Objectives

- To present recent animal research specific to visual recovery in adults from amblyopia induced in the "critical period".
  - Pharmacotherapy
  - Environmental manipulation / enrichment
- To present recent human research on Perceptual Learning (vision)
  - Normal vision
  - Amblyopic adults

WARNING

- Do NOT attempt any of these experimental drug regimens on your patients.
Vision: It’s a brain thing

Development of brain circuitry involves a complex interaction between genetics and visual experience.

- Genetics: define the gross cerebral architecture and wiring
  - Significant prenatal development in primates allows vision to be present at birth
- Visual experience: fine-tune synaptic connections
  - Sensory experience has dramatic influence on subtle wiring

Amblyopia

Visual impairment caused by EARLY abnormal visual experience due to the presence of an “amblyogenic factor”

- Anisometropia
- Strabismus
- Form deprivation

“Critical Periods”

Restricted “time windows” in early post-natal life when brain circuits show high sensitivity to manipulation by external environmental signals.
Prevailing consensus:
Amblyopia reversal is only possible before closure of the “critical period” – i.e., early in life.

Success rate of traditional patching therapy has been shown to depend on:
• Degree of vision impairment
• Type of amblyopia
• Occlusion dose
• Patient compliance
• Age of onset
• Etc.

Amblyopia – animal models
The major pathological changes that occur in amblyopia occur at the cortical level.

Recent studies are providing evidence that interventions that boost the brain’s “neural plasticity” in adulthood may allow visual functions to be restored even after the end of the “critical period.”

What is “neural plasticity?”
The brain is CONTINUOUSLY shaped and re-shaped by what it receives from the outside world (adaptation).
• Sensory systems provide the input that shapes the brain.
**Different kinds of neural plasticity**

- Developmental plasticity (immature brain first begins to process sensory information)
- Activity-dependent plasticity (changes in sensory input due to, e.g., eyesight problems)
- Plasticity of learning and memory (e.g., discrimination training)
- Injury-induced plasticity (following brain damage)

**Recovery from long term visual deprivation: lessons from animal models**

Can we induce juvenile-like plasticity in the adult brain?

Promoting plasticity in the adult nervous system could open doors to innovative therapies for treating brain disorders for which suitable treatment in adulthood is not currently available.

**Creating amblyopia in an animal**

- Long term monocular deprivation starting during the “critical period” and protracted until adulthood.
- Lenses (anisometropia)
- Prism (strabismus)
- Translucent occluder (form deprivation)
Hypothesis: Intracortical inhibitory transmission limits plasticity in the adult brain

Neurotransmitters:
- Excitatory: glutamate
- Inhibitory: GABA

Premise: intracortical inhibition determines the boundaries of the critical period.

Hypothesis:
- If the transmission of interneurons within the cortex that release GABA can be reduced in the adult, plasticity can be restored.

Keep in mind: An ocular dominance shift does NOT occur if monocular deprivation is initiated after critical period (i.e., in adulthood).

Hubel & Wiesel: Ocular dominance

- Monocular deprivation
  - Normally, briefly depriving one eye during development will result in visual field representation shifts. The animal will have a virtual mirror image of the visual field in the contralateral eye.
  - Normally, briefly depriving both eyes during development will result in visual field defects. The animal will lose vision.

**Experimental protocol**

- Adult rats were monocular deprived AND had contralateral visual cortices infused with a GABA inhibitor (experiment) or saline (control).
- Ocular dominance of individual cortical neurons was objectively assessed by quantifying the responsiveness of the neuron to visual stimulation of either eye.

**Show me the data!**

- Monocular deprivation + saline: No significant difference in OD distribution from normal.
- Monocular deprivation + GABA inhibitor caused a statistically significant shift in OD distribution towards non-deprived eye – IN ADULTS!!!

**GABA inhibition: DRAWBACKS**

- Some are PRO-CONVULSIVE
- Some not FDA-approved
- Therefore, limited clinical utility
Can GABA inhibition be achieved indirectly? YES!

- Brainstem neuromodulates intercortical neurons (GABA) via noradrenaline, serotonin and acetylcholine (Bacci, et al, 2005)
- Increasing local availability of noradrenaline accelerated recovery from monocular deprivation (Kasamatsu, 1982).
- Chronic administration of fluoxetine reinstated ocular dominance plasticity and promoted recovery of visual functions in adult amblyopic rats (Vetencourt, et al, 2008.)

(data on next slide)

Rats were raised with monocular lid suture to create amblyopia in one eye. This experiment was initiated after the rats had reached adulthood (i.e. CP over)

- Visual acuity of formerly deprived eye (amblyopic) was less for control rats than for rats on fluoxetine.
- Measured VA in formerly deprived eye after fluoxetine was not significantly different from control ("complete recovery")

Binocularity recovery

- The C/I VEP ratio was significantly higher in visual cortex of fluoxetine-treated adult rats than controls AND was in the range of adult rats with normal vision.
Epigenetic Therapy

- Genes are controlled by other factors (environmental) in addition to the DNA sequence.
- Epigenetic changes can switch genes on or off and determine which proteins are transcribed.
- Epigenetics is involved in many NORMAL cellular processes.
  - Ex. The cells in a given person’s body all have the same DNA, but that person has many different types of cells. Cells, tissues, and organs differ because some genes are “turned on” (expressed) while others are “turned off” (inhibited) during development.

Within cells, there are three systems that can interact with each other to silence genes: DNA methylation, histone modifications, and RNA-associated silencing

DNA Methylation

Adding the methyl group changes the structure of the DNA, which affects how a given gene interacts with other transcription entities in the cell nucleus.
Histone modifications

- Histones are the primary PROTEIN components of chromatin (DNA and protein mix that makes chromosomes).
- Modification of histones can change the arrangement of chromatin, which can determine whether the associated DNA is transcribed.

