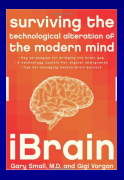
You Are What You Experience:

Effects of Environment on Neuroplasticity and Recovery from Brain Injury

ISNA Symposium
Birmingham, AL
October 2, 2010



Christopher C. Giza, M.D.
UCLA Brain Injury Research Center
Dept of Neurosurgery and Div of Pediatric Neurology

What's Important

I. **Principles of Plasticity and Development**

Experience-dependent plasticity is the process thru which changes in environment alter brain structure and function.

IV. Building the Evidence Base
V. Summing Up

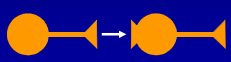
Principles of Plasticity and Development

- Kennard Principle *(1938)*

  Similar injuries in developing and mature brains produce less functional disability in the developing brain

  "Younger is better."

- Hebbian Theory *(1949)*

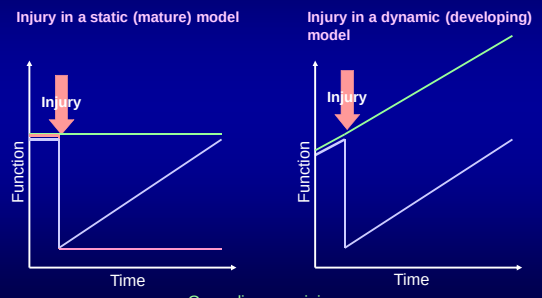


Repeated stimulation of a synapse leads to …..

…structural changes which facilitate transmission at that synapse

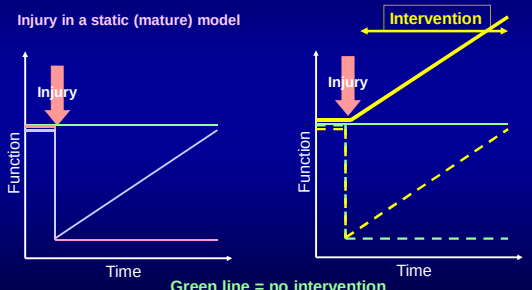
"Cells that fire together, wire together."

"Recovery to Baseline"… is inadequate after developmental TBI



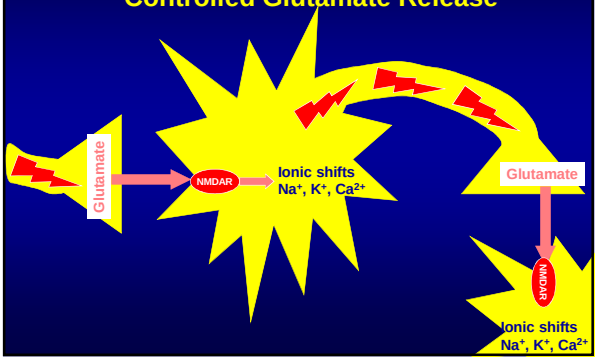
Green line = no injury

Neural repair/recovery vs experience-dependent plasticity….?



Green line = no intervention
Yellow line = yes intervention

Normal Plasticity Response: Controlled Glutamate Release



What's Important

I. Principles of Plasticity and Development
II. Nature vs Nurture
III. Mechanisms of Experience-Dependent Neuroplasticity
  A. Normal Development
  B. Environmental Effects
  C. Pharmacological Effects
  D. Recovery from Acquired Brain Injuries
IV. Building the Evidence Base
V. Summing Up

Maternal care, hippocampal synaptogenesis and cognitive development in rats

August 2000 Volume 3 Number 8 pp 799 - 806

Dong Liu, Josie Diorio, Jamie C. Day, Darlene D. Francis & Michael J. Meaney

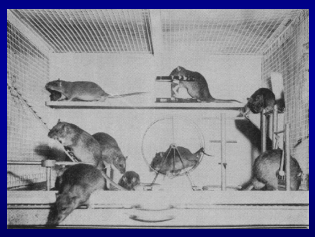
The offspring of mothers that show high levels of pup licking and grooming and arched-back nursing showed increased expression of NMDA receptor subunit and brain-derived neurotrophic factor (BDNF) mRNA, increased cholinergic innervation of the hippocampus and enhanced spatial learning and memory.

Maternal nurturing
↓
↑ Plasticity molecules (NR2A, BDNF)
↑ Cognition (MWM)

Liu D, et. al. Nat Neurosci 2000

Enriched Environment (EE) Paradigms

EE (or complex environments) have been shown to modify brain chemistry, structure and function since the seminal work of Rosenzweig, Bennett and Diamond in the 1960s.

