DO NOT STUDY FROM THESE NOTES!
LECTURE MATERIAL CHANGES EACH SEMESTER!
TO THE STUDENT

About these notes:

These notes show a rough outline of the lectures and overheads used in this course. The point of distributing these is to unburden you from taking exhaustive notes during class; therefore allowing more concentration on the material presented in lecture. However, they do not replace attending class or taking supplementary notes of your own! Some of the material presented in class will not be in these notes and vice versa. These notes are meant to be used as a tool during lectures and not as a replacement for attending any lectures.

My recommendation is to make a hard copy of these notes and place them in a three ring binder. Then you can bring them to class and make your own notes on them in the margins and on the backs of pages. The notes are most effective if you read the pages relevant to an upcoming lecture in advance. This way, we will literally be on the same page, but you will also know what is already in the notes and what is not. Then, when a new term or concept is presented in class, you know whether or not to start writing.

About the lectures:

This course is heavily based on the lectures. I spend a considerable amount of time before each lecture editing out any material that you do not need to know. I will not waste your time presenting material, only to indicate later that you do not need to know it. Thus, every term and concept (except anecdotes) presented in lecture is considered equally important to me, and should be by you. When I make up exams and quizzes, I do so exclusively from the material of the lectures. I don’t even look at the text book. Here are some general pointers:

- Attend all the lectures. Of course I do not take attendance, but I have too often seen that material missed during lectures is also missed on exams. If you miss a lecture, try to get notes from a fellow student or come to my office hours to ask questions.

- Read relevant lecture notes and text material before lecture so you can focus more on the details and do not get overwhelmed by new terms and concepts.

- Many of the slides, especially in anatomy, necessarily have more information than you need to know. As a general rule, any detail that I point to or mention is something you want to know. During the section on Neuroanatomy, most of my slides are taken directly from the CIBA book. The correspondence between the slide number on the screen and the plate number in the CIBA book is provided in the lecture notes. Many students bring the CIBA book to class and make notes directly on the relevant figures during lecture so they can recall what was emphasized. A great idea. Don’t try to preserve your CIBA book for later resale. Plan to keep it for life. It looks smart on any coffee table.
- Please ask questions in class. The purpose of live education is that you get to talk back to me. Lectures should be a dialog, not a monolog. I love and cherish questions of any sort. If you ask a question, no matter how dumb it may seem to you, 10 other people in the room will silently applaud your effort. Questions not only clarify points right away so you don’t get lost, they also give me immediate feedback for pacing the lecture. If everyone is silent, I naturally assume you already understand the point, so I move on quickly.

About the reading:

The CIBA Collection of Medical Illustrations combined with The Principles of Neural Science make a perfect text for this course. These are first class books. Consider them as a virtual owners manuals for your brain. So if you plan on going on to graduate school or medical school, or plan to use your brain in any other way in the future, I would hang on to these books for reference.

There is enough material presented during class that I see no need to look for things in the assigned reading to test you on unless I also mention it in class.

There are three distinct uses of these texts:

1) Preparing for lecture - The syllabus provides chapters for general reading. The general reading should be done as we begin each new section to give you a coherent background. Reread relevant sections before each lecture so you can concentrate during lecture on new ideas not in the book, and on getting answers to questions aroused by the book.

2) Reviewing after lecture - If you forget to ask a question during lecture, the answer may well be in your book. If you can’t find it there, be sure to come to my office and get answers.

3) Expand your knowledge - Neuroscience is an enormous subject. These texts go well beyond the material in the course. As you get inspired by a given topic in class, the texts should provide more detail and a good launch point for finding out more from the literature.

About the course:

We can barely scratch the surface of the brain in this class. This course is designed to equip you with fundamentals of Neuroanatomy, Neurophysiology, and Sensory Systems. With this knowledge, you will be ready to go on to study other subjects related to Neuroscience at the graduate level. I have pitched the challenge of the course right at the border between undergraduate and graduate levels of expectation. I have continually found that undergraduate students appreciate and rise to this type of challenge. The subject matter we are about to cover is not conceptually difficult, there is
just a lot of it. I try to cover all the subjects with breadth and a good deal of depth. What surprises some students is that they are expected to know all of the details, not just a subset. Try not to be surprised in this way. Please expect this course to be 2-3 times as involved as many of the other courses you may have taken previously, even at the 4000 level. You can all perform at this level, but you may be learning new study skills at the same time as Neuroscience. I love dispensing endless advice about both if you come to my office hours. However, if you do not have the time to commit this kind of effort this semester, please drop this course immediately and postpone taking it till you have the extra time.

A final note about neuroscience research:

Beyond this course, if you are even vaguely thinking about going on to a Ph.D. program in Neuroscience or to medical school, I strongly recommend that you try to get extensive research experience in one of our neuroscience laboratories here at C.U. Actual research training is one of the most important educational tasks we accomplish here, and too few undergraduates avail themselves of the opportunity. This is probably because they don’t understand its importance both to assessing their own interests in the field and to enhancing their attractiveness to graduate and medical programs. It is probably also because there is no formal mechanism by which you can obtain research experience. I will be harping on this at greater length during class. But please come to my office to get advice on all aspects of getting research experience, and on graduate and medical programs and careers in general.

Enjoy this course and rise to the challenge!
TABLE OF CONTENTS

Methods of Studying the Brain ------------------------------------------ 1
Neuroanatomy ------------------------------------------------------ 4
Neurophysiology ---------------------------------------------------- 12
Visual System ------------------------------------------------------- 24
Auditory System ------------------------------------------------------ 34
Somatosensory and Motor Systems ------------------------------------- 39

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METHODS OF STUDYING THE BRAIN

-> The goal of behavioral neuroscience is to understand human behavior by performing physical measurements of brain function.
-> This goal is made possible by, and limited by, the tools and methods that we have at our disposal.

*(slide 1)*

One of the biggest problems facing the study of human brain function is the skull
- Protects brain from harm
- Shields brain from direct observation

A number of methods have been devised for studying brain structure and function. As we cover each of these, try to evaluate them according to the following properties:
- Noninvasive vs. Invasive
- Structure alone vs. Structure + Function
- Spatial (space) resolution
- Temporal (time) resolution (only applies to functional measures)

NONINVASIVE METHODS:

1. Phrenology *(slide 2)*
   - Perhaps the earliest noninvasive method
   - Basic belief: the brain is like a muscle, the bumps on outside of skull should reflect cognitive strengths
   - *(slide 3; CIBA, sec. I plate 3, page 5)*
   - Problem with theory: the inside of the skull is actually smooth, not the same as the outside of skull. However, phrenology concept of localized function was correct

2. CAT (also called “CT”) scan *(slide 4 and overhead)*
   - CAT scan = Computed Axial Tomography
   - Similar to X-ray except array of beams are directed through head at all angles
   - Detected by highly sensitive scintillation counters
   - 1mm planar slices reconstructed by computer showing hard and soft tissues
   - Little radiation actually used (although radiation can accumulate in brain with repeated use
   - Shows structure not function. (However, some functional information can be garnered from lesions and malformations)
   - Good (<1mm) spatial resolution

3. MRI *(slide 5)*
   - MRI = Magnetic Resonance Imaging
   - Subject placed in strong magnetic field to align polarized molecules (i.e. water)

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• Weak perpendicular magnetic field pulsed to cause resonance of aligned molecules
• Resonance frequency related to molecule
• Shows structure not function
• Excellent (10s of microns) spatial resolution (resolution gets better every year)

4. fMRI (slide 6)
• fMRI = Functional MRI
• Measures changes in blood oxygen due to local brain activity
• Allows function to be measured by a MRI
• Same excellent spatial resolution as MRI
• Lousy temporal resolution (many seconds to minutes)

5. PET scan (slides 7 and 8)
• PET = Positron Emission Tomography
• Injected or inhaled positron emitting isotope
• Isotopes bind to glucose taken up by active brain cells
• Break down of isotope produces positrons
• Collision of positron with electron = 2 gamma rays at 180 degrees
• Coincidence detectors permit precise localization
• Shows both structure and function
• Good spatial resolution (~ 3 mm)
• Bad temporal resolution (minutes of repeated stimulation)

6. EEG (slide 9)
• EEG = Electroencephalogram
• Not historically thought of as a imaging method
• Many electrodes pasted on the scalp serve to record electric potentials outside the head
• EEG produced by active brain cells (postsynaptic currents in dendrites)
• Computerized EEG maps may indicate focally active regions
• Shows both structure and function
• Excellent temporal resolution (< 1 ms)
• Fair - Poor spatial resolution (~ 1 cm)

7. MEG (slides 10 and 11)
• MEG = Magnetoencephalogram
• Measures magnetic field outside the head produced by active brain cells
• May be mapped with multichannel (100 - 200 channels) systems
• Computerized MEG maps may indicate focally active regions
• Shows both structure and function
• Excellent temporal resolution (< 1 ms)
• Excellent spatial resolution (~ 1 mm)
INVASIVE METHODS:
-> (slide 12) Skull nails not standard invasive recording method, but emphasize limitations of non-invasive techniques

1. ECoG (slide 13)
   - ECoG = Electrocorticography
   - Measurement of electrical potential on the surface of the brain
   - Metal electrodes put on surface of the brain (skull pulled back)
   - Method used when all other methods fail to help patient
   - Also may involve selective brain stimulation
   - Measures all activity at the brain surface, not in the depth
   - Measurements can be performed chronically
   - Shows both structure and function
   - Excellent temporal resolution (< 1 ms)
   - Excellent spatial resolution (~ 1 mm; governed by electrode size)

2. SEEG (slides 14 - 16)
   - SEEG = Stereotaxic Electroencephalography
   - Measurement of electrical potentials using fine wire electrodes implanted in the brain
   - Also may involve selective brain stimulation
   - Measurements can be performed chronically
   - Shows both structure and function
   - Excellent temporal resolution (< 1 ms)
   - Excellent spatial resolution (10 µm; governed by electrode size)

3. Analysis of brain trauma (overhead)
   - Relate structural damage to functional loss
   - “Experiments of nature” not very precise
   - Difficulty relating deficit to normal function

4. Histology
   - Macroscopic and microscopic study of brain anatomy postmortem or from biopsy

Staining techniques (slide 17):
   - Nissl stains: cell bodies
   - Myelin stains: cell processes
   - Shows structure only

Tracing techniques (slide 18):
   - HRP (Horse Radish Peroxidase): retrograde transport to cell bodies
   - Autoradiography: radioactive acid transport to cell terminals

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• And many more tracing methods too numerous to mention here
• Shows structure only

2DG (slide 19)
• 2DG = 2-deoxyglucose
• Accumulates in active cells
• Shows function and structure
• Excellent spatial resolution (10 µm)
• Lousy temporal resolution (many minutes of repeated trials)
ANATOMY

General directions in the nervous system (slide 20):
- The biggest confusion in terminology is due to the fact that the neuroaxis in bipeds is bent at a 90 degree angle
- To keep things clear, we will adopt two sets of terms, one for structures above the neck and the other for structures below the neck
- Be ready for all sorts of mixing of these terms in actual use
- (overheads)
- Below the neck = dorsal <-> ventral and rostral <-> caudal
- Above the neck = superior <-> inferior and anterior <-> posterior

Planes of sectioning the nervous system above the neck (slide 21):
- Horizontal = section parallel with a line connecting the eyes
- Sagittal = section cut (for example) down the center of the face separating one half of the face from the other half
- Coronal (also called “Frontal” or “Transverse”) = section cut (for example) from ear to ear separating face from the back of the head

Planes of sectioning the nervous system below the neck:
- Cross (also called “Transverse”) = perpendicular to long axis of the spine

Basic divisions of the Central Nervous System (CNS) (slide 22):
- Forebrain = Telencephalon + Diencephalon Telencephalon = cerebral cortex + limbic system + basal ganglia
- Diencephalon = thalamus + hypothalamus
- Midbrain = Mesencephalon
  - Mesencephalon = tectum + tegmentum
- Hindbrain = Metencephalon + Myelencephalon
  - Metencephalon = pons + cerebellum
  - Myelencephalon = medulla

TELENCEPHALON
Cerebral Cortex(slide 23; CIBA 3004 - sec. II plate 1, page 23)
- Brain appears as a folded balloon
- If inflated, would appear almost three time this size
- 1mm³ = 50K neurons = 6K syn/neuron = 300 mill synapses
- 1 hemisphere = 100,000 mm² = 10 billion cells = 60 trillion synapses
- Each cell is far more powerful than a PC

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• Computational capacity of the cortex is truly unimaginable
• Fortunately the brain is folded - act as anatomical landmarks
• Central Sulcus - divides the frontal and parietal lobes
• Lateral/Sylvian Sulcus - separates temporal lobe from frontal/parietal
• Parietal/Occipital Sulcus - divides occipital and parietal lobes
• Preoccipital notch - divides occipital and temporal lobes
• Note the four lobes and their basic functions
  1. Frontal Lobe
     ➢ Precentral Gyrus - just anterior to central sulcus (“motor strip”) = motor execution
     ➢ Anterior to this - secondary motor cortex = motor planning
     ➢ Anterior to this - prefrontal cortex = pretty much a functional grab bag
       - Frontal lobectomies produce mixed results
       - Appropriate social behavior?
       - Attention?
       - Working memory?
  2. Parietal Lobe
     ➢ Postcentral Gyrus - just posterior to central sulcus (“somatosensory strip”) = primary somatosensory cortex
     ➢ Posterior to this - “association cortex” = polysensory processing?
  3. Occipital Lobe - primary and secondary visual cortex
  4. Temporal Lobe
     ➢ Superior Temporal Gyrus - primary and secondary auditory cortex
     ➢ Middle and Inferior Temporal Gyrus - secondary visual cortex
     ➢ Hippocampus - short term memory
     ➢ And more later

