Journal of Medical Sciences and Health Care Research

PRIME OPEN ACCESS

Volume 2, Issue 1

Research Article

Date of Submission: 25 January, 2025
Date of Acceptance: 20, March, 2025
Date of Publication: 27 March, 2025

Neurogenesis and Neuroplasticity in Brain Injury Recovery: Mechanisms and Therapeutic Implications

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Citation: Hamza, N. (2025). Neurogenesis and Neuroplasticity in Brain Injury Recovery: Mechanisms and Therapeutic Implications. *J Med Sci Health Care Res, 2*(1), 01-07.

Abstract

Recovery from brain injury is a dynamic process driven by the synergistic mechanisms of neurogenesis and neuroplasticity. Neurogenesis, the generation of new neurons from neural stem cells, plays a very key role in restoring damaged neural circuits, especially within the hippocampus. Simultaneously, neuroplasticity allows for the reorganization of synaptic connections in the brain and the redistribution of functional tasks to intact parts of the brain, allowing for adaptive recovery. The review comprehensively analyzes these two processes, their interaction, and the therapeutic implications in the recovery after brain injury. Key mechanisms of neurogenesis are discussed in view of experimental findings and difficulties of translation to human clinical contexts. Neuroplasticity is approached according to synaptic plasticity and cortical reorganization, emphasizing its contribution to both short-term and long-term functional recovery.

The interaction of neurogenesis with neuroplasticityis discussed, focusing on how these processes restore brain functions complementarily. Therapeutic approaches, including pharmacological interventions such as growth factors and neuroprotective drugs, and non-pharmacological therapies like cognitive rehabilitation and brain stimulation, are reviewed. Emerging strategies include gene editing and stem cell therapy, along with ethical and translational challenges. This review highlights several critical gaps in the literature at present and seeks to drive future research through translational human clinical trials to bridge basic experimental findings toward clinical applications. This review sets the stage for future priorities in developing brain injury therapies.

Keywords: Neurogenesis, Neuroplasticity, Brain Injury Recovery, Neural Stem Cells, Hippocampus, Synaptic Plasticity, Cortical Reorganization, Growth Factors, Neuroprotective Drugs, Cognitive Rehabilitation, Brain Stimulation, Gene Editing, Stem Cell Therapy, Translational Challenges and Therapeutic Innovation

Introduction

Neurogenesis is the process of generating new neurons from neural stem cells, primarily occurring in specific brain regions such as the sub granular zone of the dentate gyrus and the subventricular zone of the lateral ventricle. Recent research has highlighted its significance in the adult brains, challenging the long-held belief that neurogenesisceases after early development [1]. This process of forming neural stem cells is crucial is the brain formation from embryonic stages to adulthood, impacting the plasticity and the disease state in humans [2].

Neurogenesis is also a regulator technique in the brain, preventing overfitting and promoting the generalization in a category learning task [3]. It is assumed that in the process of neurogenesis, some phases such as proliferation and the creation would consist in quantum coherent states in the sense that the formation of the new neurons might be synchronized. Thus, ion dependence formalism of the quantum mechanics is formulated, with an emphasis on the usage of the evolution operator Hamiltonian governed by Coulomb forces [4].

Neuroplasticity refers to the ability of the central nervous system (CNS) to undergo structural and functional changes in

response to experiences, learning and environmental factors enabling the functions such as adaptations and recovery [5]. It is the ability to reorganize its neurons and form new neuronal connections based on life experiences. This also allows us to form cultural and spiritual development and recovery from the neurological conditions affecting senses, movements or cognitive functions [6].

Neurogenesis and neuroplasticity are fundamental mechanisms in the process of recovery in brain injuries. Together they play a role in the restoration of the brain function, offering potential therapeutic targets for patients with neurological damage and disorders.

This review aims to provide a comprehensive understanding of the mechanisms, interactions, and therapeutic implications of neurogenesis and neuroplasticity in brain injury recovery. By synthesizing current experimental findings, addressing translational challenges, and exploring emerging therapeutic approaches, the review seeks to bridge the gap between basic neuroscience research and clinical applications.

