The big picture...

Cortex gets huge amount of information about the world via sensory systems. Takes full context, tells 3 systems “Here’s what’s going on – what should I do with all this?”

- **Hippocampus**: Spatial cognition and episodic memory. (Pyramidal Cells)
- **Cerebellum**: Fine motor execution/perception (Perkinje Cells).
- **Basal Ganglia**: Associating values (rewards) with actions (Spiny GABAergic Neurons)

Each system responds with its own answer.
Principle of the Week: Reentry

Many areas of cortex converge into organs such as the Basal Ganglia, Hippocampus, and Cerebellum, then project back out to the cerebral cortex.
What do all three systems have in common? (hippocampus, cerebellum, basal ganglia)

1. Receive input from widespread areas of cortex
2. Send output back to cortex (reentry)
3. Series of subregions – convergent info in, divergent info out
4. Involved in learning (alterations in synaptic strengths)
5. Firing patterns related to full context of environment
the cortex-cerebellum-cortex loop: role in timing and adjustment of fine motor patterns

- **Inhibitory projection**
- **Excitatory projection**

**Cerebral Cortex**
- Pontine nuclei (mossy fibers)
- Convergence

**Cerebellum**
- Granule cells
- Purkinje cells
- Convergence = coordination across muscles of the body

**Vestibular and proprioceptive inputs**
- Inferior olive (climbing fibers - ‘error’ signal induces learning)

**Cerebellar Nuclei**
- Base of cerebellum - each contains homunculus

**Ventrolateral Thalamus**
- And brainstem and spinal cord

**Motor Cortex**
- Divergence

**Convergence**
- Coordination across muscles of the body

**Divergence**
- Vestibular and proprioceptive inputs

**Images**
- Diagrams of brain structures and connections.
Inputs to Cerebellum

- Inhibitory projection
- Excitatory projection

- Cerebral cortex
- Pontine nuclei (mossy fibers)
- Convergence
- Divergence
- Convergence = coordination across muscles of the body

- Cerebellum - granule cells
- Cerebellum - Purkinje cells
- Vestibular and proprioceptive inputs
- Inferior olive (climbing fibers - 'error' signal induces learning)
- Cerebellar nuclei (base of cerebellum - each contains homunculus)
- Ventrolateral thalamus (and brainstem and spinal cord)
- Motor cortex
Inferior Olive Climbing Fibers
Climbing Fibers of Inferior Olive

- Inferior olive sends a neuron axon (climbing fiber) up the trunk of the Purkinje cell.
- Inferior olive neurons (climbing fibers) go off when there is an expectation error.
- This will cause depression of Granule cells parallel fibers.
Cerebellar Nuclei

- Inhibitory projection
- Excitatory projection

- Cerebral cortex
- Pontine nuclei (mossy fibers)
- Convergence
- Divergence
- Convergence = coordination across muscles of the body

- Cerebellum = granule cells
- Divergence
- Ventrolateral thalamus (and brainstem and spinal cord)

- Cerebellum = Purkinje cells
- Vestibular and proprioceptive inputs
- Inferior olive (climbing fibers - 'error' signal induces learning)

- Cerebellar nuclei (base of cerebellum - each contains homunculus)
- Motor cortex
### Cerebellar Nuclei & Function

**...cerebellum – Purkinje cells**

- **cerebellar nuclei** (high baseline rates modulated by Purkinje cell inhibition) **...**

<table>
<thead>
<tr>
<th><strong>fastigial nucleus</strong></th>
<th><strong>interpositus nucleus</strong></th>
<th><strong>dentate nucleus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>neuronal activity</td>
<td>eye mvmts. / walking</td>
<td>perturbation of limb/body from holding position</td>
</tr>
<tr>
<td>localized inactivation</td>
<td>posture and gait instability</td>
<td>tremor</td>
</tr>
<tr>
<td>function</td>
<td>postural adjustments</td>
<td>balance of agonist / antagonist muscles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>timing / cross-muscle coordination</td>
</tr>
</tbody>
</table>

**Examples:**  
- Sitting in Chair  
- Holding a Bag  
- Skeet Shooting
the cortex-cerebellum-cortex loop: role in timing and adjustment of fine motor patterns

- inhibitory projection
- excitatory projection

Cerebral cortex ➔ pontine nuclei (mossy fibers)

Convergence 

Pontine nuclei ➔ cerebellum – granule cells

Divergence

Cerebellum – granule cells ➔ cerebellum – Purkinje cells

Cerebellum – Purkinje cells ➔ cerebellar nuclei (base of cerebellum – each contains homunculus)

Cerebellar nuclei ➔ ventrolateral thalamus (and brainstem and spinal cord)

Ventrolateral thalamus ➔ motor cortex

Convergence = coordination across muscles of the body

Divergence

Vestibular and proprioceptive inputs

Inferior olive (climbing fibers - ‘error’ signal induces learning)

Convergence = coordination across muscles of the body

Divergence

Parallel fibers from the front...

