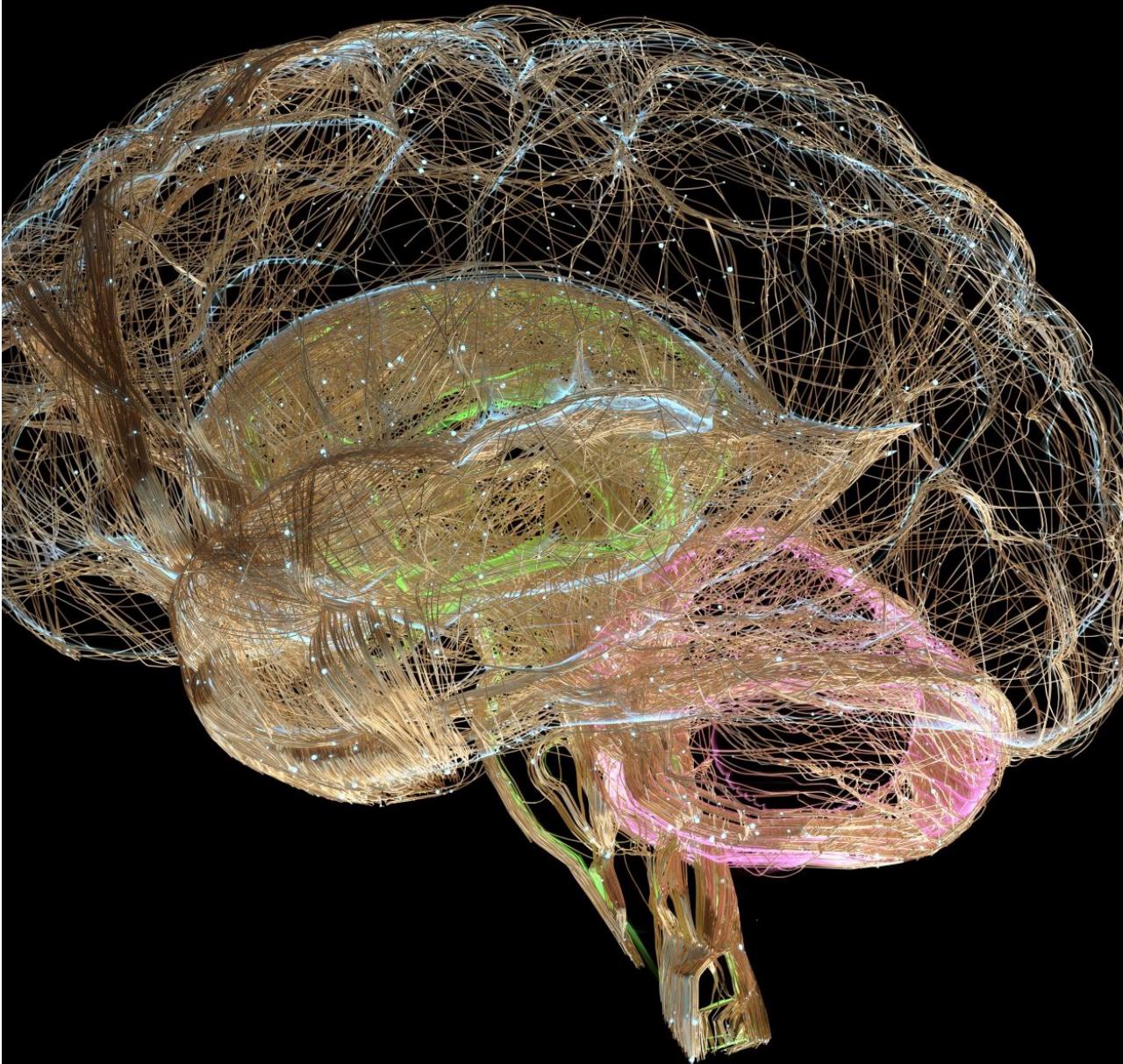
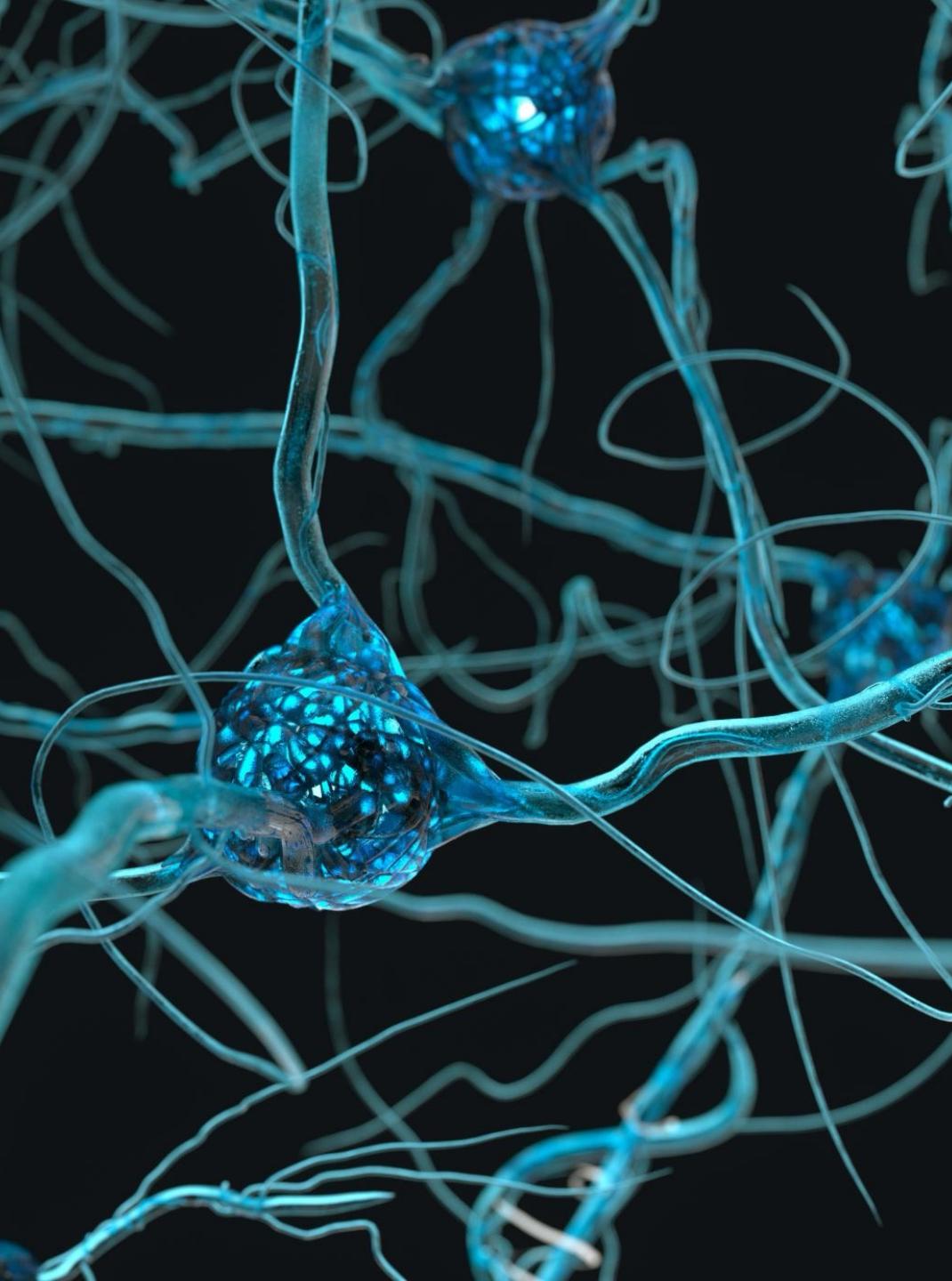


# Anatomy and Physiology of the Brain

# Overview

- The brain consists of the cerebrum, the midbrain, the brainstem, and the cerebellum
- Several brain structures involved in sleep and wakefulness are in the brainstem (locus coeruleus, reticular formation, raphe nuclei) or near the base of the brain (thalamus, suprachiasmatic nucleus, hypothalamus, and pineal gland)



