

Exploring the Role of Neuroplasticity in Stroke Rehabilitation: Mechanisms, Interventions and Clinical Implications

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ABSTRACT

Neuroplasticity, the brain's remarkable ability to reorganize and adapt throughout life, has emerged as a central focus in neuroscience research. This abstract delves into the mechanisms underlying neuroplasticity and its profound implications for learning, memory, rehabilitation, and neurological disorders. At the cellular level, neuroplasticity involves synaptic plasticity, where the strength and efficacy of connections between neurons can be modified through activity-dependent processes such as long-term potentiation (LTP) and long-term depression (LTD). Molecular mechanisms, including changes in neurotransmitter release, receptor expression, and intracellular signaling pathways, mediate these synaptic changes. Beyond synaptic plasticity, structural plasticity encompasses alterations in neuronal morphology, including dendritic branching, spine density, and axonal sprouting. These structural changes facilitate the formation of new neural circuits and underlie learning and memory processes. Neuroplasticity is not limited to developmental stages but persists throughout life, with experience and environmental factors continuously shaping the brain's structure and function. Experience-dependent plasticity is evident in various contexts, from skill acquisition to recovery from brain injuries. Understanding neuroplasticity has profound implications for education, as it highlights the importance of enriched environments and active learning strategies in promoting cognitive development. Additionally, neuroplasticity forms the basis for rehabilitative interventions following brain damage, with therapies focusing on promoting adaptive neural rewiring and functional recovery. Moreover, dysregulation of neuroplasticity is implicated in numerous neurological and psychiatric disorders, including Alzheimer's disease, stroke, and depression. Elucidating the mechanisms underlying aberrant plasticity holds promise for developing targeted interventions to treat these conditions. In conclusion, neuroplasticity represents a fundamental property of the nervous system, allowing for adaptation and optimization in response to environmental demands. Continued research into the mechanisms governing neuroplasticity promises to unveil new therapeutic avenues and deepen our understanding of brain function and dysfunction.

INTRODUCTION

Neuroplasticity can be defined as the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function, and connections. Neural plastic changes are associated with development and learning. They occur throughout the lifespan and may be enhanced following injury. They are influenced by experience and the context in which that experience occurs. The major drivers of neuroplastic change are meaningful behavior. Evidence of neural plastic changes can be observed at various levels, e.g., cellular/synaptic changes, changes in the structure and function of brain regions and networks, and changes in behavior such as improved skill and adaptability. Strong scientific evidence demonstrates that the brain has remarkable capacity for plasticity and reorganisation, yet exploiting this knowledge to enhance clinical outcomes is in its infancy.

After a brain injury, such as stroke, the person is challenged to sense, move, communicate, and engage in daily activities with the brain and body that are impacted by the stroke. Immediate and long-term effects of stroke include impairment in sensation, movement, cognition, psychological and emotional functions, and reduced independence and quality of life. There may be evidence of improvement and some regaining of lost skill. A trajectory of spontaneous and supported recovery over the days, weeks, and months after stroke has been described. Yet rehabilitation outcomes are currently suboptimal and variable, and evidence supporting novel or more effective treatments is limited.

Neural plastic changes occur following brain injury, such as stroke. The changes may occur in the days, weeks, months, and years following stroke. They may be adaptive or maladaptive. For example, a person can learn nonuse of the limb or develop dystonic postures following sensory loss. However, we have yet to harness this window of opportunity for ongoing recovery both short- and long-term after stroke. The continuum of recovery after stroke presents opportunities for targeted rehabilitation to harness and enhance these mechanisms of neural plasticity for improved outcomes.

Neural plastic changes are *experience* and *learning dependent*. *Learning* is the process of acquiring a relatively lasting change in knowledge and skills. Learning cannot be measured directly, and assessment may address different criterion indicators of learning. The potential exists for the phenomenon of neural plasticity to be shaped by the experiences that occur following stroke and to be positively impacted by rehabilitation. The question is how can we build on and shape this experience and drive positive plasticity to achieve better outcomes for stroke survivors?

Neurorehabilitation may be defined as “facilitation of adaptive learning”. *Stroke rehabilitation* founded on neuroscience is now recognised for its capacity to achieve more restorative outcomes. Experience and learning-dependent plasticity are core to this change. There are different conditions under which that plasticity may be enhanced, facilitated, and/or consolidated. These different conditions likely impact the type of neuroplasticity facilitated and behavioral outcomes observed. An advanced understanding of these will help guide the development of neuroscience-based interventions.

The aim of our scoping review was (i) to search the evidence available in relation to the three core concepts of neural plasticity, stroke recovery, and learning; (ii) to identify how these concepts are linked to each other; and (iii) to identify and discuss the themes/topics that best characterise the intersection of these three concepts, in order to better inform the neuroscience basis of stroke rehabilitation and stroke recovery. In relation to neural plasticity, we were interested in the identification of evidence of neuroplastic changes, e.g., at cellular and neural network levels. This included evidence such as synaptic changes, brain networks, and functional connectivity. We anticipated this literature would be primarily found in neuroscience and neuroimaging type journals. For the concept of stroke recovery, we were interested in outcomes related to impairment, performance, participation, and quality of life, at different times in the recovery trajectory and in relation to rehabilitation. The concept of *learning* focused on the process of change and included domains such as experience, different types of learning, attention and cognition, adaptation, environment, motivation, and goal. Investigation of the *links and intersection* between these concepts has the potential to reveal the following:

1. the type of learning experience that can enhance neural plasticity;
2. the evidence that links neural plasticity and improved outcomes for stroke survivors; and
3. how the different learning experiences linked with neural plasticity might influence/contribute to better stroke outcomes.

In achieving our aim, we sought to develop and use a methodology that would enable a broad and comprehensive scoping of the current literature. This included identification of key topics represented in the literature that relate to the three core concepts and an approach that permits searching and identification of related terms that may be used by authors. This was important to maximise the likelihood that a broad range of terms that are likely to have similar or overlapping meaning was able to be searched and accessed. Stroke continues to be a significant public health concern, ranking as the second-leading cause of mortality and the third-leading cause of mortality and disability combined, as measured by disability-adjusted life-years (DALYs) lost worldwide. Traditional approaches to stroke rehabilitation have predominantly centred

on facilitating functional recovery through compensatory strategies to alleviate the consequences of impairments rather than addressing their underlying causes. However, a growing realisation within the scientific and medical communities has underscored the extraordinary transformative potential embedded within neuroplasticity. This recognition has prompted a paradigm shift in stroke rehabilitation, emphasising the harnessing of neuroplasticity to facilitate functional recovery and promote substantial and enduring improvements in long-term outcomes for stroke survivors. This review aims to assess the role of neuroplasticity in facilitating stroke recovery and identify the challenges and limitations associated with its implementation. A comprehensive literature search was conducted to identify relevant studies, which were meticulously evaluated to determine the potential solutions for effectively harnessing neuroplasticity. The results indicate that neuroplasticity holds significant promise in stroke rehabilitation; however, individual variability in response to interventions, timing and duration of interventions and sociocultural and clinical factors pose challenges. Tailoring interventions to individual patient characteristics is crucial for optimising the impact of neuroplasticity. Despite challenges and limitations, the transformative potential of neuroplasticity in stroke rehabilitation is undeniable. The abstract concludes by emphasising the importance of a comprehensive understanding of individual variability, optimising intervention timing and duration and considering sociocultural and clinical factors. Future research and clinical practice should prioritise personalised interventions and interdisciplinary collaborations to fully exploit the vast potential of neuroplasticity in stroke recovery.

