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20mg | 40mg | 80mg

MODULE 1

BASIC NEUROSCIENCE OF BIPOLAR DISORDER AND SCHIZOPHRENIA

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MODULE 1
BASIC NEUROSCIENCE OF BIPOLAR DISORDER AND SCHIZOPHRENIA

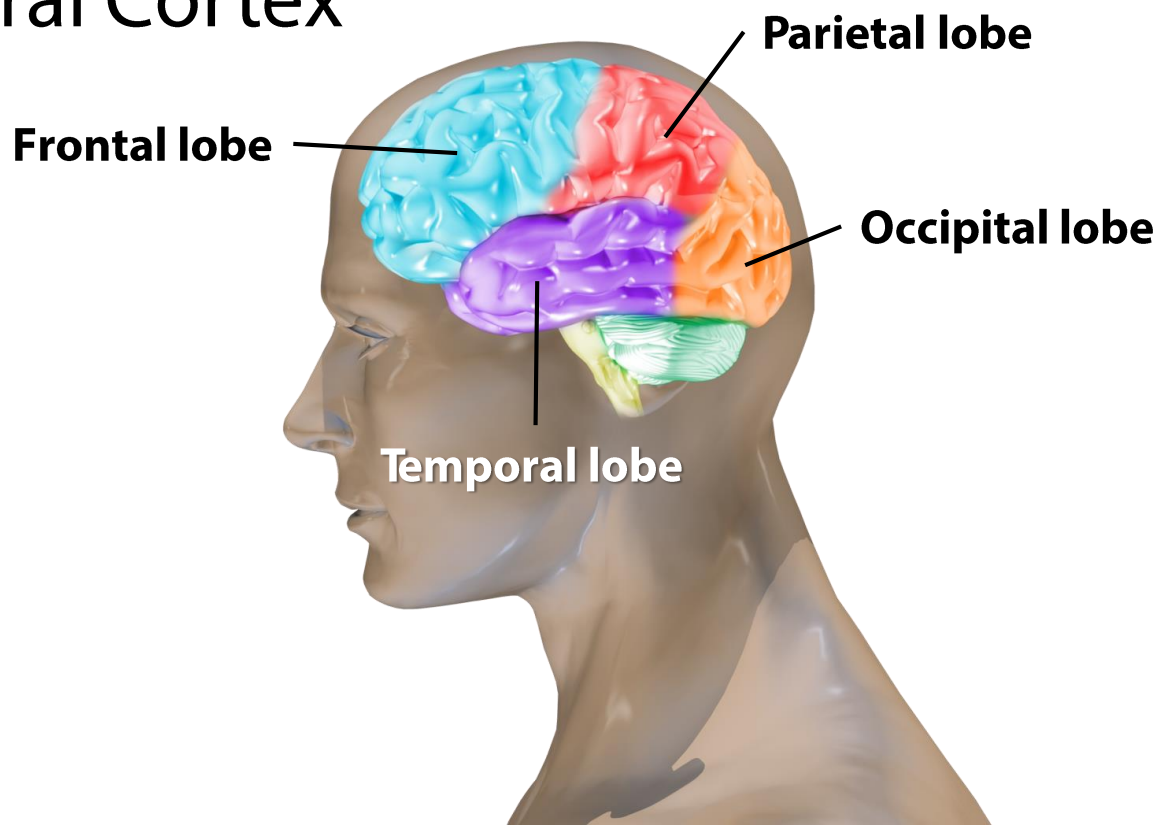
MODULE 1
BASIC NEUROSCIENCE OF BIPOLAR DISORDER AND SCHIZOPHRENIA

- Part 1: Anatomy of the brain
- Part 2: Neurons
- Part 3: Synapses and neurotransmission
- Part 4: Etiology of bipolar disorder
- Part 5: Etiology of schizophrenia

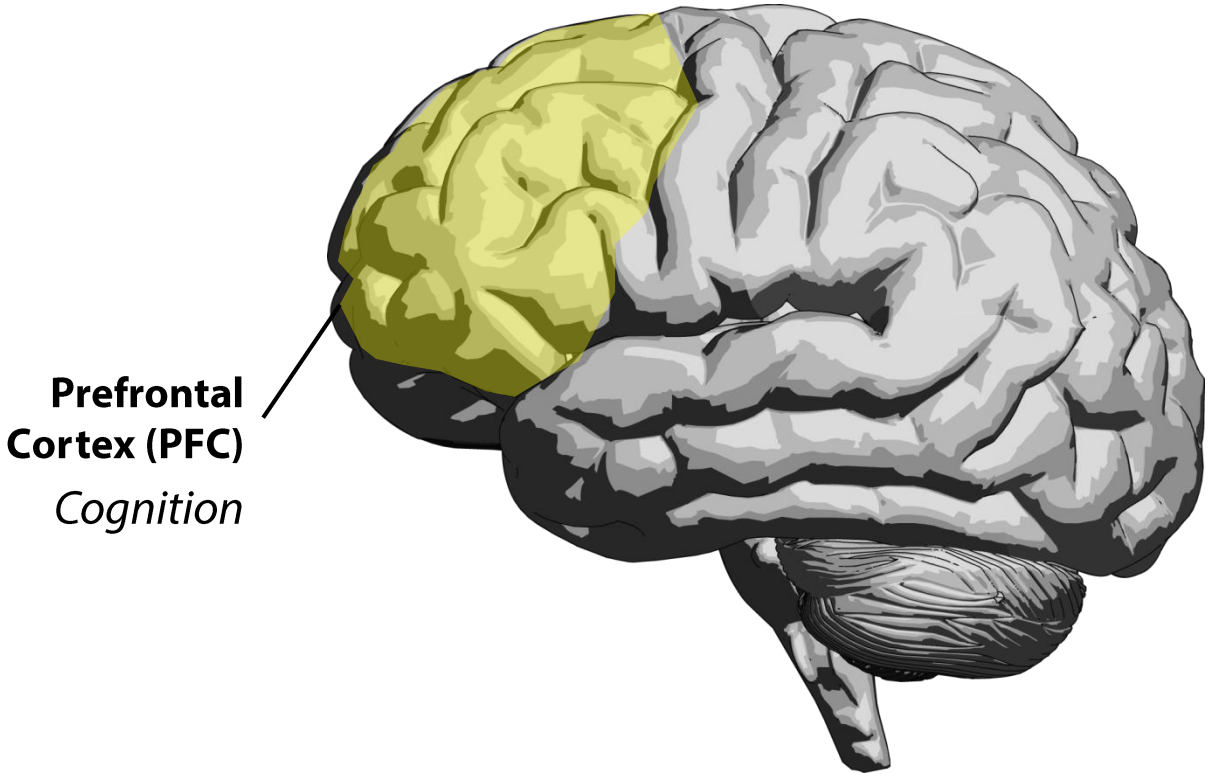
Objectives

- Identify the basic structure and functions of the brain
- List the steps in neurotransmission and describe what happens in each one
- Explain some of the current theories of the causes of bipolar disorder and schizophrenia

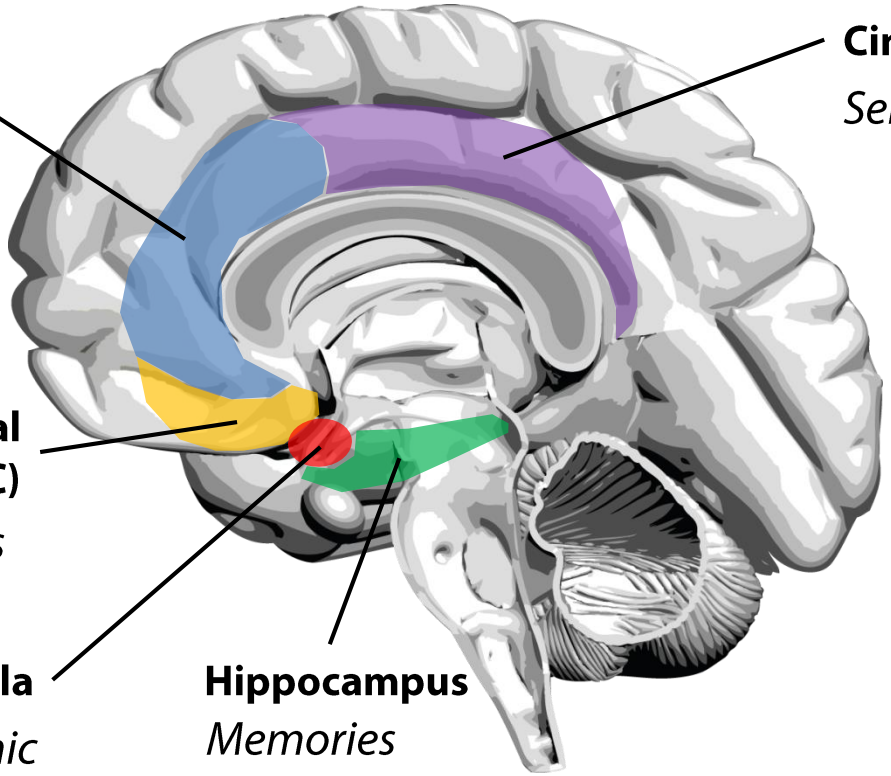
Major Regions of the Brain
Cerebral Cortex