Parallel fibers from the side...
Substantia nigra has two sub-regions:
- Pars compacta = DA neurons
- Pars reticulata = GABA neurons (analogous to GPi)

Globus pallidus has two sub-regions:
- External segment = GPe
- Internal segment = GPi

Together, the caudate and putamen are called the ‘striatum’.

The thalamic sub-region associated with the basal ganglia output is the ‘ventrolateral’ thalamus.
Basal Ganglia: Given full context of environment, should I take action x?

Substantia nigra has two sub-regions:
- pars compacta = DA neurons
- pars reticulata = GABA neurons (analogous to GPi)

Globus pallidus has two sub-regions:
- external segment = GPe
- internal segment = GPI

Together the caudate and putamen are called the 'striatum'

The thalamic sub-region associated with the basal ganglia output is the 'ventrolateral' thalamus

Convergence: all regions of cortex contribute
Basic Idea:

Stimulation of the **direct** path increases the excitatory effect on the cortex, facilitates motor action.

Stimulation of the **indirect** path decreases the excitatory effect on the cortex, suppresses motor action.
Direct Pathway (D1 receptors) vs. Indirect Pathway (D2 receptors)

- **Direct pathway** contains Gaba neurons with **D1 type** receptors which **increase** adenylate cyclase. These synapse on **GPi** gaba neurons.

- **Indirect Pathway** contains Gaba neurons with **D2 type** receptors which **decrease** adenylate cyclase. These synapse on **GPe** gaba neurons.
DA’s effect on each pathway

• Direct pathway: Activation of DA leads to an amplified response (excitation).

• Indirect Pathway: Activation of DA leads to weaker response (suppression).

• High DA levels favors Direct pathway, Low DA levels favor the indirect pathway.

• 10% decrease of DA in Substantia Nigra leads to Parkinsons Disease. Stimulating Subthalamic nucleus is a treatment.
DA neurons

- Sensitive to expected reward error.
- Ex) DA neurons fire when chocolate was given unexpectedly.
- After repetition, DA neurons will respond to predictive stimulus (student giving chocolate) instead of the actual reward.
- If association is made and predictive stimuli is present but no reward is given, the firing will depress.
- Wolfram Schultz predicted this computationally before it was shown in the brain.
Lecture 10: Sleep and its Function

Principle of the week:

**Homeostasis**: The tendency of a system to maintain internal stability.
Homeostasis Example: Thermostat

Detects fluctuations in temperature and compares them to a set-point.

Also, has mechanisms to regulate the temperature to return it to the set-point.
Electroencephalogram vs. Local Field Potentials (EEG) vs. Local Field Potentials (LFP)

- Outside the skull.
- Detects electrical activity in the brain, using electrodes attached to the scalp.
- Different stages of sleep have different EEG patterns.

- Inside the skull.
- Measurement of charge differences in two regions of the brain.
- Records populations of post-synaptic potentials.
- Reflect temporal coherence of synaptic activity.
Local Field Potentials

What are we looking at?

- One electrode in hippocampus and the other in another region of cortex.
- Smaller voltage changes won’t register with the electrode.
- But, if many EPSPs or IPSPs happen around the same time, they will summate.
- Therefore, LFP is a measurement of coherent EPSPs and IPSPs coming in to a brain region.
Fourier Transform and Theta Rhythm

You can run a Fourier Transform.
Frequencies
Strength of those frequencies

X-axis → Frequencies that are present
Y-axis → Power of the frequencies

Peak for the 8-12 Hz range.

This is range is Theta!
Sleep

- Sleep and wake states defined by particular EEG/LFP patterns and their association with:
  Eye movements
  Muscle tone
  Pattern or breathing and heart rate
  Type of mentation.