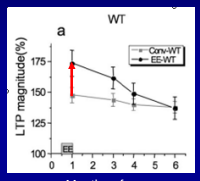


- **ECT** = environmental complexity and training (communal housing, toys, daily open field training)
- **SC** = social condition (3/cage, no toys)
- **IC** = isolated condition (1/cage, dimly lit room)

Duration of differential housing = 80 days, later 30 days

Bennett EL, et al., Science 1964

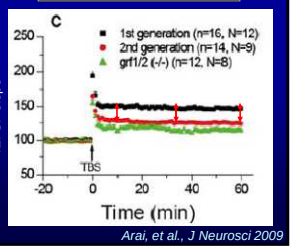
Can environmentally acquired attributes be passed on?



Months of age

EE rearing enhances long term potentiation (LTP), a physiological correlate of learning and memory.

EE rearing of mothers enhances long term potentiation (LTP) in their first generation offspring!

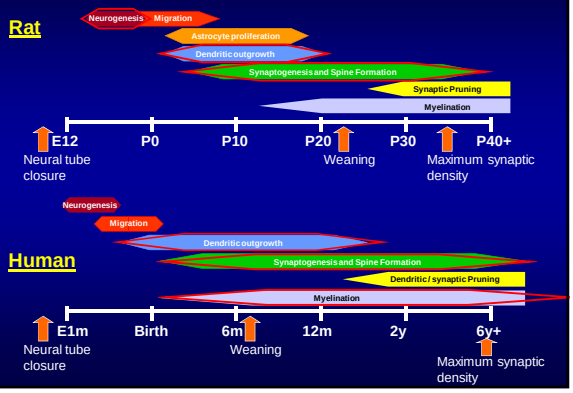


Arai, et al., J Neurosci 2009

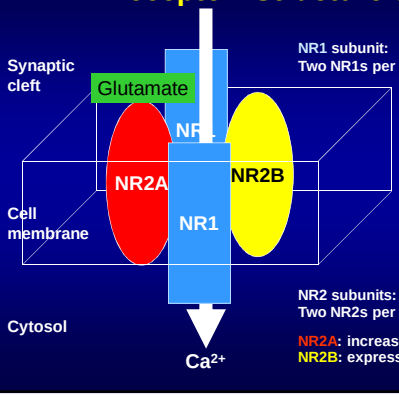
What's Important

I. Principles of Plasticity and Development
II. Nature vs Nurture
III. Mechanisms of Experience-Dependent Neuroplasticity
  A. Normal Development
  B. Environmental Effects
  C. Pharmacological Effects
  D. Recovery from Acquired Brain Injuries
IV. Building the Evidence Base
V. Summing Up

Stages of Neural Development



NMDA Receptor: Structure & Function



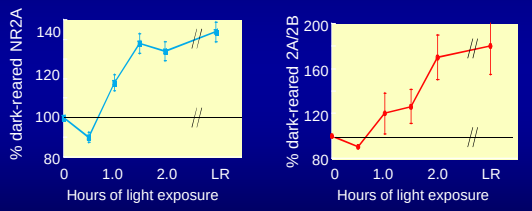
NR1 subunit:
Two NR1s per receptor complex.

NR2 subunits: "Regulatory portion".
Two NR2s per receptor complex:

NR2A: increases with maturation
NR2B: expressed from day 1

NMDA Receptor Composition:
Experience-dependent plasticity

Rapid, experience-dependent expression of synaptic NMDA receptors in visual cortex *in vivo*. Elizabeth M. Quinlan, Benjamin D. Philpot, Richard L. Huganir and Mark F. Bear. *Nature Neuroscience*, (1999). 2(4): 352-357.



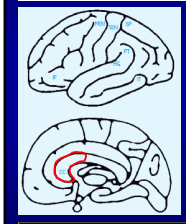
Light exposure to the developing brain rapidly changes the subunit composition of the NMDA receptor.

Quinlan, et.al. Nature Neurosci 1999

White Matter Plasticity?

Do musicians have different brains?

Lauren Stewart

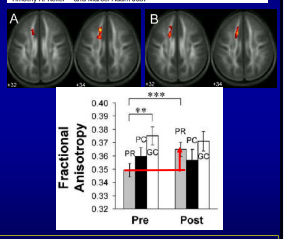


Anterior corpus callosum is larger in musicians trained from an early age.

