Neuroplasticity and its Relation to Sensory Impairment

10:30-12

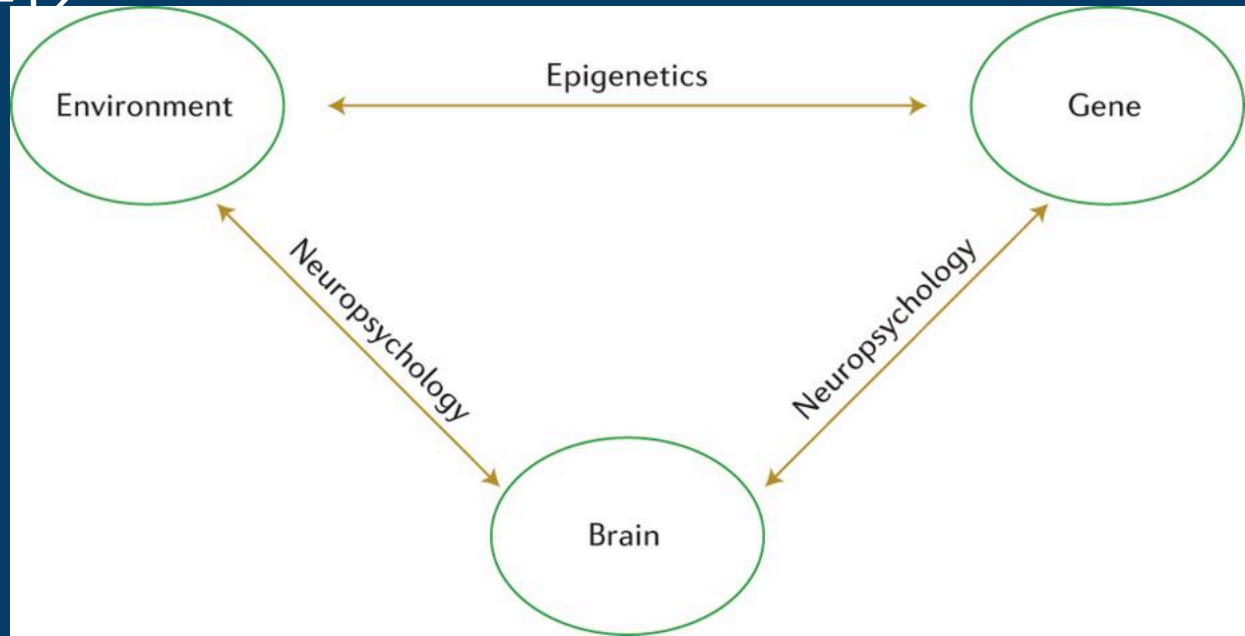


Figure 1: Mutually interactive domains — environment, gene and brain — interact in terms of environment–gene socioevolutionary processes (epigenetic), environment–brain moment-by-moment neurocognition (neuropsychology), and gene–brain universal brain and behavioural processes in child neurodevelopment.

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”

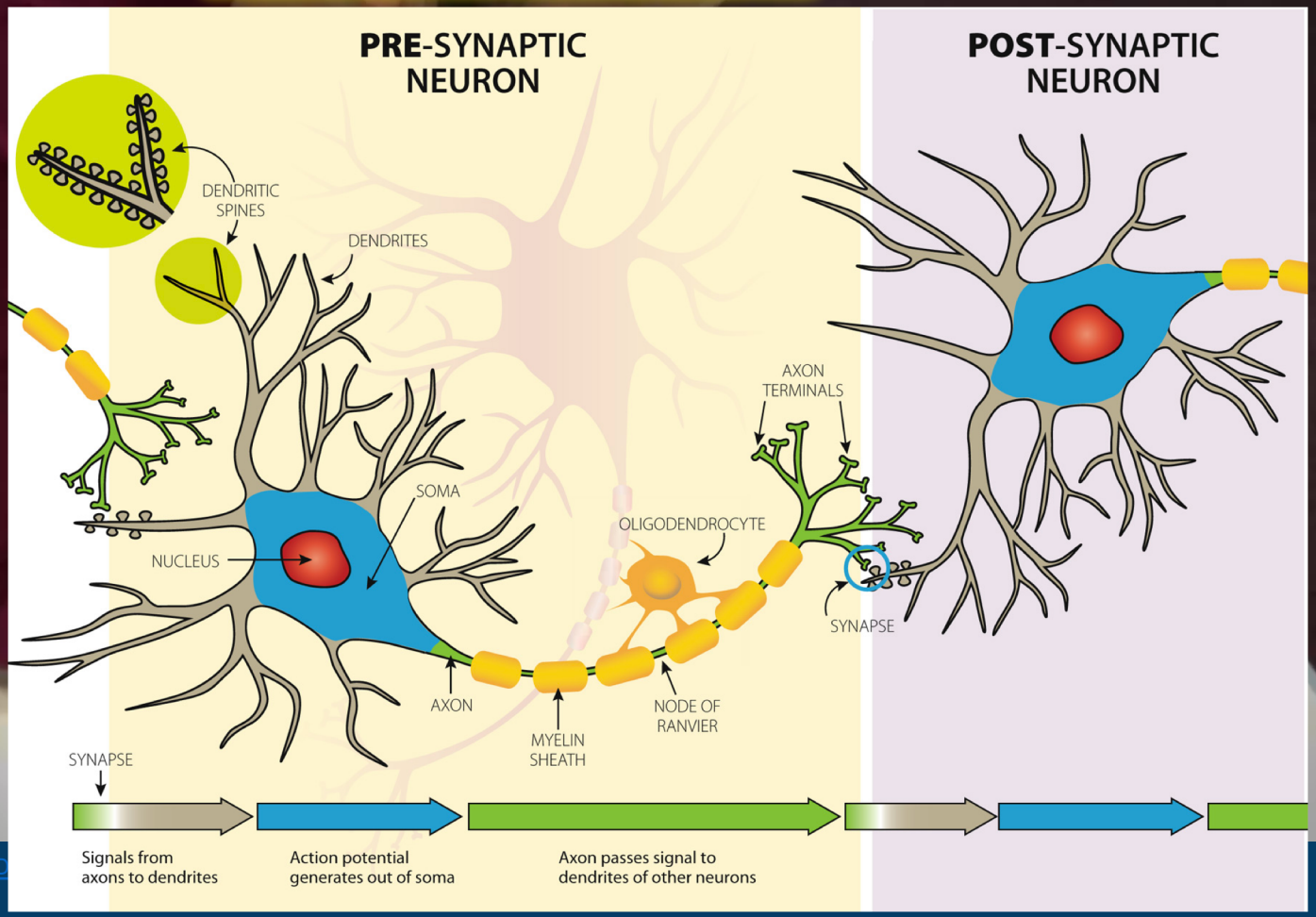
- Experience: patterns of electrical activity within neural circuits
  - Drives functional and structural brain change
- Brain changes are modulated by the spatially and temporally coordinated actions of specific cellular and molecular factors - synaptic process
- Neuroplasticity: behavioural adaptations, learning, memory, brain development/maturation, brain repair
- 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.

Cioni, 2018

EXPERIENCE

SYNAPTIC CHANGES
neurogenesis,
synaptogenesis,
synaptic pruning

BRAIN REORGANIZATION



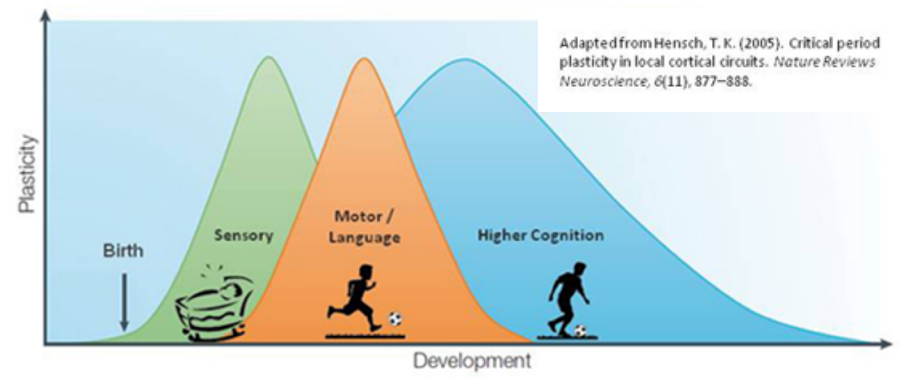
https://www.youtube.com/watch?v=VNNsN9IJkws

Factors influencing extent of neuroplasticity

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

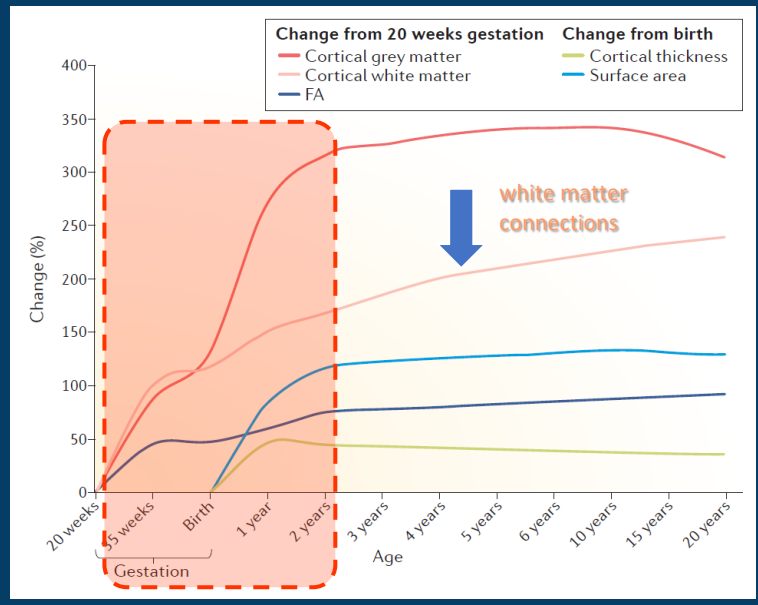
Sensitive periods: developmental period during which plasticity is heightened. It continues to a lesser degree throughout adolescence and adulthood. *"the time window(s) during which the effect of experience on brain development is unusually profound and can strongly modulate the neural circuits."*