Neurogenesis in Brain Injury Recovery

Several mechanisms are involved in neurogenesis during the repair of the brain after an injury. In areas like the subventricular zone (SVZ) and hippocampal subgranular zone (SGZ), neural stem cells (NSC) differentiate to form neuroblasts and they proliferate and migrate to form new neurons [7]. Endothelial cells, astrocytes, neurons are the building blocks of the neurovascular units (NVU) which synchronize to create an environment for neuroblast migration and differentiation. The process is supported by two growth factors which are the stromal- derived growth factor 1 (SDF1), Angiopoietin-1 (Ang1) [8]. Other stimuli of neurogenesis include exercise and an enriched environment, bone morphogenetic protein (BMP) and ENT signaling also regulates NSC proliferation and differentiation. Research on animal models of brain injury demonstrated that neurogenesis is important in the process of brain injury treatment. It also showed the association between the neurogenesis in the hippocampus and cognitive function improvement in rats with TBI [9]. Stroke also induces neurogenesis where the neuroblastsmigrate from the SVZ to the ischemic region also leads to better recovery. Medications like Erythropoietin (EPO), statins, and sildenafil have also been found to increase the neurogenesis and neuroplasticity [10]. Other animal model researches such as controlled cortical impact (CCI) and fluid percussion injury (FPI) has shown that the progenitor cell proliferation increases and the cognitive function improves through the use of growth factors including fibroblast growth factor-2 (FGF-2) and brain- derived neurotrophic factor (BDNF). There has been some inconsistency in the survival and incorporation of new neurons; where some new neurons don't get incorporated properly in to the existing networks even though the results at the beginning was very promising [11-15].

Translating the experimental findings into human therapies is a challenging but a promising step. One of the many challenges in this is the complexity of the human brain's microenvironment, as an example: neuroinflammation and disruption of the blood brain barrier that interrupt neuron integration. Neurogenesis on the other hand is limited as well, especially in older people as compared to the other animal models. This decreased neurogenetic capacity leads to inefficient recovery. Moreover, regarding safety concerns high EPO can cause high hematocrit value and even if normohematopetic EPO analogues such as CEPO have a similar effect as the hematopoietic EPO, it still requires more clinical trial validation [16]. Stem cell therapies with neural stem/ progenitor cells (NSPCs) showed promise based on preclinical research but lack clinical confirmation.

On the other hand, embryonic stem cells have several issues regarding their ethics and safety, including tumorigenicity and means of delivery. In addition, most of the newly formed neurons do not survive or fail to incorporate properly into the neural networks and incorrect migration can cause complications such as seizures. Problems with a variability of the neurogenic responses and the issues regarding the timing and delivery of the treatments, including growth factors like FGF-2, also affect clinical use. To solve these problems, developed strategies and insights on how to enhance neurogenesis for the treatment of brain injury in humans are needed [17].

Neuroplasticity in Brain Injury Recovery

The term neuroplasticity refers to the ability of the brain to adapt, self-recognize and form new neuronal connections under circumstances such as injury, learning or environment. One of the main mechanisms involved in this is the synaptic plasticity, were the strength of the synapses increases or decreases according to the amount of activity in it, Structural plasticity on the other hand is the physical change seen in the structure of the neurons like the dendritic growth, axonal branching, synthesis of new synapses. Neurogenesis also plays a crucial role here in replacing the lost cells with newly formed ones in particular regions. Other mechanisms include long term potentiation (LTP) and long-term depression (LTD) which determine the effectiveness of the synapses over time. The adjustment of synaptic strength and neuronal growth is guided by many neuromodulators for example, e, dopamine, acetylcholine, and serotonin. These mechanisms in turn help the brain in recovering from injuries as they help the affected networks to be reconstructed or avoided. Nevertheless, it must be noted that neuroplasticity has its limits; it is conditional and can be modulated by several factors including age, heritage, and environment [18, 19].

By creating new neural pathways, neuroplasticity helps the brain make up for lost functions in functional recovery following a traumatic brain injury. The initial degree of plasticity following an injury results in temporary adjustments

such as synaptic strengthening andrelease of neurotransmitters to help with the initial recovery and create temporary circuits. A sustained functional recovery is eventually established by structural alterations such as axonal elongation and the creation of new circuits made possible by long-term plasticity.

It has been observed that in people who have had a stroke or severe brain injury, the other portions of the brain that are not harmed will often take up the functions of the damaged areas. Rehabilitation techniques such as repetitive task training (RTT) and constraint-induced movement therapy (CIMT) utilize neuroplasticity to bring about these changes and improv ethe motor functions[20, 21]. Through the aid of rehabilitation therapy, the brain is also encouraged to correct the maladaptive plasticity [22, 23]. The other methods of neuromodulations include the use of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS) which are also used to improve the plasticity through manipulation of neural activity [24-26].

