PSYCH 260/BBH 203

Neurochem II

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2022-02-17 07:43:40

Prelude (01:57)

Monoamine Song

https://en.wikipedia.org/wiki/Mah_Nà_Mah_Nà

Monoamine Song

Monoamines, do-do do do-do
Monoamines, do do do-do
Monoamines, do do do do-do do do-do do do-do do do do do-do do

Monoamine Song

Monoamines, do-pa-mine is one
Monoamines, norepi, too
Monoamines, sero-tonin e-pinephrine, dop-a-mine, nor-epinephrine, melatonin, whoo!

Monoamine Song

Monoamines, mod-u-late neurons
Monoamines, throughout the brain
Monoamines, keep people happy, brains snappy, not sleepy, not sappy, do-do do-do do-do do

Announcements

- Quiz 2 due Tuesday, Feb 22, **after class**
- Blog post 1 (of 3) due Tuesday, Feb 22

Today's Topics

- Warm-up
- Neurotransmitters

Warm-up

The *presynaptic influx* of which ion triggers the release of neurotransmitters from the axon terminal?

- Na+
- K+
- Ca++
- Cl-

The *presynaptic influx* of which ion triggers the release of neurotransmitters from the axon terminal?

- ~~Na+~~
- ~~K+~~
- Ca++
- ~~Cl-~~

This type of postsynaptic receptor does NOT contain its own ion channel.

- Ionotropic
- Metabotropic
- Ligand-gated

This type of postsynaptic receptor does NOT contain its own ion channel.

- ~~Ionotropic~~
- Metabotropic
- ~~Ligand-gated~~

More on neurotransmitters

Glutamate

- Primary excitatory NT in CNS (~ 1/2 all synapses)
- Role in learning (via NMDA receptor)
- Transporters on neurons and glia (astrocytes and oligodendrocytes)
- Linked to umami (savory) taste sensation, think monosodium glutamate (MSG)
- Dysregulation in schizophrenia (McCutcheon, Krystal, & Howes, 2020), mood disorders (Małgorzata, Paweł, Iwona, Brzostek, & Andrzej, 2020)

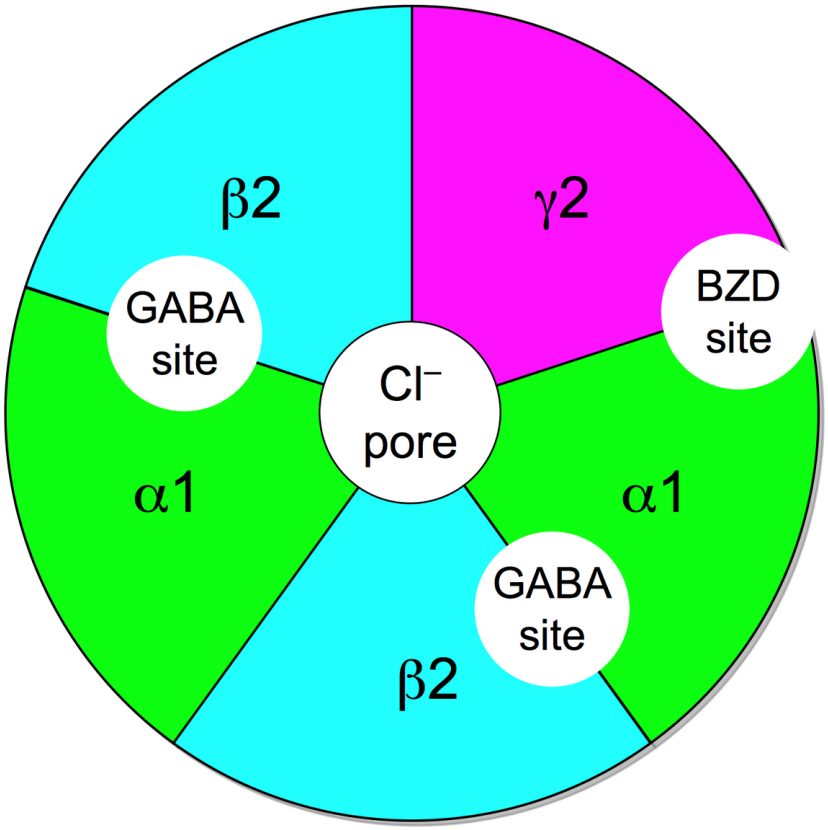
Glutamate

Type	Receptor	Esp Permeable to
Ionotropic	**AMPA**	Na+, K+
	Kainate	
	NMDA	Ca++
Metabotropic	mGlu	

γ-aminobutyric Acid (GABA)

- Primary inhibitory NT in CNS
- Binding sites for benzodiazepines (e.g., Valium), barbiturates, ethanol, etc.
- Synthesized from glutamate
- Inactivated by transporters
- Excitatory in developing CNS, [Cl-] in >> [Cl-] out