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

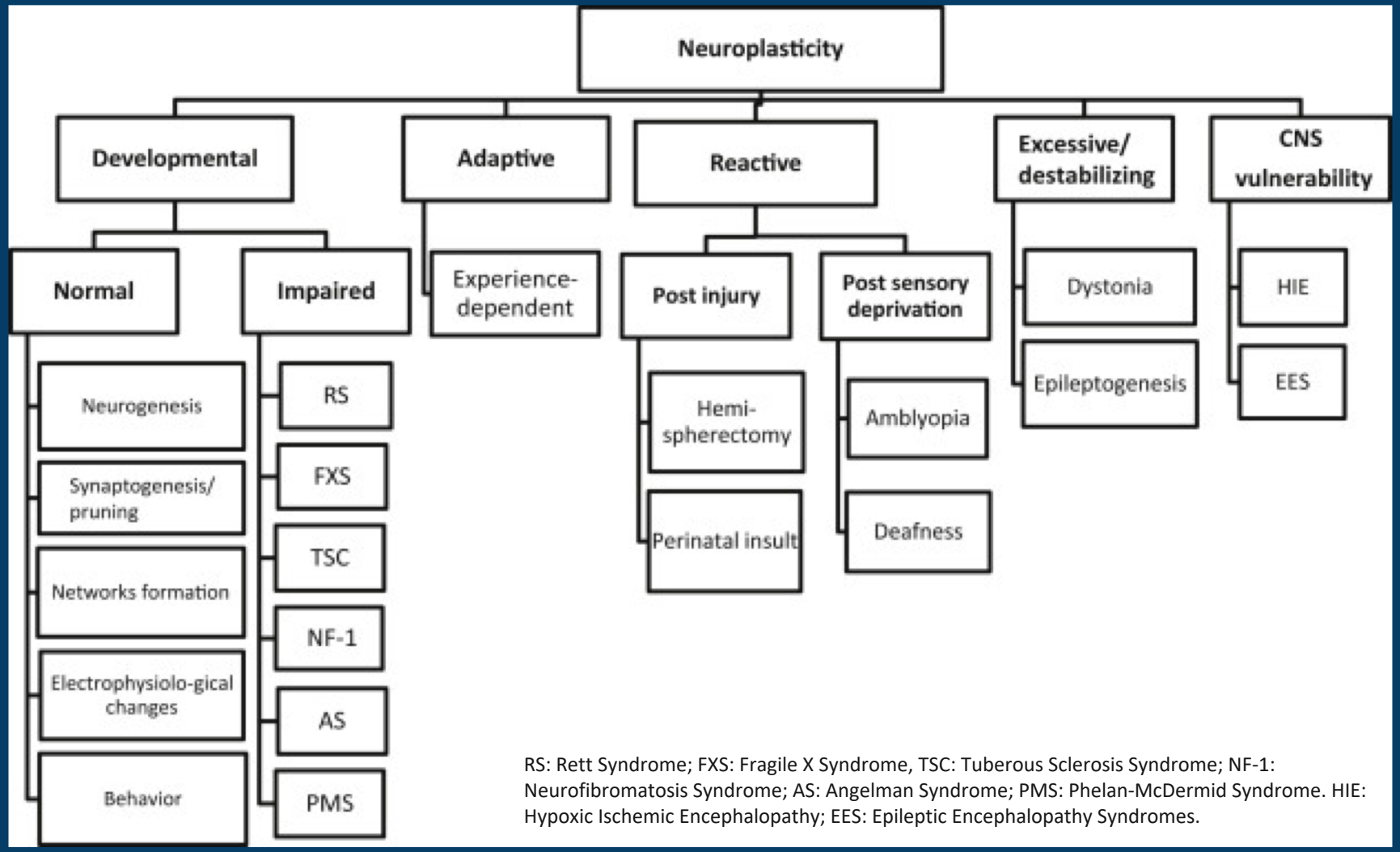
<u>Vulnerability</u>: *The brain's capacity for plasticity may be reduced in early brain injury, with developmental processes being altered, neuronal loss, and change in the developmental 'blueprint' that guides recovery…*

What neuroplasticity is not

- Neuroplasticity is not always beneficial, but can be maladaptive
  - Musician's focal dystonia, writer's cramp, phantom limb pain
  - 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.)

Dennis et al., 2013

Patterns of Neuroplasticity in the Developing Brain

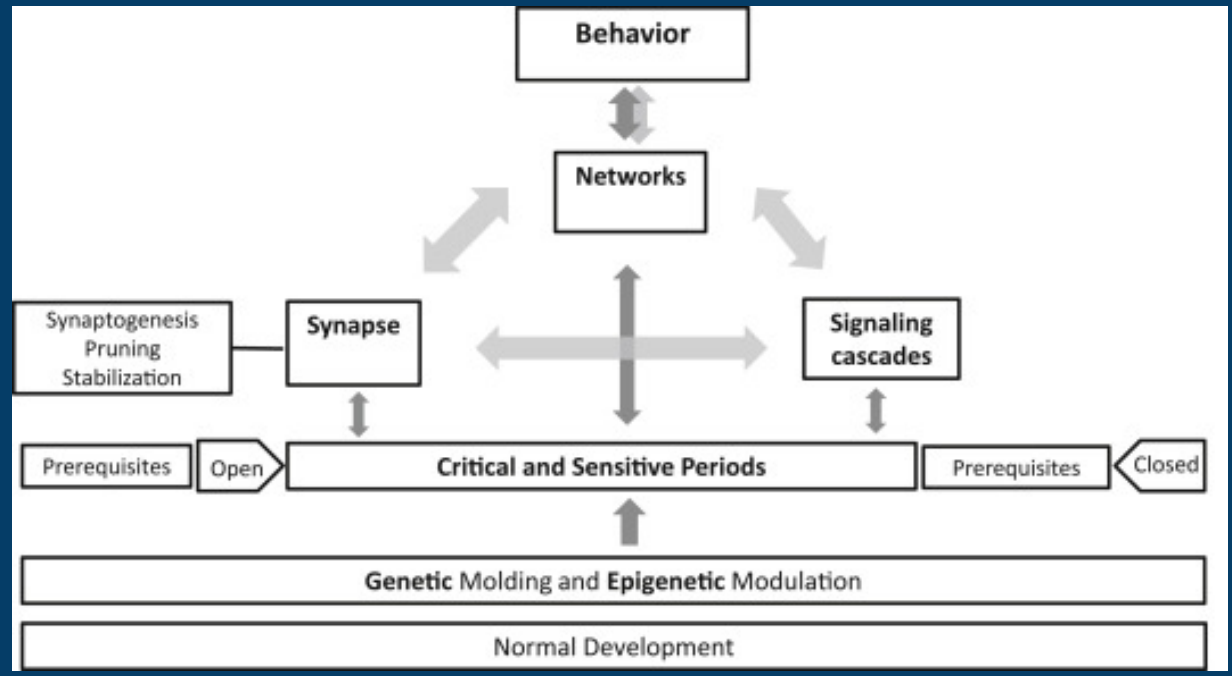


RS: Rett Syndrome; FXS: Fragile X Syndrome, TSC: Tuberous Sclerosis Syndrome; NF-1: Neurofibromatosis Syndrome; AS: Angelman Syndrome; PMS: Phelan-McDermid Syndrome. HIE: Hypoxic Ischemic Encephalopathy; EES: Epileptic Encephalopathy Syndromes.

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



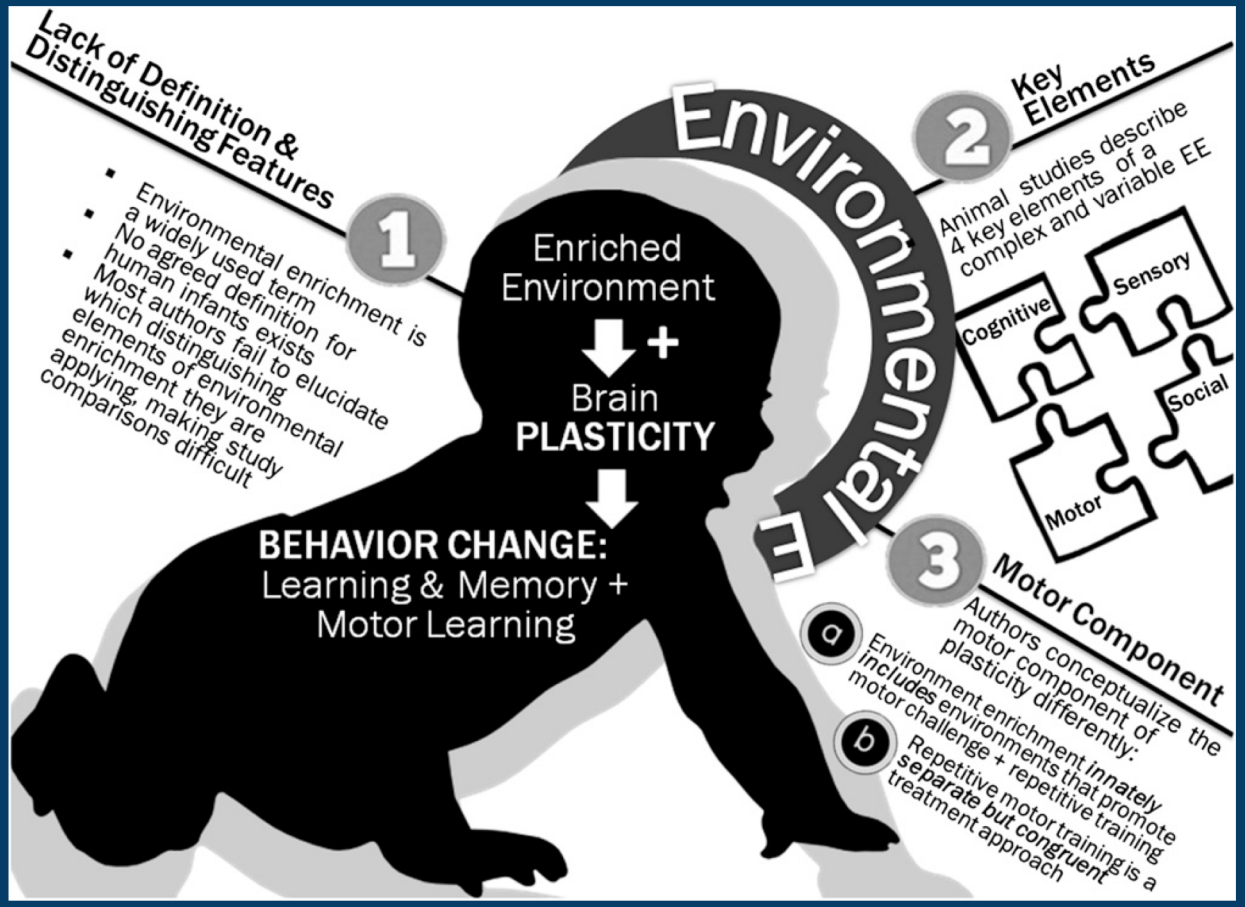
Categories of Neuromodulation Techniques

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.

