COGS 107B - Section A06
~ Week 6 ~

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Midterm next Thursday (non-cumulative!)

Practice midterm questions at the end of section today - Kahoot link posted

Most information will be on the board today, but I will do my best to synthesize the info onto slides before posting to the class website!
Basal Ganglia and the Cerebellum

... Principles: Frames of Reference, Reentry
Hippocampus, Basal Ganglia, Cerebellum

- Each of these structures have important roles in learning and memory
- **Hippocampus** - Episodic Memory (patient HM - bilateral hippocampal lesion)
  - Pyramidal Cell
- **Basal Ganglia** - combining (planned) actions with (expected) reward; motivation
  - Spiny GABAergic neuron
- **Cerebellum** - refinement of proprioceptive/motor control
  - Purkinje Cell
Hippocampus, Basal Ganglia, Cerebellum → Shared Properties

1. Each system receives input from widespread regions of cortex
2. Each system outputs back to the cortex (reentry), along with other brain regions
3. Each system is composed of several sub-regions across which information input from the cortex converges and outputs to cortex diverges
4. Each system is implicated in learning and each exhibits a unique form of learning at the cellular level
5. Neurons within each system exhibit firing patterns related to contextual information (i.e. not related to a single sensory/motor variable)
Cerebellum

the cortex-cerebellum-cortex loop: role in timing and adjustment of motor patterns

- inhibitory projection
- excitatory projection

- cerebral cortex
- pontine nuclei (mossy fibers)
- convergence
- divergence
- cerebellum – granule cells
- cerebellum – Purkinje cells
- cerebellar nuclei (base of cerebellum – each contains homunculus)
- ventrolateral thalamus (and brainstem and spinal cord)
- motor/prefrontal cortex

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

- Contains 70% of all neurons in the brain
- Sagittal view of the cerebellum shows the **Folia** → specific organization of granule cells, parallel fibers and Purkinje cells
- All areas of the cortex converge onto the pontine nuclei in the Pons (brainstem) → excitatory input from the pontine nuclei travel through **mossy fibers** to the granule cells in the cerebellum
- Granule cells send excitatory input through parallel fibers, which travel through the stacked layers of Purkinje dendritic trees
- Purkinje cells output to the cerebellar nuclei at the base of the cerebellum (each nuclei contains a homunculus)
Cerebellum → Learning Mechanism

- The Inferior Olivary nucleus is located in the medulla, under the pons – it signals ERROR.
- Inferior olivary neurons are connected to Purkinje cells through climbing fibers – these fibers wrap around the branches of the Purkinje dendrites, creating millions of synapses.
- When the IO neurons fire in response to an error in movement/expectation → produces a MASSIVE depolarization of GABAergic Purkinje cells.
- Shape of the AP changes into a complex shape, signaling a learning event.
- When there is an Error, whatever synapses are active at that time between parallel fibers/Purkinje cells are **depressed** because of the inhibitory Purkinje activation from climbing fibers → leads to an extreme depotentiation.
<table>
<thead>
<tr>
<th>Cerebellar Nuclei</th>
<th>Fastigial Nucleus</th>
<th>Interpositus Nucleus</th>
<th>Dentate Nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Active during eye movements and walking</td>
<td>• Active during perturbation of limb/body from holding position (someone bumps you when you’re holding a coffee cup)</td>
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<td></td>
<td>• Inhibition leads to posture and gait instability</td>
<td>• Inhibition leads to a tremor</td>
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<td></td>
<td>• Function: Postural Adjustments</td>
<td>• Function: balance of agonist/antagonist muscles</td>
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<td>• Active during auditory and vision triggered movements</td>
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<td>• Inhibition leads to reaction time delays and poor endpoint control (throwing a baseball)</td>
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<td>• Function: timing, cross-muscle coordination</td>
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</tbody>
</table>
basal ganglia: a complex of sub-regions damage to one or more of which is implicated in Parkinson’s disease, Huntington’s chorea, obsessive-compulsive disorder, Tourette’s syndrome, attention deficit disorder, and drug addiction.

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

- **substantia nigra** has two sub-regions:
  - pars compacta = DA neurons
  - pars reticulata = GABA neurons
    (analogous to 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

- The basal ganglia combines action and planned action together with reward
- All regions of the cortex have inputs to the basal ganglia through the striatum (made up of the caudate and the putamen)
- The basal ganglia contains Spiny GABAergic Neurons
- Important components: Globus Pallidus and Substantia Nigra pars compacta (DA inputs to basal ganglia)
cortex → basal ganglia → cortex: direct, indirect, and hyperdirect pathways

- **Cortex**
- **Striatum**
- **GPe**
- **STN**
- **GPI/SNr**
- **Thalamus**
- **Brainstem**