GABA



Type	Receptor	Esp Permeable to
Ionotropic	GABA-A	Cl-
Metabotropic	GABA-B	K+

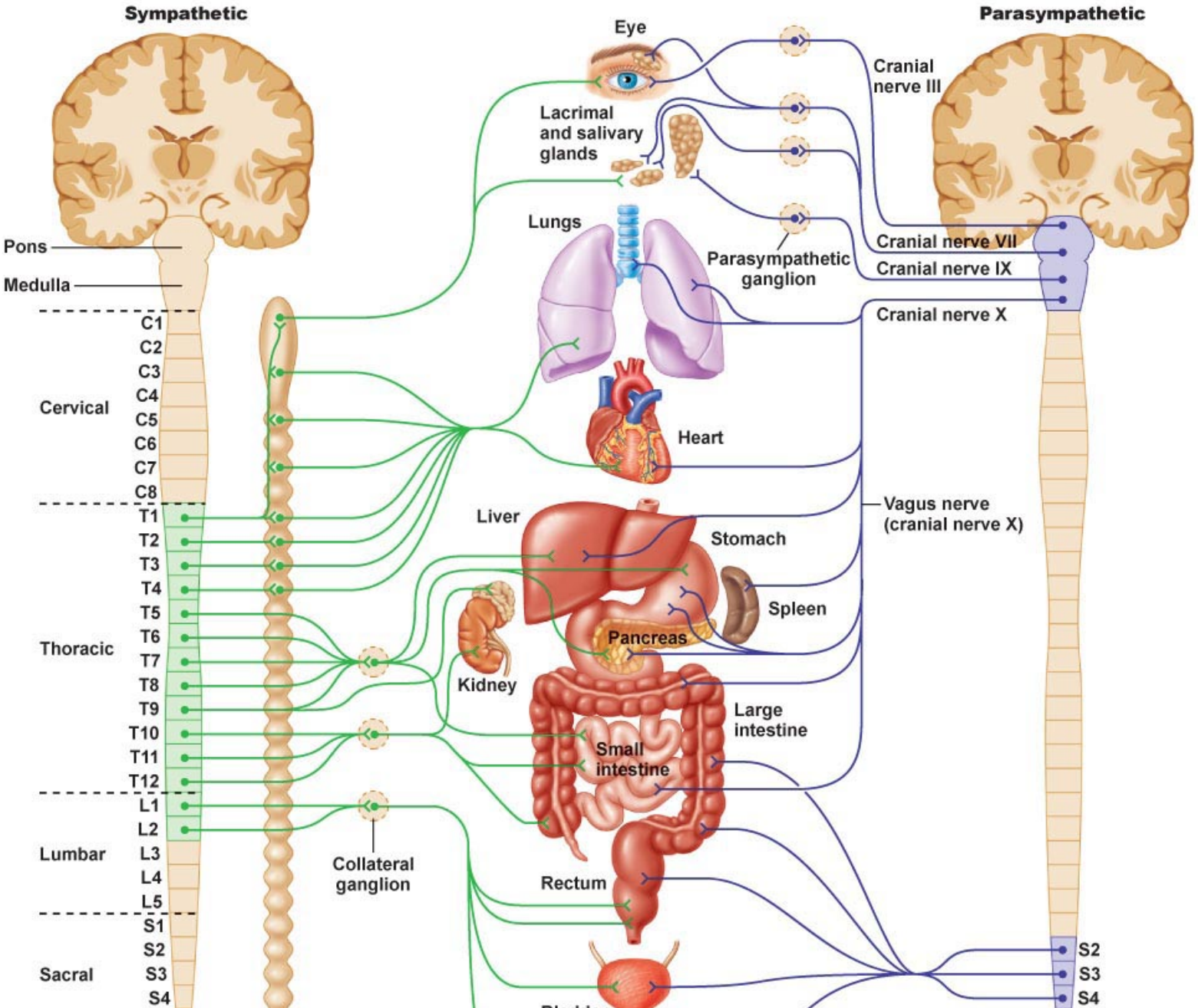
Other amino acid NTs

- *Glycine*
  - Spinal cord interneurons
  - inhibitory
- *Aspartate*
  - Like Glu, stimulates NMDA receptor

Acetylcholine (ACh)

- Primary NT of CNS output
- Somatic portion of PNS (neuromuscular junction between motor neurons and skeletal muscles)
- Autonomic nervous system
  - Sympathetic branch: preganglionic neuron
  - Parasympathetic branch: pre/postganglionic
- Inactivation by acetylcholinesterase (AChE)

ACh anatomy


Sympathetic
Parasympathetic
Eye
Cranial nerve III
Lacrimal and salivary glands
Lungs
Parasympathetic ganglion
Cranial nerve VII
Cranial nerve IX
Cranial nerve X
Pons
Medulla
C1
C2
C3
C4
C5
C6
C7
C8
Cervical
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
Thoracic
L1
L2
L3
L4
L5
Lumbar
S1
S2
S3
S4
Sacral
Heart
Liver
Stomach
Spleen
Pancreas
Kidney
Large intestine
Small intestine
Rectum
Vagus nerve (cranial nerve X)
Collateral ganglion
S2
S3
S4

Acetylcholine

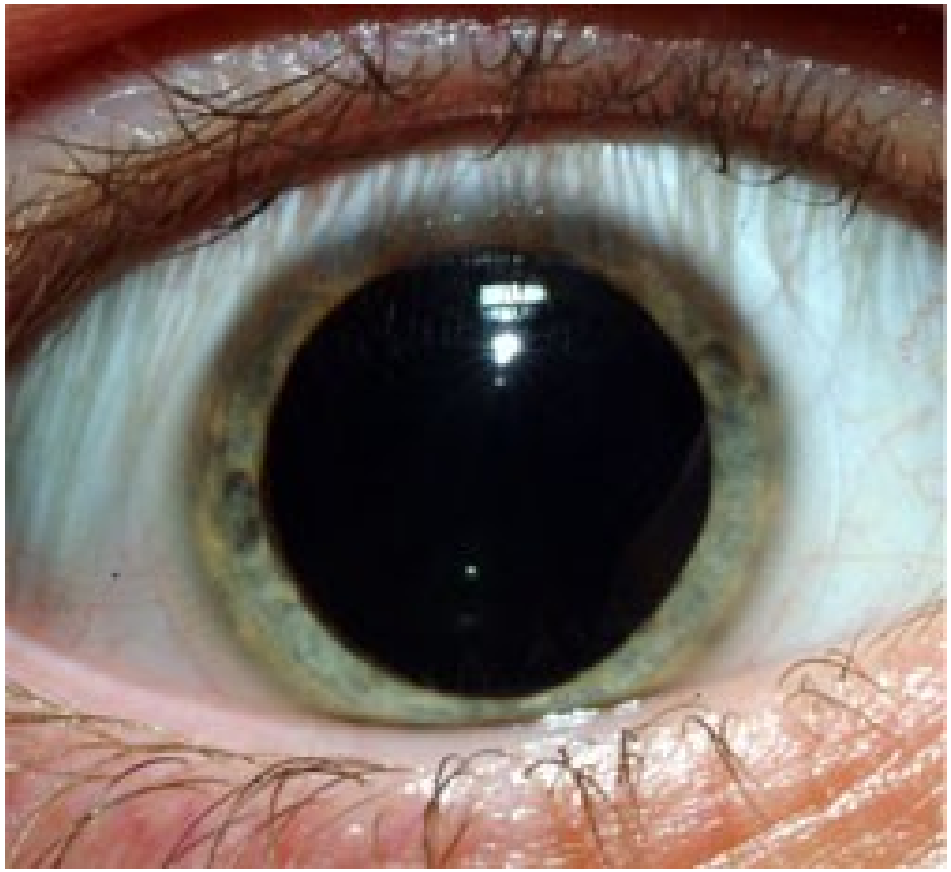
Type	Receptor	Esp Permeable to	Blocked by
Ionotropic	**Nicotinic (nAChR)**	Na+, K+	e.g., Curare
Metabotropic	**Muscarinic (mAChR)**	K+	e.g., Atropine

Curare

http://www.general-anaesthesia.com/images/indian-curare.jpg

Atropine

- aka, nightshade or belladonna



https://aapos.org/glossary/dilating-eye-drops

How to stop your prey

Substance	Effect
Japanese pufferfish toxin	Blocks voltage-gated Na+ channels
Black widow spider venom	Accelerates presynaptic ACh release
Botulinum toxin (BoTox)	Prevents ACh vesicles from binding presynaptically
Sarin nerve gas	Impedes ACh breakdown by AChE
Pesticides	Impede AChE
Tetanus toxin	Blocks release of GABA, glycine

