Neuroplasticity and its Relation to Sensory Impairment

10:30-12

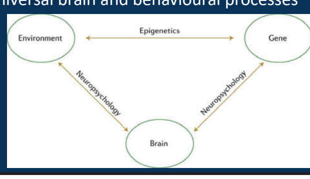
Corinna Bauer

MASSACHUSETTS EYE AND EAR | SCHEPENS EYE RESEARCH INSTITUTE

HARVARD MEDICAL SCHOOL | DEPARTMENT OF Ophthalmology

Interaction between genetics, environment, and the brain -- neuroplasticity

- environment–gene socioevolutionary processes (epigenetic)
- environment–brain moment-by-moment neurocognition (neuropsychology)
- gene–brain universal brain and behavioural processes



Boivin et al., nature, 2015

What is neuroplasticity?

"The capacity of neurons and neural circuits in the brain to change, structurally and functionally, in response to experience"

"Plasticity is the capacity of a system to respond to normal or aberrant developmental or lesion-induced changes in the internal or external environments by adopting new, stable, developmentally appropriate phenotypes and/or restoring old phenotypes"

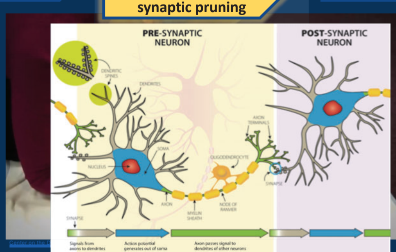
Dennis et al., 2013; Cioni, 2018

"The capacity of neurons and neural circuits in the brain to change, structurally and functionally, in response to experience"

- Experience: patterns of electrical activity within neural circuits
  - Drives functional and structural brain change
- Brain changes are modulated by the spatially and temporally coordinated actions of specific cellular and molecular factors - synaptic process
- Neuroplasticity: behavioural adaptations, learning, memory, brain development/maturation, brain repair
  - Neutral with respect to outcome: can be adaptive or maladaptive
  - In conjunction with homeostatic mechanisms regulating change across the lifespan
- Certain functional areas have different sensitive periods, during which time neuroplasticity occurs more readily
- Several factors play a role in determining brain development
  - Environmental, epigenetic, intervention, etc.

Dennis et al., 2013; Cioni, 2018

EXPERIENCE → SYNAPTIC CHANGES neurogenesis, synaptogenesis, synaptic pruning → BRAIN REORGANIZATION

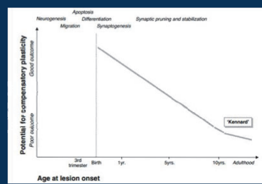


https://www.youtube.com/watch?v=VNNsN9IJkws

Factors influencing the extent of neuroplasticity

- Age
- Type and intensity of stimuli
- Brain region
- Direction of changes (e.g. synaptogenesis or pruning)
- Presence of brain injury

Kennard Principle:
Young Age Plasticity Privilege

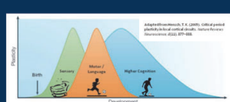


- The younger the age at insult, the better the outcome
- Brain lesions to motor areas in young monkeys resulted in sparing and recovery of function, whereas older animals did not show these patterns
- But, is this always true?
  - May be system dependent
    - Vision impairments following large occipital lesions regardless of age in her monkey experiments
  - Many of her monkeys showed delayed lesion effects – e.g. increased spasticity, less discrete finger movements when feeding, abnormal limb positioning during walking
  - The mechanisms for propelling developmental change also make the immature brain susceptible to adverse events

---

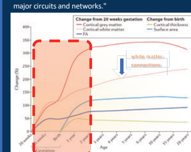
Sensitive periods: developmental period during which plasticity is heightened. It continues to a lesser degree throughout adolescence and adulthood. *"the time window(s) during which the effect of experience on brain development is unusually profound and can strongly modulate the neural circuits."*

At the end of sensitive periods, neuroplasticity levels decrease – tendency towards stabilization and maintenance of mature structural connections



"Windows of opportunity are also windows of potential vulnerability"
T. Hensch

"The basic structural and functional framework of the brain is in place by the second year of life. Brain development after age 2 years is mainly reorganization, 'fine tuning', plasticity, and remodeling of established major circuits and networks."

