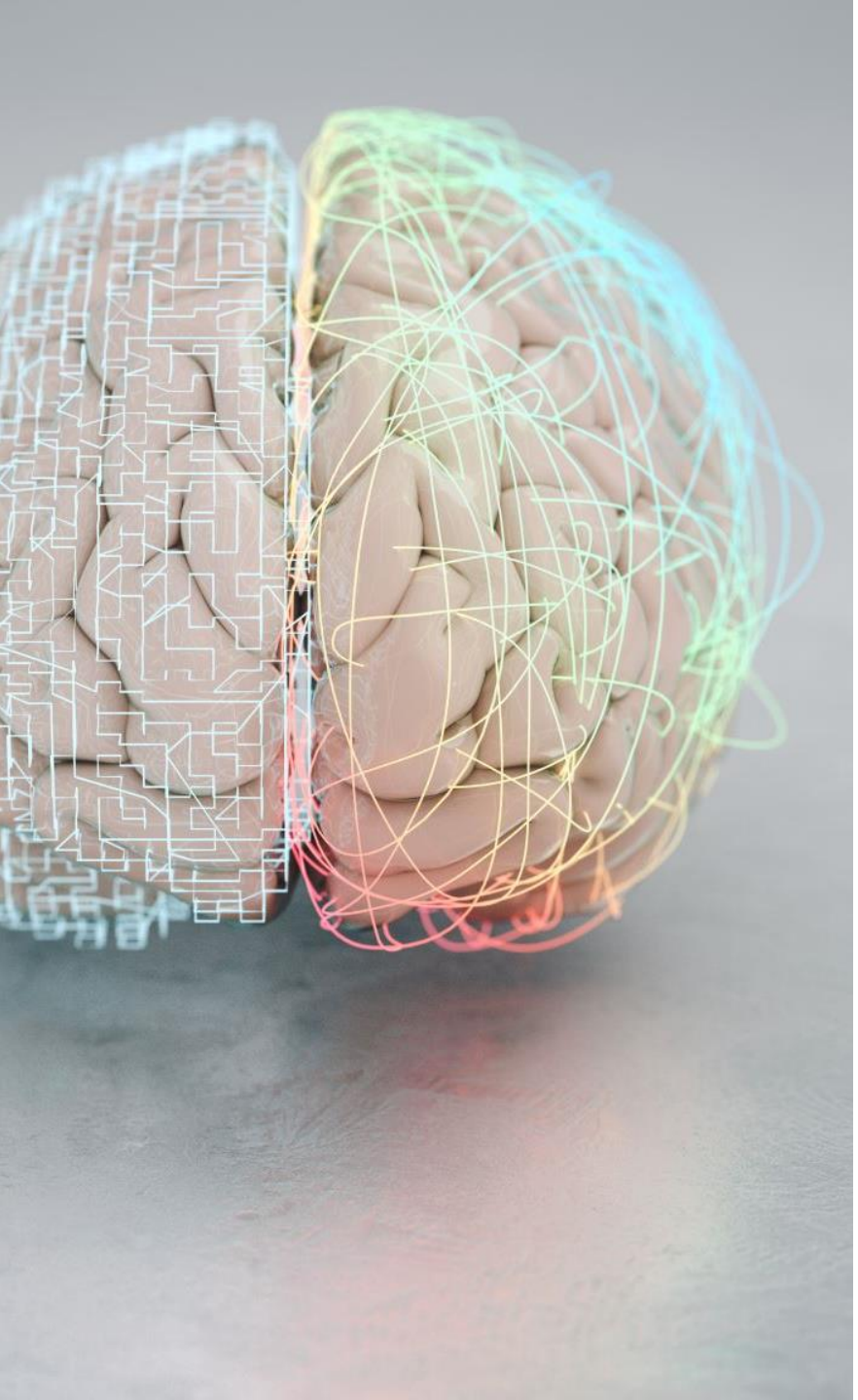

Neuroplasticity in Stroke Rewire the Brain

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- Stroke is 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. (*Feigin, Valery L et al. 2022)*

- Egypt, a low-middle-income country, is the most populated nation in the Middle East with a high overall crude prevalence rate of stroke (963/100,000 inhabitants), accounting for 6.4% of all deaths. *(Aref H. et al. 2021)*

- Inspite of increased early recognition of stroke and the advances in the management, a significant proportion of patients do not receive acute therapies due to *contraindications* or *being outside the reperfusion time window.*

- This led to a significant proportion of patients to survive with severe neurological deficits with subsequent high socioeconomic burden.

Neuroplasticity

- Neuroplasticity is a remarkable characteristics of the brain which allows the neurons to rewire their structure in response to internal and external stimuli.

- External stimuli are referred to as “epigenetic factors” strongly influence *structural* and *functional* reorganization of the brain and acting as a drive for neural plasticity.

