MERCYHEALTH

Neuroplasticity in Stroke Recovery

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Physical Medicine & Rehabilitation

MERCYHEALTH

Our Mission

We extend the compassionate ministry of Jesus by improving the health and well-being of our communities, and bring good help to those in need, especially people who are poor, dying and underserved.

Our Values

Human Dignity | Integrity | Compassion | Stewardship | Service

Stroke and Disability

- Approximately 800,000 US adults will have a stroke each year,[1] with stroke being the leading cause of long-term adult disability in the US[2]
- Due to improved treatment procedures during the acute stage (e.g., thrombolysis, thrombectomy), the associated reduction in stroke mortality has led to a greater number of patients facing impairments
- Approximately 43% of ischemic stroke survivors in the United States experience moderate to severe neurological deficits at 6 months[2]
- Long-term, population-based studies show that 39–45% of stroke survivors remain disabled (modified Rankin Scale >2) at 5 years[3,4]

Stroke Recovery

- The American Stroke Association highlights that recovery is most rapid in the first 30 days, with maximal gains by four months when rehabilitation is provided, but meaningful improvements can continue for years due to **neuroplasticity** and compensatory strategies[1]

Neuroplasticity

- Also called neural plasticity or brain plasticity
- Neuroplasticity is the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections after injuries, such as a stroke or TBI
- Influenced by environment, complexity of stimulation, repetition of tasks, motivation

Neuroplasticity

- Neuroplasticity can be broken down into two major mechanisms:

1. Structural plasticity
   - Neuronal regeneration & collateral sprouting

1. Functional plasticity
   - this includes concepts such as vicariation and diaschisis

Mechanisms of Neuroplasticity

Neuronal regeneration/collateral sprouting

- **Dendritic remodeling**
  - Dynamic structural changes in the dendritic arbors, including growth, branching, retraction, pruning, and regeneration of dendritic branches
  - Increased dendritic branching to provide more surface for synaptogenesis and re-establish axonal-dendritic connections
- **Axonal sprouting**
  - The outgrowth of new axonal processes from intact neurons to reinnervate denervated regions and restore or modify neural circuitry
- **Synaptogenesis**
  - The process by which neurons form synapses to transmit electrical/chemical signals between a presynaptic neuron and a postsynaptic target (another neuron or a muscle cell)

Mechanisms of Neuroplasticity

Neuronal regeneration/collateral sprouting

- **Synaptic plasticity** - the ability to make experience-dependent long-lasting changes in the strength of neuronal connections.
  - Proposed mechanism: when presynaptic neurons stimulates postsynaptic neurons, the postsynaptic neuron responds by adding more neurotransmitter receptors, thus lowering the threshold needed to be stimulated by the presynaptic neuron.
  - Synaptic plasticity can be positively influenced by exercise, environment, repetition of tasks, motivation, neuromodulators (such as dopamine)

- **Neurogenesis** - the concept that the brain continues to make new neurons
  - Demonstrated in the hippocampus and the subventricular zone (SVZ) of the lateral ventricles
  - Hypothalamus, striatum, amygdala, cortex, and subcallosal zone have been proposed as sites of neurogenesis based on animal studies and limited human data
  - The extent and significance of neurogenesis in humans remain areas of active investigation

Mechanisms of Neuroplasticity

Functional Reorganization

- **Unmasking** – rapid functional expression of pre-existing but previously silent neural pathways following an injury.
  - Usually under tonic inhibition → damage (stroke) leads to less inhibition → unmasking
- **Vicariation** – the idea that the brain can reorganize other portions to overtake a new and unrelated function.
  - Has been demonstrated on some longitudinal functional MRI studies[5]
- **Diaschisis** – damage to one part of the brain could cause alteration/loss of function in another, distant, uninjured area due to connected fibers/pathway
  - Resolution of distant functional loss parallels recovery of the focal lesion
  - Mechanism to explain spontaneous return of function
- **Redundancy** – the idea that multiple areas of the brain serve the same/similar functions; when one area is damaged, function is preserved due to the other area(s)

Stroke Recovery

- The medical literature consistently identifies neuroplasticity as the biological foundation for post-stroke recovery and the primary target for restorative therapies.

- Optimizing neuroplasticity through targeted rehabilitation and neuromodulation is central to improving functional outcomes after stroke.