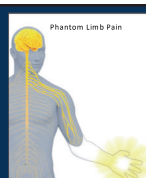


Gilmore, Knickmeyer, Gao Nat Rev Neuro 2018

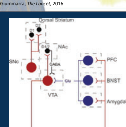
Vulnerability: *The brain's capacity for plasticity may be reduced in early brain injury, with developmental processes being altered, neuronal loss, and change in the developmental 'blueprint' that guides recovery…*

What neuroplasticity is not…

- Not always beneficial: It can be maladaptive
    - E.g. Musician's focal dystonia and writer's cramp (both due to reorganization of digit representation), phantom limb pain, addiction (synaptic and network level)
  - Maladaptive outcomes depending on a number of factors:
    - Nature and extent of neuropathogenic process
    - Stage of neurodevelopment
    - Integrity of homeostatic regulatory mechanisms
- Not limited to the young – continues in adolescence and adulthood
- Unclear whether neuroplasticity and sensitive/critical periods are the same in individuals with potential injury to the plasticity machinery
    - e.g. abnormal dendritic spine formation and elimination, impaired synaptogenesis and pruning, etc.



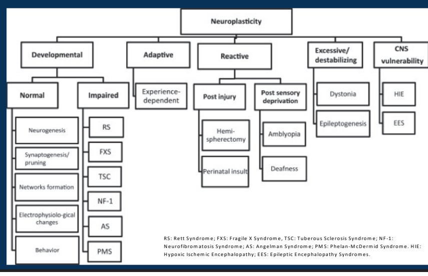
Giummarra, *The Lancet*, 2016



Mameli and Luscher, 2011

Dennis et al., 2013

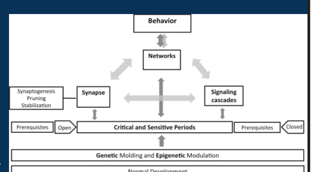
Patterns of Neuroplasticity in the Developing Brain



Ismail et al., 2017

Mechanisms that govern neuroplasticity

- Genes
- Epigenetic modulation
- Environment
- Occurs on multiple levels:
  - Molecular: CNS receptors – neural communication and networks
  - Neuronal: Anatomical-structural changes – synaptogenesis and synaptic pruning
  - Systemic: Functional – network development – influences by intrinsic mechanisms and extrinsic experiences



How Can We Modulate Plasticity?

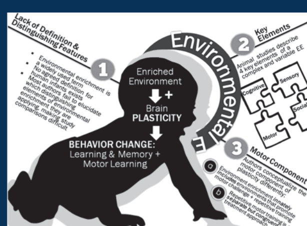
Categories of Neuromodulation Techniques

Behavioral Neuromodulation	Pharmacological Neuromodulation	Electrical Neuromodulation	Magnetic Field	Cell-based Neuromodulation
• Training-based physical therapy • CIMT • Cognitive • Neuro feedback	• CNS active medications • Nano-technology	• DBS • NIBS (rTMS/tDCS) • Spinal cord stimulation • VNS	• rTMS • Constant magnetic fields	• Stem cell transplant

- Behavioural
- Pharmacological – mixed evidence in humans
  - Side effects, dosage, long-term effects are unknown
- Electrical – DBS, rTMS, tDCS – preliminary evidence in motor function, depression, etc., but limited in vision
  - Side effects, dosage, long term effects are all unknown
- Magnetic field - rTMS
- Cell-based – stem-cell transplant – long term effects unknown – proceed with caution

Behavioural Modulation

- Evidence from enriched environments
- Habilitation programs
- Early intervention in neurodevelopmental disorders
- Activity should be variable, salient, fun, goal-directed, family centered, early as possible, and intense



PEDIATRICS Volume 132, Number 3, September 2013

Behavioural Modulation

- Mice reared in enriched environments demonstrate significant changes in brain structure:
  - Increased brain weight, neurogenesis, dendritic branching, synapse formation, etc.