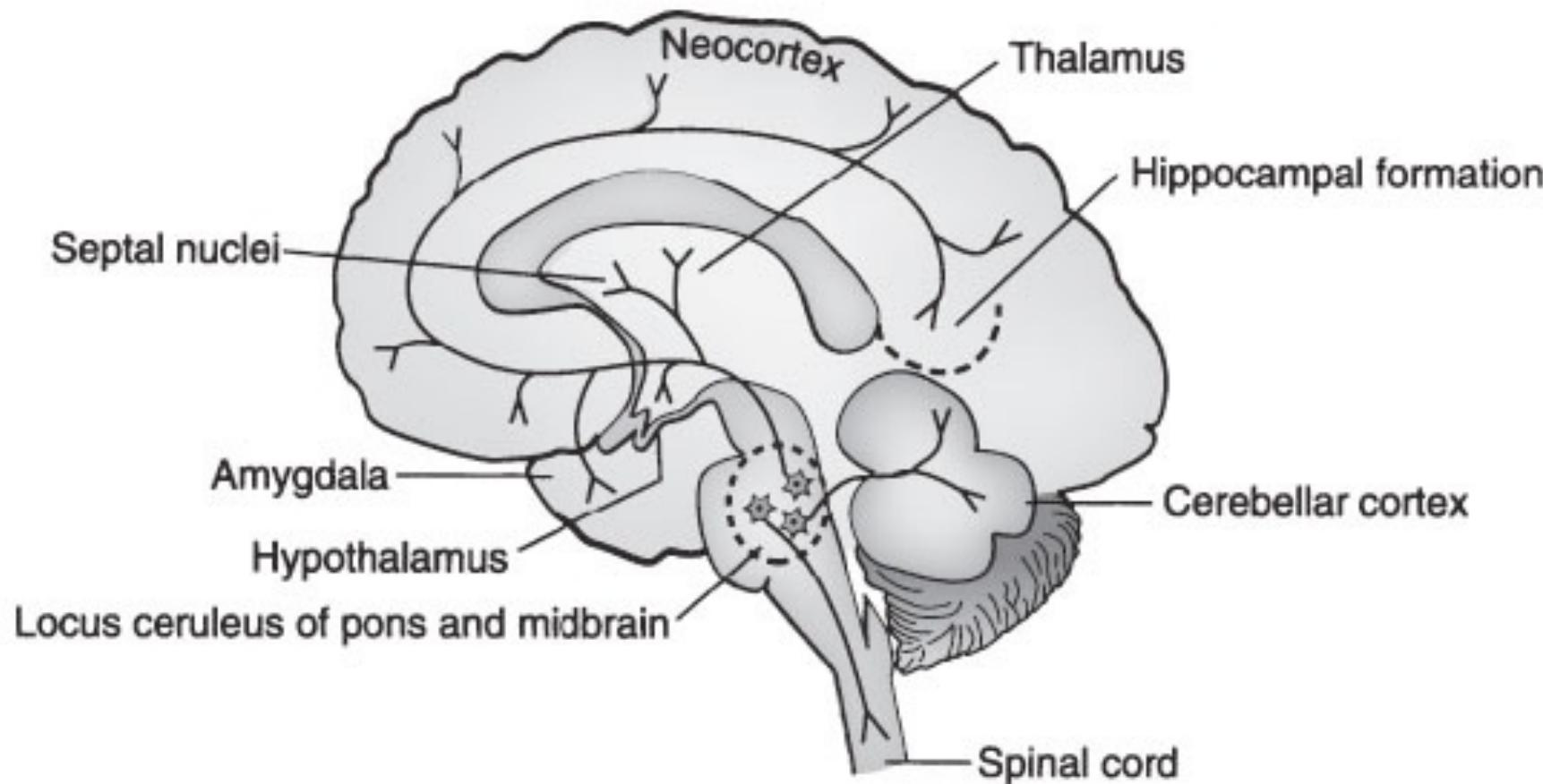


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## Locus Coeruleus

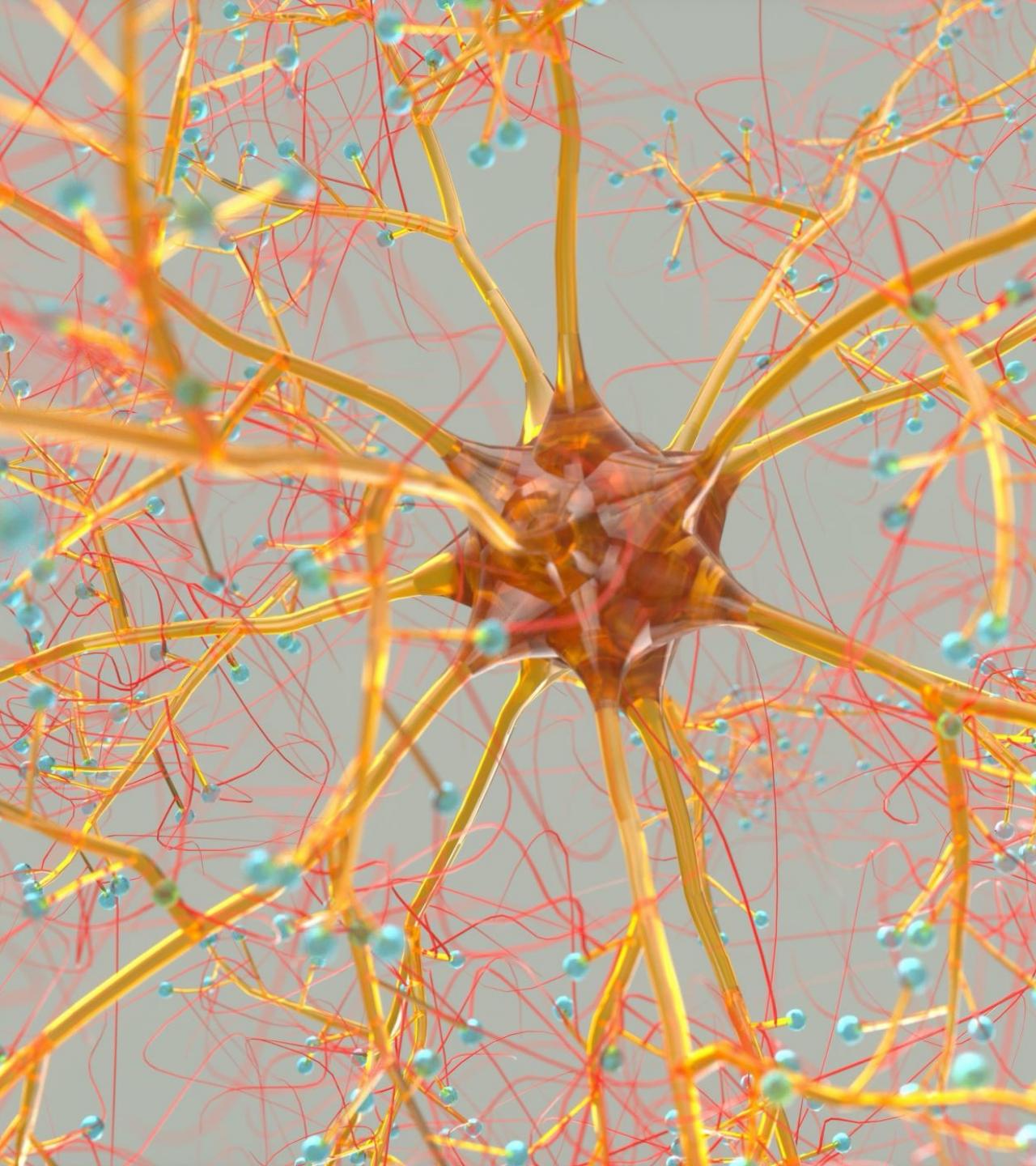
- Pronounced “LOH-kus suh-ROO-lee-us”
- Small blue-tinged area in the back of the brainstem
- Involved in rapid eye movement (REM) sleep and in wakefulness
- Contains neurons that release or are activated by norepinephrine, serotonin, and choline (i.e., norepinephrinergic, serotonergic, and cholinergic neurons, respectively)
  - These neurons fire quickly during wake, begin slow firing with sleep onset, continue to slow as sleep deepens, and nearly stop firing during REM sleep
- Contains a group of neurons (“REM-off” cells) that inhibit REM sleep
  - The action of these cells ends a REM period
  - These cells become increasingly active as REM sleep progresses and ultimately hinder the activity of the “REM-on” cells (cell that start a REM period), which are in the pons and basal forebrain