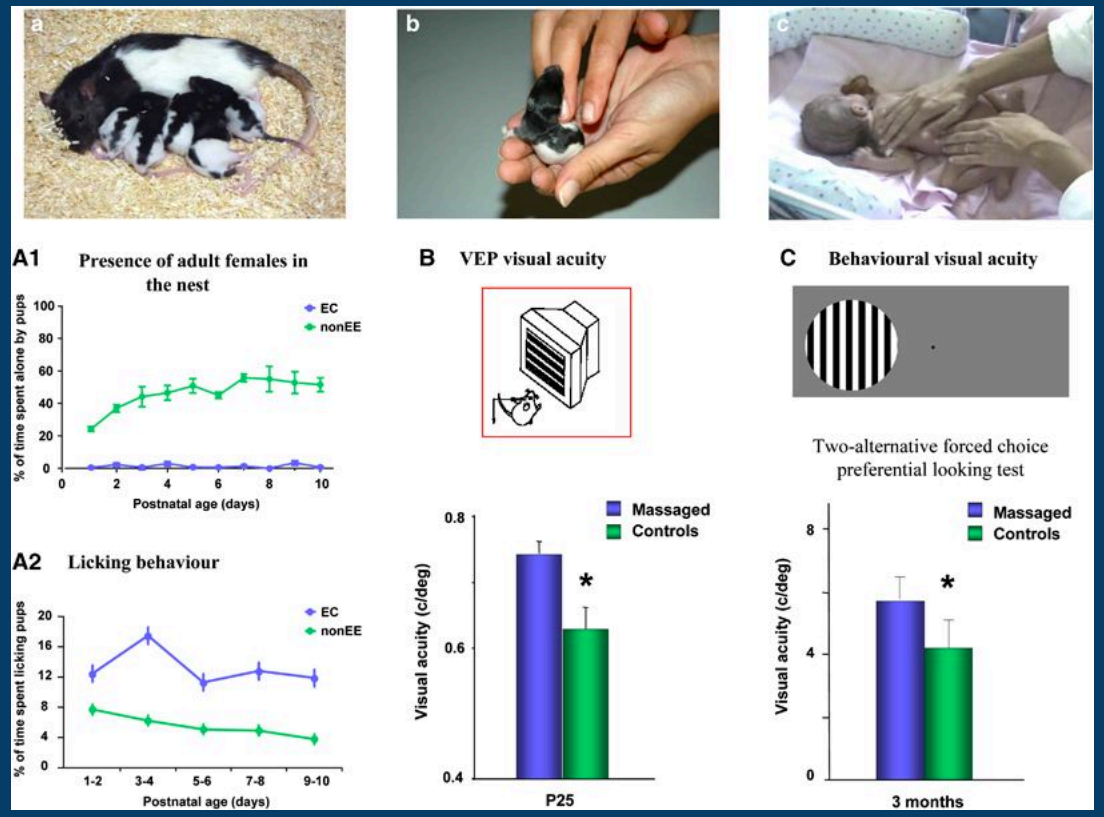
Effects of environmental enrichment in animal models of neurodevelopmental disabilities

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 attentio



Baroncelli et al., 2010

Enriched environments and motor outcomes in CP meta analysis

- Key components of EIP for preterm infants and their parents review and meta-analysis
- Early developmental intervention programmes provided post hospital discharge to present motor and cognitive impairment in PTI (Review)
- Goals activity motor enrichment – GAME protocol study

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

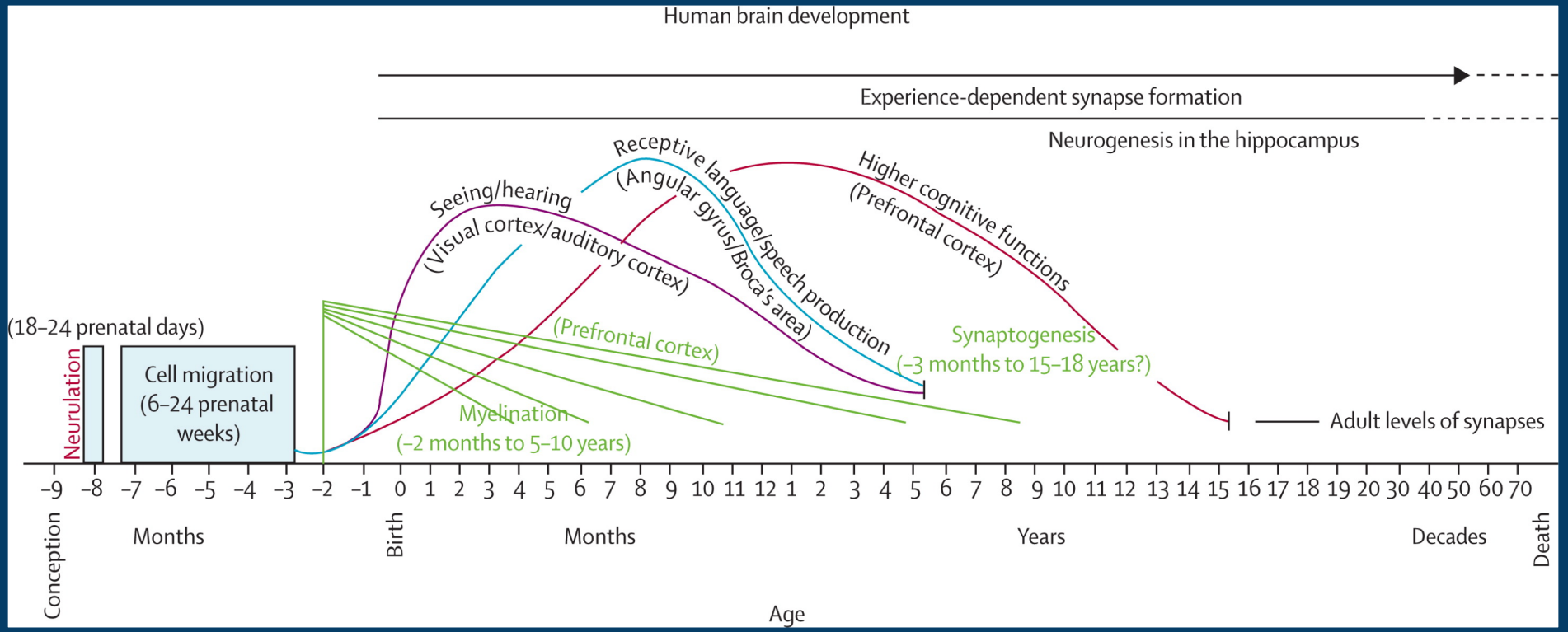
Ball et al., 2019

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

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)

Neuroplasticity in Developmental Conditions

- What we know
- What we don't know
- What the current challenges are
- Using appropriate targets

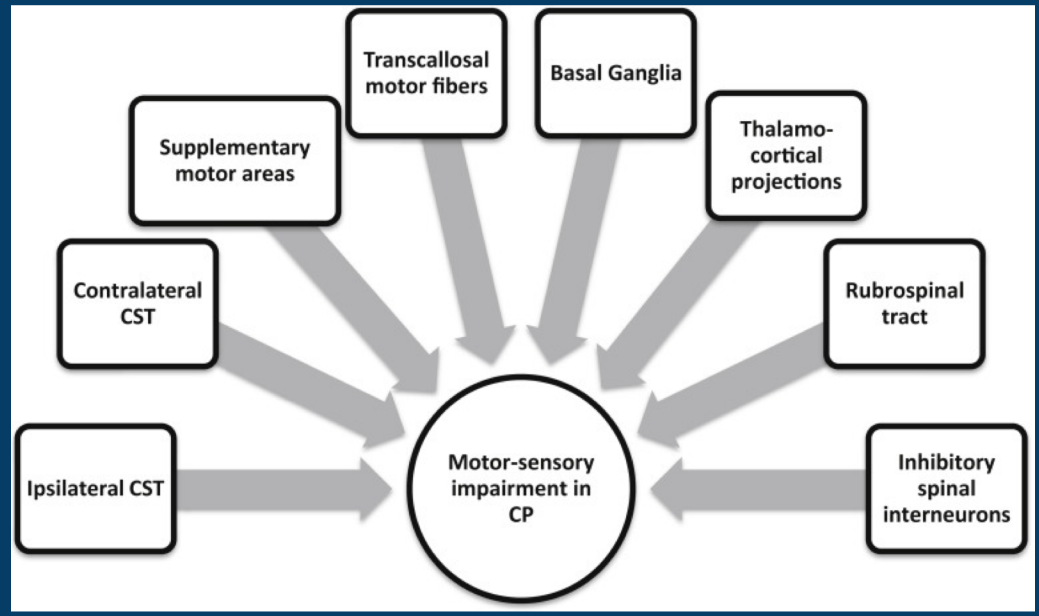


Fig. 3. Potential targets that have been shown to contribute t motor-sensory impairment in patients with cerebral palsy. W advances in understanding the inter-related and time-dependent nature of plasticity in cortical and subcortical networks during motor-sensory development, is it time to adopt a multi-modal (behavioral, pharmacological or stimulation-based), multi-targeted neuromodulatory approac

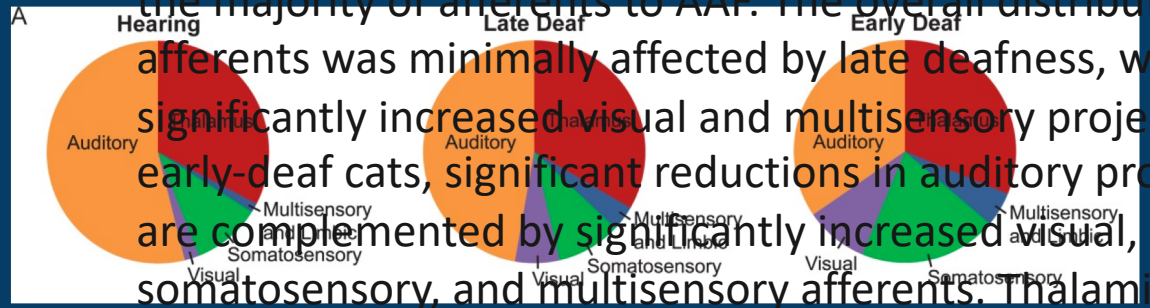
Neuroplasticity of motor cortex following stroke

- Reorganization can occur, but at what cost?

Neuroplasticity Following Sensory Loss: Hearing

- Deaf adults better at hearing controls at 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 Deaf than hearing in occipital areas
- Potentially mediated through modulation of connections between posterior parietal cortex and earlier sensory areas
- Unclear if increased visual functions related to deafness itself or to the acquisition of a visual language (e.g. sign)
- Reorganized “voice” region participated in face identify

Neuroplasticity Following Sensory Loss: Hearing



Alterations in ipsilateral visual and somatosensory cortical projection strength ± SE following early- and late-onset deafness. A,B: In hearing cats, auditory projections comprise the majority of afferents to AAF. The overall distribution of afferents was minimally affected by late deafness, with only significantly increased visual and multisensory projections. In early-deaf cats, significant reductions in auditory projections are complemented by significantly increased visual, somatosensory, and multisensory afferents. Thalamic input to AAF is similar across all three groups.