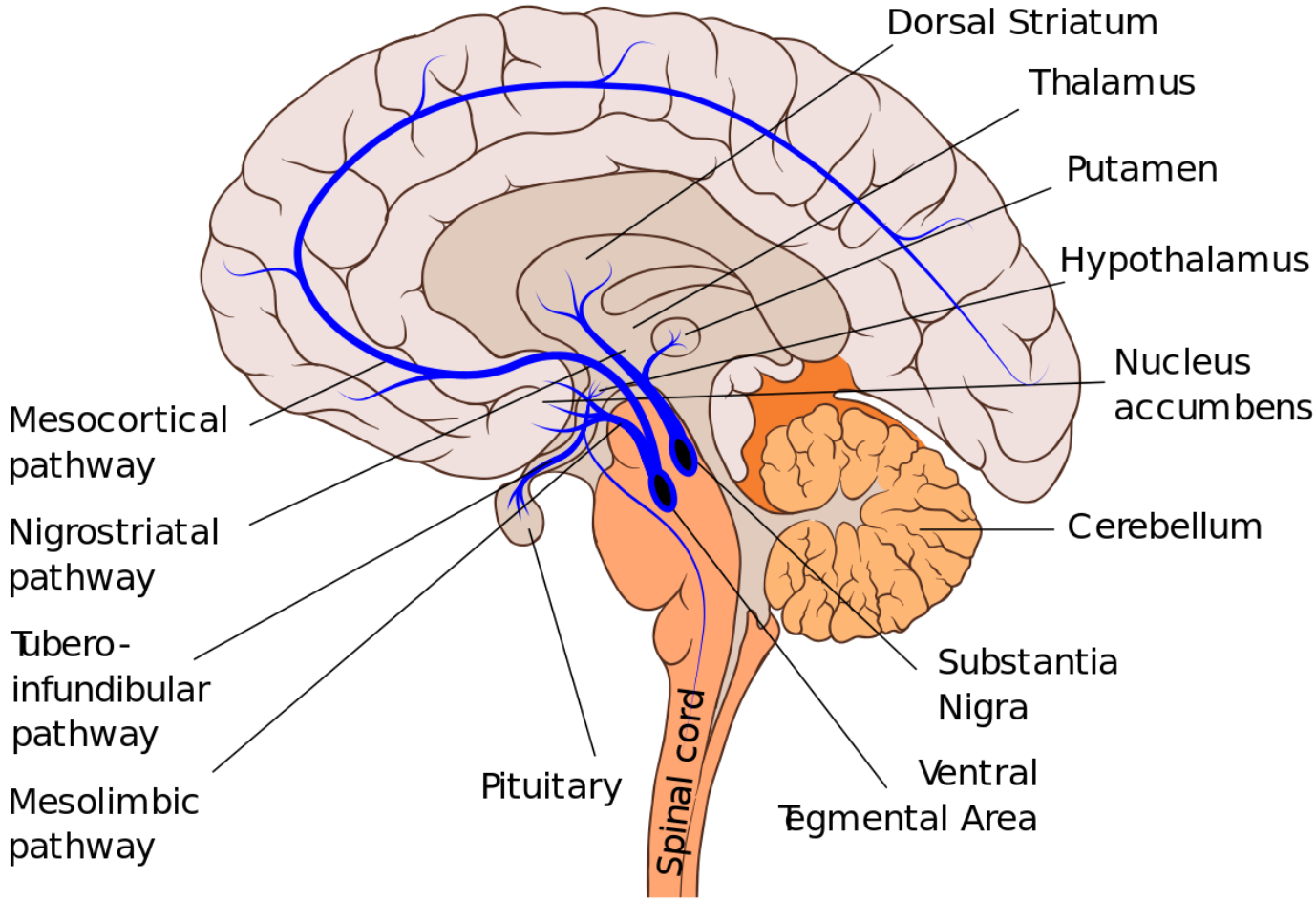
Monoamine neurotransmitters

Family	Neurotansmitter
Monoamines	Dopamine (DA)
	Norepinephrine (NE)/Noradrenaline (NAd)
	Epinephrine (Epi)/Adrenaline (Ad)
	Serotonin (5-HT)
	Melatonin
	Histamine

Dopamine (DA)

- Released by two pathways that originate in the midbrain tegmentum
  - Substantia nigra -> striatum, *meso-striatal projection*
  - Ventral tegmental area (VTA) -> nucleus accumbens, ventral striatum, hippocampus, amygdala, cortex; *meso-limbo-cortical projection*

DA pathways

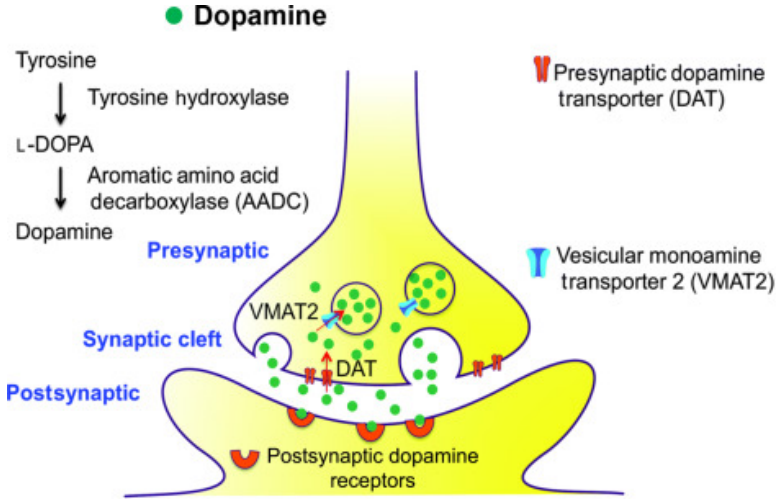

Dorsal Striatum
Thalamus
Putamen
Hypothalamus
Nucleus accumbens
Cerebellum
Substantia Nigra
Ventral Tegmental Area
Spinal cord
Pituitary
Mesocortical pathway
Nigrostriatal pathway
Tubero-infundibular pathway
Mesolimbic pathway

DA Disruption linked to

- Parkinson's Disease (mesostriatal)
    - DA agonists treat (agonists facilitate/increase transmission)
- ADHD (mesolimbocortical)
- Schizophrenia (mesolimbocortical)
    - DA antagonists treat
- Addiction (mesolimbocortical)