Frontal (Cortical) Regions



Limbic System



Anterior Cingulate Cortex (ACC)
Emotion regulation; actions & rewards

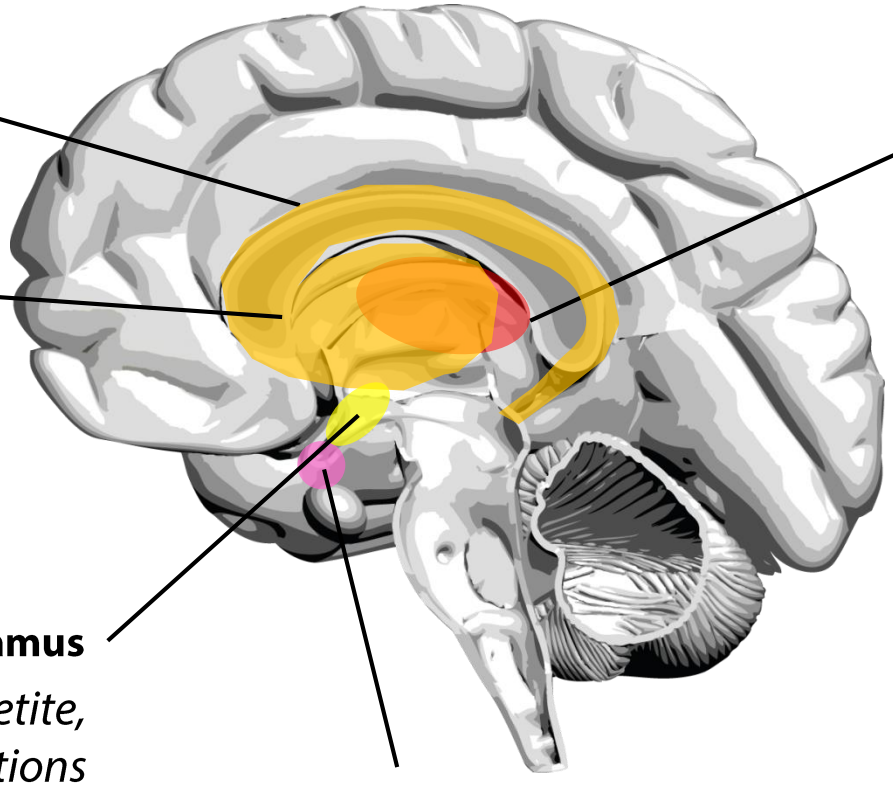
Cingulate Cortex
Selective attention

Ventromedial Prefrontal Cortex (VMPFC)
Emotions

Amygdala
Fear, anxiety, panic

Hippocampus
Memories

Basal Ganglia & Other Structures



Basal ganglia

Nucleus accumbens

Pleasure, libido, interests, fatigue, motivation

Hypothalamus

Sleep, appetite, endocrine functions

Pituitary gland

"Master gland" – hormonal regulation

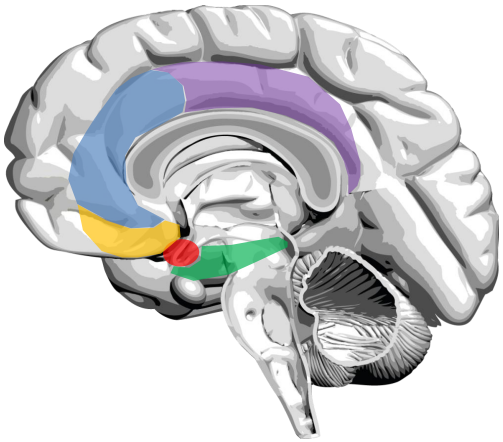
Thalamus

Relaying sensory & motor signals to cortex

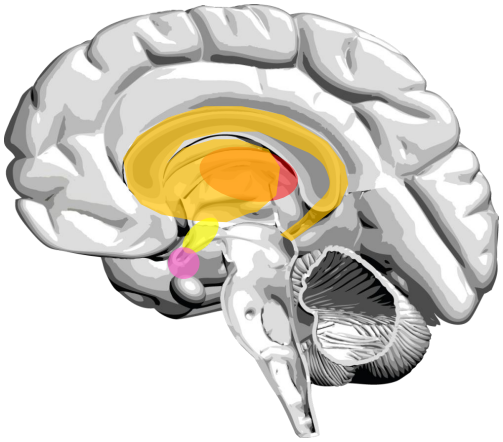
Structure and Function

OUTER → **INNER**

Higher cognitive functions



Emotions
Attention
Reward

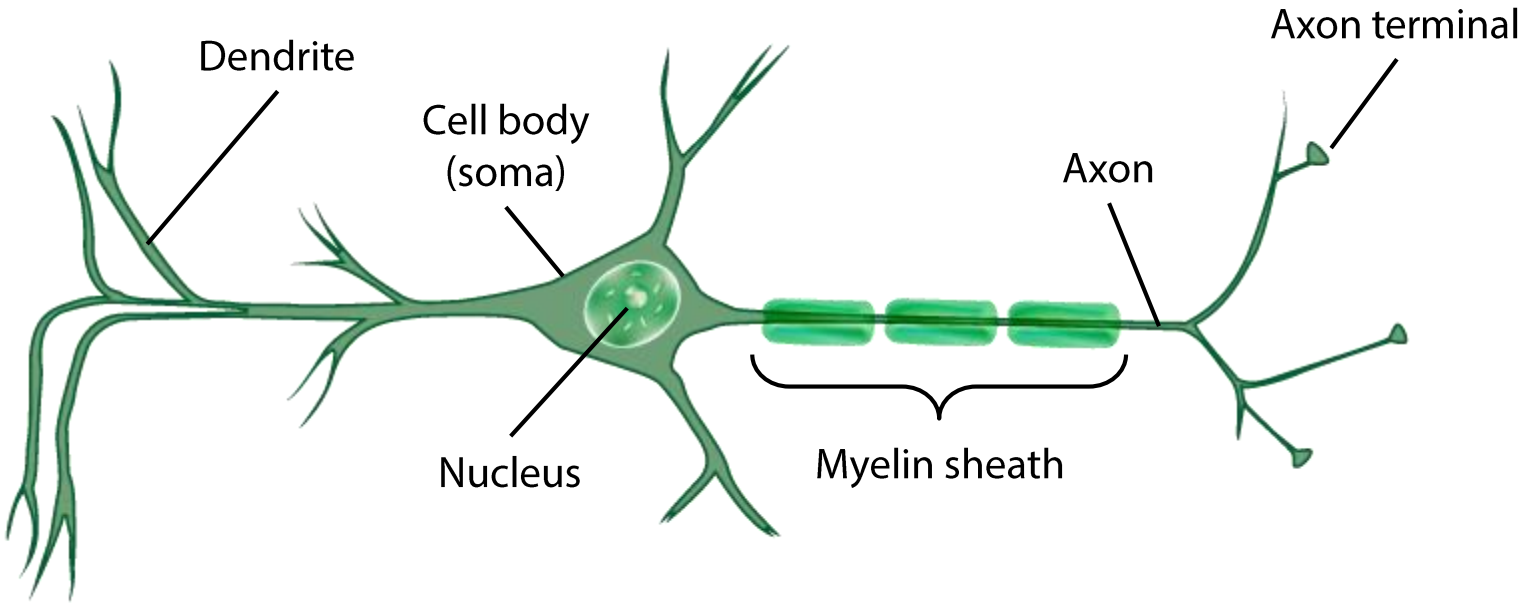


Movement regulation
Sensory regulation
Consciousness

Key Takeaways

- The **frontal (cortical) regions** of the brain are the home of higher cognitive functions, including attention, decision making, and problem solving
- The **limbic system** of the brain is involved with emotion regulation, the association of actions with rewards, the processing of fear, anxiety and panic, and memories
- The **basal ganglia** are involved with regulation of movement and sensory input, as well as pleasure, libido, interests, and motivation

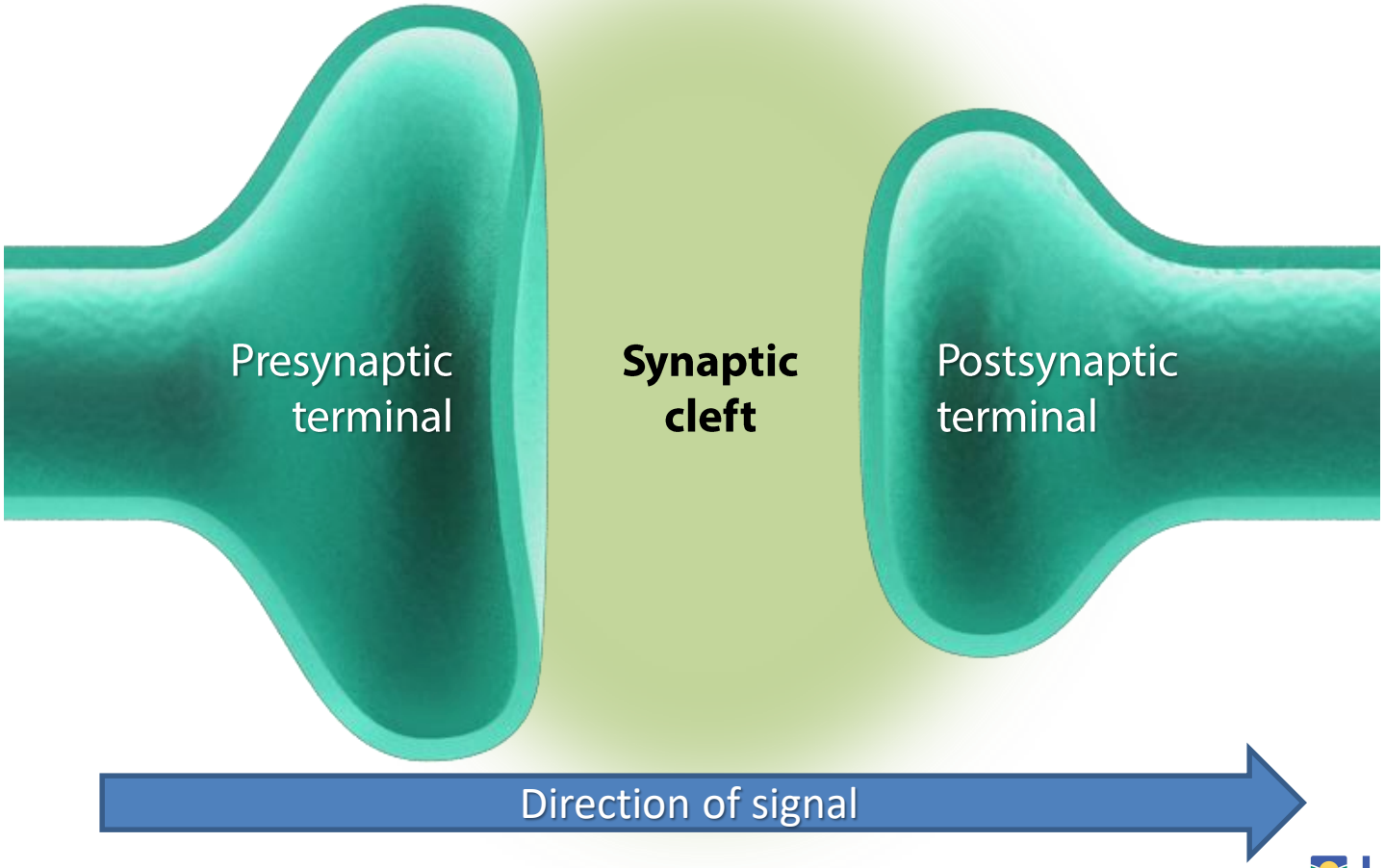
Neurons – General Structure



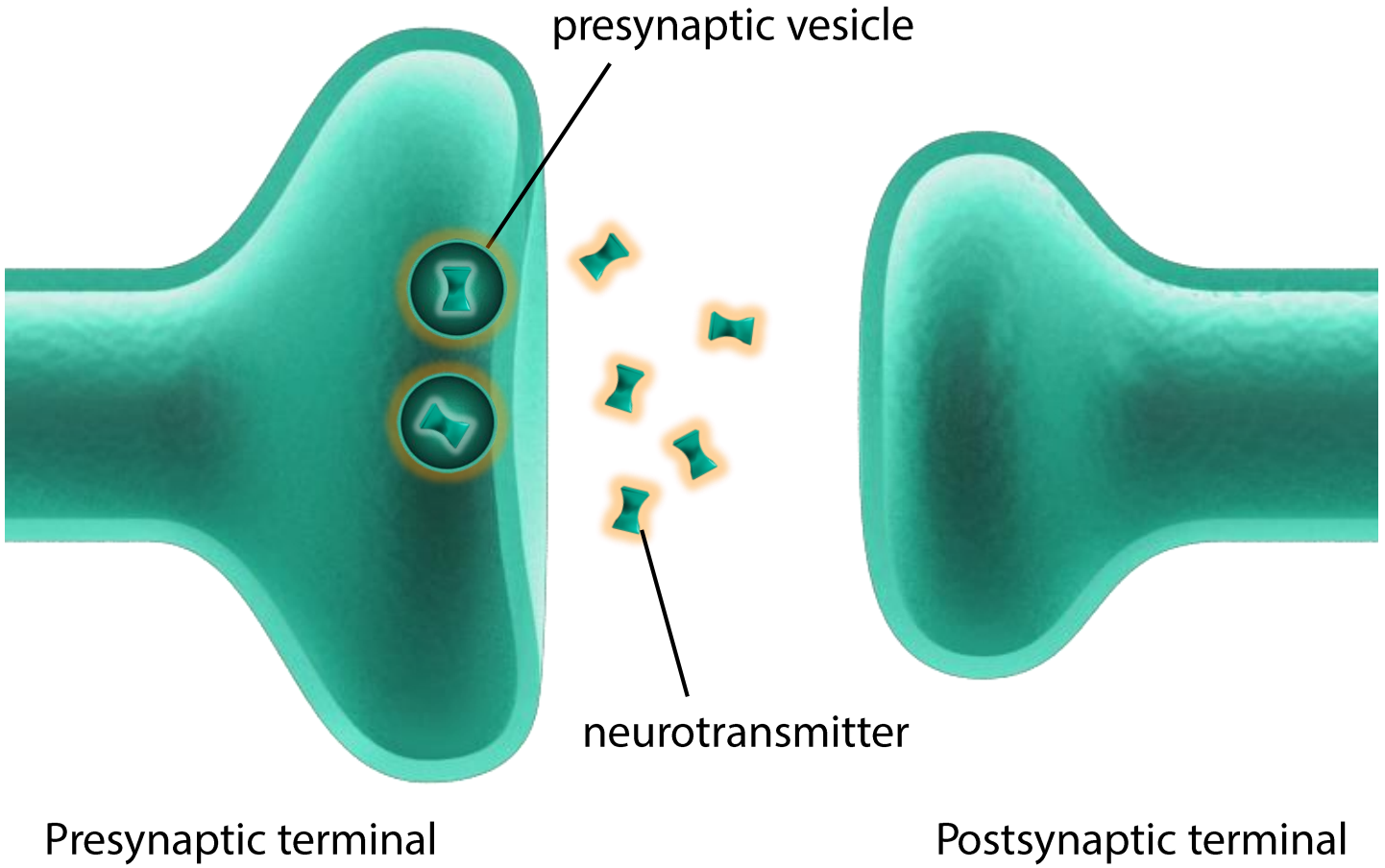
Key Takeaways

- The **neuron** is the basic functional unit of the brain, and receives and transmits information by means of both chemical and electrical signaling
- The three major components of the neuron are:
  - The **soma**, or cell body
  - The **dendrite**, which receives signals from other neurons
  - The **axon**, which sends signals to other neurons