Stewart L, Clin Med 2008

Altering Cortical Connectivity: Remediation-Induced Changes in the White Matter of Poor Readers

Timothy A. Keller[1,*] and Marcel Adam Just[1]



Training increased FA in WM regions associated with poor reading.

Keller & Just, Neuron 2009

What's Important

I. Principles of Plasticity and Development
II. Nature vs Nurture
III. Mechanisms of Experience-Dependent Neuroplasticity
  A. Normal Development
  B. Environmental Effects
  C. Pharmacological Effects
  D. Recovery from Acquired Brain Injuries
IV. Building the Evidence Base
V. Summing Up

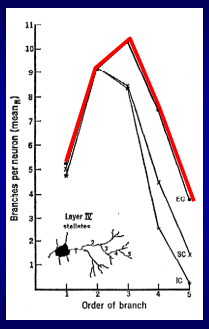
Developmental Plasticity: Enriched Environment

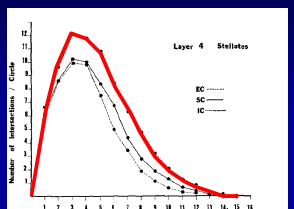
Enriched Environment effects

- Increased cortical thickness
- Increased neuronal size
- Greater dendritic arborization
- Increased glia and capillaries
- More synapses
- Improved neurocognitive performance
- Increased hippocampal neurogenesis
- *More robust effects in young animals*

Duration of EE = 17 days

Environment increases dendrites





- increased branching of neurons
- more synapses

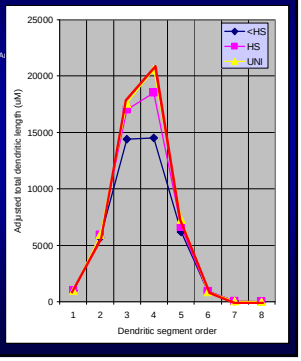
Volkmar & Greenough, Science 1972
Greenough & Volkmar, Exp Neurol 1973

J Comp Neurol 1993 Jan 1;327(1):97-111

A quantitative dendritic analysis of Wernicke's area in humans. II. Gender,hemispheric, and environmental factors.

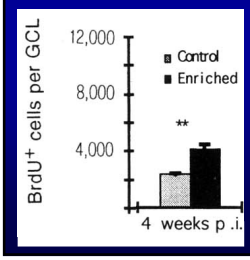
Jacobs B, Schall M, Scheibel AB.
Brain Research Institute, University of California, Los A

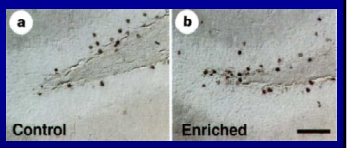
Education had a consistent and substantial effect such that dendritic measures increased as educational levels increased. Dendritic differences between independent variable levels were most clearly illustrated in the total dendritic length of 3rd and 4th order branches. Distal dendritic branches appeared to exhibit greater epigenetic flexibility than proximal dendrites. **The present findings concur with environmental enrichment research results in animals and suggest that dendritic systems in humans function as a sensitive indicator of an individual's (a)vocational activities.**



Environment increases brain cells

More hippocampal neurons in adult mice living in an enriched environment



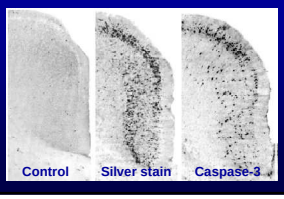


Kempermann, Kuhn & Gage, Nature 1997

What's Important

I. Principles of Plasticity and Development
II. Nature vs Nurture
III. Mechanisms of Experience-Dependent Neuroplasticity
  A. Normal Development
  B. Environmental Effects
  C. Pharmacological Effects
  D. Recovery from Acquired Brain Injuries
IV. Building the Evidence Base
V. Summing Up

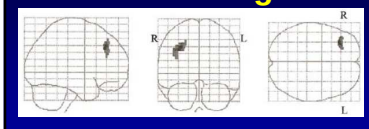
Do Our Treatments Independently Worsen Outcome?

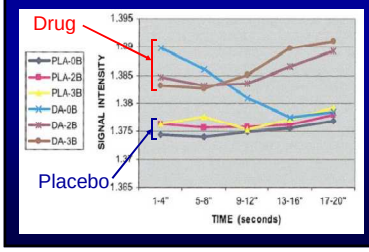


Apoptotic cell death after cocktail of midazolam, nitrous oxide and isofluorane.