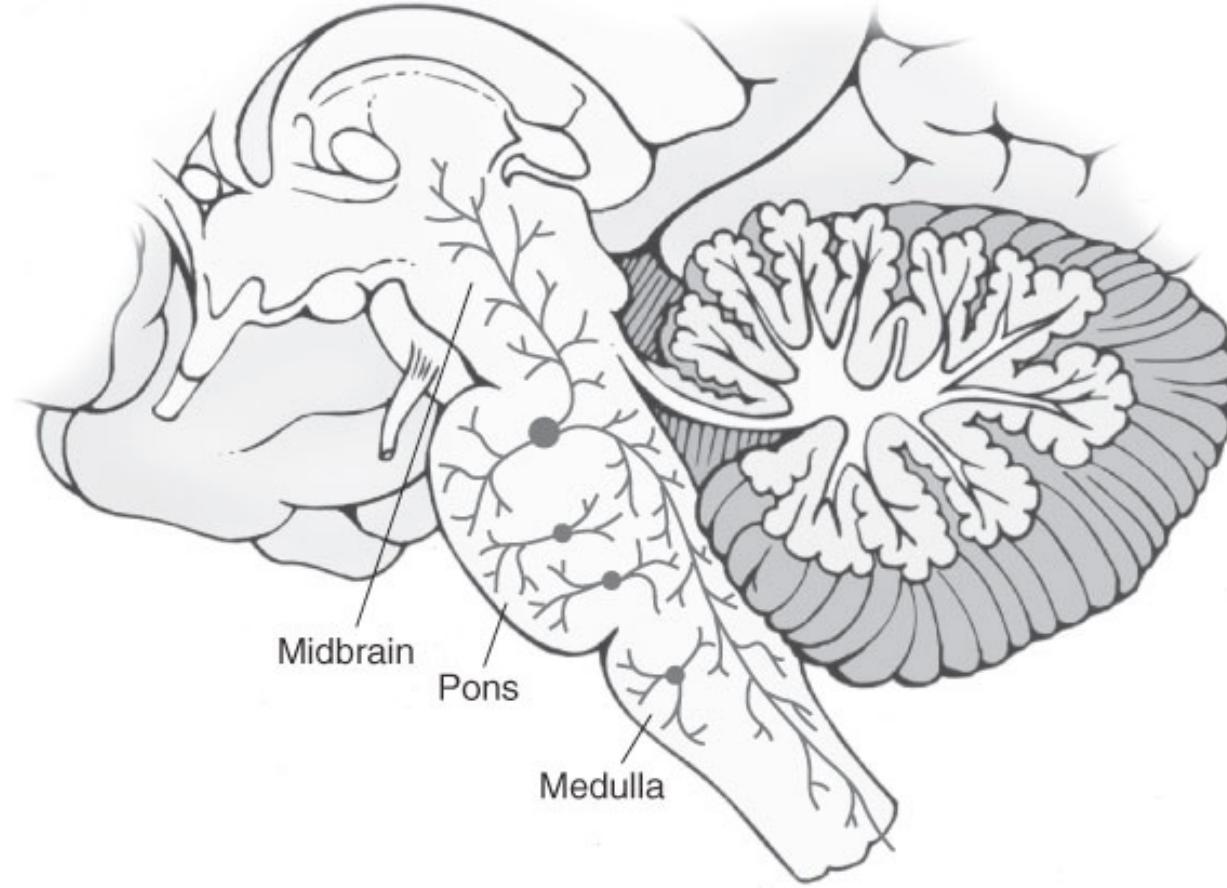
# Locus Coeruleus



# Reticular Formation

- Consists of diffuse groups of nerve cells embedded within a wealth of nerve fibers, which gives it a mesh-like appearance when examined using a microscope
- Runs throughout the inner core of the midbrain, pons, and medulla and fills the spaces between major nuclei and nerve tracts in the brainstem
- The alternation between sleep and wake cycles results from the neural interplay between the reticular formation and the cerebral cortex



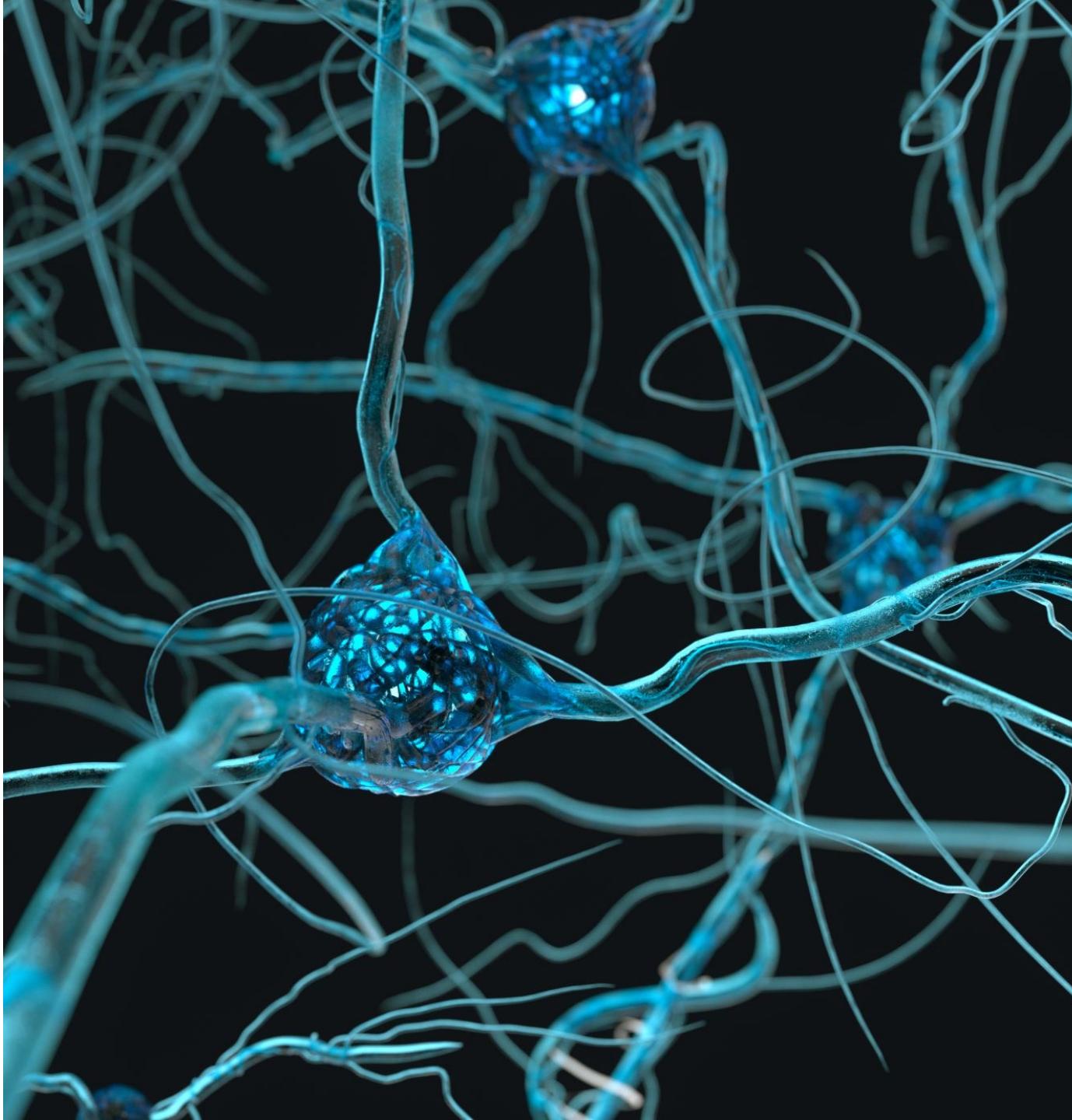


Ascending and Descending Axons in the Reticular Formation

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## Reticular Formation

- The thalamus relays signals between the cerebral cortex and the reticular formation
- Increased cerebral activation results in activation of the reticular formation and consequently wakefulness.
- During sleep, fewer impulses arise from the cerebral cortex; therefore, there is decreased activation of the reticular formation.



# Reticular Formation

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- The reticular formation has two components: the ascending reticular formation and the descending reticular formation.
  - Of these two components, the ascending reticular formation (also called the “reticular activating system”) is most directly involved in sleep and wake cycles and has a role in the overall degree of central nervous system activity.
    - The ascending reticular formation receives sensory signals traveling from the periphery toward the brain; the signals are first relayed to the thalamus.
    - From there, the signals are relayed to the cerebral cortex of the brain.
    - The pathway from the thalamus to the cortex is called the “thalamocortical pathway.”
    - Neurons of the thalamocortical pathway release excitatory neurotransmitters such as glutamate, dopamine, noradrenaline, serotonin, and histamine to the cerebral cortex.
    - These neurotransmitters are involved in wakefulness.

