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
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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 measurable 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 thickened fluids by day 7 $\rightarrow$ 36% tolerated normal diet at day 28
  • If could not tolerate grade 2 thickened fluids by day 14 $\rightarrow$ 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
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
Studied with:
- fMRI
- PET
- EEG
- MEG
- TMS
- tDCS
CNS Plasticity

Synaptic Level
- \# of connections
  - increase \# of synapses
  - Increase dendritic spine/sprouting
- Reassign where needed
  - Pruning/Remodelling
- Improve Transmission
  - NMDA Receptor Changes
  - Ca++ upregulation

Cortical (System) Level
Increase # of Connections
Reassign Where Needed

How to spell "Supercalafragalisticexpialadocious"

How to walk

How to spell "Supercalafragalisticexpialadocious"

How to walk
Improve Transmission

time = 30 seconds

→

time = 3 seconds
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?