Investigating the Potential and Efficiency of Neuroplasticity-based Interventions in Ischemic Stroke Recovery

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Abstract

Given the significant impact of stroke, especially as the 5th leading cause of death, there is a need for effective rehabilitation strategies. Neuroplasticity, the brain's ability to form new connections in response to injury, plays a crucial role in recovery following stroke damage. This paper will review current research on stroke rehabilitation methods that promote neuroplasticity to summarize various intervention strategies, including physical therapy and cognitive rehabilitation. In addition, factors that influence the efficacy of these neuroplasticity interventions will be discussed, such as individual variability, timing, and sociocultural and genetic factors.

Introduction

Currently, stroke is a major cause of disability worldwide and the leading neurological cause of lost disability-adjusted life years (Martin et al., 2024). A stroke is a medical condition that affects the arteries in the brain, leading to the damage and loss of brain cells. A recent study highlighted that neurological conditions, including stroke, now affect over 3 billion people globally, which represents approximately 43% of the global population (World Health Organization, 2024). The burden of this condition has increased by 18% since 1990, largely due to heightened exposure to various risk factors (World Health Organization, 2024). The impact of stroke tends to grow worse due to the limited access to specialized healthcare services in low-income countries, such as rehabilitation facilities and advanced technologies that promote recovery. Currently, medical treatment for ischemic strokes is limited to intravenous recombinant tissue plasminogen activator (tPA) and endovascular thrombectomy. However, the utility rates for these interventions are low due to their limited therapeutic window of only 4-6 hours (Yperzeele et al., 2014)**.** In addition, the time of symptom onset to the time when the patient gets to the emergency room (onset-to-door) and receives tPA (door-to-needle) plays a significant role in missed or delayed treatment. These disparities generate a notable challenge for stroke patients who seek early and efficient recovery (Yperzeele et al., 2014).

Most stroke patients need some form of rehabilitation to regain lost function following a stroke. New interventions have been implemented in rehabilitation to target neuroplasticity mechanisms and focus on activity-based rehabilitation (Aderinto et al., 2023). Neuroplasticity is the brain's capacity to change connections and behaviors in response to new information or damage (Marín-Medina et al., 2024). Neural networks inside the brain carry out specific functions while simultaneously retaining the capacity to reorganize themselves (Puderbaugh & Emmady, 2023). This article will delve into neuroplasticity by examining current publications about rehabilitation interventions. It will assess the neuroplasticity mechanisms, types of interventions, and their function in stroke rehabilitation with the objective of identifying the most efficient personalized rehabilitation interventions.

Stroke

In the US, stroke is the 5th leading cause of death, and there are over 795,000 stroke victims annually (Martin et al., 2024). There are many types of strokes, which can be classified into two major categories: ischemic strokes and hemorrhagic strokes. Hemorrhagic strokes occur when a blood vessel inside the brain ruptures and causes internal bleeding. Due to this, pressure can build up in surrounding tissues that can cause irritation and swelling, which can lead to further brain damage (Montaño et al., 2021). By contrast, ischemic strokes occur when a blood clot blocks a blood vessel and impairs blood flow to a part of the brain. Cells affected by strokes begin to die within minutes due to the lack of oxygen. Ischemic strokes account for about 87% of all strokes (Martin et al., 2024). Stroke symptoms occur suddenly, and include numbness or weakness of the face, arm, or leg (especially on one side of the body), confusion, difficulty speaking, visual changes, difficulty walking, dizziness, loss of balance or coordination, and severe headache (Feske, 2021). These symptoms occur due to the lack of oxygen and blood flow. When specific regions of the brain are deprived of blood flow, the cells in those areas die, which can result in the loss of the abilities controlled by the affected region. This can potentially be fatal in severe situations or cases that are left untreated for an extended period (Feske, 2021).

