Neuroplasticity in the infant brain: Research and Treatment Part II
Synaptic pruning

- Every circuit (sensory, motor, emotional, cognitive) shapes the way circuit gets put together

- Every experience--riding a bike, reading a book, etc excites certain neural circuits and leaves others inactive

- Those consistently turned on over time will be strengthened, while those that are rarely excited may be
The brain that wires itself

- Brains double in size in the first year
- Brain builds itself to adapt to its environment
- One hundred billion neurons (at birth)
- Neurons communicate across synapses
- Adds connections to eventually have a quadrillion *more than
Figure 2. Synaptic Takeover

In vivo imaging of the same multiply innervated junctions in neonates provides evidence both for the gradual relinquishment of synaptic territory by the losing axon before it is eliminated and takeover by the winning axon of synaptic territory that previously was occupied by the losing axon.

(A–E) Five views of the same junction imaged between P8 and P15. The subset CFP axon (blue) comes to occupy the sites in the upper parts of the junction that were formerly innervated by the YFP axon (yellow; 100% expresser), which completely withdrew (E, asterisk). At P12, a process of the CFP axon had begun to invade the territory of the YFP axon (D, circle and arrow in inset).

(F–J) Although in this case the subset CFP axon (blue and insets) has greater terminal area (~70%) at the first view, it progressively withdraws from the junction (arrows). The withdrawn axon can be seen in (I) and (J) (asterisks). Insets, 70% size reduction. Scale bars equal 10 μm.
Intrinsic and extrinsic factors influence cell fate

Gene expression imposes limitation on available fates (cell competence)

Final determination of a specific cell type may depend on environmental influence

These battles repeat billions of times as a baby grows. Every move a baby makes helps strengthen certain connections and weakens others.
Video review

National Geographic: Science of Babies

Start at 20:46 min
Critical Periods

- Most common in early childhood

- Certain windows of time during which the young especially sensitive to their environment

- “If you don’t use it, you lose”
Is Hemiplegic Cerebral Palsy Equivalent to Amblyopia of the Corticospinal System?

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CST development

- Corticospinal tract (CST) principal motor control pathway for skilled movements

- Has a protracted development, matching development of skilled movements

- Prolonged period of vulnerability when damage to CST (or its cortical origins) can have long term consequences to motor function

Eyre et al, 2007
Initially there are bilateral corticospinal projections.

After term the ipsilateral projections gradually regress and lose components.

Eyre et al, 2000
Fig. 1. Elimination of transient corticospinal terminations. The distribution of corticospinal axons is determined using an anterograde tracer that is injected into the primary motor cortex and follows the axons of the corticospinal tract, as outlined in Box 1. The density of corticospinal axon terminals is shown schematically as progressively darker shades of gray. The axons in the tracts are shaded black. The terms *contralateral* and *ipsilateral* refer to the side of the spinal cord in relation to the locations of the traced corticospinal neurons. The immature animal (*left*) has bilateral terminations, whereas the mature animal (*right*) has predominantly contralateral terminations.
When do babies show signs of hemiplegia?

Pre-term infants with hemiplegia first show signs of bilateral abnormal movements. Cioni 2000, Guzetta 2003

They show asymmetry only at second month post-term
Unilateral CP = Amblyopia?

- TMS characterized corticospinal tract development from each hemisphere over the first 2 years in:

  - 32 healthy children
  - 14 children with unilateral stroke
  - 25 with bilateral lesions

Eyre et al, 2007
Unilateral CP=Amblyopia?

- Unilateral lesions initially had responses after TMS of the affected cortex
- Became progressively more abnormal
- 7 were eventually lost
- Associated hypertrophy (greater size than in healthy subjects) of the ipsilateral corticospinal axons projecting from the noninfarcted cortex

Eyre et al, 2007
Unilateral CP = Amblyopia?

- TMS findings soon after the stroke did not predict impairment (0-3 months)

- Subsequent loss of responses from infarcted side and hypertrophy of ipsilateral corticospinal axons from the non-infarcted cortex (6-12 months) predicted severe impairment at 2 years

Why?