Recent advances in functional imaging of human brain activity in stroke patients, (positron emission tomographic (PET) and fMRI), reveal that cortical hemisphere contralateral to the infarction lesion plays an important role in this recovery process. There is also clinical evidence showing that the post ischemic reorganization occurring in somatosensory system of the contralesional (intact) hemisphere plays an important role for compensation for impaired functions. The underlying mechanism of this compensation occurring in the intact

hemisphere is important for optimizing the functional recovery of human stroke patients. The brain, including the motor system, learns by repetition and training.

Many basic mechanisms, however, are still poorly understood, and rehabilitative training is largely evidence based medicine. Nevertheless there are no generally accepted guidelines and no definite recommendations concerning the timing, kind and intensity of stroke rehabilitation. Stroke recovery is a complex process that probably occurs through a combination of restoration, substitution and compensation of functions. That is why it has been also difficult to translate results from rehabilitative studies in animals to recommendations for rehabilitative schedules in human stroke patients. A majority of clinical studies has been conducted in chronic stroke patients (>6months after the stroke) as recruitment of these patients was easier and baseline performance had stabilized These circumstances lead to functional outcome measurements probably gained largely from compensatory techniques to improve skills for daily living. The time courses of motor recovery differ among animal and human studies: While recovery in rodent models reaches the maximum around 4 weeks after stroke, human stroke survivors complete most of their recovery within 3 months.

NIRS could be used to predict the potential for clinical improvement in chronic stroke patients. It is also the first to demonstrate the complementary nature of neurophysiological and imaging techniques with NIRS in the prediction of functional potential and clinical outcomes. These findings have implications for clinical decision-making. Evaluation of brain function, using a combination of neurophysiological measures and imaging, can inform the setting of therapeutic effectiveness and the selection of patients for particular rehabilitation programs. This may lead to the conceptualization of re-habilitation strategies that are designed to maximally enhance rehabilitation through tailoring to individual patient deficits. Rehabilitation strategies may now be designed and optimized by employing methods to synchronize functional training of brain regions undergoing neural plasticity. However, a larger sample size, longer duration of training, or a restricted inclusion of stroke location and volume may be needed to demonstrate a difference between individually tailored rehabilitation programs and generic rehabilitation programs in efficacy in producing behavioral changes. Therapeutic approaches which directly stimulate the peripheral

nerve system or central nerve system electrically or by magnetic pulses may enhance neuroplasticity during post-stroke rehabilitation. Several studies showed that an increase of the excitability in the stroke-affected ipsilesional M1 by electrical devices resulted in improved motor outcome

The mechanisms of action of these techniques are under investigation but might involve changes in synaptic activity, gene expression and increases in neurotransmitter, receptor and neurotrophin levels or even enhanced fiber sprouting. A study of patients with stroke who had reached a plateau in motor recovery found that the volume of primary sensorimotor cortex activation in the ipsilesional hemisphere during affected hand movement was related to the level of behavioral recovery

Mechanisms of Neuroplasticity in Stroke Recovery

Review of cellular and molecular mechanisms underlying neuroplasticity post-stroke.

Post-stroke, neuroplasticity mechanisms involve cellular and molecular changes to adapt and repair damaged brain tissue. Neurons undergo structural modifications, synaptic connections adjust, and neurogenesis may occur. Glial cells play supportive roles in neuroplasticity, aiding in tissue remodeling and neuronal survival. Molecular signaling pathways, including neurotrophic factors and neurotransmitters, orchestrate these processes. Additionally, inflammation and immune responses influence neuroplasticity post-stroke. Understanding these mechanisms is crucial for developing targeted therapies to enhance recovery and functional outcomes in stroke patients.

Examination of synaptic remodeling, axonal sprouting, and neurogenesis.

Synaptic Remodeling

Synaptic remodeling involves the structural and functional changes in synaptic connections between neurons. After a stroke, the balance between excitatory and inhibitory neurotransmission is disrupted, leading to alterations in synaptic strength and connectivity. Several key processes contribute to synaptic remodeling:

Dendritic Spine Plasticity: Dendritic spines, the tiny protrusions on dendrites where most excitatory synapses form, undergo dynamic changes in response to neuronal activity. Following a stroke, there is an increase in dendritic spine turnover, with both spine loss and formation occurring concurrently. This dynamic remodeling allows for the rewiring of neural circuits as the brain attempts to compensate for the damaged regions.

Synaptic Pruning: Excessive synaptic connections may hinder functional recovery post-stroke. Synaptic pruning, a process by which unnecessary or dysfunctional synapses are eliminated, is crucial for refining neural circuits and optimizing connectivity. Astrocytes and microglia play key roles in synaptic pruning by engulfing and phagocytosing synapses that are no longer needed or are damaged.

Long-Term Potentiation (LTP) and Depression (LTD): LTP and LTD are forms of synaptic plasticity that underlie learning and memory processes. Following a stroke, there is a disruption in the balance between LTP and LTD, leading to altered synaptic plasticity. Restoring this balance through targeted interventions can promote functional recovery by facilitating the formation of new neural connections.

Axonal Sprouting

Axonal sprouting involves the growth of new axonal branches from existing neurons or the formation of collateral connections from neighboring neurons. This process is essential for rerouting neural circuits and establishing alternative pathways to bypass the damaged areas. Several mechanisms contribute to axonal sprouting:

Reactive Axonal Sprouting: In response to injury, neurons release growth-promoting factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which stimulate axonal sprouting. Reactive axonal sprouting can occur both locally, within the vicinity of the lesion, and distally, in remote brain regions.

Collateral Sprouting: Neighboring neurons can extend their axons to innervate denervated targets, forming collateral connections. This compensatory mechanism allows for the preservation of function by establishing alternative pathways for signal transmission.

Plasticity of White Matter Tracts: White matter tracts, composed of myelinated axons, undergo structural changes post-stroke. These changes include axonal remodeling, remyelination, and the formation of new connections through oligodendrocyte-mediated mechanisms.

Neurogenesis

Neurogenesis, the process of generating new neurons, occurs primarily in two regions of the adult brain: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus. While the extent of neurogenesis in the adult brain is limited compared to development, it plays a significant role in brain repair and functional recovery following injury, including stroke. Several factors influence neurogenesis post-stroke:

Inflammatory Response: The inflammatory milieu created in the aftermath of a stroke influences neurogenesis. Pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and tumor necrosis factor-alpha (TNF- α) can either promote or inhibit neurogenesis depending on the timing and context of their release.

