Behavioral Neuroscience Notes

PSYC 360

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Behavioral Neuroscience Lecture Notes

CHAPTER 7

PSYCHOPHARMACOLOGY

7.1 Overview — Unit 3

- Neurotransmitters and Neuromodulators
  - Psychopharmacology
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  - Pain

7.1.1 Psychopharmacology in Detail

- The scientific study of the effects of drugs on the nervous system and behavior.
- Psychopharmacology is the study of how drugs affect the mind and behavior.
  - Psychotherapeutic drugs
  - Better understanding of how things normally work.

Principles of Drug Action

- *Selective Action* — Drugs are selective in their action on the nervous system.
  - *Sites of Action* — The location at which a drug interacts with the body to produce its effects.
  - Side effects are often due to the drug acting on sites other than the intended target.
    - Thus, side effects are relative to what our preferred site of action is.
  - *Example*: Opioids primarily affect the opioid receptor system.
- Drugs don't CREATE effects, they *modulate* ongoing cellular activity.
  - That is, they affect behavior by affecting neural transmission in some way.
  - *Agonist* — A drug that mimics or enhances the **effects of a neurotransmitter**.
    - Facilitates post synaptic effects.
    - *Example*: Morphine mimics endorphins, which are natural painkillers.
  - *Antagonist* — A drug that blocks or inhibits the effects of a neurotransmitter.
    - Inhibits post synaptic effects.
    - *Example*: Naloxone blocks the effects of opioids, reversing their effects.
  - Agonistic effects can become antagonistic if the drug is taken in excess.
    - *Example*: I make a neuron fire a neurotransmitter, but I also block the reuptake of that neurotransmitter.

Basic Process

- *Precursor* — A substance from which another substance is formed. AKA, the ingredients used to make a neurotransmitter.
- $$\text{Precursor} \xrightarrow{\text{Synthetic Enzyme}} \text{NT} \xrightarrow{\text{Metabolic Enzyme}} \text{Inactive Metabolite}$$
  - *Synthesis* — The process of creating a neurotransmitter from its precursors.
  - Sometimes, we break down the precursor to build the neurotransmitter.

7.1.2 Other Ways of Agonist and Antagonist

- Block Ca^{2+} channels from opening (antagonist)
- *Mimetic* — Mimics the action of a neurotransmitter.
  - *Direct Agonist* — Binds to the same receptor as the neurotransmitter and mimics its effects.
  - *Indirect Agonist* — Binds to a different site on the receptor and enhances the effects of the neurotransmitter.
- Blocking agent
  - Competitive
    - *Direct Antagonist* — Binds to the same receptor as the neurotransmitter and blocks its effects.
  - Non-competitive
    - *Indirect Antagonist* — Binds to a different site on the receptor and blocks the effects of the neurotransmitter.
  - *Inverse Agonist* — Binds to the same receptor as the neurotransmitter and produces the opposite effect.
- *Depolarizing* or *Desensitizing Agent* — A drug that causes the AP to stay in a depolarized state; refusing to let the neuron go through another AP, and it stays in the absolute refractory period. (Antagonist)
- Interfere with vesicles (leaky or transporter proteins). (Antagonist)
- Interfere with docking proteins. (Antagonist)
- Selectively deactivate autoreceptors. (Agonist)
- Selectively activate autoreceptors. (Antagonist)

7.2 What Do These Chemicals Between Neurons Do?

- Transmit information.
  - Glutamate
  - GABA
  - Glycine
- Modulate information.
  - Every other neurotransmitter.

7.3 Classes of Neurotransmitters (Revisited from Lab)

- Amino Acids
  - Glutamate, GABA, Glycine
    - *Glutamate* — Synthesized from precursor glutamine by an enzyme called *glutaminase*. It is the most common excitatory neurotransmitter in the brain.
      - Related closely with the *NMDA* receptor, which is a type of glutamate receptor that is important for synaptic plasticity and memory formation.
      - One drug that binds to this site, *Phencyclidine (PCP)* (direct antagonist), is a drug that blocks the NMDA receptor and causes hallucinations and dissociation. Another drug that is thought to bind here, *Ketamine* (direct antagonist), is a dissociative anesthetic that is used in surgery and is also being studied as a treatment for depression.
      - **Reuptake and Deactivation**
        - Reuptake is done by the *excitatory amino acid transporters (EAATs)*. These are important because it reduces the change of excitotoxicity, which is believed to be involved in damage to the brain in stroke and amyotrophic later sclerosis (ALS, Lou Gehrig's disease).
    - *GABA* — Synthesized from precursor glutamate by an enzyme called *glutamic acid decarboxylase (GAD)*. It is the most common inhibitory neurotransmitter in the brain.
- *Amines* (monoamines) — Derived from amino acids
  - Catecholamines
    - Contain catechol and derived from the amino acid tyrosine.
    - *Tyrosine* — Precursor for the catecholamines.
    - Dopamine (DA), Norepinephrine (NE), Epinephrine (Adrenaline)
    - Dopaminergic, Adrenergic, and Noradrenergic systems.
  - *Indolamines*

- *Serotonin* (5-HT)
- *Melatonin*

- Peptides (AKA: Neuropeptides)
  - Endogenous Opioids
- Acetylcholine (ACh)
- Lipids
  - *Anadamide* (Sanskrit for "bliss") — Endogenous cannabinoid.
  - These appear to be synthesized on demand; produced and released as needed and not stored in synaptic vesicles.
  - Anadamide is deactivated by the enzyme *fatty acid amide hydrolase (FAAH)*.
- **Two Other Classes**
  - Nucleosides
    - Adenosine
  - Soluble Gases
    - *Nitric Oxide (NO)* — Required for an erection.