Optimizing Neuroplasticity

Endogenous Drivers: Task-oriented training

- Emphasis on repetition of functional, goal-directed tasks relevant to daily activities
  - Reaching, grasping, walking, transfers.
- Focuses on practicing whole tasks or meaningful components of tasks, rather than isolated movements or muscle strengthening exercises
- Promotes motor learning and improve functional outcomes after stroke[6]
- Thought to drive experience-dependent reorganization within the CNS.
- Evidence from both animal and human studies demonstrates repetitive, meaningful, and goal-directed tasks leads to functional and structural changes in neural pathways. [7]

Optimizing Neuroplasticity

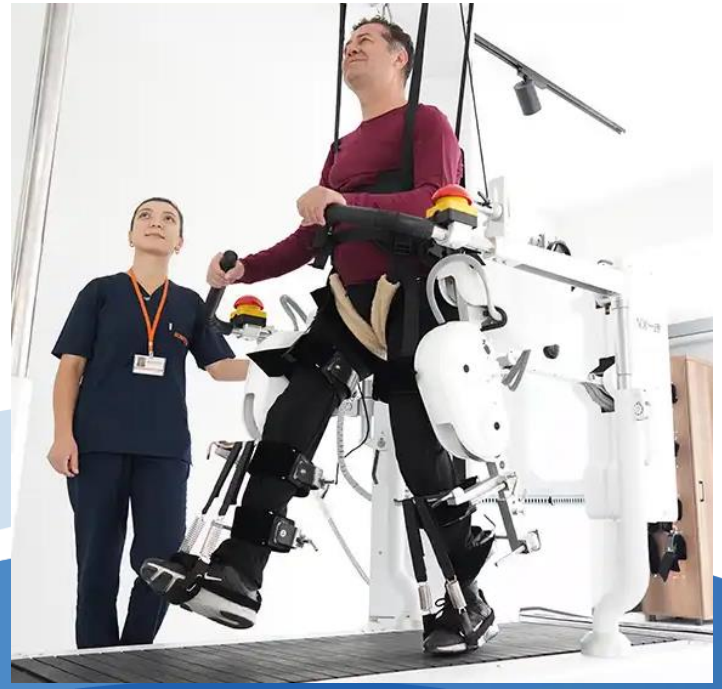
Endogenous Drivers: Aerobic Exercise

- Regular aerobic activity increases expression of neurotrophic factors (BDNF, GDNF, NGF) that facilitate synaptogenesis, neurogenesis, and angiogenesis [8,9]
  - Supports structural & functional brain adaptation
- Emerging evidence suggests peripheral lactate mediates upregulation of brain-derived neurotrophic factor (BDNF) [10,11]
  - Linking muscle activity to central neuroplastic changes

Optimizing Neuroplasticity

Robot Assisted Movements

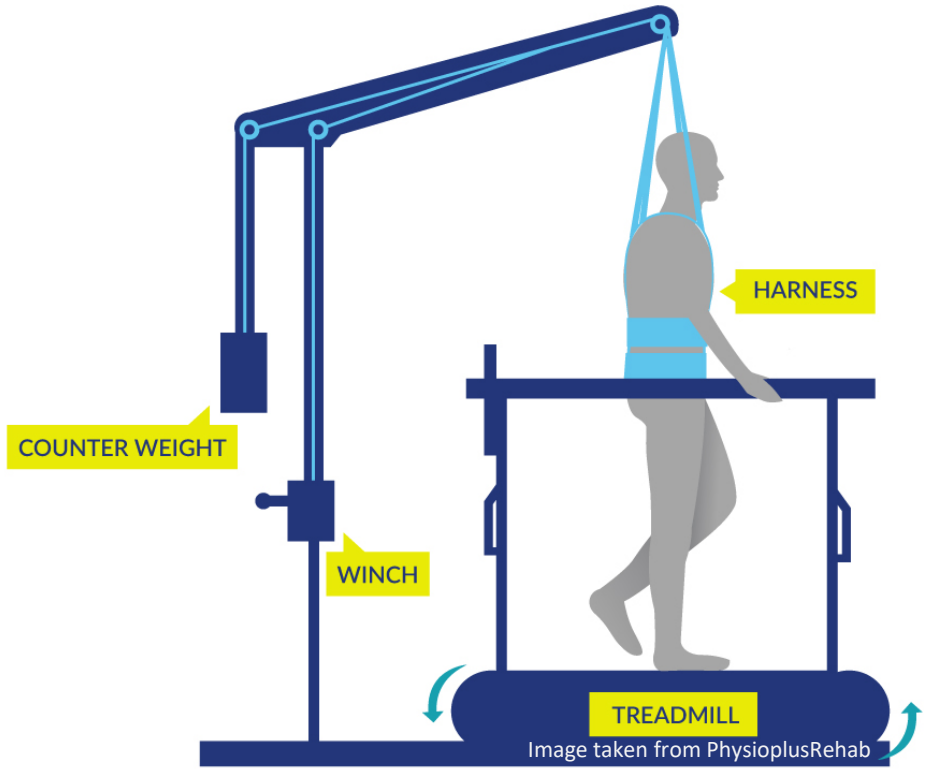
- Promotes neuroplasticity through repetitive, intensive, and task-oriented motor training that drives activity-dependent reorganization in the central nervous system.
- Robot-assisted therapies can induce changes in cortical activation, increase functional connectivity between motor regions, and facilitate adaptive reorganization in both ipsilesional and contralesional hemispheres. [12,13,14]
  - Demonstrated by fMRI & functional near-infrared spectroscopy
  - Associated with improvements in motor function, balance, & walking