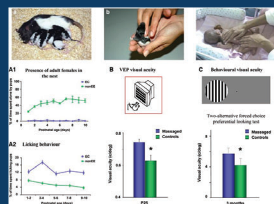
Effects of environmental enrichment in animal models of neurodevelopmental disabilities

Disorder	Behavioural effects	Cellular effects	Molecular effects
Down Syndrome[18]	Improved cognitive (spatial learning and memory) and visual function recovery	Restored long-term synaptic plasticity in a neural circuit	Reduced inhibitory transmission, bringing GABA release in the synaptosomes
Fragile X Syndrome[19]	Rescued behavioral abnormalities displayed by adult Fmr1-KO mice: hyperactivity, social and cognitive deficits	Increased dendritic spine plasticity (especially in the hippocampal and amygdala)	Not determined
Rett Syndrome[20]	Ameliorated motor coordination and motor learning	Enhanced synaptic plasticity and regulation of synapse formation and stability in the cerebral and cerebellar cortex	Increased BDNF expression
Epilepsy[21-23]	Increased resistance to seizures; attenuated deficit in exploratory activity; improved learning and spatial memory	Decreased apoptosis; increased neurogenesis	Increased GDNF, BDNF, pCREB, ARC, HOMER1A and ERG1

Cioni et al., DMCN 2016

Study on Impact of Environmental Enrichment

- Enrichment in the form of massage increased visual acuity in preterm rat pups and human infants compared to controls who did not receive the enrichment
- Unclear whether this was the massage itself or increased skin-to-skin contact and attention
- Evidence on long-term effects is inconclusive beyond 3 years



Baroncelli et al., 2010

Enriched environments following preterm birth: NIDCAP example

- Newborn Individualized Care and Assessment Program
- Aims to provide environment with minimal stress and adapts to infant's needs
- Early trials showed improved brain function and structure in low-risk preterm infants
- Subsequent studies have not reproduced these findings
- Meta-analyses do not show significant gains from NIDCAP in either short or long-term studies.
- But, it does not appear to do harm
- Music therapy and massage/sensory enrichment have shown positive outcomes in small samples of preterm infants, but need to be replicated in larger independent samples

Environmental Enrichment Considerations

- While EE may benefit some children with developmental conditions, the efficacy has not been adequately evaluated. A number of factors still need to be determined
  - Operational definitions and standardized treatments across studies
  - Use of control groups and better control over confounding variables
  - Comprehensive framework for predicting how and when environmental enrichment will alter the trajectory of neurodevelopmental conditions

Ball et al., 2019

Electrical and Magnetic Neuromodulation

- Non-invasive brain stimulation techniques may be able to modulate regional cortical excitability and therefore alter neuroplasticity
  - rTMS – repetitive Transcranial Magnetic Stimulation
  - tDCS – Transcranial Direct Current Stimulation
- TMS – intracranial electrical currents are induced in the cortex by an external magnetic field
  - Used in many conditions, particularly for behavior
    - ASD, ADHD, schizophrenia
    - Studies in pediatric stroke or cerebral palsy population may use in conjunction with CIMT
- tDCS – constance electrical currents are conducted to the cortex via scal electrodes
  - More accessible than TMS
  - Often used in conjunction with CIMT

Cell-based Neuromodulation

- An emerging paradigm using stem cells, umbilical cord blood, epithelial cells, etc. as a potential therapy to promote neurological repair in infants and adults
- Anti-inflammatory mechanisms – reduce downstream effects of brain injury
- Promote cell survival and repair
- Regenerative mechanisms to repair or replace damaged tissue
- Very few published clinical trials and no systematic reviews
- Mixed outcomes, particularly in the long-term

Precautions with Neuromodulation

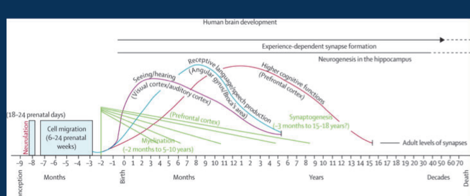
- Limited studies on appropriate dosages in the pediatric population
- Unclear what the long-term risks or benefits are
  - Neuroplastic reorganization can be maladaptive or beneficial
- Few translational models in younger population
- Some are more invasive than others and may be associated with more adverse effects
  - E.g. stem cell transplants, deep brain stimulation vs. environmental enrichment, tDCS, behavioral therapy