- The current understanding of neuroplasticity is based on ***Hebb's theory*** from 1949, which posits that repetitive stimulation of the postsynaptic neuron by the presynaptic neuron is necessary to increase synaptic efficacy

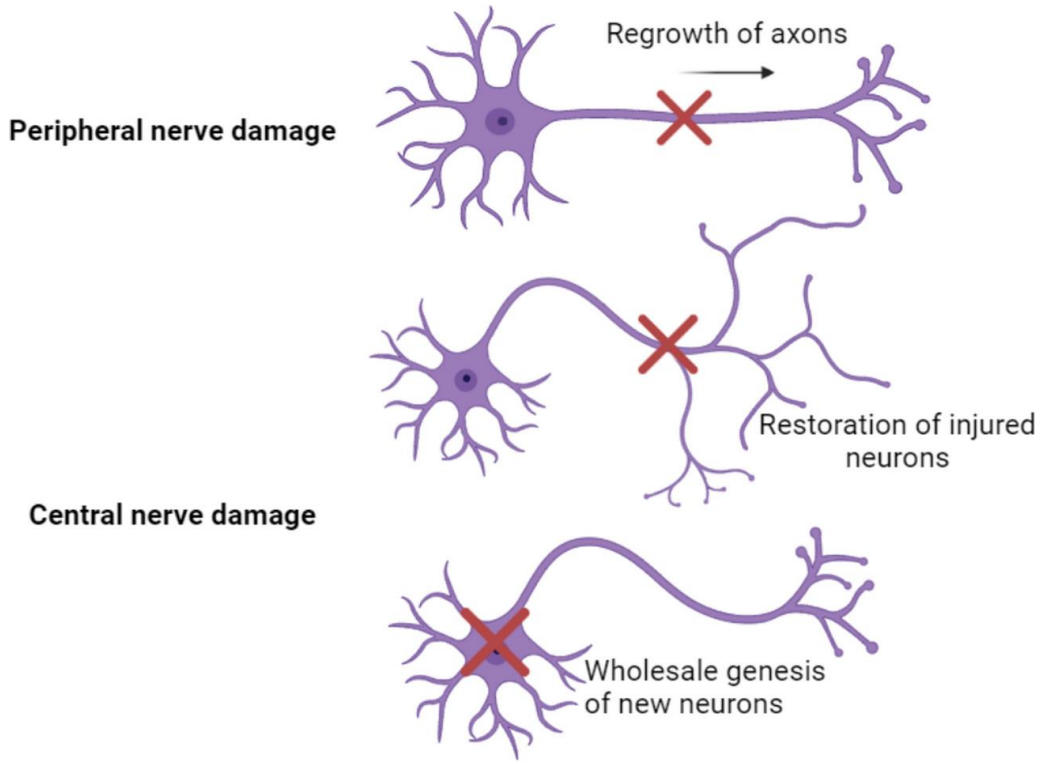
"***Neurons that fire together , wire together.***"

Main mechanisms of neuroplasticity in healthy brains

1st : *Regrowth of axons after peripheral nerve damage*.

2nd : Restoration of injured central nerve cells through the growth of new dendrites, axons, and synapses from existing cell bodies.

3rd : Wholesale generation of new neurons, in the subventricular zone and the dentate gyrus.



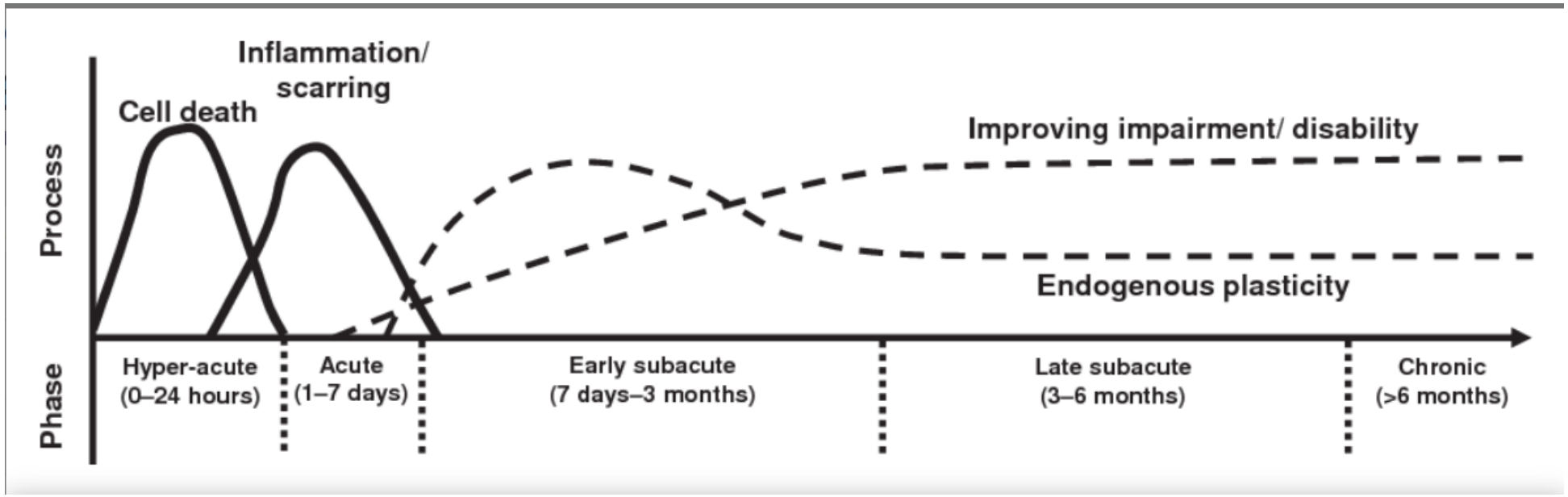
Mechanisms of neuroplasticity in healthy individuals

Recovery from Stroke

- The time after a stroke is often divided into phases.