Eyre et al, 2007
Activity Dependent Withdrawal

- Increased ipsilateral projections from the noninfarcted cortex compound disability by competitively displacing surviving contralateral corticospinal projections from the infarcted cortex

- Signs of unilateral CP appear later and progress over 1st 2 years of life

Eyre et al, 2007
Perinatal damage to the developing CST may be exacerbated by reduced activity in contralateral M1, associated with emerging developmental disregard of affected extremity.
Vicious cycle whereby lesions reduce movement, which in turn prohibits normal neural development of the circuitry underlying movement.
Consequences of brain injury

- Child with mild hemiplegia will develop 1-3 cm of contracture in gastrocsoleus-Achilles tendon complex b/w birth and skeletal maturity

- Usually accompanied by 2 cm shortening of the tibia on affected side

- 3 cm reduction in circumference of calf muscle

Gage et al, 2009
Often equinus of involved limb

Asymmetric growth of the limbs: diminished longitudinal growth, diminished circumferential growth, reduction in glove size in upper limb and shoe size in the lower limb

Gage et al, 2009
Harnessing activity-dependent plasticity to repair the damaged corticospinal tract in an animal model of cerebral palsy

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Like humans, cats initially have bilateral CST terminations with ipsilateral projections subsequently eliminated and contralateral projections maintained during development.

Early re-wiring is activity dependent.

Martin, Chakrabarty, Friel, 2011
Cat study

- Competition between two corticicles plays an important role

- Early damage to the brain may alter the development of these connections

Martin, Chakrabarty, Friel, 2011
Cat Study

- Infused inhibitory neurotransmitter directly into the motor cortex (M1)-the origin of CST unilaterally in cats

- Reproducing unilateral CP lesion

Martin, Chakrabarty, Friel, 2011
Cat Study

- Two tasks
- Adaptive locomotion
  - Walking across horizontal ladder, target is each rung - must place paw squarely on each rung to avoid slipping
- Reaching
  - Reaching for piece of food

Martin, Chakrabarty, Friel, 2011
Cat Study

- Each task requires cat to use complex sensory information to generate motor control signals for accurately guiding limb to target

- Young, healthy cats are excellent performers on both tasks

Martin, Chakrabarty, Friel, 2011
Cat Study

- After unilateral inactivation, reaching and stepping become impaired (hypermetric)

- Difficulty integrating proprioceptive and visual information with motor control signals

- Grasping becomes ineffective with loss of coordination b/w digit flexion and forearm supination

Martin, Chakrabarty, Friel, 2011
Cat Study

- Found that silenced axons failed to establish dense, strong spinal terminations
- CST that originated in the opposite, active M1 developed dense bilateral connections after 6 and 12 months
- Indicating important

Martin, Chakrabarty, Friel, 2011
How? (Biological Strategy)

- Promoted capacity of inactivated CST to compete more effectively for spinal terminations with e-stim of previously silenced CST
- Partly restored normal adaptive locomotor performance

Martin, Chakrabarty, Friel, 2011
How? (Biological Strategy)

- Also reduced competition that the previously silenced CST faced in spinal cord by inactivating the previously active/unaffected side

- Normal motor control returns!!
How? (Biological Strategy)

- Treadmill step length restored to normal values as compared to control cats
- Motor map also restored

Martin, Chakrabarty, Friel, 2011
We don’t own a transcranial magnetic stimulation machine!
Therapy worked too!!

- Behavioral manipulation strategy
- Constrained the unimpaired limb and trained impaired limb x 4 weeks
- Restored normal CST spinal connections and behavior

Martin, Chakrabarty, Friel, 2011
Needed training to see change

- 4 weeks of constraint of unimpaired limb alone without training of affected limb resulted in no reduction of step distance (compared to significant result with training)

- Suggests CST synaptic competition is at work in re-establishing normal connections after activity-based treatment

Martin, Chakrabarty, Friel, 2011
What does that mean for us?

If cat model theory is correct, altering balance in activity on two sides at an early age may normalize connectivity and help ameliorate or prevent development of impaired motor function!!!

Martin, Chakrabarty, Friel, 2011
3 Treatment groups:

- Constraint only (immediately after injury)

- Constraint and early reach training (immediately after injury 1hr/day)

- Constraint and late reach training (feline)

Only early training group had motor recovery!
What does that mean for us?

- In cat study, the period of effective activity treatments immediately follows the period of CST refinement.

- In humans this occurs between 3 months and 1 year of age.

- This early age is optimal time to intervene in children at risk for developing CP.

Martin, Chakrabarty, Friel, 2011
What does that mean for us?

- Problematic if cerebral palsy is not diagnosed until age 2 or later
What does that mean for us?

