

Recovery After Stroke and Genetic Influences of Neuroplasticity

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Factors that Predict Mortality of Acute Stroke

- Stroke severity
- ECG abnormalities
- Age
- Delay in medical care
- Elevated blood glucose in nonDM
- Brainstem involvement
- Admission from nursing home
- Hemorrhagic stroke

Factors that Predict Mortality of Acute Stroke

- Death within 30 days:
 - Age 45-64: 8-12% ischemic strokes; 37-38% hemorrhagic strokes
 - Age 65+ : 8.1% ischemic strokes; 44.6% hemorrhagic strokes
- Mortality in first year after all strokes 25-40%
- Risk of another stroke within one year 12-25%

Stroke Rehabilitation

- Goals of rehabilitation
 - Mobility, ADL's, Communication, Cognition, Swallow, Bowel & Bladder Management, Psychosocial support
- Inpatient acute rehab v snf

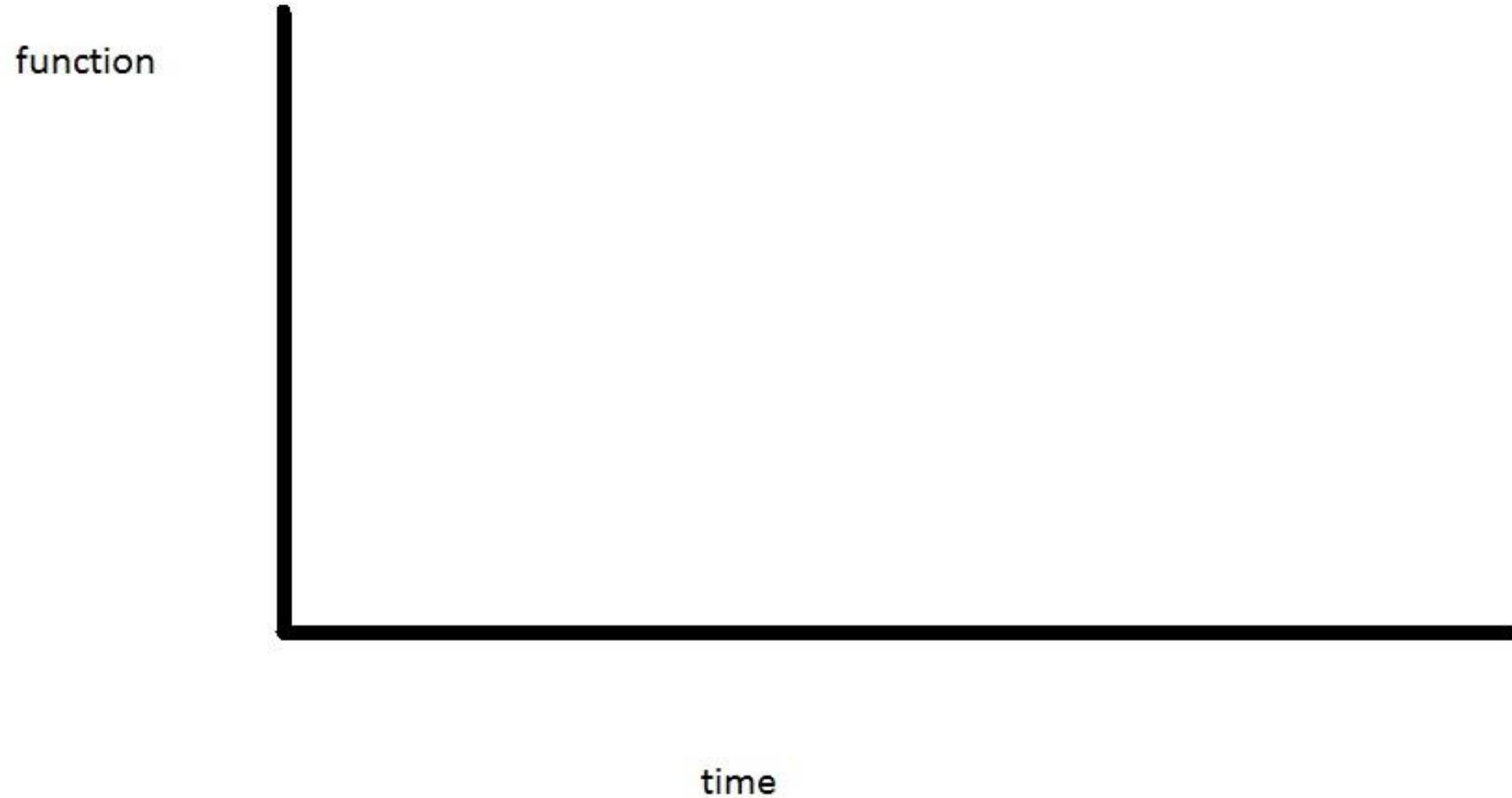
Stroke Survivors' Function Statistics

- About 50% of stroke survivors have hemiparesis
- 30% need some assistance to walk
- About 25% dependent with ADL's
- About 20% with aphasia
- 35% with depressive symptoms
- About 25% in long term nursing home