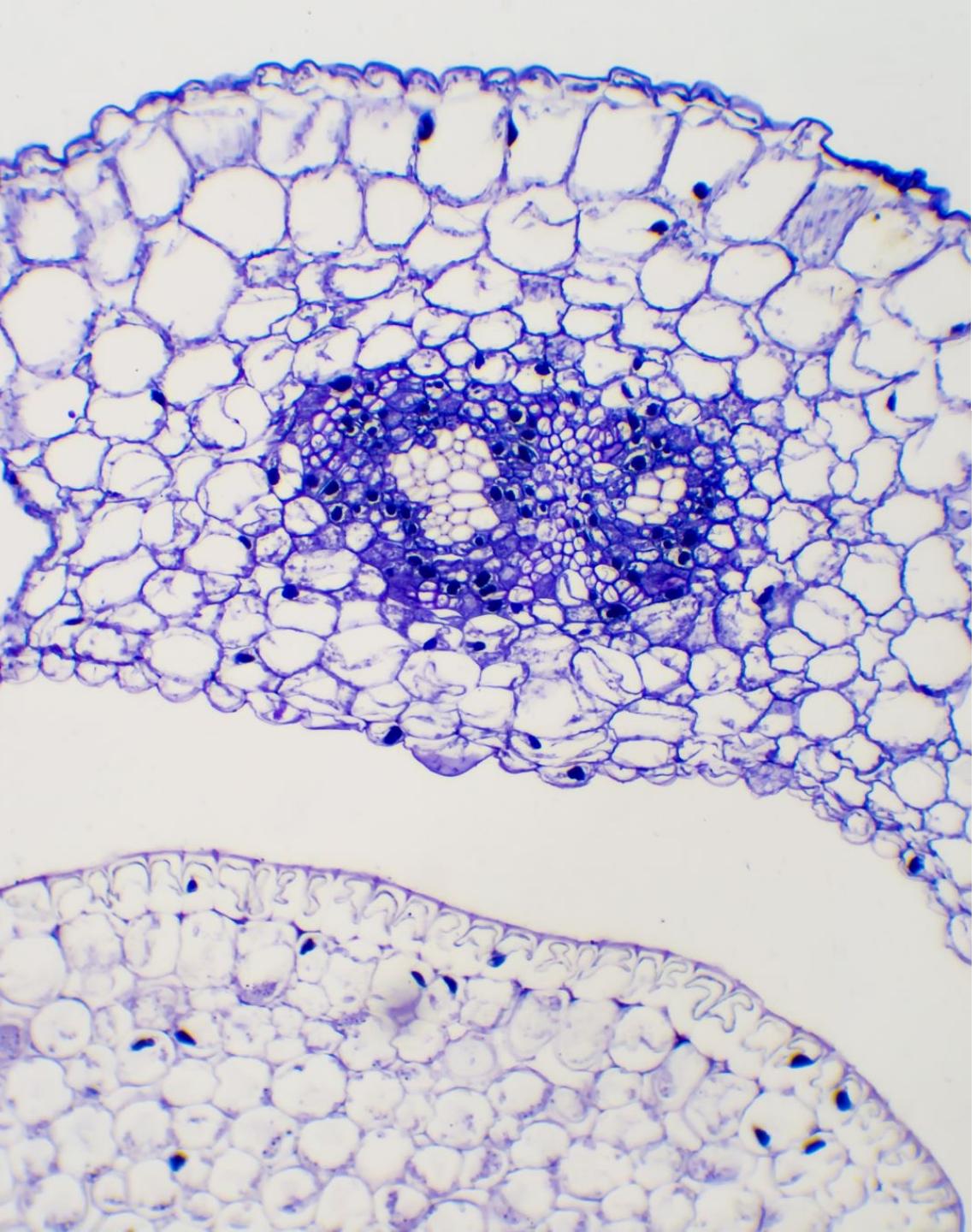
# Reticular Formation

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- The descending reticular formation receives information from the hypothalamus and is involved in the degree of activity in the autonomic nervous system (i.e., the sympathetic and parasympathetic nervous systems collectively).
  - Activation of the descending reticular formation allows the body to withstand the increase in autonomic nervous activity that occurs with wakefulness.
  - An increase in the heart rate, respiratory rate, and muscle tone activates the descending reticular formation and thereby forms a positive feedback loop (i.e., as one factor increases, another factor also increases).
  - The positive feedback loop is controlled by various dampening neural systems in the brain.
    - If it were not dampened, the result would be an extreme arousal state and consequently a seizure.

# Reticular Formation

- Another arousal pathway in the brain extends from the reticular formation to the hypothalamus and, finally, to the cerebral cortex.
  - This pathway is called the “reticulo-hypothalamo-cortical pathway.”
  - In the hypothalamus, a group of cells, called the “tuberomammillary nucleus,” releases histamine to the cerebral cortex.
  - The greatest amount of histamine in the cerebral cortex is synthesized during wake.
  - A second group of cells in the hypothalamus produces the wake-promoting excitatory neurotransmitter orexin, which is also called “hypocretin.”



## Basal Forebrain

- The basal forebrain (i.e., the base of the frontal lobe) has pathways that are involved in arousal and in REM sleep.
- Acetylcholine-synthesizing neurons in the basal forebrain project to the cerebral cortex.
- The neurotransmitter acetylcholine is involved in wakefulness and facilitates REM sleep, and the highest brain level of acetylcholine is synthesized during wake and REM sleep.
- The pons also contains a group of cholinergic neurons (i.e., REM-on cells) that facilitate REM sleep.

