The Brain-101
or why I should have been out
enjoying this beautiful day instead of
going back to school

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On August 6, 1945, the United States, in an attempt to quickly end the war in the pacific against Japan dropped the first of two atomic bombs, on the city of Hiroshima
The blast created a huge fireball and spread radioactivity over a wide area.
Figure 1. The proportion of severely mentally retarded cases and 90% confidence limits by DS86 uterine absorbed dose and postovulatory age in weeks. (Otake et al. 1987.)
Figure 5. The proportion of small head cases and 95% confidence limits by DS86 uterine absorbed dose and trimester of pregnancy. (Otake and Schull 1993.)
Figure 4. The proportion of seizure cases and 95% confidence limits by DS86 uterine absorbed dose and postovulatory age. (Dunn et al. 1990.)
General Principles Regarding the Effects of Early Experience on Development

Brain Architecture and Skills are Built in a Hierarchical “Bottom-Up” Sequence

- Social, Emotional, and Cognitive Development are Highly Interrelated
- Relationships are the “Active Ingredients” of Early Experience
- Brain Plasticity and the Ability to Change Behavior Decrease Over Time
Brain Architecture and Skills are Built in a Hierarchical “Bottom-Up” Sequence

• Neural circuits that process basic information are wired earlier than those that process more complex information.

• Higher circuits build on lower circuits, skills beget skills, and the development of higher level capabilities is more difficult if lower level circuits are not wired properly.
<table>
<thead>
<tr>
<th>Age</th>
<th>Synaptic Density</th>
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<tbody>
<tr>
<td>At Birth</td>
<td></td>
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<tr>
<td>6 Years Old</td>
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<tr>
<td>14 Years Old</td>
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The images depict the synaptic density at different stages of development.
Brain Plasticity and the Ability to Change Behavior Decrease Over Time

- Brain circuits stabilize with age, making them increasingly more difficult to alter.

- The window of opportunity for adaptive development remains open for many years, but the costs of remediation grow over time.

- It is more efficient, both biologically and economically, to get things right the first time than to try to fix them later.
Sensitive Periods for Early Development

Cognitive skills:
- Binocular vision
- Central Auditory System
- Emotional control
- Habitual ways of responding
- Peer social skills
- Language
- Symbols
- Relative quantity

Sensitive periods for early development include critical periods where skills develop rapidly. These periods typically wane after a certain age, as indicated by the chart.
Prenatal Brain Development
15 1/2 wks     22 weeks       23 weeks      ~25 weeks

27 weeks       Full term brain       Adult

http://medstat.med.utah.edu

Adolescent brain (black box)
Ungrateful, talks back, risk taking...doesn’t clean room...
Concepts and terms discussed in today’s talk

- Embryogenesis
- Neurulation
- Cell Proliferation
- Cell Migration
- Axonal Growth and synaptogenesis
- Mylenation
- Stress and the brain
Embryogenesis
Embryogenesis

- Following conception, zygote rapidly divides, forming ball of cells (blastocyst)
- About 1 week post conception, blastocyst divides into inner and outer layer
- Outer layer becomes umbilical cord, amniotic sac, placenta; inner layer becomes embryo
A. 2-Cell Stage
12-15 hours
Blastomere

B. 4-Cell Stage
24-30 hours

C. 8-Cell Stage

D. Morula

E. Early Blastocyst
Inner Cell Mass
Blastocyst Cavity
Trophoblast

F. Late Blastocyst
The blastocyst embedding itself into the tissue of the endometrium
Embryogenesis, Con’t

- Between 1st and 2nd week post conception, embryo divides into 3 layers
- Inner (endoderm) becomes organs (e.g., liver, heart, spleen), etc.
- Middle (mesoderm) becomes muscle/skeletal system
- Outer (ectoderm) becomes outer coverings PLUS nervous system
Neurulation

- Days 18-24:
  - dorsal region of ectoderm thickens and forms neural plate
  - neural plate forms a groove
  - neural tube forms
  - tube closes at rostral, then caudal ends
  - cells trapped inside tube form CNS, those outside tube form ANS
Neurulation

- Days 18-24: dorsal region of ectodermal layer of embryo thickens and forms neural plate; plate forms a groove.
- By 24th day both rostral (top) and caudal (bottom) ends have closed to form neural tube.
- Cells trapped inside tube become Central Nervous System (CNS); those trapped between outer layer of ectoderm and tube become neural crest cells, which give rise to Autonomic Nervous System (ANS).
Neural tube forming

