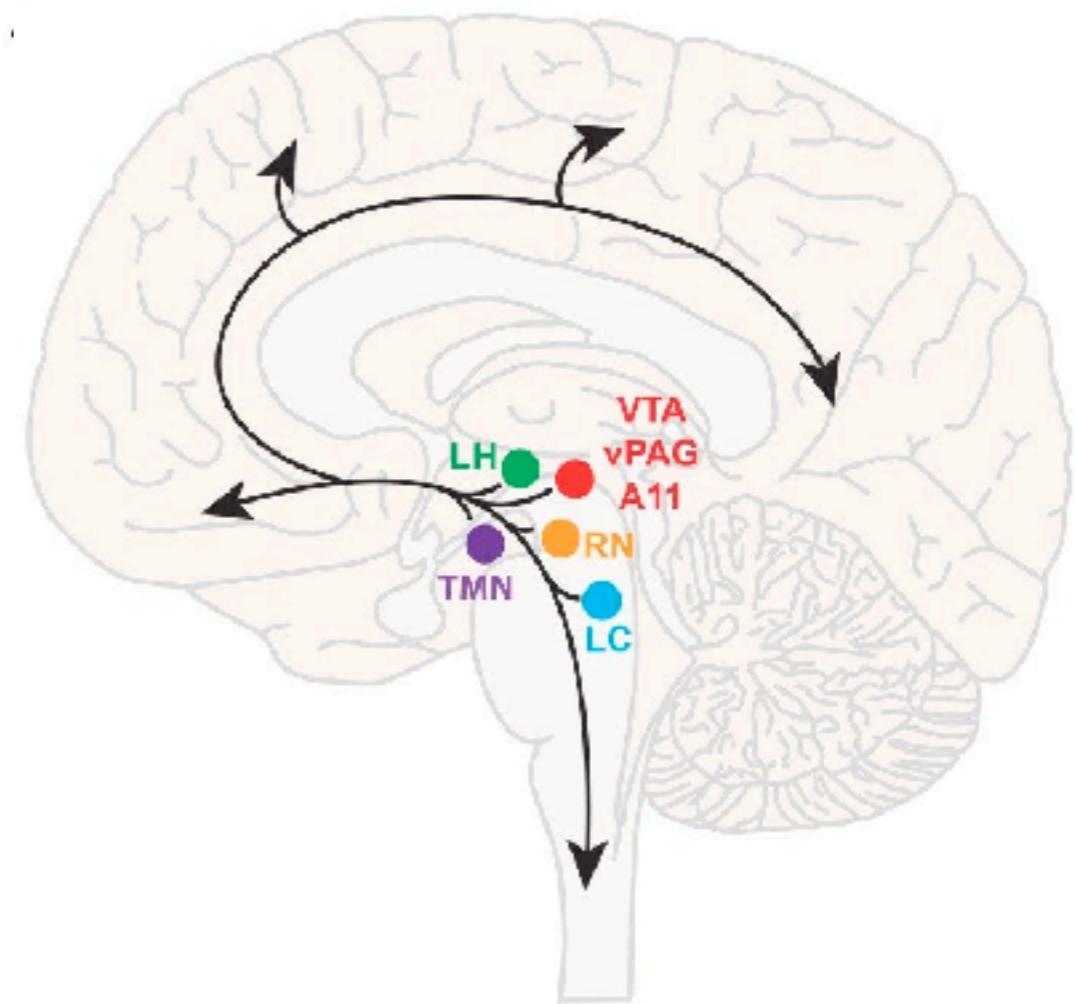
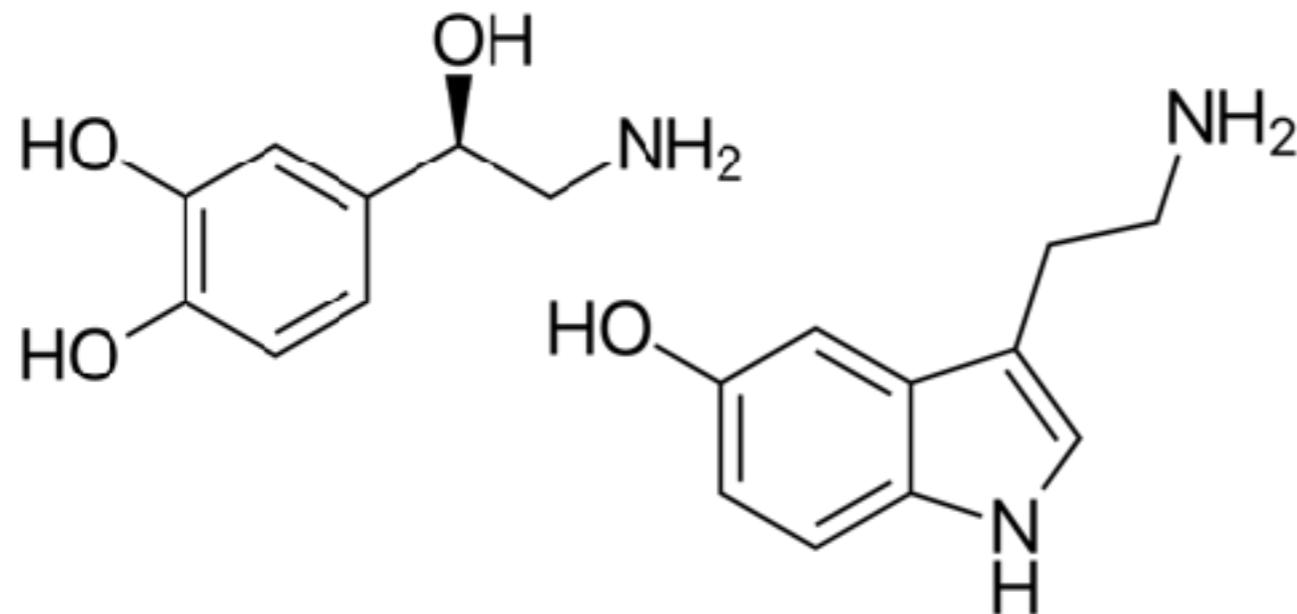
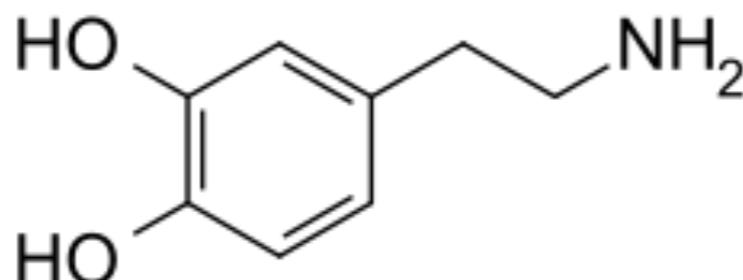
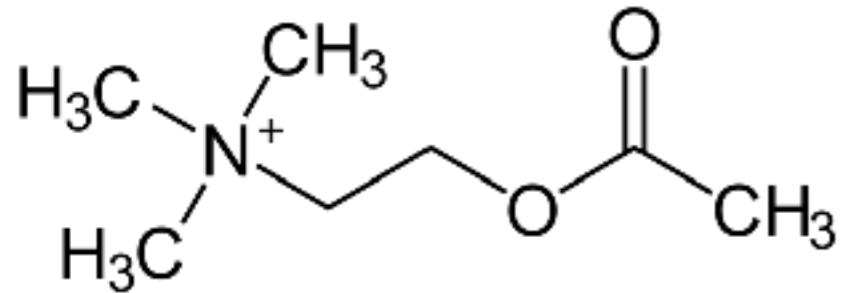


Neuromodulatory systems

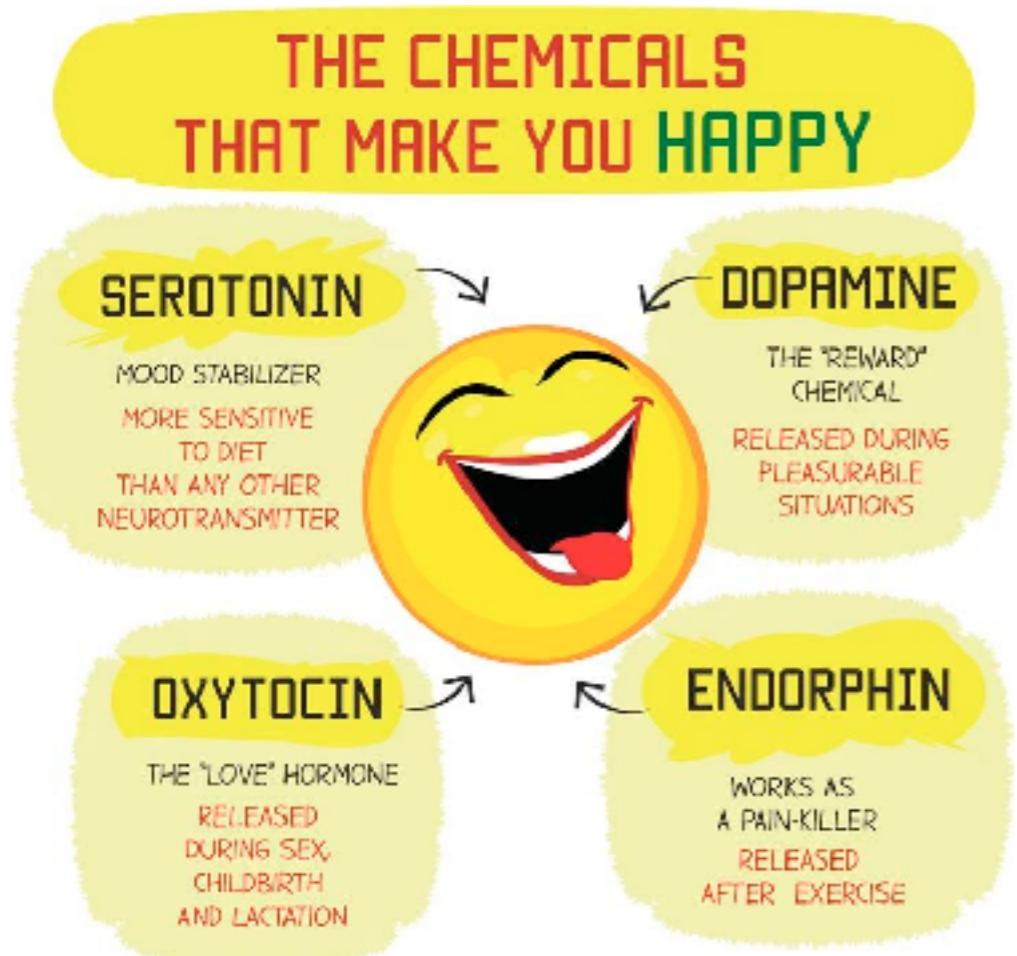


January 13, 2021

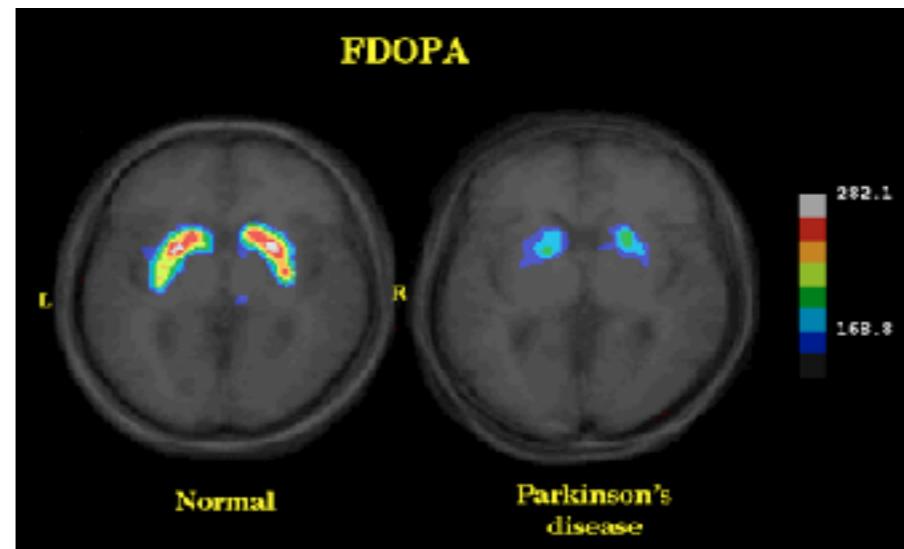
Takashi Kawashima, Department of Neurobiology

What is a neuromodulator?