Wong et al., 2015

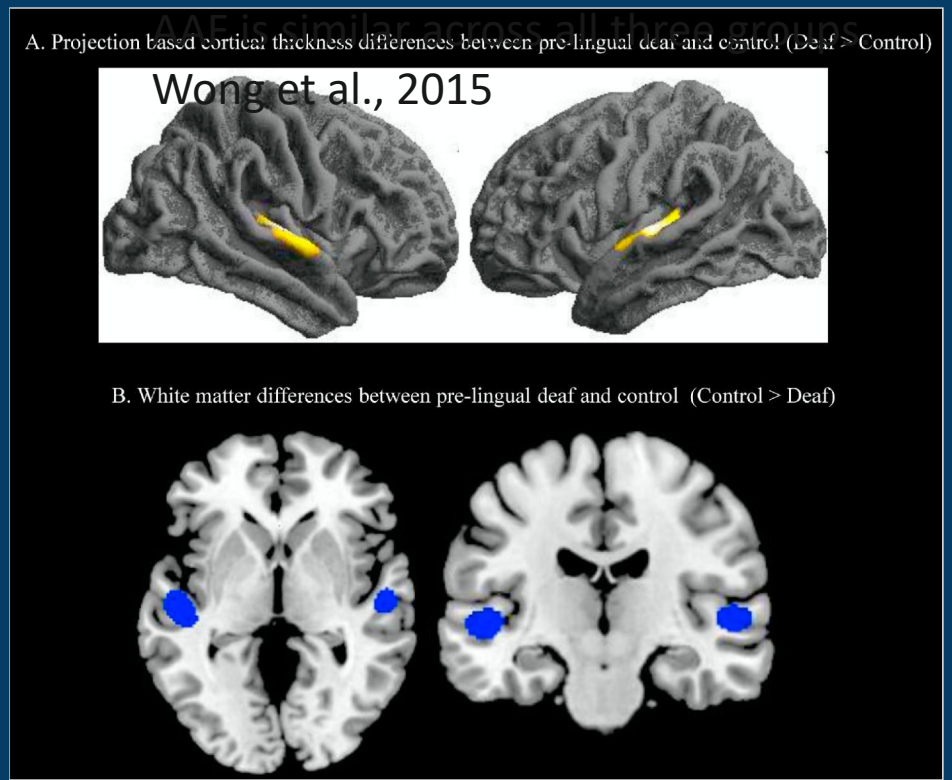


Fig. 2. (A) Represent projection based cortical thickness differences between pre-lingual deaf and control (Deaf > Control) and (B) Showing white matter difference between pre-lingual deaf and control based on VBM analysis (Control > Deaf).
Kumar and Mishra, 2018

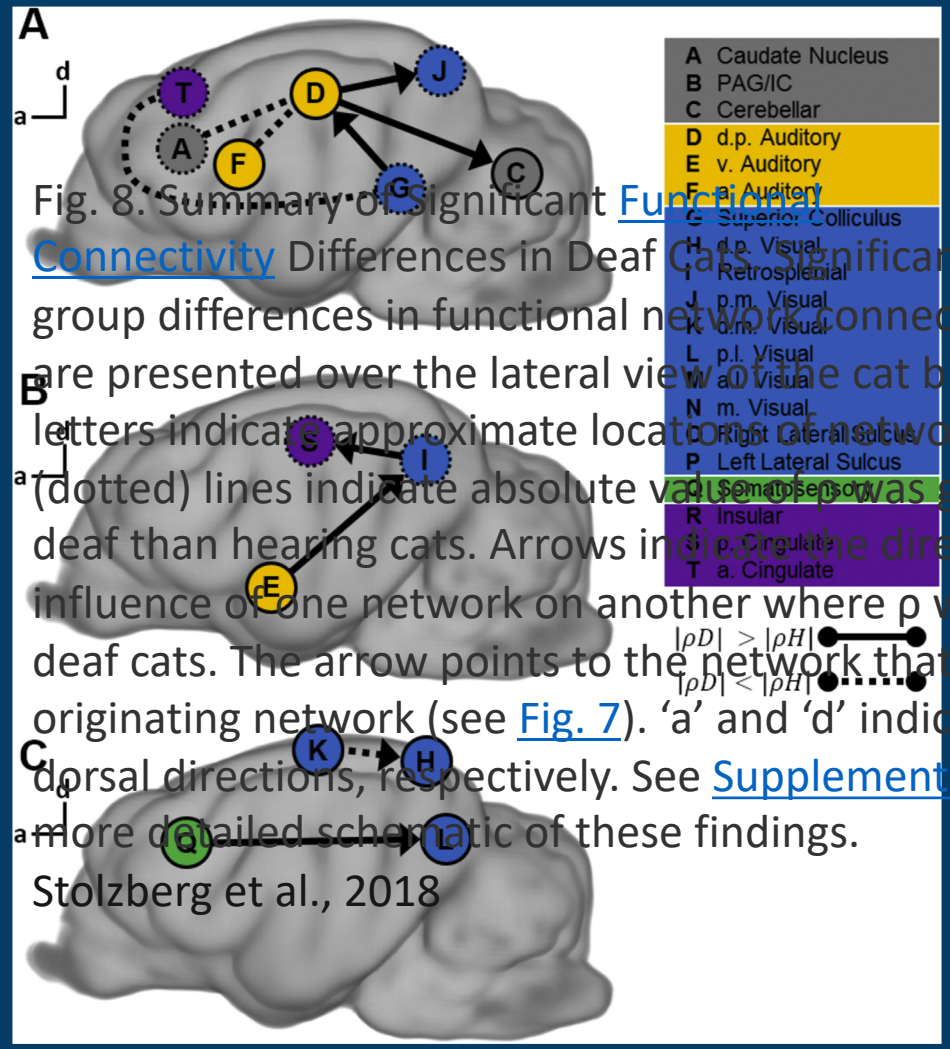
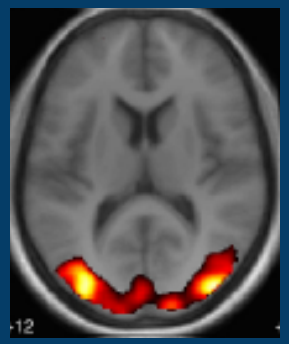


Fig. 8. Summary of significant Functional Connectivity Differences in Deaf Cats. Significant group differences in functional network connectivity are presented over the lateral view of the cat brain. Capital letters indicate approximate locations of network nodes. Solid (dotted) lines indicate absolute values of ρ was stronger in deaf than hearing cats. Arrows indicate the direction of influence of one network on another where ρ was stronger in deaf cats. The arrow points to the network that is the originating network (see Fig. 7). 'a' and 'd' indicate anterior and dorsal directions, respectively. See Supplement for more detailed schematic of these findings.
Stolzberg et al., 2018

Neuroplasticity Following Sensory Loss: Vision

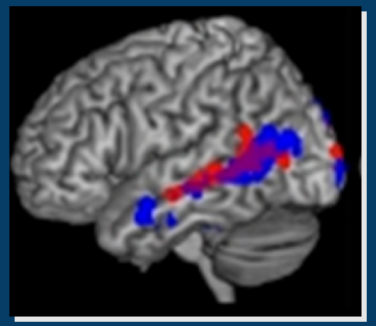
- Occipital cortex functionally recruited for many non-visual tasks
- Associated with increased performance on hearing and tactile tasks
  - May be related to reduced thresholds, rather than improved performance itself
- Also reductions in volume and white matter connectivity of visual areas

