



NEURO  
INSTITUTE

Continuing Education for Rehabilitation Professionals



# Neural Plasticity and Brain Injury Recovery

Frank D. Lewis, PhD  
National Director of Clinical Outcome Services

## Objectives

- Define neural plasticity and ways in which neurons are altered to effect human performance.
- Identify benefits of neural plasticity to your clinical practice.
- Outline how you can maximize neural plasticity in your clinical practice.
- Discuss ways to measure neural plasticity using neuroimaging technology.
- Identify limitations of neural plasticity in your clinical practice.

# Neural Plasticity and Neurogenesis

## Neural Plasticity and Neurogenesis Definition

- Neural plasticity: The ability of the brain to change in response to experience. Experience leads to changes in the brain, which, in turn, facilitate new learning, which leads to further neural change.
- Neurogenesis: Growth of new neurons.

## Neural Plasticity Definition

- Growth of new neural processes (dendrites sprouting, axonal sprouting, creating new synapses)
- Growth of new blood vessels (angiogenesis)
- New neurons (neurogenesis)

## Neural Plasticity

- Much excitement in the world of neuroscience
- BUT the brain changes all of the time
- Focused neuroplasticity with resultant meaningful functional change still a slow process

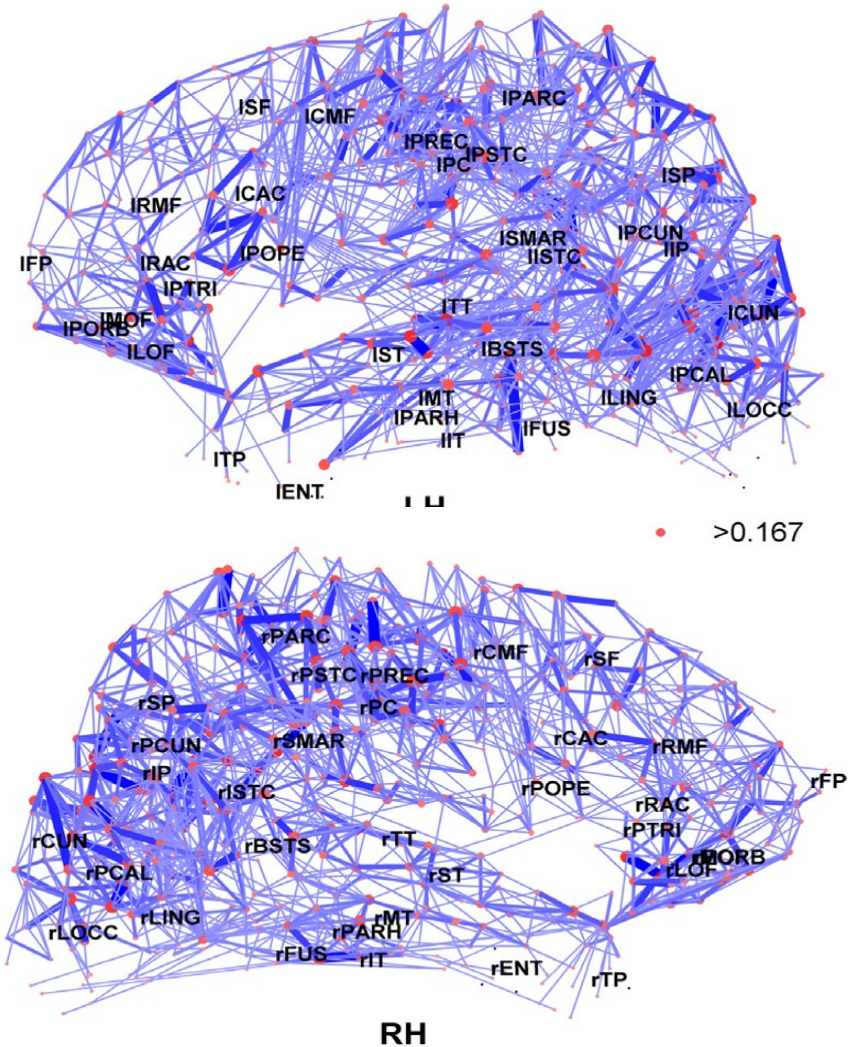
## Brain Plasticity: Not a New Concept

- “To explain skill acquisition it is necessary to assume formation of new pathways” Ramon y Cajal 1897
- However, until the early 1970s most neuroscientist believed that adult neurons were fixed
- Not well understood until advances in imaging (fMRI, DTI)