Optimizing Neuroplasticity

Body weight supported treadmill training (BWSTT)

- BWSTT - utilizes a harness system to partially offload the patient's weight, enabling repetitive, intensive walking practice even in those with significant motor deficits.
- This approach facilitates early mobilization
  - thought to capitalize on the heightened neuroplasticity in the subacute post-stroke period
- Meta-analyses and randomized trials demonstrate that BWSTT improves walking speed, endurance, and balance
  - Optimal effects when initiated within 3–6 months post-stroke, for 4–8 weeks, at body weight support levels above 30% [15,16]



Optimizing Neuroplasticity

Neuromodulation: Cortical Priming/Neurostimulation Technology

- **Cortical priming** is interventions that modulate the excitability of cortical neural networks to enhance subsequent learning, performance, or recovery of function

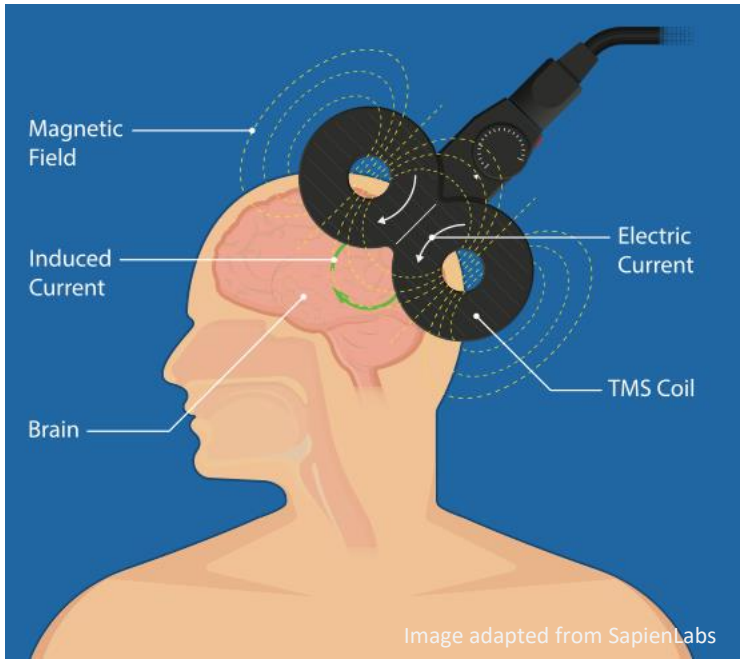
- Aims to modulate cortical firing rate by directly generating an electrical field or indirectly through a magnetic field (which produces an electrical field at the level of the cortex)

- Suggested to treat poststroke impairment by increasing the brain's neuroplastic capabilities → restoring and/or building new connections that supplement or replace those lost

- As it increases the potential for plasticity rather than driving the changes directly, neurostimulation is paired with adjunctive rehab approaches to generate positive functional changes

