Chapter 9

Development of the Prefrontal Cortex

- **Four types of cognitive functions are linked to PFC:**
  - **Working memory:** keeping relevant info accessible for short periods of time
  - Planning and carrying out sequences of actions
  - Inhibiting responses that are inappropriate in the current context but not in others
  - Following rules for social behavior
- **Perseveration** (Piaget's studies): tendency to continue making a formerly correct response when it is currently incorrect (occurs between ages of 7-12 months)
- **Diamond:** perseverative error occurred because the neural circuitry of PFC is not fully developed
- Synaptogenesis in PFC is not maximal until early in the second year and correct performance of the task involved two of the major functions of this brain area: holding info in WM and suppressing previously correct but currently incorrect responses
- **Diamond exp**: adult monkeys with bilateral lesions to dorsolateral PFC made perseverative errors similarly made by infant monkeys; control monkeys with lesions to hippocampus or posterior parietal cortex did not make such errors

Effects of Experience on the Early Development, Maintenance, and Reorganization of Neural Circuits

- **Permissive experiences:** are necessary for information in genetic programs to be manifested
- **Instructive experiences**: contribute to direction of development
- Effect of experience on development depends on when it occurs during development
- **Critical period:** time which it is essential for an experience to occur to influence development
- **Sensitive period**: interval during which an experience has a great effect on development but can still have weak effects outside the interval
- Majority of experiential effects on development have sensitive periods
- If neural circuits, once formed are not used, they do not survive and function normally

Early Studies of Experience and Neurodevelopment: Deprivation and Enrichment

- **Sensory deprivation**: rats reared from birth in the dark had fewer synapses & dendritic spines in the primary visual cortexes & as adults had deficits in depth and pattern vision
- **Enrichment:** rats raised in enriched (complex) group cages rather than by themselves in barren cages had thicker cortexes with more dendritic spines and more synapses per neuron

Effects of Experience on Topographic Sensory Cortex Maps

- **Experiment 1:** altered developing axons of ferret's retinal ganglion cells, so that axons synapsed in the medial geniculate nucleus of auditory system instead of visual system; auditory cortex became organized retinotopically
- **Experiment 2:** raised barn owls with vision-displacing prisms over their eyes; led to corresponding change in auditory spatial map in the tectum
- **Study:** early music training influences the organization of human cortex; expands the area of auditory cortex that responds to complex musical tones

Experience Fine-tunes Neurodevelopment

- Long before NS is fully developed, neurons begin to fire spontaneously and interact with env.
- The resulting patterns of neural activity fine-tune subsequent stages of neurodevelopment

- Fine-tuning constitutes the critical, final phase of normal development
- It is now known that experience can influence gene expression and experience can alter any of the phases of development in innumerable ways by this one mechanism alone

Effects of Experience on the Reorganization of the Adult Cortex

- Experience in adulthood can lead to reorganization of sensory and motor cortical maps
- **Muhlnickel:Tinnitus**(ringing in ears): produces a major reorganization of primary auditory cortex
- **Elbert**: Adult musicians who play stringed instruments that are fingered with the left hand (violin) have an enlarged hand-representation area in their right somatosensory cortex
- **Rossini:** Anesthetizing 2nd and 4th fingers reduced their representation in contralateral somatosensory cortex
- Once the brain has adapted to abnormal environmental conditions, it acquires the ability to adapt more effectively if it encounters the same conditions again

LECTURE NOTES - OCT. 22

- Simplified description--what happens to neurns in embryo, cortex--form spinal cord in brain, how disorders come about? I.e. Spine ambifida, genetic disorders, environmental toxicity
- Major forms of developmental disorders→retardation
- How some of these things are relevent to degenerative disorders

How does the brain create neurons & connections?
How do problems arise?--malformations, problems in connections
How does this lead--psychoses & later on diseases
→badly formed brain? --genetic or environmental (toxicity)
Dev'mental disorders→retardation

From psychological standpoint—formation of brain & cortex →understanding psychological disorders
Muscles—physiological psychology

- First—embryo division→ form embryonic structure
- How environment & genetic dev't interact

