Cog 107B Week 6

Monday 4-5pm
   A02

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Neuromodulators change the functional anatomy of the brain. From moment to moment, the anatomy of the brain is largely the same. But functionally, that synapse can be rendered rather ineffective *as if it did not exist*. It can also be temporarily strengthened.

The pieces of information coming into some circuit of the brain impact that part of the brain at any given moment.

A **neuromodulator** is a chemical messenger released from a neuron in the central nervous system, or in the periphery, that affects a diverse **population of neurons** that has the appropriate receptor. This large range of influence contrasts with **neurotransmitters**, which has only one presynaptic neuron directly influencing a single postsynaptic neuron connected to it.
Dopamine System

Dopamine neurons of the Ventral Tegmental Area are hugely at play in drug abuse.

When these neurons of the VTA is stimulated, a rat can press a lever 250/min.

-Will outweigh desire to eat and mate, because it has overtaken the reward system.
Neurotransmitters

**Ionotropic (ligand gated) neurotransmitter:**
- **Excitatory:** Glutamate, Ach - causes EPSPs and depolarization of membrane potential (allow Na+ and Ca++ to flow through only one kind of ion channel)
- **Inhibitory:** Gaba -- causes IPSPs and hyperpolarization of membrane potential (allow Cl- to flow through its ion channel)

**Metabotropic / Neuromodulatory (NE/NA, 5-HT, DA, HA, Ach):** causes a cascade of biochemical events, which can result in the production of chemicals that can even alter gene expression!
- Production of compounds that will activate enzymes that will cause phosphorylation (enzyme attaches somewhere on ion channel and leaves a PO3 on the channel) of non-ligand gated ion channels.
- Can have many different effects on many types of ion channels (often voltage gated channels) such as how long it stays open (kinetics, state, and distribution, but not ion selectivity or gaiting).

~~Metabotropic neurotransmitters don’t necessarily directly cause depolarization. There are many different types of metabotropicos for any one NT (5-HT has 14, for example), and then there are many different phosphorylations that can happen in the complex process of the biochemical cascade.~~

~~(The neuromodulatory receptors are mostly metabotropic)~~
Neuromodulatory Characteristics

1. Locus Coeruleus (NE factory): tip of the pons, has thousands of neurons but can certainly make a difference throughout the brain.

2. Unmyelinated: The neurotransmission will be much slower (tens of ms rather than 1ms).

3. can take up to seconds

4. Locus Coeruleus and NE neurons shut off completely during slow wave sleep, and these are completely crucial for modulating the sleep phases.

5. One common, shared input source is the PreFrontal Cortex, the very last part of the brain to fully develop. So this affects the neuromodulatory systems, which influences the functional anatomy of the brain in general. (It’s fair to say that you see what you want to see, based on the PFC influencing the neuromodulatory system).

6. Small changes in firing rates are the rule.

7. Example: Acetylcholine increases during attention, which will increase the firing rate when attenuating to a particular stimulus (visual system)
Projection Patterns

Raphe nuclei are composed of 5-HT neurons, mostly in the brainstem.

DA system: Parkinson’s, Schizophrenia, Drug Abuse. Unlike the other systems, it reaches all over the brain, though there is a dominance of input into the PFC and the Basal Ganglia system.

ACh - local
An ACh neuron may project only to one output destination, and a different neuron will project to a separate destination. The ACh neurons may be active at different times.

NE - global
In general, Locus Coeruleus neurons project in many different directions. When NE neurons are activated, most of them are activated, so they will act simultaneously everywhere.
Desai and Walcott used electrodes to study how ACh (neuromodulator) affects Ca++ and K+ (neurotransmitter) channels, by causing it to cause action potentials and NT release and depolarization.

Scientists mimicked ACh input by injecting current into the cell body to correspond with an incoming EPSP. They used OXO-m (agonist) which is a stand-in for ACh (doesn’t break down as fast)

By activating ACh metabotropic receptor with a little more current, it will cause the neuron to fire persistently for 2 whole seconds after the stimulus is gone, as if it remembers the stimulus and then responds to it in its absence.

General effect of ACh also found on the entorhinal cortex = among the very first to degenerate in Alzheimer’s, as well as the basal forebrain ACh responsive neurons.

When you depolarize the neuron to cause action potentials, certain voltage gated K+ channels will be open. K+ will want to leave and hyperpolarize it.
ACh slows this dissipation of K+ and produce a larger counterbalancing hyperpolarizing effect.
Desai and Walcott

1a gets input more directly from the environment via the olfactory bulb, the ‘sensor’.

1b layer gets inputs from other regions of cortex that correspond to, say, the What Pathway in the visual system, or Heschl’s Gyrus of the auditory system.

A rose that smells like poop? This unexpected response will cause the NE neuron to fire and wipe out the input from the visual cortex that tells you it’s a rose, identifying the odor, and reconfiguring your association and circuit.