7.4 Acetylcholine (ACh)

- First neurotransmitter discovered.
  - Otto von Loewy — Discovered ACh in 1921.
    - This guy took a frog heart and put it in saline. Then, he took simulated the parasympathetic part of the vagus nerve, and saw that the heart slowed down.
    - He then took the saline and put it in a different frog heart, and saw that the heart slowed down again.
    - "Vagusstoff" (ACh) — The chemical that was released from the vagus nerve that slowed the heart down.
    - Cholinergic — Referring to ACh.
- ***Some* Functions**
  - **Function in the ANS:**
    - Sympathetic
      - Spinal nerve leaves the cord and synapses in the paravertebral ganglion (ACh)
      - Then makes neuromuscular junction with smooth muscles and glands (NE)
        - *Neuromusclar Junction* — The synapse between a motor neuron and a muscle fiber.

        - *Paravertebral Ganglion* — A ganglion located next to the spinal cord.
        - Except sweat glands (ACh)
      - *Sympathetic Chain* — A chain of ganglia that runs parallel to the spinal cord. This is the reason for when you get anxious, ALL of your body gets anxious.
    - Parasympathetic
      - Spinal nerve leaves the cord and synapse in the parasympathetic ganglion (ACh)
      - Then makes neuromuscular junction with smooth muscles and glands (ACh)
    - The only NT in the parasympathetic branch.
    - NT of the preganglionic sympathetic branch.
  - **Function in the Somatic NS**
    - Excites the neuromusclar junction (ACh)
    - So, ACh is important for getting motor messages out to all kinds of muscles and glands.
  - **Function in the CNS**
    - ACh is important in:
      - Learning and alertness (*Basal Forebrain*)—-activates the cortex and facilitates learning.
        - *Nucleus Basalis* — Projects to the cortex
        - *Medial Septal Nucleus* and *Nucleus of Diagonal Band* — Projects to the hippocampus through the fornix.
      - Memory (*medial septal nucleus*)—-modulate the hippocampus
      - REM sleep generation (*Pedunculopontine nucleus (PPT)* and *Laterodorsal Tegmental Nucleus (LDT)*)—-projects to the pons and thalamus.
      - Reward system.
- **Synthesis and Metabolism**
- **Drugs and Disorders**

7.4.1 ACh Synthesis and Metabolism

- **Synthesis**
  - In a nutshell: A breakdown of lipids leads to Choline, which is the precursor for ACh. Acetate is the anion in vinegar (Acetic acid). Then, this is combined with Acetate to make ACh.
  - In more detail:
    - CoA attaches to an acetate ion (*Acetylcoenzyme A (acetyl-CoA)*).

    - Then, *choline acetyltransferase (ChAT)* transfers the acetate from the acetyl-CoA to the choline molecule.
    - Mnemonic: **ChAT**: From right to left: Transfers acetate to choline.

- **Metabolism**
    - ACh is broken down by the enzyme *acetylcholinesterase (AChE)* into acetate and choline. Nice and simple!
    - The choline is taken back up by active transport and reused, and the acetate is broken down and eliminated.

7.4.2 Two Types of Cholinergic Receptors

- Nicotinic Receptors
    - Agonist at low doses, but antagonist at high doses.
    - Iontropic.
    - Found at the Neuromusclar Function in the PNS.
    - *Curare* (direct antagonist) — A drug that blocks nicotinic receptors, causing paralysis.
        - Competitive blocking agent
        - Paralysis, surgery
- Muscarinic Receptors
    - Comes from a hallucinogenic mushroom (Amanita muscaria).
        - **Don't confuse with Serotonin's Mescaline: Cactus; nor Psilocybin: Mushroom.**
    - Vikings (probably took this drug before raiding) and Koryaks (Nordic people who used this mushroom in religious practices).
    - Metabotropic receptors.
    - Predominates in the CNS (although, both types are found in the CNS).
    - *Atropine* (direct antagonist) — A drug that blocks muscarinic receptors, causing pupil dilation and increased heart rate.
        - Competitive blocking agent
        - Belladonna alkaloids (deadly nightshade)

7.5 MORE Drugs and Toxins Affecting ACh

- *Botulinum Toxin* — A waste product of *Clostridium botulinum*, which are bacteria who grows without oxygen.