Angiogenesis: Neurogenesis is closely linked to angiogenesis, the formation of new blood vessels. Angiogenic factors such as vascular endothelial growth factor (VEGF) not only promote the growth of blood vessels but also support neurogenesis by providing a conducive microenvironment for neuronal precursor cells.

Endogenous Stem Cells: Neural stem cells (NSCs) residing in the SVZ and SGZ contribute to neurogenesis post-stroke. These multipotent cells can proliferate, migrate to the site of injury, and differentiate into mature neurons, replenishing the lost neuronal population.

how these mechanisms contribute to functional recovery.

The cellular and molecular mechanisms of neuroplasticity post-stroke collectively contribute to functional recovery through several interconnected processes:

Compensation: Neuroplasticity allows the brain to compensate for lost function by rerouting neural circuits, establishing alternative pathways, and recruiting intact regions to assume the functions of damaged areas.

Reorganization: Synaptic remodeling, axonal sprouting, and neurogenesis drive the reorganization of neural networks, facilitating the formation of new connections and the integration of surviving neurons into existing circuits.

Rehabilitation: Rehabilitative interventions, such as physical therapy, cognitive training, and environmental enrichment, harness neuroplasticity mechanisms to promote recovery. These interventions stimulate neuronal activity, enhance synaptic plasticity, and support the formation of adaptive behaviors.

Functional Restoration: Ultimately, the goal of stroke rehabilitation is to restore lost function and improve quality of life. Neuroplasticity-driven recovery enables individuals to regain motor, sensory, and cognitive abilities, albeit to varying degrees depending on the extent of neuronal damage and the effectiveness of rehabilitation interventions.

Neuroplasticity-Based Rehabilitation Strategies

In this systematic review, a thorough search strategy was meticulously executed to identify pertinent articles from well-established databases. The search encompassed prominent platforms such as PubMed, Web of Science, and Scopus. We considered articles published between January 2000 and September 2022 to ensure a contemporary and comprehensive review. To cast a wide net, a set of key terms and MeSH terms was employed, including "Neuroplasticity," "Brain Injury," "Rehabilitation," "Neurorehabilitation". In adherence to rigorous inclusion criteria, we prioritized studies that specifically addressed neuroplasticity mechanisms and rehabilitation strategies following brain injury. Our focus was on human studies, encompassing randomized controlled trials, systematic reviews, meta-analyses, and comprehensive investigations exploring both immediate and delayed neuroplastic changes, as well as

rehabilitation interventions capitalizing on neuroplasticity and their subsequent outcomes. Exclusion criteria were applied to studies that diverged from these parameters, including those conducted on animals, published in non-English languages, or lacking relevance. After an exhaustive screening process involving initial database searches, 120 articles were identified. Subsequent evaluations based on titles and abstracts led to the selection of 110 articles for a thorough full-text review. Ultimately, 67 articles met the stringent inclusion criteria and were thus incorporated into the final review.

1] Constraint-induced movement therapy (CIMT) and its efficacy-

Constraint-Induced Movement Therapy (CIMT), also known as CI, is a "rehabilitative strategy". It is aimed at improving the functional use of an affected extremity for those who are impacted by stroke or other neurological conditions. It uses principles of mass practice while restraining the neurologically stronger limb. It has also been defined as a **behavioural approach** to neurorehabilitation, making use of simple behavioral techniques - shaping being a predominant theme.

CIMT has been described as including the essential components of rehabilitation following neurological injury, which comprise of

1. **Repetition** - task orientated in manner.
2. **Constraining** of patients, so as to induce use of the impaired limb or function.
3. **Application** of a "package of behavioural methods" (pg 1, para 1) which allow the transference of skills learned in the clinical settings to that of the real-world environment.

There are 3 major components of CIMT:

1. **Shaping** is a training method in which a motor task is gradually made more difficult. Shaping programs are individualized, consisting of 10-15 tasks selected primarily from a basic battery of tasks. Each task is usually performed in a set of 10-30 sec trials. At the end of each set of 10 trials, the task is changed. Only one shaping parameter is changed at a time. *Shaping requires constant therapist involvement.*
2. **Task practice** is repetitive practice of individual functional tasks that takes roughly 15-20mins. Rest is provided as required. Encouragement is given on an infrequent basis (i.e. every 5 mins) with feedback at the end of the task as well about how they performed. Task practice requires less therapist involvement.
3. **Packaging** of behavioural techniques (or the administration of a transfer package) is designed to transfer gains from the clinic to daily life. It includes a behavioral contract that improves adherence to the rehabilitation process. It also includes components such as a log book daily assignments and engaging patients in problem solving. Furthermore, this allows for the identification of barriers and problem-solving to overcome these obstacles. The daily administration of a motor activity log promotes adherence.

The treatment models are commonly explained in two methods:

1. **Unmodified CIMT**: Uses a variety of approaches that promote the affected limb for 90% of the individuals waking hours. Only activities involving toileting, hygiene and bathing are permitted. This is done by constraining or reducing the use of the unaffected extremity for 2-3 weeks. The most common form of constraints used for the upper extremity are slings, mitts with velcro or resting hand splints.
2. **Modified CIMT**: This is more pragmatic model. The program consists of 3 hour per day for 5 days/week, for a minimum of 4 successive weeks. In total there will be 20 treatment sessions totaling to 60 hours. The client is expected to use his/her affected extremity for a minimum of the five "top arm use hours" at home during each week day.

Advantages to CIMT

The following have been identified as advantages in the use of CIMT:

- Overall greater improvement in function than traditional treatment.
- Highly researched and highly credible treatment approach.
- There are brain activity and observed gray matter reorganization in primary motor, cortices and hippocampus.
- Increase social participation.
- Decrease in medical cost over lifetime.

Transcranial magnetic stimulation (TMS) and other neuromodulation techniques.

TMS is a non-invasive brain neuromodulation technique that modifies brain activity using magnetic fields, which in turn generate an electric field in the area to be treated, producing **neuronal depolarization**. In this way, it is possible to **modulate brain activity**, a useful technique in the diagnosis and treatment of different pathologies.

With over 13,900 scientific studies of this technique, the **amount of scientific evidence is significant**.

Application is comfortable and simple. It is performed transcranially. A coil is placed over the patient's scalp, and this coil produces a magnetic field. This magnetic field generates an electric current which manages to selectively modulate brain activity, without causing pain to the patient.

This technique can be applied in a single pulse, in paired pulses separated by intervals, or in trains of repeated pulses at various frequencies.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive treatment that delivers repetitive pulses of an MRI-strength magnetic field from a coil placed over the scalp. Powered by a rapidly pulsed current, the magnetic field passes unimpeded through the skull and stimulates brain tissue beneath, inducing currents that may help normalize activity in the area stimulated without producing seizure activity.