Pop culture



Medical contexts



What is a neuromodulator?

Neurotransmitters

- Amino acids** (Glutamate, GABA, Glycine, etc)
- Gas** (NO, CO, H₂S)
- Purines** (ATP, adenosine, etc)
- Peptides** (Oxytocin, opioids, etc)
- Choline** (Acetylcholine)
- Monoamines** (Serotonin, Dopamine, etc)

Let's do the poll !

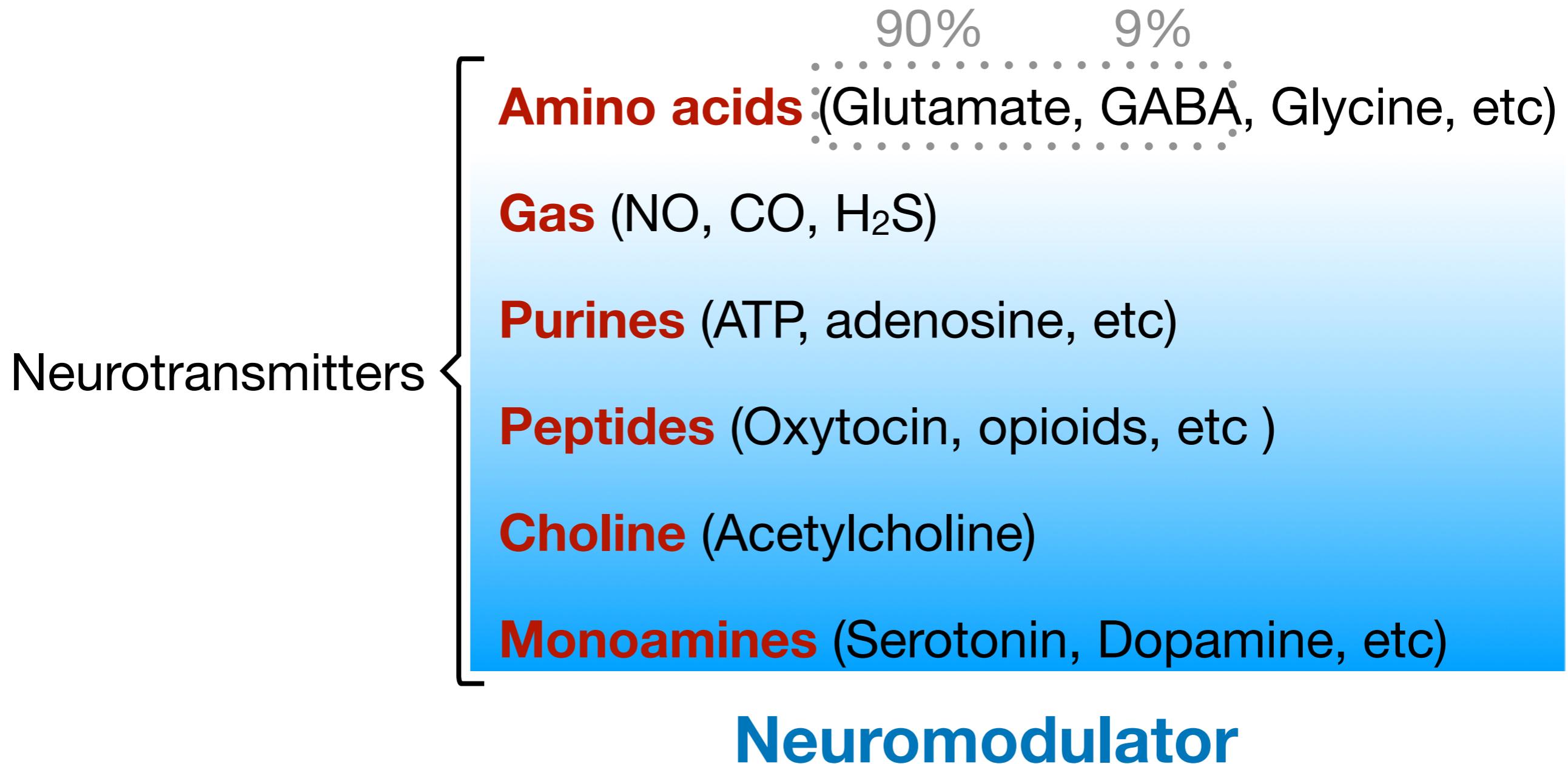
What is neuromodulator?

Neurotransmitters

- Amino acids** (Glutamate, GABA, Glycine, etc)
- Gas** (NO, CO, H₂S)
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- Monoamines** (Serotonin, Dopamine, etc)

Neuromodulator

What is neuromodulator?



What is neuromodulator?

Neurotransmitters

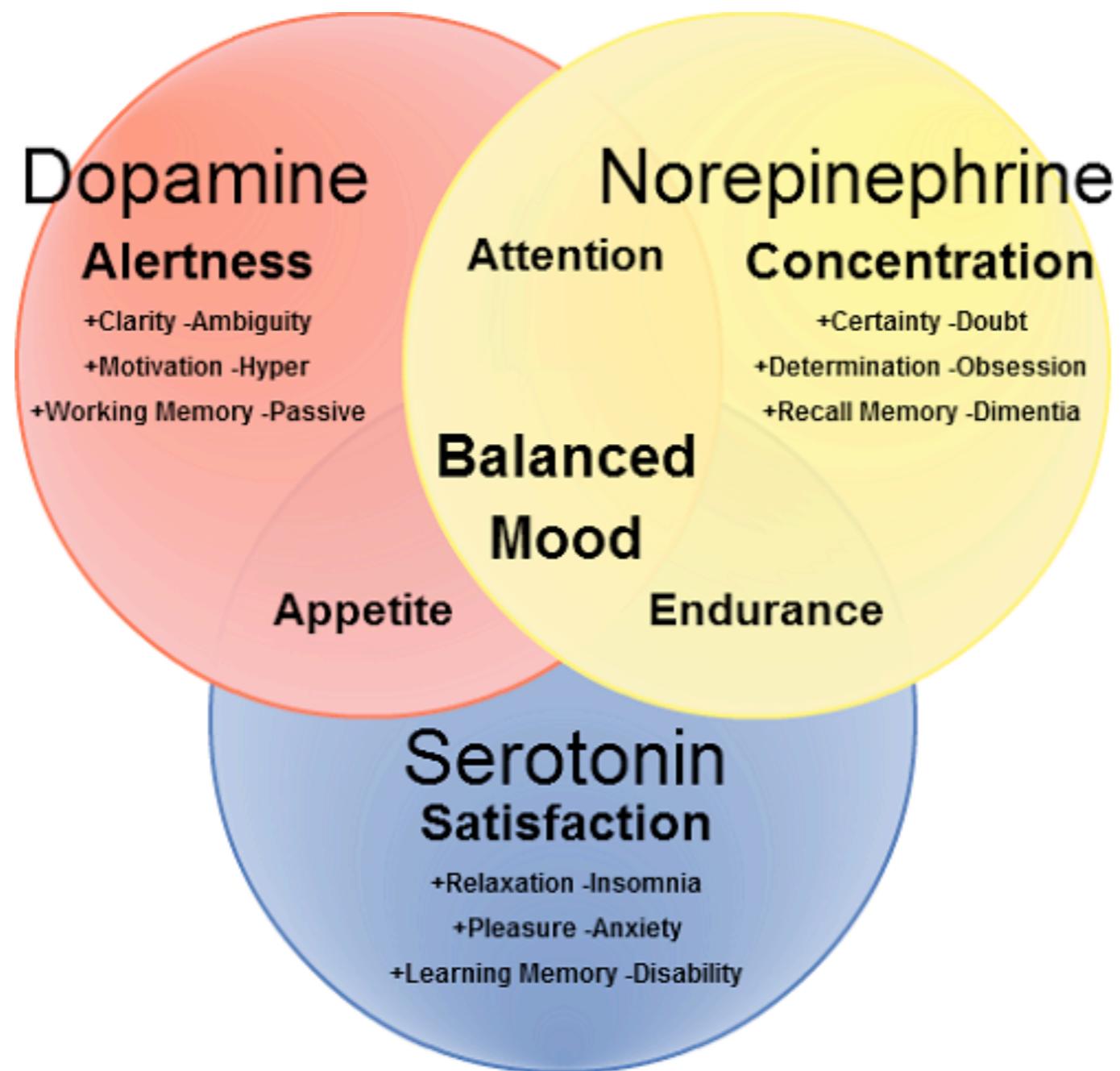
- Amino acids** (Glutamate, GABA, Glycine, etc)
 - Gas** (NO, CO, H₂S)
 - Purines** (ATP, adenosine, etc)
 - Peptides** (Oxytocin, opioids, etc)
 - Choline** (Acetylcholine)
 - Monoamines** (Serotonin, Dopamine, etc)