Olfaction



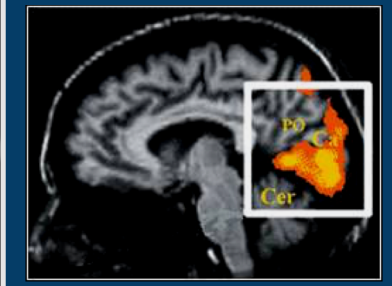
Kupers et al. Neuropsychol 2011

Language



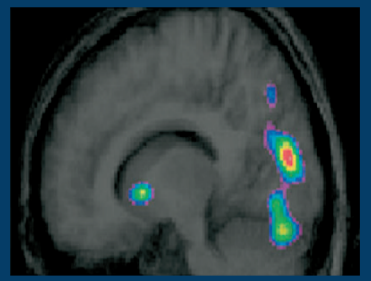
Bedny et al. PNAS 2011

Verbal Memory

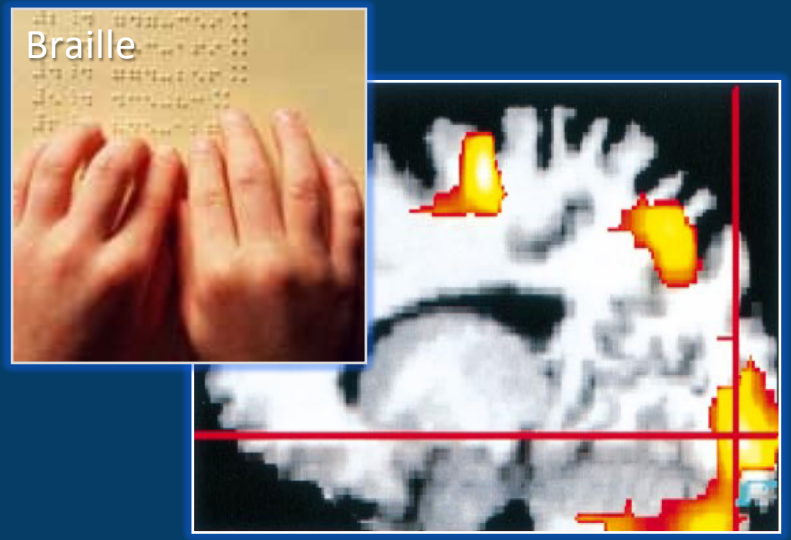


Amedi et al. Nat Neurosci 2003

Sound Localization



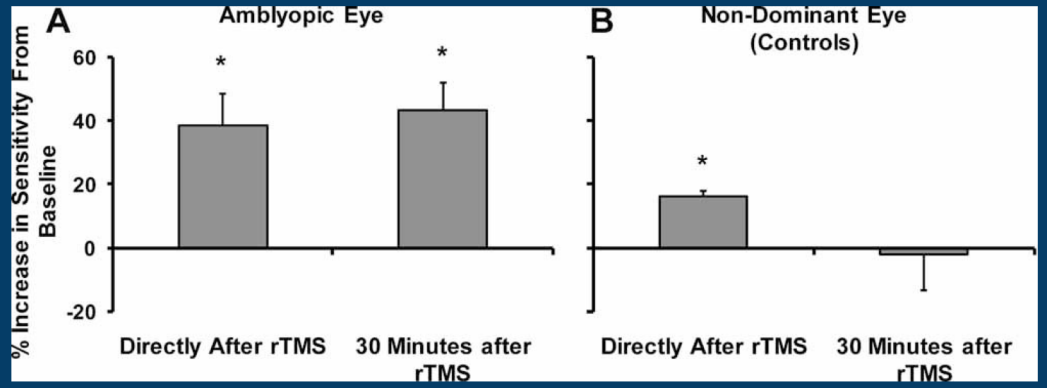
Gougoux et al., Nature 2004



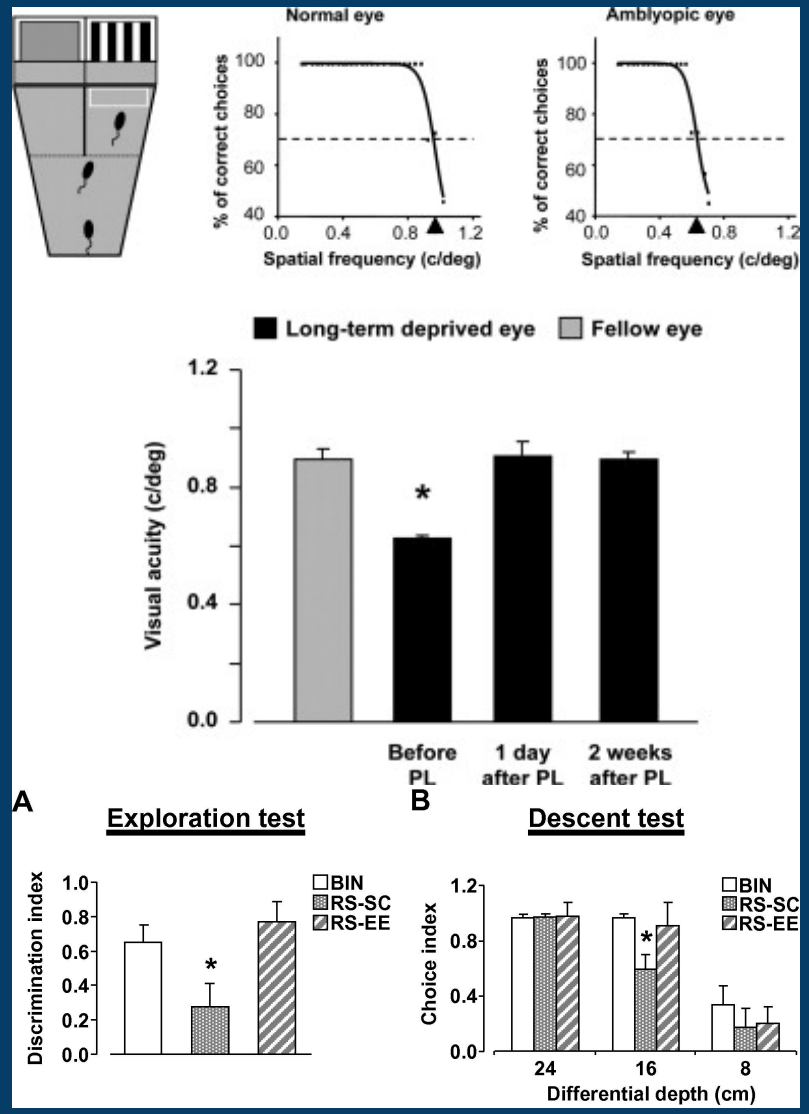
Sadato et al. Nature 1996

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

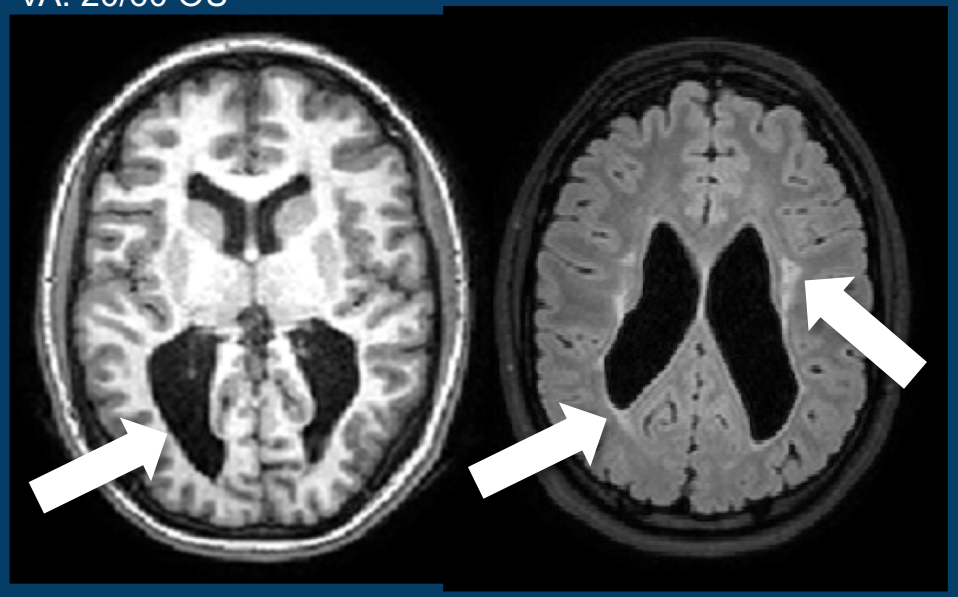
- Uncertain to what extent reorganization occurs
- Limited research in animal models specific to CVI
  - Research in underlying etiologies of CVI focus on the mechanisms of injury and immediate consequences, rather than the functional and structural reorganization that occur as a result
- Currently is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

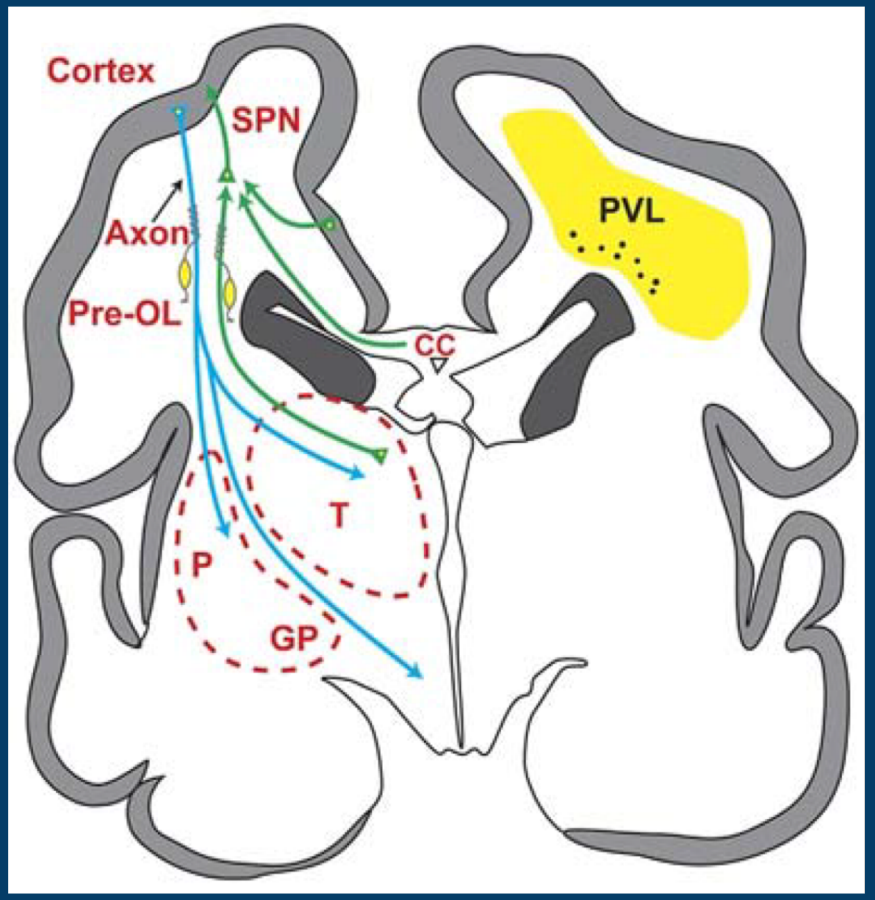
The case of PVL

C. CVI 1

(16 year old female; PVL)

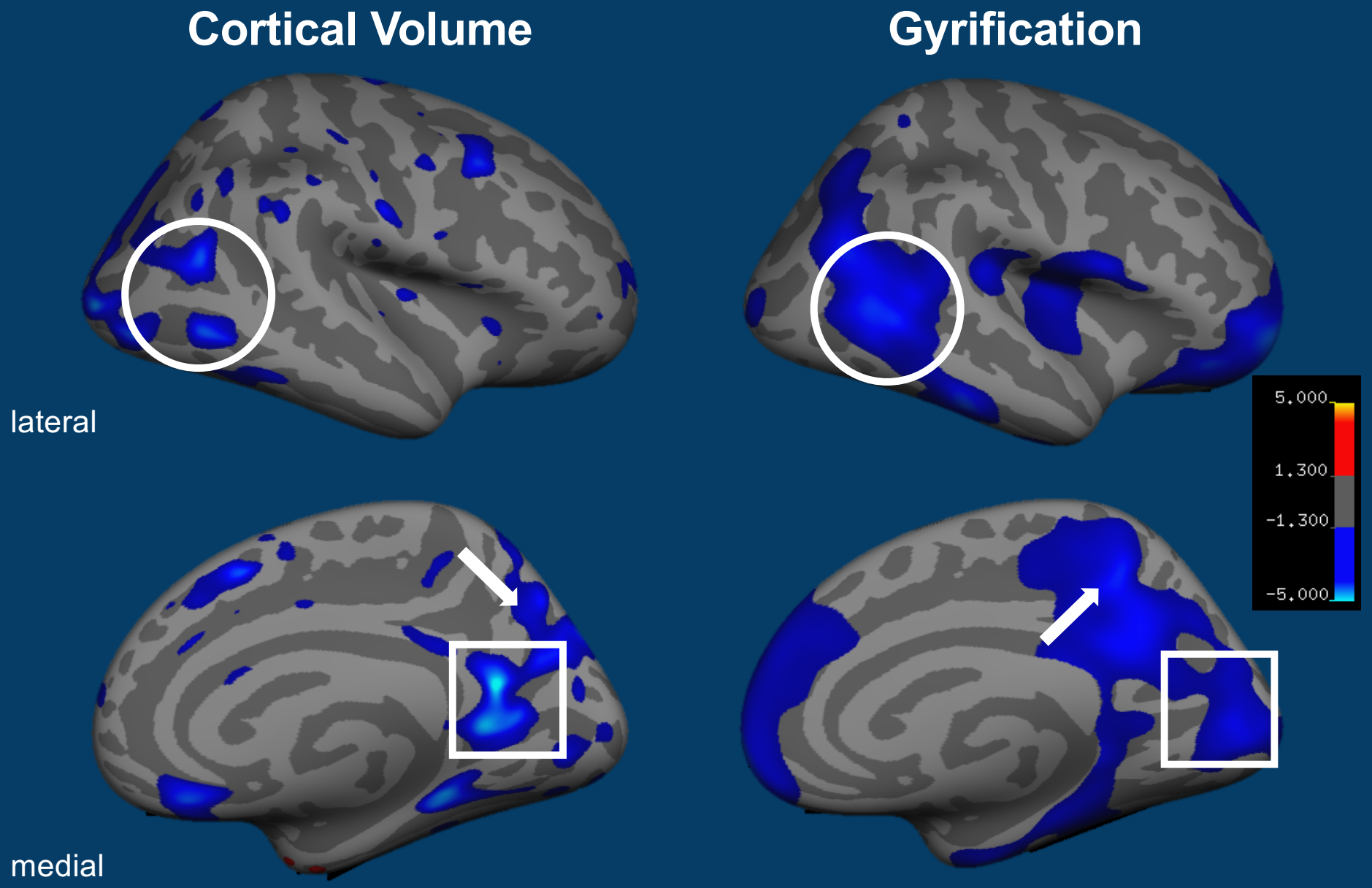
VA: 20/60 OU





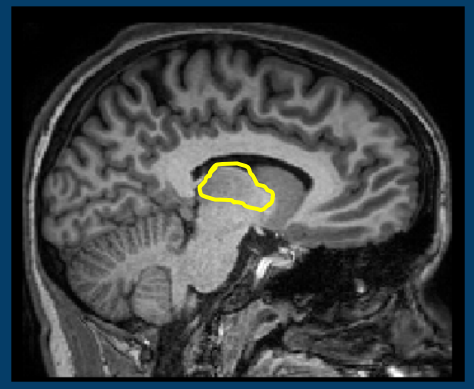
Volpe JJ. Lancet Neurol 2009;8:110-124.1)