DA Inactivated by

- Dopamine transporter (DAT)



https://doi.org/10.1016/bs.vh.2014.12.009

- Chemical breakdown

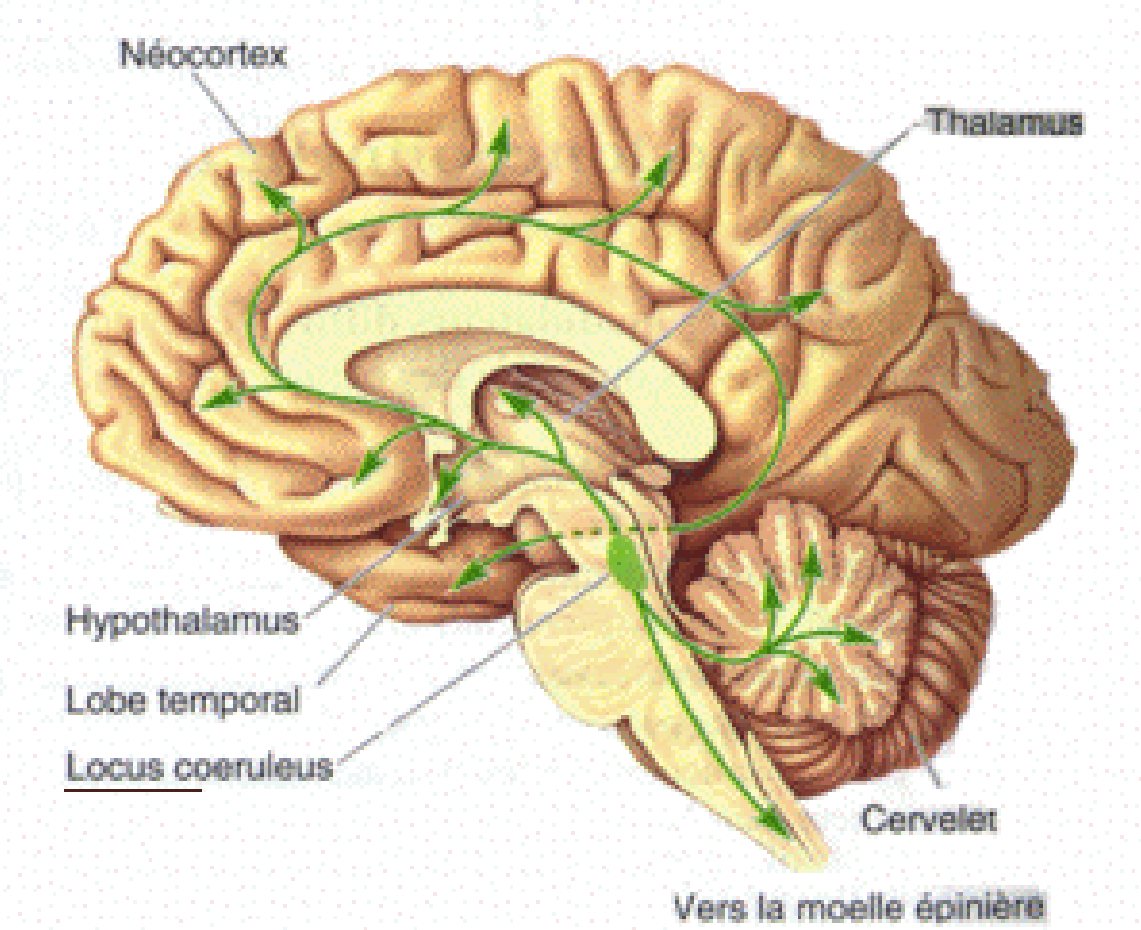
Dopamine receptors

Type	Receptor	Comments
Metabotropic	*D1-like (D1 and D5)*	more prevalent
	D2-like (D2, D3, D4)	target of many antipsychotics (drugs that treat schizophrenia symptoms)

Norepinephrine (NE)

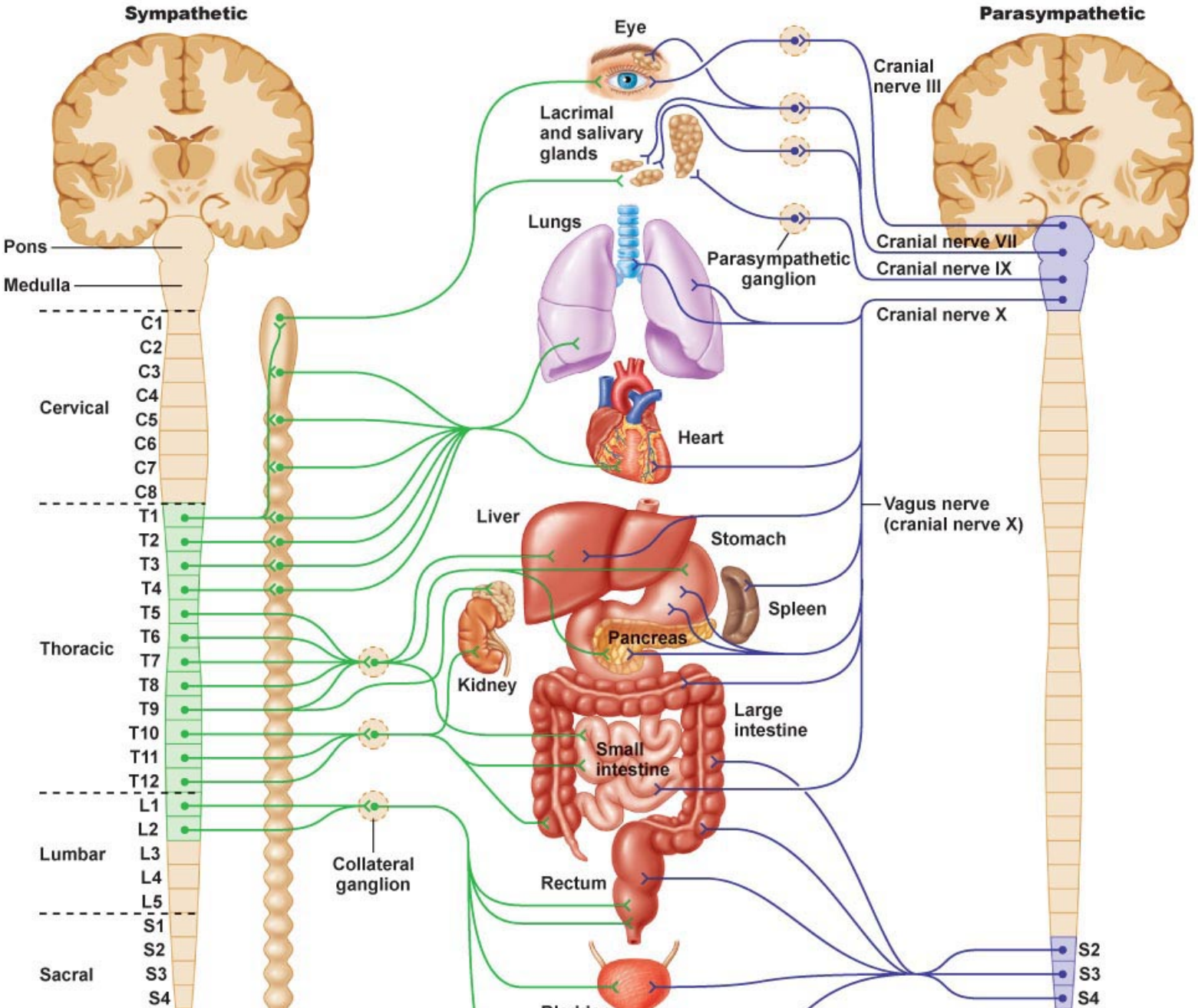
- Role in arousal, mood, eating, sexual behavior
- Released by
  - *locus coeruleus* in pons/caudal tegmentum