- The Stroke Roundtable Consortium proposed the stroke phases as (Bernhardt, Julie et al. 2017)
  - Hyperacute phase: the first 24 h
  - Acute Phase: 7 days
  - Early sub-acute phase: first 3 months
  - Late sub-acute phase: 4-6 months
  - Chronic phase: from 6 months on

- The rationale behind this differentiation is that recovery-related processes post-stroke are time-dependent.



Progression of stroke damage and tissue reorganization

- Within hours after the cerebral ischemia, a cascade of plasticity-enhancing mechanisms leads to dendritic growth, axonal sprouting, and the formation of new synapses.

- The most significant improvements occur in the first few weeks post-stroke, often reaching a relative plateau after 3 months with less significant recovery subsequently, especially concerning motor symptoms.

- After 6 months, spontaneous recovery is usually at its limit, leading to a stable chronic deficit.

- Nevertheless, with training or other interventions, improvements of some stroke-induced deficits can even be achieved in the chronic phase, primarily for more cognitive domains like language

- After stroke, the plasticity process is initiated to compensate for both the lesion itself and its remote effect.

- Changed neural activity and connectivity in terms of function and structure could be detected in the perilesional and remote regions and even in the contralateral hemisphere, which were assumed to be the mechanisms underlying spontaneous recovery

Strategies Enhancing Neuroplasticity

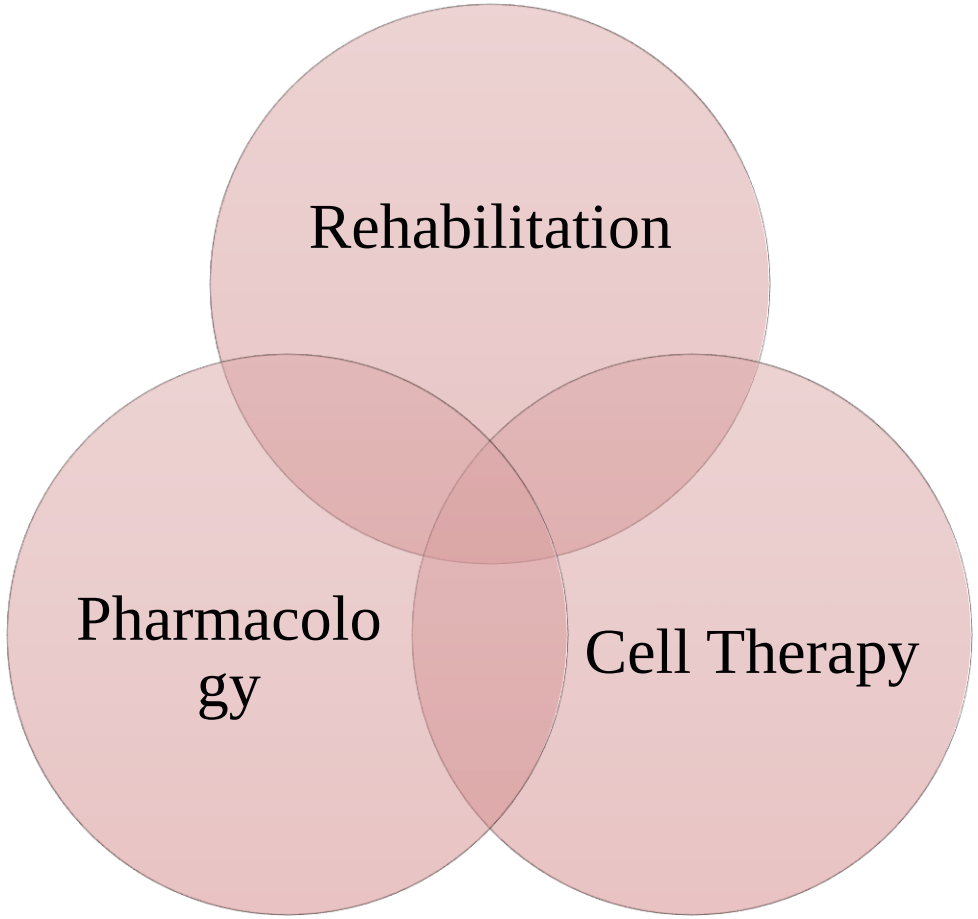
- There are now several strategies available to enhance neuroplasticity, including both ***pharmacological*** and ***non-pharmacological*** interventions that are essential for post-stroke rehabilitation

