UAD Universitas Ahmad Dahlan

Ahmad Dahlan Medical Journal
VOL 5, No. 2, 205-219
http:// http://journal2.uad.ac.id/index.php/admj

Literature Review

Emerging Neuroplasticity-based Therapies in Stroke Rehabilitation: Literature Review

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ARTICLE INFO

Article history
Received 26 Sep 24
Revised 05 Des 24
Accepted 16 Des 24

Keywords
neuroplasticity,
stroke, mechanisms,
emerging therapies

ABSTRACT

Stroke is a significant global health concern, leading to substantial mortality and long-term disability among survivors. Traditionally, stroke rehabilitation has focused on compensatory strategies to mitigate the effects of impairments rather than addressing their root causes. However, growing recognition of the brain's capacity for neuroplasticity a process involving the brain's ability to reorganize itself in response to injury has prompted a paradigm shift. A literature search of electronic database were performed and relevant studies between 2010 and 2024 were included and extracted. This review explores the mechanisms of neuroplasticity and the latest neuroplasticity-based interventions for stroke recovery. It highlights the role of neuronal regeneration, synaptic plasticity, and functional reorganization in promoting recovery. Additionally, the review discusses emerging therapies, such as Constraint-Induced Movement Therapy, mirror therapy, robot-assisted training, and non-invasive brain stimulation techniques, which have shown promise in enhancing neuroplasticity and improving functional outcomes. Although the results of these interventions have been complex and the effect sizes modest, they underscore the potential for innovative approaches to harness neuroplasticity in stroke rehabilitation..

INTRODUCTION

Stroke is considered a significant global public health issue, with millions of individuals affected each year. It is a leading cause of death worldwide and a major source of morbidity, resulting in severe mental and physical disabilities among survivors[1]. From 1990 to 2019, there was a 70% increase in stroke cases and a 43% increase in stroke-related deaths[2]. According to a systematic analysis for the Global Burden of Disease Study 2016, there were 80.1 million prevalent cases of stroke globally in 2016, with 41.1 million cases in women and 39.0 million cases in men[3]. Stroke is the second leading cause of death globally and a leading cause of long-term disability, often resulting in physical impairments, cognitive deficits, and communication difficulties[4].

Neuroplasticity, the brain's remarkable ability to adapt and reorganize itself in response to various stimuli and experiences, is a fundamental process crucial for learning, memory, and overall brain function[5]. This phenomenon allows the brain to modify its structure, function, and connections in response to intrinsic or extrinsic factors, contributing to behavioral adaptability, memory formation, and recovery from brain injuries[6]. Research has shown that neuroplasticity plays a significant role in various conditions such as depression, schizophrenia, and stroke recovery[7–9]. Post-stroke neuroplasticity involves a series of complex mechanisms that contribute to functional recovery and rehabilitation[10].

Traditional stroke rehabilitation has primarily focused on using compensatory strategies to manage the effects of impairments rather than targeting their root causes. However, there is an increasing awareness in the scientific and medical communities of the remarkable transformative potential of neuroplasticity. This recognition has led to a paradigm shift in stroke rehabilitation, with a new emphasis on leveraging neuroplasticity to enhance functional recovery and achieve significant, lasting improvements in long-term outcomes for stroke survivors[11]. This literature review aims to provide an overview of the current understanding of neuroplasticity-based interventions for stroke recovery.

METHODS

A comprehensive literature search was conducted to identify studies examining neuroplasticity in the context of stroke. The following electronic databases were utilized: PubMed, Cochrane Library, and Google Scholar. The search included peer-reviewed journal articles published in English between 2010 and 2024. Key search terms included combinations of “neuroplasticity,” “stroke,” “brain plasticity,” “recovery,” “rehabilitation,” and “functional reorganization.” Boolean operators (AND, OR) were used to optimize the search results. Studies were selected based on relevance to neuroplasticity mechanisms following stroke and their impact on recovery and rehabilitation. Studies included randomized clinical trials, observational studies, guideline statements, and review articles that discussed neuroplasticity in stroke population. Studies not specific to post-stroke populations, and abstracts without full-text availability were excluded. This search results was supplemented by reviewing references from included studies. A thematic analysis was used to identify recurring patterns and themes in the literature.

