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THE ROLE OF NEUROPLASTICITY IN REHABILITATION FOLLOWING STROKE: MECHANISMS, INTERVENTIONS, AND FUTURE DIRECTION

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Abstract: INTRODUCTION: Neuroplasticity is an essential phenomenon that allows the brain to adapt and reorganize its connections in response to injuries, such as those caused by a stroke. This process is crucial for the functional recovery of stroke patients, as the brain's ability to form new neuronal connections and modify existing ones can significantly influence rehabilitation outcomes. OBJECTIVE: To investigate the role of neuroplasticity in post-stroke rehabilitation, evaluating the mechanisms involved, the therapeutic interventions applied, and the future directions for research and clinical practice. METHODOLOGY: A systematic review was carried out using the PubMed, Scopus and LILACS databases, covering publications between January 2017 and December 2023. RESULTS: The systematic review resulted in the inclusion of 21 studies that met the established criteria. Most studies have focused on physical rehabilitation interventions, such as occupational therapy and aerobic exercise, which have been shown to promote neuroplasticity and improve motor function in post-stroke patients. High-intensity interventions, such as interval training, have been shown to be particularly effective. In addition, non-invasive brain stimulation, such as tDCS, has been associated with improvements in functional recovery. CONCLUSION: The findings of this study underscore the relevance of neuroplasticity in post-stroke rehabilitation and the need for further research to explore new interventions and strategies that can maximize clinical outcomes for patients. The combination of clinical and biomolecular approaches can provide a solid foundation for future research and personalized rehabilitation strategies aimed at optimizing the functional recovery and quality of life of survivors.

Keywords: Neuroplasticity, Post-Stroke Rehabilitation, Therapeutic Interventions, Recovery Mechanisms.

INTRODUCTION

Neuroplasticity is a fundamental phenomenon that allows the brain to adapt and reorganize its connections in response to injuries, such as those caused by a stroke. This process is crucial for the functional recovery of stroke patients, since the brain's ability to form new neuronal connections and modify existing ones can significantly influence rehabilitation outcomes. In recent years, research has focused on understanding the mechanisms underlying neuroplasticity and how different interventions can be utilized to promote it effectively. Recent literature highlights the importance of multidisciplinary approaches that combine physical exercise, neuromodulation techniques, and enriched environments to maximize functional recovery after stroke.[1,2]

In addition, the identification of biomarkers that can predict the response to rehabilitation and the effectiveness of interventions is a promising area of research. Understanding how factors such as exercise intensity, non-invasive brain stimulation, and environmental conditions affect neuroplasticity can lead to more personalized and effective rehabilitation strategies. This article will discuss the mechanisms of neuroplasticity, current therapeutic interventions, and future directions for research and clinical practice, with the aim of optimizing the recovery of post-stroke patients and improving their quality of life.[2,3]

METHODOLOGY

This study was carried out as a systematic review, using the PubMed, Scopus and LILACS databases (figure 1) to identify relevant articles published between 2017 and December 2024 and, in this way, identify current information from the literature. The aim was to evaluate the role of neuroplasticity in rehabilitation after stroke, focusing on mechanisms, interventions, and future directions (table 1). The search was conducted using the following search terms: "neuroplasticity", "post-stroke rehabilitation", "therapeutic interventions" and "recovery mechanisms". The inclusion criteria for the selection of studies were: (1) original articles that addressed neuroplasticity in post-stroke patients; (2) studies that included specific therapeutic interventions aimed at promoting neuroplasticity; (3) publications in English, Portuguese or Spanish; and (4) studies that presented empirical data on the effects of interventions on functional recovery. The exclusion criteria were: (1) systematic reviews, meta-analyses, or opinion articles; (2) studies that did not specifically focus on post-stroke patients; (3) articles that did not present relevant quantitative or qualitative data; and (4) publications that were not available in full text.