10 principles of neuroplasticity

1. Use it or lose it	Neural networks not actively engaged in training can degrade
2. Use it & improve it	Training can induce dendritic growth and synaptogenesis within specific brain regions that enhance task performance
3. Specificity	The nature of training dictates the nature of the plasticity
4. Repetition matters	Repetition is required to induce lasting neural change (skill instantiation)
5. Intensity matters	A sufficient intensity if stimulation is required to induce plasticity
6. Time matters	Different forms of plasticity occur at different times during training
7. Salience matters	The training experience must be sufficiently rewarding to induce plasticity
8. Age matters	Training-induced plasticity occurs more readily in the younger brain
9. Transference	Plasticity induced by one training experience can enhance the acquisition of similar behaviours
10. Interference	Plasticity induced by one training experience can interfere with the acquisition of similar behaviours

Note. This table summarises key principles by Kleim & Jones (2008) and is not intended as an exhaustive list.

Integrated Approach Enhancing Neuroplasticity



A. Modern rehabilitation

1. Physical Medicine
2. Aerobic Training
3. Constraint-Induced Movement Therapy (CIMT)
4. Strength Training
5. Robotics
6. Mirror Therapy
7. Noninvasive Brain Stimulation (NIBS)
8. Computer-based Training Programs/Virtual Reality
9. Neuromuscular Electrical Stimulation
10. Magnetic Field

Physical Medicine

- Intensive, repetitive task-specific training, which involves the active practice of task-specific motor activities, is recommended after stroke.

- As early as possible after stabilization of the condition but not in the 1st 24 hours.

- Repetitive task Training improves arm, hand and lower limb functional measures (low-quality evidence) as well as walking ambulation (moderate-quality evidence) up to six months post treatment.