Neuroplasticity is isolated into two categories based on the time outline they act on, short-term and long-term versatility. Short-term versatility conveys prompt brief changes inside many minutes to days after the harm. For occurrence, unmasking unused and auxiliary circuits or fortifying as of now set up neural connections. These alterations empower the brain to adjust to the misfortune of capacities but are frequently brief and lacking for a full recuperation. On the other hand, long-term versatility includes more solid changes, which are the stabilization of unused neural connections, dendritic development, and reorganization of cortical maps. These forms are set up from weeks to a long time and are fundamental for a more total recovery.

For occasion, LTP is included within the combination of learning and memory whereas axonal growing is included in engine recuperation. Factors such as age, wellbeing, and time of intercession can modify the ratio between short-term and long-term versatility. There are approaches to preserve neural actuation over time in recovery programs which in turn enhance long-term versatility and other medications counting neurotrophic figure treatments and anti-inflammatory specialists. This should be worn out arrange to upgrade the recuperation handle and at the same time upgrade the lasting useful recuperation [27].

Pathology	Drug	In vivo/ In vitro	Function of mechanism	Target	References
TBI	EPO	In vivo (Rats)	Promotes neurogenesis, enhances spatial memory restoration, induces differentiation of neural progenitor cells, and prevents apoptosis.	Dentate gyrus (DG) in the hippocampus	(9)
Focal Cerebral Ischemia	Sildenafil	In vivo (Rats)	Inhibits PDE5 to increase cGMP levels, enhancing neurogenesis in the subventricular zone (SVZ) of aged rats.	PDE5 (Phosphodiesterase 5)	(28)
Stroke	Atorvastatin	In vivo (Rats)	Increases angiogenesis, promotes endothelial cell proliferation, migration, and vascular stabilization. Decreases blood-brain barrier (BBB) permeability.	eNOS, VEGF–VEGFR2, PI3K–AKT pathway	(29)
TBI	BDNF	In vivo (Rats)	Promoted survival of immature neurons; infusion increased BrdU-positive neurons and ectopic localization in the hippocampus.	Neural progenitor cells	(30)
CCI	FGF-2	In vivo (Rats)	Increased neurogenesis: knockout mice had reduced BrdU-positive neurons, while overexpression increased dividing cells.	Neural progenitor cells	(30)

Endothelial Nitric Oxide Synthase (ENOS); Vascular Endothelial Growth Factor [VEGF]; Vascular Endothelial Growth Factor Receptor 2 (VEGFR2); Phosphatidylinositol 3-Kinase–Protein Kinase B (PI3K–AKT); bromodeoxyuridine (BRDU).

Table 1: Representing the Pathologies and the Testing Models with the Respective Drugs

Interplay Between Neurogenesis and Neuroplasticity

Neurogenesis refers to the changes in the brain and includes synaptic plasticity which is the long-term change in the strength of the synapses as a function of the neural activity and changes in the efficiency of the connections between neurons [31, 32]. Specifically, Long Term Depression (LTD) is a process that reduces the strength of the synapse through decreasing the sensitivity of receptors for neurotransmitters, on the hand Long Term Potentiation (LTP) enhances the synapses by increasing the number of neurotransmitters released and the strength of the synapses. It also includes structural plasticity which is the creation of new brain networks and synapses, as well as physical changes in the neural circuits such as axonal sprouting, dendritic remodeling and neurogenesis [33].

Axonal sprouting is the extension of new axonal tips, while dendritic remodeling refers to the change in the dendritic length and complexity [34]. The modifications in the organization of the brain circuits are referred to as functional plasticity. This involves cortical remodeling where it is possible for the brain to rewrite its sensory maps in responseto experience or injury. To maintain the homeostasis of the nervous system the processes of ion channel density, neurotransmitter release and receptor sensitivity are modulated over a period. Activity dependent myelination is a critical factor in the neuronal conduction and may be disrupted in neurological disorders [35]. The capacity of an animal to learn also enhances the survival and integration of new neurons thus implying that learning can also enhance the brain's ability to heal [36].

The incorporation of new neurons into the hippocampus with the existing neurons can also enhance the plasticity which is important in cognition such as memory and learning and these are often affected in the brain damage [36]. Neurotrophic factors include Brain derived neurotrophic factor (BDNF) which is increased during exercise and environmental enrichment, which support the neurogenesis and synaptic plasticity [37]. BDNF also enhances synaptogenesis and the function of the existing synapses. Since the neurogenesis and the synaptic plasticity are interrelated, it shows that the new neurons are being incorporated into the functional networks during the rhythmic electrophysiological activity hence, treatments that enhance the brain's natural oscillations may be beneficial. Survival depends on the timing of neurogenesis and incorporation of new neurons into existing circuits [35, 38].