- **Biological strategy:**
  - TMS
  - Anodal transcranial direct current stimulation
  - Inhibitive cathodal transcranial direct current stimulation or repetitive TMS for inhibition

- **Behavioral strategies**
  - Limited by babies' ability to follow direction, especially in those with cognitive deficits
  - Combination of biological and behavioral

Martin, Chakrabarty, Friel, 2011
Limitations

- So many questions still....
- Where do we stimulate? Dosing? Risk of seizures?
- Limited cognition of infants for behavioral therapy
- Prolonged restraint at an early age could impair development of unaffected limbs neural circuitry?
Still exciting!!
Next steps!
Baby CIMT study

Current trial will randomize babies with established hand asymmetry ages 3-8 months into massage group or CIMT

Underlying assumption: self-initiated motor actions CRUCIAL for motor development

Families participate in training study that uses modified form of CIMT, simple glove on babies as early as 3 months

Two 6 week training periods separated by 6 weeks of rest

5-7 days/week by families at least 30 minutes/day

Eliasson, 2014
**Baby CIMT study**

- **Aim:** to make sure children do not avoid using less developed hand and to stimulate them to develop ability in both hands.

- **Basket of toys that are novel to be used only during study**

- **Toys selected to promote grasp/exploration**

- **Variety of toys to promote repetition**

- **OT to visit and coach families 1x/week**

Eliasson, 2014
Baby CIMT study

- Outcome measure HAI (Hand Assessment for Infants)
- Currently being developed
- 10-15 minute video recording observing spontaneous hand movements

Eliasson, 2014
Training principles

- Encourage self-produced motor activities

- Activities need to be novel, challenging, and always fun!

- In pilot study, children are always permitted to take off “soft glove”

- Activities are never forced
5 F’s

- Absolutely essential characteristics of intervention!
  - Fun
  - Frequent
  - Focused/Functional
  - Family friendly
  - Financially feasible
**Damaged tracts**

- Originally thought to be attributed to damage to corticospinal or pyramidal tract
- These tracts are responsible for highly specialized movements in distal limbs without spasticity
- Extrapyramidal tracts such as corticobulbospinal and reticulospinal also involved
**Diffusion tensor imaging**

- Visualizes brain white matter tracts by capturing restrictions in the random movement of water protons by macromolecules and myelin
- Can be used to create 2D and 3D atlases of normal white matter architecture
- More precise classification of injury than conventional MRI
Motor or sensory damage?

Diffusion Tensor Imaging in Children with Periventricular Leukomalacia: Variability of Injuries to White Matter Tracts

Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways

Nagae, 2007
Hoon, 2009
Motor or sensory damage?

- Found more severe injury in posterior white matter fibers connecting the thalamus to sensory cortex (thalamocortical pathways) than in descending corticospinal tracts

Nagae, 2007
Why does this matter?

To design best treatments
Figure 2: Model of motor impairment associated with periventricular leukomalacia. The image on the left shows normal central sensorimotor pathways. In the image on the right the dotted blue line shows characteristic injury in thalamocortical connections. We hypothesize that this sensory pathway injury alters sensorimotor connections to motor cortex (dotted purple line). The narrow red line indicates injury in the corticospinal tracts.
Figure 2: Evidence for and against involvement of ascending, descending, and other tracts in cerebral palsy.
Reported prevalence 46-97% of children with hemiplegia have stereognosis deficits

Impairment of 12-object stereognosis correlated with impairment in motor function

Scores significantly lower for the affected hand
Neural circuits not actively involved in a task degrade.
2: Use it and improve it

Training a specific function can enhance that function.
3: Specificity

- The nature of training experience dictates the nature of plasticity
- How you practice matters
4: Repetition matters

- Induction of plasticity requires sufficient repetition

Kleim, 2008
Induction of plasticity requires sufficient intensity of training

Kleim, 2008
Different forms of plasticity occur at different times during training.

Training is more effective shortly after injury.

Kleim, 2008
7: Salience matters

- Weighted importance must be assigned for encoding to happen
- Motivation + attention + rewards increase learning

Kleim, 2008
Training induced plasticity occurs more readily in young brains

Kleim, 2008
9: Transference

- Promotion of subsequent plasticity

- Exercise promotes good environment for learning

Kleim, 2008
Maladaptive plasticity

Development of bad habits
**INTERVENTION CHARACTERISTICS**

- Create environments for exploratory, self-initiated actions that are rewarded

- Enhance tactile, proprioceptive, and all perceptual information

- Opportunities for practice of tasks you want to enforce
5 F’s

- Absolutely essential characteristics of intervention!
  - Fun
  - Frequent
  - Focused/Functional
  - Family friendly
  - Financially feasible
“Imagination is more important than knowledge”...
“For knowledge is limited to all we now know and understand, while imagination embraces the entire world, and all there will be to know and understand”