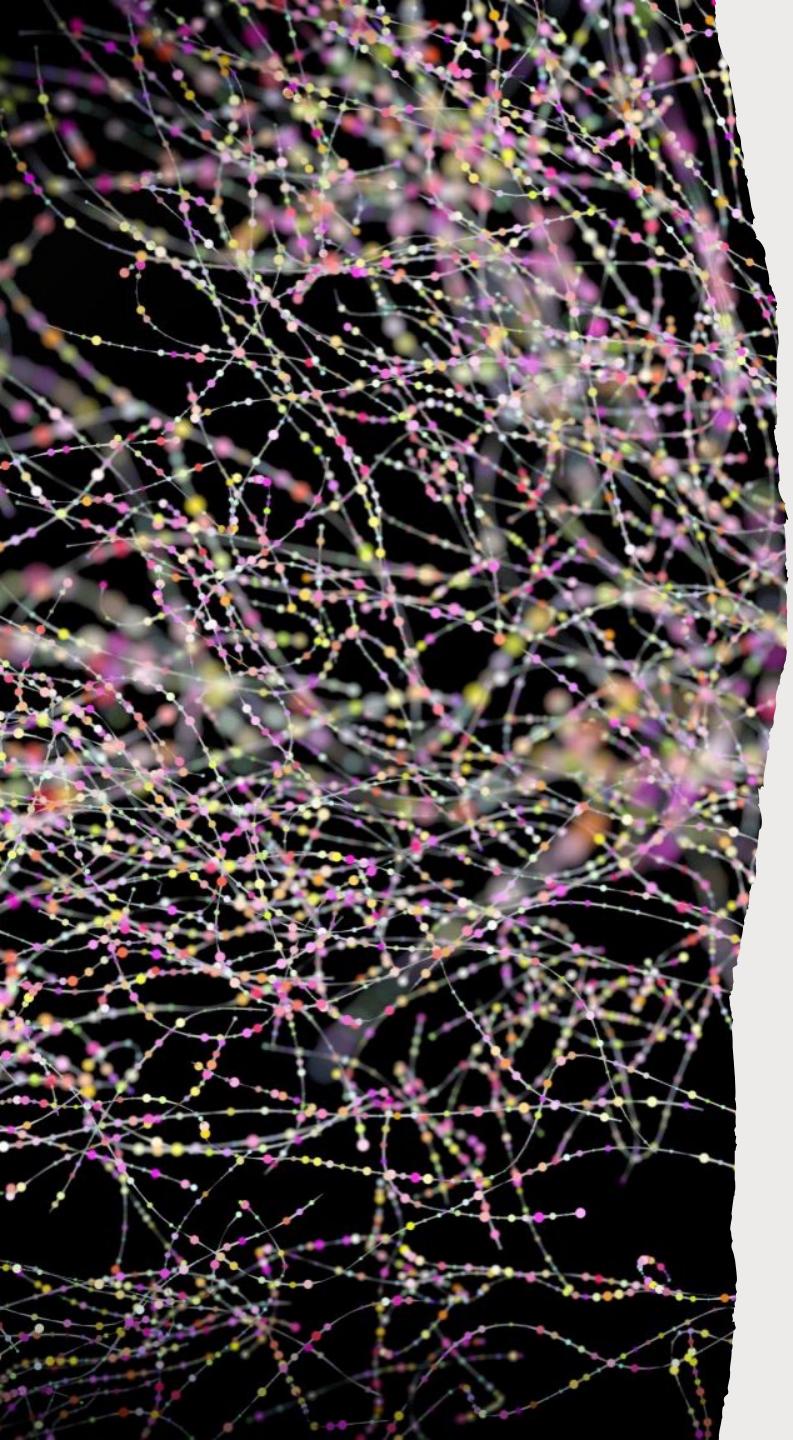
# Reticular Formation

- Reticular deactivation leads to sleep.
  - This deactivation results from neuronal activity in the forebrain, pons, medulla, and cerebellum.
    - For example, the basal forebrain contains neurons that synthesize the inhibitory neurotransmitter  $\gamma$ -amino butyric acid (GABA).
    - These neurons project to the cerebral cortex, to the histamine-producing neurons of the tuberomammillary nucleus in the hypothalamus, and to the reticular formation.
    - In these regions, GABA inhibits the activation of the reticular activating system through a negative feedback system (i.e., as one factor increases, another factor decreases) and thereby induces sleep.

# Raphe Nuclei

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- The reticular formation contains several groups of cells, collectively called the “raphe nuclei,” which consist of the caudal linear nucleus, dorsal raphe nucleus, median raphe nucleus, raphe magnus nucleus, raphe obscurus nucleus, and raphe pallidus nucleus.
- The raphe nuclei are clustered near the junction that separates the left and right sides of the brainstem.
  - This junction is called the “raphe” (in Greek, *raphe* means “seam”).
- Nerve fibers that project from the raphe nuclei release the excitatory neurotransmitter serotonin to all parts of the brain, which contributes to wakefulness.
- During wake, the raphe nuclei neurons fire rapidly.
  - They reduce their firing rate with sleep onset and increasingly reduce firing until nearly becoming quiescent in REM sleep.
  - Exactly what triggers the cells to reduce their firing rate with sleep onset is unknown.
    - A possibility is that other neurons (e.g., GABAergic neurons) indirectly or directly regulate the activity of other neurotransmitters involved in sleep.



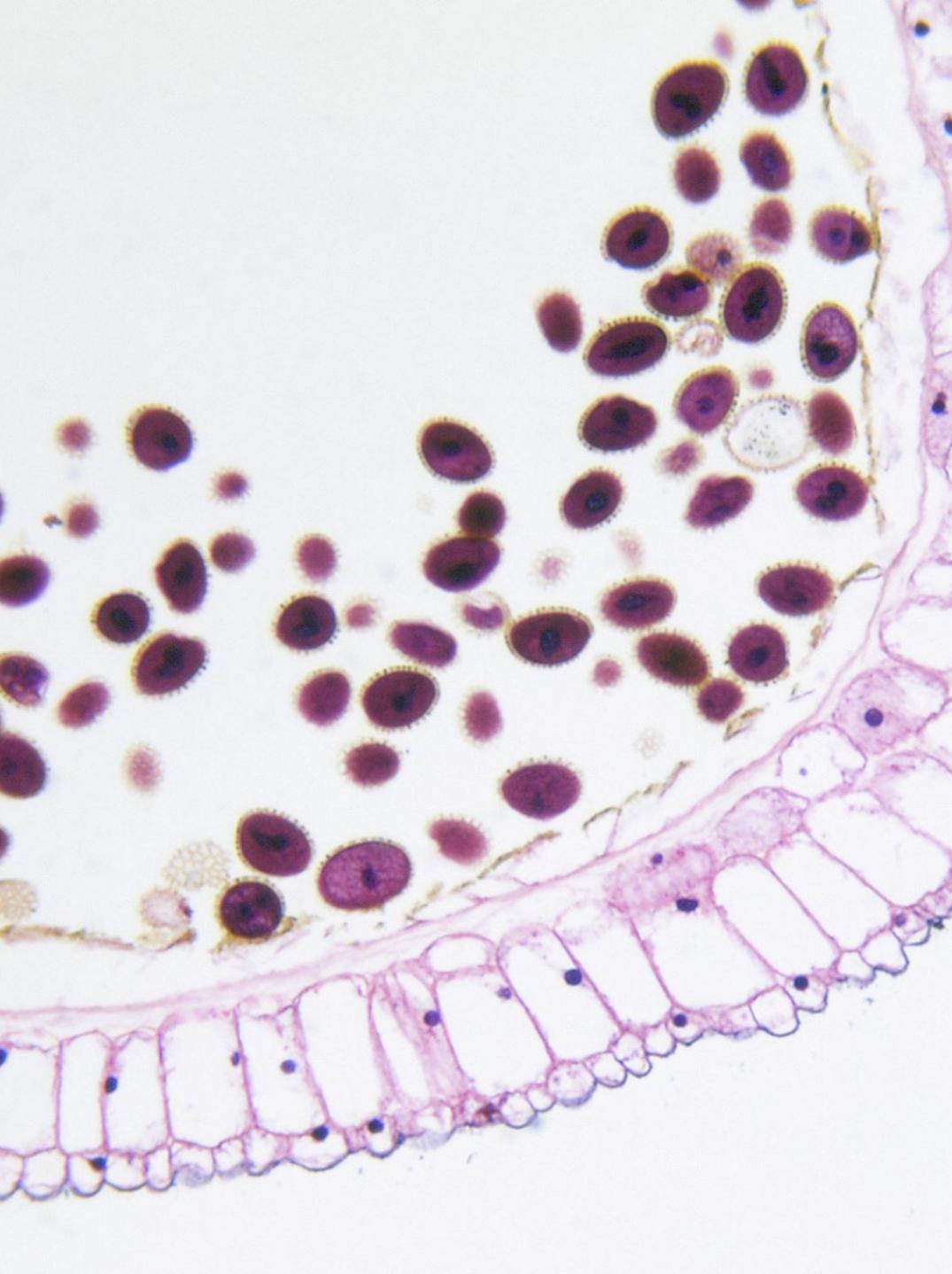
# Thalamus

- The thalamic reticular nuclei are embedded within a thin layer of myelinated fibers, called the “internal medullary lamina,” in the thalamus.
- The thalamic reticular nuclei neurons are GABAergic (i.e., they are activated by or synthesize GABA) and project from the thalamus to the reticular formation.
- During slow-wave sleep, the thalamic reticular nuclei neurons rhythmically shift between depolarization and hyperpolarization and result in the rhythmic bursting pattern of slow waves that occur during slow-wave sleep.
- The transition from sleep to wake occurs when, through the influence of excitatory neurotransmitters such as glutamate and acetylcholine, the thalamocortical neurons inhibit this rhythmic bursting pattern.

# Suprachiasmatic Nuclei

- The suprachiasmatic nuclei (SCN) are important in the alternation between sleep and wake cycles.
- These nuclei are in the anterior hypothalamus.
- They receive signals by way of the retinohypothalamic tract, the geniculohypothalamic tract (i.e., the pathway between the geniculate bodies [i.e., four small round masses just beneath the thalamus] in the upper brainstem and the nearby hypothalamus), and the raphe nuclei.

