CORTICAL PLASTICITY AND RECOVERY OF FUNCTIONS AFTER TBI IN CHILDHOOD

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Brain injury acquired during childhood or adolescence. Which specific care? Which support? - Brussels 2009
Cortical plasticity is the capability of the cerebral cortex to alter its functional organization as a result of experience.

CORRELATES OF PLASTICITY

Various levels of analysis:

- Molecular
- Synaptic
- Cellular
- Network
- Systems
CORRELATES OF PLASTICITY

In both normal and injured animals:

- cortical representational maps are altered
- synapses change their morphology
- dendrites and spines grow and contract
- axons change their trajectory
- Various neurotransmitters are modulated
- synapses are potentiated or depressed
- to a limited extent, new neurons differentiate and survive
ENVIRONMENTAL ENRICHMENT AND ACTIVITY-DEPENDENT PLASTICITY

In all sensory and motor areas of the cerebral cortex that have been studied, significant functional and structural changes have been observed as a result of experience.


Motor Learning-Dependent Synaptogenesis Is Localized to Functionally Reorganized Motor Cortex

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In comparison to rats in a motor activity control group, rats trained on a skilled reaching task exhibited:

- an areal expansion of wrist and digit movement representations within the motor cortex
- significantly more synapses per neuron than controls within layer V of the caudal forelimb area
**FIG. 1.** Performance on the skilled reaching task ($n = 6$). Mean percentage of successful reaches ($\pm$SEM) progressively increased during both the stationary and rotating table phases.

**FIG. 2.** Representative motor maps (digit, red; wrist, green; elbow/shoulder, light blue) of one animal from the skilled reaching condition (SRC; A) and unskilled reaching condition (URC; B). The two forelimb areas are outlined in white. The caudal forelimb area (CFA) is separated from the rostral forelimb area (RFA) by a band of head/neck representations (yellow). The hindlimb area (HLA) is shown in dark blue and nonresponsive sites in gray.
USE DEPENDENT VS LEARNING DEPENDENT PLASTICITY

- In all sensory and motor areas of the cerebral cortex that have been studied, significant functional and structural changes have been observed as a result of experience.

- Changes in cortical maps are driven by specific aspects of behavioral demand (i.e., skill acquisition), and are not simply the result of repetitive use.

- If this phenomenon generalizes to injured brains, then rehabilitation techniques should be optimal if they induce increasing levels of motor skill. Repetitive use alone is unlikely to induce large-scale, long-lasting changes.

In vivo intracortical mapping using microstimulation
CORTICAL PLASTICITY IS RELATED TO LEARNING!


Fig. 10. Representative high resolution motor maps from the second set of NRC (n = 6), CRC (n = 6) and PRC (n = 6) animals derived using intracortical microstimulation. Both the CRC and PRC animals exhibited an increase in the proportion of the CFA occupied by distal (green) movement representations in comparison to NRC animals. Consequently, NRC animals had a significantly greater proportion of the CFA occupied by proximal (blue) movement representations than the CRC and PRC animals. Areas in which secondary movements...
LOCAL PLASTICITY AFTER LESIONS IN THE MOTOR CORTEX

- Between 3 and 14 days, rats demonstrate increased GAP-43 immunoreactivity, suggesting neurite outgrowth.
- Between 14 and 60 days postinfarct, synaptophysin staining is elevated, signifying increased synaptogenesis.
- Surviving neurons become hyperexcitable, with associated up-regulation of NMDA receptors and downregulation of GABAa receptors.
- Axonal sprouting occurs in the peri-infarct area.
- Growth inhibition is suppressed for about 1 month post-infarct and is followed by “waves” of growth promotion which may modulate the brain’s self-repair processes.


FIG. 2. Sequence of anatomical changes in intact cortex after focal ischemic infarct. A time-dependent set of morphological changes is set into motion by focal ischemic damage to the cerebral cortex. Very early after injury, molecules associated with growth promotion, such as GAP-43, cJUN, FGF-2, and GFAP can be demonstrated. In the second to third week post-injury, significant dendritic sprouting can be observed in the contralesional hemisphere. Widespread synaptogenesis appears by the third week. This figure illustrates only a small number of events following focal infarct. For a more detailed picture see Carmichael et al. and Jones et al.
REMOTE PLASTICITY AFTER LESIONS IN THE MOTOR CORTEX

- After stroke, neuroanatomical changes occur not only in the peri-infarct cortex, but also in remote areas, such as the contralesional hemisphere.