Locus coeruleus



https://upload.wikimedia.org/wikipedia/commons/6/6d/Locus-coeruleus.gif

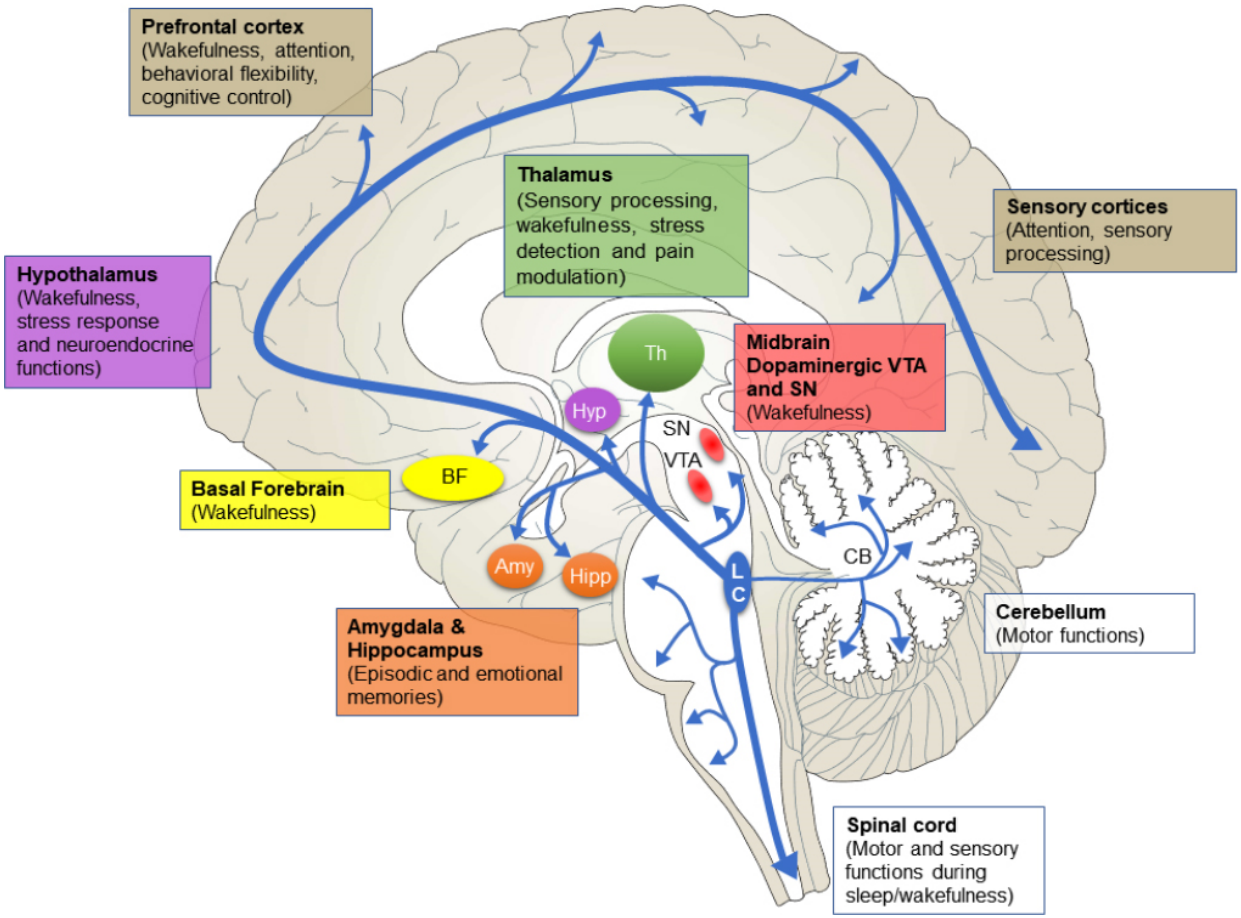
Sympathetic Nervous System



NE and monoamine oxidase

- Monoamine oxidase (MAO) inactivates monoamines in neurons, glial cells
- Monoamine oxidase inhibitors (MAOIs) *increase* NE, DA
  - Inhibiting inactivation ~ $-(-1) = +1$
- Treatment for depression, but side effects (dry mouth, nausea, headache, dizziness)

NE Anatomy



https://www.nrronline.org/article.asp?issn=1673-5374;year=2020;volume=15;issue=6;spage=1006;epage=1013;aulast=Bari