The FDA approved rTMS in 2008 as a treatment to alleviate symptoms of mildly treatment-resistant depression, in which patients have not found relief from antidepressant medication. It has also been studied as a possible treatment for a number of other disorders, such as schizophrenia, pain, stroke, and amyotrophic lateral sclerosis (ALS).

TMS was introduced in 1985, based on technology for experimentally probing brain activity. TMS was initially hoped to offer similar benefits to electroconvulsive therapy (ECT), without its drawbacks, such as impacting memory. ECT is still offered to patients who do not benefit from antidepressant medication, and is carried out under general anesthesia to limit discomfort from the convulsions it induces.

By contrast, rTMS is carried out while the patient is awake and reclining in a specially equipped chair. Sessions usually last 20-40 minutes, five days a week, typically for six weeks.

In open-label clinical trials, after 4-6 weeks of treatment, one out of two patients treated with rTMS for depression experienced a reduction in symptoms of 50% or more, and one out of three experienced remission. The effect was lower in patients who had exhibited resistance to more antidepressants.

The persistence of the effect is still being investigated. The therapeutic effect has been reported to last for at least six months, with intermittent repeat sessions as an option to prevent relapse. (1) After coming in for daily treatments during the initial treatment phase, patients should continue to be monitored and receive maintenance therapy if needed, which may include receiving a medication.

For patients with treatment-resistant depression, rTMS has been approved in Canada, Australia, New Zealand, the European Union, and Israel in addition to in the United States.

The therapy is conducted with earplugs to reduce the noise of the magnet, which makes a rapid "woodpecker"-like tapping. About one-third of patients experience a mild headache following treatment. Another third of patients notice a prickly, tingly sensation on their scalp while the stimulating pulses are being administered. One in 1,000 patients experience a provoked seizure; while this risk is similar to that from some antidepressant medications (e.g. bupropion) seizures related to rTMS exposure have terminated soon after the magnetic stimulation ends.

While clinical trials indicate TMS is generally safe and well-tolerated, the effectiveness overall is considered modest (effect size about 0.5 [2]), so in evidence-based practice guidelines it is not classified as a first-line treatment although it may be offered prior to more stringent measures such as ECT.

Due to its non-invasive nature and minimal risk of lasting side effects, rTMS has been studied as a possible treatment for a wide range of psychiatric conditions. The data are strongest for use in treatment of unipolar major depressive disorder. In schizophrenia, it has been under investigation to reduce the likelihood of hearing nonexistent voices (auditory hallucination) and of negative disease symptoms, such as apathy. It has also been studied for relieving symptoms of Parkinson's disease, dystonia, tinnitus, anxiety, migraine, eating disorders and bipolar disorders, as well as for pain, stroke and ALS, among other conditions.

BENEFITS OF TMS.

To achieve the desired result, TMS must be applied regularly in order to generate neuroplasticity and effectively modulate brain activity. The following are some of the benefits this technique provides patients and professionals:

- Non-invasive and painless technique.
- Suitable for diagnosis and treatment.
- Capable of generating evoked potentials.
- High clinical effectiveness.
- Significant scientific evidence.
- Improves symptoms of a number of different pathologies.
- Optimizes and allows customization of treatment for a number of different pathologies.
- Reduced consumption of pharmaceuticals and hospital stay.

The ultimate goal of stroke management is to promote optimal recovery of lost functions and reduce further injury. This recovery depends majorly on brain plasticity; a spontaneous regeneration process that encompasses neural plastic changes in the lesioned hemisphere to reestablish its structural and functional reorganization. Brain plasticity under pathological condition completely differs from plasticity under properly functioning brain. For instance, plasticity in normally functioning brain is a prerequisite basis of learning and memory that involves plastic adaptation such as long-term potentiation (LTP). This is opposed to plastic changes observed using MRI in cerebral stroke pathology, that involves modification in intracortical myelin, augmented neurogenesis, improved spine density in neuronal dendrites and alterations in astrocyte volume.

Stroke recovery to certain extent also depends on severity extent of the initial injury deficit as the severity of the damage is inversely related to the prognosis for recovery. But it was also observed that recovery differs even among post stroke patients with similar clinically assessed severity. This apparently stress the recovery role of other brain endogenous survival mechanism such as extent to which collateral circulation bypass to supply blood to the perilesional neurons, angiogenesis, inhibitory neurotransmitters that counteract excitotoxicity, and multiple representations of the same function in different cortical areas. Appropriate rehabilitation and drug treatment that target underline cause of stroke are also critical to recovery after post stroke cerebral damage. Rehabilitation aims to maximize optimum recovery of lost functions as a result of impairments deficit after stroke but overall, brain plasticity underlies recovery promoted by rehabilitation.

Recovery from stroke has also been attributed to be dependent on resolution of early local processes in the brain that includes resolve of perilesional edema, re-emergence of circulation within the ischemic penumbra, resolution of remote functional depression of neurological function induced by process of diaschisis. As previously stated stroke recovery majorly depends on brain reorganization process of plasticity which in turn dictates recovery promoted by rehabilitation. Mechanism through which rehabilitation mediates brain plasticity to promote recovery has been studied and explained. Rehabilitation such as physical therapists stroke interventions modifies neurotrophic factor expression in the CNS especially brain derived neurotrophic factor (BDNF), which in turn upon binding with its tyrosine kinase B (TrkB) cognate receptor recruits a cascade of signaling pathways that ultimately mediates activity-

associated plasticity of neurons. Activity-associated plasticity signifies a means of functional and structural neuroplasticity that is tailored by the depolarizing behavior of neurons, and the mechanisms governing activity-associated plasticity includes LTP and activity-associated development of corticospinal circuitry among others. Therefore, through brain plasticity after cerebral stroke, reorganization by recruiting cortical or subcortical structures to adopt the function of the injured tissue, reinforcement of remaining synaptic pathways and then creating new connections, recruitment of other pathways that are functionally alike the damaged tissue but anatomically distinct, strengthening of existing but weaker and functionally silent connections, can all be achieved to recover lost cerebral functions.