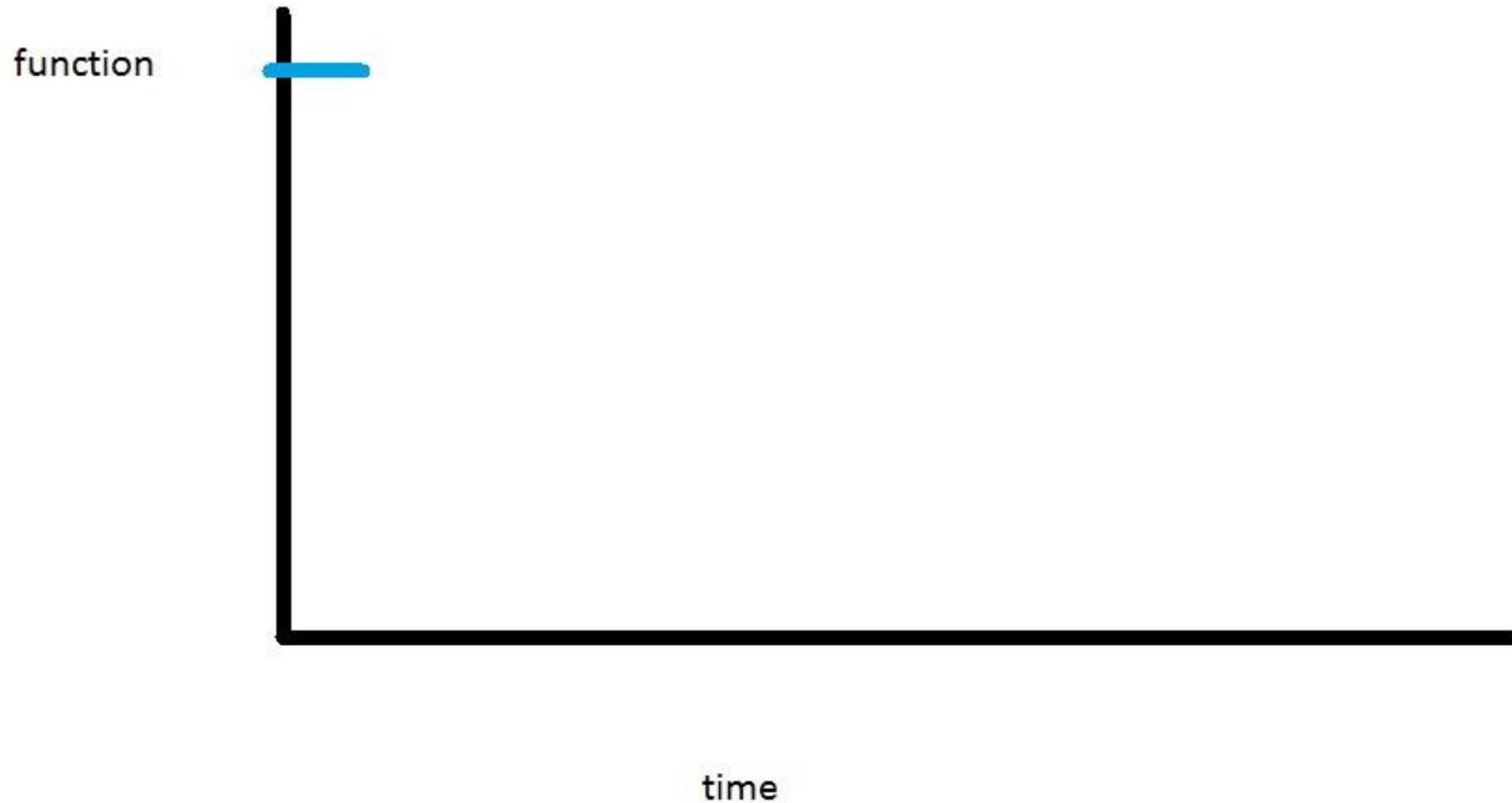
Stages of Recovery from Stroke Induced Hemiplegia

- Flaccidity
- Spasticity with minimal voluntary movement
- Some voluntary within synergies
- Some movements outside of synergies
- More complex motor combinations
- Disappearance of spasticity, individual joint movements, coordination near normal.
- Normal function restored

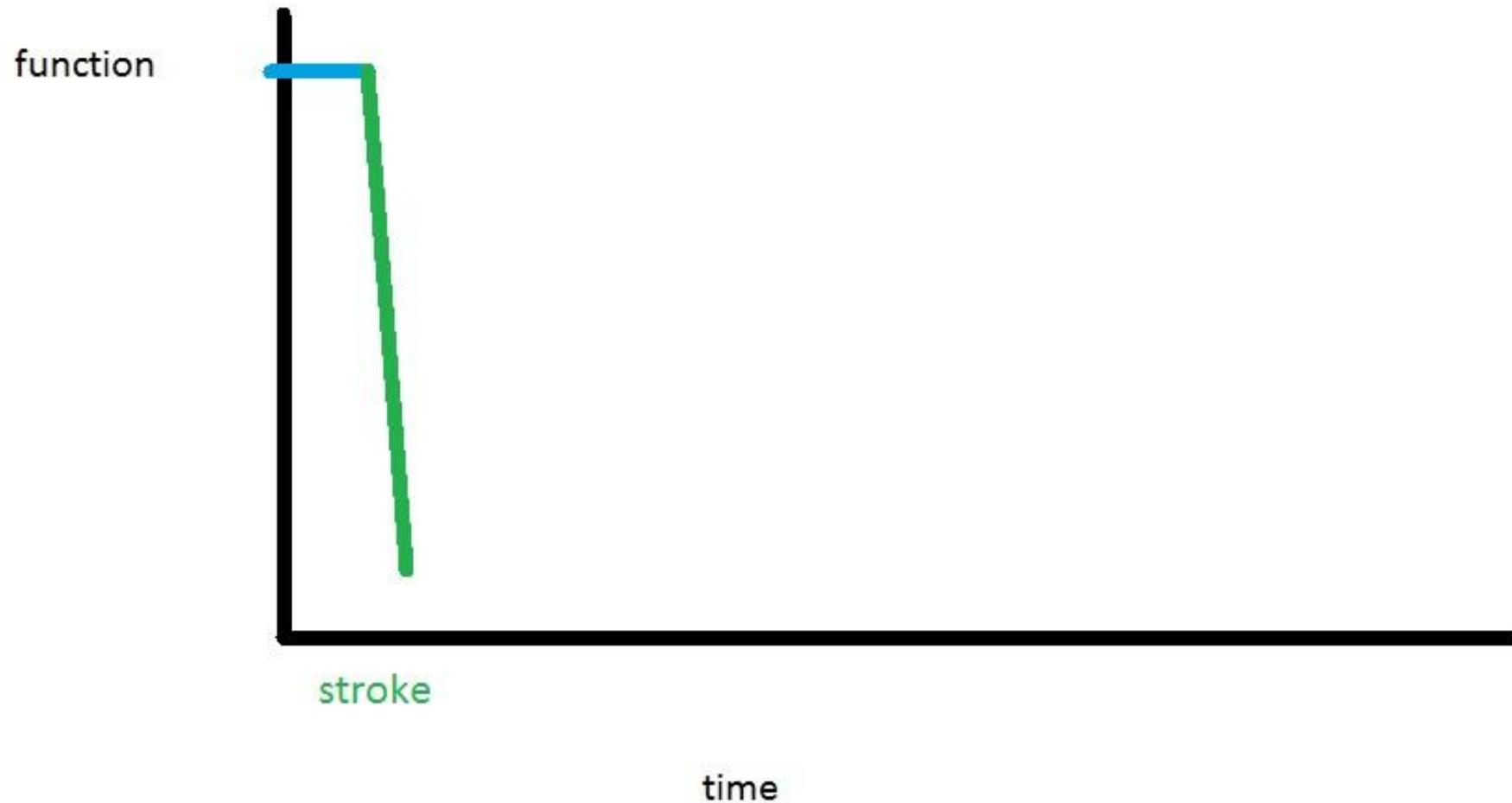
Copenhagen Studies – timeline of motor recovery