(slide 24; CIBA 3005, sec.II plate 2, page 24)
• Good view here of medial surfaces of the hemispheres
• Note the Parietooccipital sulcus is quite evident
• Calcarine Sulcus - divides the upper and lower half of visual world
• Corpus callosum + anterior + posterior commissures - fiber paths linking the hemispheres on point for point basis
• Cingulate Gyrus - part of Limbic System
• Uncus - external landmark above the amygdala
• Also note:
  ➢ Thalamus (diencephalon) - major interface to cerebral cortex
  ➢ Hypothalamus (diencephalon) - neuroendocrine organ of CNS
  ➢ Cerebral Peduncles - descending motor output from cortex
  ➢ Pons (metencephalon) - lateral tracks to cerebellum
  ➢ Cerebellum (metencephalon) - motor coordination, timing
  ➢ Medulla (myelencephalon) - final interface to spinal cord

(slide 25; CIBA 3006, sec.II plate 2, page 25)
• Good view here of inferior surfaces of the hemispheres

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LECTURE MATERIAL CHANGES EACH SEMESTER!
• Cerebral Longitudinal Fissure - divides the hemispheres sagittally
• Mammillary Bodies - part of hypothalamus and Limbic System
• Genu and Splenium of the Corpus Callosum
• Rhinal Sulcus - defines border of Parahippocampal Gyrus
• Parahippocampal Gyrus - outer landmark covering hippocampus
• Note again the position of the Uncus

The deeper, less visible parts of the Telencephalon

The Rhinencephalon (“nose brain”) and Limbic System (slide 26; CIBA 3008, sec. II plate 5, page 27)
• “Rhinen” implies nose or olfactory cortex
• Phylogenically ancient parts of cortex originally thought to be exclusively involved in olfaction.
• You can understand why if you trace olfactory bulb to septal nuclei+ amygdala
• Rhinencephalon is now generally subsumed under the Limbic System
• The physiological basis of emotion is poorly understood, yet structures of Limbic System and connections are anatomically valid and may explain certain components of emotional experience
• Phenomena associated with Limbic structural connections (overhead)
  ➢ Interactions between smell and memory?
  ➢ Interactions between smell and emotion?
  ➢ Interactions between emotion and memory?
  ➢ Autonomic components of emotion?
  ➢ Interactions between emotion and cognition?
  ➢ Interactions between cognition and emotion?
  ➢ Persistence of strong emotion?
• Externally visible parts of the Limbic System
  ➢ Uncus (covering deeper amygdala) = smell
  ➢ Parahippocampal Gyrus (covering deeper Hippocampus) = smell
  ➢ Cingulate gyrus = influence of emotion on cognition?
• Deeper parts of the Limbic System (slide 27; CIBA 3009, sec. II plate 6, page 28)
  ➢ Amygdala = smell (connections to Hippocampus)
  ➢ Hippocampus = memory formation
  ➢ Fornix = connect Hippocampus to Mammillary Bodies
  ➢ Mammillary Bodies = part of hypothalamus (autonomic)
  ➢ Mammothalamic tract = connects mamms to ant. thal. nuc.
  ➢ Anterior Thalamic Nuclei = outputs to Cingulate Gyrus
• “Papez Loop” (connections are there, integrated function doubtful)
  ➢ Amygdala->Hippocampus->Fornix->MammillaryBods-> Ant. Thal. Nuc.->
  ➢ Cingulate->Cortex->Parahippocampal->Amygdala+Hippocampus->etc.

The Basal Ganglia (slide 28; CIBA 3007, sec. II plate 4, page 26)
• Comprised of the:
  ➢ Amygdala (also part of Limbic System)
  ➢ Caudate nucleus (head, body and tail)

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Lentiform nucleus
  Globus pallidus (medial)
  Putamen (lateral)
- Entire structure wraps around lateral to the thalamus
- Internal capsule
  - Separates the lentiform nucleus from thalamus
  - Carries major descending/ascending fibers from/to cortex
- Basal Ganglia play role in motor function

DIENCEPHALON (slide 29; CIBA 3148; sec. VIII plate 41, page 193)
Thalamus
- Major interface between the cerebral cortex and the outside world
- Consists principally of gray matter (cell bodies), therefore it has an integrative function as well as a relay function
- Thalamus receives more projections back from the cortex than it projects to the cortex (just “relay nuclei”? I don’t think so)
- Separated by white matter (Internal Medullary Lamina) into three groups of “relay nuclei”
  1. Lateral Nuclei
     - Pulvinar
       - temporal, parietal, occipital lobes (In)
       - temporal, parietal, occipital lobes (Out)
       - Function = sensory integration
     - Medial Geniculate Body MGB
       - acoustic pathway (In)
       - auditory cortex (Out)
       - Function = audition
     - Lateral Geniculate Body LGB
       - optic nerve (In)
       - visual cortex (Out)
       - Function = vision
     - Ventral Posterolateral VPL - somatosensory from below neck (In)
       - somatosensory strip (Out)
       - Function = somatosensation
     - Ventral Posteromedial VPM - somatosensory from above neck (In)
       - somatosensory strip (Out)
       - Function = somatosensation
     - Ventral Intermedial VI
       - cerebellum (In)
       - primary motor cortex (Out)
       - Function = motor
     - Ventral Lateral VL
       - cerebellum (In)
       - primary motor cortex (Out)
       - Function = motor
     - Ventral Anterior VA
       - globus pallidus (In)
       - premotor cortex (Out)
       - Function = motor
     - Lateral Dorsal LD
       - cingulate gyrus (In)
       - cingulate gyrus (Out)
       - Function = emotion

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LECTURE MATERIAL CHANGES EACH SEMESTER!
1. Lateral Posterior LP
   ➢ parietal lobe (In)
   ➢ parietal lobe (Out)
   Function = sensory integration

2. Anterior Nuclei
   ➢ mammillary bodies (In)
   ➢ cingulate gyrus (Out)
   Function = limbic

3. Medial Nuclei
   ➢ Medial Dorsal MD
     ➢ amygdala, hypothalamus (In)
     ➢ prefrontal cortex (Out)
     Function = limbic
     • There are also two groups of nuclei that have historically been considered to be
       “diffuse” or “non-specific”
   ➢ Midline & Intralaminar Nuclei
     ➢ reticular formation (In)
     ➢ cortical regions (Out)
     Function = modulate cortical excitability
   ➢ Reticular Nucleus
     ➢ all thalamic projection nuclei (In)
     ➢ all thalamic projection nuclei (Out)
     Function = modulate thalamocortical circuits
     • Note here, the distinction between “relay” or “specific” nuclei vs. “diffuse” or
       “non-specific” nuclei is out-dated.
     • Better to distinguish between “mediating” vs. “modulating”

Hypothalamus (slide 30, CIBA 3162, sec. VIII plate 55, page 207)
• Consists of a large number of nuclei for such a small area
• Presses definition of nuclei in that many are fiber tracks as well
• Direct influence on pituitary effects - neurosecretory role
• We will simply consider its functional distinctions on the medio-lateral and
  anterior-posterior axes for now
• (slide 31, CIBA 3169, sec. VIII plate 62, page 214)
  ➢ medial = satiety
  ➢ lateral = hunger
• (slide 32, CIBA 3171, sec. VIII plate 64, page 216)
  ➢ head ganglion of autonomic nervous system
  ➢ anterior = parasympathetic
  ➢ posterior = sympathetic

BRAIN STEM (slide 33, CIBA 3015, sec.II plate 12, page 34)
• Note in the posterior view MGN, LGN, Pineal Gland, Superior and Inferior
  Colliculi, Cerebellar Peduncles

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LECTURE MATERIAL CHANGES EACH SEMESTER!
• Note in anterior view Olfactory and Optic tracks, Mammillary Bodies, Cerebral (not Cerebellar) Peduncles, bulge and transverse fibers of the Pons, Pyramidal tract and point of decussion
• Note sections at Mesencephalon (A), Metencephalon (B), and Myelencephalon (C-E) and refer to next slide for internal component of each
• (slide 34, CIBA 3016, sec.II plate 13, page 35)

**MESENCEPHALON** (A)

• Tectum = superior + inferior colliculi (visual - auditory tracking)
• Tegmentum = periaqueductal grey matter (pain modulation), reticular activating system RAS (arousal), red nuclei (motor)
• Substantia Nigra (dopamine to basal ganglia)
• Cerebral Peduncles (descending motor fibers)

**METENCEPHALON** (B)

• Pons (“bridge”) = descending motor fibers interdigitated by transverse collaterals to cerebellum via cerebellar peduncles
• More reticular formation = nuclei controlling sleep, posture
• Note Cerebellum is part of metencephalon, but is cut off here

**MYELENCEPHALON** (C-E)

• Medulla Oblongata
• The pyramids and decussation (motor fibers)
• Olivary Nuclei (ascending auditory system)
• Cuneate and Gracile Nuclei = relay of somatosensory info to VPL
• Cuneate and Gracile Fasciculli = ascending somatosensory (“dorsal columns”)
• More reticular formation = vital reflexes, postural control

**Cerebellum** (slide 35, CIBA 3013, sec.II plate 10, page 32)

• Part of Metencephalon, but cut of in previous slide
• Will review anatomy and function of cerebellum later with motor system
• Note for now it is like a miniature cerebral cortex
• Miniature gyri called folia
• Deep nuclei mediate connections with rest of CNS

**Cranial Nerve Nuclei** (slide 36, CIBA 3066, sec.V plate 3, page 95)

• The rest of the Brain Stem contains relay nuclei for the Cranial Nerves
• No need to identify these nuclei specifically
• However, any neuroscientist needs to know their 12 cranial nerves by heart

**12 CRANIAL NERVES** (slide 37, CIBA 3064, sec. V plate 1, page 93)

• Note basic cranial structures again

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• Begin looking at the basic input and output tracks to the CNS
• Compared to spinal nerves, the 12 pairs of cranial nerves are highly differentiated in terms of function (except for #10 (vagus), it is concerned with afferent and efferent to head and neck)
• Function simply must be memorized
• 2 methods help memorization:
  • Anatomical order of emergence agrees with arrangement of innervation
  • Mnemonic = **On Old Olympus’ Towering Tops A Fin And Voluptuous German Viewed Some (Spinal Accessory?) Hopps**
• Mnemonic = nerve #8 = semicircular canals look like a figure 8
• Vagus similar to “vagabond”, i.e. travels all over
• Best mnemonic is simply to study the nerve numbers, names, and afferent as well as efferent functions in detail on CIBA page 93.....

**VENTRICULAR SYSTEM** *(slide 38, CIBA 3011, sec. II plate 8, page 30)*
• We have already viewed the ventricles as anatomical landmarks in the computer graphics
  - 1 & 2 = Lateral Ventricles (anterior, posterior, and inferior horns)
  - 3 = Third Ventricle (between the hemispheres of the thalamus)
  - 4 = Fourth Ventricle (just ventral to the cerebellum)
• Circulation of CSF *(slide 39, CIBA 3012, sec. II plate 9, page 31)*
  - Ventricles filled with a clear colorless liquid called cerebrospinal fluid CSF
  - 1/2 quart of CSF produced a day, turn over every 6-7 hours
  - CSF = protein, glucose, potassium, NaCl, and water
  - CSF manufactured in Choroid Plexus of all ventricles (Choroid Plexus selectively filters blood, thus part of the “blood/brain barrier”)
  - CSF circulates under hydraulic pressure through ventricles, central core of spinal cord, around the Meninges of the spinal cord and brain, and reenters the blood stream via the Arachnoid Granulations
  - Note: Meninges = Dura Matter, Arachnoid membrane, Subarachnoid space, and Pia Matter
  - Blockage of Cerebral Aquaduct causes hydrocephalus
  - Shunt installed from lateral to abdominal cavity prevents this
• Functions of ventricular system:
  - Mainly provides cushion for brain (buoyancy)
  - Provides needed space during brain swelling
  - Serves a nutritive function as well
  - Removes waste products from CNS

**SPINAL CORD** *(slide 40, CIBA 2994, sec. I plate 9, page 11)*
• Spinal column is to cord as skull is to brain
• Bony but flexible support for spinal cord
• Consists of 33 segments:

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Cervical = 7  
Thoracic = 12  
Lumbar = 5  
Sacral = 5  
Coccyx = 4  

- Most of these segments are associated with the emergence of spinal nerve trunks  
  
- Spinal cord is the downward continuation of the medulla  
- Approximately 46 cm long  
- Cervical and lumbar enlargement = increased processing load for upper and lower limbs  
- Nerves emerge between segments  
  
- Spinal cord similar to brain in that covered by meninges  
- Differs from cortex:  
  - Gray matter on the inside  
  - White matter on the outside  
- Cord is also a complex computer governing all reflexes of the body  
- Enormous amounts of computation performed in gray matter  
- General principal:  
  - Info enters the spinal cord (afferent) via the dorsal roots (cell bodies of afferent nerves are located in the dorsal root ganglia)  
  - Info exits the spinal cord (efferent) via ventral roots (cell bodies are located in the gray matter of the spinal cord)  
  - Afferent and efferent fibers merge to share the same spinal nerve and innervate the same body region

- Another view of spinal cord of person sectioned at thoracic level  
- Review: white & gray matter, dorsal & ventral roots, dorsal root ganglia  
- Note second set of ganglia ventrally:  
  - Sympathetic ganglia - relay station for sympathetic output fibers  
- Spinal Sections  
  - Total dorsal region is devoted to ascending somatosenses of the lower and upper limbs = dorsal columns = cuneate and gracile fasciculi  
  - Lateral regions of the middle cord also afferent  
  - Total ventral region = descending efferents  
  - Medial middle regions = main descending efferents  
  - Propriospinal fibers surround grey matter = interconnections between spinal segments  

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AUTONOMIC NERVOUS SYSTEM (slide 45, CIBA 3042, sec. IV plate 1, page 69)

