



NEUROPLASTICITY AFTER BRAIN INJURY: CELLULAR MECHANISMS AND THERAPEUTIC OPPORTUNITIES

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Abstract: Neuroplasticity is the capacity of the central nervous system to modify synaptic strength, neuronal structure, and functional networks in response to experience or injury. Following acquired brain injury, including ischemic stroke, traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, and hypoxic-ischemic injury, neuroplastic mechanisms support partial recovery of neurological functions through synaptic remodeling, dendritic spine turnover, axonal sprouting, cortical reorganization, and glial responses. These processes are regulated by molecular pathways involving BDNF/TrkB signaling, neurotransmitter-dependent changes in excitability, inflammatory responses, and extracellular inhibitors of axonal growth. Rehabilitation exploits these mechanisms through repetitive, task-specific training, while neuromodulation, robotics, virtual reality, brain-computer interfaces, and biological therapies provide additional approaches. Artificial intelligence may further improve recovery prediction and personalization of rehabilitation. However, substantial variability between patients, limitations of experimental models, maladaptive plasticity, and difficulties in measuring cellular processes in humans remain major challenges. This review summarizes the principal cellular mechanisms of post-injury neuroplasticity and



evaluates current and emerging therapeutic strategies for promoting functional neurological recovery.

Keywords: *Neuroplasticity; Brain injury; Stroke; Synaptic plasticity; BDNF; Neurorehabilitation; Brain-computer interface*

1. Cellular and Functional Basis of Neuroplasticity

Neuroplasticity occurs at several levels, from molecular modifications of individual synapses to large-scale reorganization of functional brain networks. Three major forms are particularly relevant after brain injury: synaptic plasticity, structural plasticity, and functional reorganization (Cramer et al., 2011; Kleim & Jones, 2008).

Synaptic plasticity involves persistent changes in synaptic strength. Long-term potentiation (LTP) strengthens synaptic transmission, whereas long-term depression (LTD) reduces it. Classical LTP involves NMDA receptor activation, Ca^{2+} influx, and activation of signaling molecules such as CaMKII and PKC, which increase AMPA receptor function and trafficking to the postsynaptic membrane. LTD is associated with lower, sustained Ca^{2+} signaling and activation of phosphatases that promote AMPA receptor internalization (Malenka & Bear, 2004). These mechanisms allow surviving neural circuits to modify their responses according to patterns of activity.

Structural plasticity involves the formation and remodeling of synapses, dendritic spines, and axonal branches. After injury, surviving neurons can undergo increased spine turnover and synaptogenesis, particularly within peri-injury regions. Axonal sprouting allows surviving axons to form collateral connections with previously denervated targets (Murphy & Corbett, 2009; Benowitz & Carmichael, 2010).

Functional reorganization changes the distribution of neural activity across existing networks. Latent pathways can become functionally active, while adjacent or contralateral cortical regions may contribute to functions previously controlled by damaged areas. Motor-map studies demonstrated that intensive task-



specific training can expand functional representations within surviving cortex, supporting the principle that experience shapes recovery (Nudo et al., 1996).

Adult neurogenesis may also contribute to recovery, particularly within the subventricular zone and hippocampal dentate gyrus. Brain injury can temporarily increase progenitor proliferation and migration, but the extent to which newly generated neurons provide durable functional replacement in humans remains limited and uncertain (Zhao et al., 2008).

2. Molecular and Glial Mechanisms

Neuroplasticity after injury depends on interactions between neurons, astrocytes, microglia, oligodendrocyte precursor cells, extracellular matrix molecules, and neurotrophic factors.

Neuronal activity induces immediate early genes such as c-Fos, Egr1, and Arc, which regulate activity-dependent changes in synapses and neuronal structure. Growth-associated proteins such as GAP-43 contribute to axonal remodeling and synaptogenesis (Benowitz & Carmichael, 2010).

BDNF/TrkB signaling is one of the major molecular systems supporting neuroplasticity. Binding of BDNF to TrkB activates MAPK/ERK, PI3K/Akt, and PLC γ pathways, promoting neuronal survival, synaptic modification, dendritic growth, and gene transcription. Genetic variation in BDNF, including the Val66Met polymorphism, can modify activity-dependent BDNF secretion and has been associated with differences in plastic responses (Lu et al., 2013).