Neuromodulator

Neuromodulator

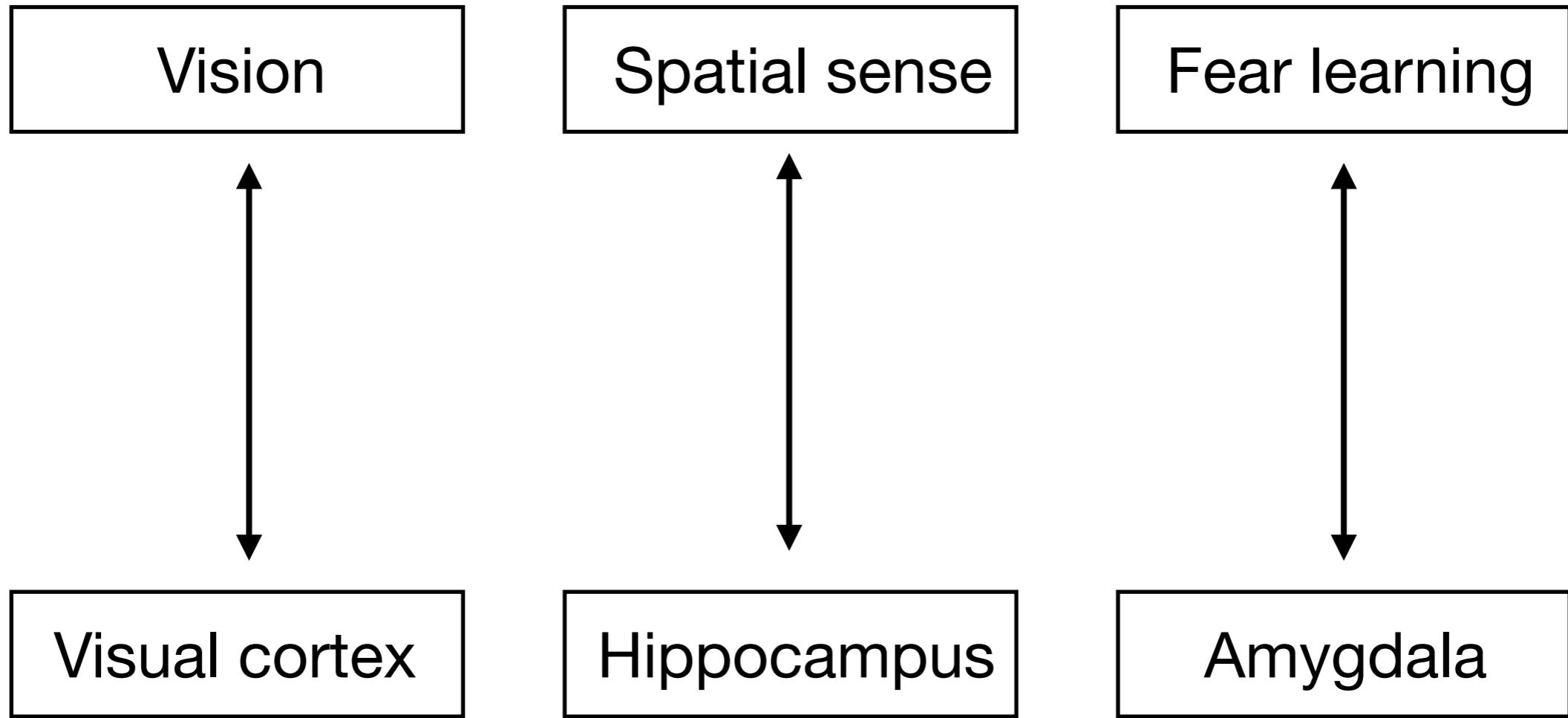
	<u>Glutamate, GABA</u>	
Function	General	More specific??
Synaptic?	Mostly synaptic	Synaptic / diffusive
Communication mode	One-to-one	One-to-many
Receptor action	(typically) Ionic, fast	(typically) GPCRs, slow

Do neuromodulators have specific functions?

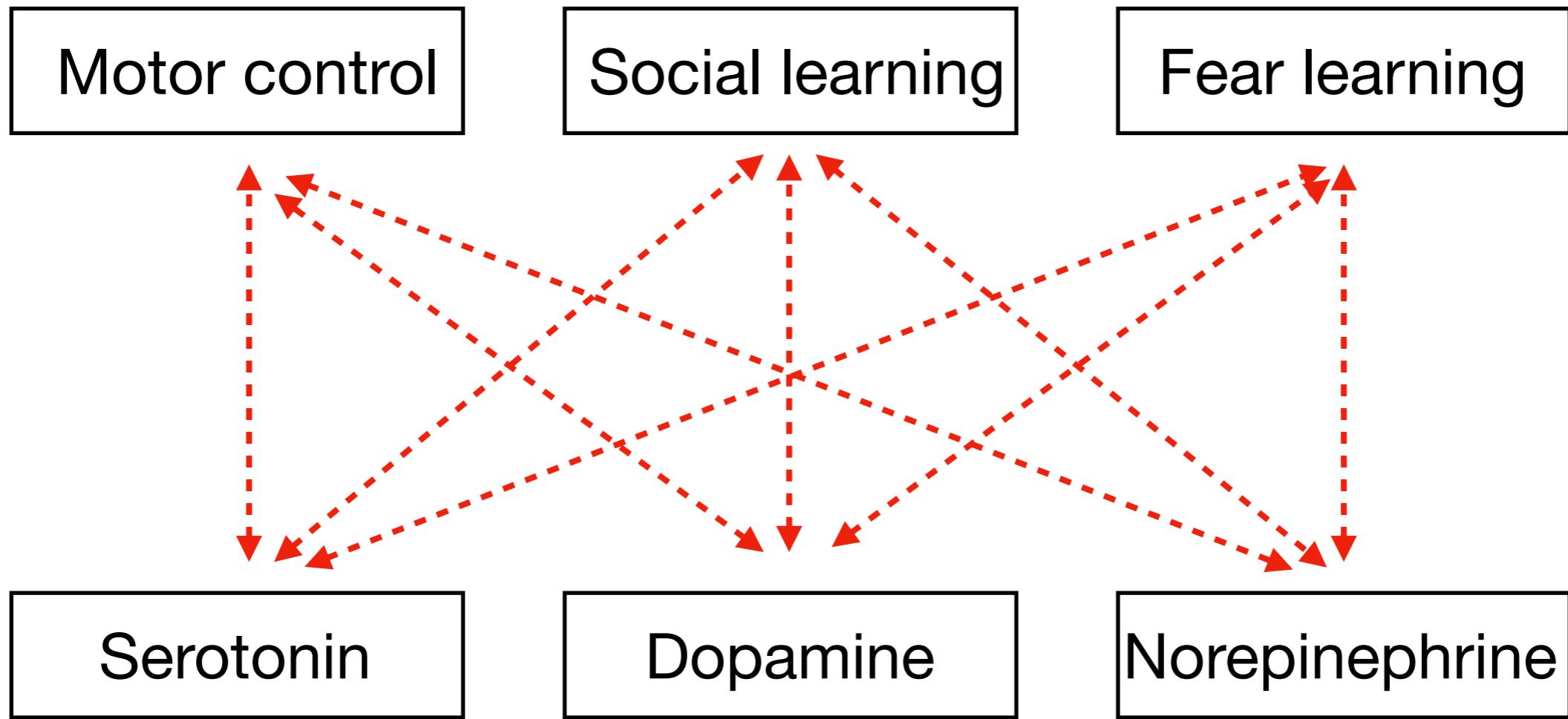


(Wikipedia)

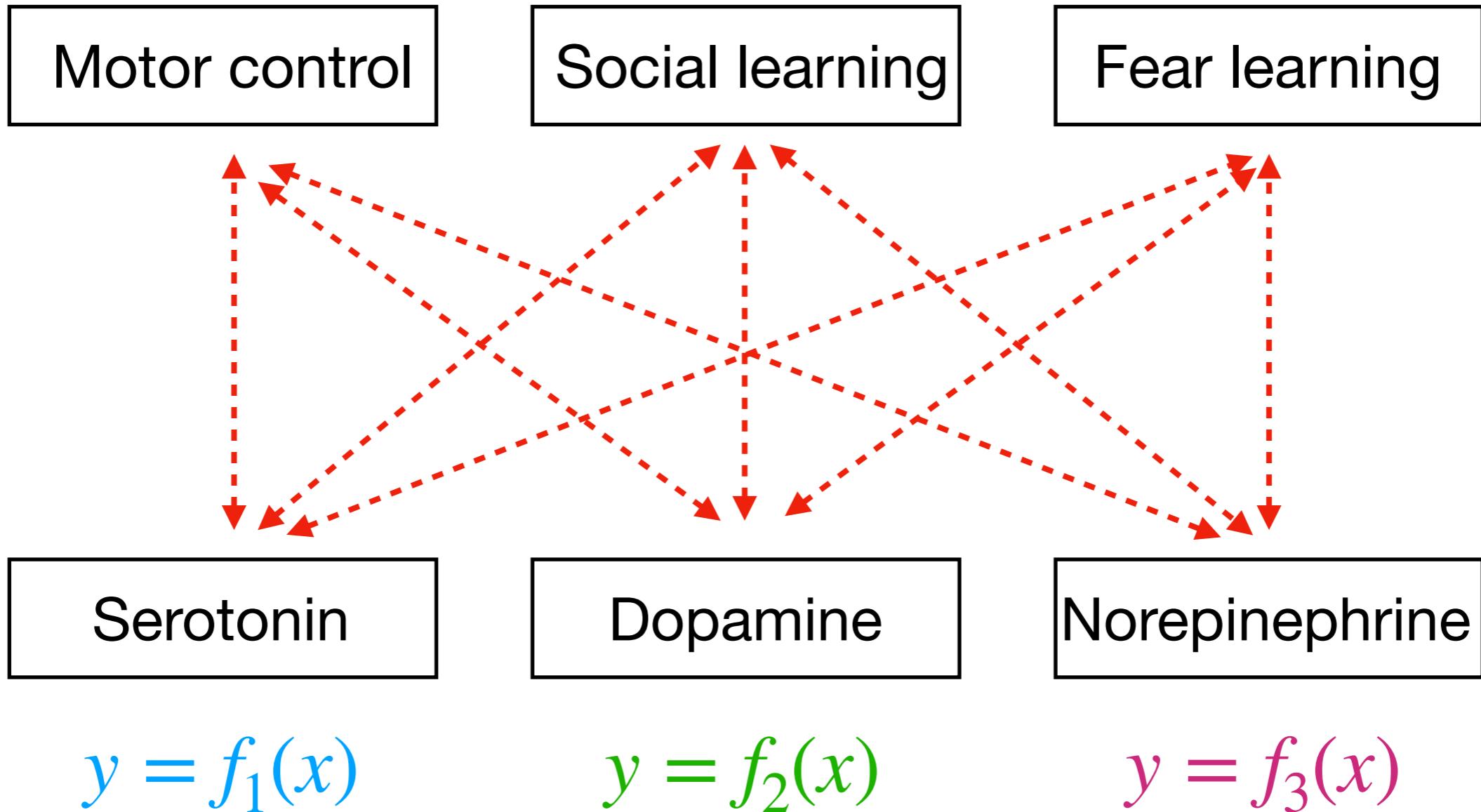
Usual way of systems neuroscience



If you do the same approach to neuromodulators...



If you do the same approach to neuromodulators...