Following a stroke, an ischemic core develops in the brain, where cells have irreversible damage leading to permanent neurological deficits. If not treated promptly, the ischemic core grows. (Kaufmann et al., 1999). The ischemic penumbra is the surrounding tissue around the core that remains viable due to reduced but sufficient blood flow. Therefore, the tissue in the ischemic penumbra has the potential to recover if prompt delivery of treatment is ensured (Kaufmann et al., 1999). The rapid identification through medical imaging of the ischemic penumbra is crucial for determining treatment because it is the target for current treatments such as tPA and endovascular thrombectomy (Hughes et al., n.d.; Papanagiotou & Ntaios, n.d.).

Current Treatments

Currently, there are two main types of medical treatments used in stroke management: tPA and endovascular thrombectomies. However, their strict eligibility criteria lead to low utilization rates. In a meta-analysis, the utilization rate for endovascular thrombectomies is 9.1% (Kayola et al., 2023). In addition, stroke onset-to-door time significantly increases missed treatment opportunities. The American Stroke Association highly suggests the immediate admission of patients suspected of stroke damage (Adeoye et al., 2019).

Tissue Plasminogen Activator (tPA)

tPA works by breaking down blood clots inside the brain's arteries that impede blood flow, thereby restoring circulation and minimizing potential brain damage. Currently, tPA is the only FDA-approved treatment for ischemic strokes (Hacke et al., 2008). Before tPA is administered to a patient, a non-contrast computed tomography (CT) scan is done to determine the type of stroke. Once it has been determined that the patient suffered an ischemic stroke, tPA is given to patients intravenously, and when delivered promptly after stroke onset, it helps to restore blood flow to brain regions affected by an ischemic stroke. Through this, tPA limits the risk of damage and functional impairment (Hughes et al., n.d.). However, tPA has strict eligibility criteria. A patient must be diagnosed with an ischemic stroke within a specific time frame, ideally within three hours of symptom onset. The patient must also exhibit measurable neurological deficits that indicate a significant impact from the stroke (Hughes et al., n.d). Additionally, several exclusion criteria may prevent a patient from receiving tPA. These include current intracranial hemorrhages, subarachnoid hemorrhages, active internal bleeding, recent (within three months) intracranial or intraspinal surgery, severe head trauma, severe uncontrolled hypertension, conditions that increase the risk of bleeding, patients over the age of 80, those with a National Institutes of Health Stroke Scale (NIHSS) score greater than 25, or those with a history of diabetes and prior strokes may also be ineligible for tPA if treated between 3 and 4.5 hours after symptom onset (Hughes et al., n.d).

The administration of tPA for ischemic stroke patients is associated with particular risks. The elevation of blood pressure throughout the use of tPA increases the risk of a hemorrhage transformation (Demaerschalk et al., 2016). Patients who received antihypertensive treatment while receiving tPA had a high incidence of hemorrhage after a study (Bahadir et al., 2022). Additionally, some patients may experience a decrease in fibrinogen levels, which can lead to coagulopathy and increase the risk of hemorrhage. (Demaerschalk et al., 2016) Cautious monitoring of selected patients who will receive tPA is critical to mitigate the risks of hemorrhages.

Endovascular Thrombectomy

Endovascular thrombectomy is a surgical procedure to treat ischemic strokes by removing a blood clot from a blocked artery in the brain (Hacke et al., 2008). A long, thin catheter is inserted into an artery during this surgical procedure. The catheter is then guided up via the blood vessels through micro-cameras to the site of the blocked artery in the brain. After the catheter is inserted, the blood clot is extracted using a small tool known as a stent retriever, which restores blood flow to the damaged part of the brain (Hacke et al., 2008). However, the use of endovascular thrombectomy has been limited by several factors. Typically, a patient must be diagnosed with an ischemic stroke within a specific time frame, ideally within six hours, but no later than 24 hours, of symptom onset. Patients presenting mild stroke severity, measured by the NIHSS, may not be allowed to receive this treatment (Papanagiotou & Ntaios, n.d.). In addition, patients who are older or have pre-existing conditions may also not be granted the procedure.

Neuroplasticity

Neuroplasticity is the ability of the nervous system to change its activity and form new connections in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections (Puderbaugh and Emmady, 2023). After a stroke or a traumatic injury, the brain will undergo this process to adapt and reorganize its structure and function in response (Aderinto et al., 2023).