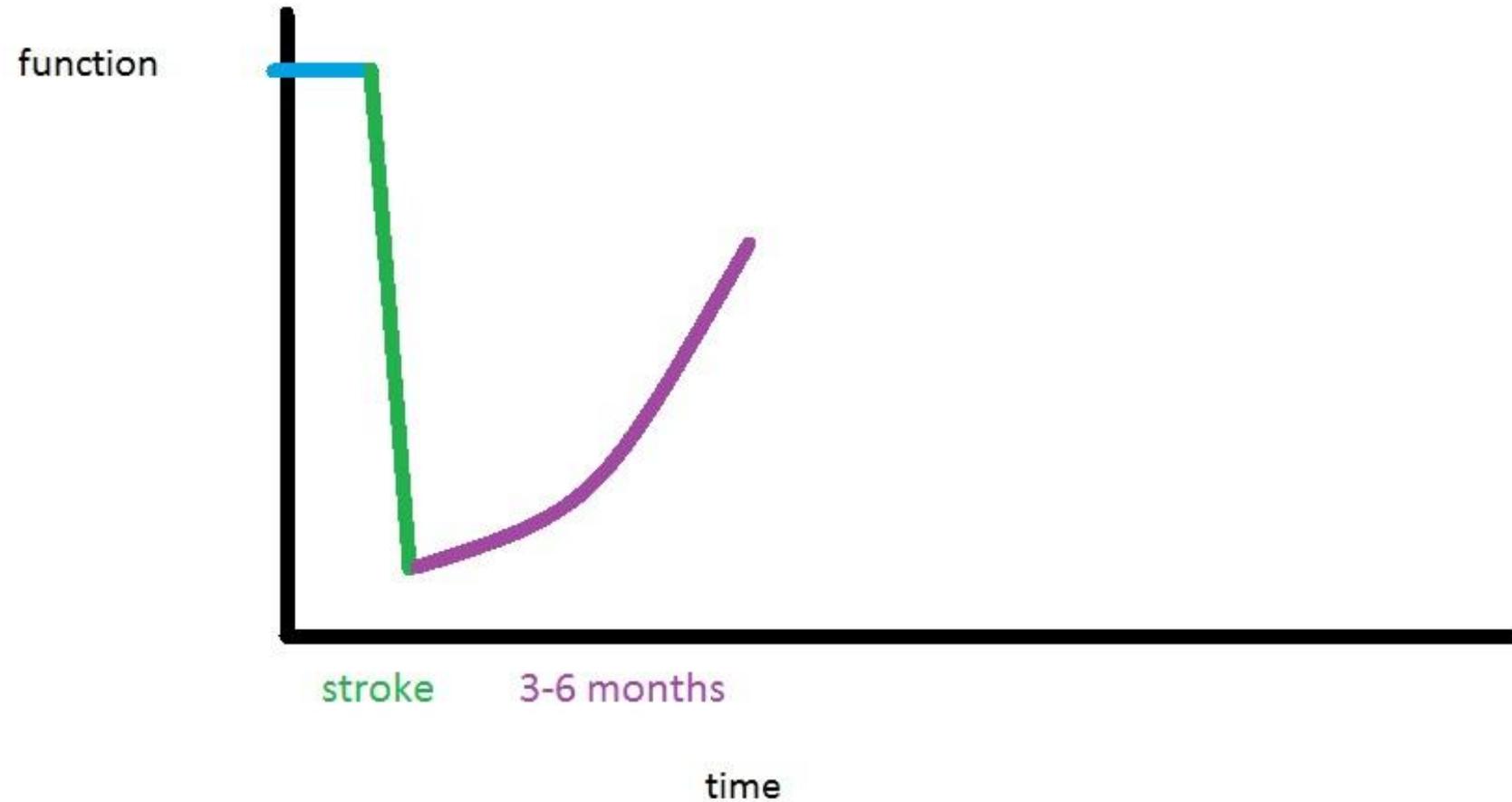
Copenhagen Studies – timeline of motor recovery



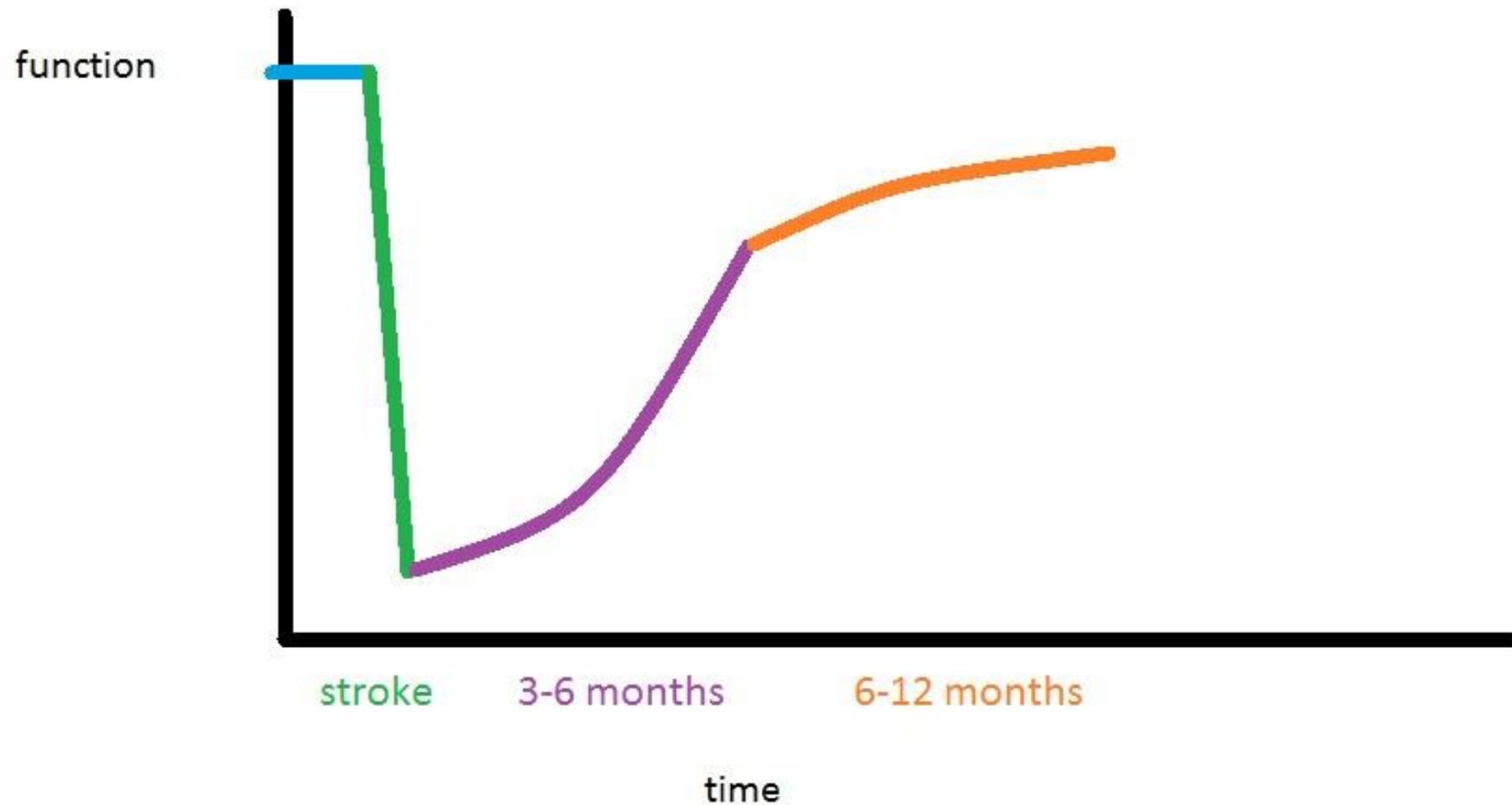
Copenhagen Studies – timeline of motor recovery