Neuroplasticity Examples

Typical Development, Developmental Conditions, and the Motor, Sensory, Auditory, and Visual Systems

Neuroplasticity During Typical Development

- Outline the development of OR and other major WM pathways in vision
- Brain development is the result of a complex interaction between genes, social interactions, physical environment and epigenetic mechanisms (e.g. gene transcription and expression) that lead to changes in neuronal structure (e.g. dendritic spine density, pruning, axonal sprouting, etc.)
- Requires both neurogenesis and pruning
  - Under-pruning is associated with many neurodevelopmental disorders, including autism, fragile X syndrome, Rett syndrome
  - Over-pruning and loss of (or failed maintenance of) dendritic spines is associated with other conditions, such as schizophrenia (more is not always better)
  - This balance may be disrupted following brain lesions in infants, children, or adults



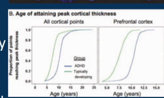
While the young brain is uniquely flexible,
it is also uniquely susceptible.

The Lancet 2007 369, 60-70DOI: (10.1016/S0140-6736(07)60032-4)

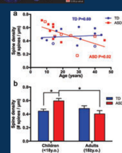
Deviations from Typical Trajectory: Evidence from Neurodevelopmental Disorders

- In child onset schizophrenia (COS), the typical increase in WM volume during adolescence is nearly completely absent, showing a loss of white matter expansion
- In children with ADHD, cortical maturation may be delayed, lagging by ~3 years, most noticeably in the prefrontal cortex
- Children with ASD demonstrate deviations from typical developmental changes in cortical thickness and dendritic spine density, with increased slope of cortical thinning and spine loss

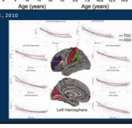
Gogtay et al., 2008



Shaw et al., 2010



Weir et al., 2018

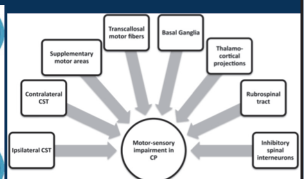


Zielinski et al., 2014

Neuroplasticity in Developmental Conditions: Using Appropriate Targets

Components of the EE intervention and hypothesized effects of increased BDNF levels and improved functional abilities in girls with Rett Syndrome

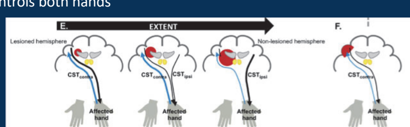
Downs et al., OJRD, 2018



Potential targets that contribute to motor-sensory impairment in patients with cerebral palsy. Highlights the need to adopt a multi-modal, multi-targeted approach to improve behavioral outcomes

Neuroplasticity of motor cortex

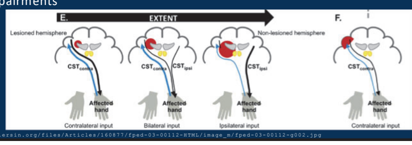
- In children with unilateral cerebral palsy, the motor system may reorganize in multiple ways
- Reorganization of the motor system from the non-lesioned side can occur, but at what cost?
  - More ipsilateral projections is generally associated with worse bimanual function due to "mirror movements" because the same corticospinal system controls both hands



https://www.frontiersin.org/files/Articles/160877/fped-03-00112-HTML/image_m/fped-03-00112-g002.jpg

Neuroplasticity of sensory system

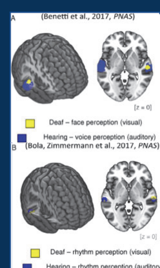
- The effect of preterm unilateral lesion differs for the sensory system
- Reorganization is mediated by structures on the lesioned side
- Ascending thalamocortical somatosensory projections may not have reached the cortex at the time of lesion, allowing the ingrowing axons to bypass around the lesion to reach the cortex
  - This reorganization is only available during the preterm window and unilateral lesions at or near term will impact these projects and cause somatosensory impairments



https://www.frontiersin.org/files/Articles/160877/fped-03-00112-HTML/image_m/fped-03-00112-g002.jpg