It is essential to understand the different types of neuroplasticity changes for enhanced recovery outcomes. First, synaptic plasticity is the ability of the synapses to strengthen or weaken over time in response to changes in their activity (Kania et al., 2017). Synaptic plasticity is characterized by two primary forms: long-term potentiation (LTP) and long-term depression (LTD). LTP is the increase in synaptic strength following high-frequency stimulation, which is necessary for learning and memory. LTD is the decrease in synaptic strength following low-frequency stimulation, which helps refine neural circuits and remove unnecessary connections caused by stroke (Kania et al., 2017). Second, dendritic remodeling (Figure 1) refers to changes in the structure and number of dendrites, which are the extensions of neurons that receive signals from other neurons. This remodeling process allows neurons to adapt their connectivity based on changes and demands. Dendritic spines, small protrusions on dendrites where the synapses form, can change in number and size, which affects the neuron's ability to process information (Figure 1) (Marín-Medina et al., 2024). Third, axonal sprouting is the process in which damaged neurons can grow new axons to reconnect with the other neurons (Figure 2). This is important following stroke damage because the brain is trying to compensate for lost connections. Axonal sprouting can lead to the re-establishment of these functional pathways and aid in recovery by allowing the brain to essentially reroute signals around damaged areas (Figure 2) (Marín-Medina et al., 2024).

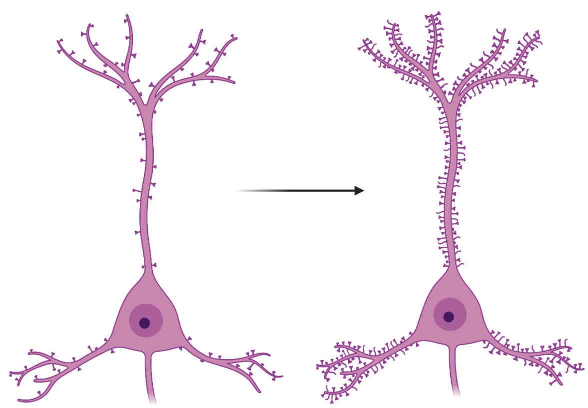

Figure 1: Dendritic Remodeling. Neuroplasticity increases the number of dendritic spines on the dendrites of neurons. Image created using BioRender.

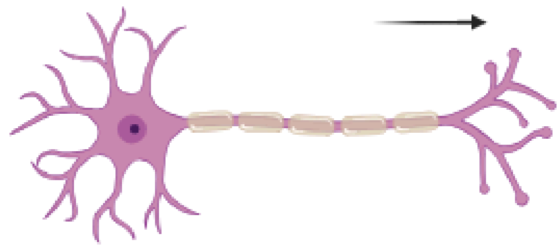

Figure 2: Axonal Sprouting. Neuroplasticity increases the growth of axons to connect with other neurons following damage. Image created using BioRender.

Neuroplasticity works in three main mechanisms following stroke damage. The first entails growing functional activity in the somatosensory system on the opposite side of the brain where the infarction occurred. The second mechanism works by strengthening and improving the structural integrity of the corticospinal tract through the same side of the brain where the infarction occurred. The third mechanism boosts the restoration of interhemispheric functional connectivity on both sides of the brain. Following stroke damage, the brain's neuroplasticity heightens, demonstrating successful restorative outcomes (Marín-Medina et al., 2024).