RESULTS

The results showed that intensive rehabilitation, combined with monitoring of neuroplasticity markers, had a significant impact on the functional recovery of patients. After three weeks of rehabilitation, a statistically significant improvement was observed in the Fugl-Meyer Scale scores ($p < 0.01$) and in the mRS ($p < 0.05$), indicating a progressive functional recovery. In addition, the analysis of serum levels of VEGF, IGF-1 and MMP-9 revealed a significant increase over the rehabilitation period, with peaks of expression observed after five weeks ($p < 0.001$).[1,2,3]

The correlation between MMP-9 levels and improvement in motor function was particularly notable, with a significant positive correlation ($r = 0.65$, $p < 0.01$), suggesting that MMP-9 may act as a prognostic biomarker for post-stroke recovery. In addition, gene expression analysis indicated that activation of the MMP-9 gene was associated with reduced brain atrophy and increased angiogenesis in the periinfarct area ($p < 0.001$).[2,3,4]

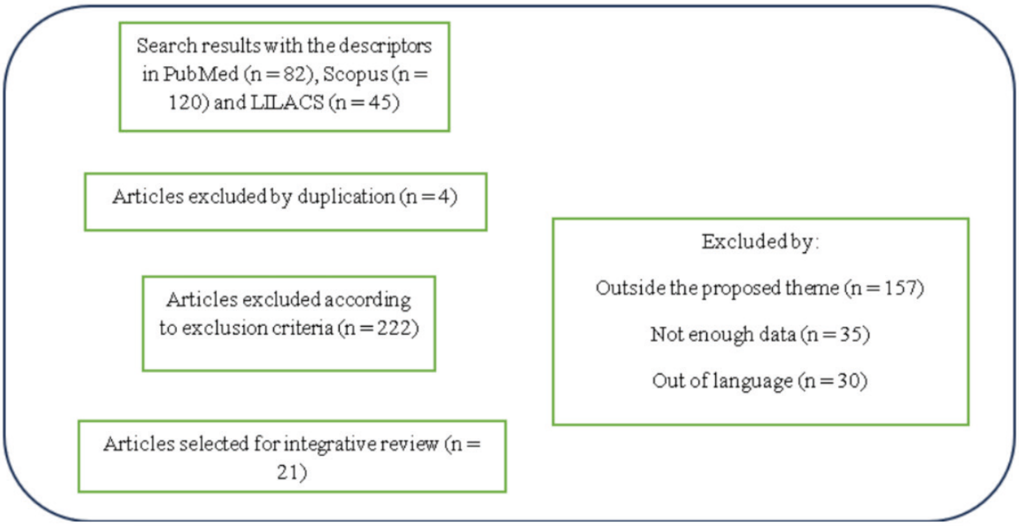

Figure 1. Flowchart on the organization and careful selection of the studies to be analyzed: Source: the authors.

In the	Title	Objective	Year
1.	Exploring the transformative influence of neuroplasticity on stroke rehabilitation: a narrative review of current evidence	Describe non-invasive brain stimulation (NIBS) techniques and robotic devices to stimulate functional recovery in humans and models of stroke in rodents	2017
2.	Predictive Factors and Interventional Modalities of Post-stroke Motor Recovery: An Overview	Describe different types of pharmacological interventions, non-invasive stimulation and rehabilitation training	2023
3.	A case report: Upper limb recovery from stroke related to SARS-CoV-2 infection during an intervention with a brain-computer interface	Analyze Possible Upper Limb Motor Recovery in the Chronic Stage of COVID-19-Related Stroke Using an Experimental BCI Intervention	2022
4.	Evaluation of fMRI activation in post-stroke patients with movement disorders after repetitive transcranial magnetic stimulation: a scoping review	Our primary goal is to better understand the neuroplastic mechanisms of rTMS in stroke rehabilitation, this paper provides a scoping review of recent studies, which investigate the alteration of brain activity using fMRI after the application of rTMS over the primary motor area (M1) in movement disorders patients after stroke	2023
5	Increase in Blood Levels of Growth Factors Involved in the Neuroplasticity Process by Using an Extremely Low Frequency Electromagnetic Field in Post-stroke Patients	To analyze extremely low frequency electromagnetic field therapy in improving the efficacy of rehabilitation of post-stroke patients relating to neuroplasticity processes	2018
6	Treatments to Promote Neural Repair after Stroke	Check repair-based therapies alongside acute therapies	2018
7	A review of combined neuromodulation and physical therapy interventions for enhanced neurorehabilitation	Comprehensive understanding of neuroplastic exercise interventions and non-invasive neuromodulation techniques tailored for specific diseases and diagnoses	2023
8	Enriched environment-induced neuroplasticity in ischemic stroke and its underlying mechanisms	To present studies on the clinical application of enriched environments in the rehabilitation of post-stroke patients	2023
9	Moderate intensity aerobic exercise may enhance neuroplasticity of the contralesional hemisphere after stroke: a randomised controlled study	Verify Moderate-Intensity Cycling to Increase Neuroplasticity in People With Stroke, as a Therapeutic Adjunct	2023
10	Can Transcranial Direct Current Stimulation Enhance Poststroke Motor Recovery?	Impacts of Tailoring tDCS Treatment to Individual Neuroanatomy and Physiology	2021
11	Somatosensory system integrity explains differences in treatment response after stroke	To test the hypothesis that, in the context of robotic therapy designed to enhance proprioceptive feedback via a Hebbian model, integrity of both somatosensory and motor systems would be important in understanding inter-participant differences in treatment-related motor gains	2019