Strategy	Proposed mechanism reported to modulate and promote neuroplasticity
Transcranial direct current stimulation (noninvasive)	Modification of neuronal membrane potentials, consequently persuading neuronal excitability which form part of the basis of neuroplasticity.
Deep brain stimulation (invasive)	This by stimulating neuronal network connected to the stimulated region, the pathological neuronal network becomes altered by changes in the neurochemical components thereby inducing morphological changes in both the dendrites (dendritic arborization) and axons (axonal sprouting).
Functional Electrical Stimulation (FES) (noninvasive)	Hypothesized to modulate neuroplasticity through repeated generation of neurons synaptic activity that might facilitate synaptic remodeling, leading to neural reorganization.
Aerobic Exercise	Aerobic exercise is linked with surge in neurogenesis and angiogenesis, together with rise in neurotrophic molecules especially BDNF and other growth factors implicated in neurite outgrowth and synaptic plasticity
Brain-derived neurotrophic factor (BDNF) therapy	By binding of BDNF to its TrkB cognate receptor, two distinctive intracellular signaling pathways namely phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK) becomes initiated, thereby regulating transcriptional gene activity of neurite outgrowth and neurogenesis.
Statins	Proposed mechanism by which statins modulates neuroplasticity involves indirect effect through statin-mediated increase in proteins such as endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), tissue plasminogen activator (tPA), and brain-derived neurotrophic factor (BDNF) among others.
Erythropoietin (EPO) therapy	EPO and EPO receptor (EPOR) that both becomes upregulated in response to cerebral ischemia, when supplemented act to indirectly augment neurogenesis through EPO-mediated increase in the expression vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF).
Phosphodiesterase type 5 inhibitors (PDE-5 inhibitors)	PDE-5 inhibitors competitively inhibit phosphodiesterase enzymes responsible for converting cyclic guanylyl monophosphate (cGMP) back to GMP, thus fostering cGMP accumulation which has diverse cellular effect in the brain including angiogenesis, and neurogenesis which are requirements of neuroplasticity
Vascular endothelial growth factor (VEGF) therapy.	Proposed mechanism through which VEGF modulates neuroplasticity involves mediating the PI3K–AKT–nuclear factor kappa B signaling pathway; an intracellular pathway that regulate transcriptional factors involves in neurogenesis

Neuroimaging and Biomarkers

Overview of neuroimaging techniques for studying neuroplastic changes post-stroke.

Neuroimaging techniques offer valuable insights into neuroplastic changes post-stroke. Functional MRI (fMRI) measures brain activity during tasks, revealing compensatory mechanisms and reorganization of functional networks. Diffusion tensor imaging (DTI) assesses white matter integrity, highlighting axonal sprouting and structural reorganization. Positron emission tomography (PET) imaging detects metabolic and molecular changes, elucidating neuroplasticity-related processes such as neurotransmitter function and neuroinflammation. These modalities collectively provide a comprehensive understanding of stroke recovery mechanisms, guiding the development of targeted interventions for rehabilitation.

Functional MRI (fMRI), diffusion tensor imaging (DTI), and PET imaging.

Functional MRI (fMRI): fMRI is a non-invasive imaging technique that measures changes in blood oxygen level-dependent (BOLD) signals to infer neural activity. In the context of stroke recovery, fMRI helps identify brain regions involved in motor, cognitive, and language functions. For example, studies have shown increased activation in ipsilesional and contralesional motor areas during motor tasks post-stroke, indicating potential compensatory mechanisms. Furthermore, longitudinal fMRI studies enable tracking of neuroplastic changes over time, providing insights into the recovery trajectory. For instance, research has demonstrated functional reorganization of language networks in aphasic patients, with increased activation in spared regions and recruitment of compensatory pathways.

Diffusion Tensor Imaging (DTI): DTI is a specialized MRI technique that measures the diffusion of water molecules in brain tissue, providing information about white matter microstructure. Following stroke, DTI enables the characterization of changes in white matter integrity, such as axonal damage, demyelination, and axonal sprouting. Fractional anisotropy (FA), a DTI metric, reflects the directionality of water diffusion and is commonly used to assess white matter integrity. Reduced FA values in the ipsilesional hemisphere and white matter tracts connecting affected regions are indicative of injury and disruption of neural pathways post-stroke. Conversely, increases in FA values over time suggest neuroplastic remodeling and structural reorganization.

Positron Emission Tomography (PET) Imaging: PET imaging allows visualization of metabolic and molecular processes in the brain by detecting radiolabeled tracers. In the context of stroke recovery, PET can assess regional cerebral blood flow, glucose metabolism, neurotransmitter function, and neuroinflammation.

For example, studies using PET have demonstrated changes in glucose metabolism and neurotransmitter receptor availability in peri-infarct regions and remote brain areas following stroke. These metabolic alterations reflect adaptive responses and neuroplastic changes associated with recovery processes.

Identification of Potential Biomarkers Associated with Neuroplasticity:

Biomarkers play a crucial role in stroke research and clinical practice by providing measurable indicators of biological processes associated with stroke pathophysiology, recovery mechanisms, and treatment response. In the context of neuroplasticity post-stroke, identifying biomarkers associated with adaptive changes in brain structure and function is essential for predicting recovery outcomes, monitoring disease progression, and guiding personalized rehabilitation interventions. Biomarkers can encompass various molecular, cellular, structural, and functional markers that reflect underlying neuroplastic processes and treatment effects.

Biomarkers associated with neuroplasticity post-stroke:

Molecular Biomarkers: Molecular biomarkers include proteins, peptides, nucleic acids, and metabolites that are involved in neuroplasticity-related processes, such as synaptic remodeling, axonal sprouting, neurogenesis, and neuroinflammation. These biomarkers can be detected in blood, cerebrospinal fluid (CSF), or brain tissue samples using biochemical assays, proteomic analyses, or molecular imaging techniques.

- **Neurotrophic Factors:** Growth factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF) play key roles in promoting neuronal survival, synaptic plasticity, and neurogenesis post-stroke. Changes in circulating levels of neurotrophic factors have been associated with stroke severity, functional recovery, and response to rehabilitation interventions.
- **Inflammatory Markers:** Neuroinflammation is a hallmark feature of stroke pathology and contributes to secondary tissue damage and neuroplasticity. Biomarkers of neuroinflammation, such as cytokines, chemokines, and microglial activation markers, can be detected in blood, CSF, or brain imaging studies. Alterations in inflammatory biomarkers have been linked to stroke outcomes, post-stroke depression, and cognitive impairment.
- **Neurotransmitters and Metabolites:** Changes in neurotransmitter levels (e.g., dopamine, serotonin, glutamate) and metabolite profiles (e.g., lactate, lactate/pyruvate ratio) reflect alterations in neuronal activity, energy metabolism, and synaptic transmission post-stroke. Biomarkers of neurotransmitter function and metabolic activity can be assessed using neurochemical assays, magnetic resonance spectroscopy (MRS), or positron emission tomography (PET) imaging.

Cellular Biomarkers: Cellular biomarkers encompass various cellular components and processes associated with neuroplasticity, including neuronal and glial markers, cell proliferation, differentiation, and synaptic connectivity. These biomarkers can be measured using histological techniques, immunohistochemistry, flow cytometry, or molecular imaging approaches.

- **Neuronal Markers:** Biomarkers of neuronal injury (e.g., neuron-specific enolase, neurofilament proteins) and regeneration (e.g., doublecortin, PSA-NCAM) provide insights into neuronal survival, axonal sprouting, and dendritic remodeling post-stroke. Changes in neuronal markers can be detected in brain tissue samples, cerebrospinal fluid (CSF), or neuroimaging studies.
- **Glial Markers:** Glial cells, including astrocytes, microglia, and oligodendrocytes, play critical roles in neuroinflammation, synaptic remodeling, and myelin repair post-stroke. Biomarkers of glial activation (e.g., glial fibrillary acidic protein, ionized calcium-binding adaptor molecule 1) and myelin integrity (e.g., myelin basic protein, myelin-associated glycoprotein) reflect glial responses to injury and neuroplastic changes in white matter tracts.