## Axonal Pathways

- Diffusion spectrum imaging has been able to map large-scale structural brain networks within and across cortical hemispheres in humans

Hagman P, Cammoun L, Gigandet X, Meuli R, Honey, CJ, Wedeen VJ, Sporns Mapping the Structural Core of Human Cerebral Cortex, PLoS Biology, July 2008, Vol 6, Issue 7, 1479-1493.





## Neuroplasticity After TBI

- After brain injury (lesions, shearing) neurons spontaneously rewire
- Poor result for functional recovery without stimulation of those pathways

## Neuroplasticity after Brain Injury

Frost et al 2003

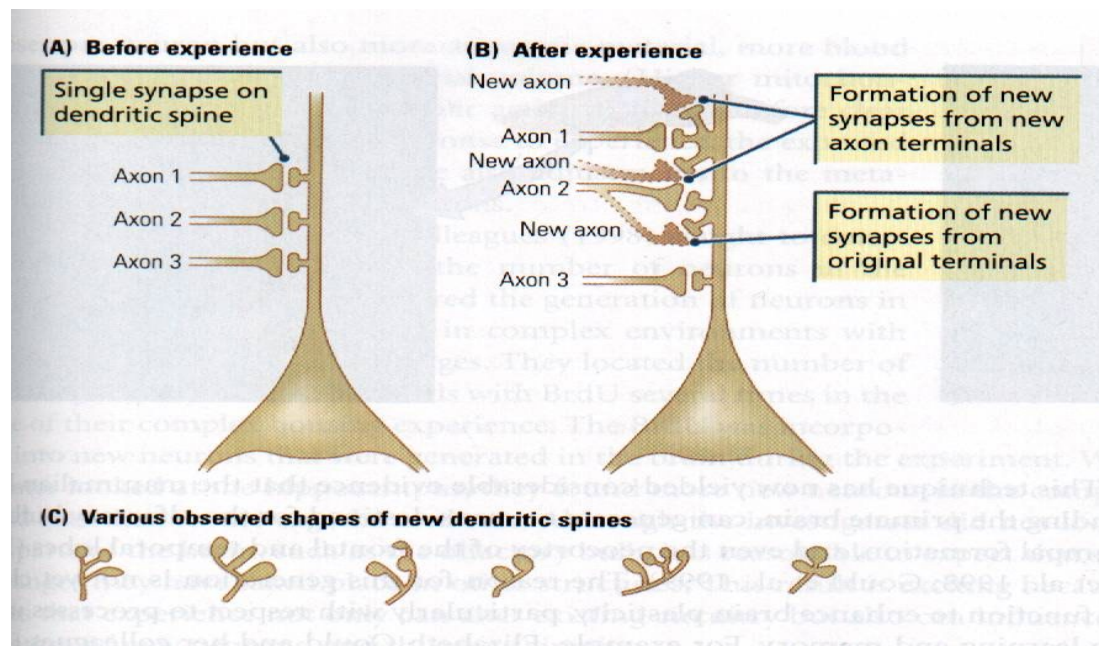
- Induced small ischemic strokes in monkey's motor cortex
- Repetitive use of affected paw in food gathering tasks
- Intra-cortical microstimulation revealed cortical reorganization in adjacent cortical areas unaffected by stroke
- Within months regain use of paw
- *Conclusion: post – injury rehabilitation drives plasticity in spared motor cortex*

## Brain Rewiring

- Repeated firing of neurons along specific nerve tracks results in those cells becoming functionally and anatomically reconnected (Nudo, 2011)
- Brain workouts – Challenging intellectual tasks/activities help the brain to reorganize (Liou, 2010).