Optimizing Neuroplasticity

Neuromodulation: Non-invasive brain stimulation



- **Repetitive transcranial magnetic stimulation (rTMS)** – uses an electromagnetic coil placed above the scalp which generates a rapidly pulsed magnetic fields to induce electrical currents in targeted brain regions, modulating cortical excitability
  - Stimulates neural tissue up to 1.5 cm deep in the brain
  - Usually targeting the primary motor cortex, though can target others (prefrontal cortex, premotor cortex, etc)
  - Applied 10-30 minutes prior to rehab to increase susceptibility to plasticity
  - Clinical studies and meta-analyses indicate that rTMS can improve motor function, activities of daily living, and cognitive outcomes post-stroke [17,18]
  - Research ongoing regarding optimizing delivery, dosing, timing, duration of treatment, and stimulation parameters
- Currently rTMS is approved for treatment of depression & OCD; not yet approved for hemiparesis for stroke survivors.

Optimizing Neuroplasticity

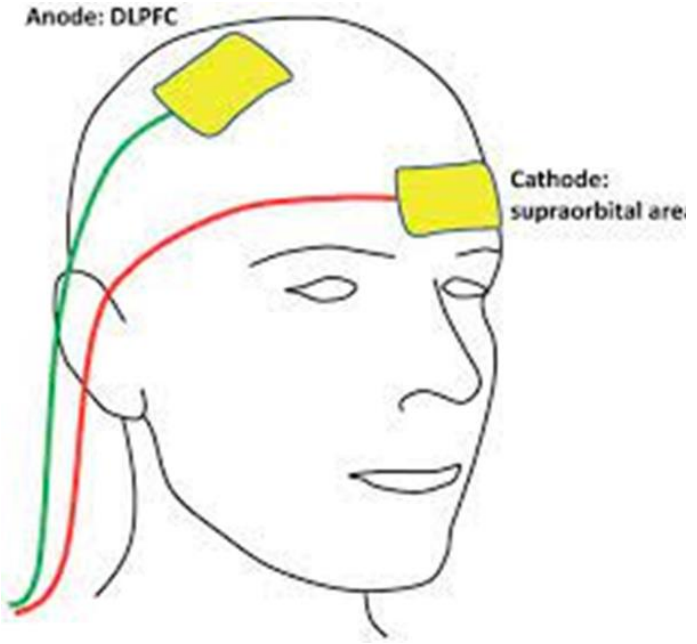
Neuromodulation: Non-invasive brain stimulation

- **Repetitive transcranial magnetic stimulation (rTMS)**
  - Side effects: local transient scalp pian and discomfort (39%), sleepiness, mild headache (28%); seizure (<1%)
  - Contraindications: metal in head; implanted electrical devices in close contact to coil (cochlear implants, medication pumps)
  - Relative contraindications: seizures; medications that lower seizure threshold; fainting; severe head Injury; pregnancy

Optimizing Neuroplasticity

Neuromodulation: Non-invasive brain stimulation

- **Transcranial direct current stimulation (tDCS)** – delivers weak, low amplitude direct electrical currents via scalp electrodes to modulate neuronal membrane potentials
  - Saline soaked sponges placed over the primary motor cortex & contralateral supraorbital area; alternatively placed bilaterally on primary motor cortices
  - **Anodal** stimulation depolarizes = increase excitability; **cathodal** stimulation hyperpolarizes = decreases excitability (inhibitory)
  - Rehabilitation potential of tDCS greater when in conjunction with therapy
  - tDCS typically applied during chronic phase of stroke is felt to be most effective
  - Has demonstrated benefits for motor and cognitive recovery [17,19]
- Class II device, not yet approved to use outside investigational setting