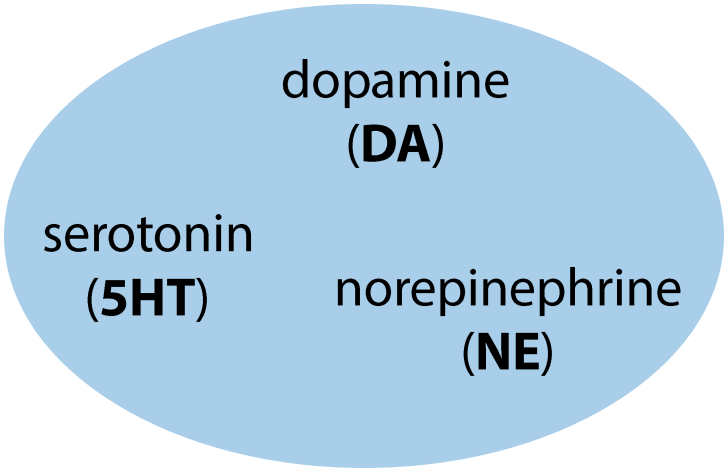
Synapses



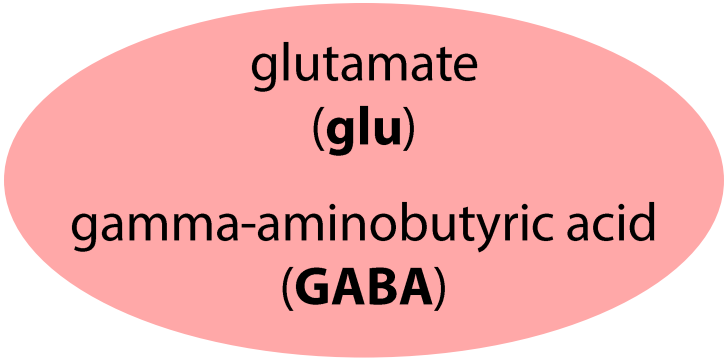
Neurotransmitters



Some Key Neurotransmitters



monoamines

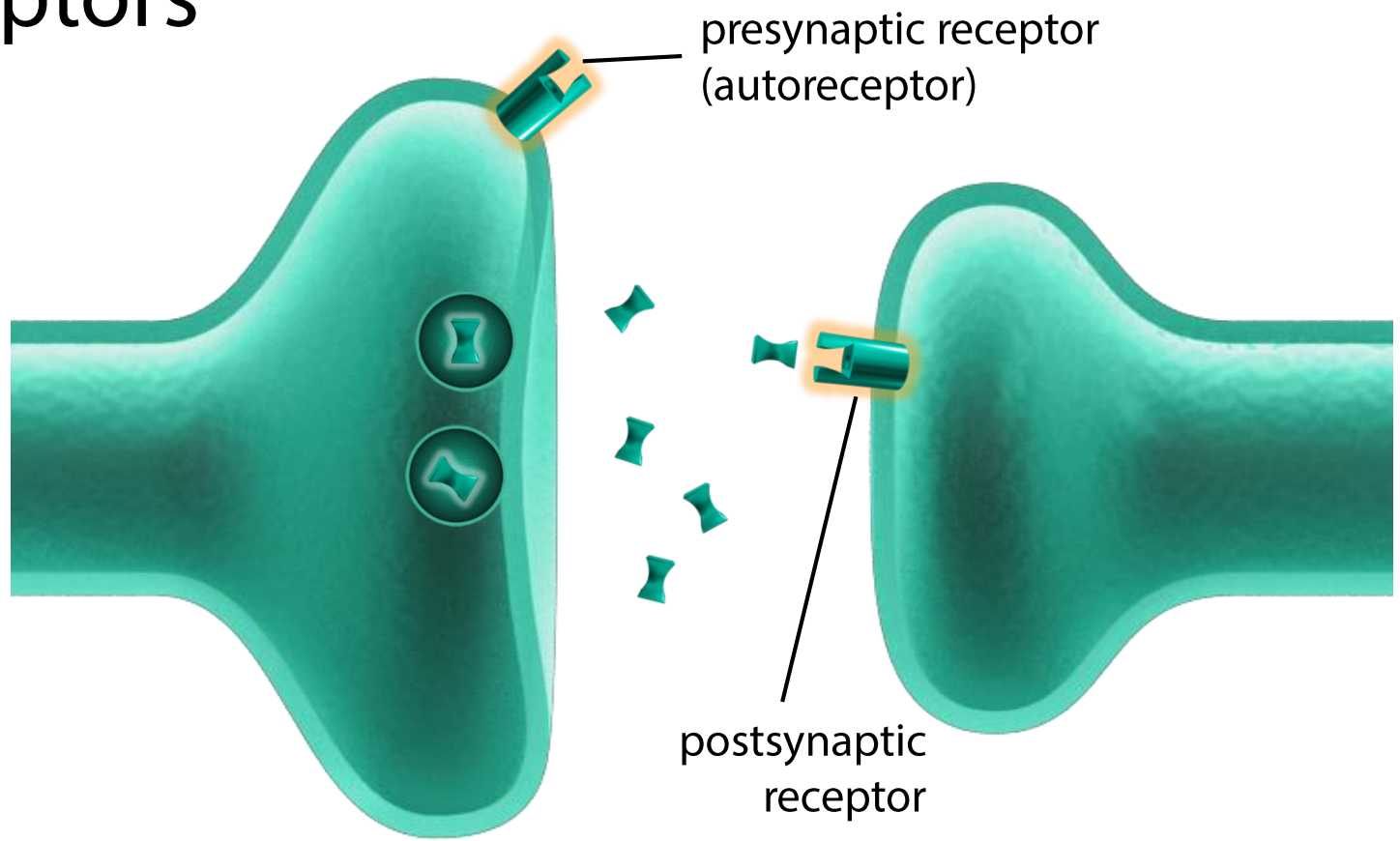


amino acids

Key Takeaways

- The brain is estimated to have trillions of connections, or **synapses**, between neurons
- **Neurotransmitters** are the chemical messengers that convey information from one neuron to another
- Some neurotransmitters that are hypothesized to have key roles in psychiatric disorders, particularly bipolar disorder and schizophrenia, include:
  - **Dopamine**
  - **Serotonin**
  - **Norepinephrine**
  - **Glutamate**
  - **GABA**

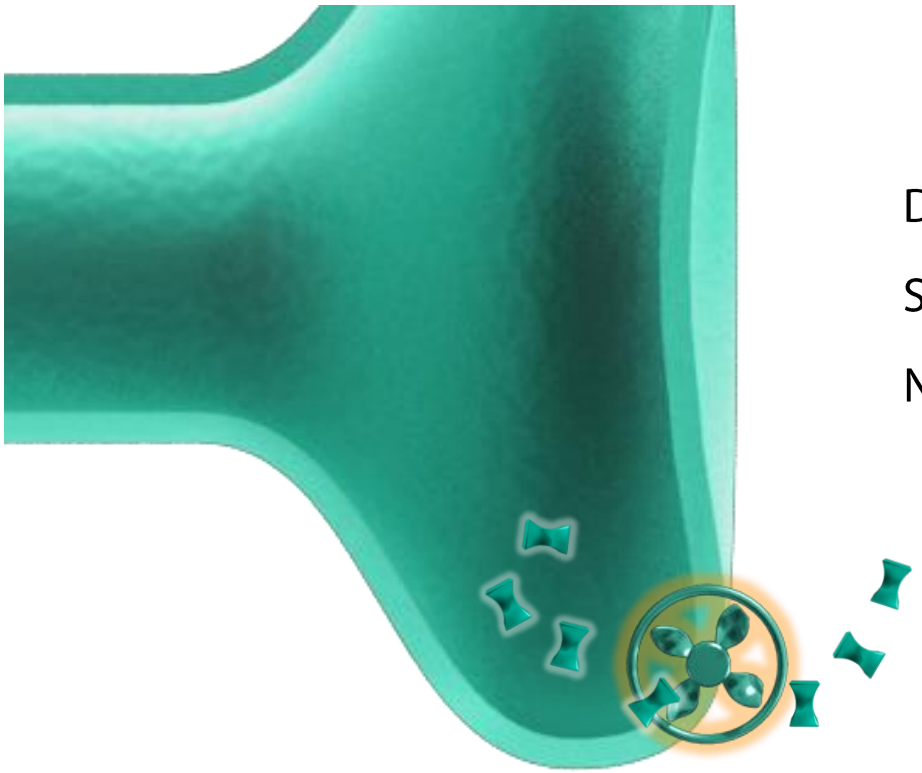
Receptors



Key Takeaways

- **Receptors** are specialized proteins to which neurotransmitters selectively bind
- **Multiple receptor subtypes** typically exist for a given neurotransmitter; these subtypes often have different structure, function, and location
- The correlation between receptor binding and clinical outcomes is uncertain