2/3's of output to, prefrontal, premotor or motor cortex

- **Indirect pathway**
- **Direct pathway**

- **Convergence**: all regions of cortex contribute

- **Excitation**
- **Inhibition**
- **Dopamine modulation**

- **'hyperdirect' pathway**

- **Caudate/ Putamen** and **GABA, enkephalin, D2**
- **GABA, substance P, D1**
Basal Ganglia – Direct Pathway

- D1 Receptors
- Resting State: GPi inhibits the thalamus
- When an AP enters the striatum $\rightarrow$ activates the DIRECT pathway
- Activation leads to increased suppression of GPi from the striatum $\rightarrow$ inhibitory action of the GPi on the thalamus is inhibited $\rightarrow$ leaves the thalamus free to send information to the cortex
- NET EXCITATION
- Favored when there is high dopamine levels in the basal ganglia $\rightarrow$ means there was an incident that led to DA increase, which means there is information present that needs to be sent to the cortex
Basal Ganglia – Indirect Pathway

- D2 Receptors
- Resting State: GPe inhibits the GPi, thalamus is not inhibited
- AP enters the striatum → activates the INDIRECT pathway
- Striatum activates suppression of GPe → lowers base inhibition of GPi → GPi free to continue inhibiting the thalamus → no information sent to the cortex
- NET INHIBITION
- When there is no dopamine present in the basal ganglia, the indirect pathway is favored
- No DA means that there is no important information to send to the cortex
The direct and indirect pathways are modulated differentially by DA.
Direct vs. Indirect Pathways (Summary)

### Direct Pathway
- D1 Receptors (excitatory)
- Leads to net excitation of the thalamus (and cortex)
- Favored pathway when there is high levels of dopamine in the system
  - D1 receptors will ENHANCE an action potential when there is dopamine present → favors this pathway when DA is present
  - Without dopamine, the action potential is less likely to reach the cell body
- High levels of dopamine occur during reward prediction and positive errors in reward prediction (the thalamus has something important to tell the cortex)

### Indirect Pathway
- D2 Receptors (inhibitory)
- Leads to net inhibition of the thalamus (and cortex)
- Favored pathway when there is high levels of dopamine in the system
  - D2 receptors will INHIBIT an action potential when there is dopamine present
  - Without dopamine, the action potential is more likely to reach the cell body → favors this pathway when DA is not present
- Low levels of dopamine occur when there is not a positive error in reward prediction; nothing exciting going on (and therefore nothing the thalamus needs to tell the cortex)
Key Terms

- Reentry
- Cerebellum
- Basal Ganglia
- Episodic Memory
- Pyramidal Cell
- Spiny GABAergic Neuron
- Purkinje cell
- Shared properties of hippocampus, basal ganglia, cerebellum (5)
- Granule cells
- Parallel fibers (axons)
- Dendritic tree
- Pontine nuclei
- Convergence
- Folia
- GABAergic
- Homunculus
- Ventrolateral Thalamus
- Cerebellar nuclei
- Fastigial Nucleus
- Interpositus Nucleus
- Dentate Nucleus
- Inferior olivary nucleus
- Complex spiking
- Striatum
- Super-autobiographical memory
- D1/D2 Receptors
- Direct, Indirect, Hyperdirect pathway
- Dopamine
- GPi, GPe
- Striatum - caudate + putamen
- Net excitation/inhibition
- Substantia Nigra pars compacta
- STN
Sleep

Principle: Homeostasis
Homeostasis

- Homeostasis: the tendency of a system, especially a physiological system of higher animals, to maintain internal stability → coordinated by response of its parts to any situation/stimulus tending to disturb its normal condition or function
- Sleep as a homeostatic function
- During our awake state, we build up sleep debt - this grows the longer we are awake, and can only be reset by sleeping again (feeling of fatigue, sleepiness, slower cognitive processing, being cranky)
  - We refer to this increasing sleep debt as the buildup of Factor S (potentially a chemical in the brain - Russian dog studies)
Local Field Potentials

- **Local Field Potential (LFP)** - a measurement, like the membrane potential, of charge differences between two regions of the brain - maximal fluctuations in voltage are produced by common fluctuations in membrane potential among a population of neurons
  - EX: EEG measures LFP from the scalp of the brain. EEG does NOT measure the firing of a single neuron, rather the cumulative electrical activity of a group of neurons/brain area
  - This is the Temporal Coherence of Synaptic Activity → reflects BIASES in excitatory and inhibitory synaptic activity
Sleep

- In mammals, sleep is broken down into NREM and REM sleep (+waking)
  - NREM breaks down into four stages: I, II, III, IV
  - A lot of differences in stages are defined by LFP/EEG
- REM sleep, overall, is more similar to the waking state than NREM sleep (memory consolidation/replay)
- Both NREM and REM sleep are **ACTIVELY** induced by specific brain mechanisms → it’s an ACTIVE PROCESS
Sleep