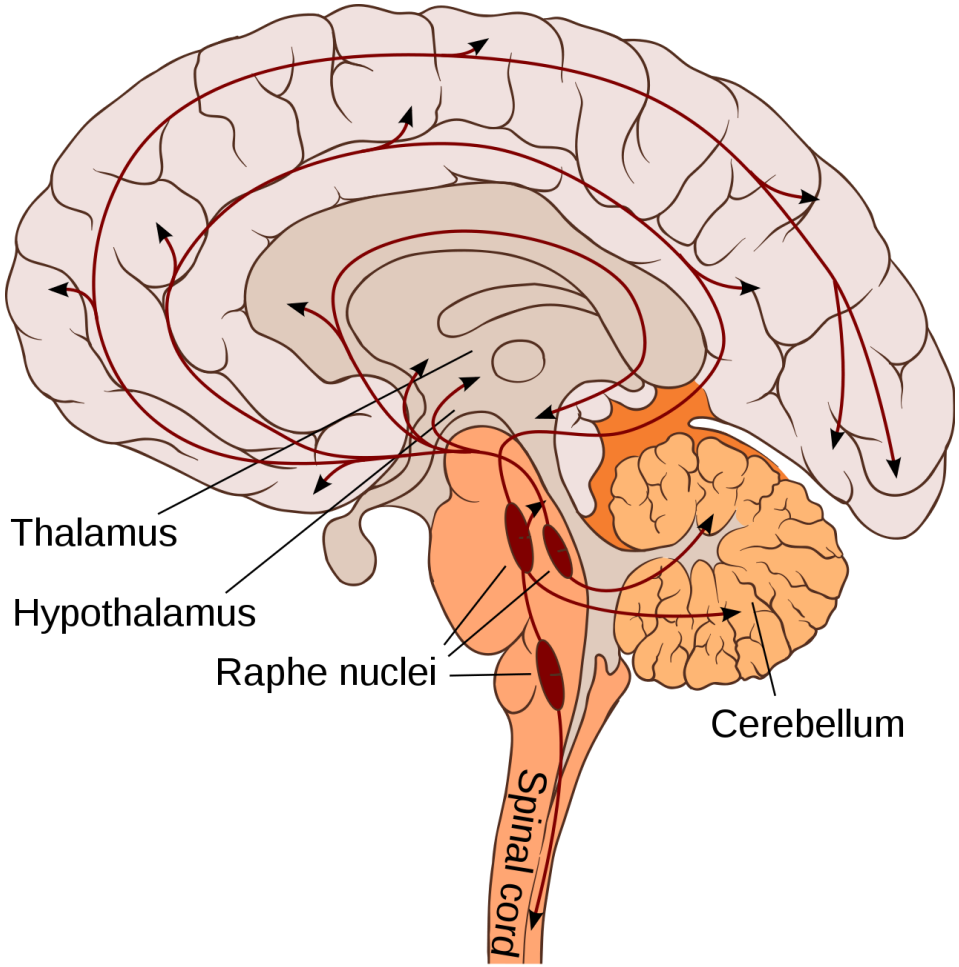
NE receptors

Type	Receptor	Comments
Metabotropic	α (1,2)	antagonists treat anxiety, panic
	β (1,2,3)	‘beta blockers’ in cardiac disease

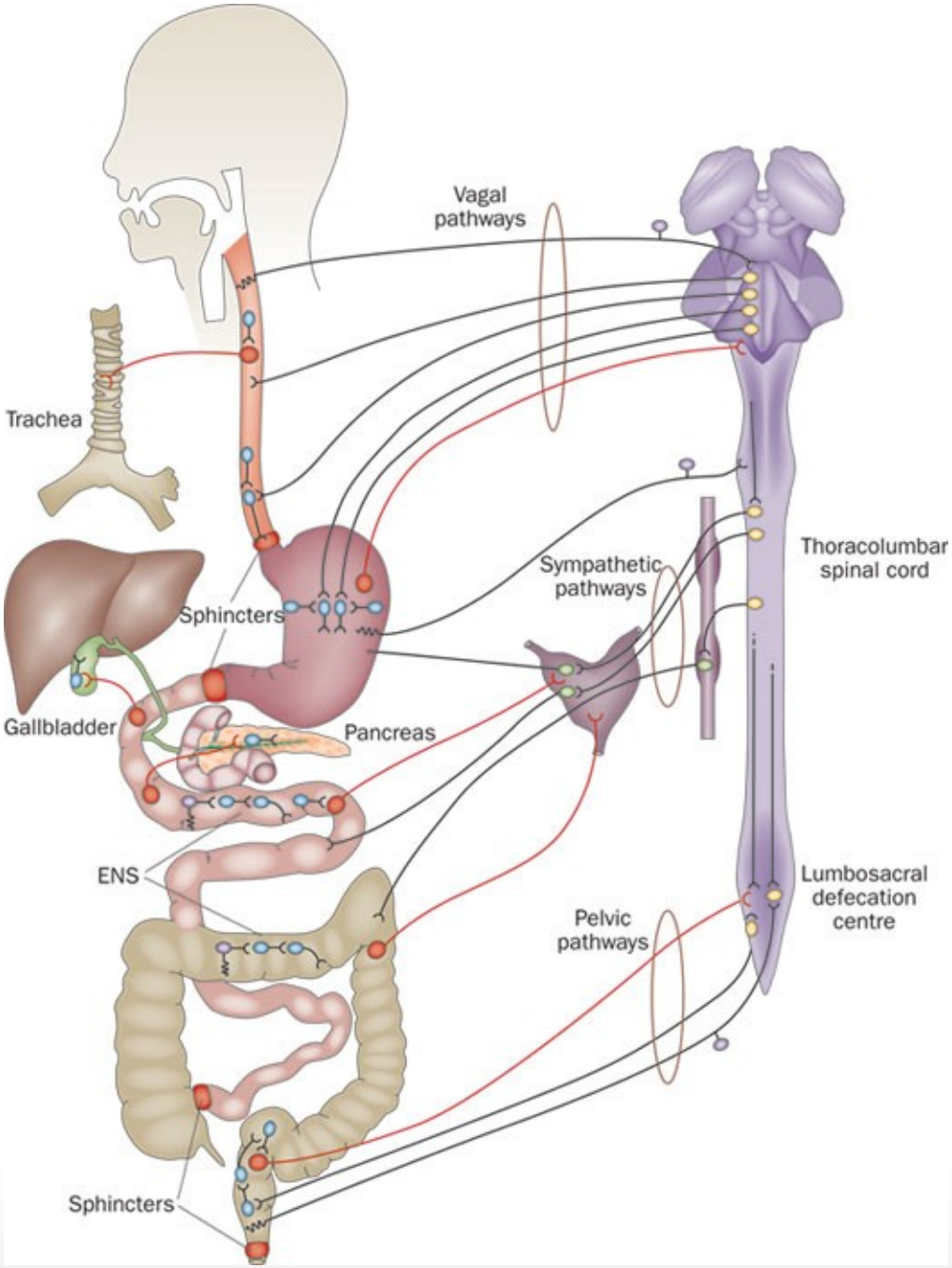
Serotonin (5-HT)

- Released by *raphe nuclei* in brainstem
- Role in mood, sleep, eating, pain, nausea, cognition, memory
- Modulates release of other NTs
- Most of body's 5-HT regulates digestion
    - Enteric nervous system

5-HT anatomy



https://en.wikipedia.org/wiki/Serotonin_pathway



(Furness, 2012)