Transporters - Monoamines

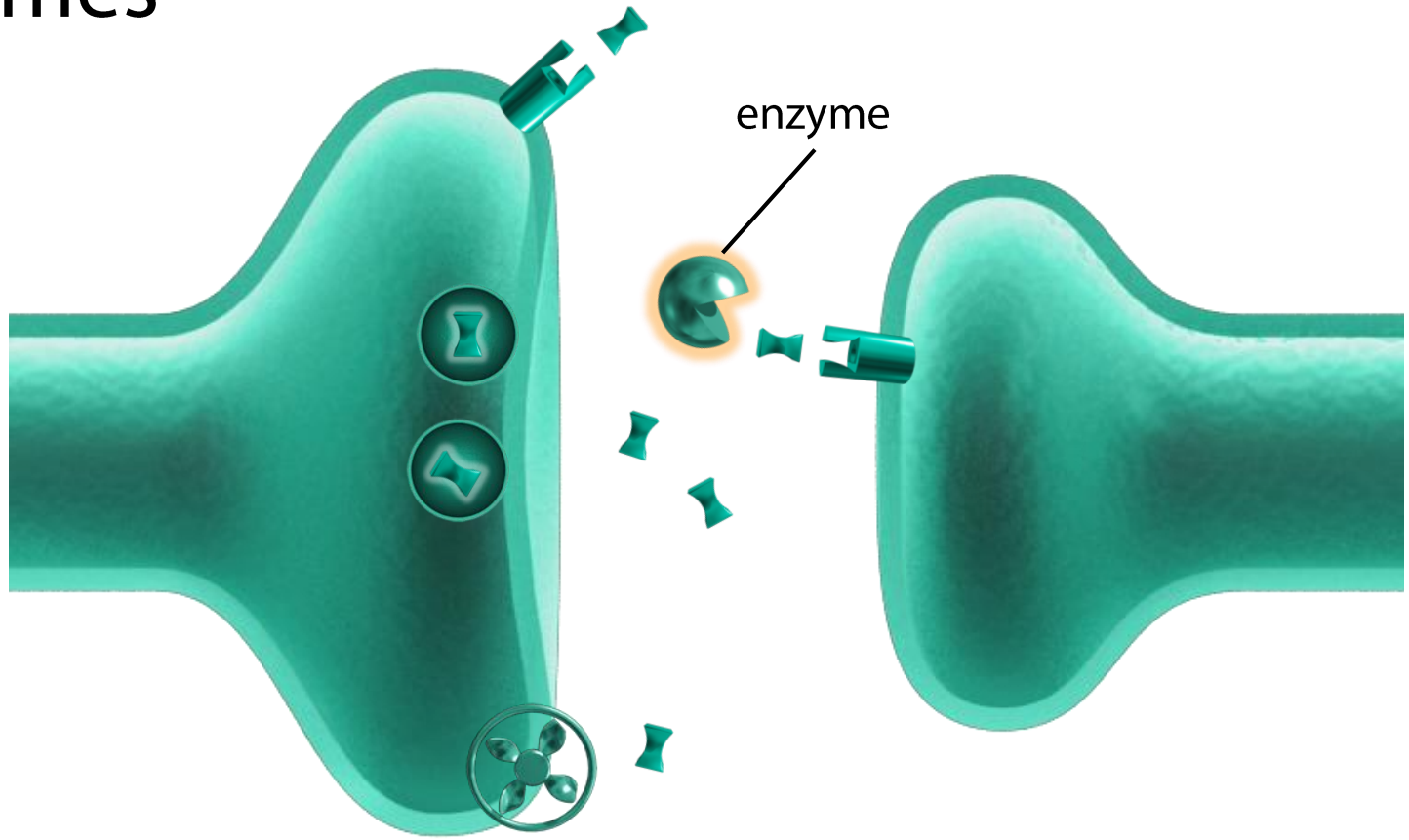


Dopamine transporter (DAT)

Serotonin transporter (SERT)

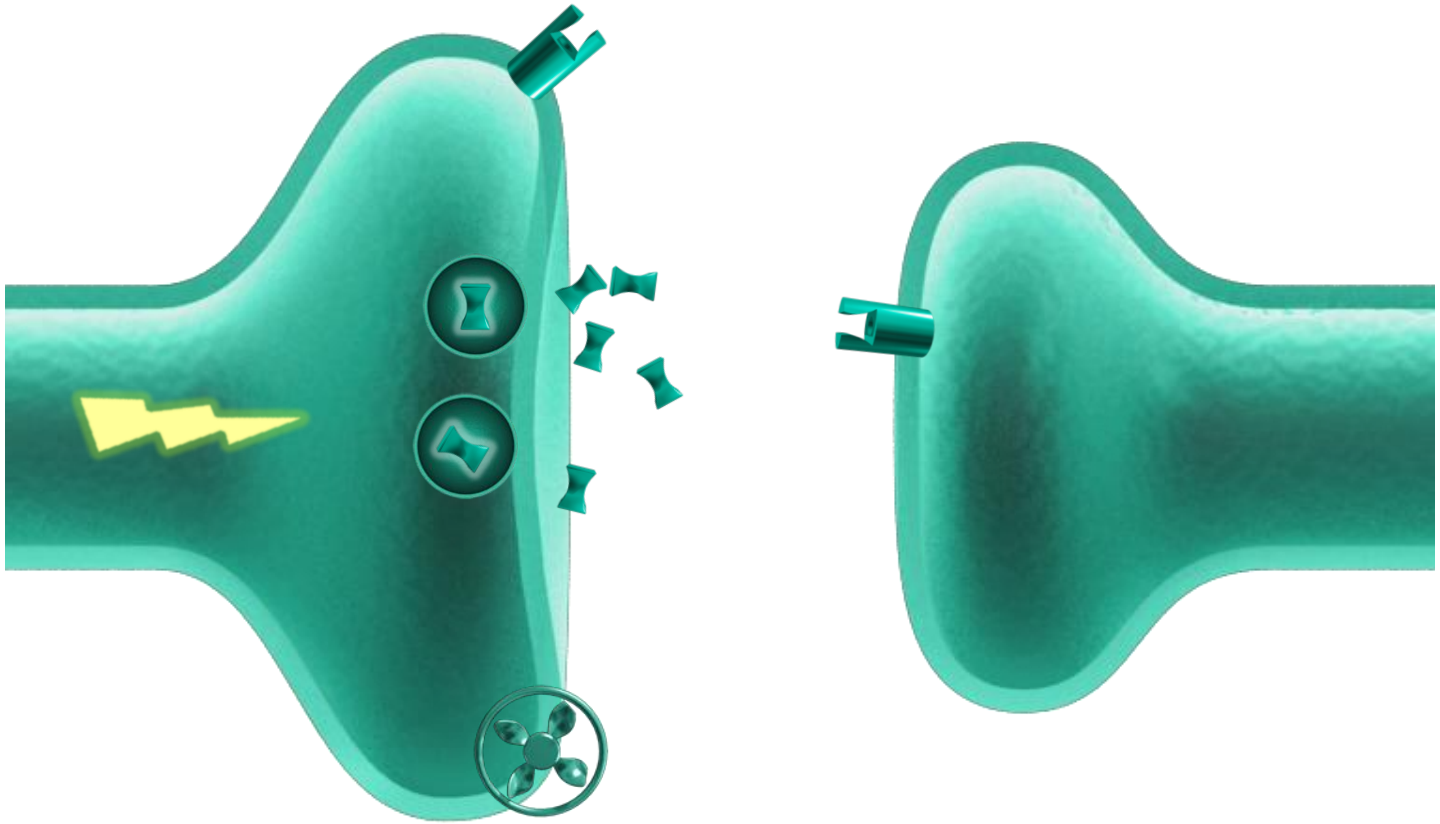
Norepinephrine transporter (NET)