LITERATURE REVIEW

Concept of Neuroplasticity

Neuroplasticity refers to the brain's inherent capacity to adapt in response to changing environmental demands[12]. In this context, plasticity is an adaptive process that occurs when there is a prolonged mismatch between the brain's immediate functional capabilities and the demands of the environment, such as when a new cognitive task needs to be performed. It involves the brain's capacity to form new neural connections, reorganize neural pathways, and adjust its structure and function to optimize performance and adapt to new situations.[13]. Neuroplasticity plays a crucial role in brain development, learning, memory, and recovery from injuries or neurological disorders[14].

For a long time, it was believed that the brain's structure was flexible and responsive to external influences only during critical periods in early life, and that this malleability was lost afterward. While animal models have suggested that age limits the capacity for adaptive changes, numerous studies have demonstrated that neuroplasticity can still occur in the adult brain[15].

Basically, neuroplasticity can be divided into two major mechanisms:[16]

a. Neuronal regeneration/collateral sprouting, this includes synaptic plasticity and neurogenesis. In synaptic plasticity, when the presynaptic neuron stimulates the postsynaptic neuron, the postsynaptic neuron responds by increasing the number of neurotransmitter receptors, thereby lowering the threshold needed for stimulation by the presynaptic neuron. This process strengthens the synapse over time. Various factors, such as exercise, environmental influences, task repetition, motivation, neuromodulators like dopamine, and certain medications or drugs, can positively affect synaptic plasticity. However, aging and neurodegenerative diseases are linked to a decline in neuromodulators, which may reduce the capacity for synaptic plasticity. The theory of synaptic plasticity has also evolved to encompass the growing complexity of synaptic communication. Adult neurogenesis refers to the idea that the brain continues to produce new neurons even in adulthood.
b. Functional reorganization, this includes equipotentiality, vicariation, and diaschisis. Equipotentiality is the idea that if one area of the brain is damaged, the opposite side can compensate for the lost function. Meanwhile, vicariation suggests that the brain can reorganize different regions to take on functions they weren't originally intended for. In its strictest definition, vicariation occurs when one part of the brain assumes a new and unrelated function. However, with the advent of advanced imaging techniques, it has been shown that neither theory fully captures the brain's behavior. It is suggested that the brain employs both equipotentiality and vicariation to compensate for lost functions. Diaschisis is the concept that damage to one area of the brain can lead to a loss of function in another region due to their interconnected pathways.

Neuroplasticity in Stroke

After a stroke, the brain shows remarkable restorative capabilities through neuroplasticity. This process allows for the generation of new neurons, the formation of new neural pathways, and the modification of cellular structures in response to environmental changes. Neuronal reorganization and plasticity following a stroke start in the very early stages and persist for several weeks, involving brain regions far from the affected area. Imaging studies (PET, EEG, and fMRI) have shown widespread changes in brain activation patterns during simple movements of the affected hand after a stroke. These changes occur over a period that aligns with the gradual reorganization of the sensorimotor system[17].

1. The acute response to injury occurs within the initial hours, during which changes in blood flow, edema, metabolism, and inflammation become evident (acute phase).
2. A repair phase begins in the first few days after a stroke and continues for several weeks. During this period, spontaneous recovery occurs, and endogenous repair processes peak (repair phase).
3. The third phase starts weeks to months after the stroke, when spontaneous recovery levels off, marking a stable yet still modifiable chronic phase (chronic phase).