Structural Cortical Changes in CVI

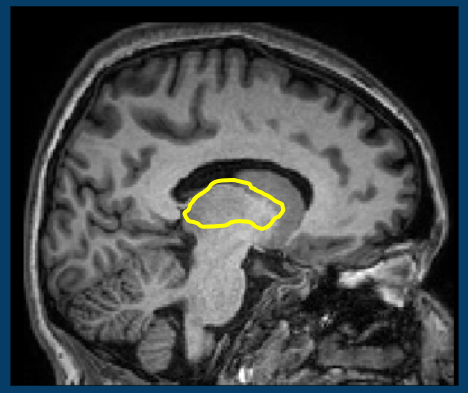


Subcortical/Thalamic Changes in CVI

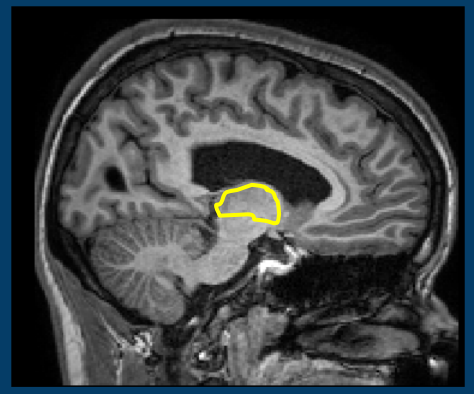
A. Sighted control
(17 year old female)
VA: 20/20 OU



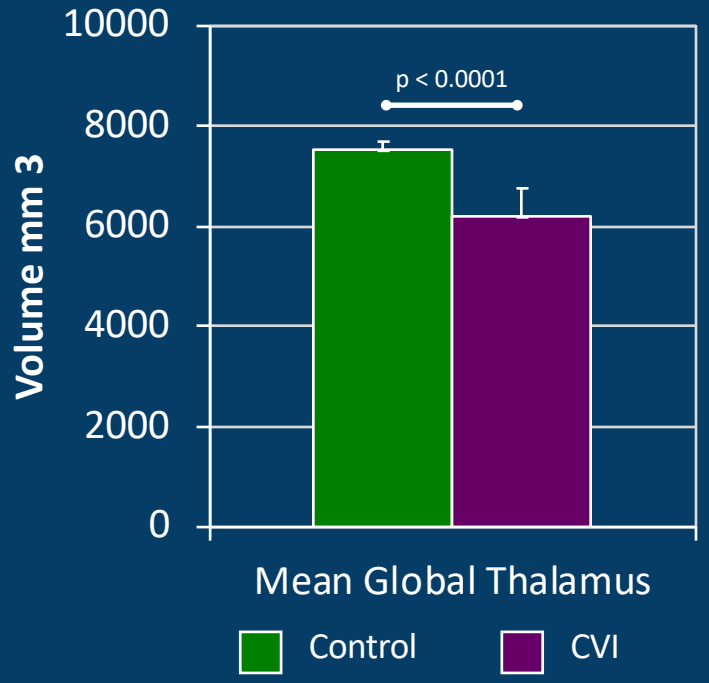
B. Ocular blind
(25 year old female; Leber's)
VA: LP

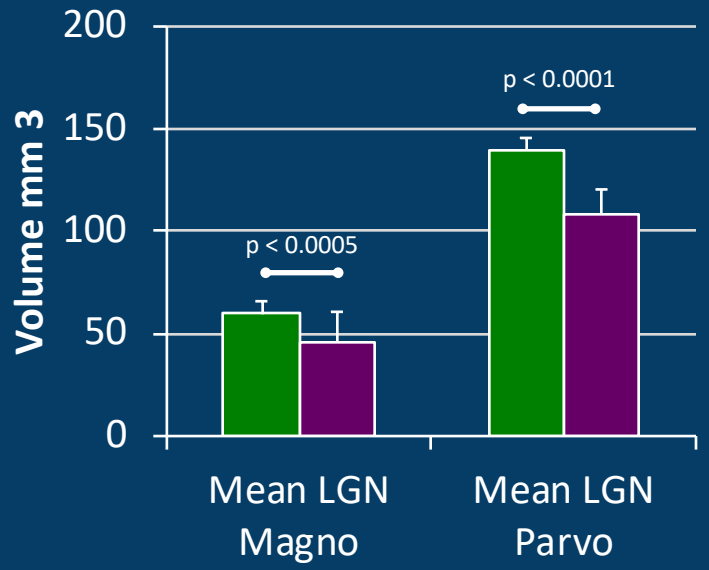


C. CVI 1
(16 year old female; PVL)
VA: 20/60 OU



D. CVI 2
(16 year old male; non PVL)
VA: 20/100 OU

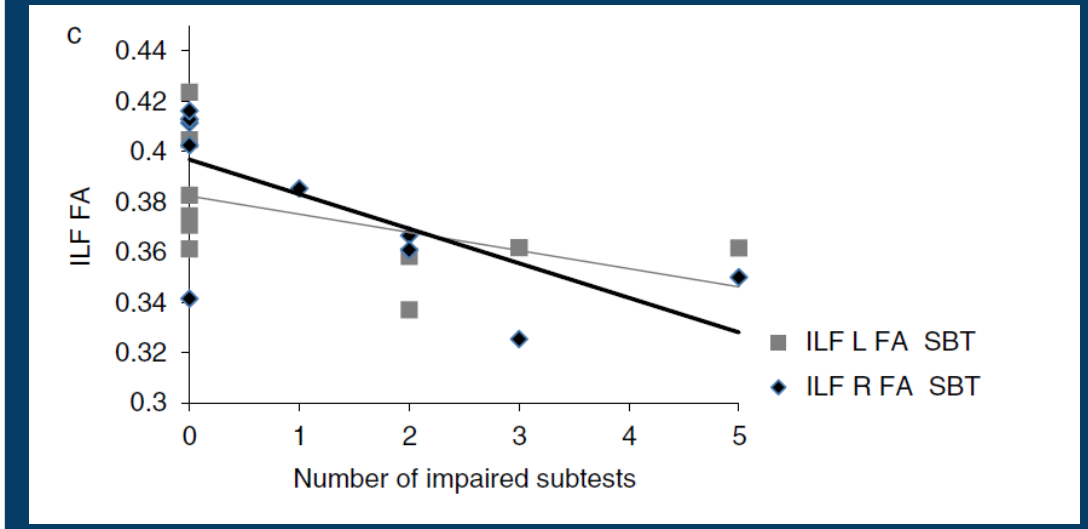




DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

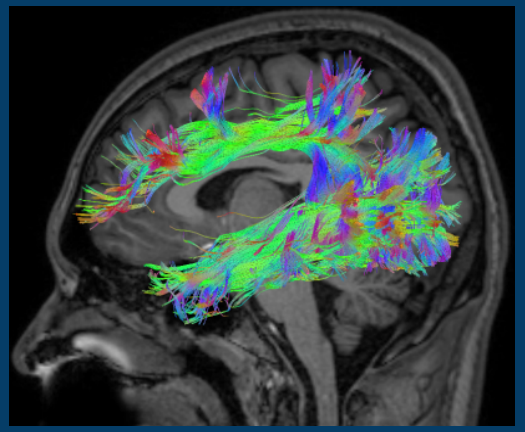
Integrity of the inferior longitudinal fasciculus and impaired object recognition in children: a diffusion tensor imaging study

ELS ORTIBUS[1] | JUDITH VERHOEVEN[2] | STEFAN SUNAERT[2] | INGELE CASTEELS[3] | PAUL DE COCK[1] | LIEVEN LAGAE[1]