- After injury, a large number of cortical areas are deprived of intracortical connections and their neurons terminals lie in ischemic territories.

- New projection pathway resulting from the ischemic infarct represent a repair strategy of the cortex to re-engage the areas.

Schematic illustration of the effects of a unilateral cortical lesion (red circle) on spared cortical tissue as depicted in a nonhuman primate brain. Time-dependent neurophysiological and neuroanatomical alterations occur in the peri-infarct region (pink region surrounding lesion) and remote cortical areas. These include alteration in neurophysiological maps of motor representations, neurotransmitter receptor regulation, dendritic sprouting (not shown), local and remote axonal sprouting (short and long green arrows, respectively) and synaptogenesis (small black dots). These changes are accompanied by waves of growth-promoting and growth-inhibiting proteins (large white and black circles, respectively) that might trigger axonal sprouting and provide guidance to regenerating axons. Similar changes have been documented in the contralesional (undamaged) cortex, and are thought to be related to behavioral compensation in the ipsilesional forelimb, and possibly recovery of function by the contralesional forelimb. Recent studies suggest that lesion size is an important factor in determining the role of remote cortical plasticity. Concentric circles in PM denote expanded motor representations. Abbreviations: M1, primary motor cortex; PM, premotor cortex; S1, primary somatosensory cortex.
MODULATING NEUROPLASTICITY

Behavior is one of the most powerful modulators of post-injury recovery (i.e. constraint-induced movement therapy).

Figure 1. Enriched-rehabilitation treatment condition. A, View of a typical enriched environment. Cages and objects were changed twice weekly to promote exploration and a broad range of tactile experience. B, The rehabilitative reaching apparatus, which was implemented daily (5 d/week) to promote deficit-specific therapy of the impaired forelimb and digits. A shelf directly below the impaired limb was filled with food pellets to reinforce skilled use of the impaired forelimb. C, Side view of the staircase-reaching task. See Materials and Methods for additional description.
PLASTICITY AFTER DEVELOPMENTAL TBI
Neuronal plasticity is enhanced in the developing brain and children appear to learn more quickly than adults:

- they can easily acquire new languages, learn to playing a musical instrument, acquire to play sports
- impaired vision early in life from strabismus or ocular disorders can lead to permanent amblyopia because of reorganization of central visual pathways
- early hearing impairment can lead to impaired central auditory perception
- children also recover from certain brain injuries more readily than adults
MAJOR EVENTS IN HUMAN CEREBRAL DEVELOPMENT

- Primary neurulation
- Prosencephalic development
- Neuroblast proliferation and differentiation
- Neuronal migration
- Cortical organization

Gestational age - weeks post conception
HERITABILITY

Identical twins (MZ)  Fraternal twins (DZ)

Share all their genes  Share half their genes

Gray matter correlation between twins

$S/M$  $W$

$r^2$

Perfectly correlated

More similar

Independent
Table 1. Candidate genes used in association studies with cognition

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Abbrev.</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 7 nicotinic receptor</td>
<td>CHRNA7</td>
<td>15q</td>
<td>Cholinergic receptor, attention, learning</td>
</tr>
<tr>
<td>Brain derived neurotrophic factor</td>
<td>BDNF</td>
<td>11p</td>
<td>Role in LTP; episodic memory</td>
</tr>
<tr>
<td>Catechol-O-methyltransferase</td>
<td>COMT</td>
<td>22q</td>
<td>Involved in degradation of dopamine, notably in prefrontal cortex; executive sub-processes</td>
</tr>
<tr>
<td>Dopamine receptor type 4</td>
<td>DRD4</td>
<td>11p</td>
<td>Dopamine receptor with a limbic distribution; attention</td>
</tr>
<tr>
<td>Dopamine transporter</td>
<td>DAT1</td>
<td>6p</td>
<td>Ruptake of dopamine at or near the synapse; attention</td>
</tr>
<tr>
<td>Monoamine oxidase A</td>
<td>MAOA</td>
<td>Xp</td>
<td>Degradation of dopamine, norepinephrine, serotonin; attention</td>
</tr>
<tr>
<td>Semaphorin</td>
<td>SEMA4F</td>
<td>2p</td>
<td>Axonal growth cone guidance</td>
</tr>
<tr>
<td>Serotonin 2A receptor</td>
<td>5HT2A</td>
<td>13q</td>
<td>Serotonin receptor with wide forebrain distribution; episodic memory</td>
</tr>
</tbody>
</table>

