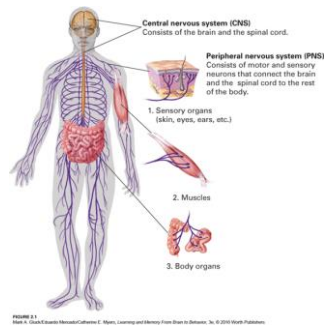
NEURAL BASES OF LEARNING AND MEMORY

Arlo Clark-Foos

You're Making Me Nervous….System

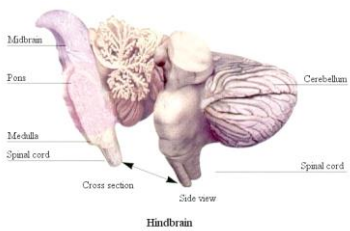
- Egyptian and Greek views of the brain

- Behavioral Research vs. Brain Research



Ye Olde Hindbrain

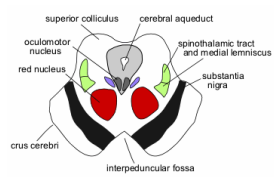
- Cerebellum, Pons, Medulla
  - Circulation, Respiration, Arousal/Sleep
  - Fine coordination of movement (e.g., eye blink from air puff)



Hindbrain

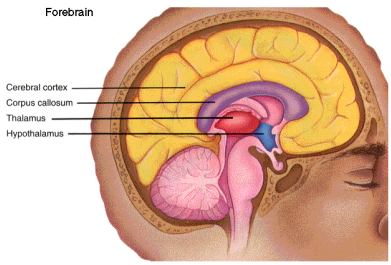
Midbrain

- Tectum, tegmentum…
  - Coordinating hearing/vision with movement
  - Orienting and reflexive behaviors (e.g., freezing)

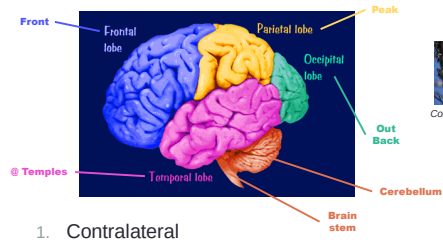


More Evolved Forebrain

- Thalamus, Hypothalamus, Pituitary Gland, Cerebral Cortex (Striatum, Hippocampus, Amygdala)



The Cerebral Cortex

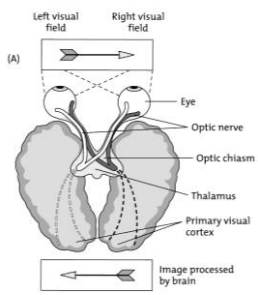


Cortex (Latin) means bark/rind

1. Contralateral
2. Distinctions among functions within hemispheres
3. Type of representation

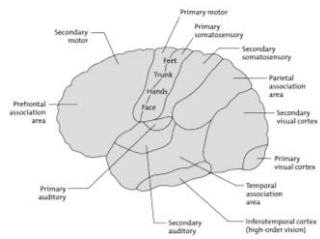
Cerebral Cortex

- Contralateral organization



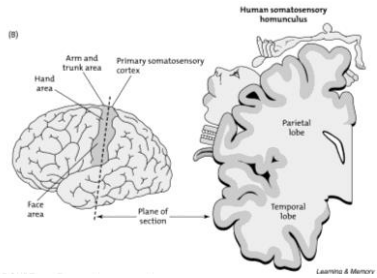
Cerebral Cortex

- Distinctions among functions within hemispheres
  - Primary, Secondary, and Association areas