RNA-associated gene silencing

Remember basic protein synthesis?

Non-coding RNAs – 13 of them!
RNA-associated gene silencing

DNA imprinting  DNA methylation  Chromatin modification

- paramutation
- ncRNA
- X chromosome inactivation
- Defects
- Complex diseases

Non-coding RNAs – 13 of them!
Silingardi, et al. (2010). Epigenetic treatments of adult rats promote recovery from visual acuity deficits induced by long term monocular deprivation.

“We found that chronic intraperitoneal administration of valproic acid or sodium butyrate (two different histone deacetylase inhibitors) to long term monocularly deprived adult rats coupled with reverse lid suturing caused a complete recovery of visual acuity, tested electrophysiologically and behaviorally.”

Extracellular Matrix in the nervous system

• Chondroitin sulfate proteoglycans act as barriers to cell migration and axon growth.

• During postnatal development CSPGs accumulate particularly around inhibitory interneurons, thereby contributing to restriction of plasticity in the adult brain.

Could “digestion” of these CSPGs restore neural plasticity?


• Differences in species in amount of plasticity in adult (rat has more than cat).

• Differences in degree of amblyopia produced by monocular deprivation.

• Digestion of chondroitin sulfate proteoglycans may prove effective if released slowly or if in combination with other treatments/therapies (ex. other drugs, VT)
Environmental Manipulation

Dark exposure followed by binocular vision or reverse occlusion allowed recovery of spatial vision after chronic monocular deprivation.


Environmental Enrichment

Combine multi-sensory / cognitive stimulation, increased physical activity, and enhanced social interactions.

Environmental enrichment promotes amblyopia recovery and reduces intracortical inhibition in adult rats.

Human Adult Amblyopes

Impact of Active Visual Stimulation

- Improved visual attention drives cortical plasticity
- "Perceptual Learning":
  - Any change in perceptual ability as a result of practice
  - Can be observed in all sensory modalities
  - Vision: practice with sensory enrichment procedures has demonstrated improved performance in a variety of tasks, including grating acuity and stereoacuity.
  - Demonstrated in people with normal vision (think “sports vision training”) and those with amblyopia.
15 yrs of documented improvement with PL on visual functions in ADULT amblyopes

- Age of subjects > 7 years at start of therapy
- No correlation between population age and functional outcome of treatment has ever been reported
- The age of the subjects enrolled in the various tested experimental procedures is not the main factor accounting for the variance across studies.


- Task: texture discrimination
- Duration of blank stimulus that gives 80% correct rate for identifying orientation determined.
- As learning occurred, the duration of blank stimulus to achieve 80% correct rate became shorter.

- Training session every 2-3 days
  - 6 training sessions in experiment 1; 14 sessions in experiment 2
  - 1520 trials in blocks of 40.
- fMRI recorded pre-training and 3 different times post-training.
  - Since training stimulus is in upper left VF, fMRI should show changes in lower right V1 cortex.
  - Measured fMRI while stimulus shown in either upper left (trained area) or lower right (untrained area) VF.
“V1 index” is a normalized dimensionless measure that compares the response in the “trained” area of V1 (lower right) to the response in the “untrained” area of V1 (upper left).

- A value of “0” means no difference in response between the 2 areas.

“Performance index” is a normalized, dimensionless measure that compares the threshold duration of the blank interval when presented in trained vs. untrained area of VF

As perceptual learning develops, initially both activation of V1 and behavioral performance increase.
Later, the activity increase in V1 disappears, but the behavior improvement is maintained.

**PL: Are achievable improvements limited to the trained stimulus, condition, or task?**

Such a narrowed specificity for the trained task has NOT been shown to be true in perceptual learning involving amblyopic subjects! (YAY!)

- Published studies involving practicing vernier acuity, position discrimination, contrast detection, and letter identification have all been shown improvements in Snellen acuity. (i.e., a global transfer effect occurred.)
- Believed to occur due to ACTIVE visual system stimulation

**If we have to pick ONE thing to train in an amblyope, what is likely to give us “the most bang for our bucks”?**

**CONTRAST SENSITIVITY**
Untreated amblyopic eyes "previously amblyopic eyes (now 20/20)"

Contrast sensitivity in amblyopia: The fellow eye of untreated and successfully treated amblyopes.

Chatzistefanou KI, et al. JAAPOS, Volume 9, Issue 5 2005 468 - 474

Full time or part time occlusion therapy can restore 20/20 acuity (the CSF cutoff frequency), yet the ability to detect contrast remains reduced across the entire function – vision is not normal!

Fortunately, training in amblyopes does not require practice with detection of all spatial frequencies.

Training at ONE spatial frequency (near cut off for the individual) transferred to improved performance for a broad range of SF's.


Video game play induces plasticity in the visual system of adults with amblyopia

Lots of different SFs and contrast levels!

http://www.virtual-reality-game.com/

Subjects ages ranged from 15-61 years.
All forms of amblyopia, except that related to ocular pathology

PL: Key Considerations
- Initial changes are temporary
- Practice makes changes permanent
- Repeated exposure even to small events can induce change
- The most substantial changes occur when the brain is engaged (attention)
- Motivation increases the efficiency of inducing change
Optimal Training!

- Training must be active, not passive
- Training must begin just within reach of existing skills
- Training must then be incrementally and proportionally increased as skill level increases
- Training should be interesting & varied!

*motivation & attention are key factors*

References