- Interferes with Ca^{2+} influx channels, preventing the release of ACh.
- Because Botox causes paralysis, it can interfere with emotional *expression* because it paralyzes muscles like the orbicularis oculi.
- Additionally, since we know that expression influences experience, when we paralyze these muscles, then the emotional *experience* is also negatively affected.
- **Does Botox Decrease Emotional Experiences?**
  - Population: Women who want wrinkles gone.
  - One IV: two levels: Botox or restylane (dermal filler).
  - Method: Everyone had wrinkle reduction. AND, Everyone watches some emotion evoking movies.
  - Results: Botox group had less emotional experience than the restylane group.
  - **Is this a good thing?**
    - Another study takes a sample of depressed people and gives them either Botox or a placebo.
    - Results: 15% of placebo had a decrease in depression, while 52% of the Botox group had a decrease in depression.
- Botox can also be used to treat migraines, cerebral palsy, and hyperhidrosis (excessive sweating).

- *Black Widow Spider Venom* — A neurotoxin that causes the release of ACh at the neuromuscular junction, causing continual release of ACh and paralysis.
- *Cobra and Krait Venom* — A neurotoxin that blocks the binding of ACh to nicotinic receptors, causing paralysis.
- *AchE Blockers* — Comes into contact with the enzyme that breaks down ACh, causing an increase in ACh in the synaptic cleft.
  - Irreversible
    - Insecticides (Parathion)
    - Nerve gas: DFP (Diisopropylfluorophosphate (don't need to know the whole name)) and Sarin.
      - Readily crosses the blood-brain barrier so PNS and CNS are affected.
      - Antidote?
        - *Atropine* — A drug that blocks muscarinic receptors, preventing the effects of excess ACh.
        - *Pralidoxime* — A drug that reactivates AChE, allowing it to break down ACh again.
  - Reversible
    - *Neostgmine* (**Prostigmin**) and *Physostigmine* (**Antilirum**) — Drugs that inhibit AChE, increasing the amount of ACh in the synaptic cleft.
      - Doesn't cross the blood-brain barrier, so it only affects the PNS.

- Used to treat *myasthenia gravis* (a disease that causes muscle weakness and fatigue).
  - Autoimmune disease that attacks nicotinic receptors at the neuromuscular junction.
- *Donepezil* (**Aricept**) and *rivastigmine* (**Exelon**) — These drugs do the same thing as the above drugs, but they cross the blood-brain barrier and are used to treat Alzheimer's disease and Parkinson's disease (only the cognitive part).

7.6 New Drug for Schizophrenia

- We'll talk about dopamine drugs later in this unit.
- This new drug now:
  - *Xanomelne and trospium chloride* (**Cobenfy**) — A drug that blocks the muscarinic receptors in the CNS, but not in the PNS.
  - Dopamine but also Ach!

7.7 Catecholamines

- Dopamine (DA)
- Norepinephrine (NE)
- Epinephrine (Adrenaline)

7.7.1 Dopamine (DA)

- Synthesis and Metabolism
- Function
- Drugs and Disorders

Dopamine Synthesis

- Tyrosine was first discovered from cheese (tyrosine = cheese).
  - Tyrosine is the precursor for DA, NE, and Epi.
  - *Tyrosine Hydroxylase* — The rate-limiting enzyme in the synthesis of catecholamines.
    - Converts tyrosine to L-DOPA.
    - L-DOPA is the precursor for DA, NE, and Epi.
  - L-DOPA is converted to DA by the enzyme *DOPA decarboxylase*.

Dopamine Metabolism

- DA is broken down by the enzyme *Monoamine Oxidase (MAO)* into *Dihydroxyphenylacetric acid (DOPAC)*.
- Then, *Catechol-O-methyltransferase (COMT)* converts DOPAC into *Homovanillic acid (HVA)*.
- Also, starting from DA, we can use COMT to convert it to 3-methoxytyramine (3-MT), then with MAO, we can convert it to HVA.

DA Function

- **Movement/Motor systems**
  - *Nigrostriatal System* — Starts in the substantia nigra and ends in the striatum (caudate nucleus and putamen).
  - Here's the route: We start at the striatum, which then sends an inhibitory GABA signal to the substantia nigra, who sends a reciprocal inhibitory DOPA signal back to the striatum nerve that sends an inhibitory GABA signal to the globus pallidus. Then, the globus pallidus excites the thalamus, who then excites the primary motor cortex, who then excites movement.
    - Note that if the inhibitory signal to the substantia nigra is limited, then the signal that the striatum sends to the globus pallidus is much stronger, which leads to a weaker signal to the thalamus, and thus to movements.
  - Parkinson's Disease symptoms:
    - Weakness,
    - Tremor at rest,
    - Muscle rigidity,
    - Problems with balance,
    - Abnormal gait,
    - Trouble learning
  - Treatment
    - *Reserpine* (**Raudixin**) for ↓ **BP** (Not in use anymore because it caused Parkinson's-like symptoms)
      - 1960's
        - Blocks monoamine transporters
          - Developed Parkinson's symptoms
          - Can't fill vesicles and DA is lowered
      - Then, discovered Substantia Nigra was pale.
    - L-DOPA can be a direct treatment for Parkinson's as well.
    - *MPTP* — Neurotoxin for DA cells in the Nigrostriatal System (which is not endogenous).