Neuroplasticity Following Sensory Loss: Hearing

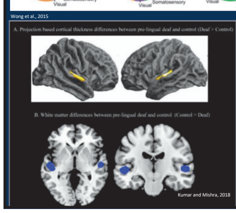
- Multiple studies outline neuroplastic reorganization of the auditory cortex to process visual and somatosensory information
  - Reorganized "voice" region participated in face identify
  - Rhythm and face perception in auditory cortex when presented visually
- Similar to auditory processing improvements in the case of blindness, visual processing may improve in the case of hearing impairment
  - detecting the onset or direction of motion of a peripheral visual stimulus
  - Faster at switching visual attention toward a near-periphery target in the presence of distractors
  - Larger visually evoked responses for in occipital areas
  - Unclear if increased visual functions related to deafness itself or to the acquisition of a visual language (e.g. sign)
- Potentially mediated through modulation of connections between posterior parietal cortex and earlier sensory areas



Neuroplasticity Following Sensory Loss: Hearing

Wong et al., 2015

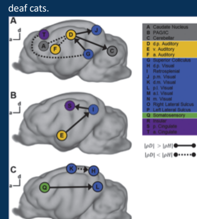
Projections to the anterior auditory field are mainly auditory in normally hearing cats, but in early deafness, the auditory projections are reduced, with increased visual, somatosensory, and multisensory inputs



Kumar and Mishra, 2018

Cortical thickness increases in individuals who are prelingual deaf and regional decreases in white matter volume compared to controls

Altered functional network connectivity in deaf cats.



Stolzberg et al., 2018

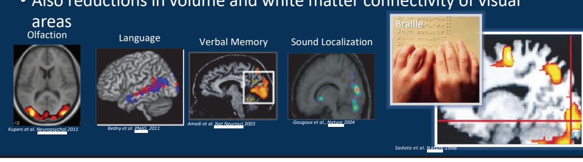
Neuroplasticity of language system

- Typically, language is left-lateralized in adults
- If the left hemisphere is injured during the perinatal period, the language system may relocate to the right homotopic area with minimal impact on function
- This reorganization is more likely in term infants than those with preterm lesions

Guzzetta et al., Neuropediatrics 2008

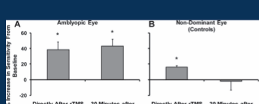
Neuroplasticity Following Sensory Loss: Vision

- Occipital cortex functionally recruited for many non-visual tasks
- Associated with increased performance on hearing and tactile tasks
  - May be related to reduced thresholds, rather than improved performance itself
- Also reductions in volume and white matter connectivity of visual areas

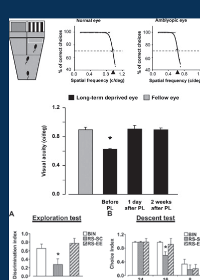


Neuroplasticity in Amblyopia

- Leads to loss in visual acuity, low contrast sensitivity, impaired stereopsis, and altered orientation tuning of cortical neurons.
  - Patching therapy during the critical period (~8 years of age) can help prevent the permanent changes in binocular vision and acuity
  - In a rat model of adult amblyopia, environmental enrichment has lead to full recovery of visual acuity, ocular dominance, and depth perception
    - Physical exercise, practicing visual discrimination tasks, and environmental enrichment
  - Non-invasive brain stimulation – temporarily improve amblyopic eye function



Thompson et al., 2010



Baroncelli et al.,2012, 2013

Neuroplasticity in CVI

What Current Evidence Suggests
Examples From Common Aetiologies
What We Still Don't Know

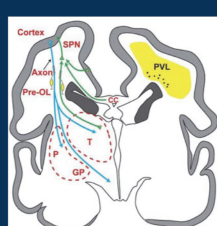
Neuroplasticity in CVI

- Uncertain to what extent reorganization occurs
- Limited research in animal models specific to CVI
  - Research in underlying etiologies of CVI focus on the mechanisms of injury and immediate consequences, rather than the functional and structural reorganization that occur as a result
- Currently is limited to correlation analyses, with few (if any) appropriate case-control studies