Enzymes



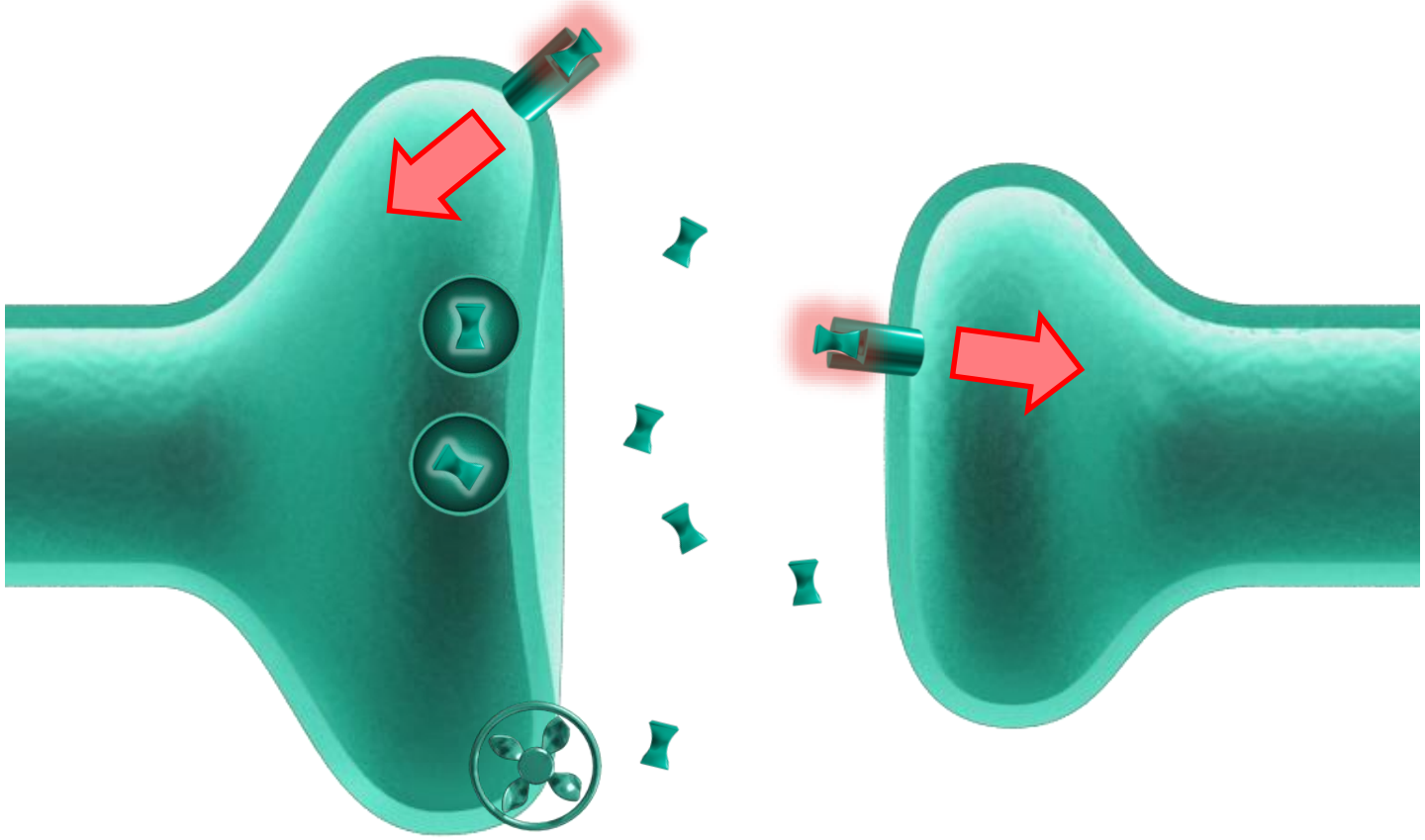
Neurotransmission

Electrical Impulse and Neurotransmitter Release



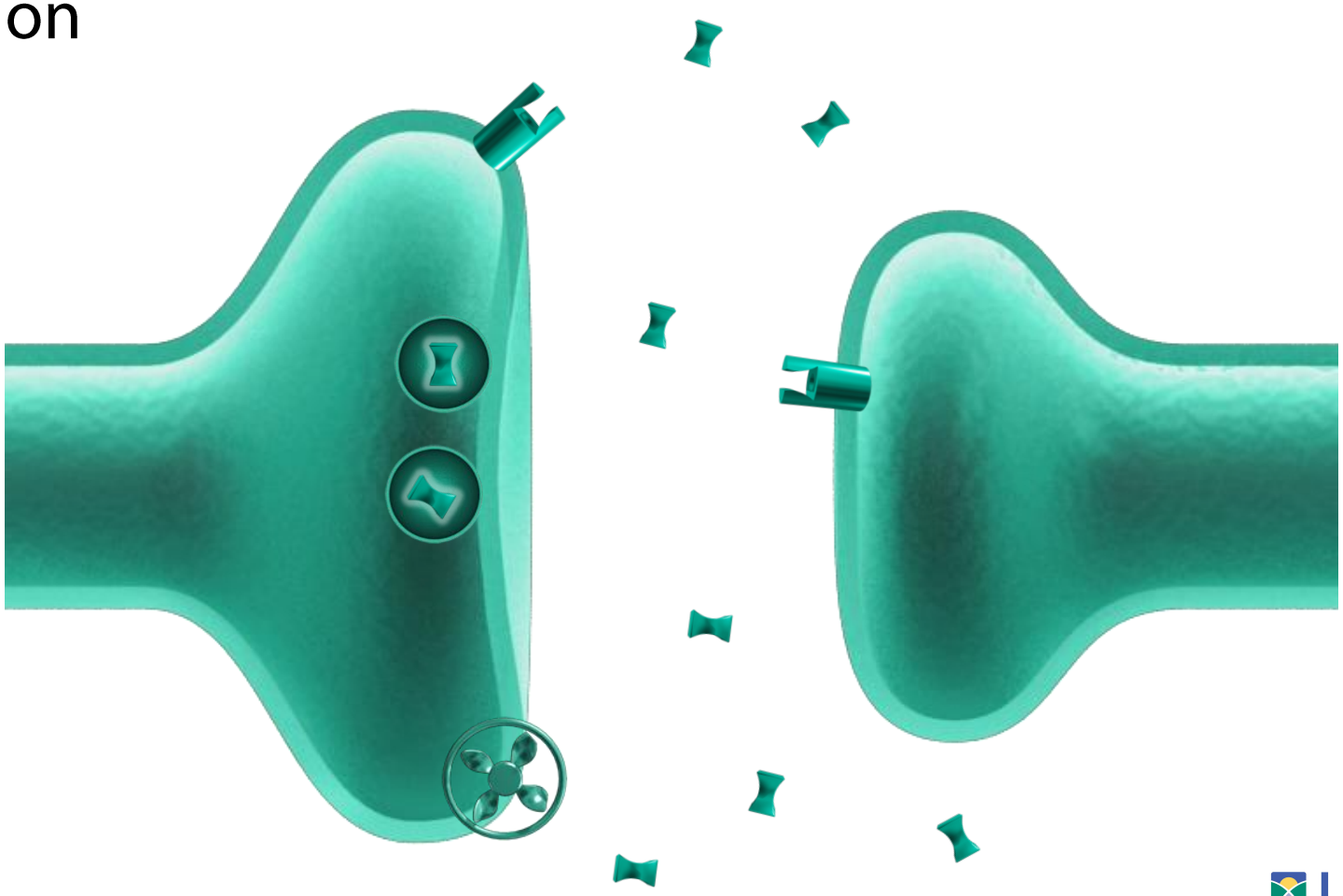
Neurotransmission

Receptor Binding and Signal Propagation



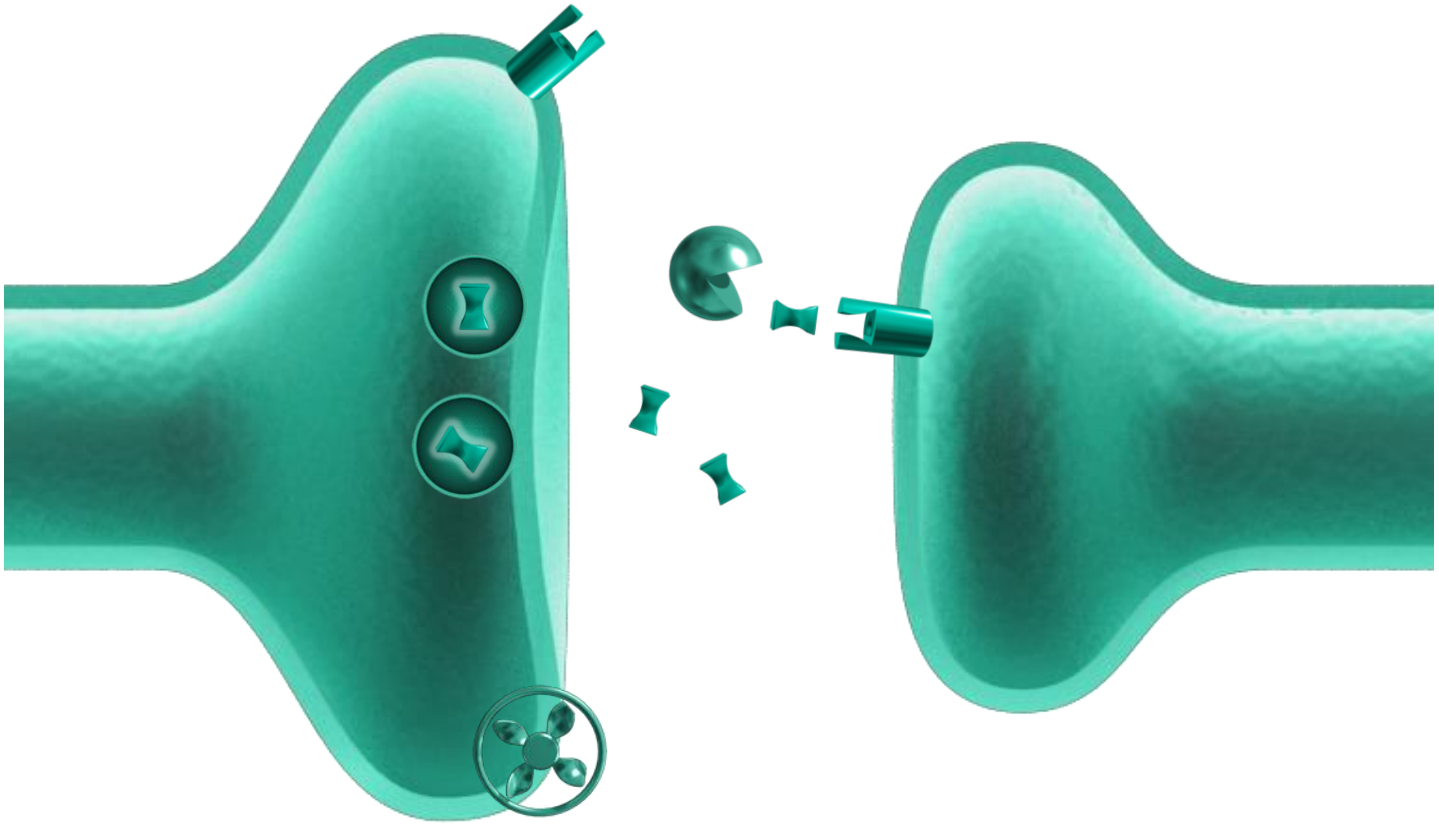
Neurotransmission

Diffusion



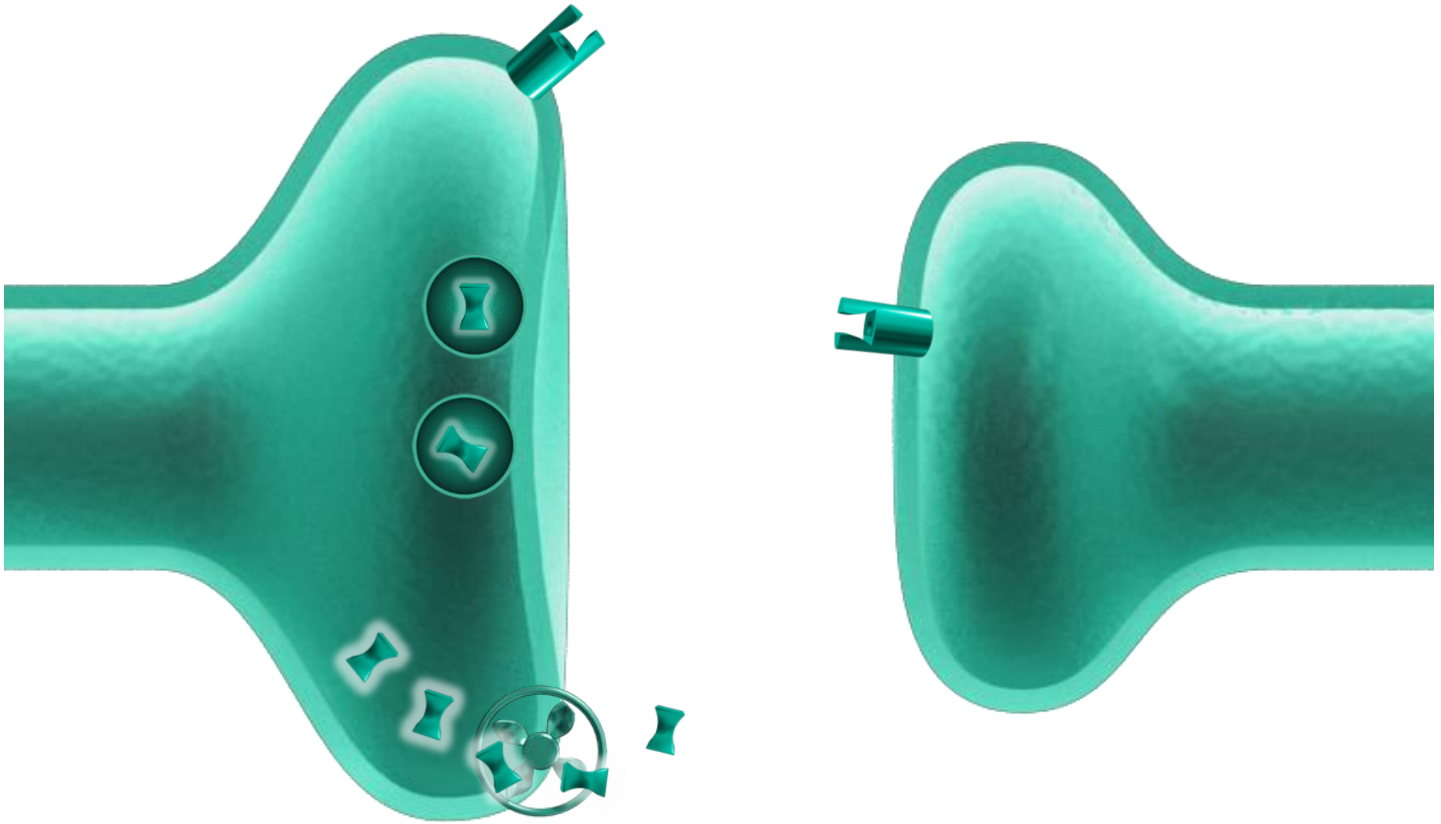
Neurotransmission

Degradation



Neurotransmission

Reuptake



Key Takeaways

Major steps in neurotransmission

1. An electrical impulse is created within the presynaptic neuron. The stimulus for this impulse can be neurotransmitters, light, drugs, hormones, or nerve impulses.
2. The electrical signal travels down the axon and arrives at the presynaptic terminal, where it triggers the release of neurotransmitters into the synaptic cleft.