More mechanistic perspectives

The goal of this lecture

- (1) Basics of neuromodulators
- (2) How they work at mechanistic levels
- (3) How mechanisms generalize across functions

(60 min lecture x 2 +15 min break)

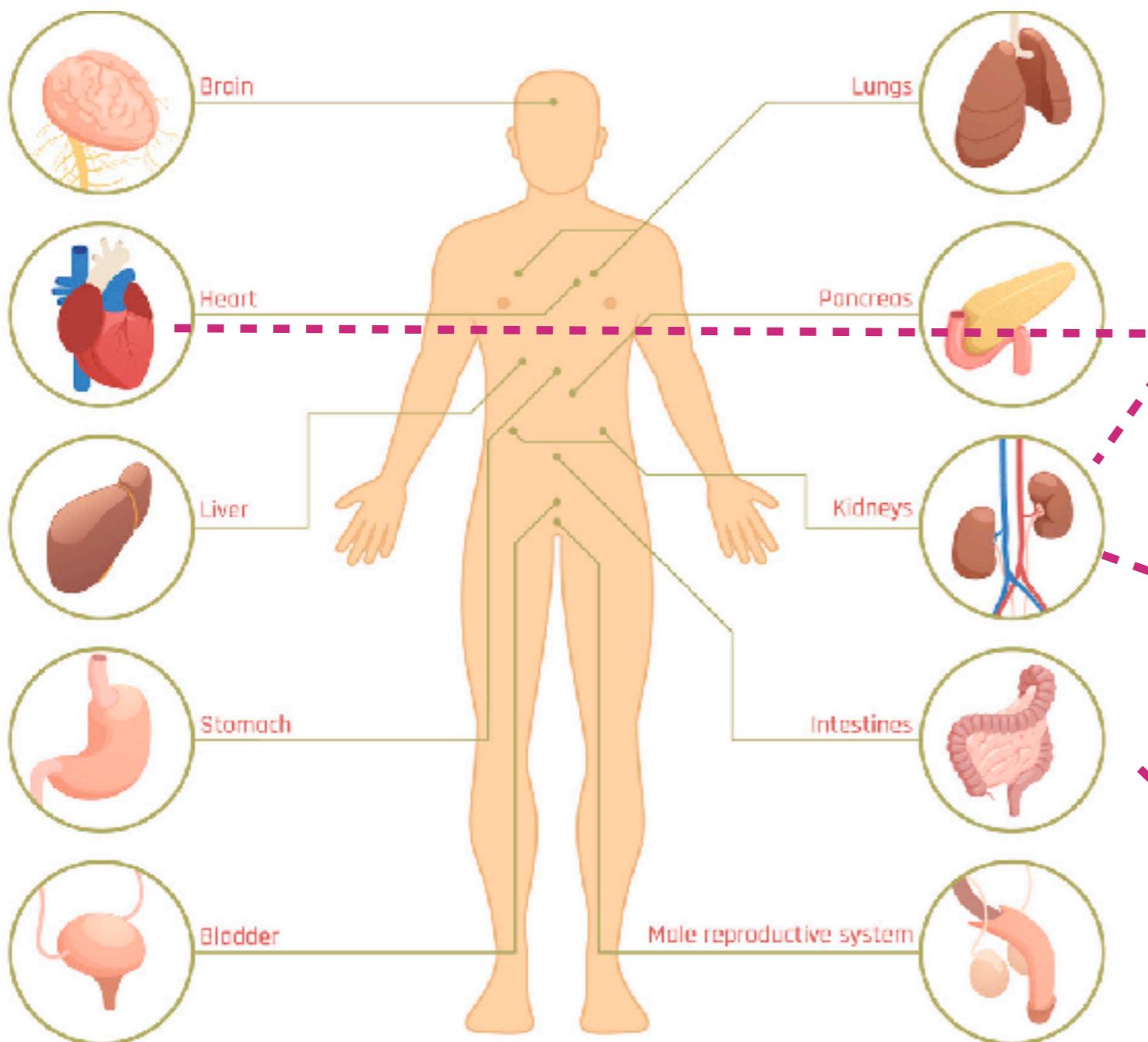
The goal of this lecture

Neurotransmitters

- Amino acids** (Glutamate, GABA, Glycine, etc)
- Gas** (NO, CO, H₂S)
- Purines** (ATP, adenosine, etc)
- Peptides** (Oxytocin, opioids, etc)
- Choline** (Acetylcholine)
- Monoamines** (Serotonin, Dopamine, Norepinephrine)

The goal of this lecture

- (1) Basics of neuromodulators
- (2) How they work at mechanistic levels
- (3) How mechanisms generalize across functions



Norepinephrine
von Euler, 1945

Acetylcholine
(Baeyer, 1867)
Loewi, 1921

Dopamine
(Dale, 1910)
Holtz, 1939

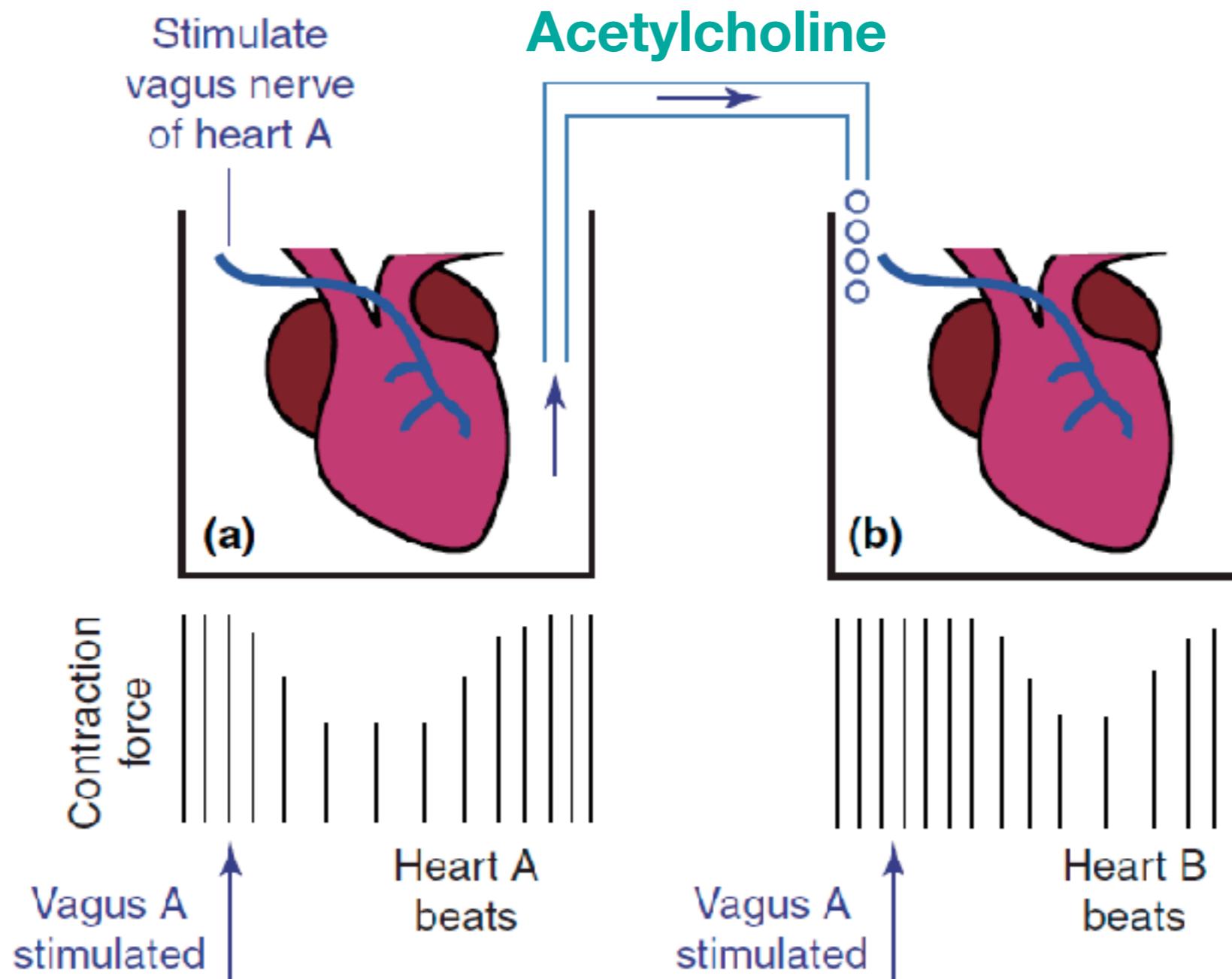
Serotonin
Erspamer, 1935

Discovery of neuromodulators: initial questions

- Does it work as a neurotransmitter?
- Is dopamine meaningful in the brain?
- Where are they produced in the brain?

- Does it work as a neurotransmitter?
- Is dopamine meaningful in the brain?
- Where are they produced in the brain?

Loewi's proof of chemical neurotransmission (1921)



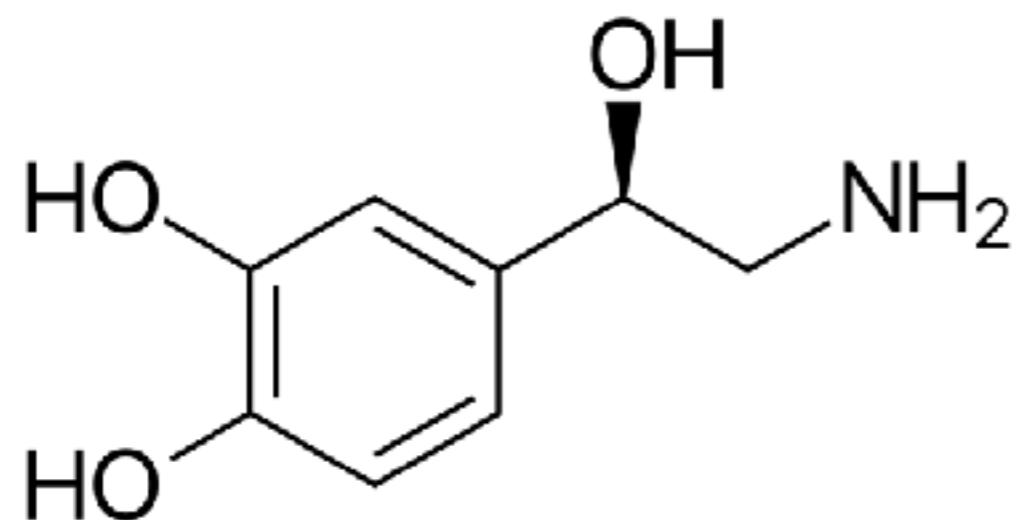
(from Dani et al., 2011)

Neuromodulators are evolutionally conserved

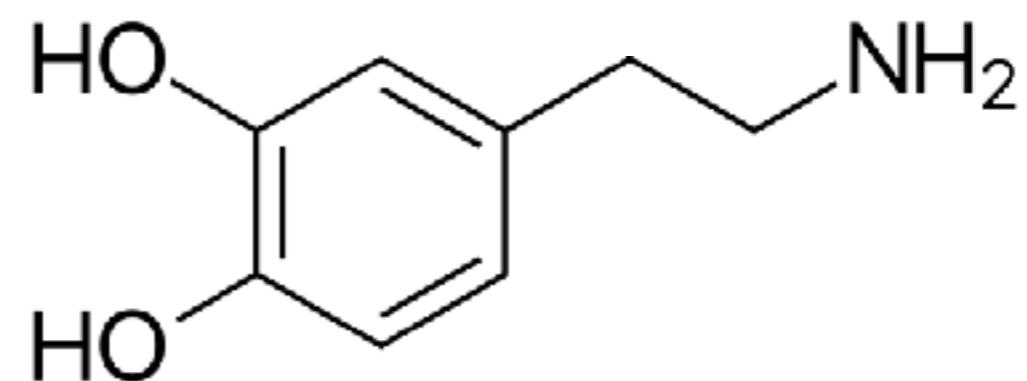
	Worm	Fly	Fish	Mammals
Major transmitter	ACh GABA	ACh GABA	Glutamate GABA	Glutamate GABA
Modulator	Serotonin Dopamine Octopamine	Serotonin Dopamine Octopamine	Serotonin Dopamine Norepinephrine ACh	Serotonin Dopamine Norepinephrine ACh

- Does it work as a neurotransmitter?
- Is dopamine functional in the brain?
- Where are they produced in the brain?