5-HT receptors

- Seven families (5-HT 1-7) with 14 types
- All but one metabotropic

5-HT clinical significance

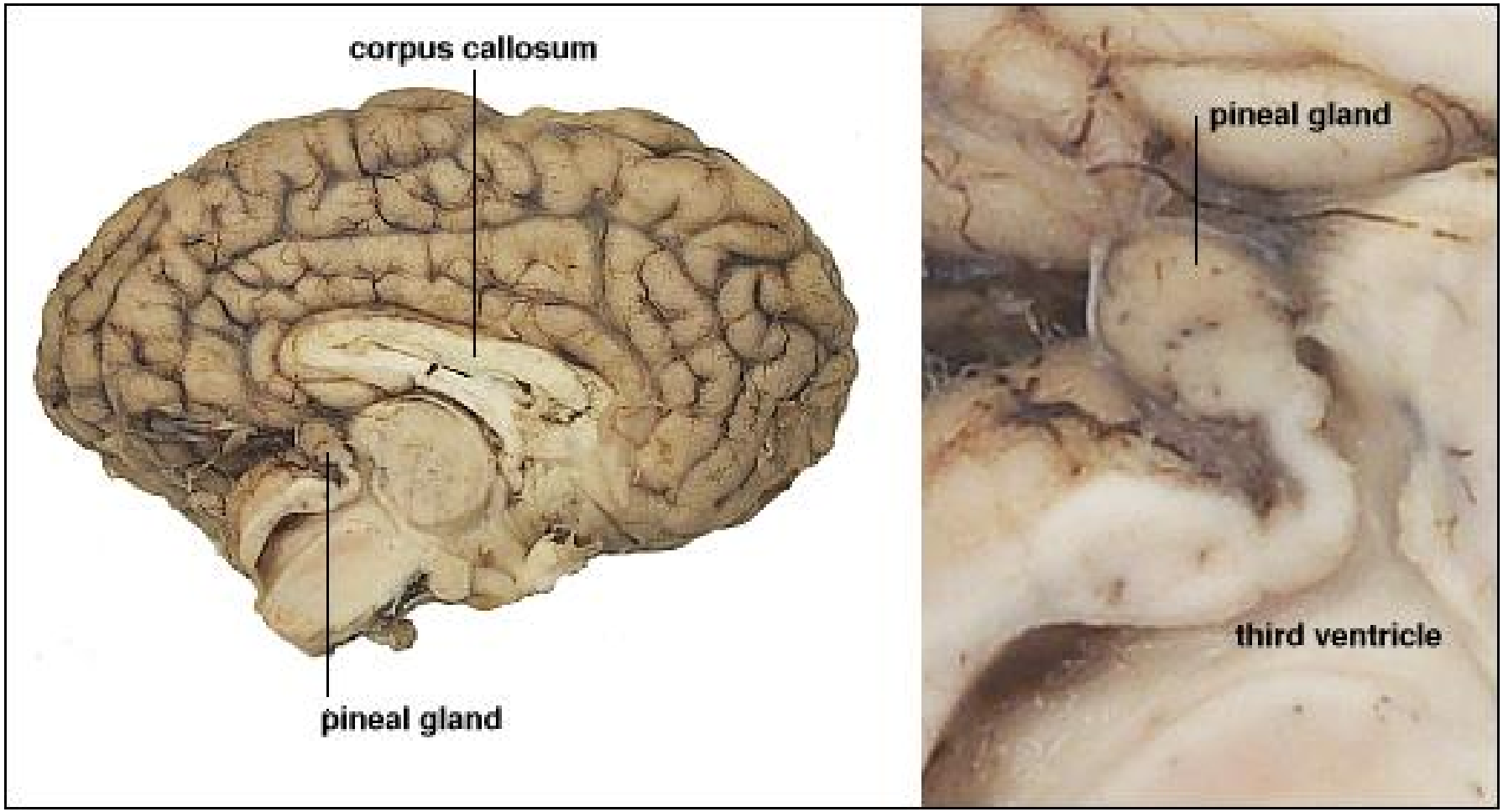
- Ecstasy (MDMA) disturbs serotonin
- So does LSD
- Fluoxetine (Prozac)
  - *Selective Serotonin Reuptake Inhibitor (SSRI)*
  - Inhibits reuptake -> increases extracellular concentration
  - Treats depression, panic, eating disorders, others

5-HT clinical significance

- 5-HT3 receptor antagonists are anti-mimetics used in treating nausea

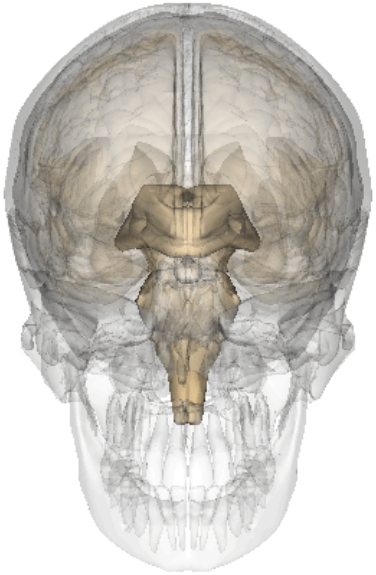
Melatonin

- Hormone released by pineal gland into bloodstream
- Concentrations vary over the day, peak near bedtime
- Release regulated by inputs from hypothalamus



http://www.vivo.colostate.edu/hbooks/pathphys/endocrine

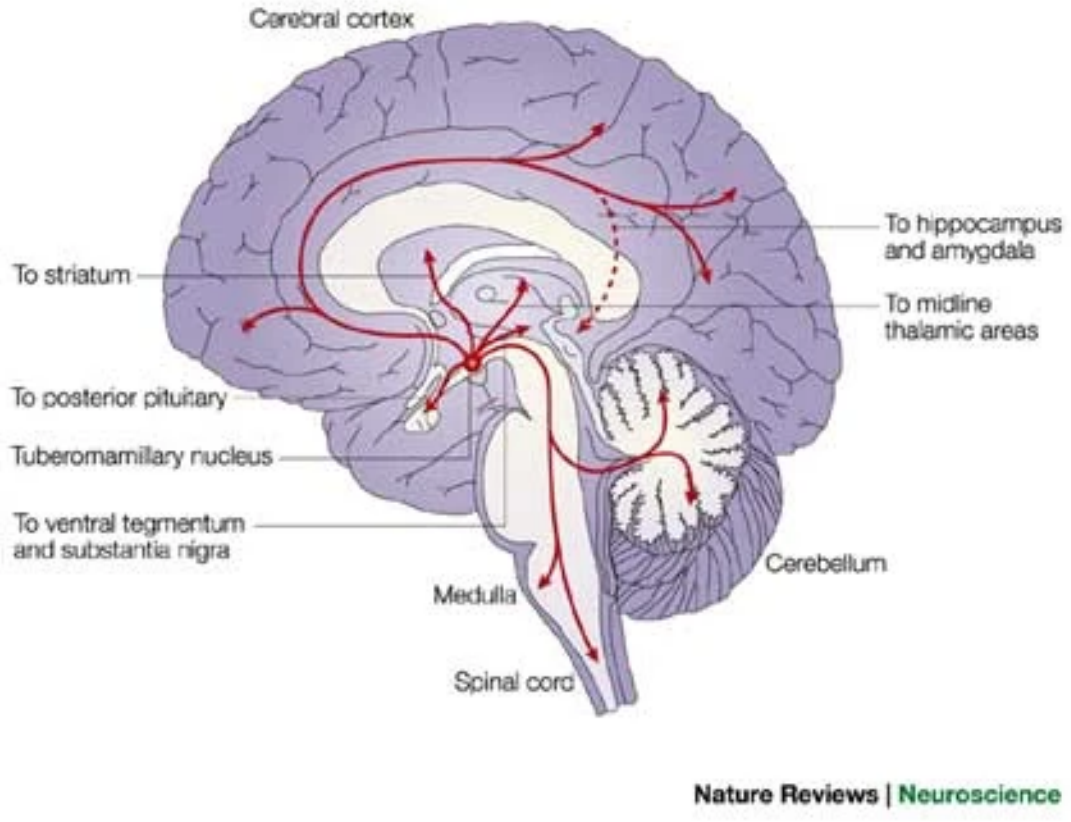
Pineal gland



Histamine

- In brain, released by hypothalamus, projects to whole brain
  - Metabotropic receptors
  - Role in arousal/sleep regulation
- In body, part of immune response