Key Takeaways

Major steps in neurotransmission (continued)

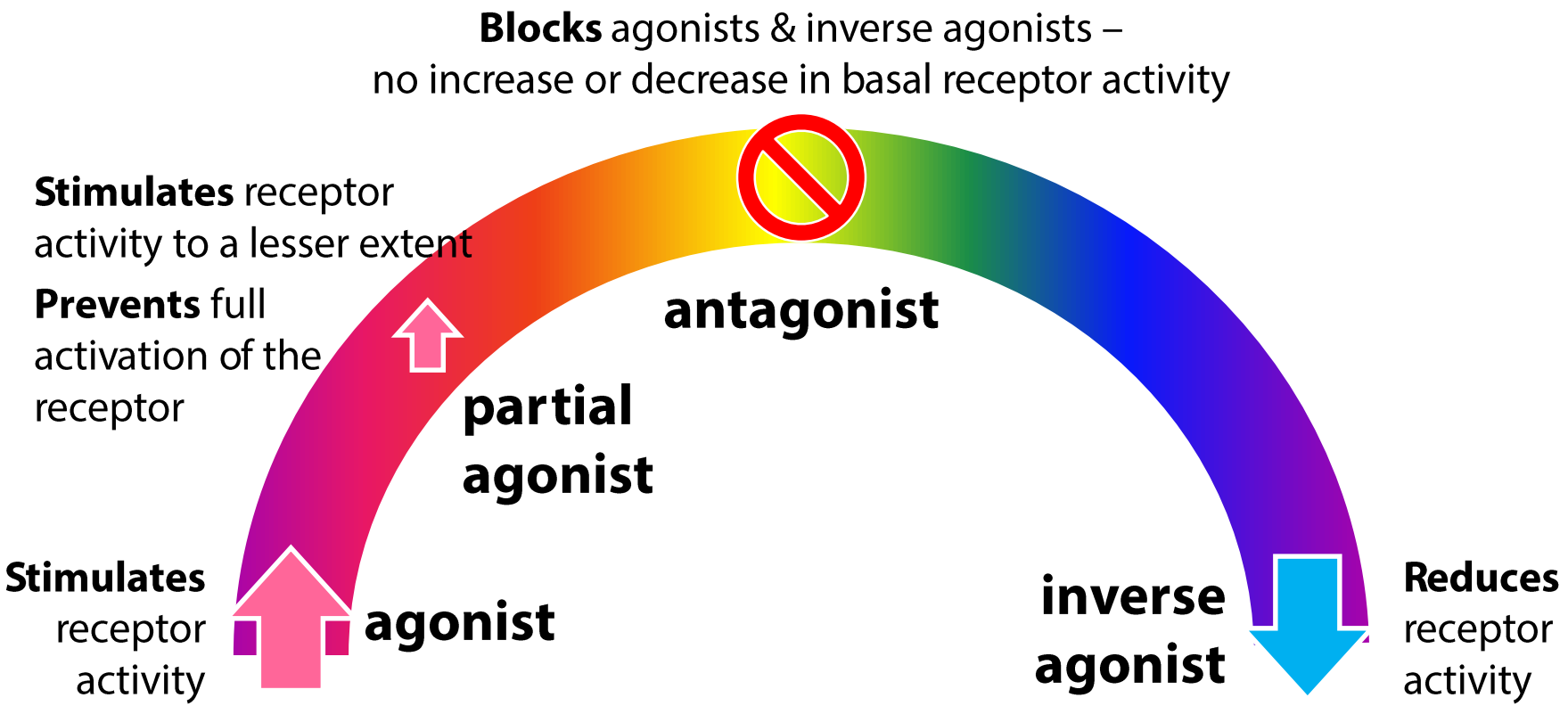
3. Neurotransmitters diffuse in the synaptic cleft. Some neurotransmitters bind to their corresponding receptor, either on the postsynaptic surface or on the presynaptic surface.
4. The receptor is activated and, in the case of a postsynaptic receptor, the signal propagates down the receiving neuron.

Key Takeaways

Major steps in neurotransmission (continued)

5. Neurotransmitters can be removed from the synaptic cleft by any of three mechanisms:
   - **Diffusion**
   - **Degradation** by enzymes
   - **Reuptake** by transporters

The Agonist Spectrum



Key Takeaways

- An **agonist** is a molecule that **increases the activity** of its bound receptor
- A **partial agonist** is a molecule that stimulates its specific receptor, but to a lesser extent than a full agonist would. Upon binding, the partial agonist also prevents the full activation of the receptor
- An **antagonist** is a molecule that blocks both agonists and inverse agonists, but by itself **neither increases nor decreases the activity** of the receptor

Bipolar Disorder

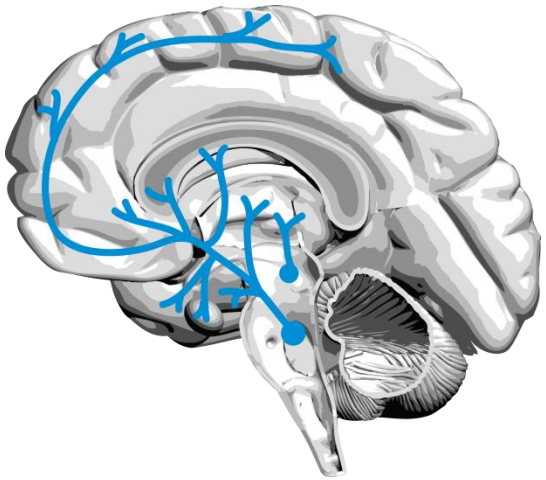
MANIC EPISODE
Abnormally elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy

MAJOR DEPRESSIVE EPISODE
Depressed mood or loss of interest

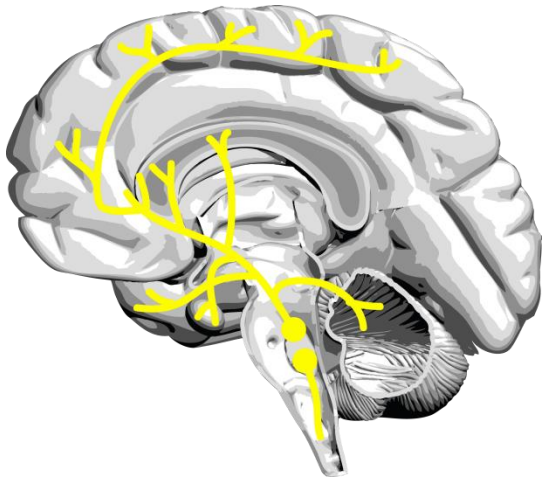
HYPOMANIC EPISODE
Elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy

Etiological Theories of Bipolar Disorder

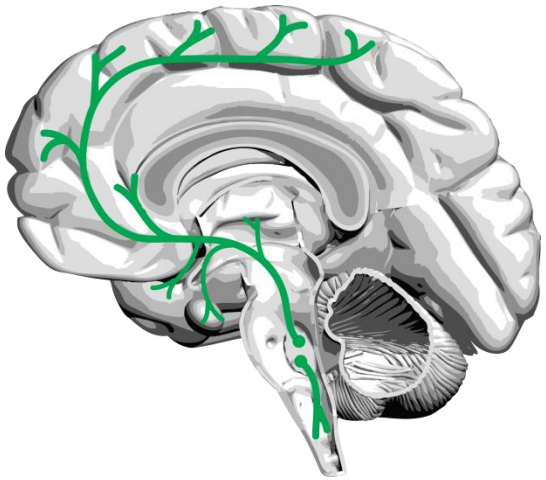
Circuits and Symptoms in Bipolar Disorder



dopamine pathways



serotonin pathways



norepinephrine pathways

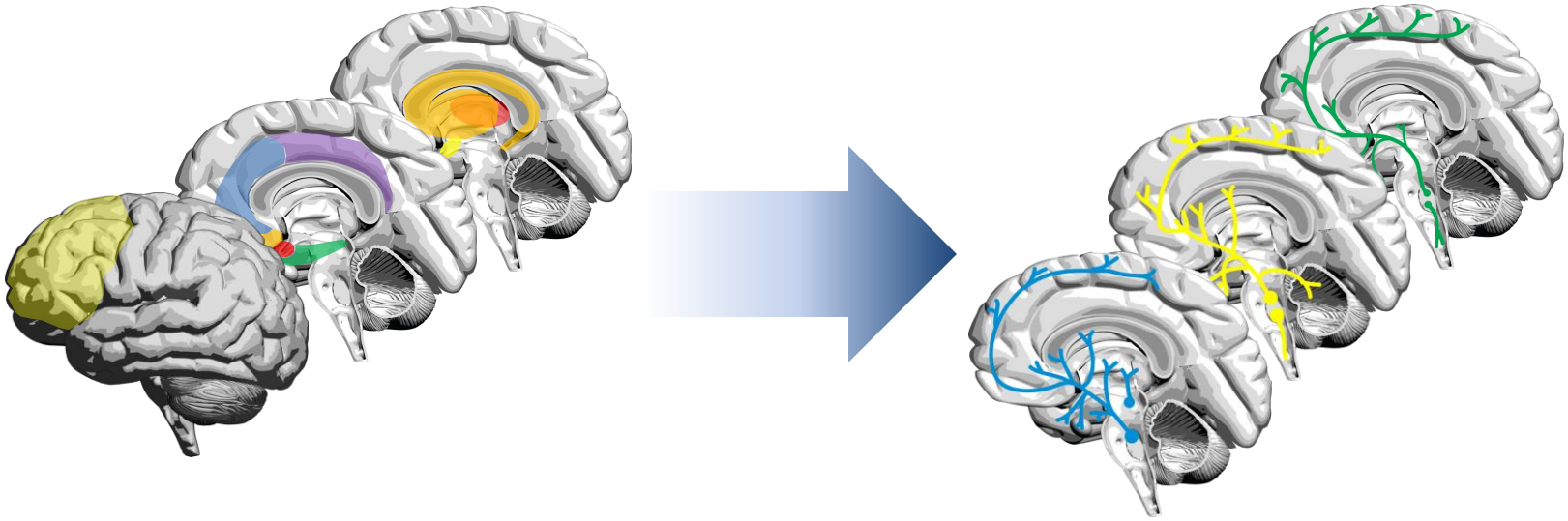
MONOAMINE HYPOTHESIS: deficiency of any or all of these three neurotransmitters is thought to account for depressive symptoms.

Etiological Theories of Bipolar Disorder

Circuits and Symptoms in Bipolar Disorder

Brain functions / disease symptoms are associated with specific brain regions…

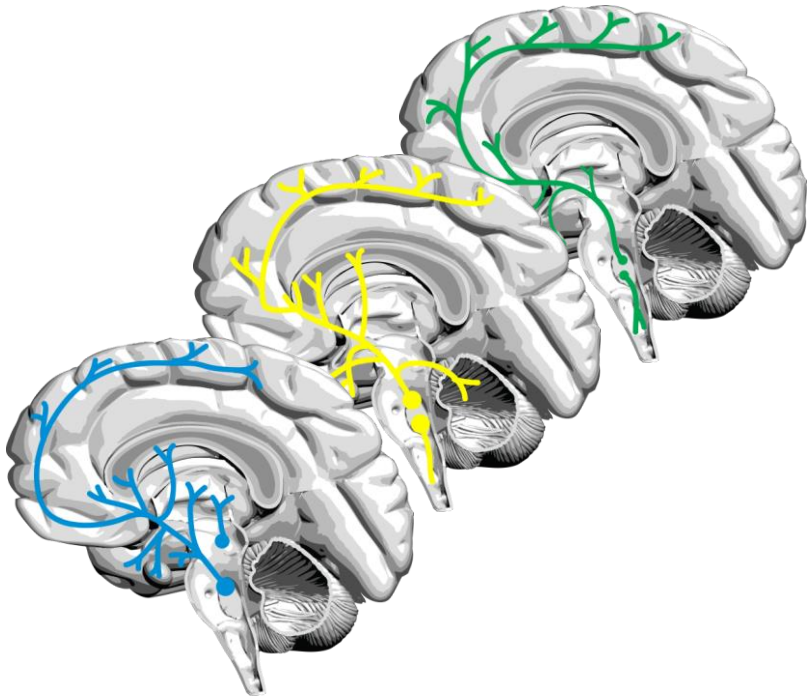
…and the monoamine neurotransmitter circuits that stimulate these regions can be identified



Etiological Theories of Bipolar Disorder

Circuits and Symptoms in Bipolar Disorder

Treatments for bipolar disorder may "tune" neurotransmission in malfunctioning circuits