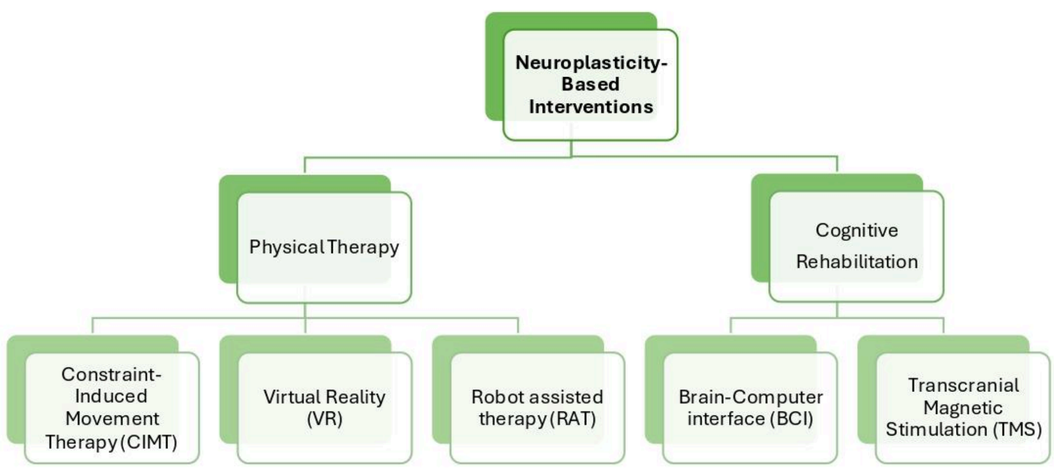

Figure 3: Neuroplasticity-Based Interventions. This diagram categorizes various interventions to harness neuroplasticity following a stroke discussed in this paper.

Interventions

Physical Therapy

Constraint-Induced movement therapy (CIMT)

The purpose of constraint-induced movement therapy (CIMT) is to limit the use of a less affected limb in order to force the use of the affected limb. Through this technique, CIMT improves the motor function ability of the affected limb after a stroke (Wang et al. 2022). CIMT consists of movement and behavioral techniques and restriction methods to promote the quality and frequency of movement in the affected limb following stroke damage. This is often achieved by placing a padded mitt or glove on the unaffected arm, which restricts its movement and encourages the patient to utilize their affected arm for various tasks. Some CIMT everyday exercises may include tasks such as grasping objects, turning door knobs, or reaching and lifting for objects. This therapy emphasizes intensive practice, requiring patients to engage for several hours daily. This repetitive practice is crucial for reinforcing motor pathways and promoting neuroplasticity for functional improvements (Kwakkel et al., 2015). CIMT is known to target motor recovery after stroke and synaptic plasticity. Nevertheless, the exact mechanisms underlying its effectiveness are not yet completely known (Aderinto et al., 2023).

Virtual Reality Therapy (VR)

Virtual reality therapy (VR) employs 3D display interfaces between a computer and a patient. This therapy uses both hardware and software mechanisms to simulate interactions with the environment, giving the user an immersive experience (Gangemi et al., 2023). Through immersive and interactive environments, users can engage in repetitive and task-specific training, which can significantly improve motor and cognitive abilities. A quasi-randomized clinical trial investigated the neurophysiological effects of VR cognitive stimulation on patients with chronic ischemic stroke, utilizing EEG recordings to assess brain activity. The results revealed significant improvements in alpha and beta frequency bands in the experimental group, indicating enhanced cognitive functioning. The control group showed no significant changes. This suggests that VR cognitive stimulation may be a valuable tool in stroke rehabilitation, promoting neuroplasticity and cognitive recovery in stroke patients (Gangemi et al., 2023). In VR therapy, different levels of immersion are used based on patient needs. Skillful immersion targets motor skills, while strategic immersion focuses on cognitive skills like decision-making. Narrative immersion uses storytelling to enhance engagement, while spatial or total immersion creates a fully immersive virtual environment (Martin et al., 2024).

Robot-assisted therapy (RAT)

Robot-assisted therapy (RAT) utilizes robotic devices to promote repetitive, task-oriented training for stroke patients (Bonanno et al, 2023.). RAT devices serve to support a patient’s movement in different axes to help provide better control and monitoring for personalized tasks tailored to patient needs. The effectiveness of RAT depends on patient factors such as their ability to move the affected limb, the type of support provided to the limb, and the duration of robot support. The active engagement that RAT provides is crucial for enhancing neuroplasticity and improving motor recovery (The European Federation of NeuroRehabilitation Societies, n.d). During RAT therapy sessions, patients might utilize robotic devices on their affected upper limbs to perform movements such as reaching objects, where the robot guides the limb. This allows patients to practice movements while still promoting their active involvement. In addition, the robotic system provides real-time feedback, helping patients refine their movements, enhancing their learning experience, and offering a personalized experience tailored to each patient. RAT has shown persistency six months after treatment, and in some cases has been noted up to eight months post-intervention. By focusing on specific tasks, such as performing functional activities, patients can work on improving their motor skills and overall upper limb functionality. (Bonanno et al., 2023) (Stanescu et al., n.d.)