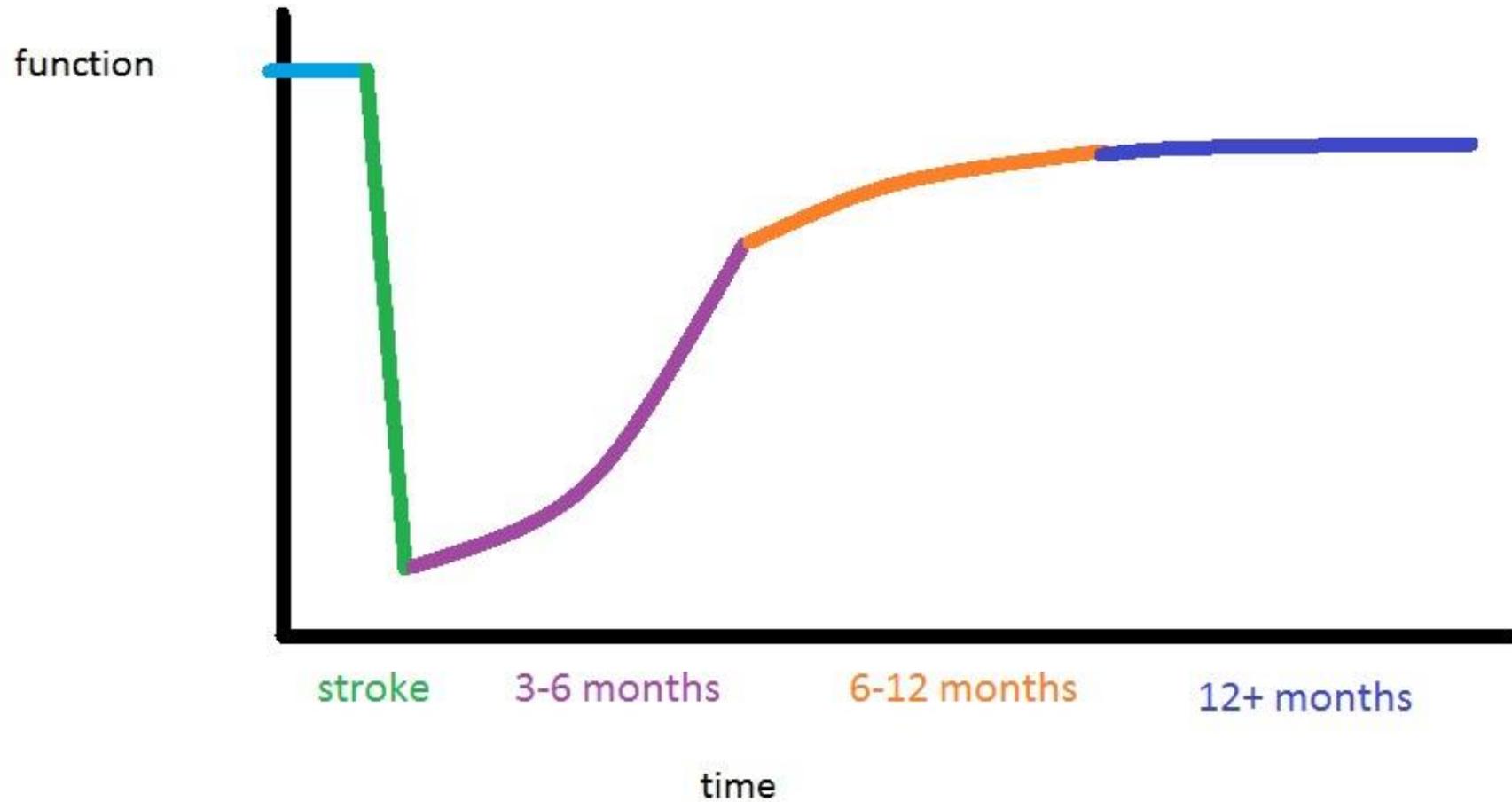
Copenhagen Studies – timeline of motor recovery



Copenhagen Studies – timeline of motor recovery



Copenhagen Studies – timeline of motor recovery



Predictors of motor recovery

- 9% of complete upper extremity paralysis at onset achieve useful recovery of hand function.
- If some hand movement by 4 weeks, up to 70% chance of full or near full recovery
- Poor prognosis:
 - No measureable grasp strength by 4 weeks
 - Severe proximal spasticity
 - Late return of proprioceptive facilitation response >9 days
 - Late return of proximal traction response >13 days

Bowel/Bladder Dysfunction post stroke

- Urinary Incontinence 50-70% during first month and similar to general population at 6 months (~15%)
- Incidence of bowel incontinence in stroke patients is 31%
 - Usually resolves within first 2 weeks.
- Incontinence persisting greater than 2 weeks of bowel or bladder is associated with poorer outcomes of disability after stroke.