- NREM Sleep: strong variation in EPSP/IPSP biases occurring over longer periods of time
- *Stage 1:* Theta waves; very much like the waking state with 3-7 cps (cycles per second)
- *Stage 2:* 2-12 cps with sleep spindles and K complexes
- *Stage 3, 4:* (deep sleep) $\frac{1}{2}$ - 2 cps; slow-wave delta waves
- The smaller the brain, the quicker the cycle: NREM-REM cycles occur every 90 minutes for humans, 30 minutes for cats and 7 minutes for mice
Sleep

- **Wakefulness**: eye movements, high amount of muscle tone, high/variable breathing and heart rate, vivid mentation (mental cognition)
- **NREM**: no eye movements, low muscle tone, low/regular heart rate and breathing, minimal mentation
- **REM**: rapid eye movements, absent/paralyzed muscle tone, high/variable breathing and heart rate, vivid mentation

In mammals, sleep and wake states are most often defined by characteristic EEG / LFP patterns and their association with:

- presence or absence of eye movements
- degree of muscle tone
- pattern of breathing and heart rate
- type of mentation
Muscle Atonia

- Specialized process from a small nucleus in the Pons (brainstem) → inhibits movement in the trunk/axial muscles during REM sleep (so you don’t act out your dreams)
- This is NOT sleepwalking - sleepwalking comes out of NREM sleep and is a strange mixture of slow wave (3,4) activity with waking activity
- Narcolepsy → degeneration of Orexin Neurons that leads to cataplexy events: the muscle atonia process is switched on during the awake state, and a person becomes fully paralyzed while fully conscious
  - ^Why you shouldn’t talk shit about a narcoleptic after a cataplexy event
<table>
<thead>
<tr>
<th></th>
<th>Waking</th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical EEG / LFP</td>
<td>fast/low-amp/irregular</td>
<td>slow-waves/spindles</td>
<td>fast/low-amp/irregular</td>
</tr>
<tr>
<td>Trunk Muscle Tone</td>
<td>high</td>
<td>minimal</td>
<td>absent (paralysis)</td>
</tr>
<tr>
<td>Eye Movements</td>
<td>frequent</td>
<td>none</td>
<td>frequent</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>high/variable</td>
<td>low/regular</td>
<td>high/variable</td>
</tr>
<tr>
<td>Breathing Rate</td>
<td>high/variable</td>
<td>low/regular</td>
<td>high/variable</td>
</tr>
<tr>
<td>Mentation</td>
<td>vivid</td>
<td>minimal / transient</td>
<td>vivid</td>
</tr>
<tr>
<td>Hippo. LFP</td>
<td>theta rhythm</td>
<td>slow-waves</td>
<td>theta rhythm</td>
</tr>
<tr>
<td>Cortex/thalamus</td>
<td>fast/irregular</td>
<td>slower/burst-pause</td>
<td>fast/irregular</td>
</tr>
<tr>
<td>ACh Neurons</td>
<td>high rate</td>
<td>lowest rate</td>
<td>highest rate</td>
</tr>
<tr>
<td>NE Neurons</td>
<td>high rate</td>
<td>very 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>very 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>
Neuromodulators and Sleep

- ACh, NE, HA, DA, 5-HT → strongly impact the sleep/wake state, and are important for the changing state to occur
- Generally fire at a relatively low rate
- ACh, NE, HA, 5-HT neurons fire at a **high rate** during waking state and a **low rate** during NREM sleep
- NE, 5-HT and HA are **REM-OFF Neurons** - completely inactive during REM sleep
- ACh has a **high firing rate** during REM sleep
- VLPO neurons have everything to do with whether or not sleep happens → highest firing rates during NREM Sleep
  - If you take out VLPO neurons, you will have no NREM sleep for over two months
  - If you take out REM-On neurons, you will never have REM sleep again
Key Terms

- Homeostasis
- REM
- NREM
- Wakefulness
- Sleep debt
- Factor S
- Local field potential (LFP)
- EEG
- Temporal Coherence of synaptic activity
- EPSPs/IPSPs
- NREM: Stage I, II, III, IV
- Spindles
- Muscle atonia
- Awake state vs. NREM/REM state
- EMG
- Narcolepsy
- Cataplexy Event
- Trunk/axial musculature
- NREM/REM cycle
- Phylogeny
- Suprachiasmatic Nucleus (SCN)
- Neuromodulators (ACh, NE, DA, 5-HT, HA)
- VLPO neurons
- Orexin Neurons
- REM-Off Neurons
- REM-On Neurons
- Sleep as an Active Process
- Potassium leak channels
- Ih and It voltage-gated ion channels
- Calcium-dependent potassium channels
Have a great long weekend!

Kahoot link: https://create.kahoot.it/share/cogs-107b-midterm-2-review/267c61e1-46fb-46bc-bc70-e487753ae188