- Two types: Rapid Eye Movement (REM) and Non-Rapid Eye Movement (NREM).
# Types of Sleep

<table>
<thead>
<tr>
<th>REM</th>
<th>NREM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Eye Movement</td>
<td>Non-Rapid Eye Movement</td>
</tr>
<tr>
<td>aka Paradoxical Sleep</td>
<td>aka Slow Wave Sleep</td>
</tr>
<tr>
<td></td>
<td>Four Stages corresponding to depth of sleep. 1, 2, 3, 4.</td>
</tr>
</tbody>
</table>

- Both REM and NREM are **actively induced** by specific brain mechanisms.
Cortical Signals

Awake: Flat amplitude. No rhythm.

Drowsy: Alpha waves (8-12 Hz)
Transition awake/sleep.

Stage 1: Theta waves (3-7 Hz).
Asleep but easy to wake up.

Stage 2: Sleep spindles (12-16 Hz) and K complexes (excitation followed by inhibition)
Harder to arouse

Stages 3 & 4: Delta waves (0.5-2 Hz)
Strong synchronization.
Deep Sleep.

REM Sleep: Saw tooth waves.
REM vs. NREM

Main points:
- Stages 3-4 of **NREM decrease** over the course of the night.
- **REM (and deep sleep) increases** over the course of the night.
Sleep Cycles

- The smaller the brain, the quicker the cycle.

- Rat: 12 min
- Cat: 30 min
- Human: 90 min
<table>
<thead>
<tr>
<th>REM</th>
<th>NREM</th>
</tr>
</thead>
<tbody>
<tr>
<td>![EEG REM]</td>
<td>![EEG NREM]</td>
</tr>
<tr>
<td>EEG: Asynchronous</td>
<td>EEG: Synchronous</td>
</tr>
<tr>
<td>Oculography: Eye muscles active.</td>
<td>Oculography: Flat</td>
</tr>
<tr>
<td>REM sleep bouts get longer.</td>
<td>Stages 3-4 decrease over the course of the night.</td>
</tr>
</tbody>
</table>
Sleep and Homeostasis

How do you react after being sleep-deprived?

- As you go across the day your factor S (need for sleep) builds up. Then when you go sleep it drops back down. This is an example of homeostasis.

- When sleep deprived, and go to sleep, you get more stage 4 (deeper slow wave sleep). They also have more/faster eye movements during REM.

Main point: Your body knows when you are sleep-deprived so it will try to get you back to set-point (natural rested state).
Random Tidbits

- Mentation: awareness and perception (present in awake and REM sleep).
- Peri-LC: REM “on” fire more during REM. Stimulate leads to REM sleep.
- VLPO: SWS “on” fire more during nonREM, hypothalamus, when lesioned has very little nonREM. Stimulate leads to nonREM sleep.
- Trunk is inhibited during REM sleep.
- Narcolepsy is a REM sleep disorder where the person quickly jumps to REM sleep. Sometimes, when they are awake their muscles can be inhibited.
## Sleep Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Waking</th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cortical EEG / LFP</strong></td>
<td>fast/low-amp/irregular</td>
<td>slow-waves/spindles</td>
<td>fast/low-amp/irregular</td>
</tr>
<tr>
<td><strong>trunk muscle tone</strong></td>
<td>high</td>
<td>minimal</td>
<td>absent (paralysis)</td>
</tr>
<tr>
<td><strong>eye movements</strong></td>
<td>frequent</td>
<td>none</td>
<td>frequent</td>
</tr>
<tr>
<td><strong>heart rate</strong></td>
<td>high/variable</td>
<td>low/regular</td>
<td>high/variable</td>
</tr>
<tr>
<td><strong>breathing rate</strong></td>
<td>high/variable</td>
<td>low/regular</td>
<td>high/variable</td>
</tr>
<tr>
<td><strong>mentation</strong></td>
<td>vivid</td>
<td>minimal / transient</td>
<td>vivid</td>
</tr>
<tr>
<td><strong>hippo. LFP</strong></td>
<td>theta rhythm</td>
<td>slow-waves</td>
<td>theta rhythm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cortex/thalamus</th>
<th>Slower/burst-pause</th>
<th>Fast/irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh neurons</td>
<td>high rate</td>
<td>low rate</td>
<td>highest rate</td>
</tr>
<tr>
<td>NE neurons</td>
<td>high rate</td>
<td>low rate</td>
<td>inactive (REM-off)</td>
</tr>
<tr>
<td>5-HT neurons</td>
<td>high rate</td>
<td>low rate</td>
<td>inactive (REM-off)</td>
</tr>
<tr>
<td>HA neurons</td>
<td>high rate</td>
<td>low rate</td>
<td>inactive (REM-off)</td>
</tr>
<tr>
<td>DA neurons</td>
<td>moderate rate</td>
<td>moderate rate</td>
<td>moderate rate</td>
</tr>
<tr>
<td>VLPO neurons</td>
<td>inactive</td>
<td>highest rates</td>
<td>inactive</td>
</tr>
<tr>
<td>REM-on neurons</td>
<td>inactive</td>
<td>inactive</td>
<td>high rate</td>
</tr>
<tr>
<td>Orexin neurons</td>
<td>high rate</td>
<td>low rate</td>
<td>low rate</td>
</tr>
</tbody>
</table>