Optimizing Neuroplasticity

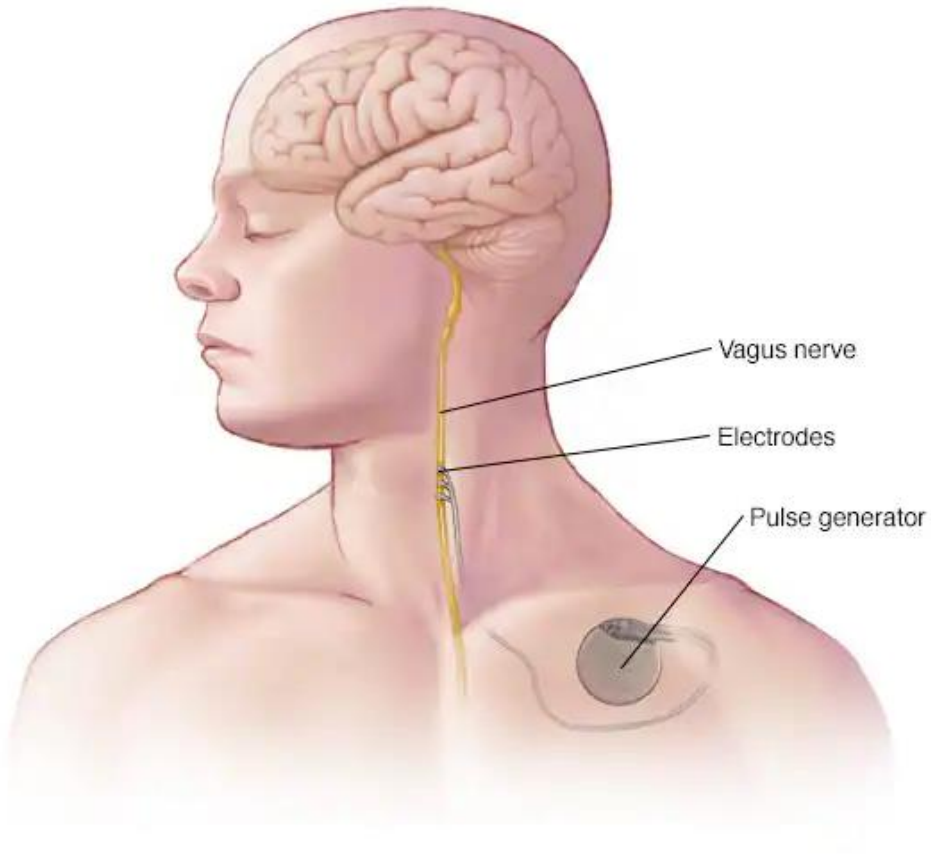
Neuromodulation: Non-invasive brain stimulation

- **Transcranial direct current stimulation (tDCS)**
  - Side effects: moderate fatigue, transient mild headaches, tingling of scalp (similar to rTMS)
  - Contraindications: metal in head, implanted electrical devices (cochlear implants, internal pulse generator, medication pumps)
  - Relative contraindications: epilepsy, medication that decrease seizure threshold, history of fainting spells, severe head trauma, hearing problems, ringing in the ears, pregnancy

Optimizing Neuroplasticity

Neuromodulation: Vagus Nerve Stimulation

- **Vagus Nerve Stimulation (VNS)** – an emerging adjunctive therapy primarily used in poststroke upper limb motor recovery → rehab potential is greater when in conjunction with therapy
- Involves delivering current to the vagus nerve either invasively (iVNS) with an implanted stimulator + cuff electrode or noninvasively/transcutaneous (tVNS) using an external stimulator with a surface electrode.
  - Sends electrical signals along the left vagus nerve to the brainstem
  - Right vagus nerve is typically not used as it can affect the heart



Optimizing Neuroplasticity

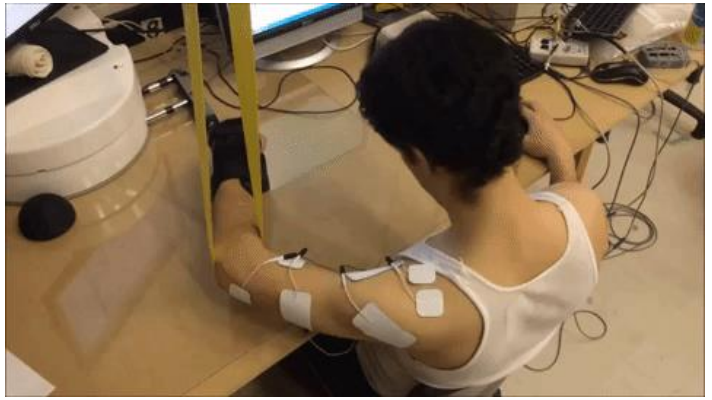
Neuromodulation: Vagus Nerve Stimulation