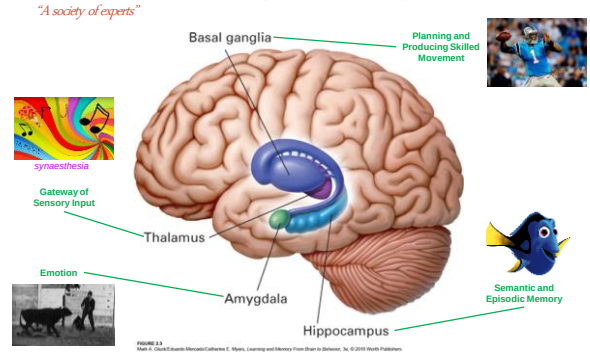
Cerebral Cortex

- Type of representation (e.g., topographic)
  - *More on this later. Yay, brains!*

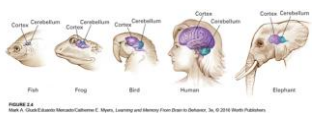


Below the Cortex (Subcortical)

"A society of experts"



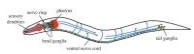
Comparative Neuroanatomy



- In a battle between the cerebellum and cortex, which determines Intelligence?
  - Frogs < Humans < Elephants?

- Vertebrates (CNS and PNS) vs. Invertebrates (PNS)

Octopus > 100 million



Nematode = 302

Human ≈ 100 billion

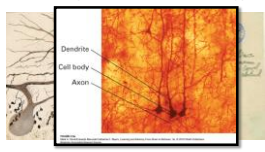
NEURONS

Neurobiology Primer

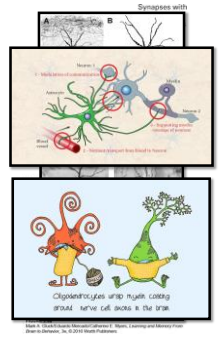
Cell → Neuron → Circuit → System

- Reticular Theory of Brain Circuitry: fixed wires
  - Santiago Ramón y Cajal and the imperfect *black reaction*
    - Identified functional components of neurons (axon, dendrite, cell body)
    - *Neuron Doctrine, directionality*
    - Cross-Species Comparisons

    - Nobel Prize with Golgi in 1906



Structure of a Neuron



New Vocabulary

Dendrites
- Receive Signals

Cell Body (Soma)
- Integrates signals, cellular metabolism

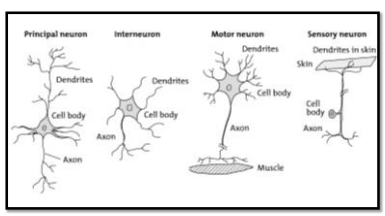
Axon(s)
- Transmits signals (neurotransmitters & vesicles)

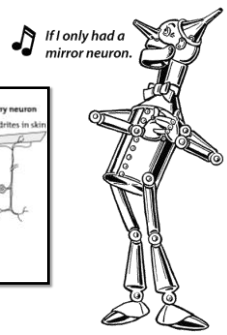
Pyramidal, Stellate, Interneurons
- Shapes and functions of neurons.

Astrocytes
- Nutrient & Oxygen Transport

Oligodendrocytes
- Fatty myelin sheath (*Multiple Sclerosis*)

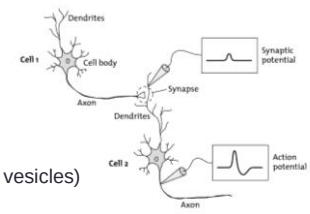
Different Flavors of Neuron (Ramón y Cajal)





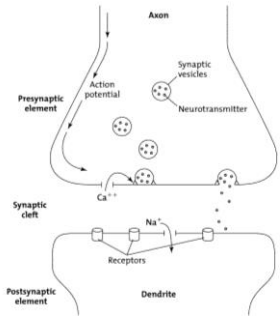
Neural Communication

- Synaptic Potentials
- Action Potential
- Neurotransmitters (and vesicles)
- Synapse/Synaptic Cleft