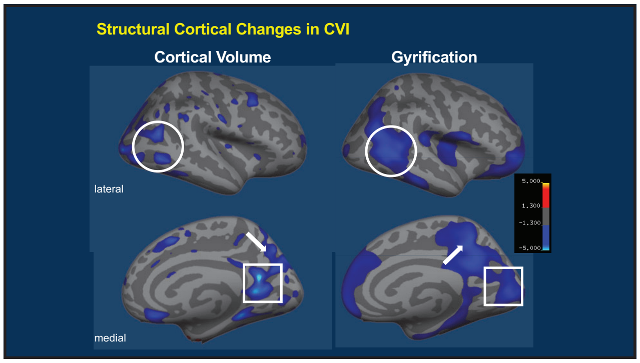
The case of PVL

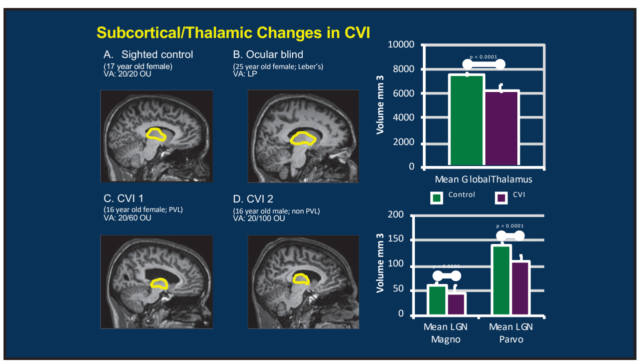
- Many developmental processes are occurring around the time of injury leading to PVL
- Can lead to widespread and varied consequences on brain development

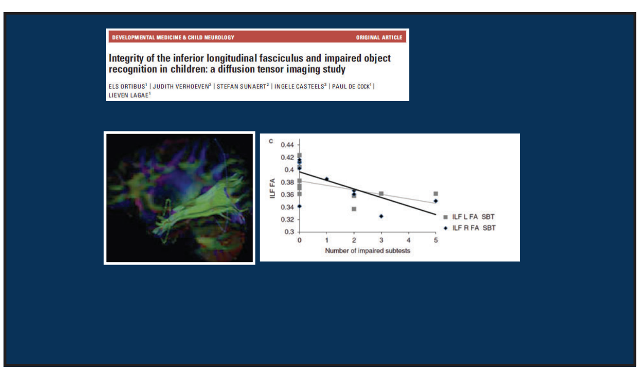
16 year old female; PVL
VA: 20/60 OU

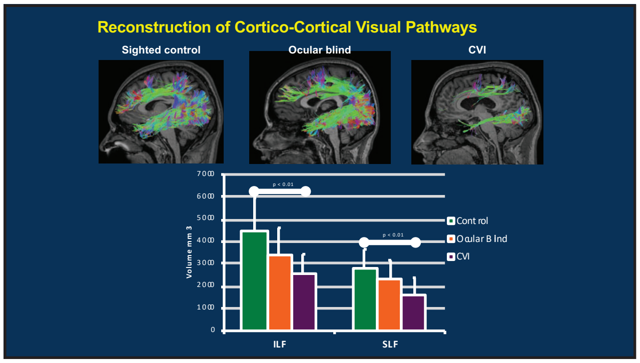


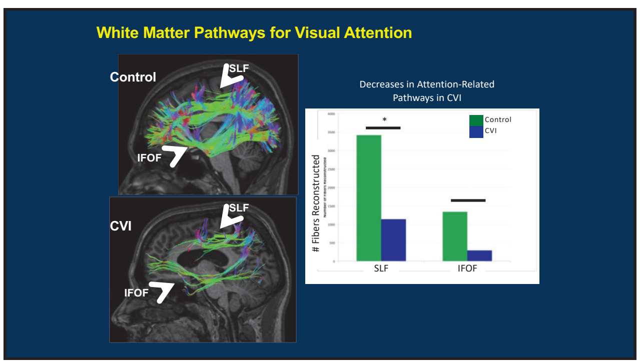
Volpe JJ. Lancet Neurol 2009;8:110-124.1)