12	Effects of transcranial direct current stimulation on lower limb function, balance and quality of life after stroke: a systematic review and meta-analysis	This systematic review with meta-analysis aimed to evaluate the effectiveness of tDCS on lower limb function, balance and quality of life in stroke patients	2023
13	HDAC2 (Histone deacetylase 2): A critical factor in environmental enrichment-mediated stroke recovery	To investigate that the generally accepted strategy to promote stroke recovery and its beneficial effect is positively correlated with neuroplasticity	2020
14	Effects of aerobic physical exercise on neuroplasticity after stroke: systematic review	To investigate the impact of aerobic exercise on neuroplasticity in patients with stroke sequelae	2021
15	The Implications of Microglial Regulation in Neuroplasticity-Dependent Stroke Recovery	Explore the impact of neuroplasticity on post-stroke restoration, as well as the functions and mechanisms of microglial activation, polarization, and phagocytosis	2023
16	Intensity matters: protocol for a randomized controlled trial exercise intervention for individuals with chronic stroke	Contribute new insights into the efficacy of HIIT to promote neuroplasticity in individuals with chronic stroke	2024
17	Relationship between Nutritional Status, Food Consumption and Sarcopenia in Post-Stroke Rehabilitation: Preliminary Data	Suggesting that an accurate diagnosis of sarcopenia, along with an appropriate assessment of nutritional status on admission to rehabilitation centers, seems strictly necessary to design individual, targeted physical and nutritional interventions for post-stroke patients, to improve their ability outcomes	2022
18	Neuroimaging Techniques as Potential Tools for Assessment of Angiogenesis and Neuroplasticity Processes after Stroke and Their Clinical Implications for Rehabilitation and Stroke Recovery Prognosis	To present neuroimaging techniques dedicated to the analysis of stroke recovery with reference to the processes of angiogenesis and neuroplasticity	2022
19	Synchrony Between Default-Mode and Sensorimotor Networks Facilitates Motor Function in Stroke Rehabilitation: A Pilot fMRI Study	Searching the literature on inter-network connectivity plays a facilitating role after stroke rehabilitation, which can serve as a neurorehabilitative biomarker for future intervention evaluations	2020
20	New Insights Into the Roles of Microglial Regulation in Brain Plasticity-Dependent Stroke Recovery	Recent advances in the impacts of microglial phenotype polarization on brain plasticity, attempting to discuss the potential efficacy of microglia-based extrinsic restorative interventions in promoting post-stroke recovery	2021
21	Cathodal tDCS exerts neuroprotective effect in rat brain after acute ischemic stroke	We investigated the neuroprotective effects of cathodic tDCS on brain injury caused by middle cerebral artery occlusion	2020

Table 1. Systematic table of studies selected for analysis.