## Brain Rewiring

- Sensory input and learning tasks change the structure and function of neurons – resulting in increased efficacy in existing neuronal circuits (Pascual-Leone et al, 1994)



## Cortical Changes Associated with Cognitive Rehabilitation

Han, Davis et al 2014

- 57 adults with mild to moderate chronic TBI (> 6 months post injury)
- Randomly assigned to one of two groups: 1) Strategic Memory Advanced Reasoning Training (SMART) or Brain Health Workshop (BHW)
- Training lasted 8 weeks
- MRIs given pre – post and 3 month follow-up

## Cortical Changes Associated with Cognitive Rehabilitation

### Results:

- Both interventions led to dynamic changes in cortical thickness – even at 3 month follow-up
- SMART – changes were in bilateral frontal cortices – suggesting cortical plasticity induced by attentional and reasoning tasks
- BHW- changes were in subcentral and superior temporal cortices and right frontal cortex - suggesting cortical changes induced by learning new information.

## Evidenced Based Rehabilitation

### Cortical Plasticity and Behavioral Recovery

- “Post injury plasticity has been documented at the molecular, synaptic and cellular level in animals and now with neuro-imaging techniques in humans” (Nudo J Rehabil Med 2003.)
- Behavioral experience appears to be critical to cortical rewiring after brain injury. Neurons move around lesions. Diffusion Tensor Imaging. (Dancause et al. Journal of Neuroscience 2005)
- Controlled primate studies: enriched structured environment improved functional outcomes. (Nudo et al. Science, 1996)

## Older Adults - *Neurogenesis*

- Researchers used chemical markers to identify new neurons.
- New neurons found in adults as old as 72.
- Growth found in the hippocampal region of the brain following semantic learning tasks.
- Some new cells die quickly, others integrate into existing neural connections.

Liou (2010) Neurobiology



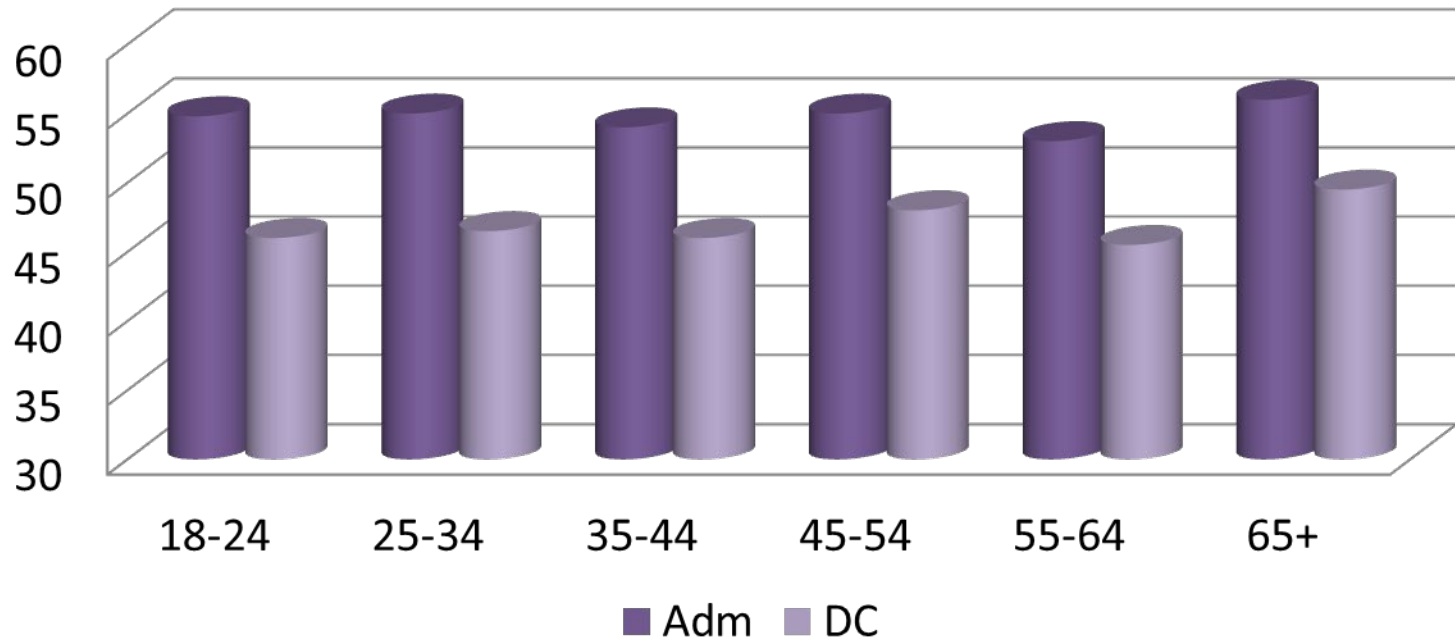
## Age and TBI Recovery (Lewis & Horn 2016)