Dysphagia

- 67% of brainstem strokes
- 28% all left hemisphere strokes
- 21% of all right hemisphere strokes

Dysphagia recovery after stroke

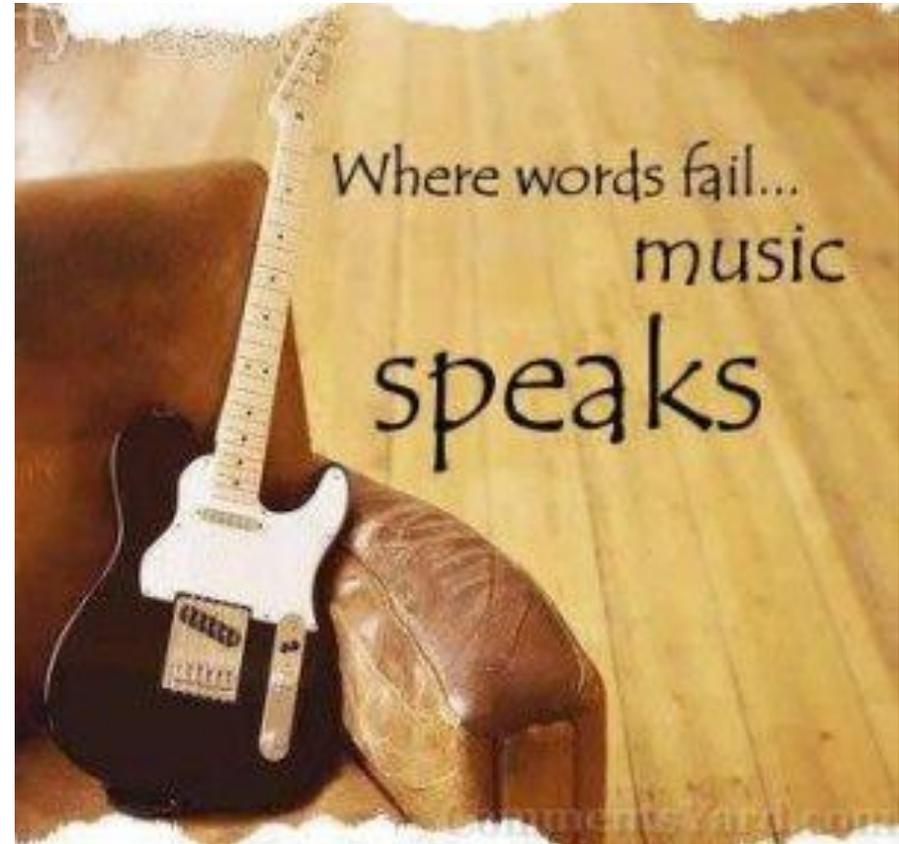
- Wilkinson retrospective cohort (186 patients at a teaching hospital)
 - If able to tolerate grade 3 thicken fluids by day 7 → 36% tolerated normal diet at day 28
 - If could not tolerate grade 2 thicken fluids by day 14 → 0 had normal diet at day 28
 - Conclusion: PEG should be considered in people unable to tolerate grade 3 thickened fluids or pureed diet 14 days post stroke
 - Eventually half of the patients requiring PEG were able to manage oral feeding
- Logemann
 - Recovery of swallow in most brainstem strokes occurs within first 3 weeks post stroke.

Aphasia recovery post stroke

- Similar to motor with greatest improvement first 2-3 months after stroke.
- After 6 months, significant drop in rate of recovery
- Unlikely for spontaneous recovery after one year, although few case reports of many years post stroke in patients undergoing SLP therapy
- Copenhagen: The outcome for language function was predicted by initial severity of the aphasia and by the initial stroke severity, but not by age, sex or type of aphasia
- Bhogal:aphasia treatments are more likely to achieve positive results if the total amount of therapy exceeds 55 h.

Aphasia Post Stroke Recovery

- Role of melodic intonation therapy?
 - Intonation and rhythm
 - Ongoing randomized clinical trial (RO1DC008796, NCT00903266) to compare MIT with a matched control treatment (i.e., speech repetition therapy) that does not include the two unique elements of MIT but shares other therapy components



Aphasia Post Stroke Recovery

- potential to unlock primitive language centers of the unaffected right hemisphere
 - Superior temporal region
 - Primary sensorimotor and premotor cortices
 - Inferior frontal gyrus
 - Arcuate fasciculus
- MIT may help with language recovery after a large left-hemispheric lesions whose only chance to recover is through recruitment of the right hemisphere.



Return to Work After Stroke

- Aphasia
- Prolonged Rehabilitation Stay
- Prior alcohol abuse

"You can't drink while you're at work!"

"Oh, don't worry, I'm not working."



Post Stroke Depression



- Independent risk factor for poorer health outcomes at 1 year and 5 years
- small trials have demonstrated that SSRIs might improve recovery after stroke, even in people who are not depressed.
- Cochrane review 2012 of 56 papers: It appears that SSRI's improve dependence, disability, neurological impairment, anxiety and depression after stroke, but need larger well designed trials before giving prophylactically in all stroke patients

Neuroplasticity

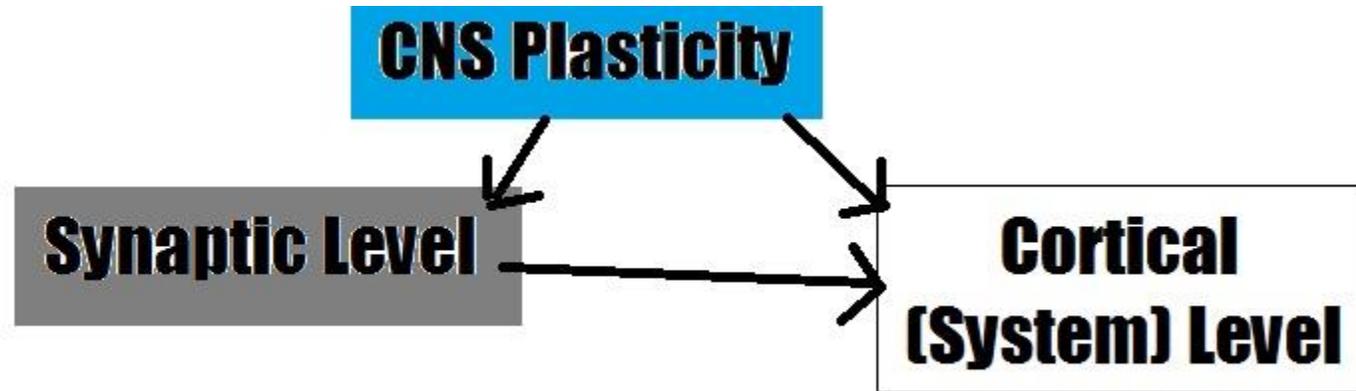
- Capability of the brain to alter function or structure in response to a range of events and is crucial component of both functional recovery after injury and skill learning in healthy individuals