Structural Biomarkers: Structural biomarkers encompass measures of brain anatomy, white matter integrity, and lesion characteristics derived from neuroimaging techniques such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and voxel-based morphometry (VBM).

- **Lesion Volume and Location:** Biomarkers of stroke lesion volume, location, and topography provide insights into the extent of brain damage, involvement of specific neuroanatomical structures, and prognosis for functional recovery. Lesion characteristics, such as infarct volume, cortical involvement, and subcortical involvement, influence neuroplasticity mechanisms and rehabilitation outcomes.
- **White Matter Integrity:** Biomarkers of white matter integrity, such as fractional anisotropy (FA) derived from DTI, reflect the structural integrity of white matter tracts and axonal connectivity post-stroke. Changes in FA values, tractography patterns, and white matter lesion burden are associated with neuroplastic remodeling, reorganization of functional networks, and recovery of motor and cognitive functions.

Functional Biomarkers: Functional biomarkers encompass measures of brain function, connectivity, and network dynamics derived from functional neuroimaging techniques such as functional MRI (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG).

- **Resting-State Functional Connectivity:** Biomarkers of resting-state functional connectivity reflect intrinsic brain networks and their alterations following stroke. Changes in functional connectivity patterns, network efficiency, and network centrality indices provide insights into neuroplastic reorganization, compensatory mechanisms, and recovery trajectories post-stroke.
- **Task-Based Functional Activation:** Biomarkers of task-based functional activation identify brain regions involved in specific motor, cognitive, or language tasks and their responsiveness to interventions. Changes in activation patterns, task-related connectivity, and lateralization indices inform the efficacy of rehabilitation strategies and predict functional outcomes post-stroke.

Correlation Between Neuroimaging Findings, Biomarkers, and Functional Outcomes

Integrating neuroimaging findings with biomarkers and functional outcomes provides a comprehensive understanding of the neuroplasticity mechanisms underlying stroke recovery. By correlating changes in brain structure and function with molecular and cellular markers, researchers can elucidate the biological basis of recovery and identify potential therapeutic targets.

For example, studies have explored the relationship between neuroimaging measures of functional connectivity, such as resting-state fMRI-derived connectivity patterns, and molecular biomarkers associated with synaptic plasticity, neurogenesis, and inflammation. By examining these associations, researchers can identify candidate biomarkers predictive of functional outcomes and treatment response. Furthermore, advances in machine learning and computational modelling enable the development of predictive models that integrate multi-modal neuroimaging data and biomarker profiles to forecast individualized recovery trajectories and optimize rehabilitation strategies.

Individual Variability in Plasticity Response

A fundamental problem in neuroscience is decoding of information contained in the structure and functional activity of the nervous system. Apart from its significance for the general understanding of brain functions, the problem is of increasing practical importance mainly in connection with developing the technology of brain-computer interfaces and using them to control prostheses. However, there emerges a very serious problem in the way to information decoding—variability of neuronal responses. Variability of neuronal responses can also be registered on a larger scale during detection of motor evoked potentials (MEPs) in response to stimulation of the cortex with a magnetic field pulse. Upon stimulation of the same cortical area with the same intensity using skin myographic electrodes, a MEP of a varying amplitude and latency is detected. In modern literature, there are a number of models describing the causes of variability. Most of them are as follows. At the single cell level, response variability is determined by noise of a peripheral sensor, stochastic nature of synaptic transmission, dynamic changes associated with neuronal adaptation, and neuroplasticity.

The MEP variability is explained as follows. “Related to TMS of M1, neurophysiologic parameters such as independent fluctuations in excitability of the M1 and interneurons as well as motor neurons on the spinal level (Eg Spinal desynchronization) also contribute to the variability of MEPs”. Stroke is the leading cause of long-term adult disability and the fifth leading cause of death in the US, with approximately 795,000 stroke events in the US each year. The aging of the population, coupled with the reduction in case fatality after stroke, is expected to increase the prevalence of stroke by 3.4 million people between 2012 and 2030. While stroke mortality had decreased in the US over the past two decades, recent trends in mortality indicate that these decreases may have levelled off, and that stroke mortality may even be rising again. Unlike myocardial infarction, which is almost always due to large vessel atherosclerotic disease affecting the coronary arteries, identification of risk factors for stroke is complicated by the fact that strokes come in many varieties. At the most basic level, stroke is divided into haemorrhagic and ischemic strokes. The majority (approximately 80%) of strokes are ischemic, although the relative burden of haemorrhagic versus ischemic stroke varies among different populations.

Haemorrhagic strokes can be either primarily intraparenchymal or subarachnoid. Ischemic stroke can be further divided into what have been referred to as etiologic subtypes, or categories thought to represent the causes of the stroke: cardioembolic, atherosclerotic, lacunar, other specific causes (dissections, vasculitis, specific genetic disorders, others), and strokes of unknown cause. Risk factors for haemorrhagic and ischemic stroke are similar, but there are some notable differences; there are also differences in risk factors among the etiologic categories of ischemic stroke. Hypertension is a particularly important risk factor for haemorrhagic stroke, though it contributes to atherosclerotic disease that can lead to ischemic stroke as well. Hyperlipidaemia on the other hand, is a particularly important risk factor for strokes due to atherosclerosis of extracranial and intracranial blood vessels, just as it is a risk factor for coronary atherosclerosis. Atrial fibrillation is a risk factor for cardioembolic stroke. Non-modifiable risk factors (also called risk markers) for stroke include age, sex, race-ethnicity and genetics. In general, stroke is a disease of aging. The incidence of stroke increases with age, with the incidence doubling for each decade after age 55.

The mean age of incident ischemic stroke in 2005 was 69.2 years. Recent evidence suggests, however, that the incidence and prevalence of ischemic stroke has been increasing in the 20 to 54 year old age group, from 12.9% in 1993/1994 to 18.6% in 2005. In a retrospective analysis of the population, the proportion of incident stroke occurring among those aged 20-54 years increased at each of three one-year time intervals, from 12.9% in 1993/1994, to 13.3% in 1999, to 18.6% in 2006. In an analysis of the Nationwide Inpatient Sample, among adults 14-44 years ischemic stroke admissions increased annually from 1995-2008. In haemorrhagic stroke patients, the incidence increases after the age of 45. The modifiable risk factors are of utmost importance, as intervention strategies aimed at reducing these factors can subsequently reduce the risk of stroke. Early identification and modification of risk factors is imperative. Modifiable risk factors can be further divided into medical conditions and behavioural risk factors. The role of many "traditional" risk factors in causing stroke, such as hypertension, diabetes, hyperlipidaemia, and smoking are well-established. The investigation of novel or "emerging" risk factors remains an area of active research. Hypertension is the most important modifiable risk factor for stroke, with a strong, direct, linear, and continuous relationship between blood pressure and stroke risk. In INTERSTROKE, hypertension was by far the most important stroke risk factor: using a definition of hypertension that included both a history of hypertension as well as a blood pressure measurement of 160/90 mm Hg, the population attributable risk, or proportion of strokes in the population attributable to hypertension, was 54%.