? ATYPICAL ANTIPSYCHOTICS

? MOOD STABILIZERS

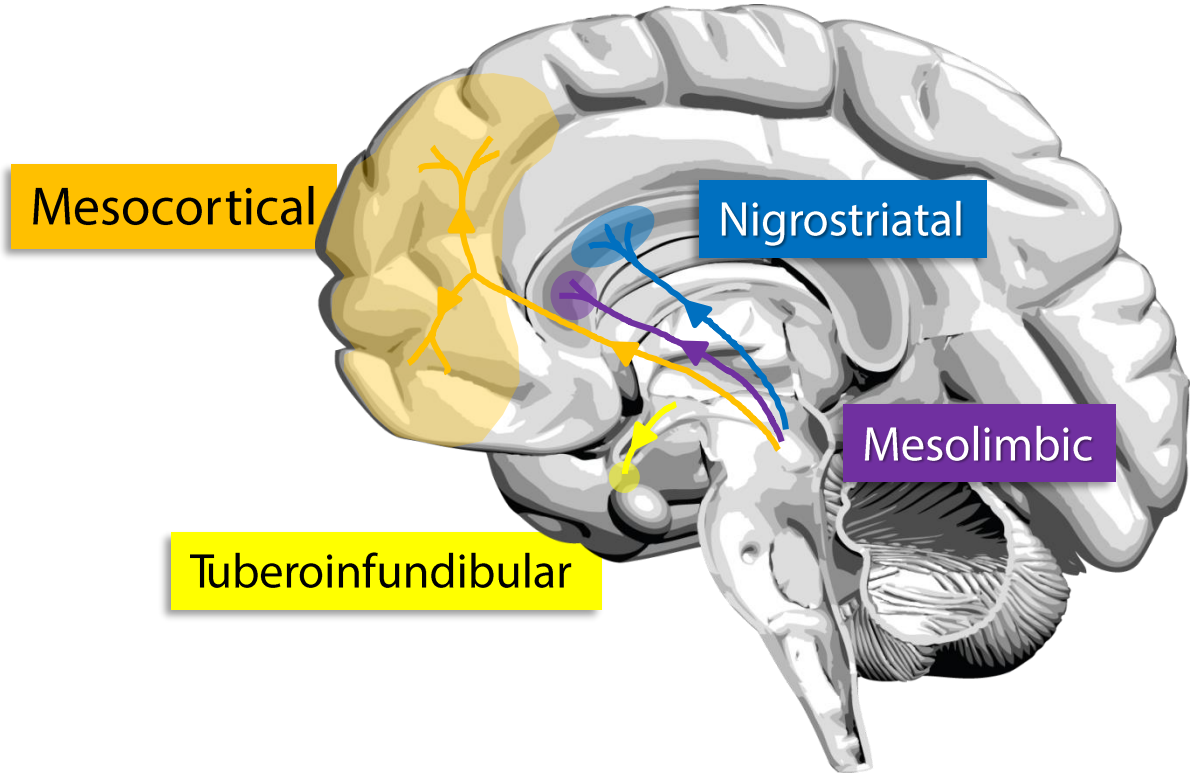
? ANTICONVULSANTS

? ANTIDEPRESSANTS

Key Takeaways

- *Symptoms* of bipolar disorder may involve dysfunction in specific neuronal *circuits* that employ various combinations of three monoamine neurotransmitters – dopamine, serotonin, and norepinephrine
- In bipolar disorder, neurotransmission in monoamine circuits is theorized to be "out of tune"; as a result, depending on the type of mood episode, some brain regions may have abnormally increased levels of neuronal activation, while others may have abnormally decreased levels

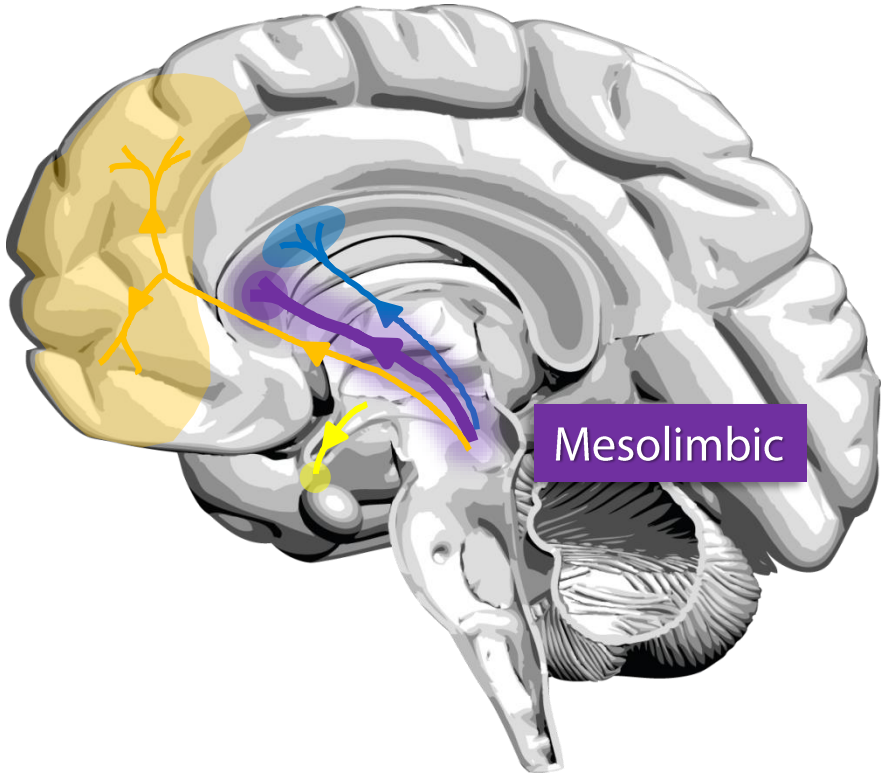
The Dopamine Hypothesis of Schizophrenia



The Dopamine Hypothesis of Schizophrenia

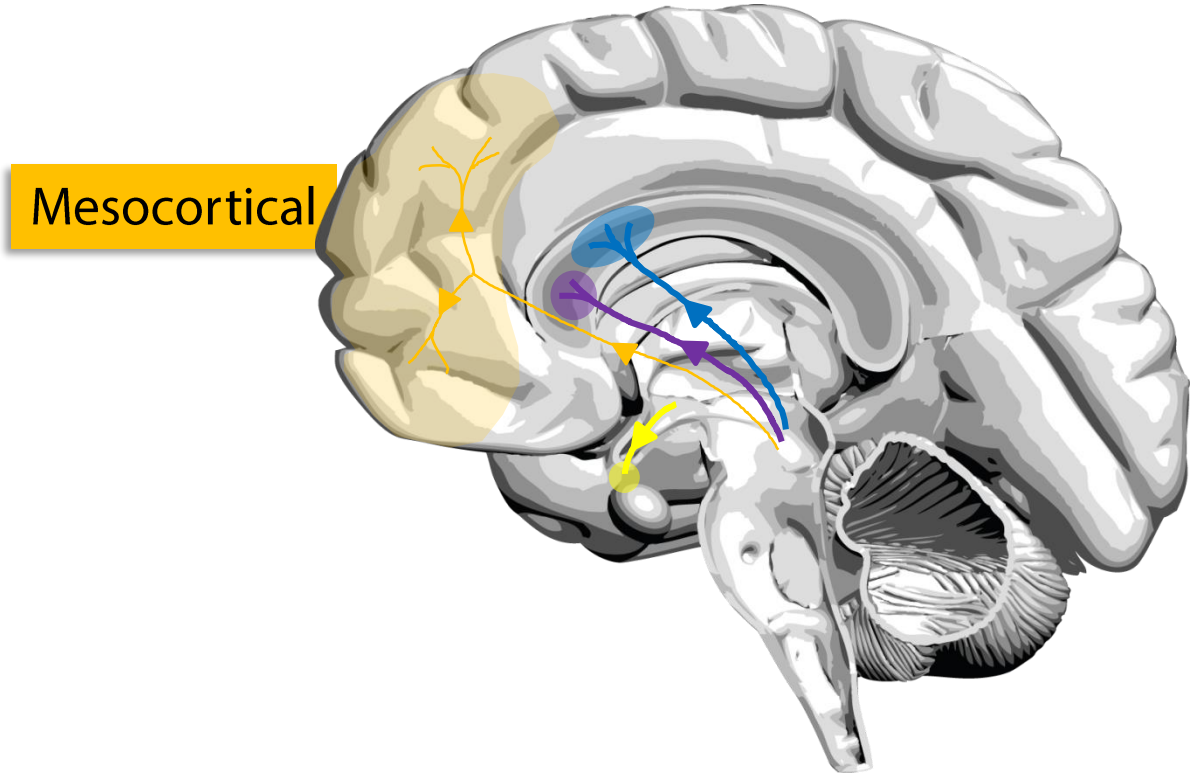
The Mesolimbic Dopamine Pathway

- Appears to be **hyperactive** in schizophrenia
- Abnormally high levels of dopamine
- Associated with positive symptoms of schizophrenia