REM: requires maximum ACh and other neuromodulators are off.
DA not modulated by sleep.

Waking and REM similar, except muscle tone.

These NMs fire at high rates during waking.
REM sleep and NREM sleep are **ACTIVE** processes mediated by the increased activity of, respectively, pontine REM-on neurons and VLPO NREM-on neurons.
Burst Activity NREM

To get from wake to nonREM sleep:

- VLPO gaba neurons inhibit ACH, NE, 5HT, HA

- k+ leaky channels open allowing K+ to leave the cell (hyperpolarization).

- Ion channels open causing Ca++ to flow in (depolarization/ AP).

- Ca++ Ion channels close and K+ channel opens (hyperpolarization).
Sleep Researchers

• Nathanial Weitman: Studied circadian rythms through cave studies

• Aserinsky (with Weitman): Discovered REM sleep

• Horne: Showed that people can be trained to function normally with only 5 hours of sleep.

• Allen Rechtschaffen: When a rat is deprived from REM sleep they will develop metabolic issues that lead to death.

   - However, completely take out the area responsible for REM sleep and their is no noticeable effect (besides a lack of REM sleep).
Possible Functions of Sleep:

• Development of brain. Newborns have lots of REM sleep.

• Restore metabolism. nonREM associated with reduced metabolism. During sleep ATP Is being built up. Squirrels are a particularly active high metabolism animals and have more nonrem and rem sleep.

• Learning. Place cells repeat patterns previously experienced.
Monotremes

Echidna
-no REM sleep

Duckbill Platypus
-lots of REM sleep
1. A neurotransmitter, upon binding to a post-synaptic receptor, begins a 2\textsuperscript{nd} messenger cascade that changes the kinetics of a voltage-gated Ca\textsuperscript{++} channel. The neurotransmitter is of what type? 
   (a) Ionotropic 
   (b) Metabotropic 
   (c) It’s not possible to know 
   (d) Cationotropic 

2. Name 4 neuromodulatory neurotransmitters and two properties common to all neuromodulatory systems.
   
   - Acetylcholine
   - Dopamine
   - Serotonin
   - Histamine
   - Norepinephrine

   Properties:
   - Change functional anatomy
   - Slow firing rates
   - Unmyelinated fibers
   - Input from PFC
   - Impacted by sleep/wake

3. NE acting on a neuron only slightly changes its membrane potential, but nevertheless doubles that neuron’s response to input from another neuron. This is one example of how neuromodulatory systems change the operations of brain circuits, or, in other words, how they sometimes change the ______ functional ______ anatomy ______ of the brain.

4. Name three cell types that each exhibit spatially-specific firing according to the allocentric frame of reference.
   - Head-direction cells
   - Grid cells
   - Place cells

5. This region/nucleus of the brainstem serves as a convergence point for cortical inputs to the cerebellum.
   
   Pontine nuclei

6. Circle the appropriate words: The \{GPi/GPe\} is part of both the direct and indirect pathways through the basal ganglia. Medium spiny neurons that project to this region utilize \{D1/D2\} dopamine receptors which \{enhance/suppress\} the response to cortical excitatory inputs.

7. True/False: Dopamine neurons fire more action potentials when expected reward is less than actual reward.  
   True
1. What effect do ionotropic excitatory neurotransmitters have on the post-synaptic cell? ______________________

2. _____________________ influence the neuronal responses to ionotropic excitatory and inhibitory inputs as opposed to directly mediating excitatory or inhibitory responses.