Neuroplasticity involves various mechanisms, such as interhemispheric lateralization, the creation of new connections between cortical regions within the injured area, and the reorganization of cortical representational maps. Studies on animal models provide strong evidence that the most significant recovery occurs during a limited period of heightened neuroplasticity following a stroke. Notably, changes in neural activity and connectivity, both in function and structure, have been observed in the perilesional and remote regions as well as the contralateral hemisphere. These alterations are thought to drive the mechanisms responsible for spontaneous recovery. One key change linked to neuroplasticity is the modulation of local cortical structure and function, where affected brain areas undergo adaptive modifications to compensate for lost functions. Additionally, neuroplasticity can also lead to changes in brain regions far from the injury site, indicating a network-wide reorganization to support functional recovery. Furthermore, a significant shift occurs in the interaction between the ipsilesional and contralesional hemispheres, as the brain adapts and redistributes functions across these regions. Another aspect of neuroplasticity is the remapping of somatotopic representation, which involves reorganizing sensory and motor maps within the brain to accommodate changes in the body (table 1)[18].

Table 1. Key neuroplastic changes associated with stroke rehabilitation[18]

Neuroplastic changes	***Description of changes***	***Neural structures involved***

Dendritic remodelling	Structural changes in dendrites, including sprouting and arborisation	Affected and unaffected brain regions
Synaptic plasticity	Strengthening or weakening of synapses based on activity and experience	Neurotransmitter systems, cortical and subcortical regions
Cortical reorganisation	Changes in cortical maps and functional organisation of brain regions	Motor and sensory cortices, association areas
Neurogenesis	Generation of new neurons in specific brain regions	Hippocampus, subventricular zone
Axonal sprouting	Formation of new connections or sprouting of existing axons	Corticospinal tract, other neural pathways

Emerging Treatments Targeting Neuroplasticity in Stroke

Various post-stroke interventions have been developed to enhance recovery, often by promoting the plasticity of the remaining neural circuits, whether intentionally or not. Alongside traditional therapies such as physical, occupational, and speech therapy, new approaches have shown promising effects in clinical trials. Many of these interventions aim to boost plasticity in the ipsilesional hemisphere, where increased activity and connectivity have been associated with better functional outcomes. However, the results have been complex, and even when significant improvements were observed, the effect sizes were generally not satisfactory in most cases[19].

Constraint-Induced Movement Therapy (CIMT)

Constraint-Induced Movement Therapy (CIMT) involves the restriction of the non-affected limb while intensively training the affected limb through repetitive task practice. This method is grounded in the principles of neuroplasticity, aiming to promote the use of the affected limb and reduce learned non-use, a phenomenon where patients avoid using their impaired limb due to its dysfunction[20]. The core mechanism of CIMT is based on the concept of forced use. By constraining the unaffected limb, patients are compelled to engage their affected limb in functional tasks, which fosters the brain's ability to reorganize and adapt. This approach not only encourages motor recovery but also enhances the neural pathways associated with the affected limb[21].

Numerous studies have demonstrated the efficacy of CIMT in improving upper limb function in stroke patients. A systematic review and meta-analysis by highlighted that CIMT significantly improves activity and participation levels in stroke survivors, suggesting that it is an effective intervention for enhancing upper limb functionality[22]. Another meta-analysis confirmed that CIMT is one of the most investigated and effective interventions for upper limb rehabilitation post-stroke, with strong evidence favoring its use[21]. Studies have indicated that the timing and intensity of CIMT play crucial roles in its effectiveness. The optimal timing for initiating CIMT is within the first few months post-stroke, as this period is critical for neuroplastic changes, while higher doses has been associated with better outcomes[20].

Mirror therapy/action observation therapy

Mirror therapy (MT) is a rehabilitation technique that utilizes a mirror to create a visual illusion of movement in the affected limb of stroke patients. The therapy involves placing a mirror in front of the patient, reflecting the movements of the unaffected limb, which creates the illusion that the affected limb is moving normally. This visual feedback is thought to stimulate neural pathways associated with motor function, promoting recovery through mechanisms of neuroplasticity[23].

Numerous studies and meta-analyses have investigated the effectiveness of mirror therapy in improving motor function and activities of daily living in stroke patients. A meta-analysis found that mirror therapy significantly improves functional ability in post-stroke patients, with a standardized mean difference (SMD) of 0.92, indicating a notable advantage over conventional therapy methods[24]. Similarly, a study reported that mirror therapy led to improvements in upper limb and hand functions across various types of stroke patients, reinforcing its applicability regardless of lesion type[25]. This is further supported by another study that highlighted that the combination of mirror therapy with biofeedback and functional electrical stimulation resulted in enhanced motor recovery of the upper extremities[26].