Neural Communication

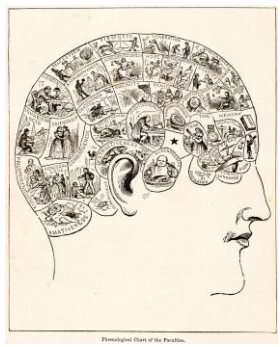
1. **Resting Potential** (~ -70mV)
2. Synaptic activity, Na+ flows into cell
3. **Action potential** (~ +40mV)
4. Ca++ flows in, binds vesicles to membrane
   - Neurotransmitter released:
     1. If neurotransmitter is *excitatory*, Na+ will flow into new cell. **Excitatory Postsynaptic Potential (EPSP)**
     2. If neurotransmitter is *inhibitory*, Cl- will flow into new cell. **Inhibitory Postsynaptic Potential (IPSP)**
5. Unbinding and recycling neurotransmitter



BRAIN STRUCTURE

Franz Joseph Gall (1758-1828)

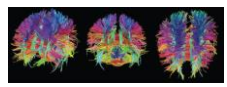
- Influenced by varying mental capacities
  - 27 different organs in the brain: Organology (phrenology)
  - *"destructiveness, carnivorous instinct, or tendency to murder"*



Structural Neuroimaging

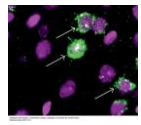
- Magnetic Resonance Imaging (MRI)
  - Density and Magnets
  - Slices

- Diffusion Tensor Imaging (DTI)
  - Type of MRI looking @ Water
  - Groups of Axons (White Matter)



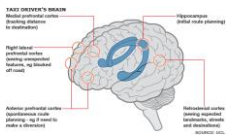
How does learning affect neurons?

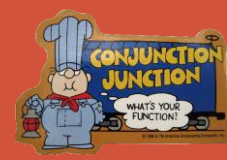
- Chemical staining (dyeing)



- Enriched environments
  - More and longer dendrites, more connections

- London Taxi Cab Drivers (Maguire et al, 2000) and Concert Violinists (Elber et al, 1995)?





FUNCTIONAL PROPERTIES

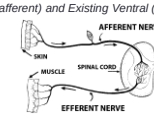
Are all behaviors learned?

- Reflexes
  - Newborns: Sucking, Diving, Palmar Grasp

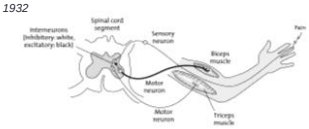
  - Adults: Knee-jerk, Eyeblink

Reflex Arcs

- *Bell-Magendie Law of Neural Specialization*
  (Bell, 1811, Magendie, 1822)
  - *Entering Dorsal (sensory/afferent) and Existing Ventral (motor/efferent)*



- *Reciprocal Innervation (Sherrington, 1906)*
  - *Nobel Prize in 1932*



Incoming Sensory and Outgoing Motor Pathways

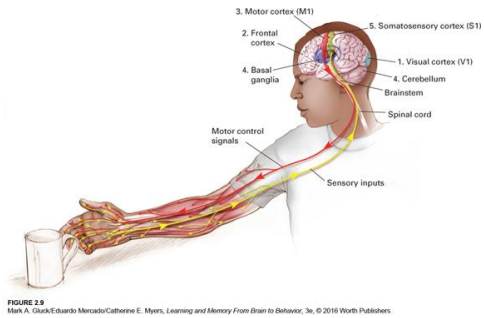
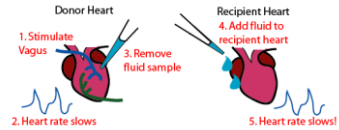


FIGURE 2.9
Mark A. Gluck/Eduardo Mercado/Catherine E. Myers, *Learning and Memory From Brain to Behavior, 3e*, © 2016 Worth Publishers

Otto Loewi (1873-1961)

- Nobel Prize in 1936 for discovering that chemical (as opposed to electrical) processes controlled neural communication.