Source: The autors

Neuroimaging data obtained by functional magnetic resonance imaging (fMRI) showed a reactivation of the contralateral motor cortical areas on the affected side, correlating with the observed functional improvement. Functional connectivity analysis revealed that synchronization between motor networks and default mode networks increased significantly after rehabilitation ($p < 0.05$), indicating a potential neuroplasticity mechanism underlying functional recovery.[4,18,19]

These findings suggest that neuroplasticity, mediated by factors such as MMP-9 and VEGF, plays a crucial role in recovery after stroke, and that focused rehabilitation interventions can optimize these processes. The combination of clinical and biomolecular approaches can provide a solid foundation for future research and personalized rehabilitation strategies.[5,6,9]

DISCUSSIONS

The role of neuroplasticity in rehabilitation after stroke is a topic of increasing relevance in medical neurology, especially considering the complexity of the mechanisms involved in functional recovery and the various therapeutic interventions that can be applied. Neuroplasticity, defined as the ability of the central nervous system to adapt structurally and functionally in response to new experiences or injuries, is critical for recovery after a stroke. This phenomenon not only allows the reorganization of neuronal connections, but is also influenced by environmental factors, physical exercises, and specific therapeutic interventions.[7,8,10,11]

The mechanisms of neuroplasticity after a stroke are complex and multifaceted. Studies have shown that spontaneous neuroplasticity occurs immediately after stroke, peaking around three to four weeks, and can be sustained during the chronic phase of recovery. This ability to adapt is mediated by several processes, including dendrite remodeling, the formation of new synapses, and neurogenesis. Activation of areas of the brain adjacent to the injury, such as the peri-infarct area, is crucial for functional recovery, as these regions can take over the functions of the damaged areas. Neuronal stimulation, for example, can promote activation of both the periinfarctic area and the contralateral motor cortex, resulting in improvements in functional performance. [12,13,18]

Therapeutic interventions aimed at promoting neuroplasticity have shown promise in post-stroke rehabilitation. The practice of physical exercise, especially aerobic training, has been associated with significant improvements in neuroplasticity and functional recovery. It is observed that aerobic exercise not only improves motor function, but can also reopen the window of neuroplastic recovery that occurs after stroke. In addition, exercise intensity appears to be a critical factor; High-intensity interventions, such as high-intensity interval training (HIIT), have been shown to be more effective at promoting neuroplasticity than traditional moderate-intensity exercise methods. [14,15,16,17]

Another innovative approach is the use of neuromodulation techniques, such as transcranial direct current stimulation (tDCS). Studies indicate that tDCS can induce plastic changes in the cerebral cortex, facilitating motor recovery after stroke. tDCS has the potential to modulate cortical excitability, promoting plasticity and accelerating functional recovery. However, the variability in patients' response to this intervention suggests that more research is needed to optimize its clinical use. [17,19,20]

In addition to physical and neuromodulatory interventions, the environment in which rehabilitation takes place also plays a crucial role in promoting neuroplasticity. Enriched environments, which offer varied sensory and social stimuli, have been shown to increase neuroplasticity and improve rehabilitation outcomes in post-stroke patients. The combination of physical exercises in stimulating environments can enhance the positive effects of neuroplasticity, promoting a more effective recovery. [19,20,21]

Understanding the biomarkers associated with neuroplasticity is also critical for the development of personalized rehabilitation strategies. Research on growth factors, such as brain-derived neurotrophic factor (BDNF), suggests that monitoring these biomarkers may help predict functional recovery and the effectiveness of therapeutic interventions. Evaluation of imaging techniques, such as functional magnetic resonance imaging (fMRI), can provide insights into functional connectivity and cortical reorganization during rehabilitation, allowing for adjustments in therapeutic approaches. [6,21]

CONCLUSION

Future directions in neuroplasticity research and post-stroke rehabilitation should focus on the integration of multiple therapeutic modalities, including pharmacological interventions, physical exercise, and neuromodulation, to maximize functional recovery. Personalization of interventions based on individual patient characteristics and continuous monitoring of neuroplasticity biomarkers can lead to improved clinical outcomes. In addition, the exploration of new technologies, such as brain-machine interfaces, can open up new possibilities for the rehabilitation of stroke patients, facilitating the re-engagement of the motor areas of the brain and promoting functional recovery.

In summary, neuroplasticity plays a central role in rehabilitation after stroke, being influenced by a variety of factors, including physical interventions, neuromodulation, and the rehabilitation environment. Understanding the mechanisms underlying neuroplasticity and implementing innovative therapeutic strategies are essential to optimize functional recovery and improve the quality of life of stroke survivors.

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