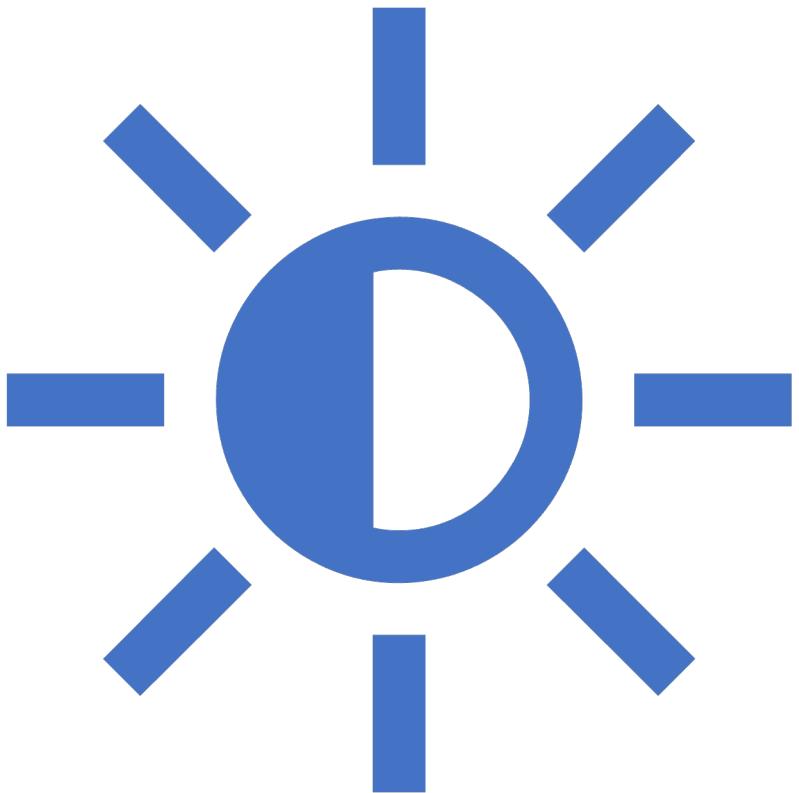




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## Suprachiasmatic Nuclei, Hypothalamus, and Pineal Gland

- The retinohypothalamic tract lies between the retina of each eye and the hypothalamus and is important in establishing the circadian rhythmicity of the sleep–wake cycle.
- The retina, a thin multilayered lining inside the eye, contains two types of light-sensitive visual cells: rods and cones.
  - Rods make it possible for a person to see in dim light settings and to detect motion.
  - Cones make it possible for a person to perceive color.



## Suprachiasmatic Nuclei, Hypothalamus, and Pineal Gland

- When light strikes the rods and cones, photopigments (e.g., the protein rhodopsin) in these cells chemically transform the light energy into an action potential.
- The signal is relayed from the rods and cones to bipolar cells and finally to the ganglion cell layer in the retina.
- Fibers extending from the ganglion cells exit from the back of the eye as the optic nerve and project into the lateral geniculate bodies, which are involved in vision.
- From there, the signals are relayed to the visual center in the occipital lobe.

# Suprachiasmatic Nuclei, Hypothalamus, and Pineal Gland

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- Some fibers from the retinal ganglion cells relay signals from the retina to the SCN in the anterior hypothalamus.
  - This pathway is called the “retinohypothalamic tract.”
- The SCN then relays signals to the pineal gland, a pinecone-shaped structure, located within the groove formed by the juncture of the two halves of the thalamus.
- Depending on the strength of the signals, the pineal gland increases or decreases its secretion of the sleep-promoting neurotransmitter melatonin.
- High-intensity light (e.g., daylight) decreases the pineal gland’s production of melatonin, whereas low-intensity light (e.g., nightfall) increases its production of melatonin.

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## Regulating Sleep and Wake

- Various areas of the brain are responsible for allowing the body to enter different sleep stages, as well as regulate sleep and wake.
- Two of the most important processes in regulating sleep and wake are the circadian rhythm and homeostatic sleep drive.
- The balance of each of these processes helps individuals sleep well, whereas disturbances of each of these systems may cause difficulty sleeping.



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## Circadian and Homeostatic Processes

- The homeostatic drive for sleep decreases during sleep and increases during wakefulness, whereas the circadian process diminishes its alerting signal during the night to help promote sleep and increases during the day to promote alertness
- The homeostatic sleep drive increases with sleep debt—the more hours awake, the higher the drive to sleep.
- Although processes exist that cause continued alertness within an individual with excessive sleep debt, the only way to satisfy the homeostatic drive to sleep is by sleeping.
- High cognitive workload promotes sleep homeostatic responses by increasing subjective sleepiness and fatigue, but it also delays sleep onset, producing a global sleep homeostatic response by reducing wake after sleep onset



# Circadian Rhythm



With its alerting effects, the circadian rhythm opposes the homeostatic drive to sleep.



Through specialized retinal photoreceptors containing melanopsin, the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, receives input from light.



The input of light to the SCN inhibits melatonin secretion by the pineal gland, producing alertness.



When the SCN receives input from low levels of light (dark), melatonin is secreted from the pineal gland, causing a decrease in alertness.

# Circadian Rhythm

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- The pineal gland produces melatonin from the amino acid tryptophan.
- Melatonin is secreted not only into the blood but also into the cerebrospinal fluid.
- Daytime plasma melatonin concentrations are at least 10-fold lower than nocturnal concentrations.
- The secretion of melatonin begins at 3 or 4 months of age, concurrent with sleep consolidation at night.
  - Nighttime melatonin levels then increase rapidly, peaking at 1 to 3 years of age, at which point it begins to decline
  - Melatonin nocturnal serum concentrations decline across puberty.
  - Peak nocturnal melatonin concentrations in 70-year-olds decrease to only a quarter or less of what they are in young adults.

# Circadian Rhythm

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- Ocular light exposure induces a range of neurobehavioral, neuroendocrine, and circadian responses, including melatonin suppression, circadian phase resetting, and enhancement of alertness and performance.
- These responses are most sensitive to blue (short-wavelength, 450 to 480 nm) visible light.
- Before bedtime, sleep improves when subjects looked through amber lenses (blocking blue wavelength light) instead of clear lenses.
- Nighttime light exposure acutely suppresses melatonin and increases alertness in a dose-dependent manner.
- Independent of melatonin suppression, daytime white light exposure has also been shown to increase alertness.

# Circadian Rhythm

- Although inherent and set genetically, the circadian system is modifiable.
- Zeitgebers, meaning “time givers” in German, entrain or align the internal clock, which cycles with a period slightly longer than 24 hours: about 24.2 hours in adults and 24.3 hours in adolescents.
- Although zeitgebers include meals, exercise, and social contact, the most potent stimuli to entrain the circadian phase is bright light.



# Ventrolateral Preoptic Area

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- In addition to the SCN, the hypothalamus contains another important system for sleep: the ventrolateral preoptic (VLPO) area.
- The VLPO and the median preoptic nuclei contain sleep-active neurons. Insomnia and sleep fragmentation are produced by a loss of VLPO neurons.
- Neurons in the VLPO contain  $\gamma$ -aminobutyric acid (GABA) and galanin—they are relatively inactive during wake.
- Most sleep-active neurons in the VLPO are active during nonrapid eye movement (NREM) and REM sleep and are activated by sleep-inducing factors including prostaglandin D2 and adenosine.
  - Caffeine is an adenosine antagonist, causing arousal.

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## Locus Coeruleus

- Located in the brainstem (pons), the locus coeruleus inhibits the VLPO, leading to wakefulness. In addition, norepinephrine-, choline-, and serotonin-containing neurons, within the locus coeruleus, fire quickly during wake.
- With the onset of sleep, the neurons fire slower and continue to slow as sleep deepens.
- During REM sleep, the neurons cease firing.
- The locus coeruleus is involved in inhibiting REM sleep with REM sleep-off neurons.
  - As REM sleep progresses, these cells become increasingly active, eventually obstructing the activity of REM sleep-on neurons, found in the pons and basal forebrain.