- **History of MPTP — or why you shouldn't use illicit drugs**
  - 1982 — young California heroin users
  - Had used what they THOUGHT was synthetic heroin
    - *MPPP* — Opioid analgesic drug
      - Not used clinically
      - Illegally manufactured for recreational drug use
    - INSTEAD it was MPTP (oh no!)
      - They instantly developed Parkinson's-like symptoms
      - Bad for them, but good for us because we can study it.
        - Led to animal model development and possible treatment ideas.
  - We don't know why Parkinson's patient's cells are dying, but maybe something similar.
  - MPTP is converted to the chemical *MPP+* by the enzyme MAO (which is what breaks down DA), which is what damaged the cells.
    - Question: Could MAO-I improve Parkinson's?
    - Yes!
    - *Deprenyl*, also called *selegiline* (**Eldepryl**, **Jumex**) — A drug that inhibits MAO, can slow down progression of the disease.
- New treatment
  - Molecule keeps proteins from misfolding
  - *Lewy Bodies* — Misfolded proteins that are found in the brains of people with Parkinson's.
    - These are toxic to DA cells
- *Huntington's Chorea* — A genetic disorder that leads to uncontrolled movements and cognitive decline.
  - Too little GABA from the Striatum to the Substantia Nigra causes an increase in dopamine back to the Striatum which, in turn, lessens the signal to the Globus Palidus, which increases overall movements.
  - *Tetrabenazine* (**Xenazine**) — Drug that inhibits the DA vesicle transporters.
  - *Pallidotomy* — A surgery that affects the Globus Pallidus to inhibit movement.
- *Choreoathetotic Movements* — too much movement
  - *Athetosis* — Slow continually writing movements
  - *Choreic* (to dance) — Rapid, purposeless, involvuntary movements

- **Behavioral Arousal and Attention**
  - Narcolepsy
    - *Methylphenidate* (**Ritalin**) — A drug that increases DA and NE in the brain, used to treat ADHD, but can also be used for narcolepsy.

- *Hypocretine* — A neuropeptide that is involved in the regulation of sleep and wakefulness.
  - Created by the lateral hypothalamus.
  - Hypocretine: *Hypo* for *hypo*thalamus, *cretine* for *secretin* (a hormone).
  - *Orexin* — Another name for hypocretine; makes you want to eat.
- From hypocretine, researchers developed an antagonist for the orexin receptor, which is used to treat insomnia. This drug is called *Suvorexant* (**Belsomra**).
- **Treatment**
  - *TAK-994* — OX2R (Orexin-2 receptor) Agonist
  - *Hcrt-1* — Intranasal hypocretine-1 (orexin-1) agonist
  - Hypocretine Cell Transplant
  - Gene Therapy: *introduce* preprohypocretin gene into the brain to make more hypocretine.
  - Opiates (exogenous) can increase the number of hypocretin-producing cells in the brain.
  - Indirect role for opiate agonists in treating narcolepsy.

- ADHD
  - Uses Methylphenidate for selective attention.
- *Mesocortical System*
  - From ventral tegmental nucleus to prefrontal cortex, limbic CORTEX, hippocampus, all frontal lobes, and association areas of parietal and temporal lobes in primates.
  - Short-term memories, planning, and problem-solving are all associated with this system.

- **Reinforcement and Reward**
  - *Mesolimbic System (MLS)* — Responsible for reward and reinforcement.
    - From vental tegmental nucleus to limbic system
      - Amygdala, hippocampus, and nucleus accumbens.
      - Opioids cause the release of dopamine at the nucleus accumbens, which is the pleasure center of the brain.
  - James Olds & Peter Milner (1954)
    - They asked: "Does electrical stimulation of the reticular formation facilitate learning?"
    - James Olds visits a conference and listens to Neal Miller, who says electrical stimulation is aversive, so it should be avoided.
    - One lone rat was put in a box with a lever, and when the rat pressed the lever, it would get a shock to the reticular formation. He ended up pressing the level 700 times per hour.

- More studies of this
  - Skinner box
    - Rats press 2000 times per hour for a shock to the MLS.
    - Monkeys press 8000 times per hour for a shock to the MLS.
    - Starving animals will choose the MLS over food 80% of the time.
    - They also press the button for these conditions too:
      - Thirsty,
      - Getting shocked (at their feet),
      - Mother instincts.
- Delgado (1969) — For people who were getting their brain stimulated for seizures, this researcher also asked them about what they thought of the stimulation. They all thought that it was pleasurable.

NEW NOTES FOR 04/16/25

7.8 Schizophrenia in Focus

7.8.1 General Description

- *Dementia Praecox* — A term used to describe a group of disorders characterized by a decline in cognitive function and emotional regulation. Found by Emil Kraepelin, a German psychiatrist (1887).
  - Premature deterioration of the mind.
- Age of onset: Late teens to mid 30s.
- *Schizophrenia* — Same definition as before, duh. Found by Eugen Bleuler, a Swiss psychiatrist (1911).
  - Split of the mind from reality, not split personalities.

7.8.2 Theory behind Negative and Positive Symptoms**

**(and Cognitive Symptoms)

- "Positive" and "Negative" are not used in the traditional sense. Instead, they are used to describe the presence or absence of certain symptoms.
  - Positive symptoms are the presence of abnormal behaviors, while negative symptoms are the diminution or absence of normal behaviors.
  - Cognitive symptoms are the presence of cognitive deficits.