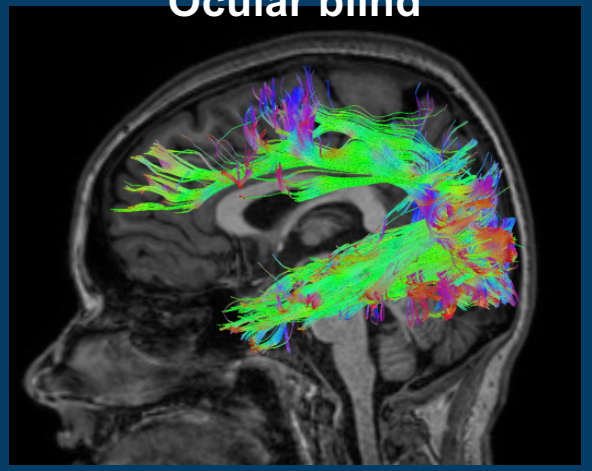


Reconstruction of Cortico-Cortical Visual Pathways

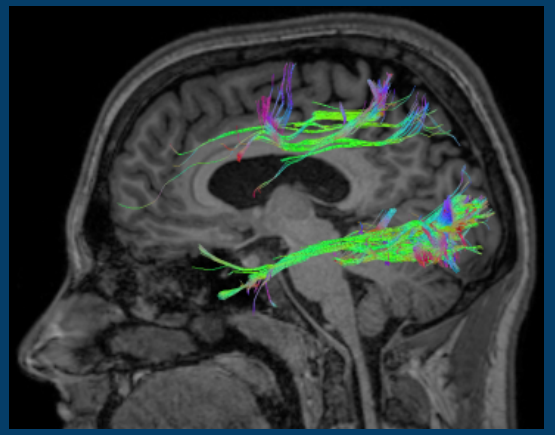
Sighted control

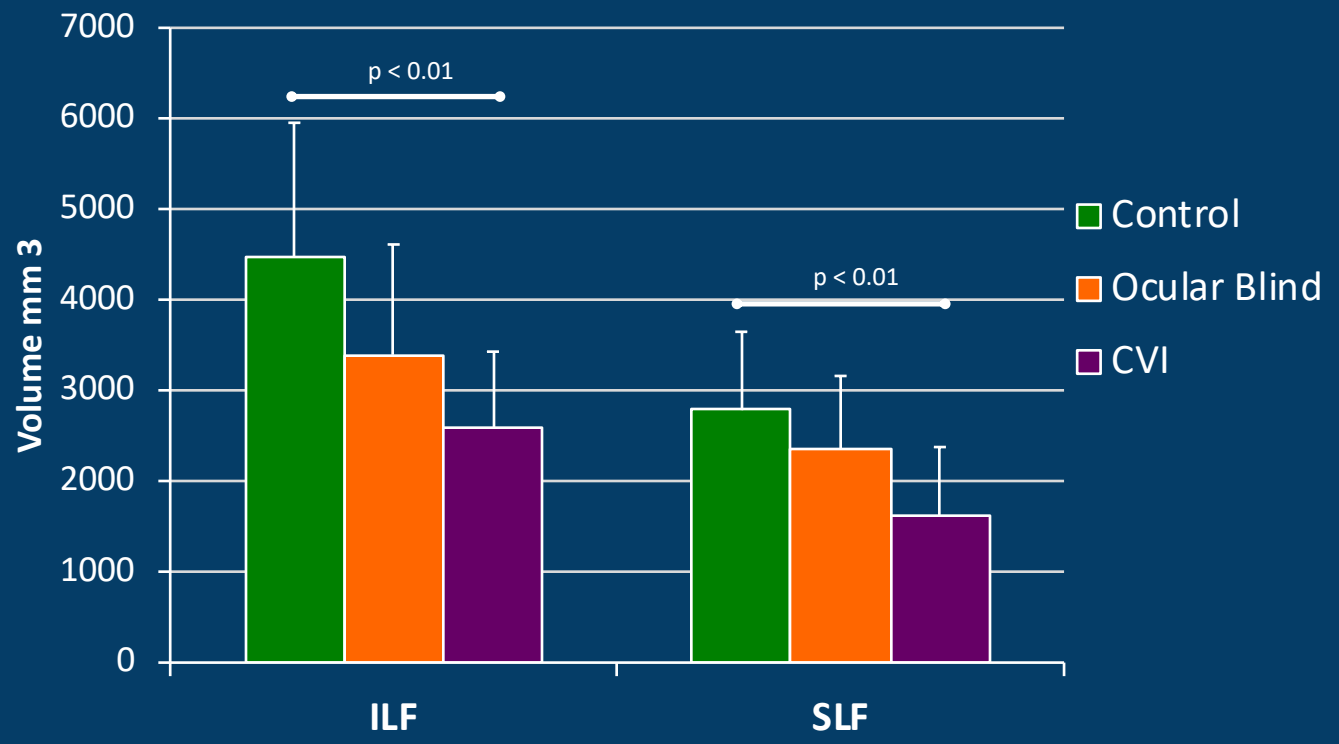


Ocular blind

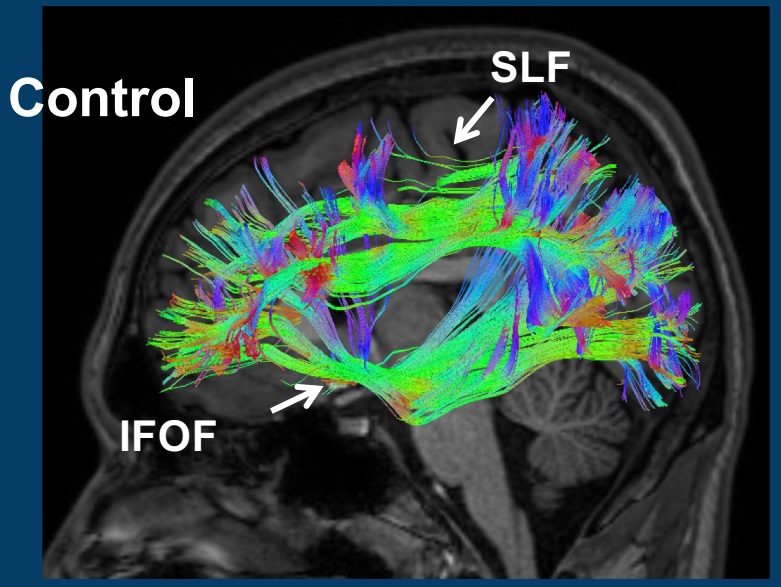


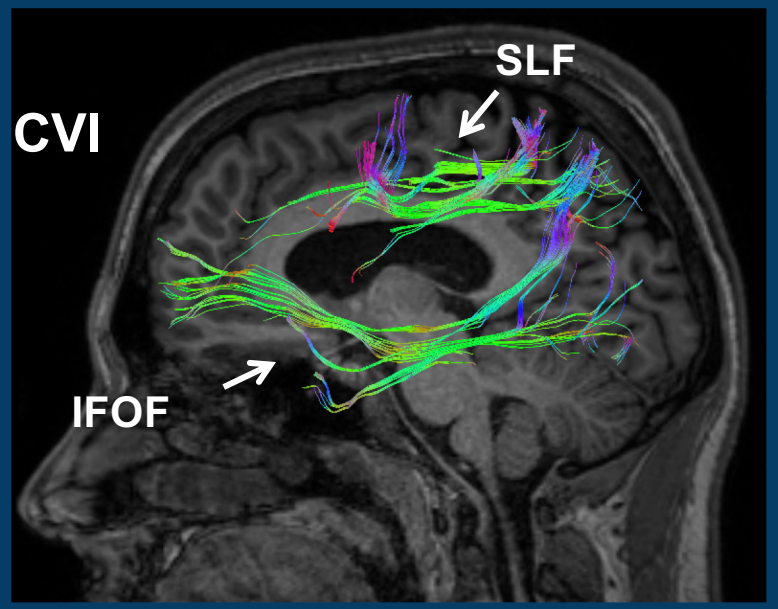
CVI



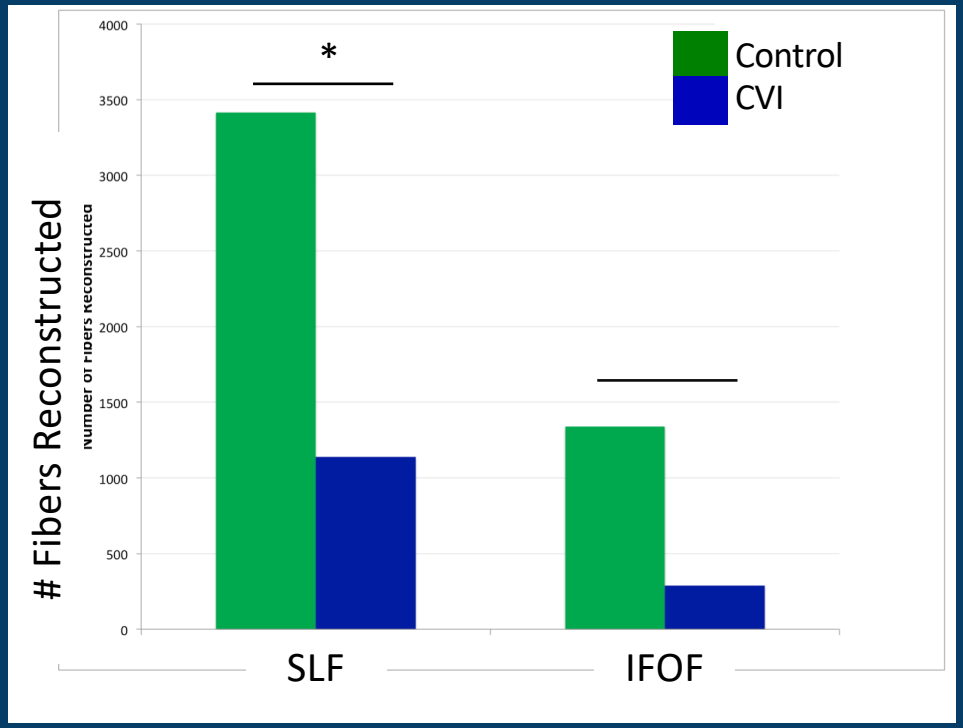


White Matter Pathways for Visual Attention

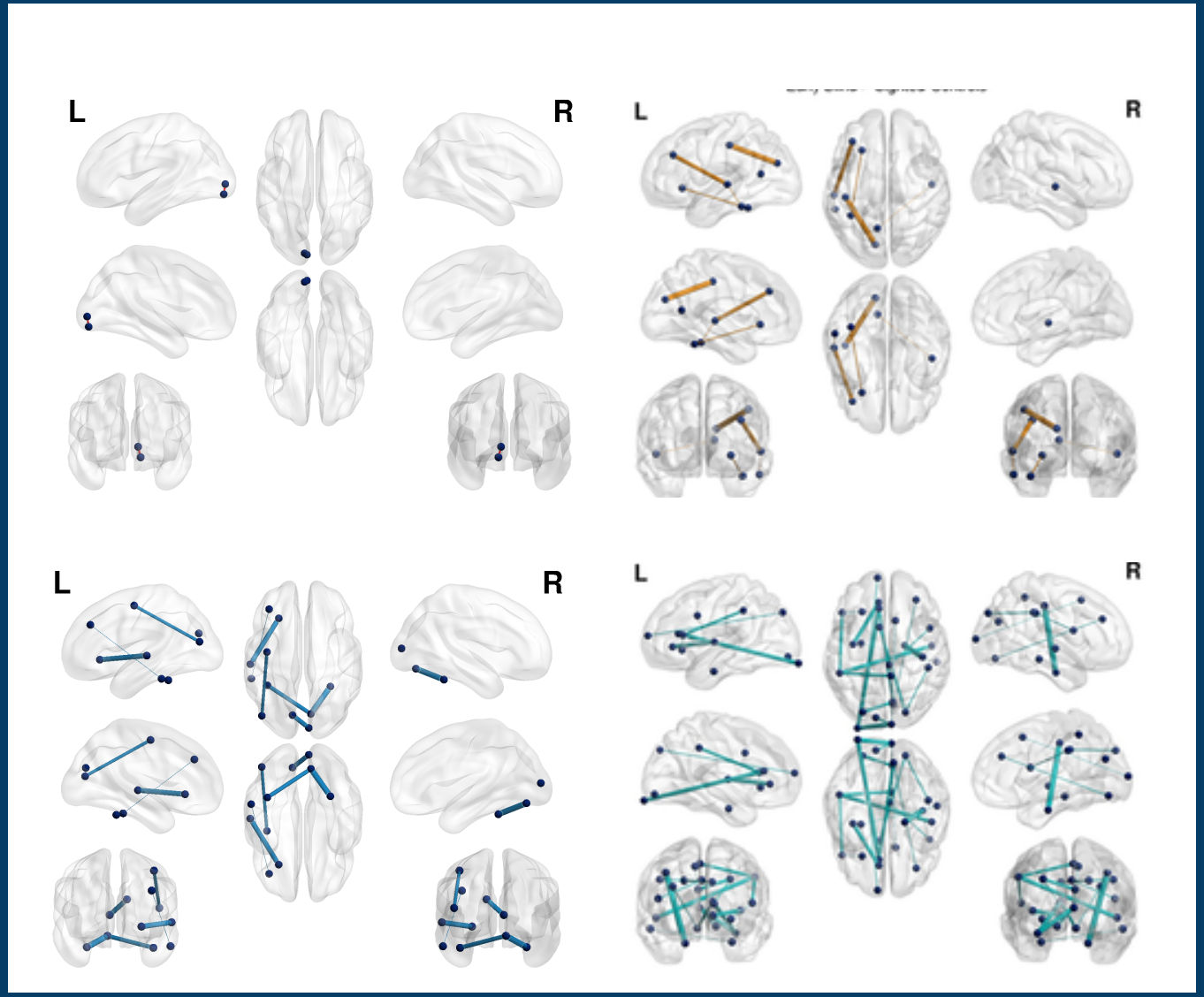