Olney JW et al., TIPS, 2004

Modulating neural activity





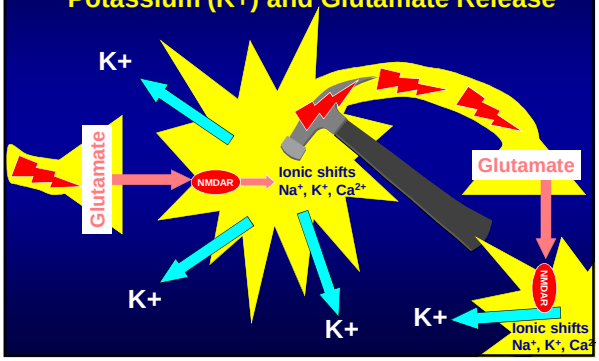
D-amphetamine selectively increased R prefrontal activation during a working memory task

Mattay et al., Neuroimage 2000

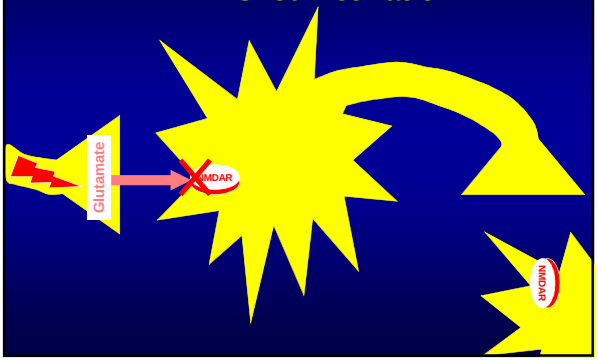
What's Important

I. Principles of Plasticity and Development
II. Nature vs Nurture
III. Mechanisms of Experience-Dependent Neuroplasticity
  A. Normal Development
  B. Environmental Effects
  C. Pharmacological Effects
  D. Recovery from Acquired Brain Injuries
IV. Building the Evidence Base
V. Summing Up

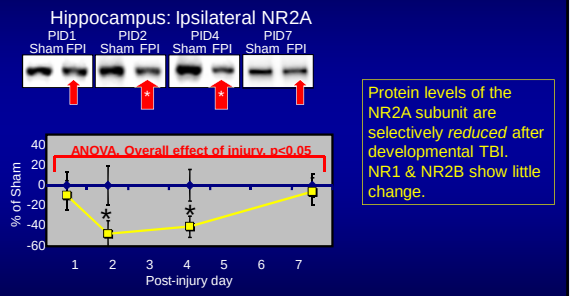
Post-Concussive Cellular Response: Potassium (K+) and Glutamate Release



Post-TBI Plasticity Response: Diminished Activation?



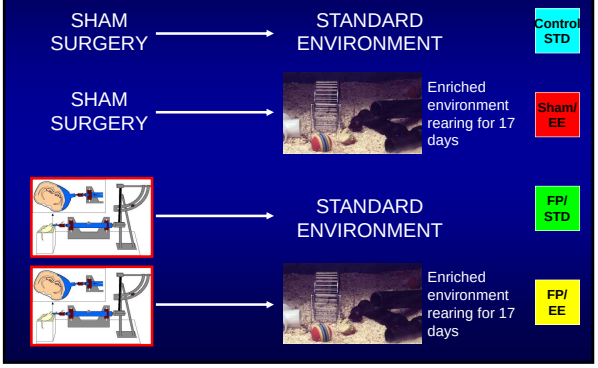
Developmental TBI: NMDA Receptors



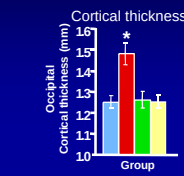
Protein levels of the NR2A subunit are selectively *reduced* after developmental TBI. NR1 & NR2B show little change.

Giza, Santa Maria & Hovda, J. Neurotrauma 2006

Experimental Design:

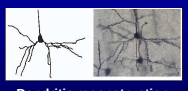


Developmental TBI & EE: Lack of Anatomical Enhancement

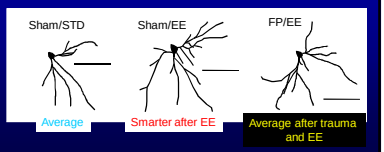


Cortical thickness and dendritic arborization *increase* in response to EE, but these benefits are NOT seen after developmental TBI.