Diabetes mellitus is an independent risk factor for stroke with a 2-fold increased risk in stroke for diabetic patients and stroke accounts for 20% of deaths in diabetics. Prediabetics are also at increased risk of stroke. Approximately 8% of population have diabetes mellitus, with nearly half of the population ≥ 65 years of age prediabetic. The duration of diabetes mellitus is also associated with increased stroke risk. In recent study, duration of diabetes mellitus was associated with ischemic stroke. Compared with nondiabetic participants, those with diabetes mellitus for 0 to 5 years and 5 to 10 years were at increased risk, and the risk for those with diabetes mellitus for ≥ 10 years increased markedly. Diabetic patients who have a stroke tend to be younger have a higher prevalence of other stroke risk factors. The increase in diabetes mellitus may explain some of the increase in the risk of stroke in younger populations. The use of combined behavioural modification and medical therapy in diabetics has been shown to reduce the risk of stroke. Hereditary factors contribute to stroke risk because of genetic mutations and because of shared familial exposures remains challenging. The task has been complicated by the heterogeneity of stroke, the multitude of conventional risk factors that cause stroke, and the variability among populations and studies. Genetic variability may, however, contribute to stroke risk through several potential mechanisms. First, specific rare single gene disorders may contribute to individual familial syndromes for which stroke is the primary or unique manifestation (Eg cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Second, single gene disorders may cause a multisystem disorder of which stroke is just one manifestation (Eg sickle cell anaemia). Third, some common variants of genetic polymorphisms have been associated with stroke risk, although the individual contribution of such

polymorphisms is regarded as modest (Eg variants in 9p21). Fourth, genetic causes of conventional stroke risk factors, such as AF, diabetes mellitus, and hypertension, are also, not surprisingly, associated with risk of stroke. Emerging evidence suggests that genetic studies could help to distinguish stroke subtypes and even contribute to patient management. For example, there is an association between gene variations that confer an increased risk of AF and ischemic stroke.

This raises the possibility that genetic tests could help to make the diagnosis of strokes likely to be because of AF. Pain encompasses sensory, cognitive, and most importantly affective components. The affective component of pain includes feelings of annoyance, sadness, anxiety, and depression in response to a noxious stimulus. In particular, depression and pain share a high degree of comorbidity, and a large number of studies have examined the close relationship between pain and depression. Acute pain induces depressed mood, and chronic pain is known to cause depression. Depression, meanwhile, can also adversely affect pain behaviours ranging from symptomology to treatment response. Pain and depression independently induce long-term plasticity in the central nervous system (CNS). Comorbid conditions, however, have distinct patterns of neural activation. We performed a review of the changes in neural circuitry and molecular signalling pathways that may underlie this complex relationship between pain and depression. We also discussed some of the current and future therapies that are based on this understanding of the CNS plasticity that occurs with pain and depression. Acute pain can adversely affect mood following surgery. In the immediate postoperative period, the rate of depression has been reported to be between 21 and 50% in study populations with low (0–11.8%) levels of preoperative depression. Indeed, postoperative pain intensity is correlated with the degree of depressive symptoms. High postoperative depression scores have also been associated with increased length of stay and poor functional outcomes after surgeries. Preoperative psychological factors may also negatively affect the resolution of acute pain. Preoperative anxiety and catastrophising are two well-studied risk factors for the development of chronic postsurgical pain. Both of these factors are known to lead to worsening depressed mood in the postoperative period. In imaging studies of acute experimental pain in human subjects, areas most commonly activated include the primary somatosensory (S1) and secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), insular cortex (IC), prefrontal cortex (PFC), thalamus, nucleus accumbens (NAc), and amygdala. S1 and S2 activations contribute to the sensory-discriminative dimension of pain. The ACC, PFC, IC, NAc, and amygdala, meanwhile, have been implicated in the affective component of pain. Distinct alterations in brain structure and activity, meanwhile, occur with chronic pain. For example, reductions in grey matter volume are observed in the IC, ACC, and PFC, areas involved in the emotional and cognitive aspects of pain.

Translation to Clinical Practice.

Approximately one-third of patients with stroke exhibit persistent disability after the initial cerebrovascular episode, with motor impairments accounting for most poststroke disability. Exercise and training have long been used to restore motor function after stroke. Better training strategies and therapies to enhance the effects of these rehabilitative protocols are currently being developed for poststroke disability. The advancement of our understanding of the neuroplastic changes associated with poststroke motor impairment and the innate mechanisms of repair is crucial to this endeavour. Pharmaceutical, biological and electrophysiological treatments that augment neuroplasticity are being explored to further extend the boundaries of poststroke rehabilitation. Potential motor rehabilitation therapies, such as stem cell therapy, exogenous tissue engineering and brain–computer interface technologies, could be integral in helping patients with stroke regain motor control. As the methods for providing motor rehabilitation change, the primary goals of poststroke rehabilitation will be driven by the activity and quality of life needs of individual patients. This Review aims to provide a focused overview of neuroplasticity associated with poststroke motor impairment, and the latest experimental interventions being developed to manipulate neuroplasticity to enhance motor rehabilitation. There are now a large number of technological and methodological approaches to the rehabilitation of motor function after stroke. It is important to employ these approaches in a manner that is tailored to specific patient impairments and desired functional

outcomes, while avoiding the hype of overly broad or unsubstantiated claims for efficacy. Here we review the evidence for poststroke plasticity, including therapy-related plasticity and functional imaging data. Early demonstrations of remapping in somatomotor and somatosensory representations have been succeeded by findings of white matter plasticity and a focus on activity-dependent changes in neuronal properties and connections. The methods employed in neurorehabilitation have their roots in early understanding of neuronal circuitry and plasticity, and therapies involving large numbers of repetitions, such as robotic therapy and constraint-induced movement therapy (CIMT), change measurable nervous systems properties. Other methods that involve stimulation of brain and peripheral excitable structures have the potential to harness neuroplastic mechanisms, but remain experimental. Gaps in our understanding of the neural substrates targeted by neurorehabilitation technology and techniques remain, preventing their prescriptive application in individual patients as well as their general refinement. However, with ongoing research—facilitated in part by technologies that can capture quantitative information about motor performance—this gap is narrowing. These research approaches can improve efforts to attain the shared goal of better functional recovery after stroke.

Designing clinical trials to test novel interventions neuroplasticity

Up to 2/3rd of the stroke subjects may experience impairment in any of the somatosensory modalities such as light touch, proprioception, and stereognosis. The sensory recovery is strongly associated with the level of motor recovery. Very negligible sensory-based interventions have been developed and found to be evident in enhancing the sensory deficit and associated motor recovery. The possible factor for the ineffectiveness of these sensory interventions could be lack of the neuroscientific basis in formulation of the program. Thus, the objective of the study is to determine the effectiveness of a neuroplasticity-principles-based sensory-rehabilitation protocol on motor and sensory recovery, and disability of the post-stroke hemiparetic subjects.