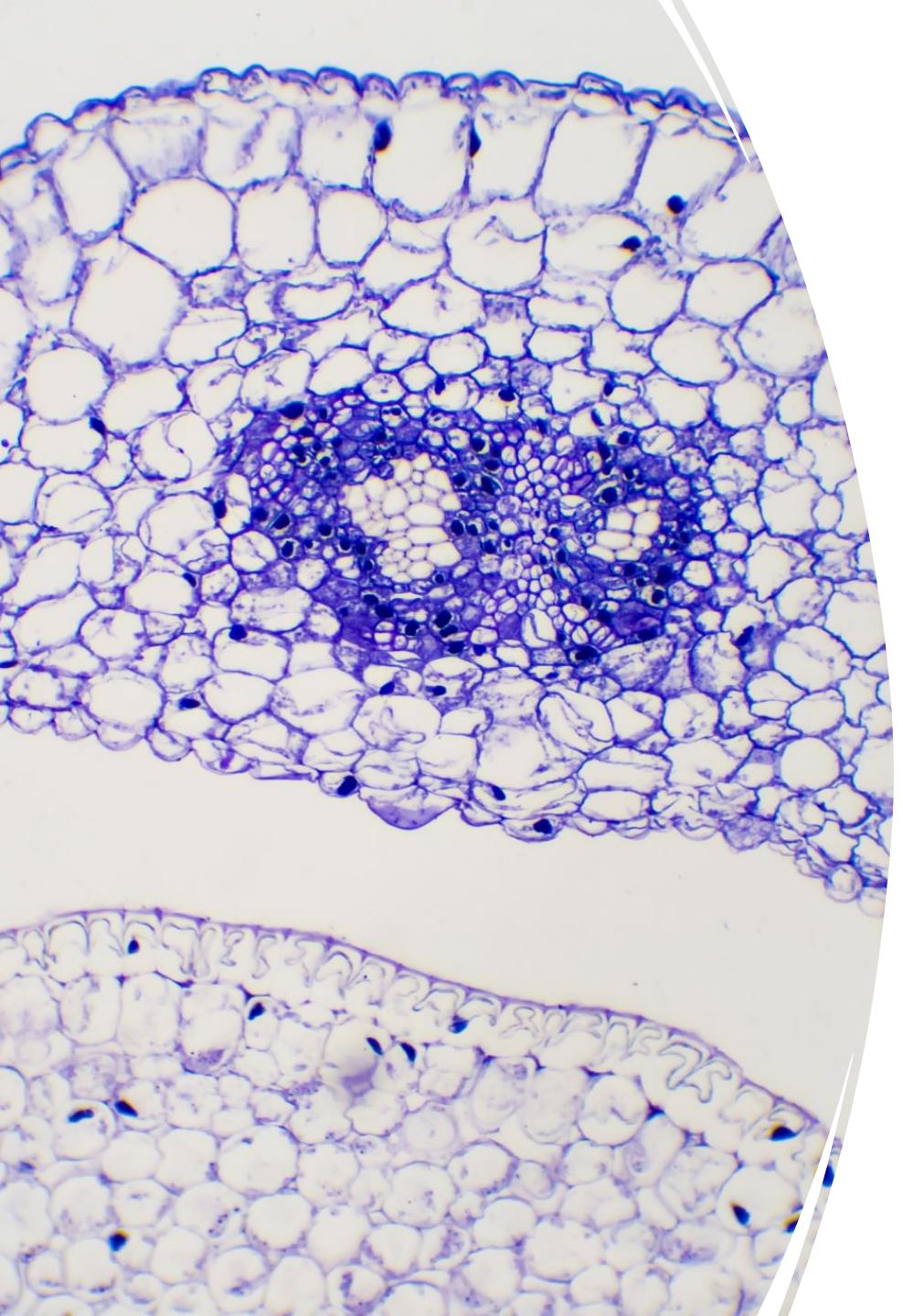


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## Basal Forebrain

- Activation of the basal forebrain leads to acetylcholine release, resulting in wakefulness or REM sleep.
- Inhibition of acetylcholine release in the basal forebrain, by adenosine, leads to slow-wave sleep.
- Major cholinergic output of the central nervous system occurs in the basal forebrain.

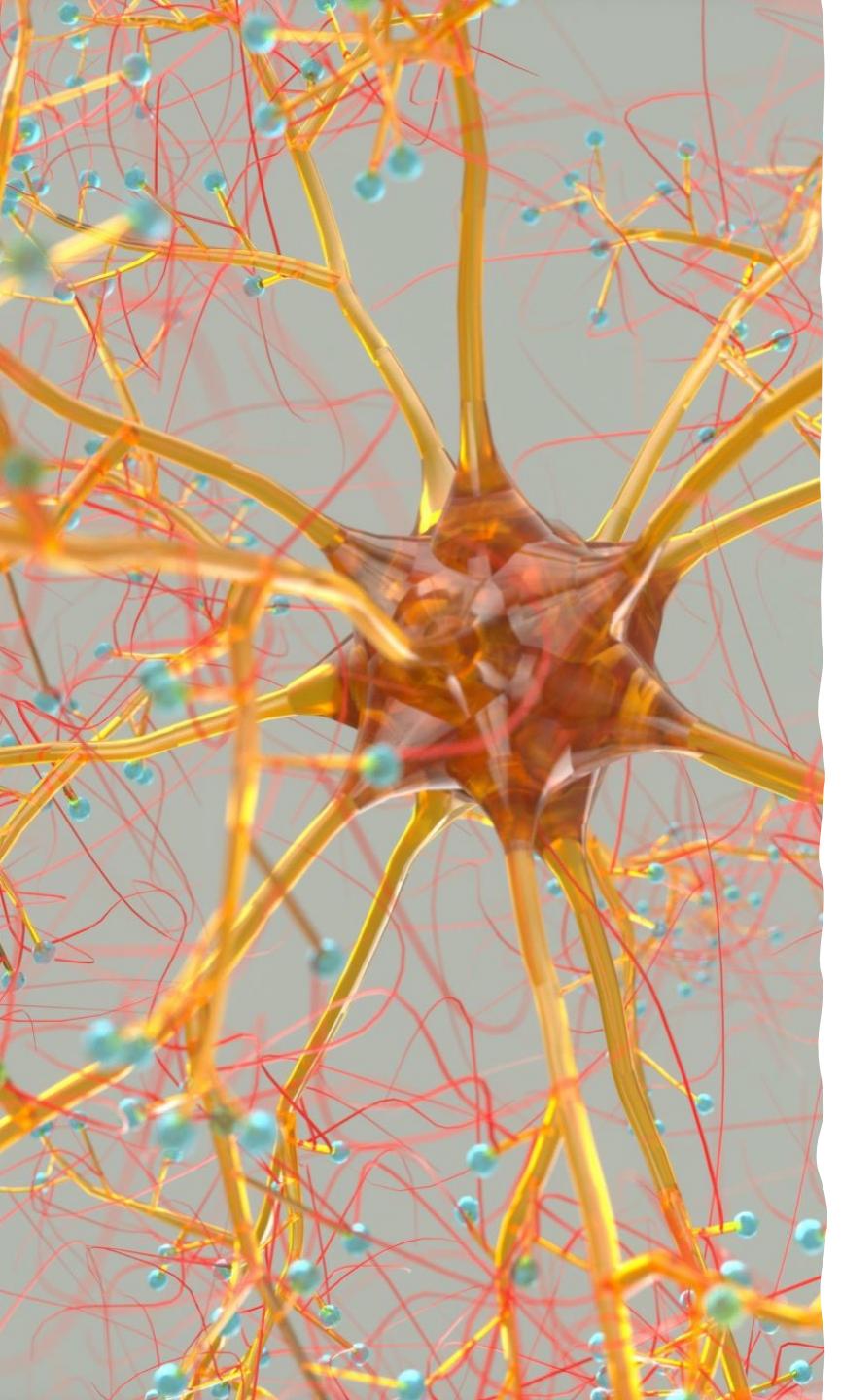




# Raphe Nuclei

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- The raphe nuclei are in the reticular formation of the brainstem
- By way of the thalamus, serotonin-containing neurons of the raphe nuclei promote the emergence of slow-wave cortical activity.
- Like the locus coeruleus, raphe nuclei cells are most active and variable during waking, particularly in response to novel stimuli.
- Also like the locus coeruleus, these cells do not fire in REM sleep because of the decrease in aminergic system activity (serotonin-containing raphe neurons and norepinephrine-containing locus coeruleus) and fire relatively slowly during slow-wave sleep.