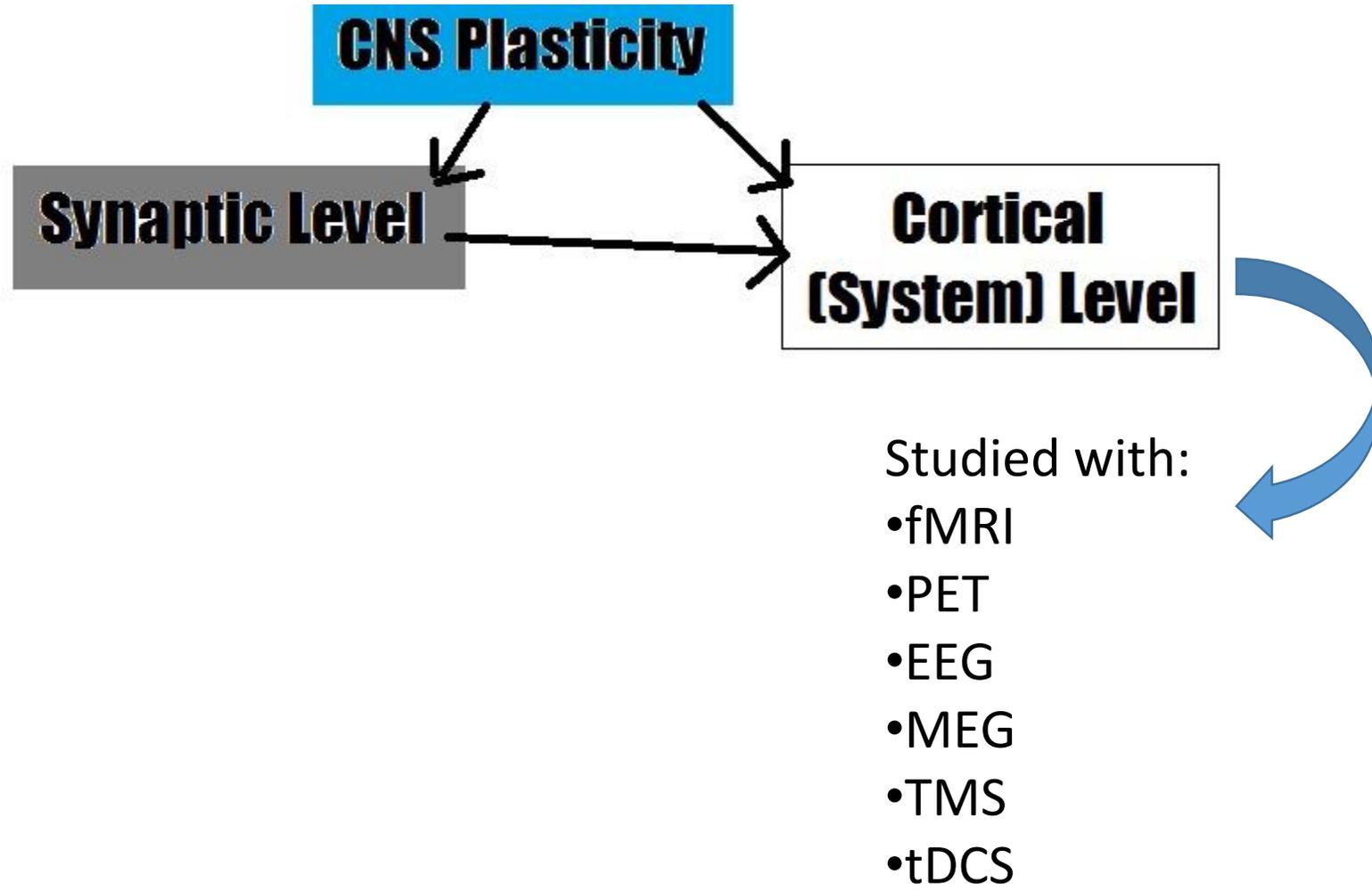
Overview

- Patients with similar injury can have highly variable recovery and response to therapy.
- Neuroplasticity is needed for recovery
 - Cortical level
 - Synaptic level
- Individuals who have a greater capacity for neuroplasticity theoretically have an advantage with regard to recovery and functional outcome following brain injury

Overview

- Factors such as age, experience, mood, features of CNS injury, severity of behavioral deficit, training intensity, medication effects, social factors, and even stage of menstrual cycle can influence plasticity
- *Above + genetics* = Influence outcomes