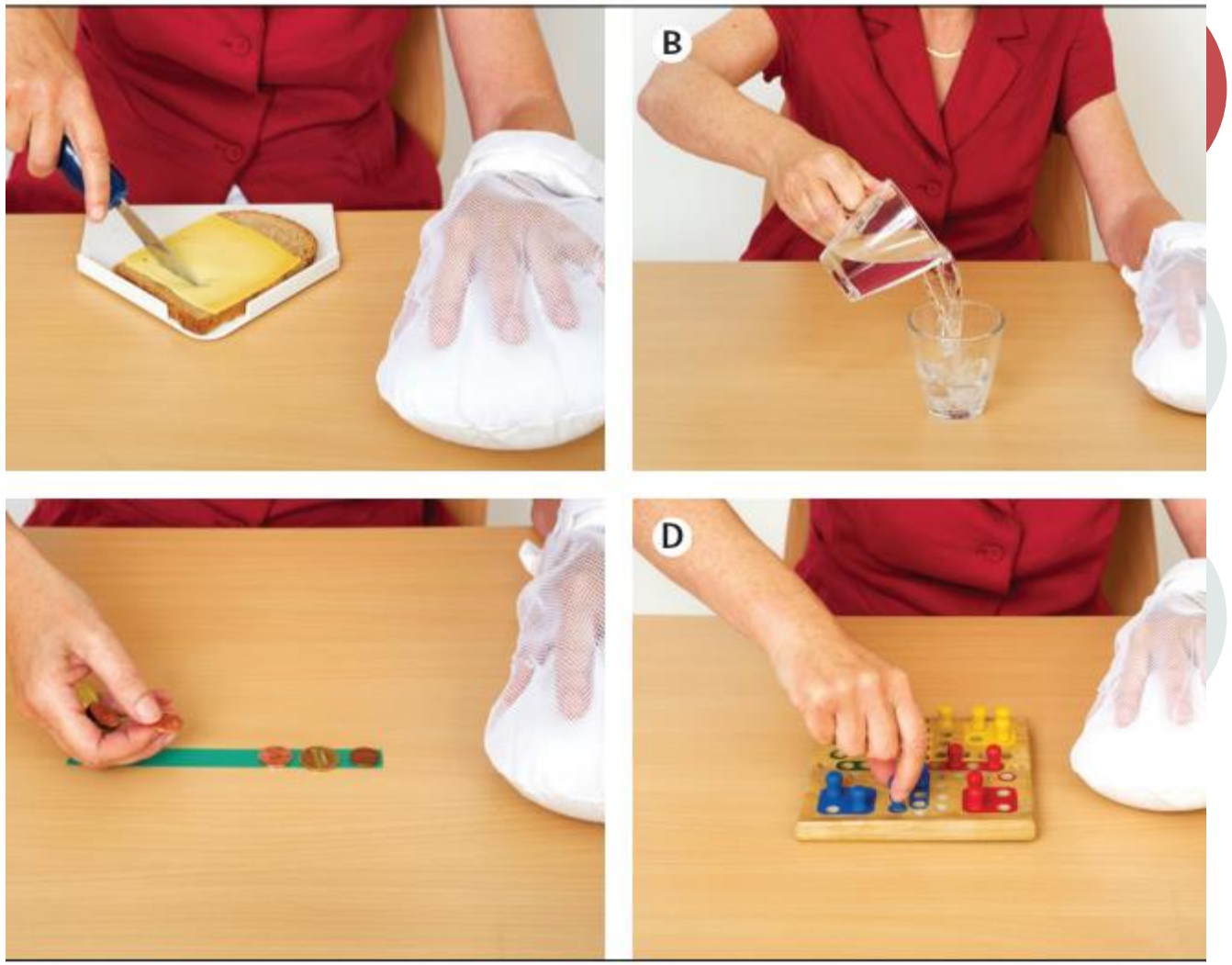
Aerobic Training

- Studies showed that aerobic training improve mobility, walking capacity and gait speed.

- Aerobic training may contribute to increased levels of BDNF, IGF-I, NGF and increase synaptogenesis in multiple brain regions

Constraint-Induced Movement Therapy (CIMT)

- Task-oriented practices with the paretic limb in constraint-induced movement therapy (CIMT) Practices include: (A) cutting bread, (B) pouring water, (C) picking up and placing back money, and (D) playing a game. Use of the unaff ected limb is restricted by a padded mitt.



Strength Training

- Progressive resistance training seemed to be the most effective treatment to improve strength the lower limb, walking distance, fast walking and balance.

- Training should be intensive and tailored to the patients' needs

Robotics

- In stroke patients, these devices are used to improve upper limb and the lower limb functions and primarily to improve gait

- Three main types of lower-limb rehabilitation robotic systems:
  - stationary systems (exoskeleton-type devices and programmable foot end-effector devices)
  - overground walking systems
  - wearable robotic walking devices

Mirror Therapy

- Mirror therapy is performed by positioning a mirror in the person's midsagittal plane (between limbs), reflecting the non-paretic side and giving the impression as if it was the affected side.

- This may give the visual illusion that affected limb functions normally

Noninvasive Brain Stimulation (NIBS)

- Transcranial Direct Current Stimulation (tDCS) or repetitive Transcranial Magnetic stimulation (rTMS)

- They aimed at restoring the interhemispheric balance by inhibiting healthy hemisphere or stimulating the lesioned one.

- Some studies have been shown that NIBS combined with other therapies may be effective to improve *gait speed, hemispatial neglect, performance in ADL, paretic limb force* in patients after stroke.

Computer-based Training Programs/Virtual Reality

- Virtual reality training and interactive video gaming allows patients to interact with the environment and allows them to receive feedback about their activities.

- Those methods are used for improving motor function (upper limb, global motor function, gait, balance) and cognitive function.

B. Pharmacology

- For at least 2 classes of drug, serotonergic and dopaminergic, both of which are monoaminergic, existing evidence from human studies supports the possibility for enhancing motor outcome after stroke.

Serotonergic Drugs

- Serotonin normally plays a role in modulating multiple cognitive functions, particularly response inhibition and memory consolidation, and modulates the impact of punishment-related signals on learning and emotion.

- Recent reports suggest potential clinical utility of selective serotonin reuptake inhibitor (SSRI) drugs for promoting improved motor outcome after stroke.

- The Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME) study
  - a double-blind, placebo-controlled trial
  - nondepressed hemiplegic/hemiparetic patients within 10 days of ischemic stroke onset.
  - 3 months of oral fluoxetine (20 mg/d) or placebo.
  - Results:

    Patients randomized to fluoxetine showed *significantly greater gains on the primary end point*, change in the arm/leg Fugl–Meyer motor score to day 90 (P=0.003), a remarkable difference of 9.7 points on this 100-point scale.

- Mechanism of action in SSRI in stroke recovery:
  - Downregulating and desensitization serotonin receptors
  - Reducing neural inflammation.
  - Enhancing neurotrophin activity
  - Increasing neurogenesis.
  - Chronic SSRI dosing increases intracortical facilitation and reduces intracortical inhibition.

Dopaminergic Drugs

- Dopamine regulates many aspects of neural functioning, including excitability, synaptic transmission, plasticity, protein trafficking, and gene transcription.

- Dopamine has a key role in wide-ranging brain processes, such as movement, reward, learning, and plasticity.

- So, Dopaminergic terminals in motor cortex contribute to cortical plasticity and indeed are necessary for motor skill learning.