Robot-assisted training

Robot-assisted training (RAT) utilizes robotic devices to provide repetitive, task-specific training, which is crucial for neuroplasticity and functional recovery after a stroke. The integration of robotics into rehabilitation programs offers several advantages, including the ability to deliver high-intensity training, monitor progress, and provide consistent feedback to patients[27]. The primary mechanism behind RAT is its ability to facilitate repetitive movements in a controlled manner, which is essential for motor relearning. Robotic devices can assist, resist, or guide movements, allowing patients to engage in exercises that they may struggle to perform independently. This assistance can be tailored to the individual needs of each patient, promoting engagement and motivation during therapy[28].

A systematic review found that RAT significantly enhances upper limb function compared to conventional therapy, particularly in chronic stroke patients[27]. The review emphasized the importance of task-oriented training facilitated by robotic devices, which can lead to better functional outcomes. Similarly, another meta-analysis confirmed that robot-assisted training is effective in enhancing balance and functional recovery in stroke survivors, with positive effects observed across various stages of rehabilitation[29]. Moreover, studies have indicated that RAT can be beneficial in both acute and chronic phases of stroke recovery. For instance, it is found that

E-ISSN 2774-3837

the use of a wearable robot for in-bed sensorimotor rehabilitation in early subacute stroke survivors effectively improved motor function and engagement in therapy[30]. This suggests that robotic rehabilitation can be initiated early in the recovery process, potentially leading to better long-term outcomes.

Virtual reality

Virtual reality (VR) allows for the simulation of real-life tasks and activities, which can be tailored to the individual needs of stroke survivors. This approach not only increases engagement and motivation but also facilitates repetitive practice, which is critical for neuroplasticity and functional recovery[31]. A systematic review found that VR-based rehabilitation significantly improved balance and functional mobility in post-stroke patients compared to conventional therapeutic exercises[32]. The review highlighted that patients had a more enjoyable experience with VR, which may contribute to better adherence to rehabilitation programs. In another study, VR training combined with upper limb sensory exercise stimulation improved the active range of motion (AROM), function, and concentration in chronic stroke patients.[31] This suggests that VR can effectively enhance both physical and cognitive aspects of rehabilitation, further supporting the use of VR by showing that virtual reality training with cognitive load improved walking function in chronic stroke patients. Studies have also shown that improvements in motor function and activities of daily living (ADLs) can be sustained over time following VR interventions. For instance, a study by found that VR-based therapy significantly improved the quality of life and functional independence of stroke patients during a three-month follow-up[33].

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation technique that utilizes magnetic fields to induce electrical currents in the brain, thereby modulating neuronal activity. This method has garnered significant interest in the field of stroke rehabilitation due to its potential to enhance recovery of motor function and facilitate neuroplastic changes in the brain following a stroke[34]. TMS operates by delivering magnetic pulses through a coil placed on the scalp, which generates electrical currents in the underlying cortical neurons. These currents can either increase (facilitate) or decrease (inhibit) the excitability of the targeted brain regions, depending on the frequency and pattern of stimulation[35]. This modulation of cortical excitability is crucial for promoting motor recovery, as it can help restore balance between the hemispheres of the brain, particularly in cases where one hemisphere has become dominant following a stroke[36].

A systematic review highlighted that repetitive TMS (rTMS) significantly improves upper limb motor function in stroke patients, particularly when combined with conventional rehabilitation therapies. The review emphasized that rTMS can enhance the effects of physical therapy by promoting cortical reorganization and improving motor performance. They found that TMS could improve cognitive functions, such as attention and memory, which are often impaired following a stroke[37]. Another meta-analysis by indicated that TMS is effective in treating post-stroke dysphagia[38]. Additional evidence from a study supports the use of TMS in enhancing motor recovery after stroke. The study found that rTMS applied to the unaffected hemisphere could facilitate recovery by promoting interhemispheric balance and reducing inhibition from the unaffected side[36].