- While much of the traffic in the spinal cord is associated with sensory-motor function, a large generally ignored fraction is also devoted to the autonomic nervous system (ANS)
- ANS = automatic, involuntary functions, vegetative functions
- ANS = rather boring
- Hypothalamus = head ganglion of the ANS
- (slide 46, CIBA 3043, sec. IV plate 1, page 70)
- ANS divided into the sympathetic and parasympathetic systems
- Anatomical basis for division:
  - parasympathetic = “craniosacral” division
  - sympathetic = “thoracolumbar” division
- Functional basis for division:
  - sympathetic = Catabolic = “fight or flight” = expenditure of energy. (i.e. blood flow to muscles, heart rate up, sweating, etc.)
  - parasympathetic = Anabolic = “rest and digest” = conservation of energy. (i.e. salivation, intestinal motility, digestive juices, etc.)
- Usually competing effects on the same organs (why?)
- ANS is not just efferent (slide 47, CIBA 3044, sec. IV plate 3, page 71)
- Now abundant evidence that it is equally afferent
- Sensation from visceral afferent is largely unconscious
- But also visceral pain, nausea, hunger
- Visceral pain may be referred to skin area supplied by somatic fibers of same segment. i.e. angina pain referred to upper back and back of arms
- As we will see in greater detail when studying motor system, most afferents in ANS form reflex chains for feedback control
- Feedback for control everywhere in nervous system (in this case, negative feedback)
- Negative feedback = stability, Positive feedback = instability
- Good segue to neural circuits and Neurophysiology Section
NEUROPHYSIOLOGY

(Overhead 1A, Possible complexities of neurophysiology)
While the function of the neocortex is no doubt quite complex, the study of Neurophysiology would be made nearly impossible if:

- The cytoarchetecture of each cortical area was grossly different
- There were millions of different cell types with different functions
- Cells were randomly distributed throughout all levels of the cortex

However, in fact, there are a number of simplifying features of cortical neurophysiology:

**Organization and function of cortical cell types**
- *(slide 48, coronal sections)*
  - Note directions, thalamus, cortex
  - Note grey (cell bodies = processing) vs. white matter (axons = interconnections)
  - Grey matter is not uniform, instead consists of distinct cellular layers
- *(slide 49, laminar sections)*
  - The distribution of cells in all cortical areas is quite similar forming 6 distinct layers
  - Vertical slices of rat cortex
  - Each slice approx. 1.5 mm tall
  - Stained for cell bodies or fiber connections
  - Layer 4 = granular layer, Layers 1-3 = supragranular layers, Layers 5-6 = infragranular layers
- *(slide 50, basic cell types comprising the cortical laminae)*
  - There are only a small variety of cells responsible for all info processing, these reside within and have distinct connections and functions within specific layers as follows:
  - Granular Layer (4)
    - middle cortical layer
    - contains basket and stellate cells (bodies look like grains of sand)
    - basket cells = lateral inhibition, “inhibit thy neighbor”
    - stellate cells = powerfully excite supragranular pyramidal cells
    - both receive direct input from thalamus
    - This is the INPUT layer of the cortex
  - Supragranular Layers (1-3)
    - upper cortical layers, nearest the surface
    - contains mainly small pyramidal cells (apical dendrites toward surface)
    - most cell bodies in layers 2-3
    - most connections in layer 1
    - input mainly from granular layer
    - output mainly to other supragranular cells and to infragranular layers
    - These are the LOCAL PROCESSING layers of the cortex
    - also major source of fibers connecting hemispheres through corpus callosum
  - Infragranular Layers (5-6)
    - deepest cortical layers, just before start of white matter

DO NOT STUDY FROM THESE NOTES!
LECTURE MATERIAL CHANGES EACH SEMESTER!
contains mainly fat cell bodies of infragranular pyramidal cells
apical dendrites extend to cortical surface
input mainly from supragranular pyramidal cells
output mainly subcortical structures (i.e. thalamus, brain stem, spinal cord)
These are the OUTPUT layers of the cortex
When a stimulus arrives from the thalamus, it triggers an archetypal excitatory/inhibitory response sequence in the cortex
fast (10-20 ms) excitatory cascade = stellate (4) -> pyramidal (1-3) -> pyramidal (5-6)
followed by inhibition = basket (~4) -> pyramidal (1-3 & 5-6)

• The layers, cell types, function, and response sequence described here is similar in all cortical areas! What a simplification that is.

Glial cells (slide 51, glial cells in the CNS)
• Before moving on to the function of pyramidal cells, we should mention glial cells:
  • They do not do information processing
  • There are 2 distinct type of glial cells shown here
  • Oligodendrocytes
    ➢ Primarily form myelin sheath for axons
    ➢ Equivalents in PNS are Schwann cells
  • Astrocytes
    ➢ Nutritive support
    ➢ Structural support
    ➢ Encapsulate synapses (neurotransmitter uptake, electrical isolation)
    ➢ Buffer extracellular K+ (membrane very permeable to K+)

Basic types of information processing cells (slide 52, polar cells)
• Unipolar, Bipolar, and Multipolar cells, major information processing cells in the CNS and PNS, have similar structures
• Dendrites = input and integration of electrical signaling
• Soma = metabolic support, and often integration of electrical signals from dendrites
• Axon = output via action potentials
• Unipolar cell
  ➢ Sensory input from peripheral receptors
  ➢ Little information processing, mainly signal transmission
• Bipolar cell
  ➢ Slightly more complicated than unipolar cells
  ➢ In plentiful supply in the retina of the eye
  ➢ Output decision determined at the soma
  ➢ More divergent dendrite and axon = more info processing
• Multipolar cells
  ➢ Kings of all information processing in CNS

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Highly ramified dendrites = much information processing
Left = motor neuron (spine), Right = Perkinje cell (cerebellum)
Will concentrate discussion on pyramidal cell in center

• The Pyramidal cell: Most Powerful Computer on Earth (overhead 1b)
  ➢ Highly ramified apical dendrites (they stick up towards surface of the cortex from dendritic tree)
  ➢ Surrounded radially by basilar dendrites (they stick out @ right angles from dendritic tree)
  ➢ Connection of apical and basilar dendrites give soma a pyramidal shape
  ➢ Pattern of dendrites reflects the layered architecture of neocortex (Contrast this to the spinal motor neuron and the Purkinje cell)
  ➢ Axon may extend for some distance and is usually highly ramified
  ➢ Receives input from 1000s of other cells
  ➢ Integrates information in 4 dimensions
  ➢ Information is combined with both excitatory and inhibitory influences uses numerous chemical tricks at synapse to enhance computation power

Axons versus Dendrites (slide 53, long axoned pyramidal cells)
• Emphasizes again the length axons can take compared to the dendritic tree
• Highlights the grossly different role of these structures
• Axons:
  ➢ Transmission of info undegraded over long distances
  ➢ Oligodendrocytes provide insulation to the axon in order to prevent cross talk between axons and prevent leakage (loss of signal over distance)
  ➢ Produce action potentials = Digital processing (see below)
• Dendrites:
  ➢ Combination (integration) of info over short distances from many sources
  ➢ No insulation on dendrites because the their sole purpose is to promote cross talk
  ➢ Conduct graded potentials = Analog processing (see below)

Digital versus Analog processing
(most important difference between axons and dendrites)
• Digital
  ➢ represent information as all or nothing impulses, as ONs and OFFs, as in the “bits” that represent information in a digital computer
  ➢ action potentials in axons are “digital” impulses
  ➢ good analogy = transmitting signals via telegraph
  ➢ strengths = simple signal, immune from noise (just detect if on or off)
  ➢ weaknesses = very inefficient way to store and compute information, because continuously varying (analog?) signals must be converted to digital impulses
• Analog
  ➢ represent information as graded signal, i.e. all voltage values are important, not just on or off
  ➢ graded post-synaptic potentials in dendrites are analog signals

DO NOT STUDY FROM THESE NOTES!
LECTURE MATERIAL CHANGES EACH SEMESTER!
good analogy = transmitting output of microphone through wire
a natural way to represent most biological signals which come in the form of continuously varying energy (i.e. sound wave, light levels, etc)
strengths = very efficient, dense packing of info, rapid processing (no need for digital conversion first)
weaknesses = susceptible to noise, unstable

• As we will see, dendrites are not simple electronic circuits although they operate on simple electronic principals.
• Let’s start with description of how axon works because it is somewhat simpler than dendrite

HOW DOES AN AXON WORK?
• First it should be understood that all parts of a nerve cell, not just the axon, are charged like a small battery ready to work
  • The cell as an electric battery (slide 54, two electrode experiment)
  • Single pyramidal cell sitting in water (salt water to be realistic)
  • One wire at great distance hooked to very sensitive electric meter
  • Other end of meter hooked to conducting glass capillary that can penetrate the cell
  • When both wires are sitting in extracellular fluid, meter registers 0 VDC
  • When electrode penetrates cell body (or other part) meter shows -60 mV
  • Thus cell is a battery - it shows a potential difference between inside and outside
  • Charge is used to perform work - i.e. computation and communication
  • Before we get to other experiments on this cell, lets look at how a battery is charged
  • The resting membrane potential

To understand even the resting membrane potential, we need an intro to electricity (overhead 6, Mr. Wizards Intro to Electricity)
• All electrical measurements reflect the separation of positive (cations) and negative (anions) charges in a conductive medium (i.e. saline)
• Opposite charges attract, therefore, charge separation requires energy
• Charge separation = Electrical Potential = Volts of stored charge
• Charge flow = Electrical current = Amperes of work returned
• Two forces, chemical and electrical, make charges want to get back together

(overhead 7, Why does a dead neuron not work?)
• Equal number of positive and negative charges inside and outside cell = no potential = no volts = no membrane potential = dead battery = dead neuron
• Note charges involved with cells are always Na+, K+, Cl-, and A- (negative anions)

(overhead 8, How can we recharge the neuron?)
• A Na-K pump removes 3 Na+ ions for every 2 K+ ions pumped into the cell

DO NOT STUDY FROM THESE NOTES!
LECTURE MATERIAL CHANGES EACH SEMESTER!
• = more + outside than inside = potential to do work = some volts = charged battery = healthy neuron
• millions of Na-K pumps all over all parts of neuron
• membrane potential established in all parts of neuron (not just axon)
• What happens if we keep pumping?

(overhead 9, What holds the potential to -70 mV?)
• the membrane leaks
• Electrical pressure = like charges repel etc.
• Chemical pressure = Like ions want to spread out evenly (i.e. move down their “concentration gradient”)
• Na and K will leak back across the membrane until each is in equilibrium (i.e. the chemical and electrical pressures on each ion balance).
• This balance for a given ion is called the equilibrium potential for that ion
• (overhead of Nernst Equation)
• The Nernst equation expresses this balance between electrical and chemical forces on a single ion that forms its equilibrium potential

NERNST EQUATION
Describes the potential necessary to balance a single ionic concentration gradient
Example: Take a cell that is totally and selectively permeable to potassium (K)

\[ E_k = (\frac{RT}{zF}) \ln (\frac{K_o}{K_i}) \]

\( E_k = \) membrane potential to balance K concentration gradient
\( R = \) gas constant (8.3144)
\( T = \) temperature
\( z = \) valence (+ or -) of ion, + for K
\( F = \) Faraday constant (# coulombs of charge carried by 1 mole of particular ion) 96485.0
\( \ln = \) natural log function (it’s on your calculator)
\( K_o = \) concentration of K outside the cell
\( K_i = \) concentration of K inside the cell

\((RT/zF) = 25 \text{ millivolts (mV)} \) if \( T = 17^\circ C \)

\( T \text{ in Kelvin} = 17 + 273.15 = 290.15 \)
\( RT = 8.3144 \times 290.15 = 2412.3 \)
\( zF = (+1) \times 96485.0 = 96845.0 \)

\( RT/zF = 2412.3/96845.0 = .025 \text{ Volts} = 25 \text{ mV} \)

**Note: the only variable here is temperature ... as temp rises so does chemical pressure
\( E_k = 25 \ln (\frac{K_o}{K_i}) \) \ or if you wish to work in base 10 log: \( E_k = 25 * 2.3 \log (\frac{K_o}{K_i}) \)

DO NOT STUDY FROM THESE NOTES!
LECTURE MATERIAL CHANGES EACH SEMESTER!
Example:
Ko = 10
Ki = 400

Ek = 58 log (10/400)
   = 58 log (.025)
   = 58 * -1. 6020
   = - 92.9 mV  ****equilibrium potential for potassium****

- Another way to think of the equilibrium potential for a given ion is as the potential you would have to make the inside of a cell to stop the ion from moving down its concentration gradient
- Depends on chemical and electrical forces on the ion
- (slide 55, driving forces)
- Na+ under both chemical and electrical pressure to enter cell
- Na+ under very strong driving force to get into cell
- K+ under chemical pressure to leave & electrical pressure to enter
- K+ under modest driving force to leave cell
- Cl- is at equilibrium when cell is at rest, because Cl- has no pump
- (Overhead 10, With all this leaking ...)
- The sum of equilibrium potentials for all ions (really Na and K), weighted by the permeability of the membrane to those ions in a given state, gives the true membrane potential
- This weighted sum can be computed directly from the Goldman Equation

**GOLDMAN EQUATION**
Describes the potential necessary to balance all ions of a nerve membrane

\[ V_m = \frac{58 \log \left( \frac{p_k K_0 + p_{Na} N_{a0} + p_{Cl} C_{li}}{p_k K_i + p_{Na} N_{ai} + p_{Cl} C_{lo}} \right)}{} \]

Application of Goldman equation to the giant squid axon resting potential
Ionic concentrations: Permeabilities:
Ko = 10  pk = 1.0
Ki = 400  pNa = .03
Nao = 460  pCl = 0.1
Nai = 50
Clo = 540
Cli = 40

DO NOT STUDY FROM THESE NOTES!
LECTURE MATERIAL CHANGES EACH SEMESTER!
Vm = membrane potential