Positive Symptoms (Escalation over normal functioning)

- *Hallucinations* — Perception of something that does not have a basis in reality.
  - Auditory (most common), visual, tactile, olfactory, and gustatory.
- *Delusions* — A false belief that is resistant to reason or confrontation with actual fact. Actually built on reality, but misinterpreted.
  - Patently unrealistic.
  - For example:
    - *Referential* — Believing that something is meant for you (e.g., the TV is talking to you).
    - *Persecutory* — Believing that someone is out to get you (e.g., the government is watching you).
    - *Grandiose* — Believing that you are more important than you are (e.g., you are the king of the world).
    - *Control* — Believing that someone is controlling your thoughts or actions (e.g., the government is controlling your mind).
  - On the difference between an *illusion* and a *delusion* is that everyone can experience and illusion (not unique and based on manipulations of our nervous systems), whereas a delusion is unique to the person experiencing.
- *Disorganized Speech* — A pattern of incoherent or illogical speech that is difficult to follow.
  - *Derailment* — A pattern of speech in which the speaker jumps from one topic to another without any logical connection between them.
  - *Tangentiality* — A pattern of speech in which the speaker goes off on tangents and does not return to the main topic.
  - *Word Salad* — A pattern of speech in which the speaker uses words that are not related to each other in any meaningful way.
- *Grossly disorganized behavior* — A pattern of behavior that is inappropriate for the situation or that is not goal-directed. It is unpredictable and unprovoked.
- *Catatonic behavior* — A pattern of behavior in which the person is unresponsive to the environment and does not move or speak.
  - Maintaining a rigid or bizarre posture.
  - Purposeless excessive motor activity.
    - For example, continuously spinning your hair in circles or pacing back and forth.

Negative Symptoms

- *Affective Flattening* — Restricted range of emotional expression, including facial expressions, voice tone, and body language.
- *Alogia* — A lack of speech or a decrease in the amount of thought, which is reflected in a decrease in speech produced.
- *Avolition* — A lack of motivation or a decrease in the ability to initiate and persist in activities.
- *Anhedonia* — A lack of pleasure or a decrease in the ability to experience pleasure from activities that are normally pleasurable.
- Notice that these negative symptoms are shared with a lot of other disorders, including depression and anxiety, or even brain damage.

Positive versus Negative (Summary)

- Positive
  - Relatively unique and historically easier to treat.
- Negative
  - Common in a number of disorders.
  - Less responsible to treatment.
  - Usually emerge first.

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7.8.3 Negative Symptoms and Brain Damage

- *Discordant Twins* — Twins that are discordant for a disorder, meaning that one twin has the disorder and the other does not.
- Brain atrophy is larger than normal ventricles and cortical sulci.
- Abnormal neurological systems (physiological tests that are used to assess the function of the nervous system).
  - Jerky or non-existent visual pursuit, and cannot do it without moving their head.
  - Absence of a blink reflex.
  - Poor pupillary light reactions.
  - Unusual facial expressions.
  - Continuous elevation of the eyebrows.

- *Cytoarchitectual Abnormalities* — Abnormalities in the structure of the brain cells and their organization.
  - **Hippocampus** — Cell bodies are aligned with healthy people, but not aligned for people with schizophrenia. It indicates that this is a developmental disorder.
  - List of reasons for why these abnormalities **MIGHT** occur:
    - Exposure to a virus during pregnancy (e.g., influenza).
      - Either the literal virus or the immune response to the virus from your mom.
      - *Seasonality Effect* — The idea that people born in late winter/early spring months are more likely to develop schizophrenia than those born in the summer months.
        - 2nd trimester of pregnancy is important to brain development.
          - In Finland 1957, there was a flu epidemic in the winter months
          - *Note:* Flu is not the only virus that can cause this. Measles, polio, and chicken pox can also cause this.
        - The seasonality is more pronounced in cities.
        - Other disorders that are affected by this include autism, bipolar disorder, narcolepsy, and depression.
    - Vitamin D deficits
      - *Latitude effect* — The idea that people who live in higher latitudes (further from the equator) are more likely to develop schizophrenia than those who live closer to the equator.
    - Stress?
      - Huttunen and Niskanen (1978) — Studied people who were born in Finland during the war and found that they had a higher incidence of schizophrenia than those who were not born during the war.
        - When the mother's husbands were away, the mothers became much more stressed and their babies had a higher incidence of schizophrenia.
    - Babies who have pre or perinatal complications (e.g., low birth weight, hypoxia, and obstetric complications) are more likely to develop schizophrenia than those who do not have these complications.

7.8.4 Which Parts of the Brain are Affected?

- *Dorsolateral Prefrontal Cortex (DLPFC)* — The part of the brain that is responsible for organization, motor planning, regulation, self-reflection, directed thought, and attention.
  - Activity here
    - Low
      - Blood flow and cerebral metabolism

- Post mortem studies
  - Deterioration of DA neurons here
  - Lower D_1 receptors
    - Correlated with severe negative symptoms
    - *D1 Receptors* — A type of dopamine receptor that is involved in the regulation of movement and cognition.
- Destroy DA input for D_1 receptors
  - *Hypofrontality* — A decrease in metabolic activity in the prefrontal cortex, which is associated with negative symptoms of schizophrenia.
  - Amphetamine?
    - Increased blood blow and increased frontal lobe tasks.
- Why does it take so long to develop?
  - Don't notice until synaptic pruning occurs (around 18-25 years old).