Transcranial Direct Current Stimulation (tDCS)

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that applies a low electrical current to the scalp through electrodes, modulating neuronal excitability and promoting neuroplasticity. tDCS works by delivering a constant, low electrical current (typically 1-2 mA) to the scalp, which can either increase (anodal stimulation) or decrease (cathodal stimulation) the excitability of cortical neurons beneath the electrodes. Anodal tDCS is generally used to enhance cortical excitability in the affected hemisphere, while cathodal tDCS can inhibit activity in the unaffected hemisphere, thereby reducing interhemispheric inhibition that may hinder recovery[39]. This modulation of cortical activity is believed to facilitate motor learning and recovery by promoting synaptic plasticity and enhancing the brain's ability to reorganize following injury[40].

A systematic review found that tDCS significantly enhances the effects of conventional rehabilitation therapies, particularly in improving upper limb function and activities of daily living. The review highlighted that tDCS is effective across various stages of stroke recovery, including acute, sub acute, and chronic phases[40]. In a randomized controlled trial, the combination of tDCS and robot-assisted gait training was shown to improve walking ability in chronic stroke patients. The study indicated that the synergistic effects of tDCS and robotic training could lead to greater functional improvements compared to either intervention alone.[41] Another study reported that tDCS combined with functional electrical stimulation (FES) led to significant improvements in upper limb recovery in patients with sub acute stroke.[39] Another important aspect of tDCS is its potential to enhance cognitive recovery. It is suggested that tDCS could improve cognitive function in stroke patients[42]. Studies have indicated that improvements in motor function and cognitive abilities can be sustained over time following tDCS interventions. A meta-analysis highlighted that tDCS can lead to lasting enhancements in upper limb function and quality of life in stroke survivors[43].

Deep brain stimulation

Deep Brain Stimulation (DBS) is a neurosurgical procedure that involves the implantation of electrodes in specific brain regions to deliver electrical impulses. This technique has been primarily used to treat movement disorders such as Parkinson's disease, essential tremor, and dystonia. However, its application in stroke rehabilitation is gaining traction, particularly for addressing motor deficits and improving functional recovery[44]. DBS works by modulating the activity of targeted brain circuits. The electrodes are typically implanted in areas such as the subthalamic nucleus (STN) or globus pallidus internus (GPi), which are involved in the regulation of movement. By delivering continuous electrical stimulation, DBS can alter the pathological firing patterns of neurons, thereby restoring more normal function in the affected motor pathways[45]. Several studies have demonstrated the efficacy of DBS in improving motor function in stroke patients. A systematic review reported the effectiveness of DBS in improving functional outcomes in stroke patients. It is suggested that DBS could lead to significant improvements in activities of daily living (ADLs) and overall quality of life[44].

Stem cell therapy

Stem cell therapy aims to promote recovery by enhancing neurogenesis, reducing inflammation, and improving functional outcomes in patients who have suffered from ischemic or hemorrhagic strokes[46]. The potential of stem cell therapy for stroke patients has been a focus of extensive research, with various types of stem cells being investigated, including mesenchymal stem cells (MSCs), neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs). Stem cell therapy has been proposed for stroke treatment for a number of reasons. Stem cells can differentiate into neurons and glial cells, which are essential for repairing damaged brain tissue. This process, is critical for restoring lost functions after a stroke. Stem cells also secrete various neurotrophic factors and cytokines that promote the survival, growth, and differentiation of endogenous neurons. This trophic support can enhance the brain's natural repair mechanisms and reduce inflammation. Stem cell therapy can modulate the immune response following a stroke, reducing neuroinflammation and promoting a more favourable environment for recovery[47]. This is particularly important, as excessive inflammation can lead to further neuronal damage. Stem cells can promote the formation of new blood vessels (angiogenesis) in the ischemic area, improving blood flow and nutrient delivery to the damaged tissue[48].