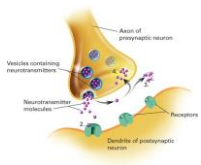


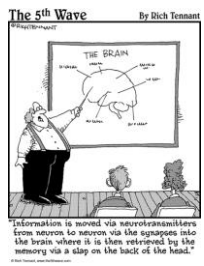
acetylcholine ↓

↑ noradrenaline

Electrochemical Control of Behavior

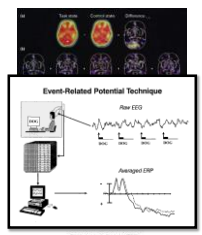
- Neurotransmitters
  - Refractory Period
  - Inactivation
  - Reputake

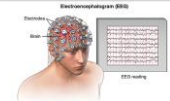




Functional Neuroimaging & EEG

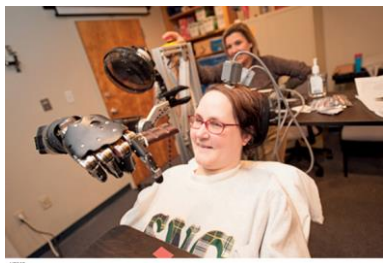
- Functional
  - Baseline & Difference Images
  - functional Magnetic Resonance Imaging (fMRI)
    - Oxygen (BOLD Signal)
    - New Image every few seconds
    - High Spatial, Moderate Temporal Precision
  - Positron Emission Tomography (PET)
    - Glucose & Positrons
    - New Image every few minutes
    - Moderate Spatial, Low Temporal Precision
  - Electroencephalography (EEG)
    - Constant recording of electrical changes
    - Event-related potential (ERP)
    - Low Spatial, High Temporal Precision





Recording Directly From Neurons

- Single-cell Recording
  - Spikes



UPMC

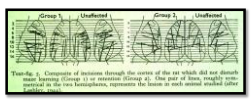
PLAYING WITH BRAINS

Neuropsychology

"new phrenology"

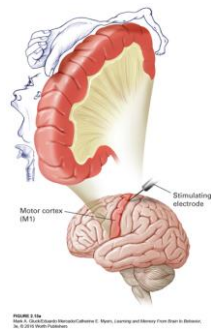
- Aliens, cars, and brains
- Brain Injuries (case studies) & Animal models

- Karl Lashley's search for engrams
  - Equipotentiality (Flourens, 1824) and the Percentage of our Brains we *actually* use
  - Learning "simply is not possible" (Lashley, 1929)
  - Are memories more cortical or subcortical?



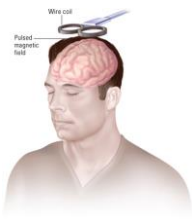
Homonculus, *little man*

- Pavlov's anesthetized dogs (1927)
  - Electrical stimulation
- Motor Cortex (M1)
  - Fine motor control requires more neurons for specialization
- Déjà vu and Virtual Reality Training
  - *Remembering by the Seat of your Pants*
- Violins and Deep Brain Stimulation
  - https://www.youtube.com/watch?v=T3QQOQAILZw
  - https://www.youtube.com/watch?v=M_fjiEOb40M

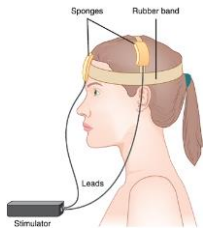


Transcranial Stimulation

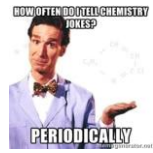
Transcranial Magnetic Stimulation (TMS)



Transcranial Direct-Current Stimulation (tDCS)

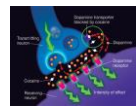


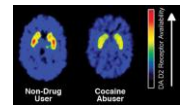
May improve memory disorders (e.g., Floel, 2014)



Better Living Through Chemistry

- Drugs
- Synaptic Transmission



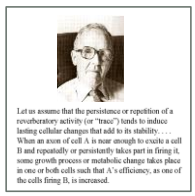


  - Presynaptic effects
    - e.g., Amphetamines and dopamine, MDMA and serotonin
  - Postsynaptic Receptors
    - e.g., Opiates mimic endogenous opiods (pleasure)
  - Inactivation and Reuptake
    - e.g., Selective serotonin reuptake inhibitors (SSRI; anti-depressants)
      Cocaine blocks reuptake of dopamine and norepinephrine

Ritalin, Adderall, Provigil?