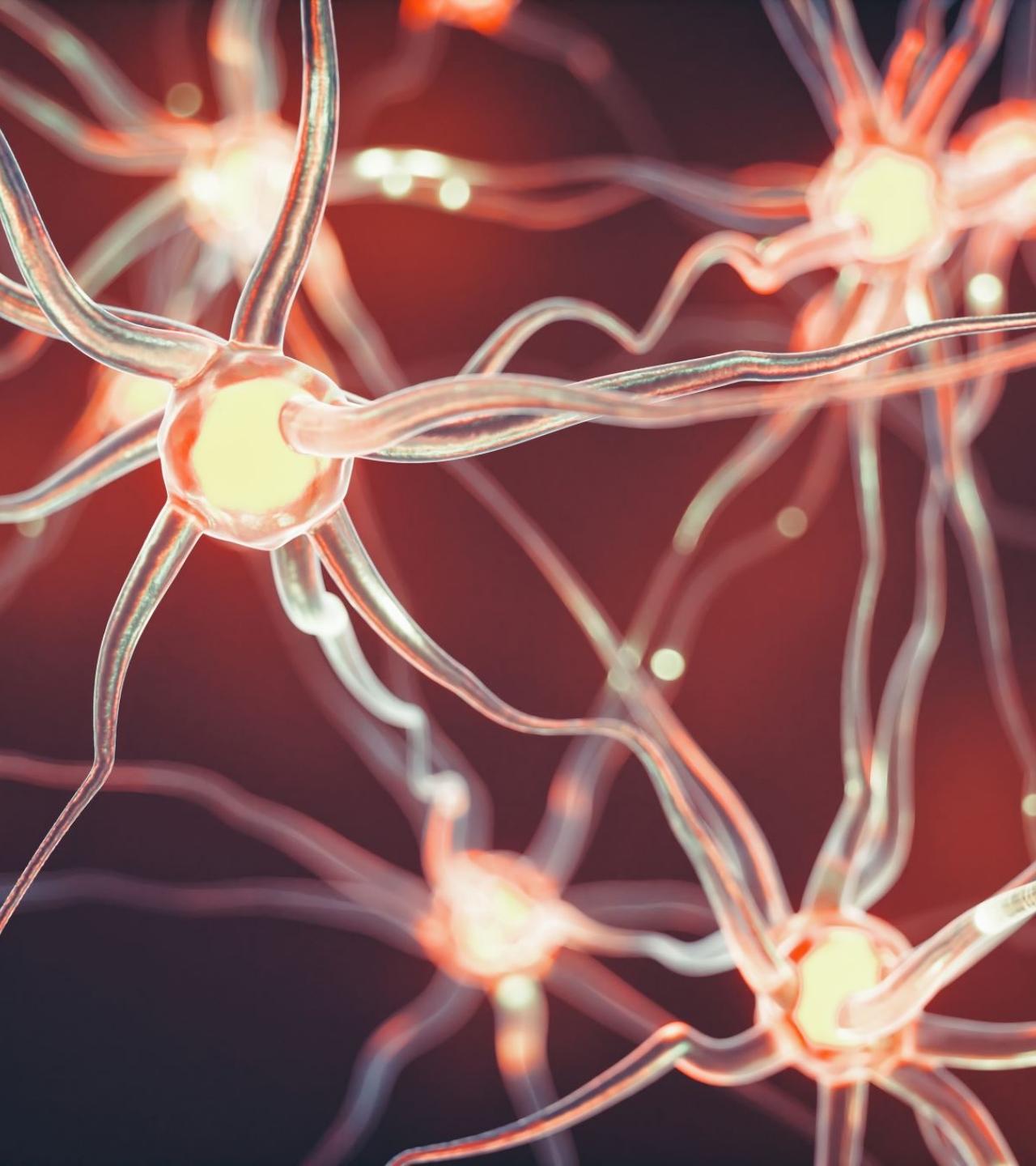
# Ascending Reticular Activating System

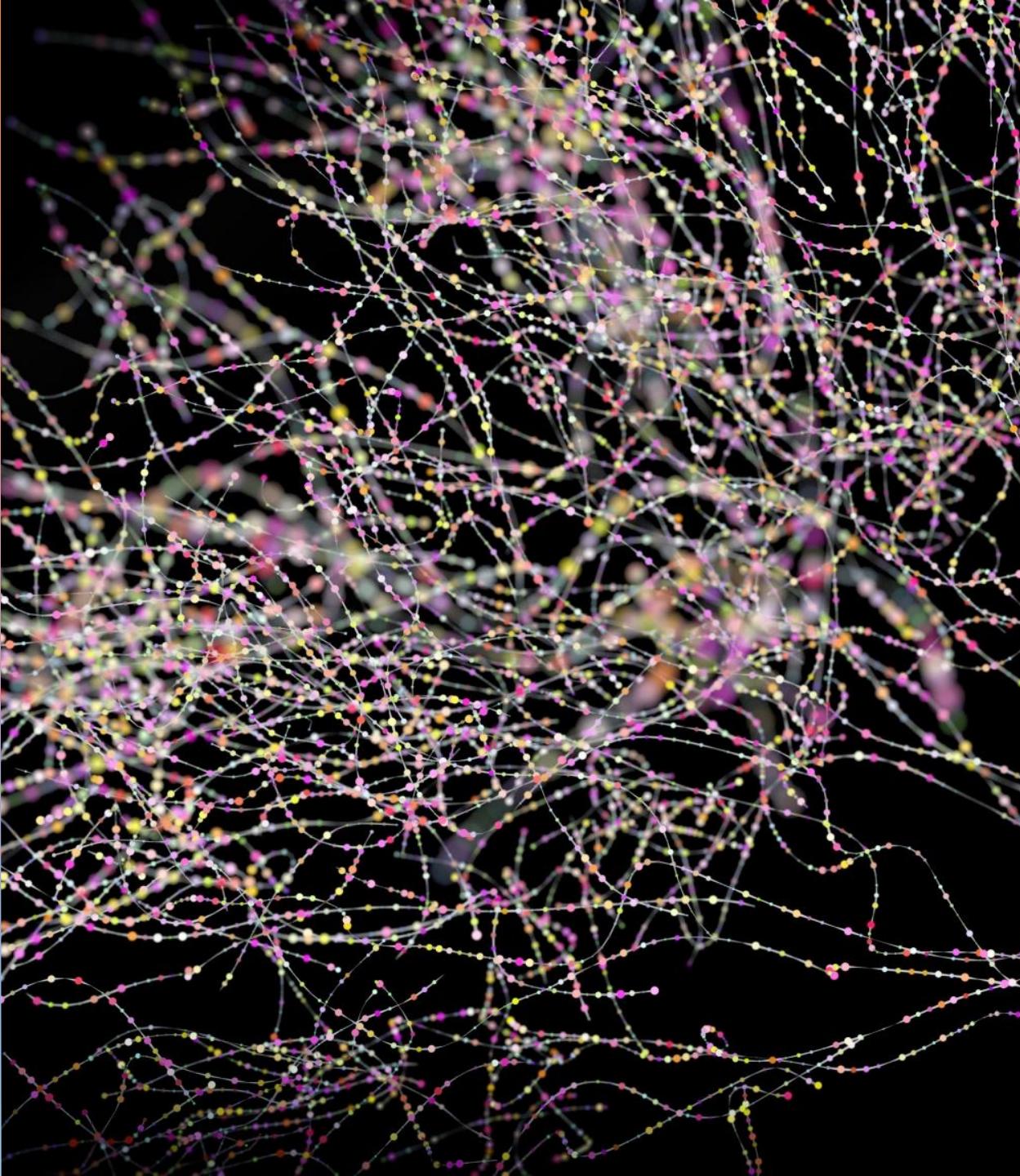
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- The ascending reticular activating system (ARAS) comprises several neuronal circuits, traveling through the thalamus, connecting the brainstem (reticular formation) to the cerebral cortex.
- The ARAS also includes the hypothalamus and basal forebrain and consists of dorsal and ventral pathways.
- Both pathways are involved in cortical activation, causing neurons in the ARAS to fire at a higher rate during wakefulness.
- Because of external stimuli, the ARAS provides an inhibitory influence by reducing afferent (sensory neurons) activity during sleep.
  - In other words, during sleep, fewer impulses arise from the cerebral cortex and decrease ARAS activation.

# Ascending Reticular Activating System

- The ARAS is also involved in REM sleep.
- Interaction of brainstem aminergic, cholinergic, and GABAergic neurons controls the activity of glutamatergic reticular formation neurons.
  - This leads to REM sleep, resulting in rapid eye movements, muscle atonia, cortical activation, and dreaming.





## Thalamus

- Located just above the brainstem is the thalamus.
- Within the thalamus is the thalamic reticular nuclei, which contain GABAergic neurons that project from the thalamus to the reticular formation.
- The rhythmic bursting pattern of slow waves seen during slow-wave sleep is caused by the thalamic reticular nuclei neurons rhythmically shifting between depolarization and hyperpolarization.
- The thalamocortical neurons inhibit this rhythmic bursting pattern through the influence of excitatory neurotransmitters, such as acetylcholine and glutamate, causing the transition from sleep to wake.

# Reference

- Mattice, C., Brooks, R., and Lee-Chiong, T. (2020). *Fundamentals of Sleep Technology* (3<sup>rd</sup> Edition). AAST.