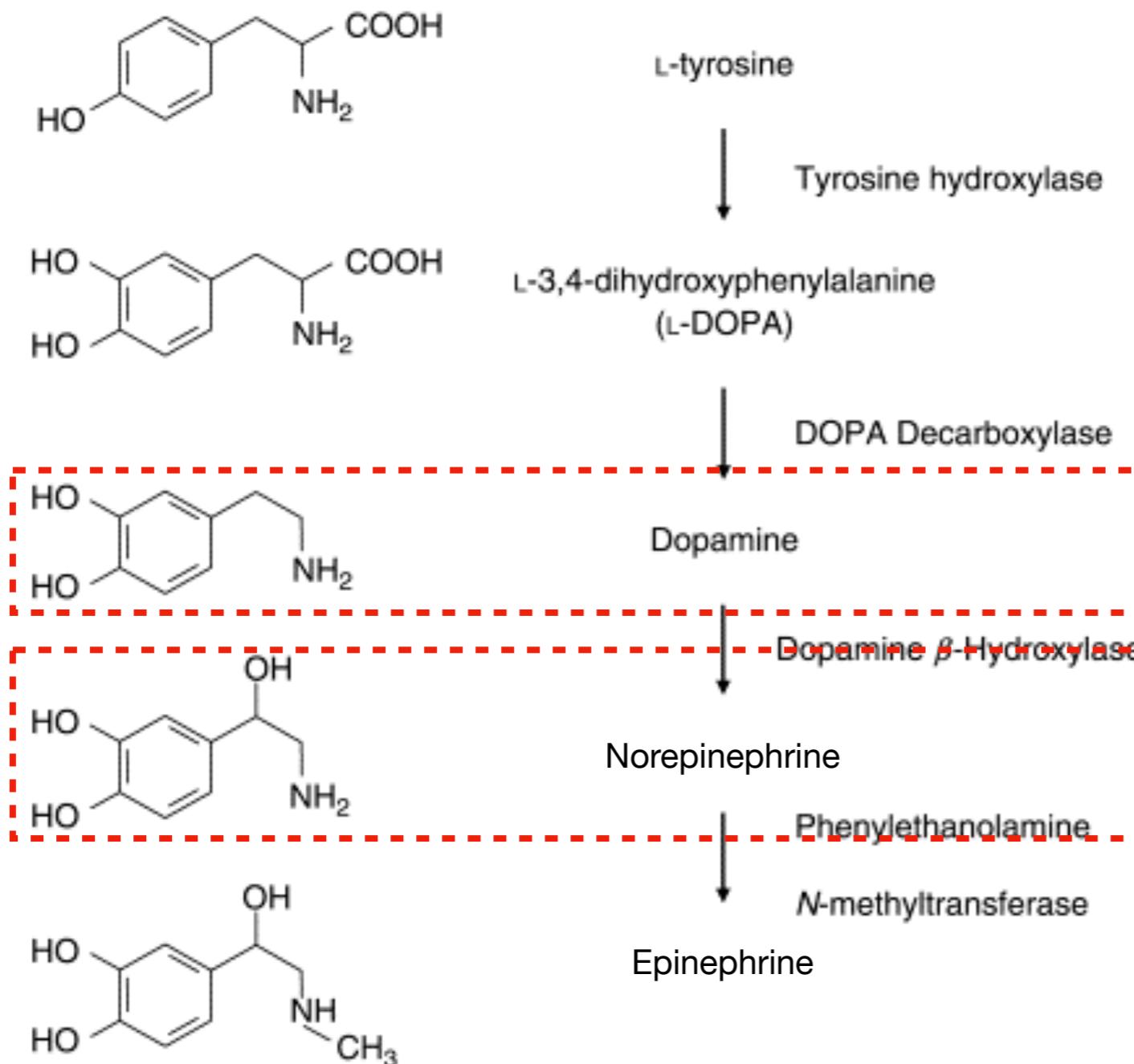
Norepinephrine



Dopamine



Dopamine used to be regarded as a precursor of norepinephrine



Experiment by Arvid Carlsson

"for their discoveries concerning signal transduction in the nervous system"



Arvid Carlsson

⌚ 1/3 of the prize

Sweden

Göteborg University
Gothenburg, Sweden

b. 1923



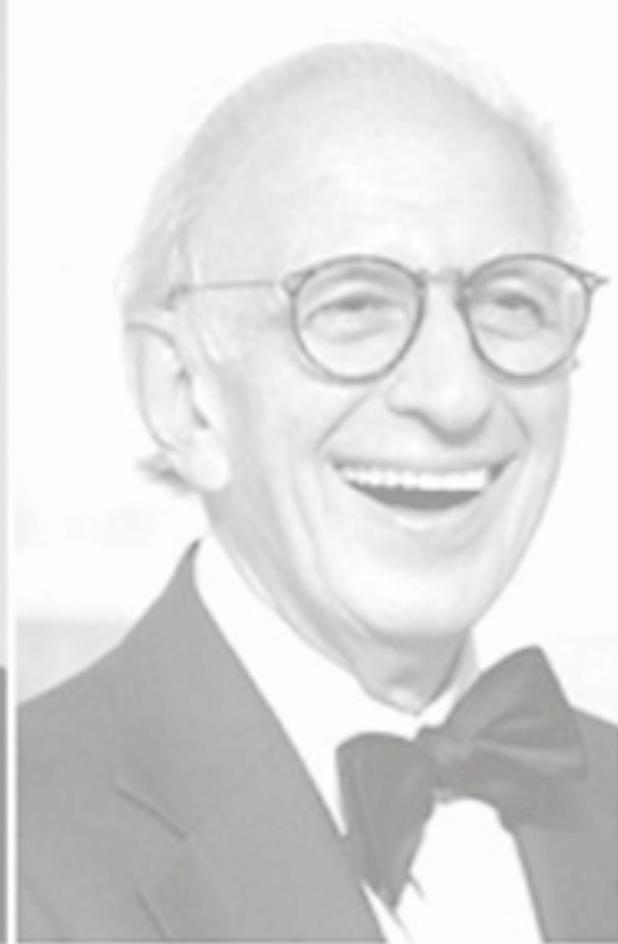
Paul Greengard

⌚ 1/3 of the prize

USA

Rockefeller University
New York, NY, USA

b. 1925



Eric R. Kandel

⌚ 1/3 of the prize

USA

Columbia University
New York, NY, USA

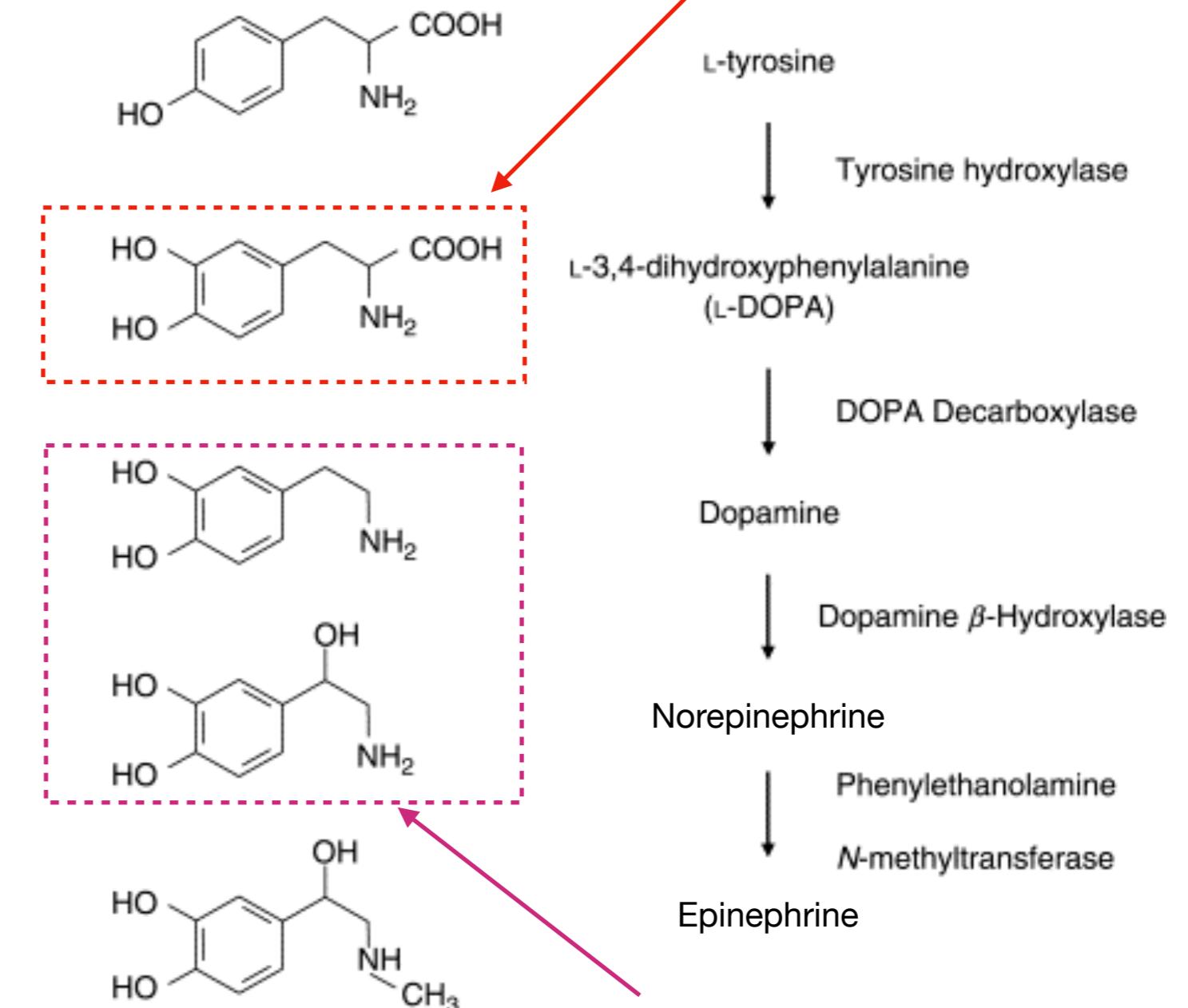
b. 1929
(in Vienna, Austria)

Reserpine-induced Parkinsonism (anti-hypertension drug)