CNS Plasticity

Synaptic Level

**Cortical
(System) Level**

**↑ # of
connections**

- increase # of synapses
- Increase dendritic spine/sprouting

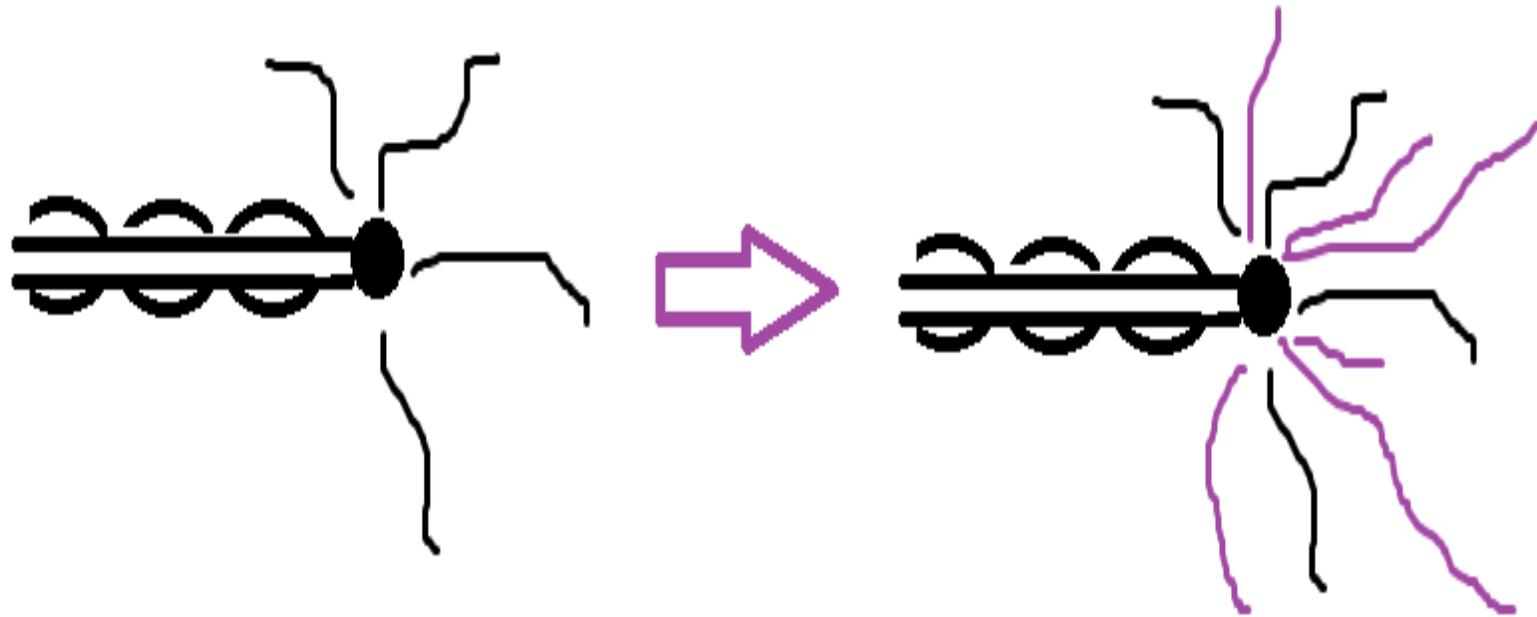
**Reassign where
needed**

- Pruning/
Remodelling

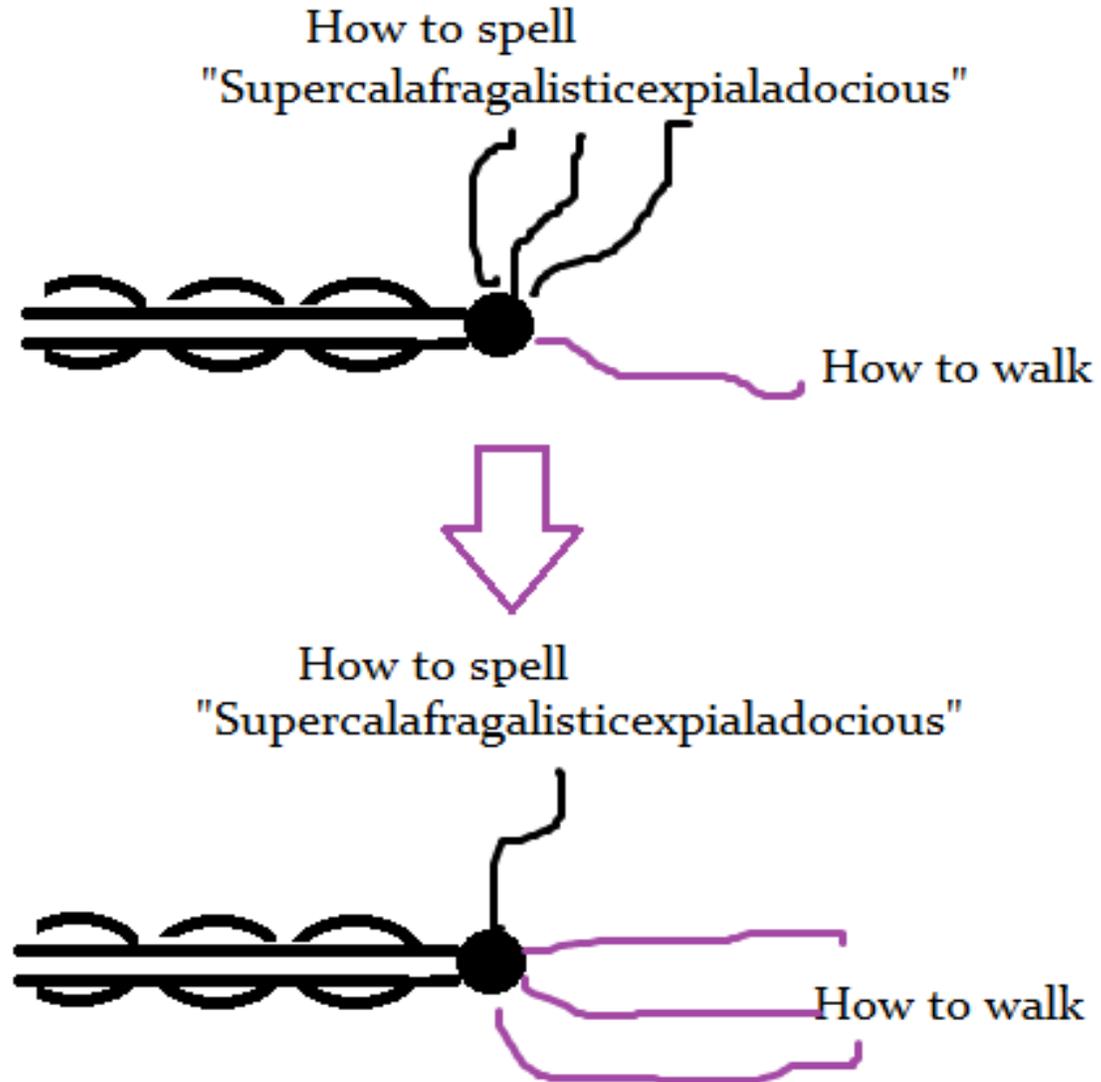
**Improve
Transmission**

- NMDA Receptor Changes
- Ca⁺⁺ upregulation

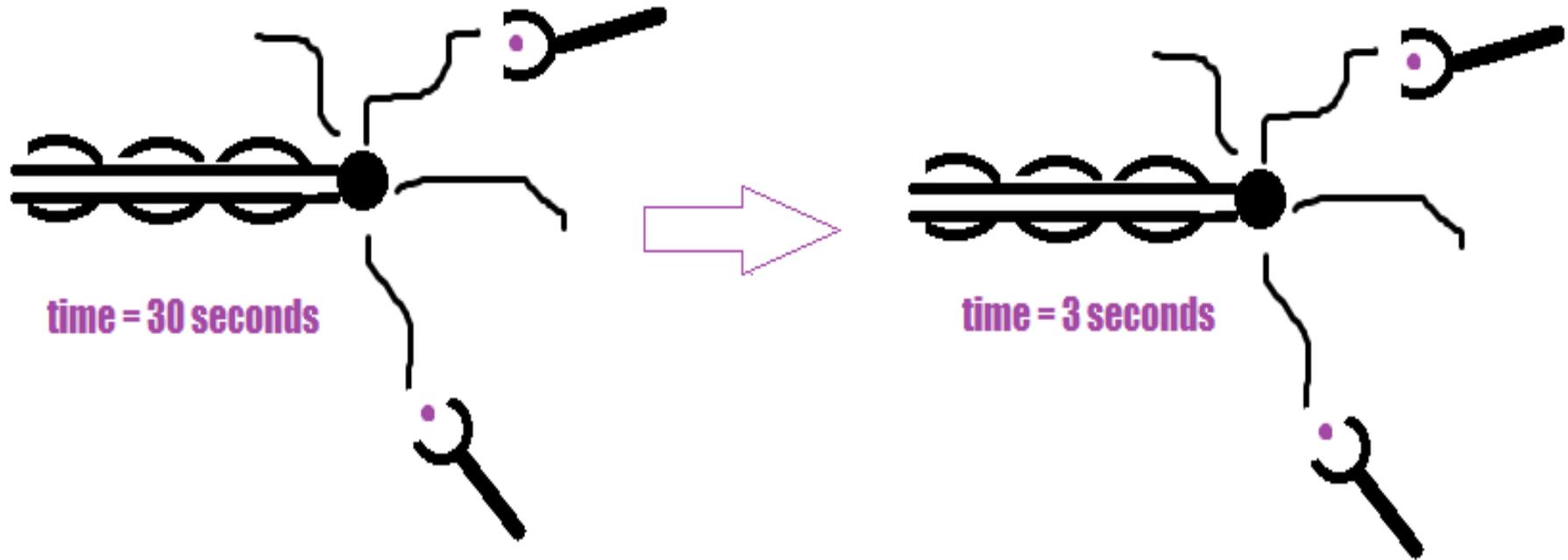
Increase # of Connections



Reassign Where Needed



Improve Transmission



Genetic Factors Affecting Plasticity

- Brain-Derived Neurotrophic Factor (BDNF)
- Apolipoprotein E (ApoE)

- How it effects plasticity at the synaptic level
- How it may influence other factors of plasticity such as learning, attention to task, and mood

Less Studied Genetic Factors

- Neurotrophin 3
- Neurotrophic Tyrosine Kinase Receptors
- Norepinephrine Transporters
- COMT
- Cholinergic Polymorphisms
- DYT1

BDNF

- Most abundant growth factor in the brain
- Increases amount of presynaptic NT release
- Increases postsynaptic depolarization
- Mediates use-dependant plasticity
- Modulates neuronal structure, function, and survival

BDNF – what happens when it's decreased/blocked in animal studies?

- Impairs spatial learning and memory
- Inhibition at hippocampus erases the cognitive benefits of exercise
- Impairs skilled motor performance and disrupted cortical reorganization
 - When exogenous BDNF then applied in motor cortex, these were partially restored

BDNF – What happens when it is increased in animal studies?

- When performing tasks, BDNF is unregulated in the tissues that control that function
- Exogenous BDNF is associated with better motor recovery in stroke rodent models

Polymorphism of BDNF

- When a Met substitutes a Val, BDNF function is not impaired, but the release and the responsiveness is.
 - Edge versus 4G
- Val/Val → good
- Val/Met → okay
- Met/Met → poor
- 30-50% of people carry at least 1 Met allele
 - These patients may have decreased CNS repair and thus diminished capacity for functional recovery after neuronal insult

Met carriers compared to Val/Val

- Reduced volume in human MRI studies of the prefrontal cortex, hippocampus, parahippocampal gyrus, caudate nucleus, and temporal and occipital grey matter
 - Decreased dendritic sprouting, less neuronal support cells, increased cell death, decreased neurogenesis all can lead to decreased volume

Met carriers compared to Val/Val

- Poorer performance on hippocampal- dependent episodic memory tasks