Example:

\[
\begin{align*}
Vm &= 58 \log \frac{(1.0\times10 + .03\times460 + 0.1\times40)}{(1.0\times400 + .03\times50 + 0.1\times540)} \\
VM &= 58 \log \frac{(1.0 + 13.8 + 4.0)}{(400 + 1.5 + 54.0)} \\
\end{align*}
\]

- Vm = 58 log (27.8/455.5)
- Vm = 58 log .061031833
- Vm = 58 * -1.214443585
- Vm = -70.43772795 mV

If a cell were permeable only to K+, than its potential would be the same as Ek which is = -90 mV
If a cell were permeable only to Na+, than its potential would be the same as Ena which is = +55 mV
At rest, a cell is mainly but not completely permeable to K (a little permeable to Na)
So the resting membrane potential (Vrm) is about -70 mV (Ek pulled a little positive by influence of Ena)

Generation of the action potential (slide 54, two electrode experiment)

- Now, return to our simple one cell experiment
- We now introduce a new feature - a current injecting electrode
- Note in C that with pulses of inward current, corresponding hyperpolarization of cell
- “hyperpolarization” always means to make the inside of the cell more negative
- With pulses of outward current, corresponding depolarization of cell up to a point
- “depolarization” = inside of the cell more positive (less negative)
- depolarization is linear up to about a change of +10 mV
- Suddenly nonlinear response, as if there was a self sustaining opening of ion channels
- All-or-nothing response = action potential (AP) = nice digital signal for transmission over distances
- Clue here as to which channels have been opened based on +55 peak
- Suggests Na channels dominate this phase (rising phase) Ena=+55 mV

DO NOT STUDY FROM THESE NOTES!
LECTURE MATERIAL CHANGES EACH SEMESTER!
• The timing of conductances to different ions during the AP was investigated initially by altering ionic concentration of intra- and extracellular fluids, now can be done by specific channel blockers (TTX blocks Na, TEA blocks K)
• AP begins with opening of Na+ channels that are “voltage sensitive” (i.e. opened by depolarizing currents)
• Depolarization resulting from these channels opening causes more channels to open
• This positive feedback of the Na channels produces a fast rise time on AP
• At AP peak, Na+ channels closed by a) voltage sensitivity and b) molecular timer
• AP begins to repolarize due to Na+ channels closing
• But AP falls faster because K+ channels have been slowly opening (“delayed rectifier”), also voltage sensitive
• When conductance to Na+ = 0 (gNa = 0) but there is still conductance to K” (gK), the AP hyperpolarizes (hyperpolarizing overshoot)
• K+ channels close due to voltage sensitivity to repolarization (negative feedback)
• Even when all channels closed, takes a while for AP to return to rest because of a) slight speedup of Na-K pump, and b) cloud of extracellular K+ must disperse
• Sequence of channel openings define two important phases of the AP
  ➢ Absolute refractory period = first ms during which nothing will trigger new AP
  ➢ Relative refractory period = any time after that till cell recovers during which a new AP can be triggered but requiring much more depolarization
• Who cares? What is functional significance of these refractory periods?
• Absolute refractory period
  ➢ sets maximum frequency any cell can fire (~ 1 kHz)
  ➢ keep AP propagating “orthodromically” (from soma to end of axon) and not returning “antidromically” (from end of axon to soma)
• Relative refractory period
  ➢ permits frequency encoding = more depolarization produces faster train of AP
  ➢ frequency encoding is the principle way that analog signals are converted to digital in the nervous system

**Conduction of the Action Potential** *(slide 57, trigger zone)*

• Note that depolarizing potentials are graded in dendrites and soma
• Depolarization can trigger AP at “Axon Hillock” because of the presence of the aforementioned voltage sensitive Na+ and K+ channels
  *(slide 58, CIBA, sec VIII, plate 5, page 156)*
• AP then propagates toward axon terminals as a wavefront of depolarization followed by a wave of repolarization (refractory period)
  *(slide 59, CIBA, sec VIII, plate 6, page 157)*
• Propagation of AP in bare axon is slow and uses up more energy
• Myelin sheath with “Nodes of Ranvier” permit AP to passively conduct between nodes (passive conduction is nearly instantaneous), jumping from node to node (“saltatory conduction”), saving energy and greatly increasing conduction speed
• Decremental (passive) conduction between nodes sets inter-node distance with a “safety factor” to make dead sure new AP can be generated at next node
• (slide 60, CIBA, sec VIII, plate 7, page 158)
• The axon bouton (end of axon, presynaptic) and short end of axon leading to it are unmyelinated, but insulated by astrocytic glial cells
• Here, voltage sensitive Na+ channels are replaced by voltage sensitive Ca++ channels, which propagate the AP to terminus
• Equilibrium potential for Ca is ~+200 mV = tremendous driving force to get into cell
• That is because Ca++ is actively pumped completely out of cell with Ca++ pump
• Ca++ pumped out of cell because its presence intracellularly causes things to happen
• In the axon bouton, Ca++ causes synaptic vesicles (filled neurotransmitter) to migrate toward presynaptic surface, merge with this surface, and dump transmitter into cleft (“exocytosis”)
• We will save discussion of electrochemical events that occur in synaptic cleft till final lecture
• Suffice it say at this point that transmitters cause opening of chemically gated ion channels in postsynaptic target (usually dendrite) which produce brief “postsynaptic potentials” (PSPs) of a depolarizing (excitatory or EPSP) or hyperpolarizing (inhibitory or IPSP) nature
• We will move at this point to assess how PSPs are produced, conducted, and integrated in dendrites and soma, since this forms the basis of analog information processing in all cells

**Generation of PSPs in Dendrites (or Soma)** (slide 61, reversal potential experiment)
• Up till now, been regarding depolarizing and hyperpolarizing currents as artificial injection of current into cells
• It is critical to understand that actual PSPs are produced by chemically gated ion channels in the postsynaptic surface of dendrites and soma
• Chemically gated channel open up the possibility for ions to cross the membrane, however, unlike artificially injected currents, whether ions move through chemically gated channels, in what direction they move, and with what force, depends on the electrical state of the cell at the time
• This slide shows experimental setup to determine what chemically gated channels, permeable to what ions, generate IPSPs and EPSPs.
• Here, presynaptic axons can be stimulated to produce either event in the postsynaptic cell, and the cells membrane potential can be artificially manipulated, searching for the “reversal potential” of each event
• (slide 62, reversal potential of EPSP)
• Note here how EPSP gets larger if we hyperpolarize cell more than resting membrane potential (i.e. -100 mV)

**DO NOT STUDY FROM THESE NOTES!**
**LECTURE MATERIAL CHANGES EACH SEMESTER!**
• If EPSPs were simply due to chemically gated channels selective for Na+, than the “reversal potential” (potential at which same transmitter release has no postsynaptic effect) would be +55 mV (Ena)
• Any further depolarization would cause the EPSP to reverse polarity (i.e. Na+ would actually leave)
• However, reversal potential for a typical EPSP is actually near 0 mV
• This is because EPSPs are actually produced by channels that are permeable to both Na+ and K+, thus the reversal potential is somewhere between the equilibrium potentials for each
• Almost all actions that depolarize cells, whether chemically or mechanically gated, open up channels that are permeable to both Na+ and K+
• (slide 63, reversal potential of IPSP)
• Typical IPSP has a reversal potential right at the resting membrane potential, which also happens to be Ecl
• IPSPs are due mainly to channels selective for Cl- (but a class of IPSPs are also produced by channels selective for K+)
• Ecl = RMP because Cl- has no pump, Cl- must equalize its intra- and extracellular concentrations to be in equilibrium at the RMP
• Opening Cl- channels when cell at rest = “silent IPSP” because no electrical event can be observed
• This is also called a “shunting IPSP”, because a depolarizing event occurring during this time will be short circuited or shunted
• Cells are rarely at rest!

Temporal (time) and Spatial (space) Summation of PSPs: The Classic Picture

➢ (slide 64, CIBA, sec VIII, plate 8, page 159)
➢ Summary picture of ion channels responsible for EPSPs and IPSPs
➢ Note that duration of synaptic current is quite brief compared to the duration of potential
➢ This is because all membranes have a property called “capacitance”
➢ (slide 65, charging curve of a capacitor)
➢ If membranes had no capacitance, the time course of membrane potentials would exactly follow that of transmembrane currents
➢ A capacitor is like a little battery on the membrane that is formed by the accumulation of positive and negative charges along the inner and outer walls of the membrane
➢ Accumulation of charges takes time and stores energy
➢ When we try to change the membrane potential, the membrane capacitor steals our current first, to charge or discharge itself to a new level
➢ This slows down the potential change of the membrane, forming a charging curve shown here
➢ How much capacitance a membrane has is reflected in its “Time Constant”
➢ Time Constant = time (ms) it takes to charge to within 37% of a final value
➢ (Overhead of Dendritic Potentials)
➢ Time Constant = T = R*C

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LECTURE MATERIAL CHANGES EACH SEMESTER!
R = membrane resistance (how easily can current get into or out of capacitor)
C = capacitance (how much charge is stored up in the first place)

* (slide 66, temporal summation) *

Long time constant = more temporal smearing = more memory of PSPs over time = enhanced TEMPORAL SUMMATION
Long or short time constants are neither good or bad, depends on whether you want events to sum or not

* (slide 67, decremental conduction and the space constant) *
Unlike axons, electrical potentials in dendrites (PSPs) conduct from one place to the other in a decremental (graded) fashion, they are not regenerated like APs

Space Constant = distance (µm) a signal can travel down a dendrite (or any other cell structure) till it drops to within 37% of its original value

Space (Length) Constant = sqrt(rm/ra)
rm = membrane resistance
ra = axial resistance of intracellular fluid
PSP currents leak out of the dendrite (across rm) as they conduct down its length (across ra), which directly affects the length constant
Long Length Constant = signals go further, they have more distant impact on potential of cell, particularly at the axon hillock
Long Length Constant = enhanced SPATIAL SUMMATION

Half Truths about Dendrites (overhead)
- What has been presented so far is the classic picture of temporal and spatial summation in dendrites
- This picture is full of the following half truths:
  - “PSPs conduct passively toward the axon hillock”
    - essentially true, leading to concept of modulating vs. mediating synapses
    - but there are voltage sensitive Ca++ channels at junctions in dendrites that can produce a localized “Calcium Spike” in the dendritic tree
  - “PSPs sum algebraically (linearly) within dendritic tree”
    - Good first approximation
    - But PSPs effect driving forces on ions at synapses in other places, producing non-linear interactions (i.e. 2+2 = 3)
  - “The length and time constants of a dendrite are constant”
    - only true if the cell is at rest (i.e. only in petri dish)
    - increased synaptic activity = more ion channels open = less membrane resistance
    - less membrane resistance = shorter length constant (rm/ra lower)
    - less membrane resistance = shorter time constant (R * C lower)

BEWARE, THE FOLLOWING LECTURE IS USUALLY GIVEN BY THE T.A., THUS THE FOLLOWING LECTURE NOTES DO NOT APPLY. GET NOTES INSTEAD FROM THE T.A.

THE SYNAPSE

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In most cells there is a small gap (30-50 nm) between axon terminal and dendrite called the synapse (throughout we will refer to the presynaptic and postsynaptic membrane).

- The main function of synapses is COMMUNICATION
- Neurotransmitters are stored in small containers called vesicles
- An action potential is triggered if EPSP’s and IPSP’s sum over space and time to a threshold value at the axon hillock
- Saltatory conduction carries the action potential to the terminal bouton
- The terminal bouton is a specialized structure at which an electrical signal is converted into a chemical signal which is transmitted to the adjoining neuron
- When AP reaches the terminal, the vesicles release transmitters which cross the synapse and affect the postsynaptic neuron by opening ion channels.

In most cells, the synapse is bridged chemically, other cells are bridged physically:

**Electrical synapse** =
- “gap junction”
- direct fusion with pre and post-synaptic neurons
- communication through ion currents
- benefit: speed (quicker behavior)

**Chemical synapse** =
- “synaptic cleft”
- many neuron transmitters are released
- benefits: amplification of effect
  - more modification is allowed which = more adaptability

**NEUROTRANSMITTERS:**
Neurotransmitters are the substances that effect communication between neurons:

4 criteria to be a neurotransmitter:
- Has to be synthesized in the neuron
- Needs to be present in pre-synaptic bouton and released in an amount sufficient to cause a post-synaptic response
- There must be a drug that mimics the neurotransmitter
- Needs to be some type of mechanism to remove the transmitter from the synaptic cleft

**Transport of neurotransmitters through the axon**
- **Synthesis** - Neurotransmitter are usually synthesized in the soma, but they can also be synthesized in the vesicles. However, in order for biosynthesis to occur a precursor must be present (usually an enzyme found in diet)
- **Golgi apparatus** - Neurotransmitters are packaged in the vesicles here.
- **Axoplasmic transport** - The active process by which the vesicles containing neurotransmitters are moved from Golgi apparatus to the terminal
- **Terminal** - When action potential reaches the bouton, Ca ions activate the Ca sensitive channels in the terminal. Ca enters the bouton and causes the filaments holding the vesicles to release them. The vesicles now migrate to the end of the terminal.
- **Exocytosis** - The process of vesicles binding to the end of the terminal and releasing the neurotransmitters into the synaptic cleft
- **Active zones** - The location at the end of the terminal where the vesicles bind.
- **Auto Receptors** - Located at the active zone site, they regulate the amount of neurotransmitters released into synaptic cleft

3 methods or regulations of clearing the neurotransmitters out of synaptic cleft:
- **Enzymatic degradation** - enzymes deactivate remaining transmitters
- **Diffusion** - transmitters carried away by bloodstream
- **Endocytosis** - reuptake into the vesicles of the pre-synaptic neuron

2 types of receptors found on the post-synaptic neuron:
- **Direct receptor**: (a.k.a. lock & key) -
  - Spatially localized
  - Allows for only one response
  - Rapid and instant responses
- **Indirect receptor**: (a.k.a. second messenger)
  - Long response time
  - Slow build up/slow response
  - Wide spread effects
  - Allows for much variability because there are more “players” involved