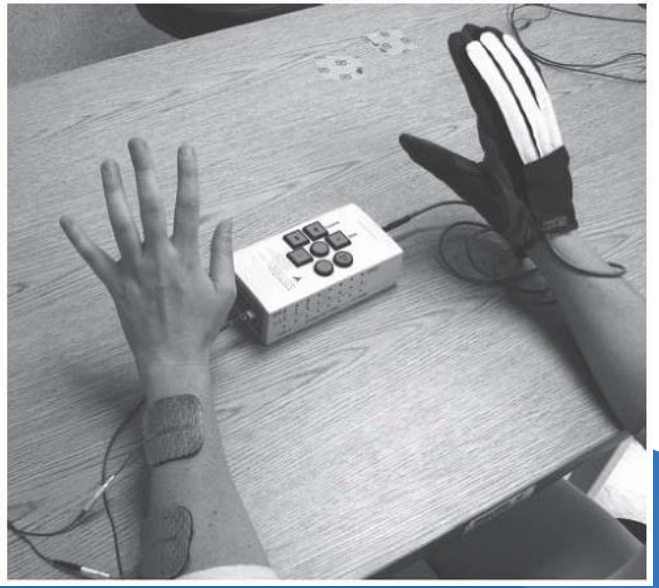
- Randomized controlled trials and meta-analyses show that VNS paired with task-specific rehabilitation yields moderate to large improvements in upper limb sensorimotor function compared to rehabilitation alone, with a favorable safety profile and mostly mild, self-limited adverse events.[20]
- Currently FDA approval to treat moderate/severe upper extremity motor deficits associated with ischemic stroke

Optimizing Neuroplasticity

Neuromodulation: Peripheral Nerve Stimulation

- Electrical current generates muscle contractions and send signals back up to the brain
- Modalities are differentiated by level of activation and whether stimulation is applied for functional use; these include:
  - **Functional Electrical Stimulation (FES)** – stimulation incorporated into a task by multiple channels to generate functional movement; surface or implanted electrodes
    - **Contralateral controlled FES (CCFES)** - uses surface electrodes over the paretic finger and thumb extensor and instrumented glove over non-paretic hand to deliver stimulation proportional to the degree of volitional opening of the contralateral hand → stimulation-assisted functional motion of hand

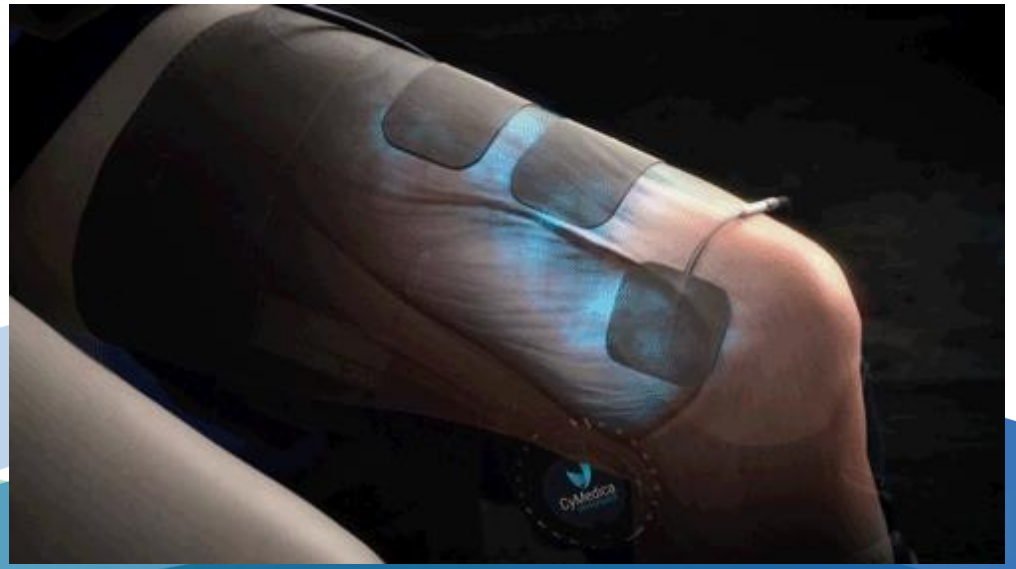




Optimizing Neuroplasticity

Neuromodulation: Peripheral Nerve Stimulation

- Electrical current generates muscle contractions and send signals back up to the brain
- Modalities are differentiated by level of activation and whether stimulation is applied for functional use; these include:
  - **Neuromuscular Electrical Stimulation (NMES)** – elicit muscle contraction not necessarily for functional movement; surface or implanted electrodes