- A randomized, double-blind, placebo-controlled study of 53 patients within 6 months of stroke onset found that 100 mg L-Dopa/day, given as Sinemet and combined with physical therapy, was significantly better than placebo plus physical therapy on motor recovery after 3 weeks, measured using the Rivermead Motor Assessment. (Scheidtmann, K et al. 2001)

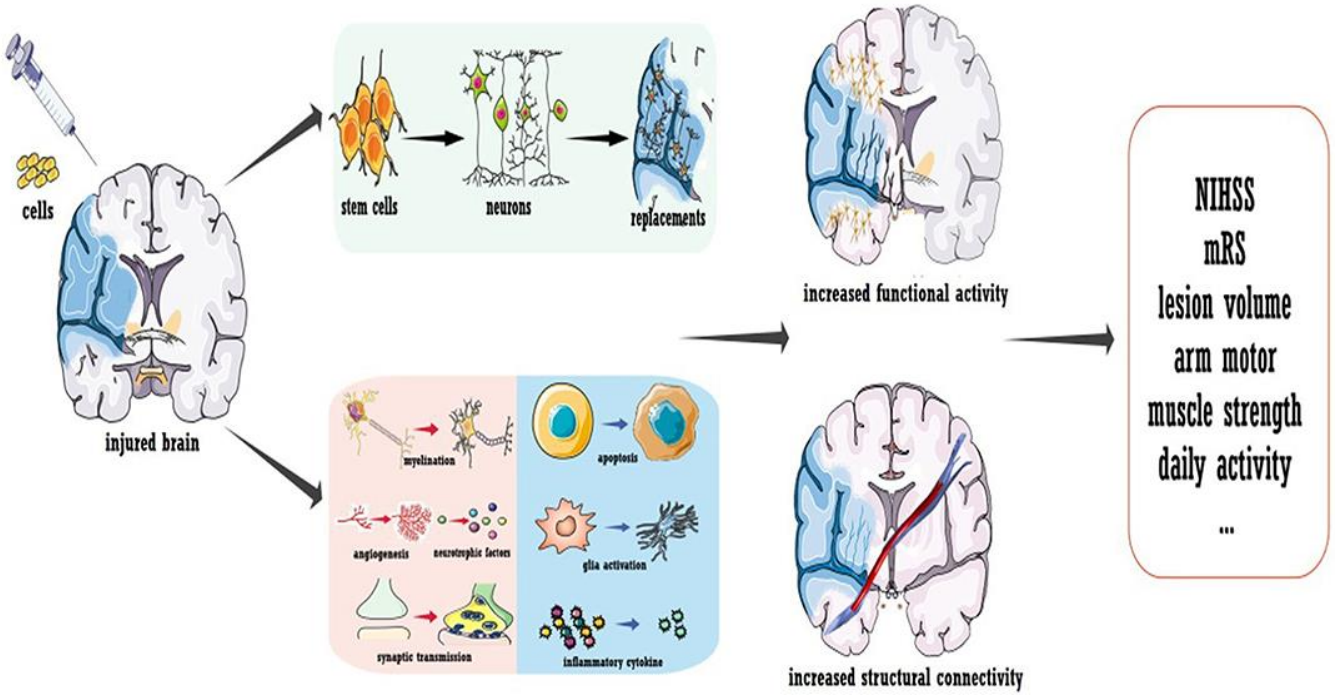
Other drugs improve brain recovery

- **Noradrenergic Drugs**
- **Cholinergic Drugs**
- **Amphetamine**
- **Niacin**

C. Cell Therapy

- Cell therapy is emerging as a viable neurorestorative therapy for stroke, and the number of investigations in this field have surged in recent decades. Stem cells have the ability to transform into multiple cell types. Theoretically, both endogenous and exogenous therapeutic strategies are capable of promoting post-stroke plasticity