Fineman, Giza, et.al., J Neurotrauma, 2000

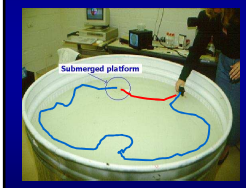


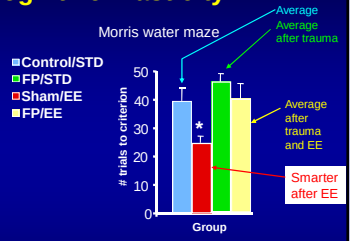
Dendritic reconstruction



Ip, Giza, et.al., J Neurotrauma, 2002

Developmental TBI & EE: Loss of Cognitive Plasticity



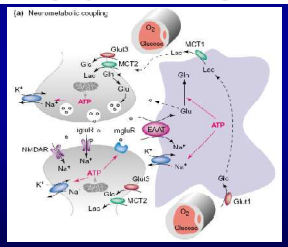


Morris water maze performance *improves* after enrichment, but does NOT improve with enrichment after developmental TBI.

Giza, Griesbach and Hovda, Behav Brain Res 2005

Glutamate and fMRI

Does glutamate image your thoughts?

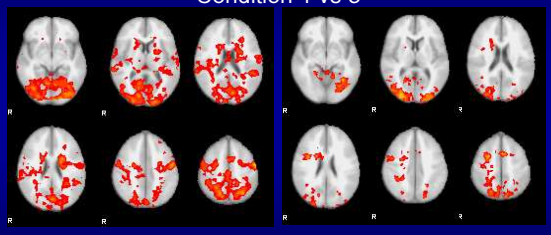


Glutamate neurotransmission may drive the (BOLD) signal seen on fMRI

Bonvento,G. et.al., TINS, 2002

Post-TBI Impaired Activation: Functional MRI

Condition 1 vs 3

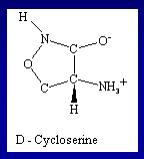


Controls TBI

During a spatial working memory task, children post-acutely following moderate-severe TBI show much less network activation

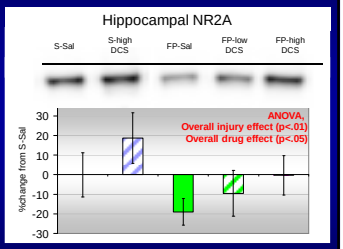
Cazalis F, et al., Soc for Neurosci, abst, 2007; also in Anderson & Yeates, eds, Ped TBI 2010

D-Cycloserine (DCS) Treatment Reverses TBI Dysfunction



D-cycloserine

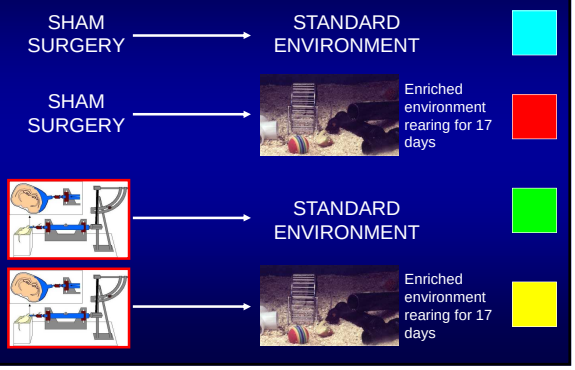
- NMDAR co-agonist
- Binds at glycine site
- FDA approved agent (for TB)
- Good bioavailability
- Penetrates BBB



Treatment with DCS restores normal NR2A levels in rats

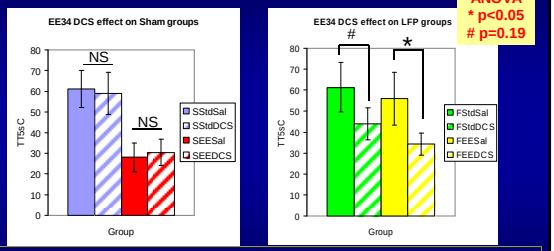
Santa Maria N.S., et al, J Neurotrauma abst 2007

Experimental Design:



D-Cycloserine (DCS) Treatment Restores post-TBI Plasticity

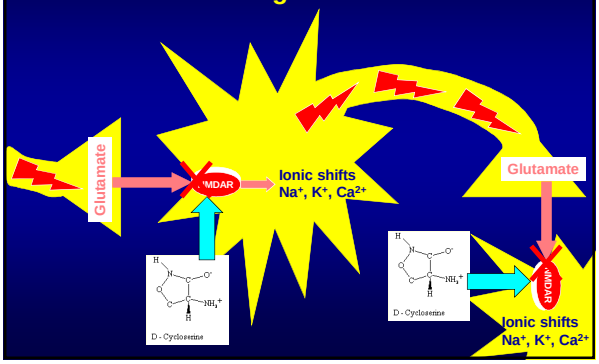
One-way ANOVA
* p<0.05
# p=0.19



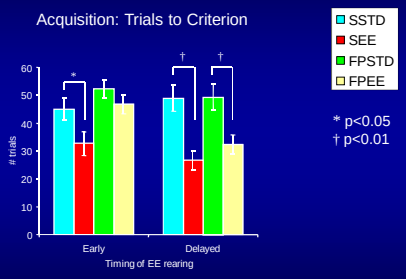
Treatment with DCS has no effect in sham rats, but given after developmental TBI, DCS improves spatial memory in adulthood preferentially in EE reared animals

Santa Maria N.S., et al., J Neurotrauma abst 2008

Post-TBI Plasticity Response: Pharmacological Restoration?



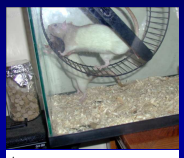
Developmental TBI + EE: Partial Recovery of Plasticity

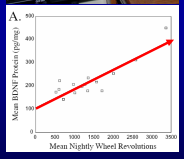


Spatial learning task acquisition in FPEE recovers if EE is delayed after injury

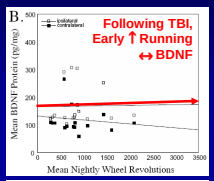
Giza, Griesbach, Hovda, Behav Brain Res 2005

Early exercise is not always better…

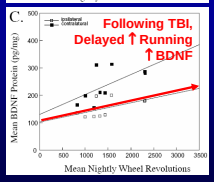




In Normals, ↑Running, ↑BDNF



Also… Worse cognition



Better cognition

Griesbach, et. al. Neurosci 2004

PAPER

Outcomes following childhood head injury: a population study

C A Hawley, A B Ward, A R Magnay, J Long

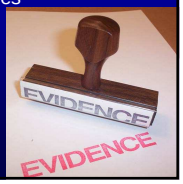
J Neurol Neurosurg Psychiatry 2004;75:737–742. doi: 10.1136/jnnp.2003.020651

Results: Frequent behavioural, emotional, memory, and attention problems were reported by one third of the severe group, one quarter of the moderate, and 10–18% of the mild. Personality change since HI was reported for 148 children (28%; 21% mild HI, 46% moderate, 69% severe). There was a significant relationship between injury severity and KOSCHI outcomes. Following the HI, 252 (48%) had moderate disability (43% mild HI, 64% moderate, 69% severe), while 270 (51%) made a good recovery (57% mild HI, 36% moderate, 22% severe). There was a significant association between social deprivation and poor outcome ($p = 0.002$). Only 30% (158) of children received hospital follow up after the HI. All children with severe disability received appropriate follow up, but 64% of children with moderate disability received none. No evidence was found to suggest a threshold of injury severity below which the risk of late sequelae could be safely discounted.

This is one of many studies that connects environment with outcome after pediatric TBI. It is critical to document and quantify relevant differences in environment, as they may influence outcomes.

What's Important

I. Principles of Plasticity and Development
II. Nature vs Nurture
III. Mechanisms of Experience-Dependent Neuroplasticity
   A. Normal Development
   B. Environmental Effects
   C. Pharmacological Effects
   D. Recovery from Acquired Brain Injuries
IV. Building the Evidence Base
V. Summing Up



Evidence-Based Rehabilitation

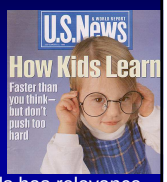
Important variables to consider:
- Age-at-injury
- Type of injury
- Timing of rehab
- Intensity/duration of treatment
- Goal of therapy

Choosing appropriate interventions may be guided by an awareness of potential underlying mechanisms for recovery.

Building rigorous evidence requires:
1. A comparison group (controls)
2. A consistently applied protocol for intervention (treatment)
3. A quantifiable goal of therapy (outcome measure)
4. An adequate number of subjects (statistical power)

Summing Up

1. Experience-dependent plasticity is the process thru which changes in environment alter brain structure and function.
2. These changes can occur due to normal development/aging, medications and/or neurocognitive training.



3. Studying changes in environment in animals has relevance for understanding plasticity in humans.
4. By targeting specific biological mechanisms of experience-dependent plasticity more effective rehabilitative interventions can be developed.
5. Timing of interventions is often critically important.
6. Building a rigorous evidence-base of therapeutic efficacy is essential for widespread application of rehabilitative interventions.