- No difference on semantic memory and verbal fluency
- Separate studies using TMS and fMRI showed similar motor map organization at baseline , but Met carriers had reduced short-term, experience-dependent plasticity in the motor cortex
- Met allele is associated with poorer outcome after SAH

BDNF and Depression

- BDNF is reduced in the hippocampus and prefrontal cortex in post partum depressed patients
- rTMS shown to improve depression symptoms in Val/Val better than Val/Met or Met/Met patients
- Possibly the decreased hippocampal volumes associated with Met allele may make some individuals more susceptible to depression

BDNF and Exercise

- Exercise increases BDNF in cerebral cortex, cerebellum, and spinal cords of rodents in as little of 30 minutes
 - May explain the functional improvements seen with initiation and intensity of therapies
- Val/Met patients respond to exercise on memory tasks when compared to Val/Met controls

BDNF and Pharmacology

- Briefly SSRI, Norepi reuptake inhibitors, catecholamine enhancers have had different results depending on polymorphism

ApoE

- Primarily involved in lipid transport, but also plays a significant role in:
 - Growth and regeneration of peripheral and CNS tissues
 - Neuronal repair
 - Neuronal remodeling
 - Neuronal protection
- 3 alleles: ApoE2; ApoE3; ApoE4
 - ApoE4 is bad 😞

ApoE4 studied in rodents

- Less NMDA receptor activation in response to Reelin
- Less compensatory sprouting and synaptogenesis after cortical lesioning

ApoE4 studied in humans

- Accelerated cognitive decline with age
- Impaired episodic memory
- Decreased hippocampal volume and cortical thickness
- Impaired attention
- Carriers have fMRI and PET activation patterns similar to those diagnosed with Alz Disease
- More than 2x as likely to have an unfavorable outcome 6 months following TBI
- Poorer recovery at 1 and 3 months following stroke

Conclusions

- In general, most recovery occurs within the first 6 months post stroke
- Motor recovery occurs proximal to distal
- Depression and incontinence are associated with poorer outcomes
- There are genetic factors that influence neuroplasticity, which may account for differences in outcomes for interventions
- Future research may help identify and subsequently target factors that facilitate neuroplasticity

JUST DO IT.



EVEN IF YOU SUCK.

**“Hope for the best,
but plan for the now”**

-Dr. C

Thank you!

Questions?