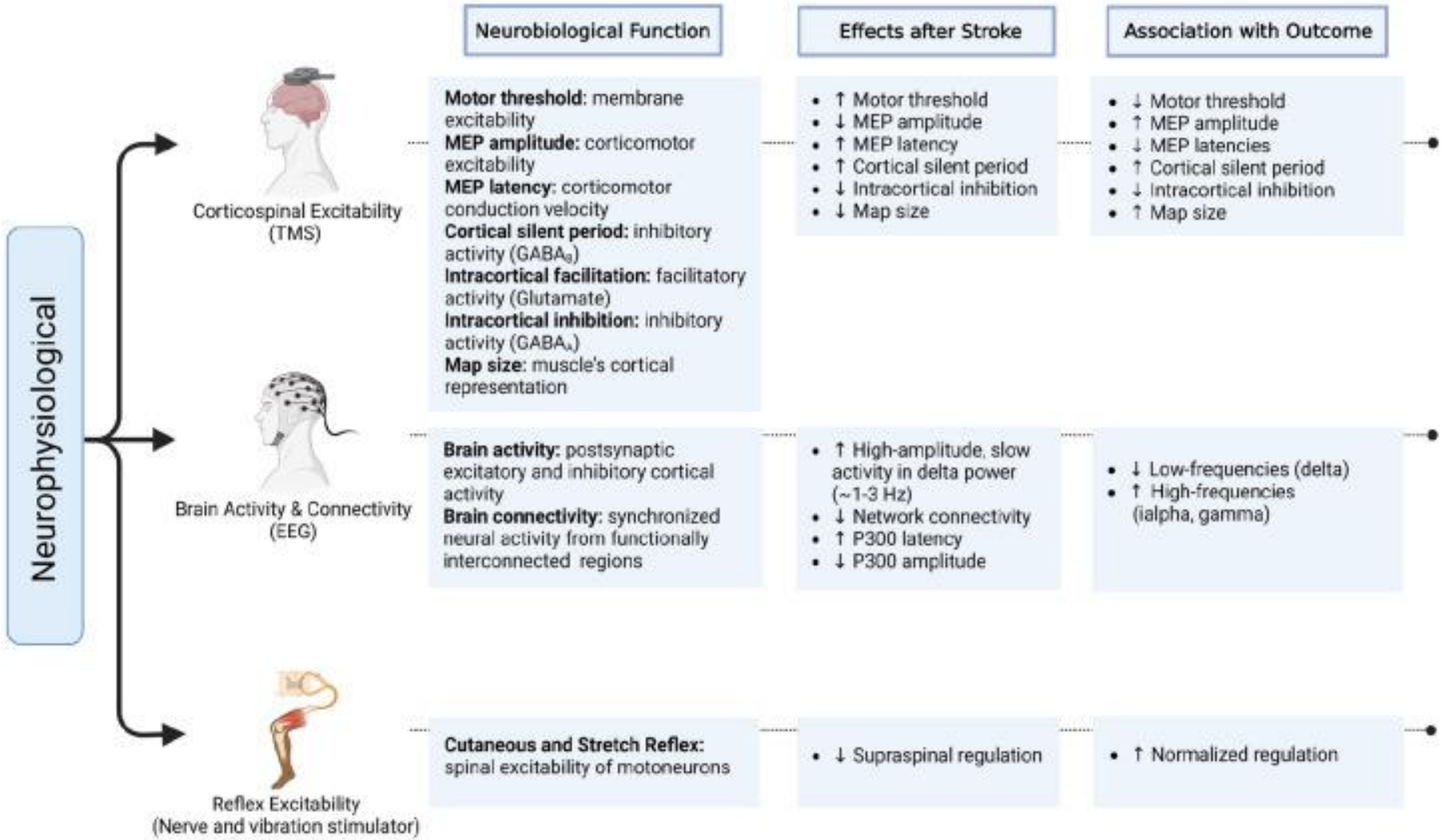
Cell transplantation to promote stroke recovery. Cell therapy was shown to induce the replacement of dead neurons in the infarcted area; more importantly, it ameliorated the microenvironment of the whole brain to promote functional modulation. Treatment not only enhances the neural activity of the injured hemisphere but also improves the structural connection of the whole brain.