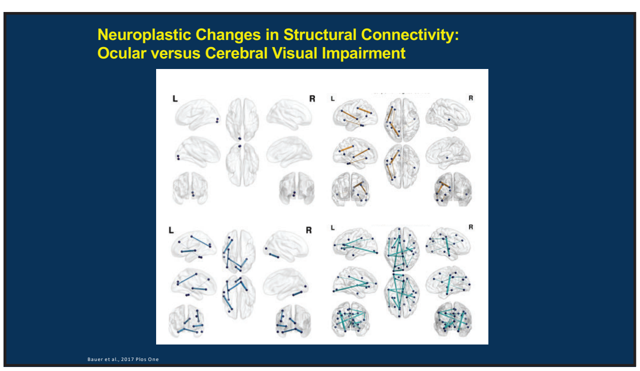

Structural Cortical Changes in CVI
Cortical Volume
Gyrification
lateral
medial


Subcortical/Thalamic Changes in CVI
A. Sighted control
(17 year old female)
VA: 20/20 OU
B. Ocular blind
(25 year old female; Leber's)
VA: LP
C. CVI 1
(16 year old female; PVL)
VA: 20/60 OU
D. CVI 2
(16 year old male; non PVL)
VA: 20/100 OU
Volume mm 3
p < 0.0001
Mean GlobalThalamus
Control
CVI
Volume mm 3
p < 0.0001
Mean LGN Magno
Mean LGN Parvo


DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY
ORIGINAL ARTICLE
Integrity of the inferior longitudinal fasciculus and impaired object recognition in children: a diffusion tensor imaging study
ELS ORTIBUS | JUDITH VERHOEVEN | STEFAN SUNAERT | INGELE CASTEELS | PAUL DE COCK | LIEVEN LAGAE
c
ILF FA
Number of impaired subtests
ILF L FA SBT
ILF R FA SBT


Reconstruction of Cortico-Cortical Visual Pathways
Sighted control
Ocular blind
CVI
Volume mm 3
7000
6000
5000
4000
3000
2000
1000
0
p < 0.01
p < 0.01
Control
Ocular Blind
CVI
ILF
SLF


White Matter Pathways for Visual Attention
Control
SLF
IFOF
CVI
SLF
IFOF
Decreases in Attention-Related
Pathways in CVI
Fibers Reconstructed
Control
CVI
*
SLF
IFOF


Neuroplastic Changes in Structural Connectivity:
Ocular versus Cerebral Visual Impairment
L
R
L
R
L
R
L
R
Bauer et al., 2017 Plos One

Predicting Outcomes

- Can be challenging to predict long-term outcomes at birth
- Study from the Groningen Perinatal Project following children at 1.5, 4, 6, 9, 12, and 14 years
- Sometimes impairments and abnormal neural development are only seen near birth
- On the other hand, some neurological conditions and impairments do not manifest until later in childhood/adolescence

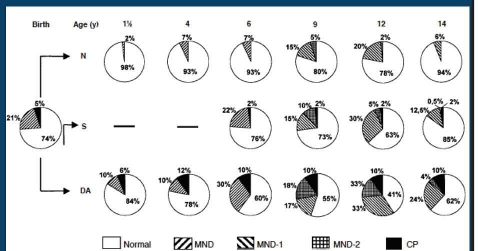


Figure 1: *Neonatal neurological condition and neurological findings at 1½, 4, 6, 9, 12, and 14 years of age (adapted from references [40, 75–80]; for number of children examined see Table I). Hatching in legends refers to neurological condition at follow-up. At birth, white denotes normal (N) neurological condition; hatching, mildly abnormal (MA) or suspect (S); and black, definitely abnormal (DA) neurological condition.*

Hadders-Algra – Groningen Perinatal Project outcomes, 2002

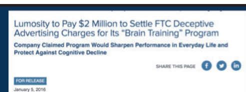
Dispelling Neuromyths

Learning from the Past to Improve the Future

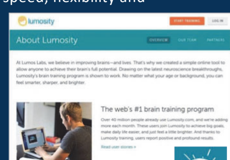
Plasticity in Popular Culture: The Neuromyth

- Neuroplasticity can change your brain!
- Rewiring your brain will change your life!
- Stories of (usually adult) brains rewiring following damage
- Follow this method and rewire your child's brain to improve function
- What does scientific evidence suggest?