Cognitive Rehabilitation

Brain-machine interface (BMI)

In brain-machine interfaces (BMI), the transduction of brain signals is translated into computational commands that enable the control of technological devices such as prosthetics and computers. (Ma et al., 2023). BMI has two methods for receiving brain signals: invasive and non-invasive. The invasive method, while potentially providing cleaner signals, carries surgical risks and may not always be suitable for clinical use. Invasive electrodes include cortical surface microelectrodes (ECoG), cortical penetrating, and deeply penetrating types, which record different brain action potentials. Non-invasive approaches like electroencephalography (EEG) are more common and well-supported by research, though alternatives like near-infrared spectroscopy are also used. (Marín-Medina et al., 2024) During therapy sessions, patients might wear a cap equipped with electrodes that monitor the patient’s brain activity. Furthermore, they are guided to visualize specific movements of their affected limb, and in doing so, BMI allows patients to control devices such as robotic arms or computer cursors through thought alone. This therapy helps patients practice motor tasks and provides immediate feedback to offer personalized service (Sebastián-Romagosa et al., 2020).

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a technique used to investigate the brain’s plasticity following stroke damage. TMS creates magnetic field pulses that induce electrical activity in the focal area of the brain. This technique activates corticospinal neurons trans-synaptically, eliciting neuronal output in motor-evoked potentials. It can also be used to study populations of inhibitory and excitatory interneurons of various motor and nonmotor cortical regions within and across cerebral hemispheres (Reis et al., 2008). During TMS, a magnetic coil that generates magnetic pulses to help stimulate the targeted areas of the brain is placed on the patient's scalp (Kricheldorff et al., 2022). The patient may be asked to perform simple motor tasks while the magnetic pulses are delivered. This combination of brain stimulation and motor tasks aims to enhance neuroplasticity and promote functional recovery (Kricheldorff et al., 2022; Hoyer and Celnik, 2011).

Variables that Affect Interventions

Social, cultural, genetic, environmental, and economic environments in which stroke patients reside are referred to as sociocultural factors, and these factors can have an impact on their recovery and rehabilitation (Rethnam et al., 2023). For instance, patients from lower socioeconomic backgrounds may face limitations such as reduced access to rehabilitation centers and services, inadequate transportation, or financial constraints that hinder their ability to participate in specific types of therapy. Cultural values may also impact patient motivation and desire to follow treatment plans. For example, in a study in Ghana, 43% of stroke survivors preferred to use herbal medicines after their stroke due to cultural beliefs (stroke rehabilitation). Genetic polymorphisms can also influence neuroplasticity after stroke. Genetic factors like variations in genes related to brain-derived neurotrophic factor (BDNF), dopamine, and apolipoprotein E, play a crucial role. These genetic variations can affect neuroplasticity, motor learning, and overall recovery following stroke recovery (Stewart & Cramer, 2017)*.* Clinical factors are critical in determining the appropriate interventions for stroke patients. Additionally, the timing of intervention post-stroke is crucial since early rehabilitation has been shown to yield better outcomes. Individual patient characteristics, such as age and prior health status, must be considered to optimize rehabilitation interventions and maximize effectiveness following stroke damage (Rethnam et al., 2023).

Conclusion

Neuroplasticity is a crucial process required for stroke recovery and rehabilitation. More research and studies are needed to fully characterize the effects of interventions designed to promote neuroplasticity following a stroke. Current treatments in the acute management of stroke are limited. Ongoing research to develop improved pharmacological treatments is needed. The need for personalized rehabilitation strategies that consider genetic profiles is evident, and further research to better understand the implications of these genetic factors on rehabilitation efficacy and to enhance stroke recovery outcomes is crucial. Despite the advancements in stroke rehabilitation methods, there is still room for improvement in developing personalized interventions. Public education can significantly impact patient outcomes by encouraging them to seek immediate medical attention if a stroke is suspected.

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