**MAJOR NEUROTRANSMITTERS**:  
I. Acetylcholine (Ach)
  - First neurotransmitter ever discovered
  - Found in neuromuscular junction, sympathetic ganglion, autonomic target organs, thalamus, and cortical pyramidal cells
  - Principally has excitatory effect on Na channels (nicotine receptors at neuromuscular junction)
  - In CNS, may have excitatory effect on K channels (muscarine receptors)

II. Monoamines (usually a positive effect on sympathetic nervous system)
  A. Catecholamines
    1. Dopamine (DA)

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**LECTURE MATERIAL CHANGES EACH SEMESTER!**
• Found mainly in substantia nigra. Also found in retina and olfactory bulb
• Principally inhibitory effect via second messenger system
• Associated with Parkinson’s disease

2. Norepinephrine (NE)
• Found mainly in Locus coeruleus (projects to wide area of the brain)
• Principally inhibitory effect via second messenger and increase of membrane resistance

B. Indolamines
1. Serotonin (5-hydroxytryptaminie; 5-HT)
• Found mainly in the Raphe nucleus of the pons
• Principally inhibitory effect

III. Amino Acids
A. Glutamic Acid (glutamate) - excitatory effect only!
B. Gamma-aminobutyric Acid (GABA) - inhibitory effect only!
C. Glycine

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LECTURE MATERIAL CHANGES EACH SEMESTER!
VISUAL SYSTEM

The dominance of vision over other senses (the reason for starting with vision)

*slide 68, visiotactile experiment*

- Early theory that one learns how to see using correlation with touch
- Actually vision totally dominates perception.
- Seeing is believing. If there is any disparity between what you see and any other sense, vision wins every time.
- Orienting reflex is another sign that vision dominates our sensory world
- In many mammals, vision is truly the Cadillac of the senses
- We therefore begin applying our knowledge of Neuroanatomy and Neurophysiology to explore the sensory system of vision

**The eye as a camera (overhead)**

- Early thought regarded the eye as similar to standard photographic device
- There are several useful similarities between eye and camera:
  - Image focused by lens upside down and backwards on back plate (retina)
  - Back plate covered with black material (Choroid) to decrease light diffraction
  - Iris controls light level
  - Focus achieved by moving lens (F-B in camera, adjust thickness in eye)
  - * (slide 69, film grains)
  - Image recorded by discrete points at receptive surface
  - *(slide 70, photo receptors)*
  - Course grain film = high sensitivity = low acuity (rods)
  - Fine grain film = low sensitivity = high acuity (cones)
  - Note: The sensitivity of photoreceptors in the eye is remarkable. Light energy down to single photon can be registered by a single photoreceptor
- *(slide 71, frog + human retinogram)*
- Analogy to camera has been taken to the extreme by:
  - Franz Boll (1876, Rome) - rods contained red pigment called rhodopsin. It bleaches in light
  - Willy Kuhn (1876, Heidelberg) - made first retinogram with rabbits eye, fixed in alum. (Note: crime detective story that emerged from this work)
  - Willy annoyed by this: “I disregard all journalistic potentialities of this subject, and willingly surrender it in advance to all of the claims of fancy free coroners on both sides of the ocean, for it certainly is not pleasant to deal with a serious problem in such company.” Curiously, Willy went on to produce the first human retinogram from a beheaded man.

**The eye as a computer**

- Yet, the analogy to the eye as a camera ends abruptly as we examine the capacity of the receptive surface, the retina.
- Early thought was that the retina had the sole job of transmitting mosaic image of the world to the brain.
- *(slide 72, compound eye of the crab)*
• Even in the simplest animals, the retina represents a complex computer that transforms and analyzes incoming images in a way not possible with simple photographic film
• The eye is actually a very elegant computer transforming the visual world radically and strategically before transmitting the information to the CNS
• We begin examining these transformations with simple experiments performed on the crabs compound eye, useful because each photoreceptor can be optically isolated at the input and electrically isolated at the output for analysis
• (slide 73, frequency encoding by a single crab photoreceptor)
• First sign that computation is occurring is that light is transformed into a “frequency encoded” train of APs
  ➢ This is a nice shot because it shows both depolarization level and APs produced by light stimulus
  ➢ Frequency encoding is the fundamental way all neurons convert an analog signal (i.e. light level) into and digital signal (i.e. AP frequency)
  ➢ Note: response begins with burst of AP = time of stimulus onset, followed by an steady train of slower AP = stimulus intensity
• (slide 74, response to different light levels)
• More intense stimulus = higher frequency AP (as usual)
• Note again: always burst followed by steady train of AP
• (slide 75, flicker fusion at the crabs receptor)
• Second sign that computation is occurring is flicker fusion
  ➢ light flashing faster than about 30 Hz is seen as continuous light
  ➢ receptor throws out information about flicker because steady image more useful
  ➢ there are numerous examples of flicker fusion around us (i.e. T.V, indoor lights, cinema)
• (slide 76, lateral inhibition in the crab eye)
• Third sign that computation is occurring is contrast enhancement
  ➢ AP frequency of receptors A and B stimulated together is less than when they are stimulated separately
  ➢ This is because of axon collaterals between receptors that serve the purpose of “lateral inhibition” (inhibit thy neighbor policy seen throughout nervous system)
  ➢ (overhead of mechanisms behind lateral inhibition and contrast enhancement)
  ➢ Lateral inhibition enhances contrast in any parallel neural system. There is far more relevant information in edges than there is in overall illumination level.
• (slide 77, Kufflers on/off center cells)
• (experiments performed by Keffer Hartline in 1949, won Nobel Prize)
• A 1:1 ratio between receptors and outputs are rare (as in crab)
• Even the simplest visual systems have tremendous convergence
• Retina is less a film than it is a filter - It sends only the relevant information
• Relevance depends on species
• Processing is reserved for the cortex in most higher level species

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• Retina used primarily for contrast enhancement, but with a greater amount of spatial resolution than the crab
• **Receptive field of Ganglion cell**
  - The areas on retina (population of photoreceptors) where illumination causes excitation or inhibition
  - Receptive fields vary in size across the retina
  - Smallest in fovea = few minutes or arc = high resolution
  - Largest in periphery = 2-3 degrees = low resolution
  - In most mammals, receptive fields are as shown here, with an **annular** shape and an **antagonistic center-surround** configuration
  - The purpose of antagonistic center-surround is to simply enhance contrast before sending info into CNS
  - Some animals such as the frog, retinal processing is taken to extremes. (i.e. bug detectors)

**Advantages of high level retinal processing:**
- Efficiency - less information transmitted to cortex
- Speed - rapid processing in analog form directly at the receptors

**Disadvantages:**
- All processing done independently of the senses
- Difficult to evolve a more complex system
- Tends to be “hard-wired”, not adaptable (*slides 78-80, Sperry experiments*)

**The Mammalian Retina**
- Reasons for studying the retina in detail:
  - The mammalian retina is a truly powerful neural computer
  - Retina is the only part of the brain that is exposed to light
  - When you look into someone’s eyes, you literally look into their brain
- (*slide 81, ground squirrel retina*)
  - One of the most striking features of the retina = laminations
  - Note cell types in layers, which way light flows
  - It is remarkable how light can penetrate these layers to form precise images.
- (**CIBA 3127: sec VIII, plate 20**)
  - Note again, retinal layers on schematic and direction of light flow:
BIPOLAR CELLS  (Bipolar Layer)
ê

HORIZONTAL CELLS  (Outer Plexiform Layer)
ê

RODS AND CONES  (Photoreceptor Layer)
ê

Choroid

• Note in fovea, layers are pulled to the side to increase spatial resolution
• (overhead, retina layers)
• **Ganglionic Layer:**
  ➢ Ganglion cells
  ➢ Fat somas - because they are supporting many axons
  ➢ Axons face away from the amacrine cells
  ➢ An opportunity for convergence and divergence
  ➢ Final output stage to the CNS
• **Inner Plexiform Layer:**
  ➢ Amacrine cells
  ➢ Synaptic junctions between bipolar and ganglion cells
  ➢ Lateral inhibition takes place here (much center-surround antagonism)
  ➢ Another opportunity for convergence or divergence
  ➢ Maybe movement sensitivity also
• **Bipolar Layer (also called Inner Nuclear Layer):**
  ➢ Bipolar cells
  ➢ Another opportunity for convergence and divergence
  ➢ Integrate activity from a few (fovea) or many (extra-foveal) receptors
• **Outer Plexiform Layer:**
  ➢ Horizontal cells
  ➢ Synaptic junctions between bipolar and photoreceptors
  ➢ Dense lateral inhibition here (much center-surround antagonism)
  ➢ Another opportunity for convergence and divergence
  ➢ Horizontal cells essentially set up the receptive field of bipolar and ganglion cells
• **Photoreceptive Layer (also called Outer Nuclear Layer):**
  ➢ Rods and cones point away from the lens - buried in the choroid plexus
  ➢ Transform light to an electrical signal
• **Choroid Layer:**
  ➢ Absorb ambient light
  ➢ Collection area for waste products to be dumped
• Why are the photoreceptors located in the back of the retinal layers?
  ➢ high metabolism in photoreceptors
  ➢ high spatial resolution because they are in choroid plexus

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- evolution theory - more layers were simply added on top of the receptors
- Note also the presence of two kind of photoreceptors, rods and cones

**Rods vs. Cones** *(slide 83, shape of rod and cone)*
- Both rods and cones:
  - Have outer and inner segments + synaptic terminal
  - Outer segment connected to inner segment via cilium (contain microtubules)
  - Out segments contain stacked disks full of photopigments:
    - The disks eventually become detached from the membrane
    - Phagocytosis in epithelium (metabolism)
    - As many as 4 disks per hour
- Identification and function defined by shape
- Shape of rod = more surface area = more sensitive = less spatial resolution
- Shape of cone = less surface area (comes to point) = less sensitive = far more spatial resolution because of conical shape
- Rods prevalent in extrafoveal region of retina = peripheral vision = detect presence of object
- Rods sensitive only to light intensity not color = night vision
- Cones prevalent in foveal region of retina = foveal vision = foveate to figure out what an object is
- Cones sensitive to light intensity and color = day vision

**Summary of Functional Differences of Rods and Cones:** *(overhead)*

<table>
<thead>
<tr>
<th>RODS</th>
<th>CONES</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitive to illumination (high sensitivity)</td>
<td>sensitive to select colors</td>
</tr>
<tr>
<td>concentrated in periphery</td>
<td>concentrated in fovea</td>
</tr>
<tr>
<td>night vision</td>
<td>day vision</td>
</tr>
<tr>
<td>physically shaped like a rod</td>
<td>physically shaped like a cone</td>
</tr>
<tr>
<td>produce rhodopsin</td>
<td>produce cone opsin</td>
</tr>
<tr>
<td>low spatial acuity</td>
<td>high spatial acuity</td>
</tr>
<tr>
<td>larger receptive field</td>
<td>smaller receptive field</td>
</tr>
<tr>
<td>peripheral vision = detects objects</td>
<td>focused vision = concentrated on an object</td>
</tr>
<tr>
<td>high convergence on bipolar &amp; ganglion</td>
<td>low convergence on bipolar &amp; ganglion</td>
</tr>
</tbody>
</table>

**Phototransduction in the rod:** *(overhead 5, Phototransduction etc.)*
- Phototransduction is the same in both rods and cones
- Rods contain Rhodopsin whereas cones contain Cone opsin
- Rhodopsin = opsin + retinal (light absorbing molecule)
- Retinal takes 2 configurations:
  - **11-cis** = in the dark
  - **all trans** = in the light
- In the dark, Na+ channels in the outer segment are held open by a “second messenger” called cGMP
- Thus, in the dark, rods (and cones) are tonically depolarized = “dark currents”
- Light produces a cascade of chemical events, resulting in hyperpolarization

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retinal converted to all trans form
all - trans form activates G - protein
G-protein activates cGMP phosphodiesterase (hydrolyzes cGMP)
Since cGMP is hydrolyzes , and cGMP holds Na+ channels open, Na+ channels close
Inward Na+ current is reduced, thus hyperpolarizing the cell toward K+ equilibrium potential (-90 mV)

- Transmitter in both rods and cones is glutamate
- Transmitter release is graded depending on level of depolarization (more depolarized = more transmitter released)
- Therefore always, when the light comes on there is less glutamate released

**How to build antagonistic center-surround receptive fields**

- For some reason, this part of the lecture confuses many students
- The main reason is that retinal circuitry and function seems to violate many “Common Sense Notions About Neurophysiology” that we got stuck with somehow but are not completely true
- *(overhead, Common sense neurophysiology)*
- *(back to overhead 7, How to construct... etc)*
- Remember, the receptive fields of ganglion cells are always annular, with an antagonistic center-surround configuration
- *(slide 84, On center and Off center fields)*
- Half the ganglion cells have an “on-center” (light in the center excites it), and the other half have an “off-center” (light in the center inhibits it)
- Start by focusing on the simple circuit of a single photoreceptor and bipolar cell to construct the circuits necessary for either on or off centers *(slide 85, center circuits)*
  - In either circuit, when light shines on the photoreceptor, it hyperpolarizes and releases proportionately less glutamate as always
  - Important note: the effect of glutamate on the postsynaptic surface of the bipolar cell determines if the circuit is on or off center
  - If glutamate is normally excitatory, then light = less glutamate = less excitation = inhibition = OFF center response (open triangles)
  - If glutamate is normally inhibitory, then light = less glutamate = less inhibition = excitation = ON center response (filled triangles)
  - “As goes the bipolar cell, so goes the ganglion cell”, excite bipolar = excite ganglion, inhibit bipolar = inhibit ganglion
  - Note general principal: The effect of any neurotransmitter throughout the nervous system is determined by the response of the postsynaptic surface (dendrite, soma) not the type of transmitter
- Now focus on the simple circuit of two photoreceptors (one in the center and one in the surround) and a single horizontal cell connecting them to make the antagonistic surround *(slide 86, surround circuits)*

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When light shines on the photoreceptor in the surround, it hyperpolarizes and releases proportionately less glutamate as always.