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  - Something about hormone changes (estrogen and testosterone) that may be involved in the development of schizophrenia.
  - Maybe not so long to develop, but rather a long time to be diagnosed.
    - This could be due to the fact that parents do not think that their children have abnormal behavior until they reach teenage years. With the advent of cameras, we are able to video children when they are younger, and are able to see that people with schizophrenia have abnormal behavior when they are younger.
    - Such as: more negative affect, poorer social adjustment, abnormal movements

- Other places: Hippocampus (memory), amygdala (emotion), lateral temporal cortex (auditory processing), and thalamus (sensory processing).

7.9 Positive Symptoms and Dopamine

- 1950s neuroleptics (antipsychotic drugs) were used to treat schizophrenia. (Old name: major tranquilizers)
  - *Chlorpromazine* (**Thorazine**)
  - *Haloperidol* (**Haldol**)
  - Both of these drugs block post synatpic DA receptors and block the release of DA from presynaptic membrane.
  - *Dopamine Hypothesis* — The idea that schizophrenia is caused by an overactivity of dopamine in the brain.

- **Strengths of DA Hypothesis**
  - Better antagonists are more effective at treating symptoms.
  - *Amphetamine Psychosis* — DA Agonists (e.g., amphetamines) can cause positive symptoms in healthy people.
    - Agonists include:
      - Cocaine
      - Amphetamines
      - L-Dopa
  - Neurological symptoms in patients with Schizophrenia like excessive blinking led researchers to further believe that DA was involved in the disorder.
- **Post Mortem Studies in HVA**
  - Given the dopamine hypothesis, we would expect to see an increase in HVA in the brains of people with schizophrenia, but this is not the case.
    - *The Revised Dopamine Hypothesis* — Instead of an increase in dopamine, we see an increase in the number of dopamine receptors in the brains of people. However, this was also not true.
  - *Modified Dopamine Hypothesis* — The idea that schizophrenia is caused by an imbalance of dopamine in the brain, rather than an increase or decrease in dopamine levels.
    - What you need to know first:
      - Prefrontal neurons inhibit subcortial DA activity.
        - Lesion studies of the DLPFC result in an increase in HVA for mesolimbic areas.
    - The hypothesis:
      - Loss of neurons in the brain leads to a decrease of dopamine input in the DLPFC, which leads to hypofrontality.
        - This leads to negative symptoms.
        - And an increase in dopamine in the mesolimbic system, which leads to positive symptoms.
      - Overview: Too little dopamine in the mesocortial system leads to an increase in dopamine in the mesolimbic system, which leads to positive symptoms.

7.9.1 New Drug Treatment

- From the prior section, we know that Schizophrenia needs
  - An agonist in the mesocortical system (where there is too little dopamine)
  - An antagonist in the mesolimbic system (where there is too much dopamine)
  - **A partial agonist could do this.**

Atypical Antipsychotics

- *Clozapine* (**Clozaril**)
- *Olanzapine* (**Zyprexa**)
- *Cariprazine* (**Vraylar**)
- *Risperidone* (**Risperdal**)
- *Arirpiprazole* (**Abilify**)
- *Brexpiprazole* (**Rexulti**)

- These drugs are all used to treat schizophrenia and are partial agonists at the D2 receptor.
- An increase in treatment for positive and negative symptoms.
- Partial agonists are responsible for a decrease in dopamine in the mesolimbic system, and an increase in dopamine in the mesocortical system.
- A decrease in Tardive Dyskinesia
- *Tardive Dyskinesia* — Rapid involuntary movements of the tounge, jaw, trunk, or extremities developed in association with the use of neuroleptics (20% - 30% of long-term users).
- Drugs that impact serotonin receptors: Mescaline (from cactus) and Psilocybin (from mushrooms).
- Also impact serotonin receptors (increase in 1A, decrease in 2A).
  - *Dopamine-Serotonin Interaction Hypothesis* —

NEW NOTES FOR 04/23/25

7.9.2 Phencyclidine Theory of Schizophrenia

- Deficit of Glutamate?
  - People with Schizophrenia have 1/2 as much glutamate in their brains as healthy people.
  - Then how are DA antagonists helping?
    - Dopamine is a direct antagonistic to glutamate. That is, DA inhibits the release of Glutamate.
    - Think: Major tranquilizers (antipsychotics) are antagonists of DA, which leads to an increase in glutamate.
- Evidence?
  - *PCP (Phencyclidine)* — Glutmate antagonist that blocks NMDA receptors (a type of glutamate receptor).

- Hallucinations
- Depersonalization
- Cognitive disorganization
- Negative and hostility
- Frontal lobe impairments

- Chronic PCP use leads to a decrease in DA and metabolic activity in the DLPFC.
- *Ketamine (antagonist)* — Anesthetic for children and nonhuman animals NOT adults.
  - Causes psychotic reactions in adults (but not children).
- Treatment possibility?
  - Direct agonists cause seizures and brain damage, so we want to avoid those.
  - However, indirect agonists, such as gylcine leads to a decrease in symptomns.
  - *Lumateperone* (**Caplyta**) — Though this drug is used to treat schizophrenia, the mechanism of action is not well understood. However, we do know that this drug DOES work on Serotonin, dopamine, and glutamate receptors.