3. Neuromodulatory systems of the brain have [high]/[low] firing rates.

4. Alzheimer’s is a neurological disorder that is associated with which neuromodulatory system?
   (a) Acetylcholine
   (b) Dopamine
   (c) Norepinephrine
   (d) Serotonin

5. What are five properties of ion channels?
   ______________________
   ______________________
   ______________________
   ______________________
   ______________________

6. Complete the following examples of neuromodulators changing functional anatomy:
   • In the pyriform cortex, inputs to layer 1a are enhanced in the presence of ______________ or ______________.
   • Acetylcholine decrements the responses of ___________________ channels, thereby enabling greater and more persistent responses to current injection.
   • In the basal ganglia, the ____________ path is favored by high ____________ levels.
1. What effect do ionotropic excitatory neurotransmitters have on the postsynaptic cell?  __EPSP/depolarization__

Neuromodulators/metabotropic neurotransmitters

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   (a) Acetylcholine (b) Dopamine (c) Norepinephrine (d) Serotonin

5. What are five properties of ion channels?
   __ Ion Selectivity__
   __ Gating__
   __ Kinetics__
   __ State__
   __ Distribution__

6. Complete the following examples of neuromodulators changing functional anatomy:
   • In the pyriform cortex, inputs to layer 1a are enhanced in the presence of __Norepinephrine__ or __Acetylcholine__.
   • Acetylcholine decrements the responses of __Ca++ dependent K+__ channels, thereby enabling greater and more persistent responses to current injection.
   • In the basal ganglia, the __direct__ path is favored by high __dopamine__ levels.
1. Which of the following regions receive input from neurons of the entorhinal cortex? (circle all that apply)

(a) Dentate Gyrus
(b) CA3
(c) CA1
(d) Cortex – What pathway
(e) Cortex – Where pathway

2. Neurons that project back to other neurons within the same nucleus exhibit _______________ connectivity. This is an example of _______________.

3. Which structure of the brain contains all three cells that play a role in spatial cognition (head-direction cells, grid cells, and place cells)?

4. Grid cells exhibit multiple firing fields in any given environment. These fields are arranged in a particular pattern, known as _______________. Draw the pattern.

5. Head direction cells are cells whose firing is tuned to the orientation of the animal’s head relative to _______________.

6. Name the three nuclei that form the hippocampus: ________, ________, ________
Spatial Cognition

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   ______Entorhinal Cortex__________

4. Grid cells exhibit multiple firing fields in any given environment. These fields are arranged in a particular pattern, known as ________________ triangles. Draw the pattern.

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Cerebellum and Basal Ganglia

1. Name the patterns of connectivity represented by the following diagrams:

[Diagrams of connectivity patterns]

2. Name three brain structures that receive input from widespread areas of cortex and output back to multiple cortical areas.

[Structured list of three brain structures]

3. Which of the following disorders is not primarily associated with damage to the basal ganglia?
   (a) Parkinson’s disease
   (b) Drug addiction
   (c) Obsessive Compulsive Disorder
   (d) Sleep disorders

4. Among the basal ganglia structures, caudate and putamen together are called the ________________.

5. Match each cerebellar nucleus to its function:

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<th>Muscle balance</th>
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<td>Dentate nucleus</td>
<td>Timing/coordination</td>
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6. In the cortex-cerebellum-cortex loop, cells in the ________________ respond to “error” signals by inducing a massive depolarization of ________________ cells.
Cerebellum and Basal Ganglia

1. Name the patterns of connectivity represented by the following diagrams:

Convergence  Divergence  Segregation

2. Name three brain structures that receive input from widespread areas of cortex and output back to multiple cortical areas.
   - Hippocampus
   - Cerebellum
   - Basal Ganglia

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   - Dentate nucleus: timing/coordination

6. In the cortex-cerebellum-cortex loop, cells in the _____________ respond to “error” signals by inducing a massive depolarization of _____________ cells.
1. ______________________ refers to the tendency of a system to maintain internal stability, owing to the coordinated response of its parts to any stimulus tending to disturb its normal condition or function.

2. In mammal, non-REM sleep processes are mediated by the increased activity of neurons in the _______ region, while REM sleep is initiated by ___________ neurons.

3. True / False Local field potential (LFP) amplitudes typically depend on the coherence level of synaptic inputs to the dendrites of a population of neurons.

4. The slow waves that define non-REM sleep reflect burst-pause activity that results from the ‘deinactivation’ of ____ and ____ voltage-gated ion channels and their interaction with _________________ ion channels.

5. Which of the following are characteristics of both waking state and REM sleep? (circle all that apply)
   (a) low-amplitude, irregular EEG
   (b) Frequent eye movements
   (c) Vivid mentation
   (d) High trunk muscle tone

6. Measures of local field potential (like EEG) measure _______________ _______________ in synaptic activity. They do NOT measure ________________!
Sleep

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