A

Ectoderm
Mesoderm
Endoderm

B

Neural groove
Paraxial mesoderm

C

Neural tube
Paraxial mesoderm
Lateral plate mesoderm

D

Somite
Endoderm
Notochord
Neurulation Con’t

- Errors in neurulation are known as neural tube defects, and can take two forms: complete failure or partial failure.
- Complete failure: **anencephaly** (cortex fails to develop). Incompatible with life.
- Incomplete: **spina bifida** (lesion in spinal cord where cord failed to close completely).
- The next two slides illustrate these conditions. (WARNING: SLIDES ARE UNPLEASANT!)
Anencephaly
Spina Bifida
Cell Proliferation

- Immature neurons undergo replications that lead to a massive increase in the total number of potential neurons.
- By about 7 weeks, these neurons begin to migrate outward.
- A common method of cell migration is for an immature neuron to attach itself to a radial glial fiber.
- Neuron moves along radial glia fiber until it reaches its final destination point; it then detaches itself and comes to occupy a particular region of the cortex.
- 6 layers are eventually formed.
- Errors in this cycle of proliferation can result in disorders such as microcephaly ("small brain").
Cell Migration (Con’t)

- The cortex is formed in an “inside-out” pattern, meaning the inner most layer forms before subsequent layers (see next slide).

- Following the migration period, many radial glia are transformed into astrocytes (a type of glial cell that is involved in helping neurons function better), while others apparently disappear (die).
Figure 5. The generation of cortical neurons in an inside-first, outside-last gradient. The neurons born within the ventricular zone (vz) are destined for the deepest layers of the cortical plate (cp). Subsequently generated neurons migrate past the older cells, progressively forming the more superficial cortical layers. Evidence from cell lineage experiments indicate that clonally related neurons (darkened cells) can span several cortical layers, suggesting that precursor cells may often divide asymmetrically within the ventricular zone. Note that not all clones in lineage studies are clustered radially, as shown here. Abbreviations: mz, marginal zone (future layer 1); iz, intermediate zone.
Cell Migration (Con’t)

- Cell migration typically ends by the 25th prenatal week, a time when an increasing number of infants are now being born. Since cell differentiation has not yet begun, the brain at this age is typically “unconvoluted” (i.e., very few gyri and sulci) as the next slide illustrates.
The Preterm Brain
Beginning by day 20, three very primitive regions form, which are then expanded as cell migration continues. These regions are:

- The prosencephalon (forebrain)
- The mesencephalon (midbrain)
- The rhombencephalon (hindbrain)
At 5 weeks

- The prosencephalon divides into the telencephalon and diencephalon (e.g., hypothalamus, thalamus)
- The mesencephalon segments into the metencephalon and myelencephalon (midbrain and hindbrain)

In weeks 11-16 the telencephalon expands and differentiates to form
- The cerebral cortex, basal ganglia, corpus callosum, etc.

By approx 25 weeks, all 6 layers of the cortex are formed.
Errors of Cell Migration

- Microcephaly
- Schizophrenia
Axonal outgrowth and Synaptogenesis

- Once neurons have finished their migration they complete their maturation by forming axons and dendrites.
- The developing nervous system becomes more densely packed and the surface of the brain acquires convolutions (sulci and gyri) to accommodate the increasing mass (see next slide)
- Synaptic connections are formed and strengthened.
Apoptosis and Postnatal Neurogenesis

- Nearly 50% of all neurons die in a form of programmed cell death (*apoptosis*)
- Apoptosis also occurs naturally to those cells generated postnatally. For example, it is now known that in the dentate gyrus (region within hippocampus) in particular continue to be made anew through midlife.
Apoptosis and Postnatal Neurogenesis (Con’t)

- The number of new cells generated is influenced by experience.
- …but most such cells only last 2+ weeks before being retracted.
Postnatal Development

- **Formation of Axons and Dendrites**
  - During the first postnatal year, growth of dendritic trees and spines continues and can be seen in all 6 layers of cortex.
  - Formation of the appropriate axonal projections may be disturbed in a number of ways, such as early head trauma, anoxia, toxins, malnutrition, or genetic anomalies.
FIGURE 2.2 A typical neuron in the cerebral cortex. The soma gives rise to a single apical dendrite that branches, and many basal dendrites that emerge, near the base of the soma. A single branched axon with smooth contours is also observed. The jagged appearance of the dendrites is due to tiny protrusions termed "spines" where the synaptic apparatus is located. Adapted from Cajal.
Synaptogenesis

- The first synapses may occur as early as 23 weeks gestation, however, most develop postnatally, particularly in the first year of life.
  - In visual cortex, there is rapid burst of synapses 2 – 4 postnatal months, with peak of overproduction occurring 4 months.
  - Primary auditory cortex (Heschl’s gyrus) follows similar timetable.
  - In middle frontal gyrus maximum density is not reached until 12 months.
Synaptic Density

At Birth  6 Years Old  14 Years Old
A Synapse

A SYNAPSE

Bouton (Foot)

Receptor Sites

Dendrite of next Neuron

Vesicles

Axon

Mitochondria

Synaptic Cleft

Neurotransmitters

Source: http://www.ship.edu/~cboeree/theneuron.html
Synaptogenesis (Con’t)

- The initial overproduction of synapses in the cortex may be a functional property of the immature brain, allowing recovery and adaptation after focal injury or malformation as well as providing a mechanism by which the brain is made ready to receive specific input.