The COMT gene

(a) Chromosome 22
(b) 5' Promoter
(c) COMT-MB start codon
Transmembrane segment
COMT-S start codon
PCR
-210 BP
5'-CTCATCACACATCGAGATC
5'-GATGACGGTGGTGAAGTGG
(d) NlalI
(e) G1947 > A1947
AGVKD
(f) High-activity (3-4X) Thermostable
Low-activity (1X) Thermolabile

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GENES AND COGNITION

Bambino Gesù OSPEDALE PEDIATRICO

Gene expression changes by functional category after mild or severe developmental TBI.

Genes associated to Neurotransmission / plasticity and growth factors/hormones represent a much larger percentage of downregulated than upregulated genes.

60 genes

96 genes
Development of the cerebral cortex in children is characterized by an early postnatal burst in synaptogenesis followed by activity-dependent pruning of excessive synapses in the postnatal period. This probably contributes to cortical plasticity by providing an excess of synapses to be selected based on experience during childhood.
A major potential mechanism of alterations in developmental neuroplasticity following TBI involves changes in neurotransmission. Clinically, dysfunctional neurotransmission has been implicated in many sequelae of pediatric TBI, including memory impairment and attention problems.

Changes in the frequency or strength of activation across synapses can result in long-term increases or decreases in their strength, referred to as either long-term potentiation (LTP) or long-term depression (LTD), respectively.

TBI to the developing brain is distinct from adult TBI in many ways:

- The developing brain is more malleable to external stimuli, a characteristic that has often been touted as a significant advantage with regard to recovery of function. However, children who suffer TBI are well known to develop chronic cognitive and behavioral disturbances [Ewing-Cobbs, 1998; Jaffe, 1993; Levin, 2002].

- Infants and toddlers might arguably have the most plasticity and yet actually seem to have some of the worst developmental outcomes after significant TBI (Barlow, 2005; Levin, 2003).
In a static (adult) model, a given function remains constant over time. If an injury occurs, there may be a permanent deficit (dotted line) or an acute reduction in function that slowly recovers over time. At some point, if and when the level of function returns to the premorbid level, recovery is said to be complete (dashed line).

In a **developing model**, the level of function in normal subjects is changing over time. After developmental injury, while functional recovery may return to the premorbid baseline (dashed line), the baseline function of normal peers has already moved on (solid line). The duration of recovery, the rate of functional change and the presence/timing of critical windows all become important measures to determine whether the injured immature brain can actually fully recover to an age matched baseline after injury.
It is also possible that the immature brain may appear to have a complete functional recovery, but that the strength of this recovery is limited.

One final related concept to be introduced is that of ‘growing into the lesion’. This idea purports that if a particular function is not normally well developed at the time of injury, then such a deficit may not necessarily be observed until a later developmental stage.

An additional critical consideration when managing or investigating recovery from developmental brain injury is the presence of salient environmental stimuli.

It is important to realize that brain maturation occurs in situations where environmental conditions and training are superimposed upon normal developmental changes. Both normal maturational changes and response to environmental stimuli will affect outcomes from pediatric TBI.
CONCLUSIONS
Cortical plasticity is related to learning of new skills

Skill learning but not strength training induces cortical reorganization

Behavior is one of the most powerful modulators of recovery

Neuronal plasticity is enhanced in the developing brain and children appear to learn more quickly than adults

TBI to the developing brain is distinct from adult TBI

Infants and toddlers have some of the worst developmental outcomes after significant TBI

‘Growing into the lesion’, a deficit may not necessarily be observed until a later developmental stage

Rehabilitation team must pay attention to these variables in order to tailor the best treatment strategy after TBI in developmental age