Optimizing Neuroplasticity

Neuromodulation: Peripheral Nerve Stimulation

- Electrical current generates muscle contractions and send signals back up to the brain
- Modalities are differentiated by level of activation and whether stimulation is applied for functional use; these include:
  - **Transcutaneous Electrical Nerve Stimulation (TENS)** – stimulation applied at sub-motor or sub-sensory thresholds with surface electrodes; mostly used for pain (variable efficacy)

Optimizing Neuroplasticity

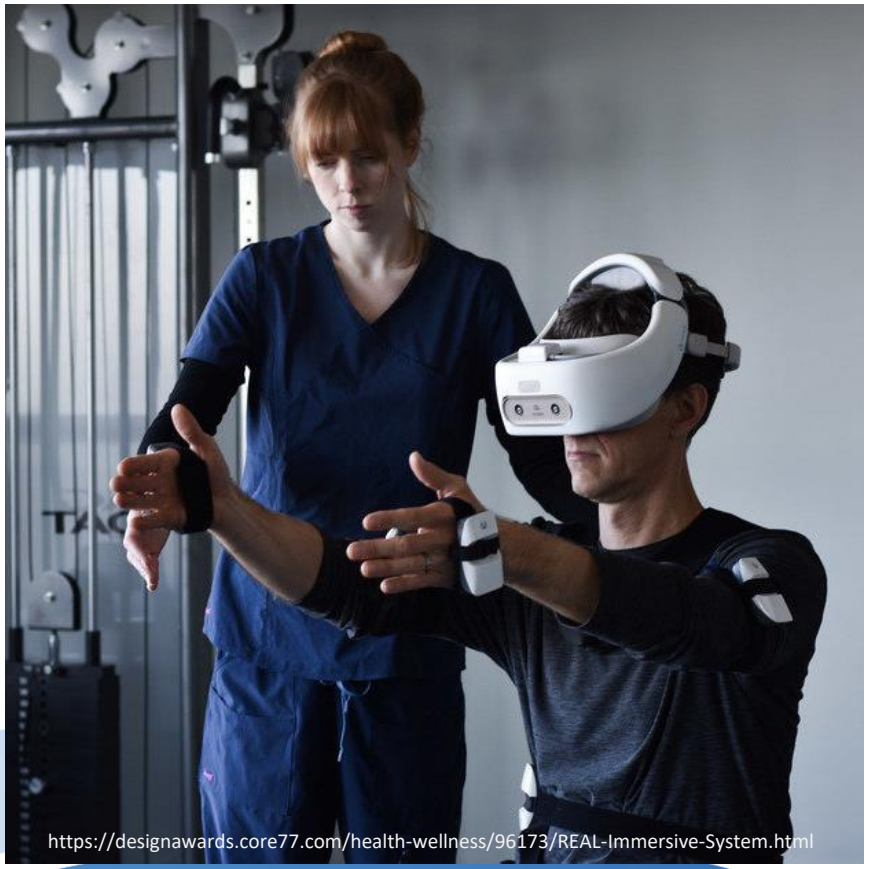
Virtual Reality (VR)

- VR aims to promote neuroplasticity in stroke rehabilitation by providing intensive, repetitive, and task-specific training
- Immersive versus Non-immersive

Optimizing Neuroplasticity

Virtual Reality (VR) – Immersive VR

- **Immersive VR** – involves head-mounted displays or projection-based environments to create a sense of presence and embodiment within a simulated, interactive environment.
  - This approach often incorporates multisensory feedback (visual, auditory, haptic, even olfactory) to feel as though they are "inside" the virtual world and directly interacting with it.
  - Usually associated with higher engagement and motivation[21]
  - May be limited by cost, equipment requirements, and potential side effects such as dizziness or nausea



https://designawards.core77.com/health-wellness/96173/REAL-Immersive-System.html

Optimizing Neuroplasticity

Virtual Reality (VR) – Non-immersive VR

- **Non-immersive VR** – uses standard computer screens, tablets, or televisions, where the patient interacts with the virtual environment via controllers, motion sensors, or touch screens.
  - The sense of presence is lower, the experience is less enveloping.
  - Non-immersive VR is generally more accessible, less expensive, and easier to implement