Zygote:

- **Blastula** (ball of cells)/blastocyst = has central hole, within which (middle) a cluster of cells (embryonic stem cells—also dividing, can be taken out of blastocyst to start new set of embryonic stem cells)
  - Stem cells" —potentiality to become mature cells of anything
  - Can introduce DNA into stem cells—alter them
    - Rid "bad cells"
    - Knockout mice
      - → can be transgenic (extra copies of genes) mice, or mice with mutant genes (making non-functional genes→to study single gene function, causing bad

mutations in cells) to improve human/mouse condition or for pure sake of studying function by creating problems in mice cells)
        - Mutant/abnormal cells (dark cells)→inserted back into blastocyst—introduced to normal cells (transferred to pseudopregnant host)→breeded to make mutant/non-mutant mice, observe consequences
            - Chimeric mice—2 colours → then breeded to make whatever kind of mutant/non-mutant mice desired
            - Genetic technology = recombinant DNA + homologous recombination
            - Dev'd in last 20 years & now standard in all brain science
    - Once divides further, ball folds over + elongates → form gastrula (process called gastrulation)
        - Now have folded ball and longitudinal axis
        - Folds eventually form 3 major layers over next 1-2 weeks:
            - Ectoderm (outer), Mesoderm (middle), Endoderm (inner) *ref to textbook diagrams, Fig. 9.1**
            - Mesoderm—muscle cells
            - Endoderm—viscera

Ectoderm: Neural plate → spinal cord
- Folds over, forming groove
- Seals to form crest, central canal, neural tube (cylindrical ectoderm)
- At this point, cells are simply—daughter cells

Middle of ectoderm (tube) → brain and spinal cord (CNS)
*ALL HAPPENING PRE-NATAL
- neural groove forms
- neural tube forms (w/ventricles + CSF) where all spinal nerves begin
Undifferentiated stem cells→daughter cells→specialized cells

Embryonic neurons—weeks 2-4:
- midline of ectoderm → neural plate
- neural tube stem cells → neurons (eventually)
- Neuron dev't:
Proliferation→migration→differentiation→processes→synapses→axon growth
- Cell death (transitional cells)+ synaptic pruning (removal of connections)

Neural Tube:
- All start near walls of ventricle
- Cells duplicate → daughter cells → radial migration (outward)
- Tangential migration (cortex) —migrate outward first, then tangentially*
    - Duplication + migration
- Migration:
    - Later in dev't→special migrations→form major brain structures

- E.g. Pontene regoin →radial migration
  - Then 2nd migration→grow out and up →form huge lip (rhobic lip)—cerebellum
    - Special migration as it goes both up and over to form cerebellum
    - Dev't of rhombic lip, then cerebellum, then...
- **3 stages of cerebral cortical dev't:**
  - 1st —duplication cells around lateral ventricles
    - Form very special way
    - Radial migration away from lateral ventricles
    - Special assist--radial glial cells
  - 2nd —migration--median ganglionic eminence —migration from under ventricles, proliferation medial-ganglia
    - Start in underside of ventricles, around side of ventricles, tangentialy across cerebral cortical surface; start near wall, radiate outward, then sideways (tangentially across)
  - 3rd migration—rostral migratory pathway
    - Out from rostral (ventricles?) →Olfactory bulbs
    - Neurogenesis still occurs→GABA neurons in olfactory bulb

Cell migration--cerebral cortex (diff from cerebellar:

- By looking @ single neuron:
  - Somal translocation: (radial or tangential) migrating cell (NOT a neuron)
    - MOVES OUTWARD TO surface, NOT CENTER, of spinal cord
  - Glia-mediated migration (radial only)
    - Move up to cerebral cortex, controlled by lattice of radial glial cells
    - They form piles of cells (stack on top of each other) → then accumulate and form layers of cortex
    - Radial glial cells--establish where they will pile up (exactly)
      - Represent field of single radial glial cell (columnar organization of cortex)
      - After stacking occurs, they die off and disappear
- Starting cells—ventricular zone
  - Daughter cells moving away from this zone, climb through several mm to reach upper surface (cortical plate), then marginal zone
  - Later cells pile on top of previous cells (cheerleading pyramid style) →cortex
  - Deepest cells—big cells—big dendrites and big connections (earlier cells)
  - Later cells
  - Excitatory glutamate neurons** radial migratory cells
  - GABA neurons (inhibitory) AND olygodendrya and astrocytes (glial--discovered in last 5 years)**tangential
  - Just beginning to understand genetic & environmental cues that differentiate them

