You Are What You Experience: Effects of Environment on Neuroplasticity and Recovery from Brain Injury

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ISNA Symposium
Birmingham, AL
October 2, 2010

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.

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

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

[Graphs showing comparison between static (mature) and dynamic (developing) models of injury and function]

Neural repair/recovery vs experience-dependent plasticity…?

[Graphs showing comparison between static (mature) and dynamic (developing) models of injury, function, and intervention]

Normal Plasticity Response: Controlled Glutamate Release

[Diagram showing normal plasticity response with controlled glutamate release]
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Maternal care, hippocampal synaptogenesis and cognitive development in rats

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)

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 1984

Can environmentally acquired attributes be passed on?

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

Arai, et al., J Neurosci 2009

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Stages of Neural Development

Rat

Human

Maternal nurturing

Plasticity molecules (NR2A, BDNF)

Cognition (MWM)
NMDA Receptor: Structure & Function

NR1 subunit: Two NR1s per receptor complex.

NR2 subunits: “Regulatory portion”. Two NR2s per receptor complex:
- NR2A: expressed from day 1
- NR2B: increases with maturation

Synaptic cleft
Cell membrane
Cytosol

Ca++

NR2A
NR1
NR2B

NMDA Receptor Composition: Experience-dependent plasticity


Quinlan, et.al. Nature Neurosci 1999

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

White Matter Plasticity?

Do musicians have different brains?

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

Keller & Just, Neuron 2009

Training increased FA in WM regions associated with poor reading.

Stewart L, Clin Med 2008

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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

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

Environment increases dendrites
- increased branching of neurons
- more synapses
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 Angeles 90024-1769.

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

Dendritic segment order

Adjusted total dendritic length (µM)

1 2 3 4 5 6 7 8

Environment increases brain cells

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

Modulating neural activity

D-amphetamine selectively increased R prefrontal activation during a working memory task.
Post-Concussive Cellular Response:
Potassium (K+) and Glutamate Release

K+ ionic shifts Na+, K+, Ca²⁺
Glutamate

Post-TBI Plasticity Response:
Diminished Activation?

Glutamate
NMDAR

Developmental TBI: NMDA Receptors

PID1
Sham FPI
FPI
PID2
Sham
FPI
PID4
Sham
FPI
PID7
Sham

Post-injury day

1 2 3 4 5 6 7

% of Sham

ANOVA, Overall effect of injury, p<0.05

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

Developmental TBI & EE: Loss of Cognitive Plasticity

Morris water maze

Average after trauma and EE
Smarter after EE

Lack of Anatomical Enhancement

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

Experimental Design:

SHAM SURGERY → STANDARD ENVIRONMENT

Sham/STD
FP/STD
FP/EE

Enriched environment rearing for 17 days

FP/EE

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

Giza, Santa Marie & Hovda, J Neurotrauma 2006

Developmental TBI: NMDA Receptors

Giza, Santa Marie & Hovda, J Neurotrauma 2005

Giza, Griesbach and Hovda, Behav Brain Res 2005

Fineman, Giza, et al., J Neurotrauma 2000

Giza, Giza et al., J Neurotrauma 2002

Surgery

STD

Enriched environment rearing for 17 days

EE

Control

Sham

FP

STD

EE

Fineman, Giza, et al., J Neurotrauma 2000

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

**Glutamate and fMRI**

**Does glutamate image your thoughts?**

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

Bonvento, G. et al., TINS, 2002

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**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 & Yudits, eds, Ped TBI 2010

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**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

Treatement with DCS restores normal NR2A levels in rats

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

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**Experimental Design:**

SHAM SURGERY  STANDARD ENVIRONMENT

SHAM SURGERY  STANDARD ENVIRONMENT

Enriched environment rearing for 17 days

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**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

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**Post-TBI Plasticity Response:**

Pharmacological Restoration?

Ionic shifts Na⁺, K⁺, Ca²⁺

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**D-Cycloserine (DCS) Treatment**

Restores post-TBI Plasticity

EE34 DCS effect on Sham groups

EE34 DCS effect on LFP groups

Glutamate

Ionic shifts Na⁺, K⁺, Ca²⁺

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

Acquisition: Trials to Criterion

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

Giza, Griesbach, Hovda, Behav Brain Res 2005

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Early exercise is not always better...

In Normals, ↑ Running, ↑ BDNF

Griesbach, et. al, Neurosci 2004

Early exercise is not always better...

In TBI, ↑ Running, ↓ BDNF

Griesbach, et. al, Neurosci 2004

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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 through 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.

Outcomes following childhood head injury: a population study

C A Nowkey, A S Ward, A R Magnay, J Long

Results: (seizures, unconsciousness, disability), sensory, and cognitive problems were reported by one-third of the severe group, one-seventh of the moderate, and 10-15% of the mild. Personality change in some (7% severe, 4% moderate, 1% mild) was found. There was a significant relationship between injury severity and BDI scores. Following the TBI, 20% (6%) had moderate disability (4.4% mild, 6.8% moderate, 6.8% severe), while 25% (1%) had a good recovery (5.7% mild, 9.4% moderate, 7% severe). There is no significant correlation between social depression and post-concussive outcomes (p>0.05). Only 30% (15%) of children received hospital follow up after the TBI. All children will develop well if appropriate follow up, but 60% of children with moderate disability will remain mentally and socially disabled. This evidence has been used to suggest a threshold of injury severity below which the risk of late sequelae could be studied.

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.

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