Newborn neurons are most sensitive to the possibility of rescue in the context of learning between the age of one and two weeks. Also, the peri-infarct area of an injury is a region of structural and functional plasticity for weeks following an injury [39]. Among injuries the most important factors that affect the ability of the brain to change are the experience, and especially the learning of new skills, including motor skills. Such activities involve the creation of new motor skills which in turn alters neurophysiology and neuroanatomy. Although neurogenesis is a process of 'use it or lose it' type many of the new cells that are formed die if they are not engaged, thus it is necessary ty work on the new neurons and engage in neuroplasticity for a long time and focus after the brain injury [36]. Not all neuroplasticity has positive implications. When compensatory mechanisms unintentionally interfere with proper healing, they may become maladaptive and maladaptive plasticity can therefore hinder the best possible recovery [18].

Therapeutic Implications

The brain, for example of good recovery and rehabilitation for those with neurological conditions, such as stroke, traumatic brain injury (TBI), and neurodegenerative disorders, relies for the most part on neuroplasticity. This is the brain's ability to reorganize and adapt. Neuroplasticity, which denotes the brain's ability to exchange its shape by building new neural links, the individuals feel as the main component of the recovery process. The authors, in their article, describe treatments that show great promise due to their use of this pliability and the increase in patient results.

A new kind of neuroplasticity is inducing high-volume physical activity and mental fitness, whose action to increase the production of neurotrophic substances such as BDNF is certified. Changes in the way we eat, especially those containing omega-3 fats and antioxidants are ways to which we can protect and heal the brain [40, 41]. Based on a study conducted it was proved the use of individually tailored treatment strategies that would use multimodal therapy strategies involving pharmacological, technical and rehabilitation treatments designed for the patient's unique and personal needs are very crucial. Despite the use of early strategies of drug administration, further excessive clinical trials are needed to be done to confirm the effectiveness of these treatment strategies [41].

Cognitive rehabilitation plays a crucial role in enhancing neuroplasticity and neurogenesis, particularly in individuals with neurological injuries or diseases. This leverages these processes to restore or improve cognitive functions such as memory, attention, and problem- solving skills. This approach is beneficial in conditions like TBI (Traumatic Brain Injury), stroke, and neurodegenerative diseases. It involves a combination of cognitive and behavioral strategies tailored to enhance specific cognitive abilities [42]. Techniques like physical therapy and occupational therapy can be helpful in enhancing the neuroplasticity and allowing the formation and strengthening of synapses [43]. Clinical cases of TBI patients demonstrated the effectiveness of neurorehabilitation in improving motor and cognitive functions through neuroplasticity. Integration of these therapeutic approaches is recommended to optimize the recovery outcomes in patients with neurological injuries [43]. While it is a very important tool in the neuroplasticity and neurogenesis, it is important to consider the individual variability of these interventions. Therefore, personalized treatment plans are crucial to maximize the benefits of cognitive rehabilitation in promoting brain recovery and function.

Practices like mindfulness meditation decrease the levels of stress and let go of any emotional stress, because of the activation of a healthier operating set of neural networks [44, 45]. The constant practice of definitive cognitive or maybe motor activity can also strengthen the neural connections that can in turn lead to plasticity and performance improvement [46].

Aerobic activity, resistance training, lifestyle changes, and technological advancements play significant roles in enhancing neuroplasticity and neurogenesis. These interventions contribute to the brain's ability to adapt and reorganize itself, which is crucial for learning, memory, and overall cognitive health. Each of these factors influences the brain through various mechanisms, promoting both structural and functional changes. Aerobic exercises induce changes in the blood flow, hormonal control and growth factor expression, which are cortical in neuroplasticity and neurogenesis. Regular aerobic exercise has shown to slow cognitive deficit and has a role as a neuroprotectant especially in aging populations [47].

While not explicitly detailed in the provided contexts, resistance training is known to complement aerobic exercise by improving muscle strength and endurance, which indirectly supports brain health through increased physical fitness and reduced risk of cognitive decline. Modifiable changes in lifestyle like diet, mental engagement and physical activity are crucial in maintaining brain health especially during aging. These factors can modulate neuroplasticity substrates like BDNP which are vital [48].