Parkinsonism

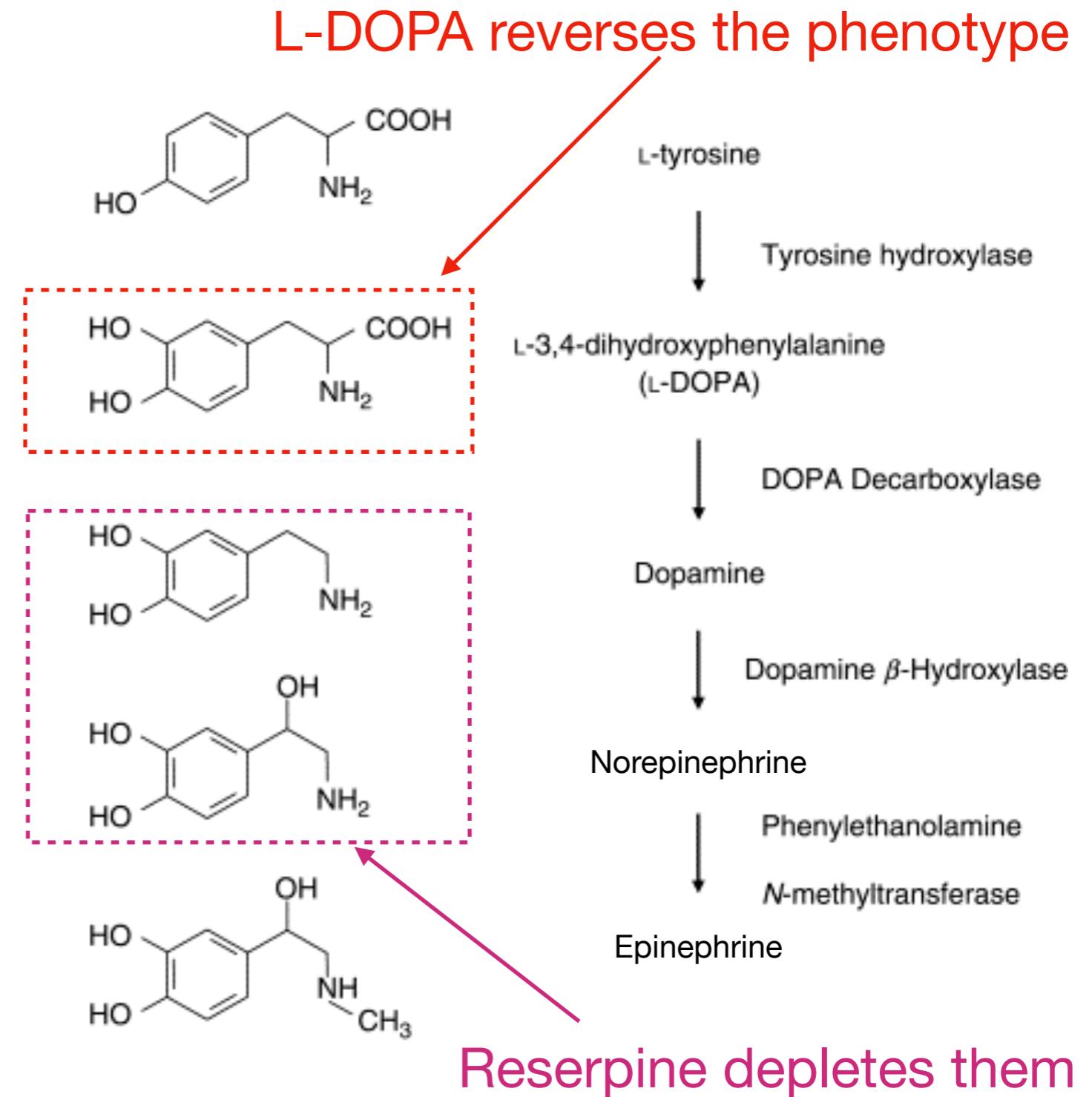


L-DOPA reverses the phenotype



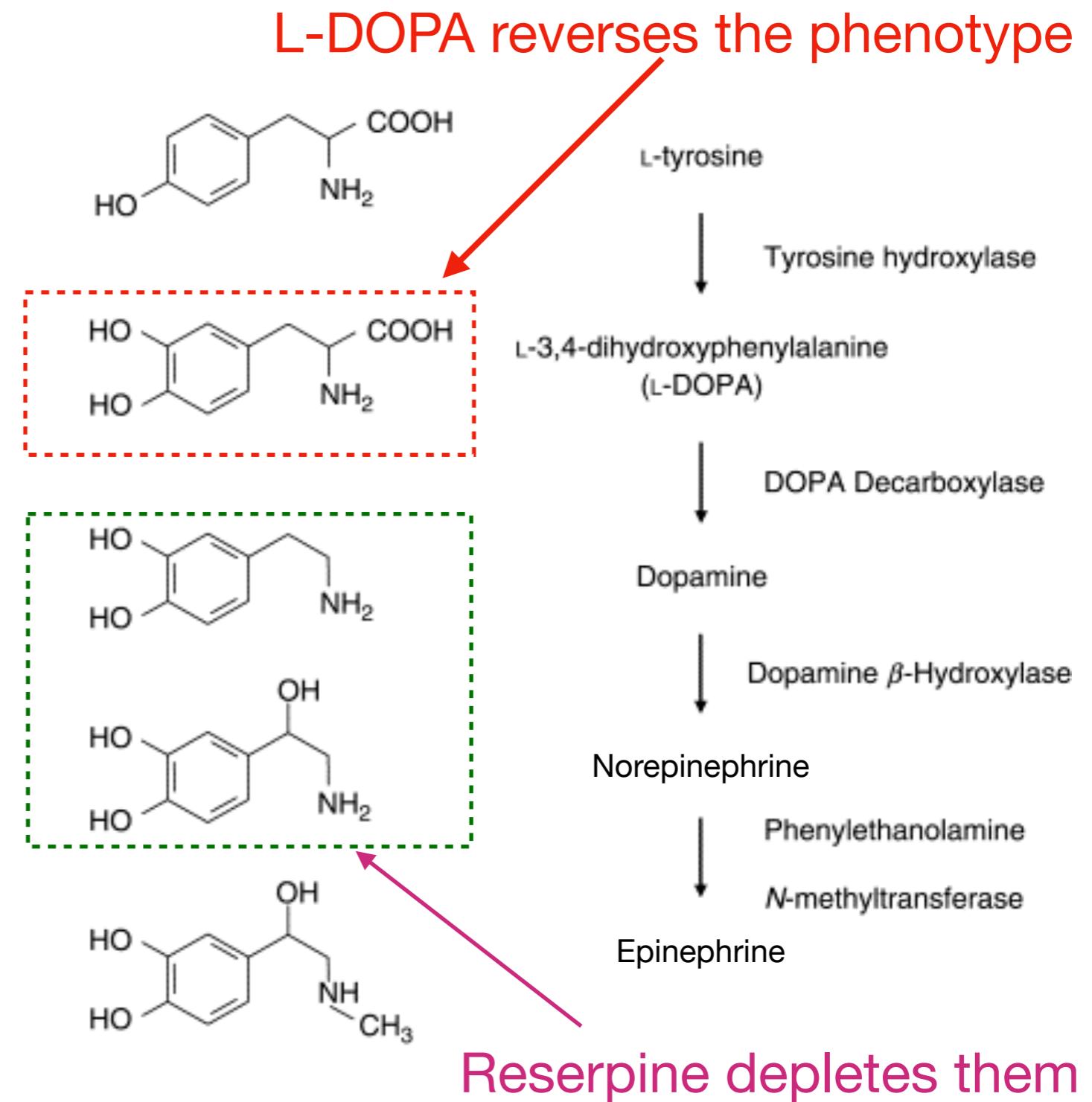
Reserpine depletes them

Breakout room discussion: what observation proved the independent role of dopamine?



Like noradrenaline (8), 3-hydroxytyramine is made to disappear almost completely from brain by intravenous injection of reserpine (5 mg/kg). On the other hand, the injection of the precursor 3,4-dihydroxyphenylalanine (150 mg of the DL form per kilogram, intravenously) caused a very marked increase in the 3-hydroxytyramine content of the brain (to about 2 µg/g in less than 1 hour). This was accompanied by central excitation (9). Both these phenomena were markedly enhanced by pretreatment with iproniazid (Marsilid). Simultaneous changes in the noradrenaline level of the brain were much less pronounced if present at all (10). Carlsson, 1958

L-DOPA mostly increase dopamine, but not norepinephrine

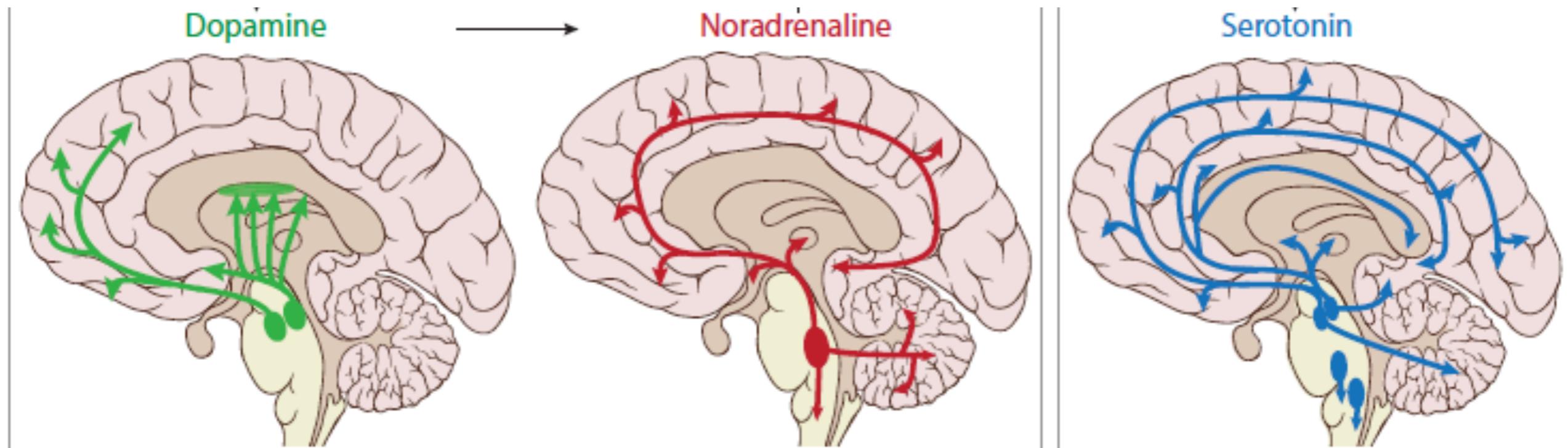


Dopamine is localized in the striatum in the brain

Distribution of noradrenaline and dopamine in the dog brain

	Norepinephrine	Dopamine
	$\mu\text{g/g}$	$\mu\text{g/g}$
Cerebral hemispheres (not corpus striatum, hippocampus)		
rostral part	0.13	0.07
caudal part.....	0.12	0.08
Caudate nucleus.....	0.10	5.90
Lentiform nucleus.....	0.08	1.63
Hippocampus.....	0.14	0.13
Hypothalamus.....	0.76	0.26
Diencephalon (not hypothalamus).....	0.17	0.09
Mesencephalon.....	0.33	0.20
Pons.....	0.41	0.10
Medulla oblongata.....	0.37	0.13
Cerebellum.....	0.06	0.03

