modulators, have demonstrated promising therapeutic potential. Preclinical studies showed that low-impact ampakine CX717 enhances LTP and respiratory motor output in rats. Phase 2 trials in humans have verified its safety, tolerability,

and engagement of glutamatergic pathways[44,45]. These findings support the hypothesis that ampakines could promote synaptic plasticity post-CNS injury.

Efforts to antagonize intrinsic growth repressors like PTEN and SOCS3 using viral vectors or small molecules in rodent models have shown axonal regrowth and functional recovery [46], though human data are still forthcoming.

Cell-Based and Bioengineering Approaches:

Neural stem cell transplantation has been validated in animal studies to rescue synaptic connectivity and restore function in spinal cord and brain injury models. While human trials are limited, early-stage phase I/II efforts report encouraging safety and preliminary efficacy [47,48]. Biomaterial scaffolds, often combined with neurotrophic factors and extracellular matrix cues, have been engineered to guide regenerating axons across lesion sites. These scaffolds support synaptogenesis and functional reconnection in rodent models of trauma or stroke [49].

Table 1: Summary of Therapeutic Strategies to Enhance Adaptive Rewiring After CNS Injury.

Strategy Category	Specific Intervention	Mechanism of Action	Key Evidence/Outcome
Rehabilitation & Activity-Dependent Plasticity	Constraint-Induced Movement Therapy (CIMT)	Forces use of the affected limb, promoting activity-dependent cortical reorganization and use-dependent plasticity.	Improved mobility and balance when applied intensively [41,42].
	Non-Invasive Brain Stimulation (tDCS/ TMS)	Modulates cortical excitability and synaptic plasticity.	Enhanced upper-limb function when combined with CIMT [42,43].
Pharmacological & Molecular Interventions	Ampakines (e.g., CX717)	Positive allosteric modulators of AMPA receptors enhancing glutamatergic transmission and LTP.	Preclinical and phase 2 human trials show safety and pathway engagement [44,45].
	Antagonism of Growth Repressors (PTEN, SOCS3)	Removes molecular brakes on axonal growth and regeneration.	Rodent models demonstrate axonal regrowth; human data pending [46].
Cell-Based & Bioengineering Approaches	Neural Stem Cell Transplantation	Provides new cells for circuit integration and neurotrophic support.	Animal models show restoration; phase I/ II human trials show preliminary efficacy [47,48].
	Biomaterial Scaffolds	Provides substrate and cues for axonal regeneration across lesions.	Supports synaptogenesis and reconnection post-injury [49].
Neuromodulation & Technology-Based	Optogenetics/ Chemogenetics (DREADDs)	Enables precise control of neuronal populations for circuit rewiring.	Optogenetic stimulation improves recovery; DREADDs suitable for long-term modulation [35,37].

Challenges and Future Directions:

Despite remarkable progress, several key challenges remain in harnessing synaptic plasticity and circuit rewiring for functional recovery after CNS injury. One major barrier is distinguishing adaptive from maladaptive plasticity. While synaptic remodeling can restore function, it may also reinforce aberrant networks, leading to spasticity, pain, or epilepsy [50]. Functional imaging and electrophysiological readouts must evolve to discriminate between beneficial and detrimental rewiring at both microcircuit and network levels.