- Glutamate is normally excitatory (open triangle) to the horizontal cell, so less of it = inhibit horizontal cell.
- Note that the horizontal cell targets the presynaptic photoreceptor in the center, not any bipolar cell.
- Glutamate released by horizontal cell is normally inhibitory to this center photoreceptor (dark triangle).
- Light on surround = inhibit horizontal cell = less glutamate on center photoreceptor = less inhibition on center photoreceptor = depolarize center photoreceptor.
- Thus, the antagonism is mediated completely by interactions between photoreceptors and horizontal cells.
- Shining light on the surround has, via horizontal cells, a depolarizing effect on photoreceptors in the center (the opposite of what light does to them which is to hyperpolarize).
- The receptive field of a given bipolar cell (and thus ganglion cell) is constructed by lateral connections between horizontal cells.

- These circuits are actually quite simple. What makes them seem complicated is that they violate some of our common sense notions of neurophysiology:
  - Receptor responds to light (stimulus) by hyperpolarizing.
  - Neurotransmitter release is graded not quantized.
  - Inhibitory or excitatory effect of neurotransmitter determined by postsynaptic surface, not by transmitter type.
  - Less inhibition = excitation, less excitation = inhibition.
  - All signaling in the retina except at the ganglion cells is carrier by graded potentials and graded transmitter release, not by APs.

- Review these circuits in detail to make sure you understand them.

**The output of the retina** (slide 87, CIBA 3128, sec VIII, plate 21, page 172)
- Axons of retinal ganglion cells form the optic track.
- The receptive fields of these ganglion cells both on-center and off-center.
- In mammals, there are two fundamental classes of ganglion cells, magnocellular (big soma) and parvocellular (small soma) that are anatomically distinct.
- Magnocellular pathway:
  - Receptive fields in extrafoveal (peripheral) vision = rods = night vision.
  - Cover 80% of the retinal area.
  - Fat soma because large input processes = converge info from many bipolar cells.
  - Large receptive field = high sensitivity - low acuity.
  - Show particular sensitivity to movement.
  - 20% of fibers in the optic tract are “M” fibers, corresponding to the magnocellular system.
  - Fat soma also because supports thick axon = fast conducting.

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subcortical projections to pretectum (pupillary reflexes) and superior colliculus (visual tracking), as well as LGN and cortex
- the job of the magnocellular system is to detect objects (particularly if they are moving) and bring foveal vision (parvocellular) on target for analysis

- Parvocellular pathway
  - receptive fields in foveal (central) vision = cones = day vision
  - cover 20% of the retinal area
  - small soma because small input processes = converge info from few bipolar cells
  - small receptive field = low sensitivity - high acuity
  - 80% of fibers in the optic tract are “P” fibers, corresponding to the parvocellular system
  - small soma also because supports thin axon = slow conducting
  - no subcortical projections
  - the job of the parvocellular system is to provide detailed analysis of an object

The Visual Pathway
- Before examining processing at different stages of the visual pathway, first get familiar with the gross features
- optic track travels from retina -> LGN -> occipital lobe
- retina maps on to the visual cortex in a straight forward way
  - left halves of both retinas project to the left hemisphere (therefore the nasal half of right retina must go through optic chiasm
  - right halves of both retinas project to the right hemisphere (therefore the nasal half of left retina must go through optic chiasm
  - bottom halves of both retinas project to bottom half (below calcarine sulcus) of visual cortex in both hemispheres
  - top halves of both retinas project to top half (above calcarine sulcus) of visual cortex in both hemispheres
- Note: however, the visual field maps on to the visual cortex upside down and reversed, as if it was projected through an optical lens
- That is because it is projected through an optical lens
- Don’t get confused by this, to figure out how a given quadrant of the visual field projects onto the cortex, determine first how it projects onto the retina. The rest is straight forward
- The last dimension of retinotopic mapping onto the visual cortex concerns foveal vs. extrafoveal vision
- Fovea = posterior and extrafoveal = anterior in visual cortex
- Note also “cortical magnification factor”, foveal representation in cortex takes up a majority of area due to the number of fibers devotes to it in optic track

The lateral geniculate nucleus (LGN) (slide 88, LGN proj)
- Thalamic “relay” nucleus to visual cortex
- consists of 6 layers (completely unrelated to the 6 layers of the cortex)

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layer 1-2 = ventral = magnocellular projections from contralateral (1) and ipsilateral (2) retinas
layers 3-6 = dorsal = parvocellular projections from contralateral (4,6) and ipsilateral (3,5) retinas
• Each of these layers has a nearly complete retinotopic map
• The retinotopic maps of each layer are in register with each other
• This arrangement, and the fact that the LGN is composed of a significant amount of grey matter, suggests that the LGN does a significant amount of processing
• However, the function of the LGN is poorly understood
  • very few known connections between the layers
  • relays visual information to visual cortex
  • first station where cortex can control (interact with) its own input (remember, as always, more corticothalamic fibers than thalamocortical fibers)
  • receptive fields of LGN cells annular on or off center, like retina, but some sharpening of contrast
  • (slide 89, interlamina of LGN)
  • recent evidence suggests fibers from reticular formation project in-between layers of LGN, may subserve selective attention to visual information

The visual cortex

• Thick layer 4 = named “striate” cortex (slide of coronal section of tree shrew)
  • Layer 4 = dark band called Band of Balliard
  • Massive input from LGN
  • Very dense layer
  • (slide 91, 2DG with one eye shut)
• As the ipsi- and contralateral retinas are segregated in the LGN, so are they in the visual cortex
  • close one eye and inject 2DG
  • staining in visual cortex shows vertically oriented columns of activated cells extending through grey matter
  • thus, there is a columnar organization to the visual cortex, with “ocular dominance columns” interdigitated between the two retinas
  • (slide 92, 2DG with orientation lines)
• Similar 2DG experiment conducted with both eyes open but staring at a screen filled with parallel lines of a given orientation
  • reveals a second dimension of columnar organization in visual cortex with “orientation specific columns”
  • (slide 93, schematic of hypercolumn)
• the arrangement of cortex into vertical columns of cells that share a similar function is a general principle called the “columnar organization of the cortex”
• This was first discovered by Vernon B. Mountcastle in somatosensory cortex
• Later adopted by Hubel and Weisel to explain their microelectrode findings
• They invented the concept of a “hypercolumn”
  ➢ found that only stimulus capable of exciting cells in cortex were little lines of
different orientation (receptive field of “simple cells” to be covered later)
  ➢ all cells in a column like lines of same orientation from same retina from same
area of retina
  ➢ hypercolumn = all processing required to assess lines of all orientation
(adjacent orientation columns) from both retinas (ocular dominance columns)
  ➢ the visual cortex is comprised of a retinotopic map of little hypercolumns
  ➢ shown here is a single hypercolumn processing one small area of the visual
field
  ➢ The hypercolumn has 3 functionally defined dimensions: 1) ocular dominance
columns, 2) orientation columns, and 3) the laminar dimension, which always
includes input (granular), processing (supragranular) and output
(infragranular) functions
• “Simple cells” discovered by Hubel and Weisel make up each orientation column
• (slide 94, simple cells)
• How do you get a simple cells in visual cortex with linear receptive fields, when
the only input is from LGN cells that have annular shaped receptive fields?
  ➢ strategic innervation of LGN cells to stellate cells in layer 4 that then
strategically converge onto to the dendrites of simple cells to form preference
for linear stimulation of retina
• How do you reconstruct a visual scene from little lines (simple cells)?
  ➢ Hubel & Wiesel proposed convergence of simple cells onto “complex cells”
and “hypercomplex cells” etc.
  ➢ this type of endless reductionism leads to concept of grandmother cell
hypothesis: i.e. that there must be subsequent cells in the processing hierarchy
with such advanced response properties that they only respond to your
grandmother.....
  ➢ There must be a more unifying idea of how the visual cortex works as a whole
to extract and represent features of the entire visual scene, not reducing into
little lines
  ➢ This has led to an understanding of how the visual cortex may encode visual
scenes in terms of spatial frequencies

Spatial frequency analysis
• To understand this, you must have a rudimentary understanding of “Fourier
Analysis” also called “Frequency Analysis”
• Principles of Fourier analysis:
  ➢ any shape of wave can be constructed from pure sine waves (overhead 11)
  ➢ visual scenes can consist of pure sine waves representing intensity variations
over space (overhead 12)
  ➢ slices of complex visual scenes can be represented by complex waveforms
indicating intensity variations over space (overhead 13)

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Then why can’t a complex visual scene be broken down into a recipe of pure spatial sine waves, i.e. by Fourier Analysis? It CAN... easily and elegantly

Most neurons in the primary visual cortex respond best to sine wave gratings at a particular frequency, orientation, and location in the visual field... more so than to straight lines

**Color Vision**
- up till now we have treated outputs from the parvocellular (foveal) system as though they are sensitive only light levels
- one of the main features of the parvocellular system is sensitivity to the hue (color) of light and not just its intensity
- to understand the biophysics of color vision, it is best to first examine the physical properties of light (*overhead 14*)
  - light travels through space as an oscillating waveform traveling at 669 million mph
  - the “wavelength” represents how far the light travels in one oscillation and depends on the color of the light
  - visible wavelengths range from about 350 nm (violet) to 700 nm (red)
  - wavelength = “hue” = pure color
  - “brightness” = the amplitude of the waveform
  - “saturation” = purity = how many other hues are mixed in
- to resolve the color of light, we have three different cone subclasses that contain cone opsins that is pigmented in such a way as to filter out all but a certain range of wavelengths
- It is like having cones with 3 different colors of sun glasses on
- (*overhead 19, response to various wavelengths*)
- this picture shows the absorption curve of the three cone systems, peaking at red, green, and blue
- Why settle for 3? Why not 1 or 2?
- This answer is provided by examining a simple figure-ground problem, where light intensity is ambiguous with actual color
- (*slide 95, single and double opponent fields*)
- Thus receptive fields of ganglion cells in the parvocellular system are annular on or off center in configuration, but instead of just comparing luminance levels in the center and surround, they compare colors
- In the retina (and in the LGN) the only two colors are contrast with each other. These fields are therefore called “single opponent” receptive fields
- The pairs of colors contrasted are always red vs. green, and yellow vs. blue
- Where does yellow come from, there is no yellow cone?
- (*overhead 20, connections between cones*) yellow is derived by mixing outputs of red and green cones at the bipolar cell input
- (*slide 96, ambiguity of single opponent fields*)
- although it seems unlikely, single opponent receptive field can still be tricked, still ambiguous for intensity vs. color if light dot isolated to center vs. surround

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• in the cerebral cortex, this ambiguity is resolved by converging the single opponent receptive field from the LGN onto pyramidal cell dendrites to form cells with “double opponent” receptive fields
• All of the double opponent color cells are located in yet another distinct columnar system within a given hypercolumn called the “pegs” or “blobs”
AUDITORY SYSTEM

• What is the advantage of auditory system over visual system?
  ➢ non-directional, orienting to stimulus
  ➢ preferred modality of communication

Physical properties of sound (slide 99, sound wave + overhead, auditory)

• similar to light, sound travels through the air as an oscillating waveform
• the waveform consists of alternating compressions and rarefactions of air
• the speed of sound is far slower than light, at about 1100 feet per sec
• “pitch” = frequency of the wave measured in Hz = tone
• frequency range of human hearing is 20 - 20,000 (20 k) Hz
• “loudness” = amplitude of wave, measured in “decibels” or db
  ➢ 0 db = 20 log (Pt/Pr)
  ➢ Pt - test pressure
  ➢ Pr - reference pressure (just audible at 3000 Hz)
  ➢ 20 db = Pt 10 times Pr
  ➢ 40 db = Pt 100 times Pr
  ➢ 60 db = Pt 1000 times Pr
  ➢ Human ear has “dynamic range” of 120 db 1- 1,000,000
• “timbre” = Complexity (or purity)
• Any complex sound wave may be constructed from pure sine waves
• Basis of Fourier Analysis (overhead 5, Fourier analysis again)
• The external auditory system has three processing jobs to perform:
  ➢ amplify sound waves in an adjustable fashion
  ➢ decode the frequency of complex sounds (Fourier analysis)
  ➢ transduce sound information to AP encoded signals
• We begin by examining the structure and function of the ear

Anatomy of the ear

• The ear can be coarsely divided into outer, middle, and inner compartments, each
  with very distinct structures and functions
• Outer ear:
  ➢ Pinna (also called the Auricle) + External auditory meatus
  ➢ acts as an inverted megaphone, with substantial gain (10-20 db) at 2-5 kHz
    (human speech)
• Middle ear:
  ➢ Air filled cavity
  ➢ Vented to outside via Eustachian tube
  ➢ Tympanic membrane (ear drum) interface to outer ear
  ➢ Ossicles = Malleus, Incus, and Stapes
  ➢ Oval window interface to inner ear
Because the inner ear is fluid filled, 97% of sound pressure would be reflected off oval window if it contacted it directly
Gain of 30 at 2-5 kHz (human speech again)
Achieved by 17:1 size difference between tympanic membrane and oval window, and by the lever action of the ossicles
(Note: conductive hearing loss = fusing of stirrup. There is still “bone conduction” in these patients)
*(slide 100, CIBA 3134, sec. VIII, plate 27, page 178)*
Note: the ossicles are connected to the “tensor tympani” and the “stapedius” muscles that provide adjustable gain. This is used to: a) protect inner ear from harm, b) increase “dynamic range” of exquisitely sensitive inner ear hair cells, c) preadjust volume level before speaking, and d) adjust for centripetal force produced by head rotation