- **Synaptic Pruning**
  - Loss of synapses, in the absence of apoptosis, refers to changes in the density of synapses per neuron, possibly driven by changes in excitatory and inhibitory inputs.
Synaptogenesis Con’t

- The period of overproduction and pruning varies by area
  - In visual cortex, synapses reach their peak by the 4th to 5th prenatal month, but do not reach adult values till the 5th to 6th postnatal year
  - In frontal cortex, peak obtained about 1 postnatal year, but adult numbers of synapses not obtained until mid- to late adolescence (see next slide)
Myelination

- …refers to production of a fatty sheath that insulates axons and provides more rapid impulse conduction
- Leads to more rapid information transmission
- Facilitates serial and parallel processing throughout brain.
Myelination During Prenatal and Early Postnatal Period

- Prenatal: myelination of peripheral nervous system; motor roots followed by sensory roots, followed by somesthetic (touch) cortex, primary visual (seeing) and then primary auditory (hearing) cortex.

- First postnatal Year: regions of brain stem, cerebellum and splenium of corpus callosum all begin; by 1 year myelination of all regions of the corpus callosum underway
Frontal areas of the brain may, by some estimates, not reach adult levels until the third or fourth decade of life.

Is some evidence of continued myelination in hippocampus through mid-life.

Disruptions in this process can be due to many factors to include congenital hypothyroidism, undernutrition, and periventricular leucomalacia (by product of prematurity).
Myelination During Childhood to Adolescent Period

- Through pre-adolescent period, observe increase in gray matter volume (more dendritic spines?) and decrease in white; this reverses in adolescence, with decrease in gray and increase in white (retraction of synapses, increase in connectivity?).

- Changes of note: parietal, temporal, and occipital lobes show relatively little change, whereas dorsal, medial and lateral regions of frontal lobes show large changes.
Human Brain Development

Experience-dependent synapse formation

Neurogenesis in the Hippocampus

- Synaptogenesis (-3 months to 15-18 years?)
- Higher cognitive functions (Prefrontal cortex)
- Receptive language areas (Broca area)
- Auditory cortex
- Visual cortex
- Myelination (-2 Months to 5-10 years)

Birth

Months

Years

Decades
What about stress and adverse experiences? What do we know about the neurobiology of these events?

- Fear system: mapped out by neuroscientists
- Stress system: mapped out as well
The Fear Response

Visual Cortex

Visual Thalamus

Amygdala

Scientific American
How Genes Make Memories Stick

1. Stimulus
2. Activation of CREB
3. CREB Activates Gene

Dendrite
Axon
Synapse
Hypothetical synapse-to-nucleus signaling molecule
Gene
Nucleus
CREB活性化
Gene activation
Strengthening Proteins
Figure 6-11
Different Outputs of the Amygdala Control Different Conditioned Fear Responses.
HPA - STRESS PATHWAY
Emotional Stimulus

HPA Pathway Control

Amygdala

Hippocampus

Hypothalamus PVN

Cortisol

CRF

PIT

Adrenal Cortex

Cortisol

Emotional Stimulus

Hypothalamus PVN

Cortisol

CRF

PIT

Adrenal Cortex

Cortisol
Interaction of the Brain and Immune System

Hypothalamus

Pituitary Gland

CRF

ACTH

Cortisol

Adrenal Gland

Locus Ceruleus

CRF

Immune Cells

Immune Organs

Cytokines

Sympathetic Nervous System
Toxic Stress

Long and prolonged activation of the body’s stress management systems in the absence of buffering protection of adult support. Precipitants include extreme poverty, physical or emotional abuse, chronic neglect, severe maternal depression, substance abuse, or family violence. Disrupts brain architecture and leads to stress management systems that respond at relatively lower thresholds, thereby increasing the risk of stress-related physical and mental illness.
Adverse Childhood Events and Adult Depression
Adverse Childhood Events and Adult Ischemic Heart Disease
Adverse Childhood Events and Adult Substance Abuse

Self-Report: Alcoholism
Dube et al. 2002

Self-Report: Illicit Drug Use
Dube et al. 2005
Overall Summary

- Brain development begins within weeks of conception
- Most of the anatomy of the adult brain is present by birth (in full-term pregnancy)
- Physiology of adult brain laid down last trimester through first few postnatal years...however
- Adult neurophysiology (e.g., synapses, myelin) not established till mid to late adolescence (which correlates with behavioral development)
- Some recent evidence for changes in brain (e.g., birth of new neurons) through mid-life.
- Beyond mid-life???
The End