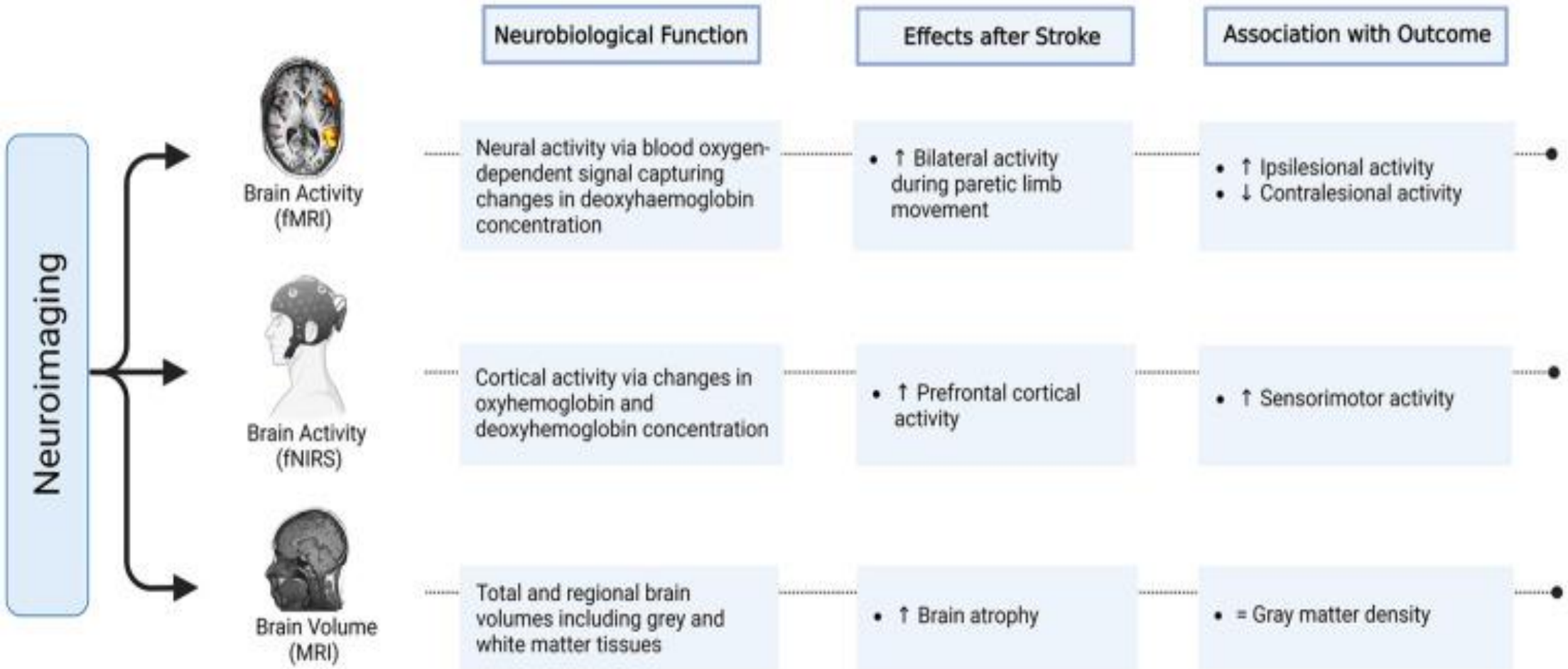
Measuring Neuroplasticity

- The use of biomarkers has enabled the assessment of cellular and molecular events that occur in the central nervous system after brain injury.

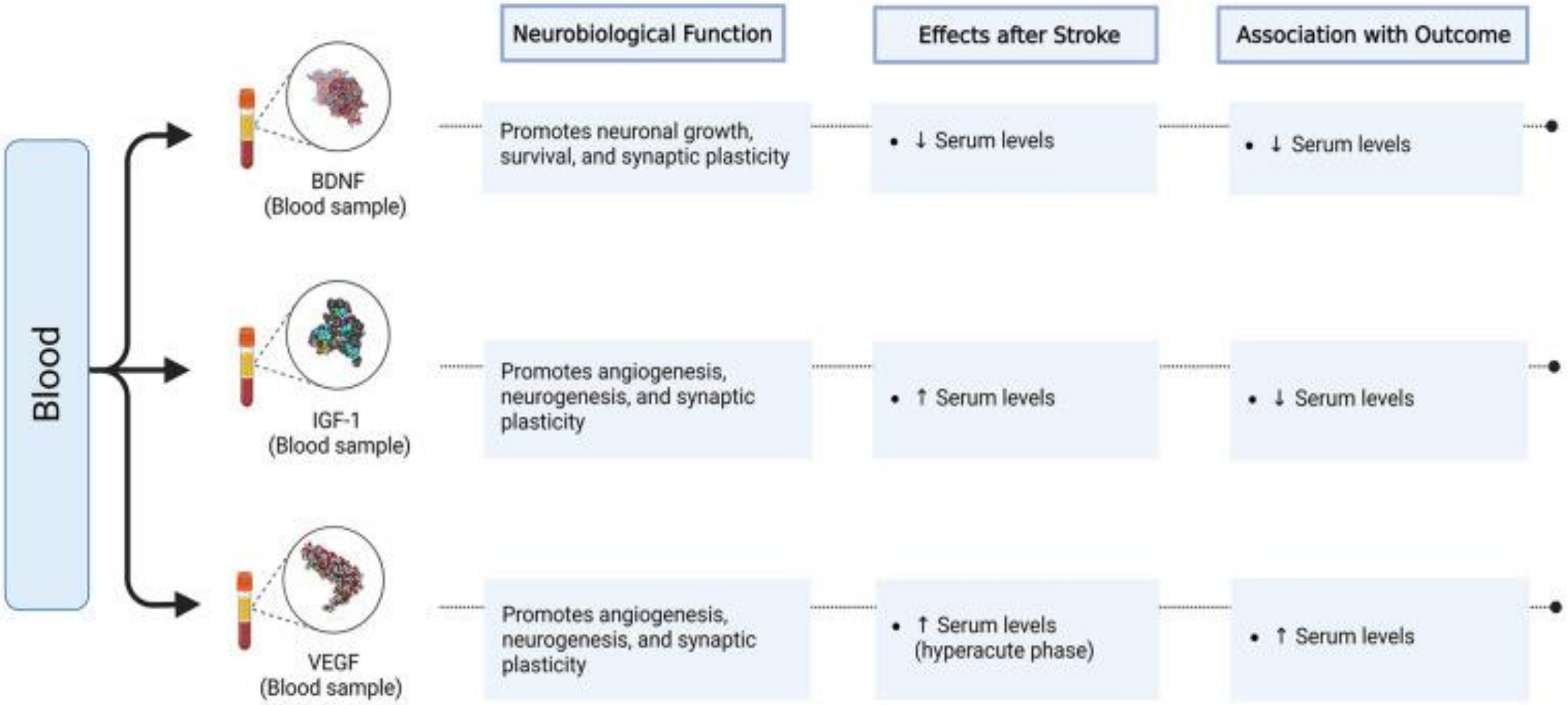
- Some of these biomarkers have proven to be particularly valuable for the diagnosis of severity, prognosis of recovery, as well as for measuring the neuroplastic response to different treatments after stroke.



Neurophysiological Biomarkers



Neuroimaging Biomarkers



Blood biomarkers.

- Plasticity is a natural property of the human brain, and its lifelong capacity enables a much longer therapeutic window for post-stroke neural restoration than previously assumed.

Thank You