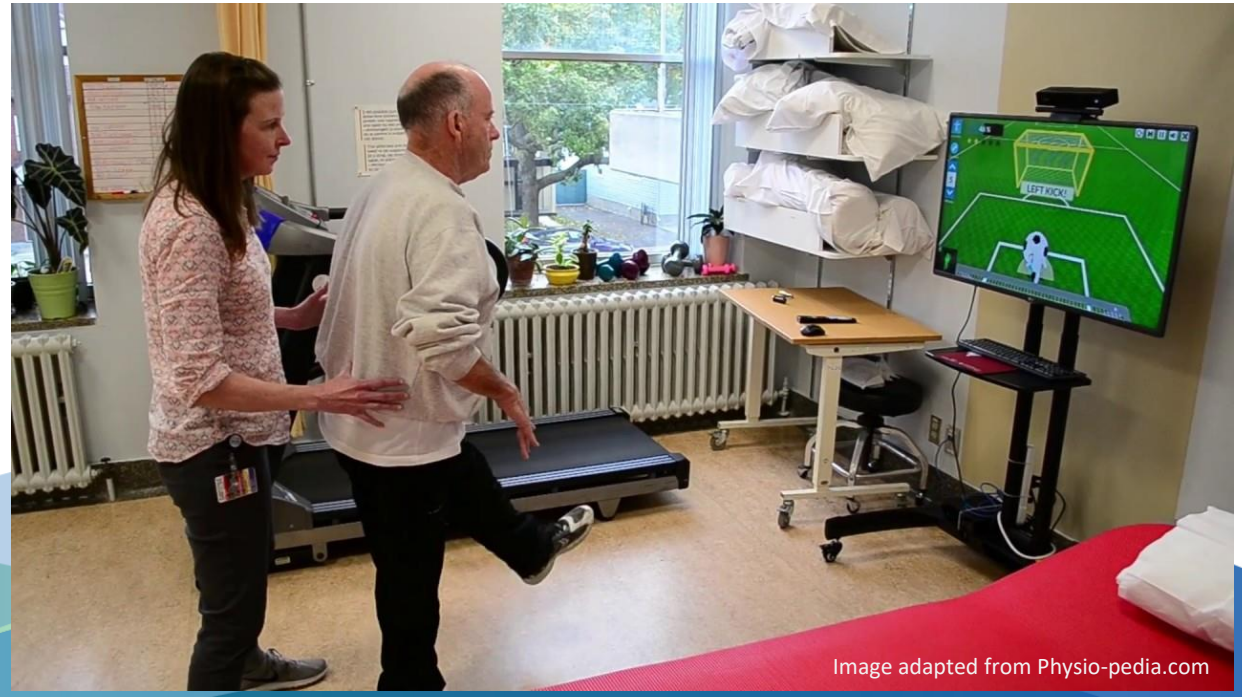


Image adapted from Physio-pedia.com

Optimizing Neuroplasticity

Virtual Reality (VR)

- VR-based interventions are associated with enhanced interhemispheric balance, cortical connectivity, cortical mapping of affected limb muscles, and activation in the primary motor cortex, sensorimotor cortex & supplementary motor area. [21,22]
  - These neural changes are consistently correlated with improvements in motor function and ADLs
  - Some studies show superior improvements in motor function and activities of daily living with immersive compared to non-immersive VR or conventional therapy. [23,24]

Optimizing Neuroplasticity

Virtual Reality (VR)

- Functional MRI and other neurophysiological assessments (e.g., EEG, TMS) suggest that VR can induce restoration or re-lateralization of activation toward the ipsilesional hemisphere, increase cortical excitability, and facilitate reorganization of corticospinal pathways, all of which are hallmarks of neuroplasticity. [21]
- The immersive, feedback-rich, and adaptive nature of VR may also enhance patient engagement and motivation[25]

Conclusion

- While stroke recovery is most robust in the first 4 months, meaningful improvements can continue for years
- Stroke rehab emphasize a multimodal, individualized approach integrating technological advances, early and intensive therapy, and expanded access models
- Early, task-specific, and high-repetition training remains foundational, with strong evidence supporting its use for motor recovery and activities of daily living.
- Cardiovascular exercise is recommended to improve gait speed and overall physical function, with limited harm and clear benefit.
- Technology-assisted rehabilitation (robotics, BWSTT, electrical stimulation) has shown mixed but promising results, especially as adjuncts to conventional therapy
- Ongoing research is focused on optimizing protocols and integration of new technologies and addressing inequities in access and outcomes
- Multidisciplinary care, personalized rehabilitation plans, and early initiation of therapy are consistently recommended by the American Heart Association/American Stroke Association and the Department of Veterans Affairs

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