Glial cells have equally important roles. Astrocytes maintain extracellular ion and neurotransmitter concentrations, support metabolism, regulate neurovascular coupling, and contribute to blood-brain barrier repair. After injury, reactive astrogliosis helps isolate damaged tissue and limit secondary injury. However, chronic reactive astrocytes and extracellular matrix components, particularly chondroitin sulfate proteoglycans (CSPGs), can inhibit axonal growth (Sofroniew & Vinters, 2010; Silver & Miller, 2004).



Microglia respond rapidly to injury and participate in inflammation, debris clearance, and synaptic remodeling. Their effects are highly context-dependent: inflammatory signaling can worsen secondary injury, whereas phagocytosis and tissue-remodeling responses can support recovery. Microglia can also remove dysfunctional synapses through complement-associated mechanisms.

Oligodendrocyte precursor cells (OPCs) proliferate after injury and may differentiate into mature oligodendrocytes, supporting remyelination and restoration of conduction along damaged axons. Thus, white-matter remodeling represents an important component of functional recovery (Carmichael, 2016).

Neural plasticity is also influenced by the balance between excitation and inhibition. After the acute excitotoxic phase, transient changes in inhibitory signaling can create a more permissive environment for activity-dependent remodeling. Dopamine, norepinephrine, and serotonin further modulate cortical excitability, attention, motivation, and motor learning.

At the same time, molecules such as Nogo-A, MAG, and OMgp inhibit axonal growth in the adult CNS. Their signaling through receptor complexes involving NgR1 can activate the RhoA/ROCK pathway, which alters the actin cytoskeleton and restricts axonal extension. Inhibition of these pathways is therefore being investigated as a strategy to increase structural plasticity (Benowitz & Carmichael, 2010).

3. Neuroplasticity Across Different Brain Injuries

Although common mechanisms are involved, the potential for functional reorganization differs according to the type, location, and extent of brain injury.

Ischemic stroke produces focal tissue damage with surrounding peri-infarct regions that may retain viable neural structures. Recovery therefore depends strongly on local synaptic remodeling, axonal sprouting, and cortical reorganization. The relatively preserved architecture around the lesion provides an important substrate for rehabilitation-induced plasticity (Murphy & Corbett, 2009; Carmichael, 2016).



Traumatic brain injury (TBI) may combine focal contusions with diffuse axonal injury. Damage to long white-matter pathways can disrupt communication between distant brain regions, making recovery dependent on both local adaptation and reorganization of distributed networks. Persistent neuroinflammation may further influence long-term recovery.

Intracerebral hemorrhage (ICH) causes primary tissue damage through hematoma formation and mass effect, followed by secondary injury associated with edema and blood-derived products. As the hematoma is gradually cleared, surviving perihematomal tissue may participate in functional reorganization.

Subarachnoid hemorrhage (SAH) can produce widespread disturbances through elevated intracranial pressure, vascular dysfunction, delayed cerebral ischemia, and cortical spreading depolarizations. These processes can interfere with metabolic stability and synaptic function, creating additional barriers to recovery.

Hypoxic-ischemic brain injury (HIBI) differs because the initial insult is global rather than focal. Selective vulnerability of structures such as hippocampal neurons, cerebellar Purkinje cells, and deep gray matter can produce widespread network dysfunction. Because fewer intact cortical regions are available to compensate for lost functions, recovery may depend heavily on surviving distributed networks and long-term functional adaptation.

4. Therapeutic Strategies to Harness Neuroplasticity

The clinical goal of neurorehabilitation is not simply to increase neural activity but to direct plasticity toward useful functional behaviors. Rehabilitation is therefore based on principles of repetition, specificity, progressive challenge, and meaningful practice (Kleim & Jones, 2008).

Constraint-induced movement therapy (CIMT) is an established approach for selected patients with upper-extremity impairment after stroke. It combines intensive use of the affected limb with restriction of the less-affected limb, reducing learned non-use and encouraging functional motor practice. The EXCITE trial demonstrated



sustained improvements in selected stroke patients receiving CIMT (Wolf et al., 2006).

Task-specific training focuses on repeated practice of meaningful activities rather than isolated movements. Aerobic exercise may complement rehabilitation by influencing neurotrophic signaling and cardiovascular function. Cognitive rehabilitation similarly applies repeated, structured practice to attention, memory, and executive networks.