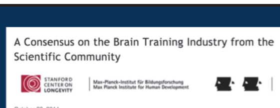
Example of Luminosity



- Subscription-based "brain training" program consisting of "science-based games designed to exercise memory, attention, speed, flexibility and problem-solving"
- Claims:
  - Delay memory decline
  - Protect against dementias
  - Develop sustained attention and focus
  - Improve school, work, and athletic performance
  - Regain cognitive abilities following stroke, chemotherapy, TBI, etc.
- Problem: No solid scientific support
  - Does improved performance on game translate to daily activities?
  - Signed statement from 70 scientists refuting claims



Lumosity

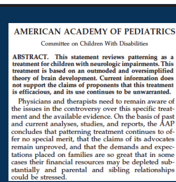


- *"We object to the claim that brain games offer consumers a scientifically grounded avenue to reduce or reverse cognitive decline when there is no compelling scientific evidence to date that they do. The promise of a magic bullet detracts from the best evidence to date, which is that cognitive health in old age reflects the long-term effects of healthy, engaged lifestyles. In the judgment of the signatories, exaggerated and misleading claims exploit the anxiety of older adults about impending cognitive decline. We encourage continued careful research and validation in this field."*

http://longevity3.stanford.edu/blog/2014/10/15/the-consensus-on-the-brain-training-industry-from-the-scientific-community/

Neuromyth or Neuroscience?

- Look for scientific studies with sound methodology, including:
  - Treatment *AND* control groups
  - Controlled interventions
  - Adequate statistical analysis
  - Evidence-based approaches
  - Clear and measurable outcomes
  - Repeatable outcomes across different populations with different researchers/clinicians
- More details in next session!

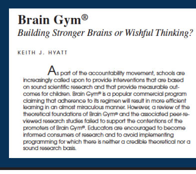


AMERICAN ACADEMY OF PEDIATRICS

Committee on Children With Disabilities

ABSTRACT. This statement reviews patterning as a treatment for children with neurologic impairments. This treatment is based on an outmoded and oversimplified theory of brain development. Current information does not support the claims of proponents that this treatment is efficacious, and its use continues to be unwarranted.

Physicians and therapists need to remain aware of the issues in the controversy over this specific treatment and the available evidence. On the basis of past and current analyses, studies, and reports, the AAP concludes that patterning treatment continues to offer no special merit, that the claims of its advocates remain unproved, and that the demands and expectations placed on families are so great that in some cases their financial resources may be depleted substantially and parental and sibling relationships could be stressed.



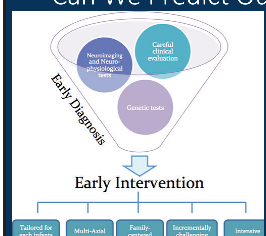
Brain Gym®

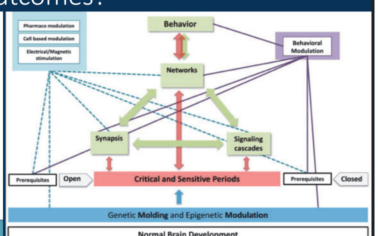
Building Stronger Brains or Wishful Thinking?

KEITH J. HYATT

As part of the accountability movement, schools are increasingly called upon to provide interventions that are based on sound scientific research and that provide measurable outcomes for children. Brain Gym® is a popular commercial program claiming that adherence to its regimen will result in more efficient learning in an almost miraculous manner. However, a review of the theoretical foundations of Brain Gym® and the associated peer-reviewed research studies failed to support the contentions of the promoters of Brain Gym®. Educators are encouraged to become informed consumers of research and to avoid implementing programming for which there is neither a credible theoretical nor a sound research basis.

Can We Predict Outcomes?

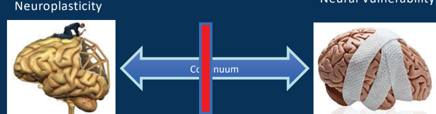




Cioni et al., DMCN 2016

Neuroplasticity

Neural Vulnerability



Individual recovery depends on multiple influences:

- Injury-related factors
  - Timing, severity, extent, type of injury, etc.
- Constitutional factors
  - Developmental stage, cognitive capacity, genetics, etc.
- Environment
  - Family support, socio-economic status, access to habilitation and intervention