### 413 TBI Participants in Neurorehabilitation

	18-24 N = 73	25-34 N = 86	35-44 N = 70	45-54 N=97	55-64 N=68	65+ N=19
<b>AGE</b>	20.8	29	39.7	49	58.7	69.8
<b>LOS</b>	3m	6.2m	6.5m	4.8m	3.9m	3.2m
<b>Onset to Adm</b>	19m	33m	29.9m	29.2m	12.5m	15m
<b>Sex</b>	71%m	86%m	81%m	81%m	83%m	68%m

## Age and TBI Recovery (Lewis & Horn 2016)

### Abilities T-Score by Age Group Admission to Discharge



## Mankato Nun Study

- 678 nuns participate in longitudinal study started at age 22 continued until death
- Annual assessments of cognitive and physical functioning
- Donated brains upon death
- Largest group of brain donors in the world

## Mankato Nun Study Results

- Idea density at age 22 linked with greater brain weight and less cognitive decline
- Positive emotions linked to longevity

## 7 Tenets Of Plasticity for Rehabilitation Professionals

1. Change only occurs when the brain is in the mood. Alert “on the ball”, acetylcholine.
2. Change strengthens connections between neurons engaged at the same time.
3. Neurons that fire together, wire together.
4. Initial changes are just temporary, do it over and over again

## 7 Tenets Of Plasticity for Rehabilitation Professionals

5. Brain plasticity is a two way street. Bad habits change the brain too. (Chronic pain behaviors over work pain neurons)
6. Memory is critical to learning, takes 8 seconds of focused attention to move information to LTM.
7. Motivation is a key factor in brain plasticity.

## II. Innovations in Brain Injury Rehabilitation

## Neuroplasticity and Constraint Induced Therapy CIT

- CIT has been consistently associated with cortical reorganization as determined by Transcranial Magnetic Stimulation, Functional MRI, and Diffusion Tensor Imaging
- Brain changes paralleled improvement in affected limb



## Brain Derived Neurotrophic Factor (BDNF)

- Involved in Neurogenesis
- Neuroplasticity and resilience encouraging branching
- When BDNF is absent it is difficult to normalize the HPA axis. (hypothalamic-pituitary-adrenal axis, involved regulates temperature, digestion, immune system, mood, sexuality, and energy)
- Stress/Pain decreases BDNF.

## BDNF

- Excitatory neurotransmission from excess glutamate (prolonged stress) results in not enough serotonin and norepinephrine to support BDNF synthesis
- Decrease in BDNF results in neurons shriveling, synapses get disconnected

## BDNF and Exercise

- BDNF improves the function of neurons, encourages new neurons to grow and protects them from stress and cell death.
- Exercise training increases size of hippocampus and improves memory. Erickson K I, Voss MW, Prakash RS, et al, PNAS Feb 15, 2011, vol 08, no. 7, 3017-3022.
- Evidence for a release of BDNF from the brain during exercise. Rasmussen P, Brafford P, et al, Experimental Physiology, August 7, 2009, doi:10.1113/expphysiol.2009.048512
- Exercise increases BDNF production.