Histamine



https://www.nature.com/articles/nrn1034

Other NTs

- Gases
  - *Nitric Oxide (NO)*, *carbon monoxide (CO)*
- Neuropeptides
  - *Substance P* and *endorphins* (endogenous morphine-like compounds) have role in pain
  - *Orexin/hypocretin*, project from lateral hypothalamus across brain, regulate appetite, arousal

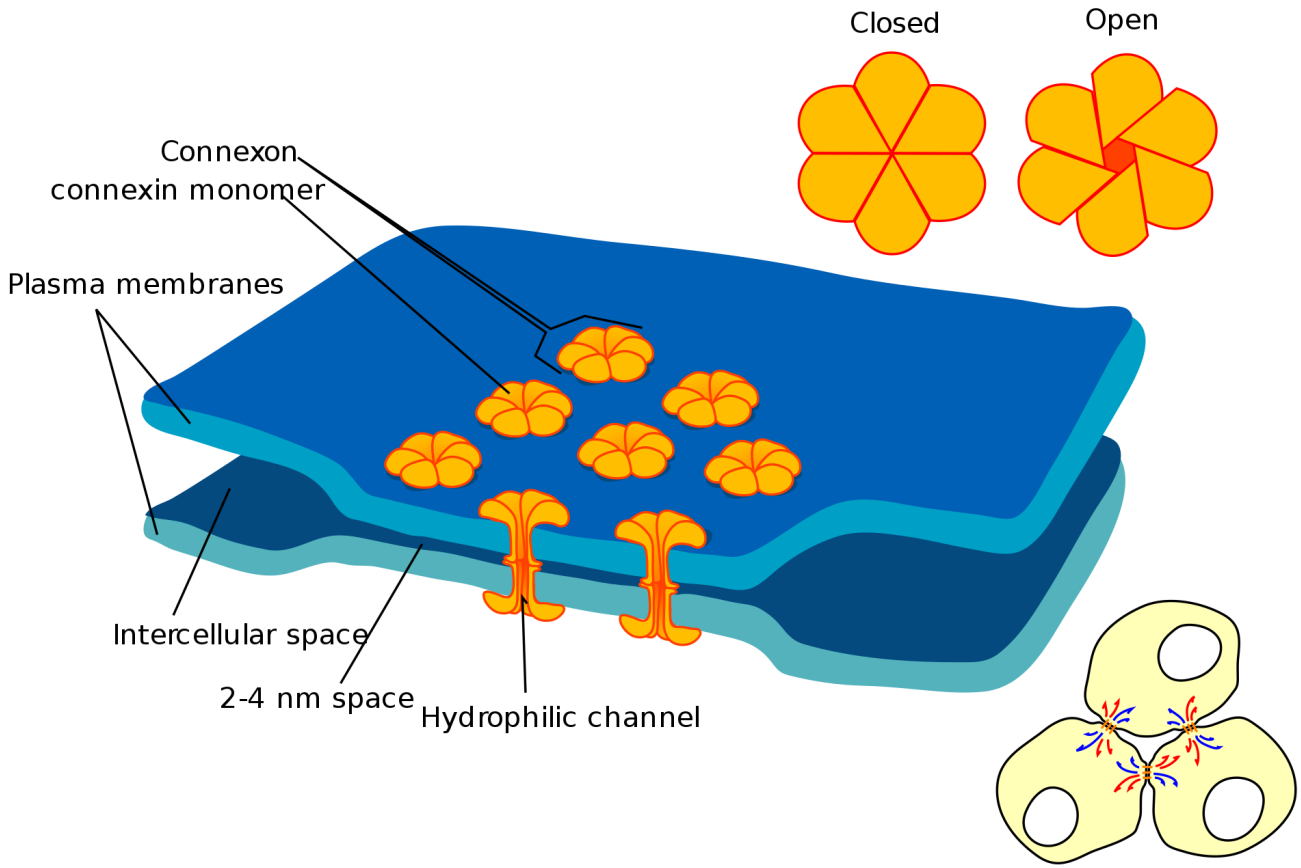
Other NTs

- Neuropeptides (continued)
  - *Cholecystokinin (CCK)* stimulates digestion
  - *Oxytocin* and *vasopressin* released by posterior hypothalamus onto posterior pituitary, regulate social behavior

Non-chemical communication between neurons

- Gap junctions
- Electrical coupling
- Connect cytoplasm directly

Gap junctions



Gap junctions

- Fast, but fixed, hard to modulate
- Examples, retina, cardiac muscle

Ways to think about synaptic communication

- Specificity: point-to-point vs. broadcast
- Direct (immediate) action vs. (delayed, prolonged) modulatory
- Agonists vs. antagonists

Agonists vs. Antagonists

- *Agonists*
  - bind to receptor
  - mimic action of endogenous chemical
- *Antagonists*
  - bind to receptor
  - block/impede action of endogenous chemical

Valium is a GABA-A receptor agonist. This means:

- It decreases inhibition
- It activates a metabotropic Cl- channel
- It facilitates/increases inhibition
- It blocks an ionotropic channel

Valium is a GABA-A receptor agonist. This means:

1. It decreases inhibition
2. It activates a metabotropic Cl- channel
3. It facilitates/increases inhibition
4. It blocks an ionotropic channel

Next time…

- Hormones

References

Furness, J. B. (2012). The enteric nervous system and neurogastroenterology. *Nature Reviews. Gastroenterology & Hepatology*, *9*(5), 286–294. https://doi.org/10.1038/nrgastro.2012.32

Małgorzata, P., Paweł, K., Iwona, M. L., Brzostek, T., & Andrzej, P. (2020). Glutamatergic dysregulation in mood disorders: Opportunities for the discovery of novel drug targets. *Expert Opinion on Therapeutic Targets*, *24*(12), 1187–1209. https://doi.org/10.1080/14728222.2020.1836160

McCutcheon, R. A., Krystal, J. H., & Howes, O. D. (2020). Dopamine and glutamate in schizophrenia: Biology, symptoms and treatment. *World Psychiatry: Official Journal of the World Psychiatric Association*, *19*(1), 15–33. https://doi.org/10.1002/wps.20693