The Dopamine Hypothesis of Schizophrenia

The Mesocortical Dopamine Pathway



Appears to be **hypoactive** in schizophrenia

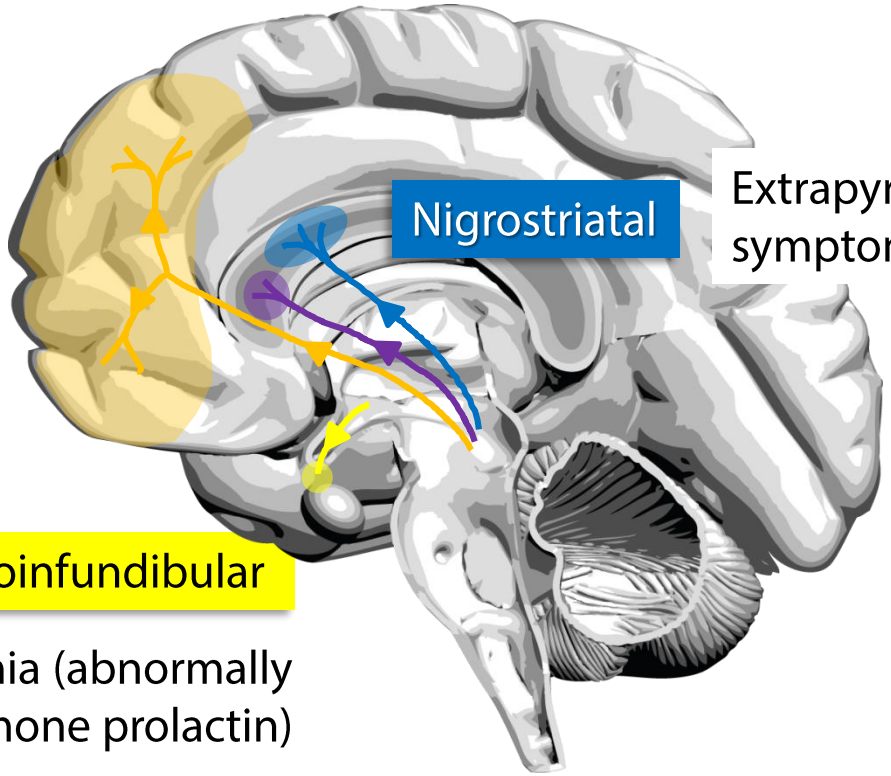
Deficit of dopamine

Associated with other symptoms of schizophrenia

The Dopamine Hypothesis of Schizophrenia

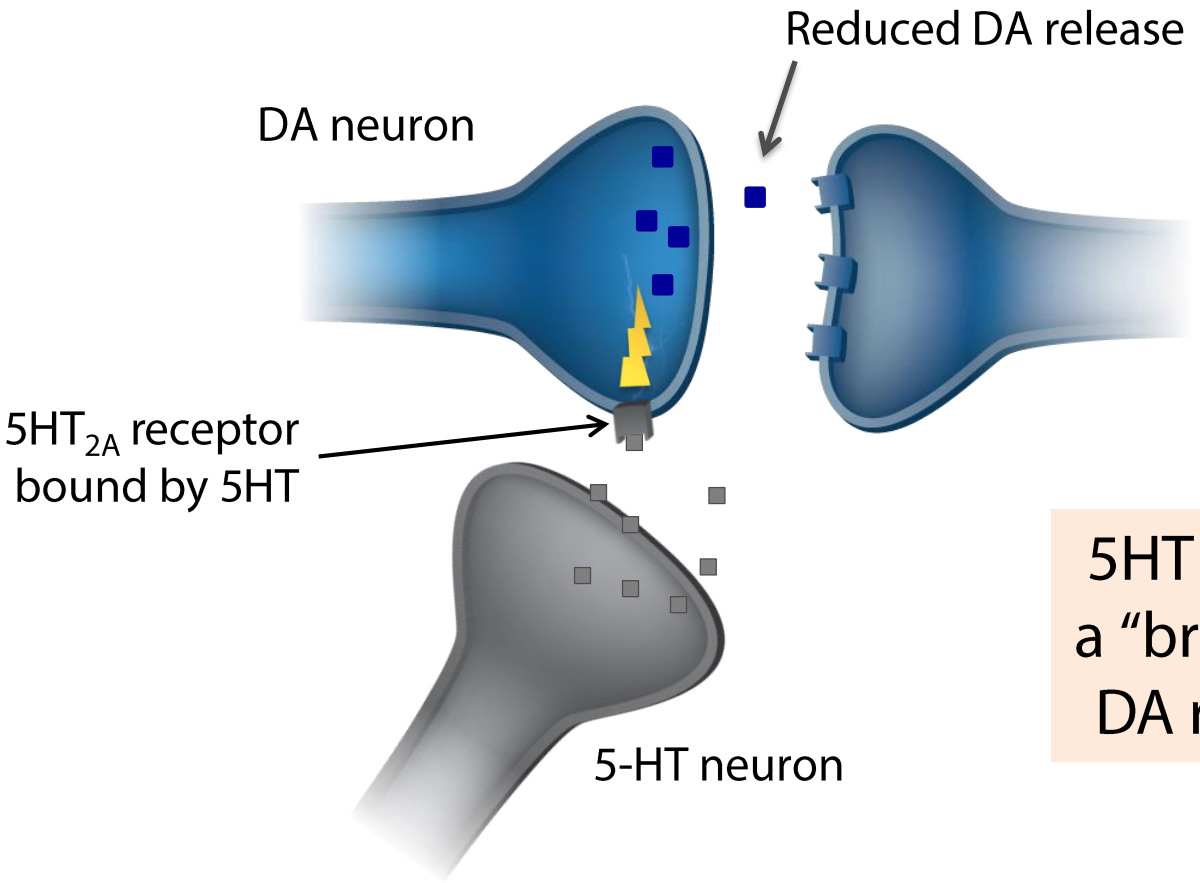
Other Dopamine Pathways

Thought to be involved in certain side effects associated with antipsychotic medications



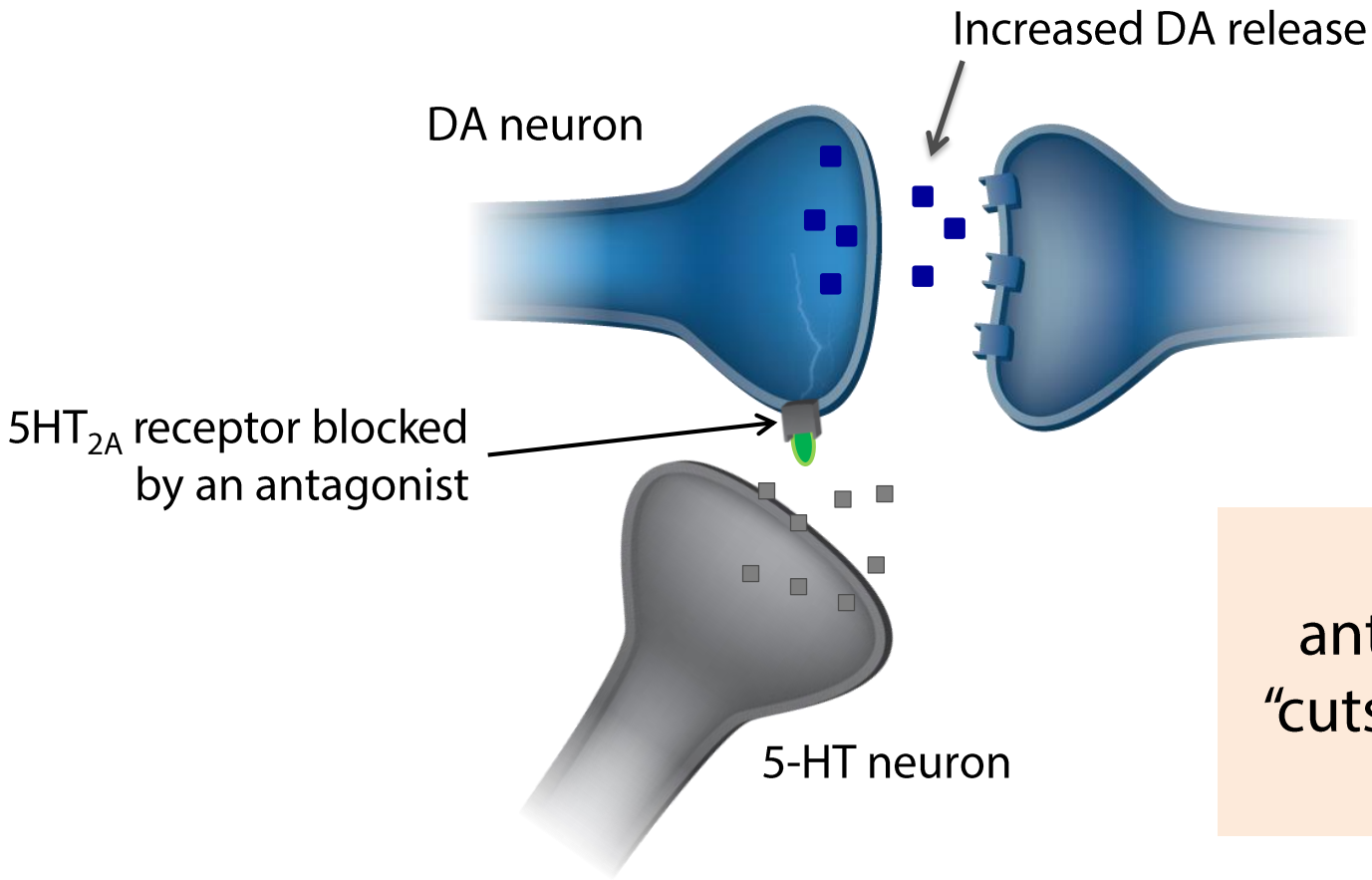
Hyperprolactinemia (abnormally high levels of the hormone prolactin)

Serotonin and Schizophrenia



5HT acts as a "brake" on DA release

Serotonin and Schizophrenia



$5HT_{2A}$ antagonism "cuts the brake cable"

Key Takeaways

- In schizophrenia, the mesolimbic dopamine pathway appears to be **hyperactive**, releasing abnormally high levels of dopamine and giving rise to positive psychotic symptoms
- In schizophrenia, the mesocortical dopamine pathway appears to be **hypoactive**, resulting in a deficit of dopamine and giving rise to other symptoms of schizophrenia
- Serotonin can have an effect on dopaminergic neurotransmission, for example, through activity at the 5-HT_{2A} receptor

GLOSSARY

agonist - an agent, such as a neurotransmitter or drug, that binds to and stimulates a receptor; by definition, an agonist increases the activity of the bound receptor

antagonist - an agent that blocks both agonists and inverse agonists, but by itself neither increases nor decreasesthe activity of the receptor itself anterior cingulate cortex (ACC)- the forward portion of the cingulate cortex which is thought to be involved in emotion regulation and the formation of associations between actions and rewards or fear

axon - a specialized extension of the neuron that sends information to other neurons autoreceptor - a receptor that is involved with the self-regulation of neurotransmitter release by a neuron basal ganglia - a curved, horn-shaped collection of structures within the brain located beneath the cerebral cortex and wrapped around the thalamus cerebral cortex - the heavily wrinkled outer layer of the brain

corticostriatal loops - regulatory circuits within the brain that are connected to the cerebralcortex degradation - the chemical destruction or breakdown of substances such as neurotransmitters

dendrite – a specialized and often branched extension of the neuron that receives signals from other neurons diffusion - spontaneous, random, thermally-driven motion

dopamine (DA)- key monoamine neurotransmitter in the brain endocrine - of or relating to various ductless glands (e.g., thyroid, adrenal, pituitary) that have hormonal secretions that pass directly into the bloodstream

enzyme - a specialized protein that functions as a catalyst for biochemical reactions; degradative enzymes break down specific substances such as neurotransmitters

frontal lobe - the forward portion of the cerebral cortex, which is the center of higher cognitive functions such as attention, decision-making, and emotions

GLOSSARY

gamma-aminobutyric acid (GABA) –	an amino acid that is the chief inhibitory neurotransmitter in the central nervous system
glutamate (glu) –	an amino acid that is the major excitatory neurotransmitter in the central nervous system
hypomanic episode –	a mood disturbance similar to a manic episode but less severe and often shorter in duration
hypothalamus –	a region of the brain that is thought to be involved in the regulation of sleep, appetite and endocrine functions
inverse agonist –	an agent, such as a neurotransmitter or drug, that binds to a receptor and reduces its activity
limbic system –	a collection of structures within the brain that includes the hippocampus and amygdala, and is involved with attention, memories, fear, anxiety, and panic
major depressive episode –	a mood disturbance in which the patient experiences depressed mood or loss of interest
manic episode –	a mood disturbance in which the patient experiences abnormally elevated, expansive, or irritable mood and associated behavioral changes
monoamine hypothesis –	a classical theory of the etiology of depression in which a deficiency of dopamine, serotonin, and/or norepinephrine was thought to account for the symptoms of depression
myelin –	a fatty sheath that surrounds and insulates the axon, increasing the transmission rate of electrical signals that propagate through it
neuron –	a nerve cell; the basic functional unit of the brain
neurotransmitter –	a general term to describe a chemical messenger that conveys information from one neuron to another

GLOSSARY

norepinephrine (NE) –	a key monoamine neurotransmitter; also known as noradrenaline (especially outside of the United States)
nucleus accumbens –	a region of the striatum thought to play a role in pleasure, libido, interests, fatigue, and motivation
partial agonist –	a molecule that stimulates its specific receptor, but to a lesser extent than a full agonist would
postsynaptic –	referring to the receiving neuron during neurotransmission
prefrontal cortex (PFC) –	a portion of the frontal lobe that is responsible for cognition and has been strongly linked to psychiatric symptoms
presynaptic –	referring to the sending neuron during neurotransmission receptor- a specialized protein that binds specifically to substances such as neurotransmitters or drugs
reuptake -	the process by which neurotransmitters are returned to the presynaptic terminal from the synapse
sagittal plane -	a longitudinal plane that divides a bilaterally symmetrical body (such as the brain) into left and right sections
serotonin (5-HT) -	a key monoamine neurotransmitter formed from tryptophan and found especially in the brain, blood serum, and gastric mucous membranes; also called 5-hydroxytryptamine
soma -	the cell body, which contains the nucleus and other organelles that carry out the basic processes that maintain the life of the cell
striatum -	the largest portion of the basal ganglia
synapse -	the junction across which a nerve impulse passes from an axon terminal to a neuron
synaptic cleft-	the small gap (typically only 20 to 40 nanometers) that separates an axon terminal and the target neuron with which it synapses

GLOSSARY

thalamus -	an area of the brain associated with the relaying of sensory and motor signals to the cerebral cortex, as well as the regulation of consciousness and alertness
transporter -	a specialized protein that shuttles specific neurotransmitters across the cell membrane ventromedial prefrontal cortex (VMPFC) - a portion of the prefrontal cortex located behind the orbitofrontal cortex and thought to play a role in the processing of emotions
vesicle -	a lipid membrane-bound capsule

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Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular Biology of the Cell. 4th ed. New York, NY: Garland Science; 2002. Hayden BY, Platt Ml. Neurons in Anterior Cingulate Cortex Multiplex Information about Reward and Action. 1 Neurosci. 2010;30(9):3339-3346. Kandel ER, SchwartzJH, Jesse II TM. Principles of Neural Science. 4th ed. New York, NY: McGraw-Hill; 2000. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 3rd ed. New York, NY: Cambridge University Press; 2008