7.10 Norepinephrine

- Cell bodies in the pons, medulla, and some in the thalamus.
- *Locus Coeruleus (LC)* — The main source of norepinephrine in the brain. It is located in the pons and is involved in arousal, attention, and the sleep-wake cycle.
- The plan for this section is to go over:
  - Receptors
  - Functions
  - Synthesis and metabolism
  - Depression

7.10.1 Adrenergic Receptors

- *α Receptors* — Strong affinity for norepinephrine, but epinephrine can also bind to them (so far only found in the brain).
- *β Receptors* — Strong affinity for epinephrine, but norepinephrine can also bind to them.
- Agonists increase BP
  - α agonist = vasoconstriction
  - β agonist = force and rate of cardiac contractions
- Inversely, β-blockers and α-blockers decrease BP.

- *Doxazosin* (**Cardura**) — α-blocker that is used to treat high blood pressure and benign prostatic hyperplasia (BPH).
- *Metaprolol* (**Lopressor**) — β-blocker that is used to treat high blood pressure and heart failure.

NEW NOTES FOR 04/25/25

7.10.2 Function

- Increases vigilance, arousal, selective attention, and orienting.
  - With amphetamines, they increase levels of dopamine, but also norepinephrine, which leads to increased orientation.
    - Works by blocking reuptake and causes the transporters to work in reverse.
  - *Atomoxetine* (**Strattera**) — (ADHD tx) Reuptake inhibitor especially in the PFC.
  - *Guanfacine* (**Intuniv**) — (ADHD tx) α-2A-agonist reduces activity in the sympathetic nervous system.
    - Binds to autoreceptors and improves PTSD along with anxiety.
- Feeding
  - Antagonists and agonists can increase feeding.
- Stress response
  - Used in the neuromuscular junction of sympathetic nervous system.

Anxiety

- β-blockers used to be used to treat anxiety.
  - *Propranolol* (**Inderal**) — A non-selective β-blocker that is used to treat high blood pressure and anxiety.
- Now,
  - We use antidepressants and benzodiazepines to treat anxiety.

7.10.3 Synthesis and Metabolism

Synthesis

- Most NT synthesized in terminal button cytoplasm, then stored in synaptic vesicles.
- **NE is Different!**
- In a nutshell, it follows from the synthesis of dopamine. The rest of the process is on the handout.

Metabolism

- On the handout.

Part II

Behavioral Neuroscience Lab Notes

CHAPTER 8

LAB 3: SLEEP LAB

NEW NOTES FOR 04/10/25

8.1 What Do We Know About Sleep?

- Sleep is an active process.
- Sleepiness and alertness are controlled in part by a biological clock.
- Things can go wrong
  - There are whole books that discuss sleep disorders.
- *Suprachiasmatic nucleus (SCN)* is the master clock of the body.
  - The SCN is located in the hypothalamus and is responsible for regulating circadian rhythms.
  - Note the name of the SCN, it is *above* the *chiasm* of the optic nerve.
- *International Classification of Sleep Disorders (ICSD)* – A system for classifying sleep disorders.
- Three kinds of rhythms:
  - *Ultradian* rhythms: cycles shorter than 24 hours (e.g., heart rate, respiration).
  - *Circadian* rhythms: cycles of about 24 hours (e.g., sleep-wake cycle, body temperature).
    - Our circadian rhythm is an endogenous clock that is influenced by exogenous factors.
    - *Free-running* is when the circadian rhythm is not influenced by external cues (e.g., light, temperature).
    - It is about 24.2 hours in humans.
  - *Infradian* rhythms: cycles longer than 24 hours (e.g., menstrual cycle, seasonal changes).
- *Zeitgeber* is a stimulus that helps to regulate the biological clock (e.g., light, temperature).
- Human clocks run long when left free running. Rats are short.

8.2 What is Sleep?

- For regular people, sleep is behaviorally defined as a state of reduced movement, species specific posture, reduced response to stimuli, and reversibility.
- For sleep researchers, they take a more physiological definition of sleep.
  - *Polysomnography (PSG)* is a method of recording various physiological signals during sleep, including:
    - **Electroencephalography (EEG):** measures electrical activity in the brain.
    - **Electromyogram (EMG):** measures muscle activity.
    - **Electrooculogram (EOG):** measures eye movements.
    - Rechtschaffen and Kales (1968) defined sleep stages based on EEG patterns.
    - In 2007, the American Academy of Sleep Medicine (AASM) updated the sleep stage criteria.

Name	Frequency	Amplitude	Description	State
Beta β	12 – 50 Hz (variable)	Lower and Variable	Desynchronous	Awake and Paying Attention
Alpha α	8 – 12 Hz	50 Microvolts	Synchronous	Relaxed Wakefulness (eye closed, not fully attending, and usually largest occipitally)
Theta θ	3.5 – 7.5 Hz	Low in voltage Microvolts	Synchronous	Drowsy, Light Sleep (Stage 1)
Delta δ	1 – 3.5 Hz	20 – 200 Microvolts	Synchronous	Deep Sleep (Stages 3 and 4)

Table 8.1: Summary of EEG Wave Characteristics

8.3 Two States of Consciousness

8.3.1 Being Awake

- Physiological definition of wakefulness:
  - Supposed to be awake for $\frac{2}{3}^{\text{rd}}$ of the day.