Non-invasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS), can modify cortical excitability and may enhance rehabilitation in selected patients. rTMS can be directed toward either the affected or contralateral hemisphere depending on the individual pattern of cortical excitability, while tDCS can modulate activity during behavioral training. Clinical effects are dependent on stimulation parameters, lesion characteristics, and patient selection (Lefaucheur et al., 2020).

Technology-assisted rehabilitation provides additional opportunities for high-dose and precisely measured practice. Robotic systems can deliver large numbers of reproducible movements and adjust assistance according to performance. Virtual reality provides interactive environments with immediate feedback and opportunities for repeated task practice. These technologies are most effective when integrated with active, goal-directed rehabilitation rather than used as passive substitutes for therapy (Lo et al., 2010).

Brain-computer interfaces (BCIs) create a direct link between neural activity and external devices. EEG-based systems can detect motor intention and control robotic devices or functional electrical stimulation. By pairing cortical motor activity with appropriate sensory feedback, closed-loop BCIs may strengthen task-relevant neural connections and provide opportunities for patients with severe motor impairment (Chaudhary et al., 2016).

Biological approaches remain largely investigational. Anti-Nogo-A strategies and enzymatic modification of CSPGs aim to remove molecular barriers



to axonal growth. Stem-cell-based therapies, particularly mesenchymal and neural progenitor approaches, are increasingly understood as potentially acting through paracrine signaling rather than direct replacement of lost neurons. Extracellular vesicles and gene-based therapies are also being investigated as methods of modifying inflammatory and neurotrophic pathways. These approaches have shown promising experimental results but require further clinical validation before routine use (Goldman, 2016).

5. AI, Personalization, and Future Directions

A major limitation of conventional rehabilitation is the substantial heterogeneity of recovery between patients. Artificial intelligence and machine learning may help address this problem by integrating clinical, imaging, physiological, and behavioral data to estimate individual recovery trajectories.

Prediction frameworks such as PREP2 combine early motor assessment with measures of corticospinal tract integrity to classify patients according to expected recovery potential (Stinear et al., 2020). More advanced machine-learning approaches can incorporate MRI, diffusion imaging, functional connectivity, electrophysiological measurements, and longitudinal clinical data.

Computer vision also enables automated analysis of movement. Markerless systems can quantify joint trajectories, movement speed, range of motion, and compensatory patterns without requiring extensive wearable equipment. These measurements could allow rehabilitation systems to adapt difficulty and assistance continuously according to patient performance.

AI may further support closed-loop rehabilitation by integrating physiological signals with robotics, virtual reality, and BCIs. Multimodal systems combining imaging, EEG, TMS-derived measures, wearable sensors, and clinical assessments could eventually identify which intervention is most appropriate for a particular patient and when it should be delivered.

Several major challenges remain. Human neuroplasticity is difficult to measure directly because techniques such as fMRI and EEG provide indirect



measures of cellular processes. Animal models provide important mechanistic information but do not fully reproduce the complexity, age distribution, and comorbidities of human patients (Ward, 2017). In addition, increased neural activity or axonal sprouting does not necessarily produce useful functional recovery. Plasticity can become maladaptive when compensatory behaviors or abnormal network activity are reinforced.

Future research should therefore focus on biomarker-guided rehabilitation, optimized treatment timing and dose, multimodal interventions, and longitudinal monitoring. Combining biological priming with intensive behavioral training and adaptive technologies may be more effective than targeting individual mechanisms independently.

Conclusion

Neuroplasticity provides the biological foundation for neurological recovery after brain injury. Synaptic remodeling, dendritic restructuring, axonal sprouting, cortical reorganization, neurotrophic signaling, and glial responses allow surviving neural networks to adapt following structural damage. However, these mechanisms are influenced by injury type, lesion location, age, systemic health, rehabilitation intensity, and molecular inhibitors of axonal growth.

Current rehabilitation strategies, particularly task-specific training and selected forms of CIMT, demonstrate that experience can shape functional reorganization. Neuromodulation, robotics, virtual reality, and BCIs provide additional tools for increasing the precision and intensity of rehabilitation, while cellular, molecular, and gene-based approaches remain promising experimental strategies.

The next stage of neurorehabilitation will likely depend on personalization. Integrating biomarkers, neuroimaging, electrophysiology, wearable sensors, and AI-based prediction could allow treatment to be matched to individual biological recovery potential. The central challenge is therefore not simply to increase



neuroplasticity, but to direct plasticity toward stable, meaningful, and functionally beneficial neural reorganization.

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