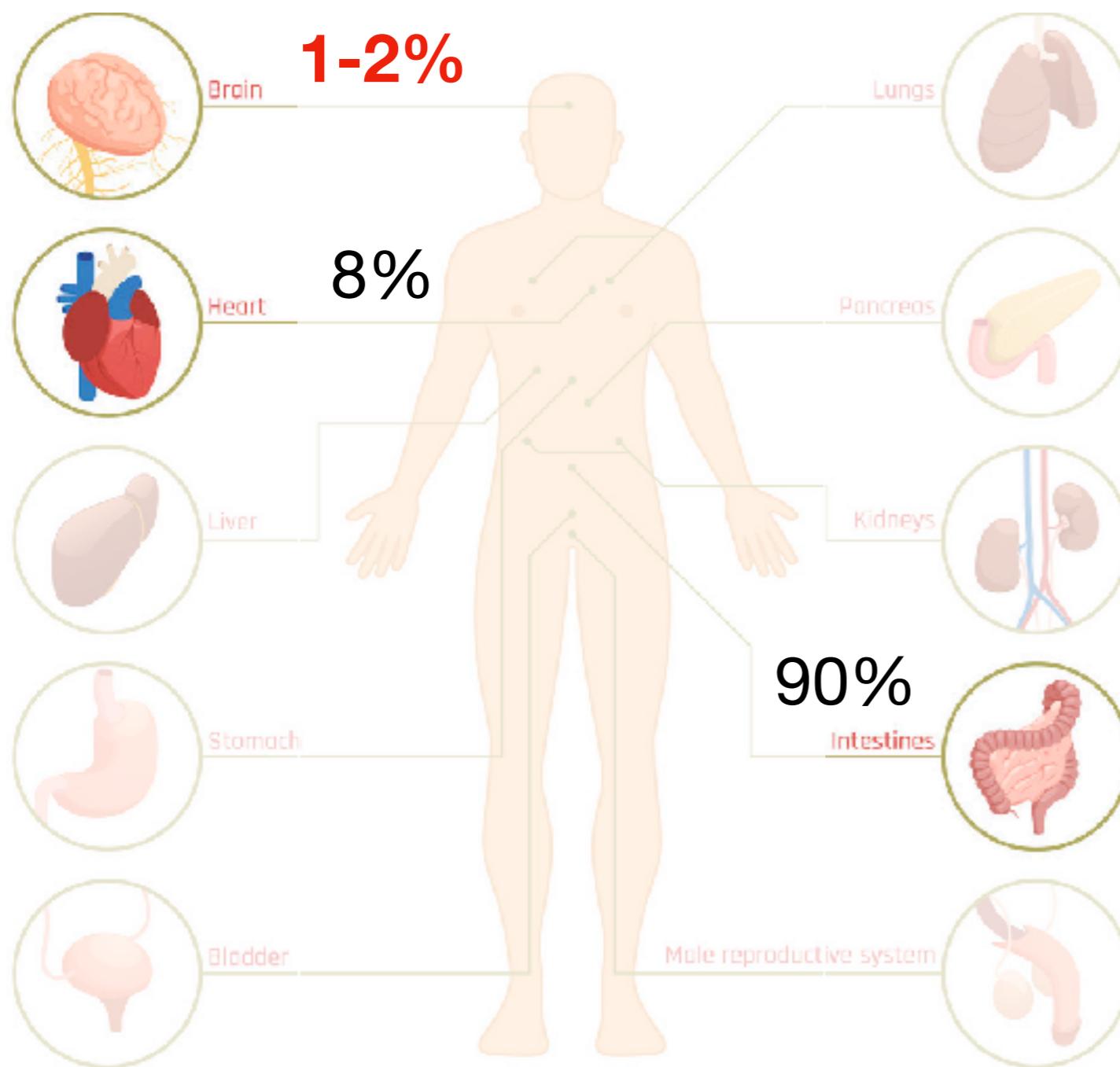
Carlsson, 1959



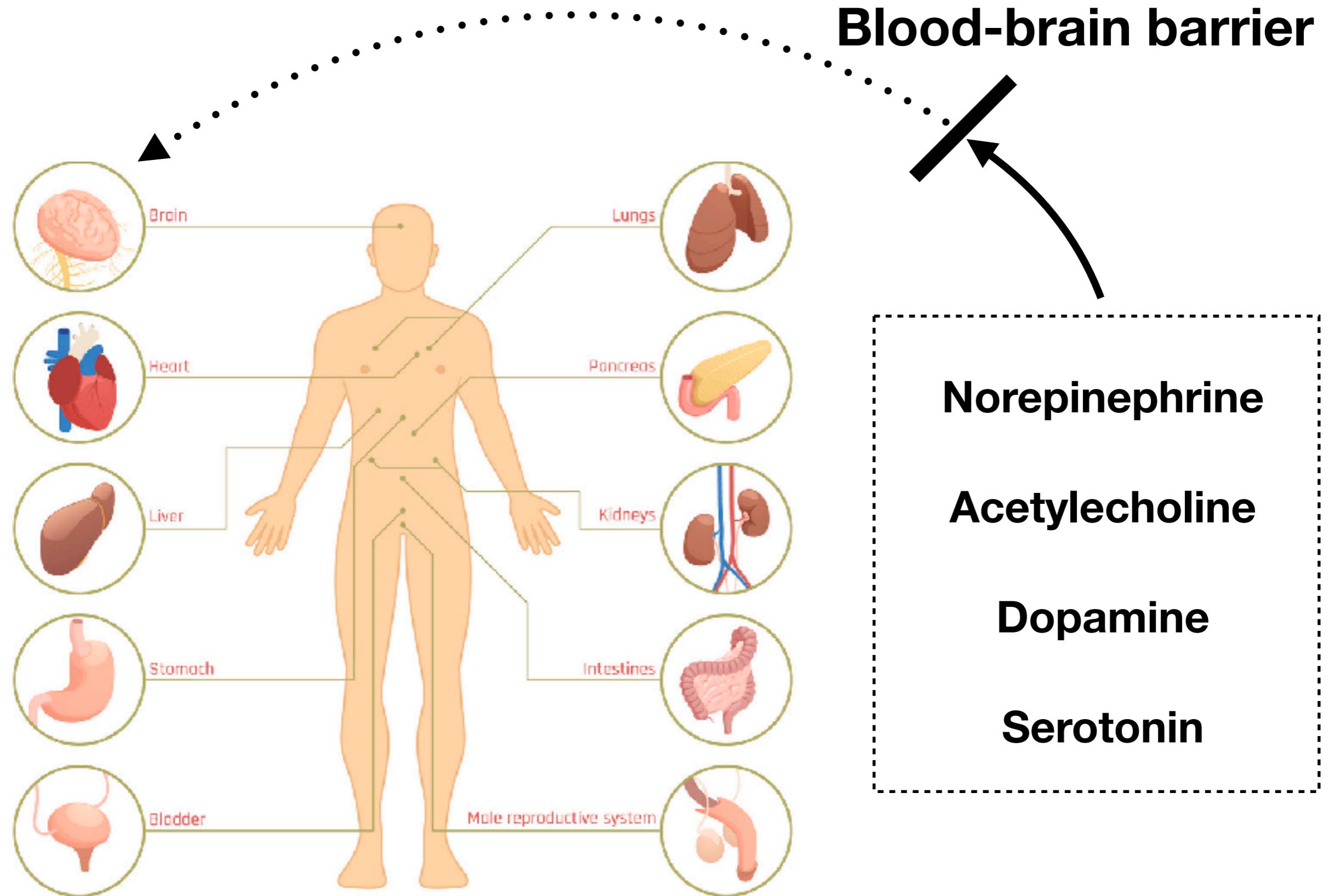
- Does it work as a neurotransmitter?
- Is dopamine meaningful in the brain?
- Where are they produced in the brain?

Do systemic neuromodulators affect the brain?

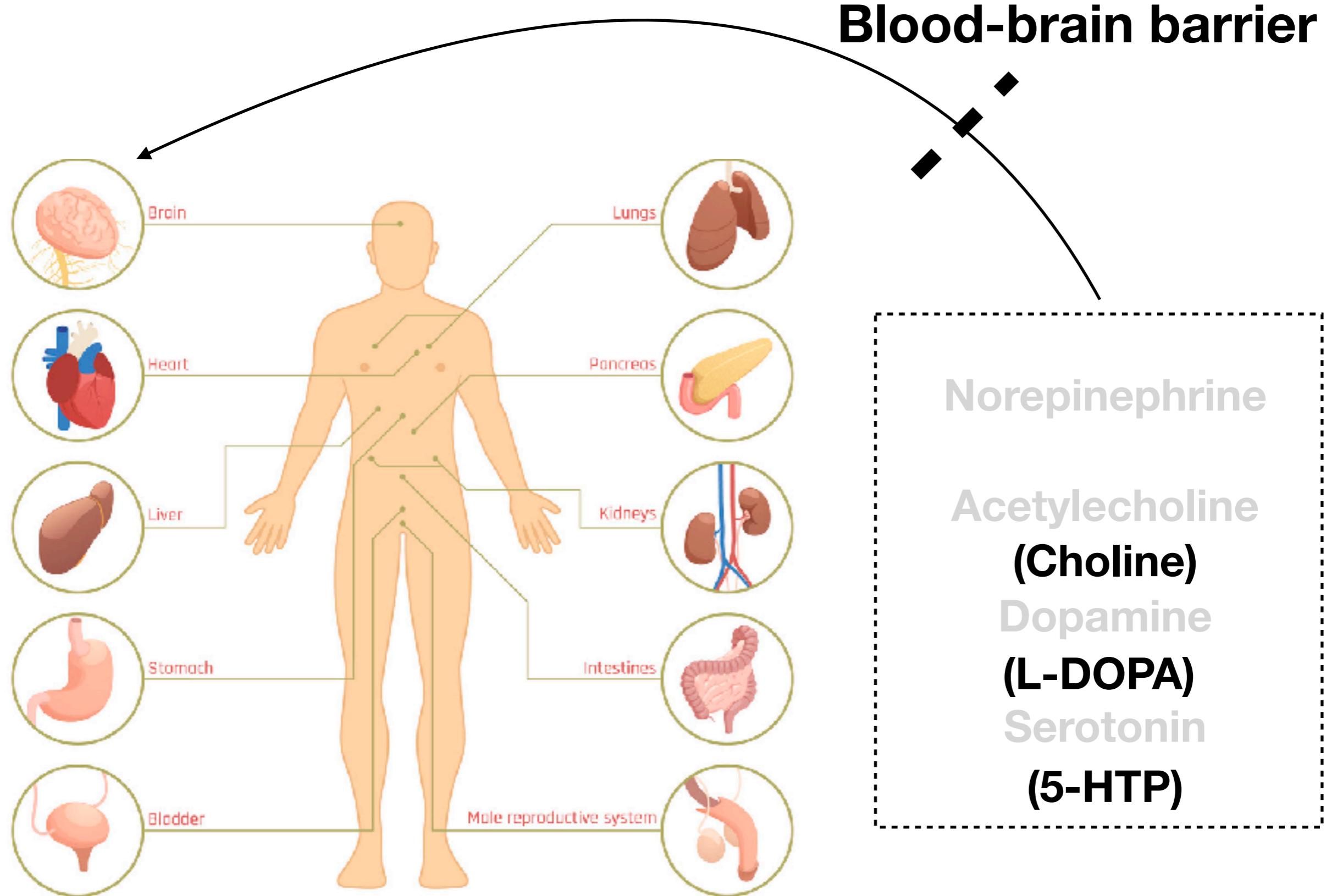
Serotonin distribution



Monoamines / acetylcholine do not enter the brain



Their precursors enter the brain

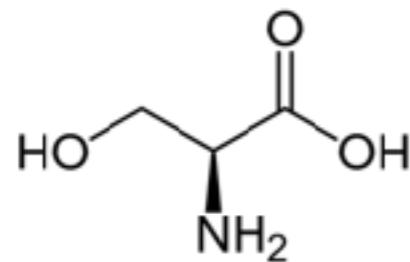


Then, why we see this kind only for serotonin?