- $< 5\%$ of the day is spent in REM sleep.
- Predominantly alpha and beta waves in the brain when drowsy.
- Muscle activity – high muscle tone when awake.
  - Lose muscle tone when you are sleeping.
    - EMG is high when awake
- Variability in the eye movement

8.3.2 Being Asleep

- Delta waves and theta waves predominantly.
- EMG is low
- Slow rolling eye movements everytime you fall asleep.
- *Hypnic Jerk* – a sudden muscle contraction that occurs when falling asleep.
- *NREM Sleep* – non-rapid eye movement sleep, which is divided into three stages:
  - *N1* – light sleep, theta waves, low EMG, and slow rolling eye movements (5-10% of the night).
    - Transition between wakefulness and sleep.
    - Hypnic jerks can occur in this stage.
    - Muscle tone is reduced, but not completely lost.
  - *N2* – light sleep, theta waves, sleep spindles, K-complexes, low EMG, and slow rolling eye movements (45-55% of the night).
    - Sleep spindles and K-complexes are characteristic of this stage.
    - Muscle tone is further reduced compared to N1.
  - *N3* – deep sleep, delta waves (3-8%), low EMG, and slow rolling eye movements (10-15% of the night).
    - Characterized by high-amplitude delta waves.
    - Muscle tone is at its lowest in this stage.
- *REM Sleep* – rapid eye movement sleep.
  - Aserinsky (1952): Discovered 70% in infants, 20-25% for healthy adults
  - Characteristics:
    - EEG – Low voltage, random, fast with sawtooth waves.
    - Fast activity, low amplitude, and desynchronous.
    - EMG – atonia (loss of muscle tone).
    - Paradoxical sleep: brain is active, but body is paralyzed.
    - Intercostal muscles are paralyzed, but not the diaphragm (obviously).

- EOG – Bursts of rapid eye movements

NEW NOTES FOR 04/17/25

8.4 Sleep Architecture: The Hypnogram

- *Hypnogram* – a graphical representation of the stages of sleep over time. (Basically a histogram of sleep stages.)
- Enter sleep through NREM sleep.
- Healthy adults trend gradually from N1 to N3, then back to N2, and then REM sleep. After $\approx$ 90 minutes of sleep, you hit REM, and then the cycle repeats.
- 4-6 cycles per night.
- As then night progresses, the amount of time spent in N3 decreases, while the amount of time spent in REM sleep increases.
- The first half of the night is dominated by NREM sleep, while the second half is dominated by REM sleep.
- *Voluntary Sleep Curtailment* – when you sleep less than your body needs, you will spend more time in N3 and REM sleep to make up for the lost sleep.
  - *REM Debt* – the amount of REM sleep that is lost due to sleep deprivation.
  - As a consequence of not getting enough REM, you are at risk of these conditions because REM **forces** you to get the pay your debt:
    - *Hypnagogic Hallucinations* – vivid, dream-like experiences that occur when falling asleep.
    - *Hypnopompic Hallucinations* – vivid, dream-like experiences that occur when waking up.
    - *Sleep paralysis* – a temporary inability to move or speak when waking up or falling asleep.
- Infants, people with sleeping disorders, and people with sleep deprivation all experience this sleep curtailment in one way or another.
- When healthy adults are sleep-deprived, their mood is worsened. However, for people with depression, their mood is improved when they are sleep-deprived.
  - In fact, REM disruption is actually a treatment for depression.
- *Sleep Efficiency* – the ratio of total sleep time to total time spent in bed.
  - Sleep researchers consider 85% or better for sleep efficiency to be good. Anything lower is considered poor.

- *Wake after sleep onset (WASO)* – This is the amount of time spent awake after initially falling asleep.
- *Sleep Latency (SL)* – This is the amount of time it takes to fall asleep after getting into bed.
- Time spent in deep sleep and time it takes to get to deep sleep are both important for sleep quality.
- Also, time spent in REM sleep.
- *Latency to Persistent Sleep (LPS)* – This is the amount of time it takes to fall asleep after getting into bed and staying asleep for a certain period of time (e.g., 20 minutes).
- *Time Spent out of Bed (TSOB)* – Self-explanatory.
- *Total Sleep Time (TST)* – Also self-explanatory.

- Assign the following to either owls, larks, or neither:
  - Better on IQ tests; more likely to procrastinate; less conscientious; more open; better at baseball; more sexual partners; more likely to be unfaithful; poorer diet; smoke and drink more; more positive affect.

Characteristics	Larks	Neither	Owls
Better on IQ Tests:			✓
More Likely to Procrastinate:			✓
Less Conscientious:			✓
More Open:			✓
Better at Baseball:	✓		
More Sexual Partners:			✓
More Likely to be Unfaithful:			✓
Poorer diets:			✓
Smoke and Drink More:			✓
More Positive Affect:	✓		
More Social Jet Lag:			✓

Table 8.2: Chronotypes