Phases of Brain Development

1. Neural Induction  E18-E24  Genetically
2. Proliferation     E24-E125  determined
3. Migration        E40-E160
4. Differentiation   E125-postnatal
5. Synaptogenesis    
6. Cell Death/Stabilization  
7. Synaptic Rearrangement  

Environmentally
Sensitive and
Self organizing
“...one could say that the growth cone is as sort of battering ram, endowed with an exquisite chemical sensitivity and advancing by rapid ameboid movements that allow it to swerve around and surmount obstacles in its path, thus forcing a passage between cells until it reaches its destination.”

Ramon y Cajal, 1899
A very young neuron and its growth cone
Growth Cone

- Axons express cell adhesion molecules that bind multiple axons together (fasciculation).
- The extracellular matrix contains proteins that act as chemoattractants as well as chemorepellants.
- Growing axons express surface molecules called “integrins” that seek out permissive proteins such as laminin.
- Integrins bind laminin to promote axonal elongation
Axonal growth
How the axon finds its target

- Pathway selection
- Target selection
- Address selection

- Direct cell-to-cell communication
- Detection of extracellular signals from other cells nearby
- Communication via diffusible chemical signals from cells at a distance
How the Axon Finds its Target

• Two strategies
  – Long distance targeting
    • Axons follow highly specific and stereotyped pathways to reach their target fields across long distances
  – Local targeting
    • Once the target field, axons arborize widely in a non-selective, trial and error way
Long Distance Targeting

- **Chemotropism**
  - Diffusible chemical gradients that attract or repel

- **Guidepost cells**
  - The trajectories of many axons are broken up into short segments (in a stepwise fashion) marked by guidepost cells or distributed positional cues

- **Preformed pathways (labeled lines)**
  - Radial glia (non neural scaffolding)
  - Pioneer neurons (neural scaffolding)
Chemoattractants and Chemorepellents

Netrin-1

Trochlear motor neurons

ATTRACTION

REPULSION

floor plate of the developing spinal cord "Netrin-1 gradient"

Semaphorin III

Dorsal Root Ganglion

la afferents (muscle stretch)

afferents to low threshold mechanoreceptors

afferents to temperature and pain receptors

repulsion

semaphorin III gradient

NO REPULSION
Variety of chemoattractants and chemorepellents
Local Targeting
(Looking up an address)

• Matching stage
  – Low precision
  – High exhuberancy

• Sorting and Adjustment stage
  – Stabilize some connections
  – Remove others
Phases of Brain Development

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7. Synaptic Rearrangement     Environmentally

Sensitive and
Self organizing
Exhuberancy in Synaptogenesis

Activity-dependent synaptic modification:
- correlated activity
- competition
- space
- growth factors
- targets

Neural Darwinism

*Figure 4.4. Variation of Brain Connections Over a Lifetime.*
Hebbian Learning Rules  
(Adjusting weights at the synapse)

• Synaptic efficacy increases if there is correlated activity in the pre- and post-synapse.

• Synaptic efficacy decreases if there is uncorrelated activity in the pre- and post-synapse.
A MODEL FOR SYNAPTOGENESIS

1. An axon from a pontine cell approaches the granule cell.

2. Once in position, binding between neurologin on the granule cell and (presumably) neurexin on the axon triggers synaptic development (shown in 3).

3. The axon tip flattens against the target cell, and synaptic vesicles cluster near the membrane. The vesicles can release neurotransmitter through exocytosis. Also, in the postsynapse, a dense meshwork of protein scaffolding appears.
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7. Synaptic Rearrangement  Sensitive and Self organizing

Environmentally
Competition for nerve growth factor leads to cell death/axon retraction
Apoptosis (programmed cell death)

FADD – Fas Associating death domain
IAP – Inhibitors of Apoptotic Proteins
SMAC - second mitochondria-derived activator of caspases
Caspases – cystein proteases
Apaf – apoptotic protease activating factor

Mitochondrial permeability is affected

TNF – tumor necrosis factor; a cytokine produced by macrophages

Arthritis Research
Phases of Brain Development

1. Neural Induction    E18-E24    Genetically
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5. Synaptogenesis      Environmentally
6. Cell Death/Stabilization  Sensitive and
7. Synaptic Rearrangement  Self organizing
Arranging Ocular Dominance Columns

Neurons in other layers are usually driven better by one eye, but also by the other.

During infancy, the animal has normal visual experience using both eyes together.

NORMAL VISUAL EXPERIENCE
Effects of monocular deprivation

(a) Normal

(b) Monocular deprivation

Ocular dominance
Effects of amblyopia and binocular deprivation

(c) One eye deviated

(d) Binocular deprivation

Number of cells

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<th>Opposite side</th>
<th>Equal</th>
<th>Same side</th>
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Ocular dominance

(c) One eye deviated

(d) Binocular deprivation

Left eye (open)

Right eye (covered)

Strengthening of synapses that successfully drive postsynaptic cell

Loss of ineffective inputs

Visual cortex cell
Plasticity in the Somatosensory System
(a) Details of cortical map

Digit 5
Digit 4
Digit 3
Digit 2
Digit 1 (thumb)

(b) Experiment 1

Dorsal surface

Immediately after serving the nerve
Five months later
Changes in Brain Weight