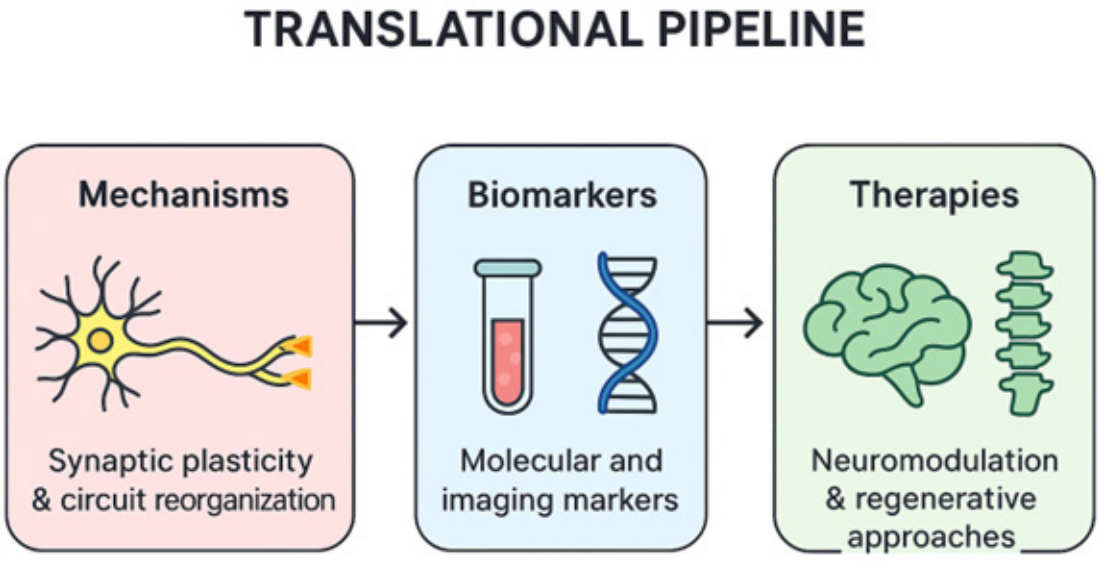


Figure 4: Translational Pipeline Linking Mechanisms, Biomarkers, and Therapeutic Strategies in CNS Injury.

Figure 4: Translational Pipeline Linking Mechanisms, Biomarkers, and Therapeutic Strategies in CNS Injury:

Conceptual diagram illustrating the translational continuum from mechanistic discovery to clinical intervention in central nervous system (CNS) injury recovery. The first stage (Mechanisms) encompasses molecular and cellular processes such as synaptic plasticity, dendritic spine remodeling, and circuit reorganization that underlie adaptive or maladaptive responses. The second stage (Biomarkers) represents molecular, electrophysiological, and neuroimaging indicators (such as BDNF expression, theta–gamma coupling, and functional connectivity metrics) that quantify neuroplasticity and predict recovery outcomes. The third stage (Therapies) integrates these mechanistic and biomarker insights into targeted interventions, including neuromodulation (e.g., tDCS, TMS, optogenetics), pharmacological modulation of growth pathways, and regenerative or cell-based therapies. This translational framework emphasizes the

bidirectional flow of information between fundamental research and clinical practice to achieve precision neurorehabilitation.

Longitudinal tracking of circuit function in humans presents another formidable challenge. Although advances in high-resolution fMRI, magnetoencephalography, and neural interface technologies (e.g., ECoG arrays) are improving temporal and spatial resolution, the dynamic nature of post-injury reorganization demands better real-time, non-invasive monitoring tools[51]. Multi-modal integration of imaging, electrophysiology, and behavioral data will be essential for mapping recovery trajectories.

Sex differences, aging, and comorbidities represent understudied yet critical variables. Aging brains exhibit attenuated plasticity, altered inflammatory responses, and increased oxidative stress, which constrain regenerative potential [52]. Additionally, hormonal and genetic differences influence neurotrophic signaling and synaptic modulation in males versus females, suggesting that individualized therapeutic strategies may be warranted.

Finally, ethical considerations must guide the deployment of invasive or enhancement-based interventions, such as deep brain stimulation or gene editing. Questions around autonomy, informed consent, and unintended consequences in cognitively impaired patients need robust ethical frameworks, especially as neuromodulation becomes increasingly personalized and powerful.

Conclusion:

Synaptic plasticity and circuit rewiring are fundamental mechanisms underlying functional recovery after central nervous system injury. Evidence across molecular, cellular, and systems levels demonstrates that adaptive reorganization of synapses and networks can partially restore lost functions, while maladaptive plasticity may contribute to chronic neurological complications. Advances in neurotechnology, including optogenetics, single-cell transcriptomics, and longitudinal imaging, are rapidly refining our understanding of these processes. Integrating these mechanistic insights with targeted neuromodulation, pharmacological strategies, and rehabilitation frameworks offers a promising path toward precision neurorehabilitation. Continued emphasis on multiscale integration, patient heterogeneity, and ethical implementation will be essential for successful clinical translation.

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