Decreases in Attention-Related Pathways in CVI

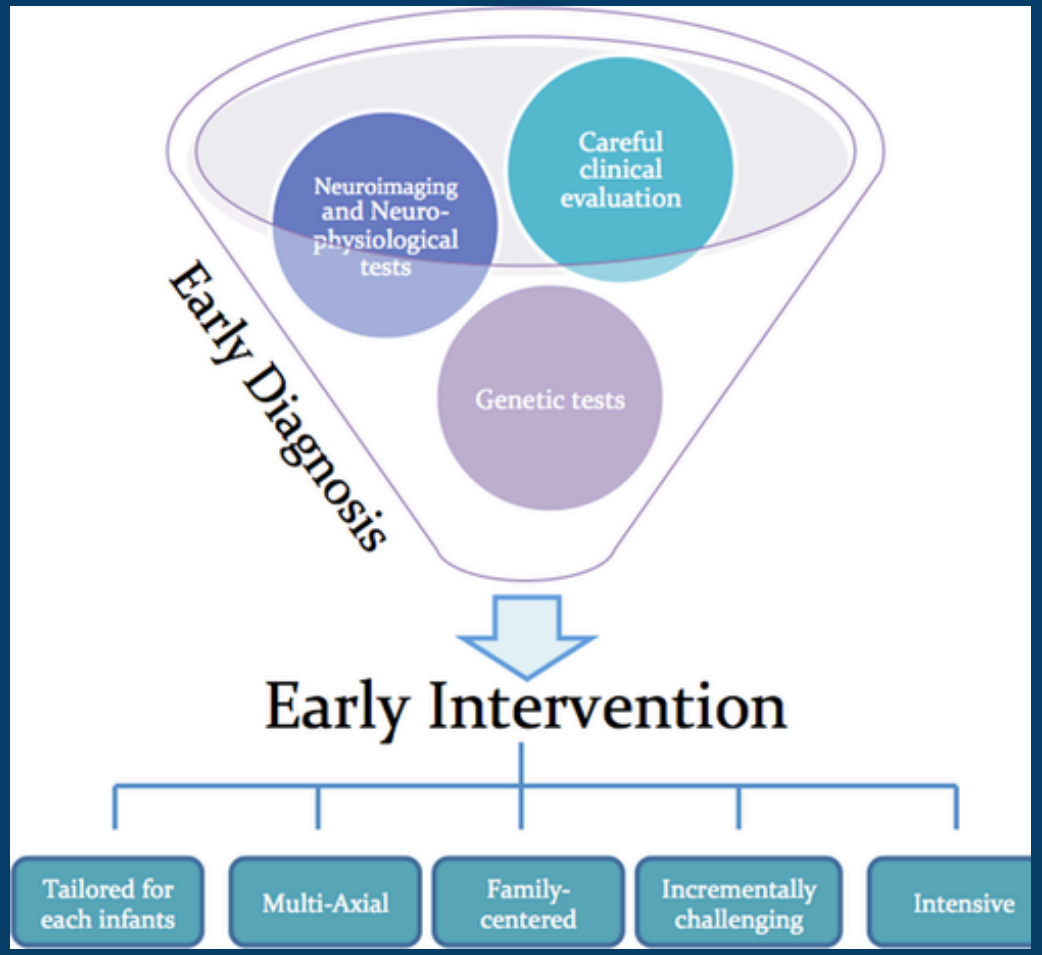


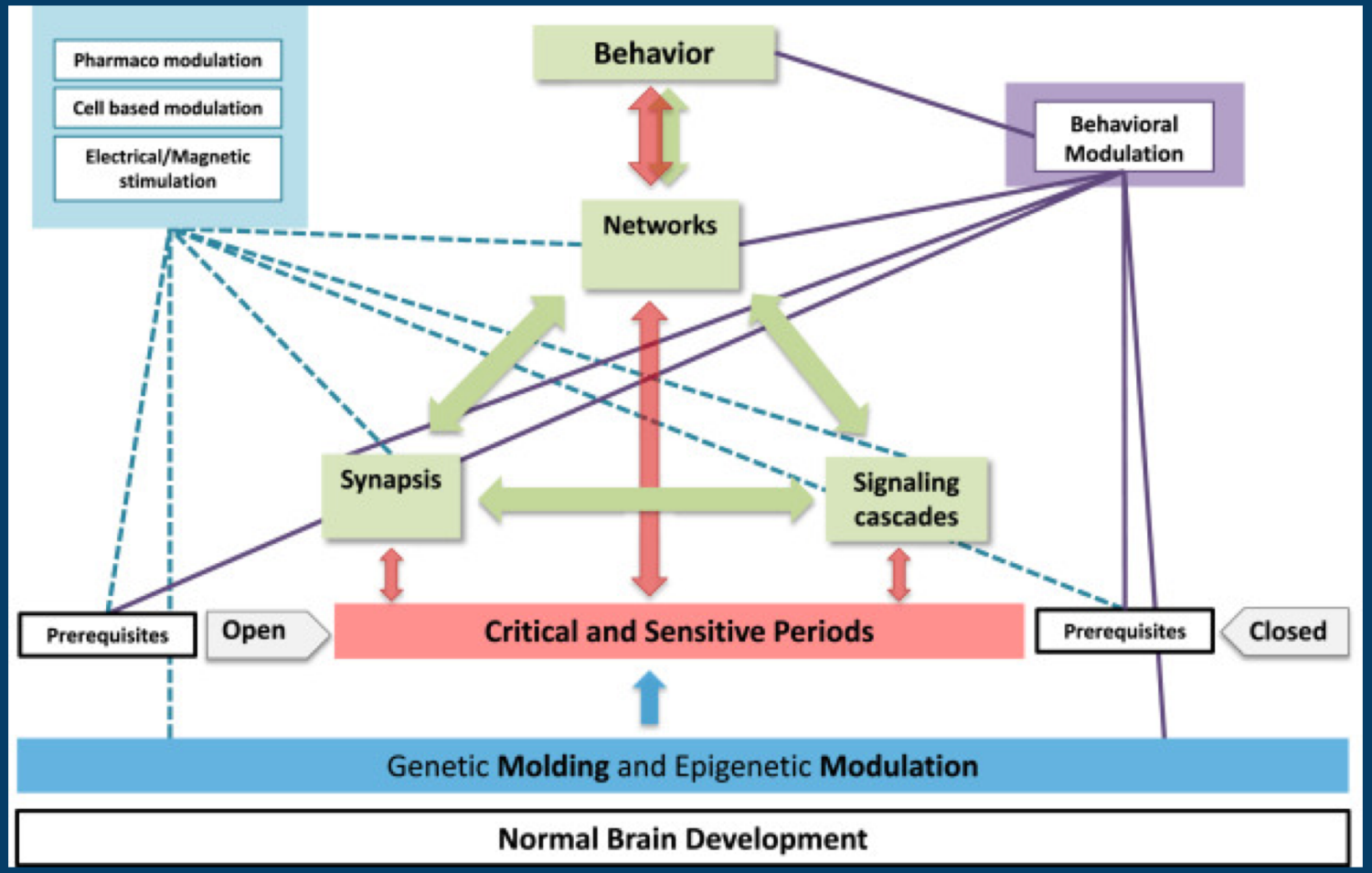
Neuroplastic Changes in Structural Connectivity: Ocular versus Cerebral Visual Impairment



Bauer et al., 2017 Plos One

Can We Predict Outcomes?

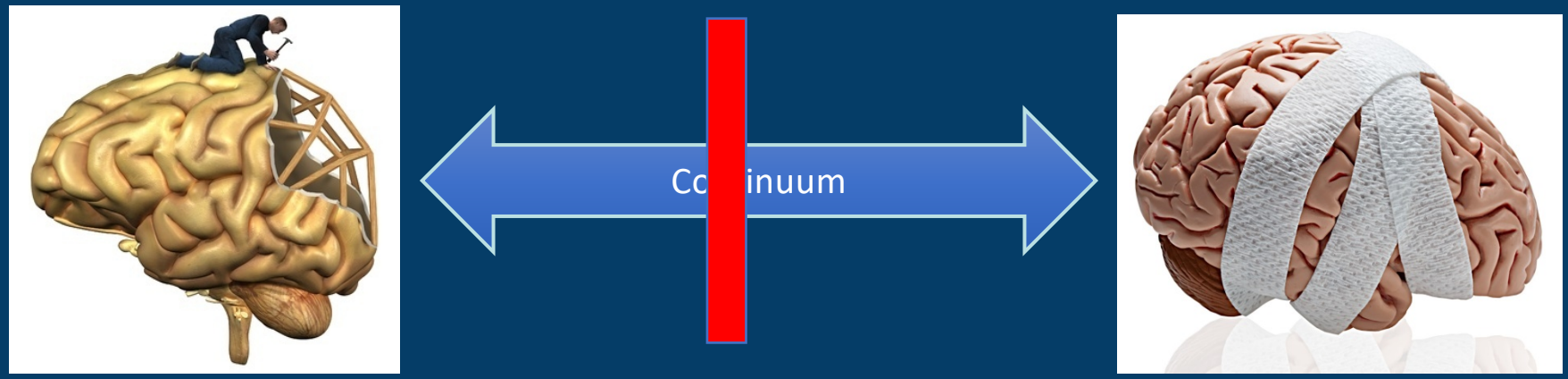




Cioni et al., DMCN 2016

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