Migrating cells—superior colliculi (major visual area in lower animals--secatic eye movements--in tectum of midbrain):

- Frog test example:

- Colliculus triggers eye movement (precise 2D map of retinotopic field)
- If misdirect neurons from retina (grow into wrong place), frog will flick tongue in opposite direction
  - Retinal fibres growing in wrong direction (180 degrees)
  - When you rotate retina, axon still grows to retinal tectum →still thinks retina is organized → frog reacts in same way
  - Retinal axons know their way to area in tectum, even when retina is rotated →can find way "in mess of tissue in brain" → has chemical map to find way around superior colliculus
    - 2 Chemicals discovered responsible for this —ephrin-A, B
      - Determine L and R, Up and Down
      - Chemicals form 2D map of tectum
      - Specific chemical tissues→determine growth of axons in brain
      - One of BEST examples—how specific chemicals determine how axons determine where to grow

Turns out that growing axons --special way of growing
As migrate outward, has special structure--growth cone (extended process of growing cell). That extended process (somal translocation) looks like axon growth cone. As it moevs toward tissue, the structure at the tip has receptors and moves--as makes contact with chemicals, either moves toward/away from chemicals.

Cone is therefore a receptor zone—has "a little brain of its own"—chemical acceptor and repulsive functions→ moves by making contact with chemicals—e.g. Would grow toward/away fro ephrin-A,B.

Some chemicals influencing migration also influences growth —

genes→types of receptors→specialization based on receptors (for growth) when interacts with chemicals (somal translocation e.g.)

Pruning:
- Organization of synaptic contacts--reoganized by postsynaptic cell
  - More focused pattern of synaptic contact after synaptic pruning
- Excitatory connections b/w retinal and thalamus —vision
- Depriving neural activity→depriving excitations→loss of connections
- Activity dependent connections→more neural activity→more excitations→+ firings→more wirings (due to competition)→stronger connections

Adult Neurogenesis:
- Discovered ~30 years ago
- In particular, 2 places: olfactory bulb (rostral migratory stream) + inside dentate gyrus (hippocampus)
  - Still don't know all function, but specific functions influenced by hormonic factors in brain

- Constantly forming new synapses (synaptogenesis) whenever learning occurs, e.g.
  - By contrast, much less regeneration of axons—not in CNS
    - E.g. Spinal cord injuries permanent—new methods to overcome forming
  - If axons cut from PNS, regeneration will occur (new connections with muscle)—yes in PNS
- New big debate: why need to make new neurons from scratch?—Is slower, more resourcefully expensive.
  - Why not new synapses? New connections—new memories
  - Turns out—controlled by hormones
  - Sex hormones facilitate neurogenesis in 2 special areas
  - Therefore systemic hormones, stress, sex →neurogenesis
  - Sick kid's theory—clearing out old memories (to create new ones)
  - Only 10% of new neurons in dentate gyrus make it to maturity—affirms question of why they still occur

Retardation & Disorders—Environment:

- Many dev'tal disorders—fetuses don't survive
- 25% fetuses naturally aborted by 3rd month →many malformed fetuses in such a catastrophic way that it compromises baby's survival →nature's way of preventing malformation survival
- Ones that survive 3rd-4th month still very immature → therefore retardation is categorized in fully formed babies
  - Many issues = environmental problems
  - Mothers told to take care of body, nutritionally, to care for baby
  - Spina bifida → one of most common malformations → spinal cord tube incomplete & divided → split spinal cord → dietary issue* (environmental)
    - Discovered if you give rat mothers folic acid, problem resolved; when folic acid deficit, spina bifida occurs
  - Phenylketonuria—problem solved environmentally
    - Too many ketones (AAs) in urine—pheyl ketones
    - Lack enzyme to breakdown phenylalanine
    - Leads to pooor dev't in brain from lack of breakdown (accumulation* heavy)
    - 2 diagnoses: urine examination & gene examination (enzyme mutation in mother)
      - Regulate mother's phenylalanine dietary intake (nutritional solution) prevents PKU
  - Cerebral palsy—death of cerebral cortical cells—but babies remarkaly recover due to growth of new cells (new cortical areas), though they almost die at birth
    - Cerebral cortex involved b/c @ time of birth, cerebral cortex cells are ones that are still coming in (after all other cells)—dev'ping last--cortical cells
  - Role of toxins—poor brain dev't of brain, cortex
    - Lead, alcohol in fetus

Genetically Caused Retardation:

Down Syndrome:

- Trisomy 21
- Brain can't handle protein overloads
- Very small extra chromosome—effects aren't as lethal as others
- Presence of amyloid precursor protein—too much → Alzheimer's disease (early onset in 40's)

William's Syndrome:
- 7q- (deletion —50% reduction of a chromosome)
- 1/10 of chromosome 7
- Deletion of about 25-7 genes —tenth of q arm
- One of most interesting—odd combination of cognitive symptoms
- Poor spatial abilities, excellent social and verbal abilities
- Left hemisphere more influenced
- Higher oxytocin → more sociability? Vs. Autism (low sociability, low oxytocin receptors and epigenetic factors)

Cri du Chat (patients have high pitched voice—short vocal cords):
- 5p-
- Deletion 1/4 of chromosome 5

Autism:
- Undetermined genes
- Increasing in case number, but cause is still unclear
- Determined by more than genetic factors, associated with multiple genes
- Associated w/synaptic dev't
- Expression of genes—influenced by environmental factors (epigenetics)

Fragile X syndrome:
- X chromosome breakage
- Especially in boys* (girls have 2)

Adult Degenerative Disorders—genetic:
- Huntington's—one of best understood
  - Chromosome 4p (p-arm) → has series of CAG repeats → results in polyglutamine (multiple AAs)
  - Most of us have 20 repeats → if >40, Huntington's, if 100, more severe, if 200, early onset of Huntington's
  - Trinucleotide repeats (characteristic of many other diseases, like Fragile X)
    - Are now a whole new category of poly-AA diseases
- Parkinson's
  - Late onset death of substantia nigra neurons (dopamine neurons)
  - When 80-90% dies, disease caused
  - Death of mitochondria (oxidation problems—too much)
  - 90% environmental—toxins (pesticides)

- Other environmental factors unknown
- Most of us lose dopamine >80, thus many of us get Parkinson's in old age

- Alzheimer's—multiple genes (and proteins)
  - Also environmental + genetic
  - Early or late onset
    - Early = <60
    - Late onset (most common) >60
  - Beta amyloid fragments accumulate in extracellular space
    - Clusters of beta amyloid protein plaques → accumulation of neuron-killing amyloid plaques
    - Black clusters in extracellular space of cerebral cortex
    - When enough accumulate, synapses and cells die →degeneration
    - Inside cells:
      - Accumulation of Tau protein inside cell & produces tangles of neurofibres inside cell
    - Therefore can be caused by either/or/both (exact interaction unclear) of Tau or Beta amyloid proteins
      - "Tau-ists" v. "BAPtists" debate → which influenced more
    - Presenilins → also influence → in case, early onset (40s-50s) → chromosome 1 and 19 (?)
    - Apolipotropin eta-4 gene → susceptibility factor → determines when you will get it
      - No copies of gene → 85
      - 2 copies → 65
      - Every copy takes off 10 years of life
      - Metabolism and breakdown of amyloid
    - Susceptibility factor + environmental insult + interactive insult (behavioural)
      - WHOLE MYRIAD OF FREAKING FACTORS
- Multiple Sclerosis:
  - Loss of myelin (glial cells) —bio movie in grade 12