Trial has two phases: intervention and follow-up. The intervention consisted of neurofeedback treatment, including intake and outcome measurements, using a waiting-list control group. Treatment involved around 40 hour long sessions, 2-5 times per week. Training involved either theta/beta or sensorimotor-rhythm regimes, adapted by adding a novel "inverse-training" condition to promote self-regulation. Follow-up (ongoing) will consist of self-report and executive function tests. It is proposed to recruit 122 poststroke subjects in a randomized controlled, assessor blinded trial to be conducted in a rehabilitation-institute. The key eligibility criteria is age between 20 to 80 years, hemiparesis (right or left), ischemic or haemorrhagic stroke, 1 to 12 months poststroke, and impairment in any of the sensory modalities. The participants in the experimental group will receive neuroplasticity-Principles-based sensory-Rehabilitation (**NEPSER**) protocol comprising active, repetitive, and meaningful training of the specific sensory modalities utilizing visuo-perceptual, cognitive, motor, and functional tasks will be imparted for 8 weeks, 5 sessions / week, each of 2 h. The control subjects will undergo only standard rehabilitation based on neurophysiological, biomechanical, and rehabilitative approaches. All the participants will be assessed for motor (Fugl-Meyer assessment, upper extremity section) and sensory recovery [Nottingham Sensory assessment (Erasmus MC modification of the revised version)] at baseline, 8-week, and 12-week follow-up. The Semmes Weinstein monofilament, two-point discrimination test and modified Rankin scale (disability) will be applied as secondary measures. A repeated-measures 2-way ANOVA will be used to estimate difference for the post intervention and follow-up scores between the groups. Symptoms were assessed by computerized attention test (T.O.V.A.) and self-report scales, at intake and outcome. Performance during neurofeedback trials was recorded. Participants were recruited and completed intake measurements during summer 2012, before assignment to treatment and control, September 2012. Outcome measurements ran April-August 2013. After dropouts, 23 treatment and 21 waiting-list participants remained for analysis. Initial analysis showed that, compared to waiting-list control, neurofeedback promoted improvement of self-reported ADHD symptoms, but did not show transfer of learning to T.O.V.A. Comprehensive analysis will be reported elsewhere. The proposed study will lead to development of a novel rehabilitation protocol

that will not only enhance the sensory recovery but also the motor and functional recovery. This may reduce the impact of stroke disability and enhance the quality of life.

TRIAL REGISTRATION:

- The trial has been registered under Clinical Trial Registry of India (CTRI) as CTRI/2019/09/021442 on 30th September 2019.
- Computer Enabled Neuroplasticity Treatment (CENT), ISRCTN13915109.

Development of guidelines for optimizing rehabilitation based on neuroplasticity principles

So far there is no clear understanding of the principles underlying effective neurorehabilitation approaches. Therapeutic protocols can be readily described by the following aspects: the body part trained (e.g., the legs), the tools or machines used for the training (e.g., a treadmill), the activity performed (e.g., walking), and when the therapy commences (e.g., during the acute phase after a stroke). However, an intervention typically includes more elements. For instance, the use of the less affected limb can be restricted, and the therapist can encourage the patient to spend more time exercising or give feedback about task performance. While some interventions, like CIMT, clearly define their active ingredients that should lead to effective recovery, most others do not. Neurorehabilitation research aims to find interventions that promote recovery and to establish whether the presence or absence of improvement can be explained by any neuronal changes that occur in the post-stroke brain. Neuroscience can help us to create interventions that lead to changes in the brain; however, with no clear understanding of what an intervention does, attributing causality remains difficult. One way to formalize an intervention is by breaking it into parts, studying the behavioural and neural effects of these parts, and deriving principles from them—in the case of stroke neurorehabilitation, these would be principles that optimize acquisition, retention, and generalization of skills.

Identification of Principles of Neurorehabilitation

Our computerized search yielded 548 records, of which 74 were deemed adequate for further screening after we examined if their titles either contained any of the search terms or appeared to discuss post-stroke rehabilitation strategies. After analysis of their abstracts and full-texts, the principles mentioned in 17 articles were extracted. We excluded papers if their title or abstract reported or compared surgical or pharmaceutical interventions as well as if they discussed stroke taxonomies, proposed study protocols or clinical trials, covered principles unrelated to stroke and/or stroke rehabilitation itself (e.g., principles for disease prevention, pre- and post-operative care, care facilities, patient management, therapist education, nursing practice, dietary recommendation, veterinary etc.), or looked into patient or caregiver perception. The articles and reviews selected spawned various research fields in neurorehabilitation: Motor learning, therapies (physical therapy), upper limb immobilization, environmental enrichment, aerobic training, CIMT, cognitive rehabilitation (Middleton and Schwartz), music therapy, tools and methods (hand robotics), VR, neurofeedback, and principles (dose and timing). Together with previously collated literature, we identified 15 principles.

The identified principles from the meta-analysis are as follows:

- Spaced practice
- Dosage/duration
- Task-specific
- Variable practice
- Increasing difficulty
- Multisensory stimulation
- Explicit feedback/knowledge of
- Implicit feedback/knowledge of performance
- Modulate effector selection
- Action observation/embodied practice

Conclusion

In conclusion, neuroplasticity stands as a cornerstone of neuroscience, offering a profound insight into the brain's remarkable capacity for adaptation and reorganization across the lifespan. This abstract has explored the intricate mechanisms underlying neuroplasticity, from synaptic modifications to structural changes, and elucidated its far-reaching implications for various aspects of cognition, rehabilitation, and neurological disorders. The dynamic nature of neuroplasticity underscores its pivotal role in learning and memory processes, highlighting the importance of enriched environments and active learning strategies in fostering cognitive development. Moreover, neuroplasticity serves as the foundation for rehabilitative interventions, providing hope for individuals recovering from brain injuries as therapies aim to promote adaptive neural rewiring and functional restoration. However, the dysregulation of neuroplasticity is implicated in a myriad of neurological and psychiatric disorders, underscoring the urgent need to decipher the underlying mechanisms to develop targeted interventions. From Alzheimer's disease to stroke and depression, understanding aberrant plasticity holds the key to innovative therapeutic approaches that could revolutionize treatment outcomes. In essence, neuroplasticity embodies a fundamental property of the nervous system, enabling adaptation and optimization in response to environmental challenges. As research progresses, unveiling the intricate mechanisms governing neuroplasticity promises to unlock novel therapeutic avenues and deepen our comprehension of both normal brain function and dysfunction. Thus, the pursuit of neuroplasticity continues to be a captivating journey, promising new insights and transformative breakthroughs in the field of neuroscience.

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9. Appendices

- Additional data tables, figures, or supplementary materials.
- Glossary of terms used in the project.

10. Acknowledgments

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