- Inner ear: *(slide 101, CIBA 3132, sec. VIII, plate 25, page 176)*
- Cochlea consists of a long tube “membranous labyrinth” that is closely curled up in a “bony labyrinth”
- Stapes pushing in and out on the oval window cause a pressure wave in the fluids of the cochlea, traveling to its distal end and back, with the “round window” relieving the pressure on return
- The pressure wave travels all the way to the end of the cochlea and back because the cochlea is divided into three separate fluid filled compartments
  - Vestibular (Reisners) and Basilar membranes separate cochlea into 3 fluid filled compartments
  - These are called the scala vestibuli, scala media, and scala tympani, respectively
  - Sound waves travel up Scala Vestibuli and down Scala Tympani to round window
- Sound transduction takes place in the “Organ of Corti”, composed of the basilar membrane on the bottom and the tectoral membrane on the top, between which the actual transducers, the “stereocilia” are sandwiched
  - The Organ of Corti is completely within the scala media
  - Note: the scala tympani and scala vestibuli are filled with a fluid called “perilymph”, which is very similar to normal extracellular fluid, whereas the scala media is filled with “endolymph” which is abnormally high in K+. This relates to the function of stereocilia as we will see later

**Organ of Corti** *(slide 102, EM of stereocilia)*
- Consists of 4 rows of hair cells (stereocilia), with their bases in the basilar membrane and their tips making contact with the overlying tectoral membrane
- The “inner hair cells” consist of a row of 3400 cells closest to the inner axis of the spiraled membranous labyrinth.
- Sound waves in the cochlear fluids cause the basilar membrane to move up and down, which causes the tectoral membrane to shear back and forth across the inner hair cells
- Inner hair cells are the actual transducers of sound in the Organ of Corti

**DO NOT STUDY FROM THESE NOTES!**
LECTURE MATERIAL CHANGES EACH SEMESTER!
• the “outer hair cells” consist of 12,000 stereocilia arranged in 3 rows outermost to the inner axis of the spiraled membranous labyrinth.
• outer hair cells actually are connected to the tectoral membrane, and act as little muscles capable of pumping the membrane up and down to amplify its mechanical response to sound
• Only 5% of afferent fibers connect to outer cells
• Outer hair cells may serve as mechanical amplifier of vibrations in basilar membrane
• Hair has actin filaments that serve as small muscles
• Unclear if feedback is local or from brain stem
• Normal ear emits sound!
• In tinnitus, emitted sound may get loud

**Receptor potentials**
*(overhead)*

• when stereocilia are bent by tectoral membrane, it mechanically open channels in the hair cells that are permeable to K+
• this causes a “receptor potential” that is depolarizing because K+ enters the cell
• K+ enters the cell when permitted because extracellular fluid (endolymph) is abnormally rich in K+
• slight depolarizations producing by K+ are amplified by electrically activated Ca++ channels (remember Ca++ always rushes in under enormous force when allowed)
• repolarization of the cell occurs in the base where a separate set of Ca++ activated K+ channels are opened
• K+ wants to leave at the base when allowed, because the base is surrounded in normal extracellular fluid (perilymph)
• *(slide 103, AP frequency following under 300 Hz)*
• At low frequencies (<300 Hz), receptor potentials are linearly related to sound waves
• action potentials can remain time-locked to receptor potentials at these low frequencies
• this led to the earliest theory of neural encoding of sound called the “frequency theory” (do not confuse with “frequency analysis” to be discussed momentarily)
• frequency theory = frequency of APs directly related to frequency of sound = true for frequencies < 300 Hz
• *(slide 104, DC fusing of receptor potentials)*
• however, at frequencies > 300 Hz, receptor potentials cannot follow sound waves and fuse together instead into a tonic depolarization of the cell for the duration of the stimulus
• a given stereocilia has a preferred frequency of sound to which it fires the maximum number of action potentials, but the action potential frequency itself does not follow the sound frequency, instead it reflects the intensity of sound at the preferred sound frequency for that cell

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• *(slide 105, preferred frequencies of different stereocilia)*
  • the preferred sound frequencies of stereocilia changes systematically as we
    measure from cells at different places along the length of the basilar membrane
  • this fact is the basis for the “place theory” of how the Organ of Corti performs
    frequency analysis of incoming sounds
• *(slide 106, resonance properties of the basilar membrane)*
  • so the first trick employed by the place theory is that the basilar membrane is
    tuned like a series of piano strings such that place proximal to the oval window
    like to resonate to high frequencies, and places distal to the window resonate at
    low frequencies
  • but this response, in an in vitro cochlea shown here, is not sufficiently precise to
    explain the remarkable ability we have at two tone discrimination (i.e. can
    discriminate sounds differing by as little as a single Hz)
  • the second trick employed by the place theory is that the outer hair cells
    sympathetically pump the membrane (remember they are little muscles) at
    different places when they get activated, amplifying the effect of passive
    resonance
  • this improves frequency discrimination, but still not enough
  • the third trick employed by the place theory is that the stereocilia themselves are
    designed like selectively tuned tuning forks, being short and stiff in the high
    frequency (proximal) region and long and floppy in the low frequency (distal)
    places on the basilar membrane
  • this improves frequency discrimination, but still not enough
  • the fourth trick employed by the place theory is that the stereocilia are
    “electrically tuned” to preferentially respond to different frequencies. The
    depolarization - repolarization cycle that we mentioned earlier is faster or slower
    in fast or slow stereocilia, respectively
  • see overhead for a summary of mechanisms behind the “Frequency Theory” and
    “Place Theory” of encoding pure frequencies

**The Auditory Pathway**
*(slide 107, CIBA 3133, sec. VIII, plate 26, page 177)*
• that auditory pathway proceeds through a number of brain stem nuclei on the way
  to the cortex
• Three main features to note:
  > Tonotopicity is maintained all the way to the cortex
  > must pass through subcortical nuclei before reaching cortex
  > Unlike other sensory systems, there is bilateral representation of both ears in
    both hemispheres
  > the mixing of both ears occurs in all subcortical nuclei except the first
  > why the big interest in info from both ears?

**Cochlear nuclei**
• Only areas to receive monaural information
• Prevalence of inhibition produced in these cells
• Some enhancement center-surround antagonism in 2 tone experiment

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• May enhance response to frequency change in particular direction (i.e. asymmetrical surround)

**Superior Olives (sound location)**
- Receives input from both ears
- **Lateral Nuclei**
  - excited by *intensity* differences between ears
  - localization based on “head shadowing”
  - useful for frequencies above 1000 Hz
- **Medial Nuclei**
  - excited by *timing* differences between ears
  - localization based on “phase”
  - useful for frequencies below 1000 Hz

**Inferior Colliculus (changing location)**
- Receives input from both ears
- Concerned with *changes* in the differences between ears (movement of sound localization)
- Interacts with superior colliculi in tracking moving sound source

**Medial Geniculates**
- Main way station to cerebral cortex (feedback from cortex)
- Maybe some sharpening of center-surround antagonism
- selective attention?
- polymodal responses

**Auditory Cortex (localizing complex auditory stimuli in contralateral auditory space)**
- Organized as primary (pure auditory) and secondary (polymodal) cortex
- Primary is tonotopically organized low=lateral high=medial
- Orthogonal to this = binaural interaction columns = auditory space
- If we progressively lesion areas of the ascending auditory system from the cortex down, and assess remaining function, we find:
  - Frequency discrimination: just need up to colliculi
  - Intensity discrimination: just need up to the olives
  - Complex localization: need all the way up to cortex

**Sound Localization**
- There are 2 complementary methods for localizing sounds, both relying on comparisons between the two ears
- “Phase differences”
  - relies on the difference in the phase of a sound wave as it travels from one ear to the next
  - this only works for low frequency (< 1000 Hz) sounds where the wavelength is longer than the width of the head
- “Head shadowing”

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Ø relies on the difference in amplitude of sound between the two ears, produced by one side of the head absorbing sound
Ø best for higher frequencies (> 1000 Hz)
SENSORY-MOTOR SYSTEM (SOMATOSENSORY AND MOTOR SYSTEM)

First, a general note about the motor system:
It is incorrect to view the somatosensory and motor systems as separate. They interact intimately at all levels of the neuroaxis. For this reason, we will cover them in parallel from the spinal level to the cortex, sometimes concentrating more on somatosensory, sometimes more on motor, but always attempting to connect them where appropriate.

Control of movement is hierarchical
- There are no such things as “simple” spinal reflexes
  - Note residual function of headless rooster *(overhead of Mike)*
  - Note residual function of spinal cat *(overhead, the spinal cat walks on)*
- The spinal cord is actually a quite complex neural computer *(overhead, spinal cord as neural computer)*
  - gray matter is a significant fraction of the CNS
  - much of the white matter is concerned with local connections
  - nearly all motor acts are executed by your spinal cord, with only descending guidance from higher centers
- *(slide 108, hierarchical components of motor system)*
- The motor system starts at level of spinal reflexes
- But, it can be modulated by:
  - Brain stem nuclei
  - Motor cortex
  - Premotor and Supplementary motor cortex
- While, hierarchy exists, there are also parallel routes from top to bottom
- Higher centers (in the brain) maintain veto rights over lower centers (in the body)
- 3 main reasons for hierarchy
  - Response speed
  - Downloading of processing
  - Evolutionary advances
- At every level of this hierarchy, there is feedback between afferent and efferent. You can see this at the spinal level in the spinal reflexes. But, this pattern is continued all the way to the cerebral cortex.

Systems of somatosensation *(overhead, somatosensory)*
- Exteroceptive systems = skin sensations
- Proprioceptive systems = position of body segments
- Interoceptive systems = internal body events (i.e. blood pressure, glucose, etc.)

Exteroceptive afferents
- Major functions of skin sensations:
  - self awareness
  - exploration of the environment

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- survival = reflexes
- essential feedback to motor system

• Major varieties of skin sensations:
  - Fast mechanical (vibration or “roughness”)
  - Slow mechanical (pressure or flutter)
  - Temperature
  - Pain (mechanical, thermal, chemical)

• The somatosensory system is unique in that each of these “sub-modalities” of skin sensation are transduced by dedicated receptor types
  - fast adapting mechanoreceptors = fast mechanical (vibration or “roughness”)
  - slowly adapting mechanoreceptors = slow mechanical (pressure or flutter)
  - thermoreceptors = temperature
  - nociceptors = pain

• (slide 109, CIBA 3120, sec. VIII, plate 13, page 164)
• first note that the type and distribution of cutaneous receptors differs between “glabrous” and “hairy” skin

- Glabrous skin:
  - fast adapting mechanoreceptors = Miessner’s corpuscles (superficial), Pacinian corpuscles (deep)
  - slowly adapting mechanoreceptors = Merkel’s disks (superficial), Ruffini terminals (deep)
  - thermoreceptors = separate hot vs. cold
  - nociceptors = free nerve endings (all polymodal)

- Hairy skin:
  - fast adapting mechanoreceptors = Pacinian corpuscles (deep)
  - slowly adapting mechanoreceptors = Hair follicle receptors (superficial), Ruffini terminals (deep)
  - thermoreceptors = separate hot vs. cold
  - nociceptors = free nerve endings (all polymodal)

• The receptive fields of cutaneous receptors are simple
  - no antagonistic center-surround (i.e. no peripheral processing)
  - the size of the receptive field is determined partly by the “innervation ratio”, but mainly by depth below the skin (slide 110, receptive fields)

• The mechanism of signal transduction in mechanoreceptors (we will not consider the others) is also quite simple (slide 111, CIBA 3121, sec VIII, plate 14, page 165)
  - simple transducer consists of membrane that opens channels to both Na+ and K+ when bent by mechanical stimulus
  - this alone would be slowly adapting in that it would remain depolarized (constant “generator potential”) for the duration of the pressure
  - to turn this into a rapidly adapting mechanoreceptor (i.e. Pacinian or Meissners corpuscle), simply add lamella which permit end of transducer to straighten back out again
• The slowly adapting mechanoreceptor provides an example of the three methods by which somatosensory information is encoded for further processing by the CNS (slide 112, receptor potentials and APs)
  ➢ FREQUENCY ENCODING = Increasing stimulus intensity = greater depolarization = higher frequency of action potentials. But cells peak out in their firing rate, so....
  ➢ POPULATION ENCODING = Increasing stimulus also usually leads to more fibers responding (number of axons involved)
  ➢ LABELED LINE ENCODING = Encoding of stimulus quality (fast or slow mechanical, temperature, pain) depends on what receptor type a given axon is attached to

**Proprioceptive afferents**

• Major functions of proprioception:
  ➢ feedback to motor system about the “static” length of muscles (how long they are right now)
  ➢ feedback to motor system about the “dynamic” length of muscles (how fast the length is changing) Why is this important?
  ➢ feedback to the motor system about the force applied to muscles
  ➢ information about fast and slow mechanical, temperature and pain from muscles and joints

• Muscle and joint receptors (slide 113, CIBA 3141, sec. VIII, plate 34, page 185)
• Here we see a dissected bicep muscle with major afferents and efferents highlighted
• As in somatosensory system
  ➢ Paciniform receptors = fast adapting response = pressure and vibration
  ➢ Free nerve endings = pain

• We also have 3 receptors in joint:
  ➢ Golgi type = joint tendon stretch
  ➢ Paciniform = joint movement
  ➢ Free nerve ending = joint pain

• Golgi Tendon Organ (GTO)
  ➢ uniquely responsive to muscle force
  ➢ high threshold GTO only fires with damaging force = shut the activity down
  ➢ low threshold GTO fires with slight changes in force = accurate force feedback for delicate grasping

• **Muscle spindles**
• spindles deserve special attention because their function is somewhat more complex and more elegant than what we have considered so far
• Note first difference between extrafusal and intrafusal muscle fibers:
  ➢ Extrafusal muscle fibers - concerned with actual work, innervated by alpha motor neurons
  ➢ Intrafusal muscle fibers - are what spindle are made of, do no heavy lifting, adjust length of spindle (therefore sensitivity), innervated by gamma motor neurons