Changing Neural Connections

- Synaptic Plasticity
  - Affecting Connections (Santiago Ramón y Cajal, William James)
  - Donald. O. Hebb, *neurons that fire together, wire together*

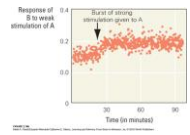


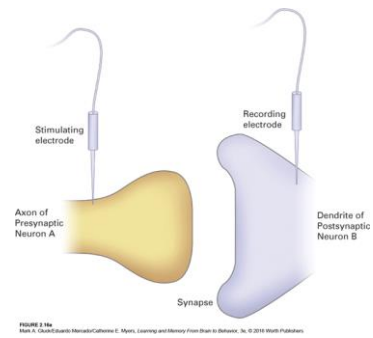
Let us assume that the persistance or repetition of a reverberatory activity (or "trace") tends to induce lasting cellular changes that add to its stability. . . . When an axon of cell A is near enough to excite a cell B and repeatedly or persistantly takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

- Distorted forms and Graceful degradation

Long-Term Potentiation and Depression

Terje Lømo
(Bliss & Lømo, 1973)

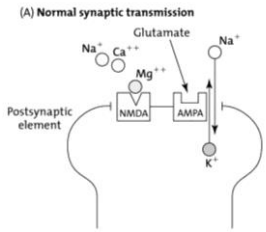




Changes can last hours

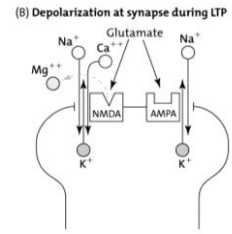
Molecular Basis for Associative LTP

1. Synaptic activity in hippocampus releases GLUTAMATE (excitatory) and Ca++
   - NMDA (blocked by Mg++)
   - AMPA (open)
2. AMPA allows in Na+
3. Excitatory Postsynaptic Potential (EPSP)



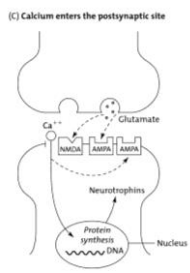
Molecular Basis for Associative LTP

4. Activation of postsynaptic dendrite releases Mg++ from NMDA receptors
5. Glutamate binds with NMDA receptor

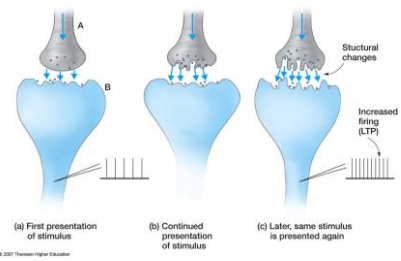


Molecular Basis for Associative LTP

6. NMDA pumps Ca++ into cell
   - Causes AP faster than Na+
7. Ca++ used to synthesize neurotrophins.
8. Neurotrophins affect synapse (more, larger, stronger connections)



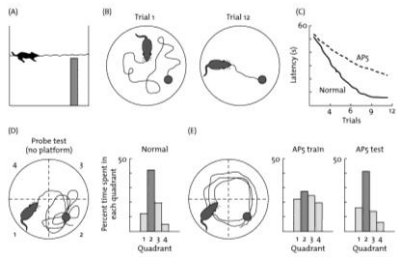
Another Graphic of LTP



https://www.youtube.com/watch?v=vso9jqfpl_c
https://www.youtube.com/watch?v=4d4zwhl3nO8

LTP and Memory

- Evidence from chemical antagonists (Steele & Morris, 1999)
  - e.g., AP5 selectively blocks NMDA receptors



How About Improving LTP?

- Joe Tsien (Tang et al., 1999) and colleagues bred mice with extra NMDA receptors. (Doogie mice)