--A change in functional anatomy.
Drugs

the long reach of neuromodulatory systems

drugs of abuse associated with neuromodulatory systems:

ACh: nicotine

5-HT: LSD, *ecstasy, ‘magic’ mushrooms

NE: yohimbine

DA: *heroin, *amphetamines (e.g., ‘ice’), *cocaine (also ‘crack’)

HA: ?

treatment drugs associated with neuromodulatory systems:

ACh: donezepil (Alzheimer’s)

5-HT: prozac (depression, obsessive-compulsive disorder, anxiety)

NE: desipramine (depression)

DA: thorazine (schizophrenia), L-DOPA (Parkinson’s disease), Ritalin (attention deficit disorder)

HA: antihistamines (insomnia)

neurological disorders associated with neuromodulatory systems:

ACh: Alzheimer’s

5-HT: depression

DA: schizophrenia, Parkinson’s disease
Brain Circuits

Re-entry: Brain areas:
A → retina
B → visual cortex
C → auditory cortex
D → posterior parietal
E → vestibular system

CORTEX has many subregions that converge and become integrated in the Hippocampus, Basal ganglia, Cerebellum. And they output back into the cortex.
Navigation

We tend to have two ways of navigating space:

1) open environment arena-like space
   - we register the **direction** we need to take (rather than the **distance**, which is less important than the direction in large open space).

2) organized spaces with routes and boundaries
   - we register lines/pathways in regard to their **orientations** and **connections**
   - Involved in episodic memory
Hippocampus: a C within a C within a C

Hippocampus proper is made up of the layers known as the Dentate Gyrus, which has granule cells that has dendrites that wrap around.

The dentate Gyrus projects into the CA3 subregion: another layer of pyramidal cells, with dendrites fanning outward as well.

The CA3 region borders the CA1 region which has another set of pyramidal cells.

CA1 region breaks out into the Subiculum (sometimes referred to as part of the hippocampus proper, sometimes it is not.)

Removal renders the loss of episodic memory abilities, as well.
Entorhinal Cortex and Spatial Navigation

EC splits into **medial** and **lateral** division.
- Lateral: more associated with **what pathway** of the **visual system** (Infero-Temporal pathway)
- Medial: more associated with **where pathway** of the **visual system** (Parietal pathway)
  
  A lot of overlap, and also associated with prefrontal and somatosensory cortices that also reach the EC

TRI-SYNAPTIC PATHWAY through the Hippocampus

**EC** projects directly to the **Dentate Gyrus** (and also into CA3 and CA1).

**Dentate Gyrus** projects into the **CA3** subregion. It projects to itself, a special case of re-entry in a way, such that it is called an **autoassociative region**. (5% rate of connecting to another DG cell)

**CA3** projects into the **CA1** subregion. CA3 is also an **autoassociative region**.

**CA1** projects back to the EC in a larger re-entry system.

At any moment, information coming into CA1 from the entorhinal cortex is processed slightly after the same information comes in via DG and CA3. So CA1 **predicts** what it should receive again, and then it forms a comparison between the two sources.
  
  - If they mismatch, CA1 may not pass on that information.
Rule 1: Many different ways to map space and depth
Example: Depth Perception via
Motion parallax, texture gradient, occlusion, retinal disparity (stereopsis)...

Rule 2: Define the frame of reference
Egocentric frames (relative to me): retinal space, eye position, hand space
Arbitrary frames (relative to external sources): allocentric, route-centered, object-centered

Rat always has both egocentric and allocentric frames of reference.
Rat has a rather abstract sense of path-space or route-space, and can monitor how far along the path it is.

Our senses and musculature inform our egocentric frame, and then by some cognitive magic, we determine where we are relative to the environment.

The number of different kinds of spatial relationships between you and your environment change rapidly.
Head Direction Cells:

Taube guy discovered head direction cells in the postsubiculum, which encodes head direction relative to the environment (allocentric).

-Universal mapping.
Grid Cells: Medial-Entorhinal Cortex

Firing nodes with high activity have relationships with each other, yielding tessellated triangle patterns. (Which is an efficient way of stacking spheres).

This map is **universal**, meaning it is the same configuration just about anywhere you go.

One cell maintains the same interval space between nodes,
Regardless of your environment.

Tracks how far you have moved relative to where you were.
- A metric for self movement through space.
- In the same area, we have head direction cells.
- Medial EC has information for movement and direction.
Place Cells:

If you rotate the polarizing cue, the place cell’s response field (place field) rotates right along with it. **Not a universal** mapping. Adjacent areas in the world may trigger adjacent neurons in one setting, but not in another (they reconfigure).

By reading the neuron firing patterns, we could locate a rat’s position in space within 1 cm of accuracy (highly tuned).

Any particular point in the environment, each neuron has a firing rate at each position (0 Hz - ~20Hz). Listing out the firing rates of each place cell is called an ensemble/population firing rate vector. This signifies your **mental map** of where you are in the world.
What and Where pathways:

Area MST integrates optic and vestibular ‘flow’.

Area VIP of the PPC: brings together personal spaces of the somatosensory and visual systems:
- It maps out the space onto the somatosensory system: stimuli in front of your right eye elicit firing from the same neuron in the VIP as touching the right eye.

Posterior Parietal Cortex and Hippocampus Regions both show bold signals when you imagine yourself moving through the environment. Spatial imagination comes from these very same structures!