Pharmaceutical interventions are increasingly recognized for their potential to enhance recovery from neurological conditions, particularly after events like stroke and brain injuries. These interventions target various neurotransmitter systems and neurotrophic pathways to promote brain repair and functional recovery. The following sections outline key pharmaceutical strategies currently under investigation or in clinical use. Antidepressants share a mechanism of downstream of pharmacological drug targets. Rapidly acting antidepressants such as ketamine have a very vast clinical potential in directly targeting neurotrophic signaling pathways. Treatments that target synaptic potential can restore functional synaptic connections in stress sensitive neural circuits to improve mood regulation and cognitive function. Targets to the glutamatergic system currently seem to be the most promising area of novel drug discovery and development. Other systems such as the cholinergic and inflammatory systems are gaining traction as well. While cellular and animal studies have provided exquisite insights into the molecular mechanisms that influence plasticity, ongoing work demonstrating the therapeutic impact of targeting these mechanisms with neuromodulation, pharmacological, and/or behavioral interventions in human subjects is needed [49].

Drugs like D-amphetamine, Levodopa, Fluoxetine, Niacin, Inosine, and Citicoline, which aim to enhance motor recovery and support neuronal growth, although their precise mechanisms and effectiveness vary across studies. D-amphetamine shows mixed results in enhancing motor recovery. Levodopa has promised to improve the motor function post stroke. Fluoxetine has neuroprotective effects, but it has mixed results over clinical trials. Niacin may improve the motor and sensory functions and behaviors, but it lacks human data. Inosine promotes axon sprouting and motor function recovery in animal studies. Citicoline has shown potential in reducing infarct volume and improving recovery. Stem cell therapy has shown promise in the post stroke recovery process. Various stem cells have shown benefits in restoring neuronal functions. Clinical trials indicate improved motor function with higher doses of stem cells. Complications and the accurate dosing remain a quite significant challenge [50].

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS) are non-invasive methods that can modulate cortical excitability and thus, give hope for the restoration of mobility and the recovery of speech in the case of stroke patients [51]. Deep brain stimulation (DBS) is one of the ways used for disorders like Parkinson's where the person undergoes a treatment that involves the focused stimulation of certain parts of the brain to better his or her motor and cognitive functions [52]. Intensive rehabilitation therapies such as constraint-induced movement therapy are the most efficient methods for motor and functional recovery, and they lead to changes in the functioning of the cortex due to activation, thus, become the most common mode of rehabilitation nowadays [41].

Challenges and Future Directions

The challenges regarding neuroplasticity and neurogenesis research are limited translational success despite the promising clinical data the translation into the clinical practice faces many hurdles. These include the species- specific difference in neurobiology and the complex microenvironment of the injured human brain. Stem cell therapies raise various ethical issues regarding the sourcing and use as well as the tumorgenicity and the immune reaction from the stem cells. Achieving precise regulation is often challenging particularly in identifying the optimal therapeutic window and ensuring the targeted effects without adverse consequences such as aberrant neural connections or maladaptive plasticity. The variability in brain injury mechanisms, severity, and affected regions complicates the development of universal therapeutic strategies.

Developing advanced models that can resemble human injuries will be a bridge that can gap between preclinical findings and clinical applications. Efforts should focus on improving cell survival, integration and functional outcomes through innovative delivery methods and bioengineering techniques. Identifying biomarkers to track the process of neurogenesis and neuroplasticity in real time can lead to efficient monitoring and personalized medicine. Combination therapy with

stem cells, neurotrophic factors, and rehabilitation strategies may enhance therapeutic outcomes. Techniques in neurotechnology like brain – computer devices or interfaces, transcranial magnetic stimulation and optogenetics could complement very well with the biological therapies, promoting functional recovery through targeted neural modulation.

Conclusion

The interplay between neurogenesis and neuroplasticity holds great potential in promoting brain recovery after injury. Advances in stem cell therapy, neurotrophic factors and neurorehabilitation highlight the potential to repair and rewire neural circuits. However, significant challenges remain to be addressed, including translational barriers, safety concerns, and injury-specific complexities. Future research must focus on refining treatment strategies, personalizing interventions, and leveraging multidisciplinary innovation to transform our understanding of recovery from traumatic brain injury and translate it into tangible clinical benefit. The therapeutic potential of neurogenesis and neuroplasticity remains a beacon of hope for millions of people affected by traumatic brain injury worldwide.

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