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• Muscle spindles are actually composed of 2 types of intrafusal muscle fibers
  • “Nuclear chain” muscle fibers:
    ➢ Innervated mainly by “flower spray” type II afferent receptors
    ➢ slowly adapt to stretch
    ➢ thus, type II afferents = static muscle length
  • “Nuclear bag” muscle fibers:
    ➢ Innervated mainly by “annulospiral” type Ia afferent receptors
    ➢ rapidly adapt to stretch
    ➢ thus, type Ia afferents = dynamic muscle length
• While muscle spindles are afferent organs, they are made of intrafusal muscle fibers for two reasons:
  ➢ (slide 114, CIBA 3142, sec. VIII, plate 35, page 186)
  ➢ keep spindle from losing response during muscle contraction
  ➢ keep spindle tuned up for maximum sensitivity over a wide range of muscle lengths (wide dynamic range)
• Whenever we contract the extrafusal muscle fibers (via alpha motor neurons) we “co-contract” the intrafusal muscle fibers (via gamma motor neurons)

**The ascending somatosensory pathways**

• (slide 115, peripheral nerve)
• their is a single pair of peripheral nerves for each segment of the spine
• each peripheral nerve contains both afferent and efferent axons carrying information to and from specific regions of the skin and underlying muscles
• the receptive field of all of the afferent fibers within a given peripheral nerve, as mapped on the skin, is called a “dermatome” (slide 116, dermatomes)
• the borders of dermatomes are sufficiently precise to determine exact levels of spinal cord injury
• (slide 117, CIBA, sec. VIII, plate 15, page 166)
• afferent and efferent fibers of a peripheral nerve diverge at the spinal cord
  ➢ afferents enter through the dorsal root and have their cell bodies in the dorsal root ganglion
  ➢ efferents emerge through the ventral root and have their cell bodies in the ventral horns of the grey matter of the spinal cord
• remember that afferent information is carried as “labeled lines”
• these labeled lines follow two very distinct pathways on their ascent to the supraspinal centers:
  • The “anterolateral system”
    ➢ thought to have evolved earliest
    ➢ carries mainly pain and temperature (and some touch and pressure) information
    ➢ fibers “decussate” immediately upon entering spine
    ➢ pain and temperature info ascends in the “lateral spinothalamic tract”
    ➢ touch and pressure info ascends in the “ventral spinothalamic tract”
    ➢ major termination of these fibers in the reticular formation of the mesencephalon = arousal to painful stimulus

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**LECTURE MATERIAL CHANGES EACH SEMESTER!**
also ascend to the VPL and on to the secondary (and some to primary) somatosensory cortex, to be reviewed later

- The “posterior (dorsal column) system”
  - thought to have evolved later
  - most touch and pressure, and all proprioceptive, information immediately enters the dorsal columns ipsilaterally (does not decussate till the brain stem)
  - dorsal columns are comprised of the “cuneate and gracile fasciculi”
  - fibers are somatotopically organized such that lower body is represented medially (gracile fasciculus) and upper body laterally (cuneate fascillus)
  - these fibers do not see their first synapse till they enter the lower medulla and synapse in the “cuneate and gracile nuclei”
  - post-synaptic outputs of the cuneate and gracile nuclei are 1) to the cerebellum, 2) superior colliculi and 3) decussate to enter the “medial lemniscal pathway” and ascend to the VPL and cortex
  - cuneate and gracile nuclei are grey matter = processing goes on here
  - (slide 118, receptive fields of cuneate and gracile nuclei)
  - while peripheral afferent fibers have simple receptive fields, those post-synaptic in the cuneate and gracile nuclei have the classic antagonistic center-surround configuration
  - (slide 119, two point discrimination)
  - the purpose of this processing is predictable, to improve spatial contrast, as depicted here for a two point discriminative stimulus

- The VPL and VPM of the thalamus (slide 120, VPL and VPM)
  - “relays” somatosensory information to the cortex
  - major point where cortex can modulate its own input
  - sharpening of spatial contrast

- Somatosensory cortex (slide 121, the somatosensory homunculus)
  - ascending inputs from VPL and VPM terminate somatotopically in the post-central gyrus
  - organization originally determined from recordings of large electrodes on the cortical surface (overhead, Penfield and Woolsey)
  - this suggested that the cells are arranged in a course map, in register with the dermatomes
  - cortical magnification reflects receptor density in the periphery and is species dependant (slide 122, animuculi)
  - later microelectrode studies by Vernon B. Mountcastle indicated a finer functional organization to somatosensory cortex
    - cells are arranged in vertical columns, with all cells in a given column responding to the same area of the body and the same sub-modality of somatosensation from that body part
    - this is referred to as the “columnar organization of the cortex”, and, as we have seen, is a general organizing principle
    - VBM originally hypothesized the columnar organization of the cortex, not Hubel and Weisel
    - VBM has not yet received a Nobel Prize, H & W have

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there are actually 4 parallel areas of the postcentral gyrus, each somatotopically organized (areas 1, 2, 3a and 3b) but responding to different sub-modality

area 3a = deep tissue (muscle stretch receptors), mainly input from thalamus, small receptive fields
area 3b = skin (slowly and rapidly adapting receptors), mainly input from thalamus, small receptive fields
area 1 = skin (rapidly adapting receptors), mainly input from areas 3a and 3b, large receptive fields
area 2 = deep tissue (pressure and joint position), mainly input from area 1, large receptive fields
areas 3a and 3b are mostly concerned with enhancing spatial contrast, whereas, areas 1 and 2 are concerned with integrating skin and proprioception for “active touch” (determining the shape of objects)

• So far, we have been concentrating on primary somatosensory cortex, or “SI”
• tucked into the lateral sulcus is a second somatotopically organized area called secondary somatosensory cortex or “SII”
• the function of SII is poorly understood
• there is some evidence that its processing may be “more advanced” than SI
  ➢ much input from SI, but not vice versa
  ➢ body is bilaterally represented
• there is also evidence that its processing may be “less advanced” than SI
  ➢ main input from pain and temperature (older, cruder system)
  ➢ preserved in animals with lesser sensory-motor skills
• as well as projecting to SII, SI also projects to the “posterior parietal cortex”
  ➢ this area is thought to be “association cortex” with polysensory response properties
  ➢ however, much more goes on here than previously suspected
  ➢ lesions of the posterior parietal lobe in the right hemisphere can lead to bizarre forms of “sensory neglect”, suggesting it is responsible for “awareness” of the contralateral body

  (slide 123, long loop reflex)
• However, the major output of SI is a point for point projection beneath the central sulcus to motor neurons of the precentral gyrus, or primary motor cortex
• this direct link between afferent and efferent is called the “long-loop reflex”, and demonstrates again the intimate connection between somatosensory and motor systems
• let’s begin examining these reflexes at the spinal level, since that is where most processing takes place

Spinal reflex pathways (slide 124, CIBA 3140, sec. VIII, plate 33, page 184)
• Spinal reflexes are mediated by direct (monosynaptic) connections between afferent inputs and motor neurons

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• Much of the complex computation involved in these reflexes is established by pollysynaptic interconnections between afferents and motor neurons by interneurons
• The “stretch reflex”
  ➢ extensor muscle set to desired length
  ➢ outside force tries to stretch (or extend further than desired)
  ➢ this activates muscle spindle in extensor muscle
  ➢ afferent from muscle spindle excites motor neuron to same muscle, causing it to proportionately contract and hold desired length
  ➢ note that a complementary inhibitory signal is sent to opposing flexor motor neuron via an inhibitory interneuron
  ➢ there is no reflex that acts on just a single muscle, coordinated actions of all muscles around a joint are provided for smooth movement
• The “tendon organ reflex”
  ➢ extensor muscle is tensed to desired force (not length) on object
  ➢ increased force beyond desired activates GTO (low threshold)
  ➢ GTO afferent input inhibits extensor motor neuron (through inhibitory interneuron), bringing force back to desired level
  ➢ GTO also excites flexor motor neuron for coordinated movement
  ➢ if high threshold GTO goes off due to extreme force, both flexor and extensor motor neurons are massively inhibited to shut movement down and protect joint
• “recurrent inhibition”
  ➢ effected through “Renshaw cell”, one of the first inhibitory interneurons discovered
  ➢ motor neuron output excites a Renshaw cell, which returns to inhibit the motor neuron
  ➢ this is a great example of “negative feedback” which serves to stabilize the output of the motor neuron
  ➢ Renshaw cell also inhibits neighboring motor neurons
  ➢ this lateral inhibition serves the same purpose as it does in afferent system, in this case to sharpen the contrast in motor neuron output to their target muscles
• The “flexor withdrawal reflex”
  ➢ extensor muscle (i.e. leg) moves limb onto painful stimulus (i.e. foot on nail)
  ➢ nociceptive fibers are activated
  ➢ nociceptive input inhibits the extensor (causing the pain) and excites the flexor motor neurons, resulting in “flexor withdrawal” from the painful stimulus
  ➢ note that the opposite effect is imposed contralaterally, excite extensor and inhibit flexor, resulting in contralateral extension to maintain balance
• These are very simplified examples of reflexes
• Most reflexes involve coordinated actions not only of multiple muscles around a joint, innervated by motor neurons in a single spinal segment, but also coordination of multiple joints controlled by many spinal segments
• The complex circuitry shown here is exploited by descending motor commands to bring about movements

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Control of movement (overhead, myotatic unit)

- all of the muscles surrounding a single joint are grouped together as a “myotatic unit”
- three dimensional positioning of a joint requires the precise coordination of tensions on muscles of the myotatic unit
- muscles contracting during a given movement are called the “homonymous” muscles
- those opposing the homonymous muscles are called “antagonist” muscles
- (overhead, a macroscopic view)
- When we are unsure of the consequences of our actions (i.e. new and untried motor tasks) we tend to stiffen up our joints by “co-contracting” both homonymous and antagonist muscles
  - stiff joint = less vulnerable to perturbations in load
  - stiff joint = less need for rapid feedback
  - stiff joint = clumsy inelegant movement
- When we are sure of the consequences of our actions (i.e. well learned motor tasks) we tend to loosen up our joints by “reciprocally inhibiting” homonymous or antagonist muscles
  - requires fast and precise feedback for slight changes in load
  - much smoother and more precise movements
- While much of the computation for coordinated activation of the myotatic unit can take place in the spine, learning, triggering, and modifying the motor programs requires the entire descending motor system

The descending motor pathway (slide 125, CIBA 3152, sec. VIII, plate 45, page 197)

- The most dominant part of descending control is from the pyramidal system
- Late in the 1800s, Hughlings Jackson proposed that motor cortex may be somatotopically organized, based on systematic spread of seizures
- Wilder Penfield stimulated parts of the precentral gyrus and activated different muscle groups
  - established “primary motor cortex” in the precentral gyrus
  - determined that primary motor cortex is somatotopically organized in register with the primary somatosensory cortex (SI)
  - cortical magnification reflects increased motor control of distal extremities and face
- descending projections begin with giant “Betz” cells in deep cortical layers
- these pass through the middle section of the internal capsule
- they then form together in the ventral mesencephalon as the cerebral peduncles
- descend in the pons, giving off tangential collaterals to the cerebellum
- regroup in the ventral myelencephalon to form the “medullary pyramids”, from which this major motor pathway gets its name the “pyramidal tract”

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• about 80% of the fibers then decussate and descend in the spinal cord as the “lateral corticospinal tract”, innervating motor neurons at all levels of the spinal cord that control muscles of the distal extremities
• the remaining 20% of the fibers do not decussate, descending ipsilaterally in the “anterior corticospinal tract”, innervating motor neurons at all levels of the spinal cord that control muscles of the trunk and proximal limbs involved in posture

Motor cortex
• motor cortex is subdivided into primary motor cortex (precentral gyrus) and secondary motor cortex (anterior to precentral gyrus)
• Primary motor cortex
  ➢ as noted earlier, primary motor cortex is organized as a somatotopically arranged series of cellular columns, each column controlling the force of a given muscle
  ➢ in this sense, primary motor cortex is like a piano upon which voluntary movements are played.. each key represented by a cortical column controlling an individual muscle
  ➢ but then, what information processing task does this large cortical area play?
  ➢ the main processing task of primary motor cortex is to compute the relative muscle contractions within a myotatic unit required to make a limb go in a desired direction, to a desired extent, at a desired speed, with a desired force
  ➢ remember that the myotatic unit controlling a joint is only composed of a few muscles, and yet it can move in all possible directions
  ➢ computation in the primary motor cortex consists of interactions between the cortical columns controlling the muscles of a given myotatic unit to get the job done
• Secondary motor cortex
  ➢ is divided into “premotor cortex” laterally and “supplementary motor area” (SMA) medially
  ➢ both perform “higher” level processing required in planning and executing movements
  ➢ both execute through the motor strip (play the piano) but also have direct projections to subcortical and spinal motor areas
  ➢ premotor cortex is primarily concerned with 1) preparing motor systems for movement (i.e. postural adjustments, proper joint tensions) and 2) planning strategies for movement (i.e. computing how fast and in what direction coordinated limb movements should be made to get the job done)
  ➢ SMA is concerned with 1) programming motor sequences (i.e. required to get around objects in the environment, adjust for inclines, etc.) and 2) coordinate bilateral movements of the body (SMA has dense transcollosal connections, unlike pre-motor cortex)
  ➢ The planning and execution of all movements requires very precise computations that integrate time and space (how fast the limbs should move, when they should move, in what sequence they should move, how far they should move, etc)
  ➢ How do we integrate time and space in the CNS?

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Were is time even represented in the CNS?

- Remember from anatomy, both primary and secondary motor cortex have intimate connections with the CEREBELLUM, the penultimate space-time computer

- We will cover the cerebellum in the last lecture of this course if there is time...

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