Numerous animal studies have demonstrated the efficacy of stem cell therapy in promoting recovery after stroke. For example, a study showed that transplantation of neural stem cells into the ischemic brain improved functional recovery and reduced infarct size in a rat model of stroke[49]. A randomized controlled trial investigated the intra-arterial infusion of autologous stem cells in sub acute ischemic stroke patients. The results showed significant improvements in neurological function and activities of daily living[50]. A systematic review found that stem cell-based therapies could lead to significant improvements in motor function and quality of life in stroke survivors[51]. The integration of stem cell therapy with other rehabilitation strategies has shown enhanced recovery outcomes. A study reported that combining stem cell therapy with repetitive transcranial magnetic stimulation (rTMS) led to greater improvements in motor function compared to either intervention alone[52].

Brain computer interface

Brain-Computer Interface (BCI) enables direct communication between the brain and external devices, bypassing traditional pathways of communication such as muscles. In the context of stroke rehabilitation, BCIs have been developed to facilitate motor recovery, enhance neuroplasticity, and improve functional outcomes for patients with motor impairments resulting from stroke[53]. BCIs typically utilize electroencephalography (EEG) to record brain activity, which is then translated into control signals for devices such as robotic arms or functional electrical stimulation (FES) systems. BCIs can be integrated with FES to facilitate movement in paralyzed limbs. By detecting brain signals associated with intended movements, BCIs can trigger electrical stimulation of muscles, enabling patients to perform movements that they cannot initiate voluntarily. This combination of BCI and FES has shown promise in enhancing motor recovery and functional independence in stroke patients[54].

A systematic review and meta-analysis found that BCI interventions significantly improved upper limb function and activities of daily living in stroke patients. The authors concluded that BCI technology is a promising tool for enhancing rehabilitation outcomes[55]. It is suggested that BCI training can induce changes in brain connectivity and promote neuroplasticity. For instance, a study demonstrated that BCI training with functional electrical stimulation led to changes in interhemispheric functional connectivity, which correlated with improvements in motor outcomes. This suggests that BCIs can facilitate the reorganization of neural circuits involved in motor control[56].

Future direction

Future directions for neuroplasticity-based therapies in stroke rehabilitation are poised to revolutionize recovery strategies, focusing on enhancing the brain's ability to reorganize and adapt following injury. Key advancements include the integration of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which have shown promise in promoting motor and cognitive recovery by facilitating neuroplastic changes. Robot-assisted therapies and virtual reality (VR) applications are gaining traction, providing engaging environments that stimulate neural pathways while improving motor functions. The use of brain-computer interfaces (BCIs) is also emerging, allowing patients to control devices through thought, thereby fostering active participation in rehabilitation. Furthermore, the combination of these technologies with traditional rehabilitation methods is expected to yield better outcomes by addressing individual patient needs through personalized therapy plans[18].

Studies have also investigated the roles of microglial regulation in brain plasticity-dependent stroke recovery, emphasizing the potential impact of microglia as key therapeutic targets for stroke rehabilitation[10]. Pharmacological interventions and rehabilitation approaches are being developed to stimulate endogenous neuroplasticity in post-stroke patients[57]. The modulation of plasticity induced by non-invasive brain stimulation through pharmacological interventions targeting ion channels or neurotransmitters presents a promising avenue for enhancing neuroplasticity in stroke patients[58,59].

CONCLUSION

The remarkable adaptability of the brain, as evidenced by neuroplasticity, offers a promising avenue for enhancing recovery after stroke. While traditional rehabilitation has centered on compensatory methods, a deeper understanding of neuroplastic mechanisms has shifted focus towards interventions that promote genuine neural recovery. Emerging therapies, including advanced techniques such as robotic training, virtual reality, and brain stimulation, are beginning to show promise in clinical settings. However, despite some success, these interventions often yield modest effect sizes, indicating that there is still much to learn about optimizing neuroplasticity for stroke recovery. Continued research into the underlying mechanisms of neuroplasticity and the development of more targeted therapies will be essential in advancing stroke rehabilitation and improving long-term outcomes for survivors.

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