## Hyperbaric Oxygen

- In a study presented at the 8<sup>th</sup> World Congress on Brain Injury March 2010, 15 blast injured veterans experienced:
  - 15 point increase in IQ
  - 40% reduction in post-concussion symptoms
  - 30% reduction in PTSD symptoms
  - 51% reduction in depression after HBOT.
    - Paul G. Harch, MD; Clinical Associate Professor; LSU School of Medicine, New Orleans LA

## Hyperbaric Oxygen Therapy: Not So Fast!

- Study conducted by the U.S. Air Force – November 2012 issue of *Journal of Neurotrauma*
- Randomized prospective double-blind study with Mild TBI patients
- No significant differences between HBO and Sham tx
- Shams did a little better
- **Placebo effect**

## Omega 3 fatty acids

- Omega-3 fatty acids are essential to the brain
- There has been a dramatic shift in the ratio of omega-3 : omega-6 fatty acids in the last century.
- Competing omega-6 fatty acids - mainly from soy, corn, and sunflower oil.

## Omega-3 fatty acids

- More than 160 studies about food's affect on the brain were analyzed.
- Omega-3 fatty acids -- found in salmon, walnuts and kiwi fruit -- provided benefits, including improving learning and memory and helping to fight against such mental disorders as depression and mood disorders, schizophrenia, and dementia.
- Omega-3 fatty acids support synaptic plasticity and seem to positively affect the expression of several molecules related to learning and memory.
- Brain foods: the effects of nutrients on brain function. Fernando Gómez-Pinilla. Nature Reviews Neuroscience 9, 568-578 (July 2008)

## Omega-3 fatty acids

- Omega-3 fatty acids supplementation restores mechanisms that maintain brain homeostasis in traumatic brain injury.
  - Wu A, Ying Z, Gomez-Pinilla F. J Neurotrauma. 2007 Oct;24(10):1587-95.



## Omega-3 supplementation

- Reduced suicidal thinking and depression among Irish subjects with a history of deliberate self-harm,
- Reduced anger and anxiety among polysubstance abusers,
- Successfully treating depression during and after pregnancy,
- Reduced the severity of bipolar symptoms in children.
  - **Joseph Hibbeln**, acting chief of the Section on Nutritional Neuroscience, Laboratory of Membrane Biochemistry and Biophysics, Nat Inst Alc Abuse & Alcoholism.

**OH NO!!!!**  
**PROSTATE CANCER**

## OMEGA 3s and Prostate Cancer

- July 11 2013 –Journal of the National Cancer Institute (Basky et al.)
- 843 men with prostate cancer
- 1,383 men who did not have prostate cancer
- Prostate cancer patients had higher levels of omega 3 fatty acids in their blood than those in the non-cancer group
- 71% increased risk in developing high grade prostate cancer

**Not So Fast!!!!**

## Other Research Tells a Different Story

- Chavarro et al. American Journal of Clinical Nutrition 2008
- 22 year prospective study of 20,167 men
- Fish intake, > 5 xs per week unrelated to incidence of prostate cancer
- 48% lower risk of prostate cancer death

## Other Research Tells a Different Story

- MacLean et al. JAMA 2006
- Systematic review of the literature
- No significant association with the incidence of prostate cancer and omega 3 fatty acids (1 decrease, 1 increase, 15 no association)

# New Treatments: ProTECT

## Progesterone given to TBI patients in ER



Neuro-protective effects including:

- Attenuates injury cascade
- Reduces inflammation
- Limits cell death (protects mitochondrial)
- Promotes re-myelination
- Toxicity protection

## ProTECT Early Results Promising

- Review of Numerous Phase II Clinical Trials
  - Mortality reduced by 50%
  - Shorter recovery time
  - Improved cognitive outcomes
  - Improved functional outcomes at 3 and 6 months

(Wei & Xiao, 2013)



## Upon Further Review

### **Progesterone Offers No Benefits in Traumatic Brain Injury**

*JAMA*. 2015;313(8):786

- 882 moderate to severe TBI randomized patients
- At six months favorable outcomes were observed for:
  - 51% of progesterone patients
  - 55.5 % of placebo patients

“Everybody is a genius. But if you judge a fish by its ability to climb a tree, it will live its whole life believing that it is stupid.”

-Albert Einstein