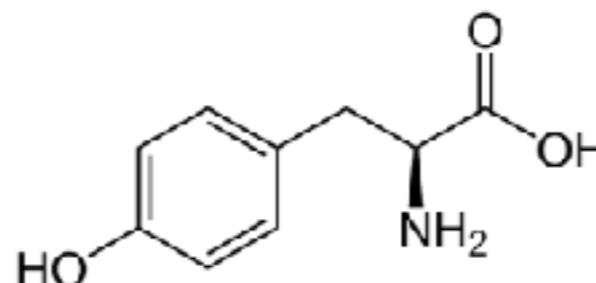
Non-essential

Serine



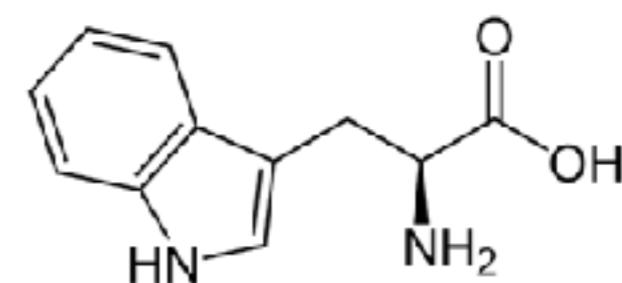
Non-essential

Tyrosine

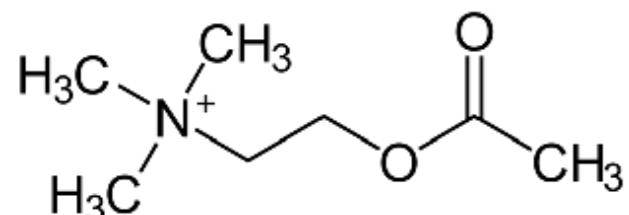


Essential

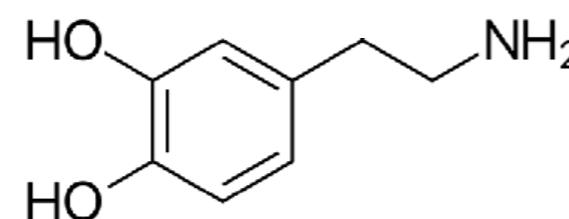
Tryptophan



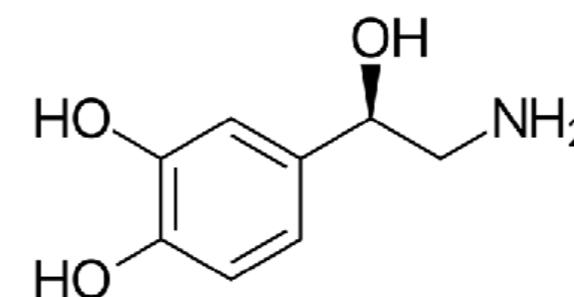
Acetylcholine



Norepinephrine



Dopamine



Serotonin



Serotonin's popularity in psychology research

(because it's easy to deplete)

Serotonin depletion induces 'waiting impulsivity' on the human four-choice serial reaction time task: cross-species translational significance.

Worbe Y, Savulich G, Voon V, Fernandez-Egea E, Robbins TW.

Neuropsychopharmacology. 2014 May;39(6):1519-26. doi: 10.1038/npp.2013.351. Epub 2014 Jan 2.

PMID: 24385133 [Free PMC article.](#) Clinical Trial.

Effects of **serotonin depletion** on punishment processing in the orbitofrontal and anterior cingulate cortices of healthy women.

Helmbold K, Zvyagintsev M, Dahmen B, Bubenzer-Busch S, Gaber TJ, Crockett MJ, Klasen M, Sánchez CL, Eisert A, Konrad K, Habel U, Herpertz-Dahlmann B, Zepf FD.

Eur Neuropsychopharmacol. 2015 Jun;25(6):846-56. doi: 10.1016/j.euroeuro.2015.02.007. Epub 2015 Feb 28.

PMID: 25869157 Clinical Trial.

Diminished synthesis of the neurotransmitter serotonin leads to impaired self-control and impulse control in aversive contexts, and to increased aggression and reduced prosocial behavior after short-term **depletion** of 5-HT.

Ward R, Sreenivas S, Read J, Woolrich M, Behrens TE, Rogers RD, et al. Tryptophan depletion impairs social comparison and leads to resource **depletion** in a multiplayer harvesting game.

Psychol Sci. 2014 Jul;25(7):1303-13. doi: 10.1177/0956797614527830. Epub 2014 May 8.

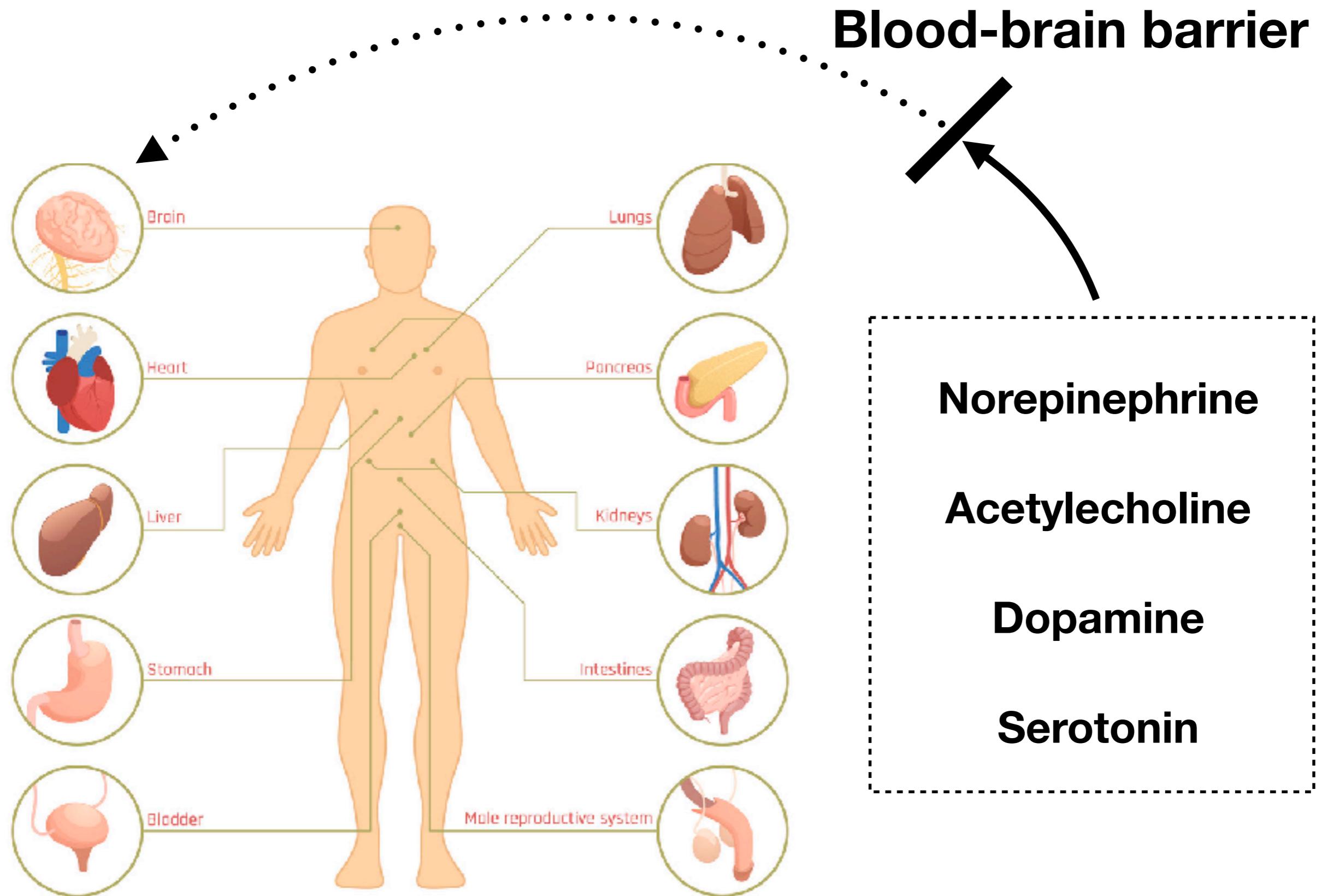
Bilderbeck AC, Brown GD, Read J, Woolrich M, Cowen PJ, Behrens TE, Rogers RD.

PMID: 24815611 [Free PMC article.](#)

Healthy adults, alongside social partners, completed a multiplayer resource-dilemma game in which they repeatedly harvested from a partially replenishable monetary resource. Dietary tryptophan depletion, leading to reduced **serotonin** activity, was associated with aggression and reduced social comparison. Given the close link between tryptophan depletion and serotonin activity, this study provides evidence that tryptophan depletion, leading to reduced **serotonin** activity, was associated with aggression and reduced social comparison.

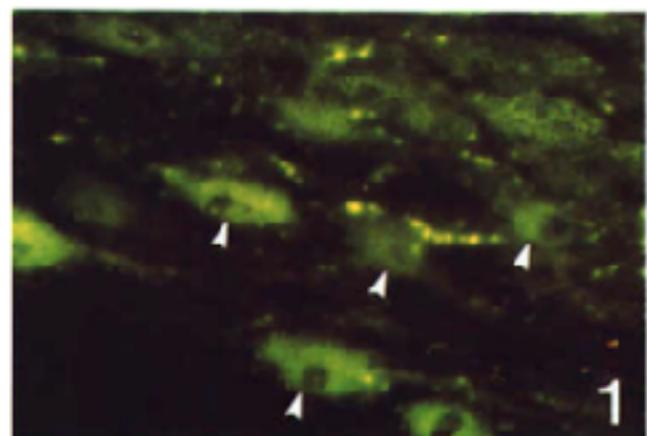
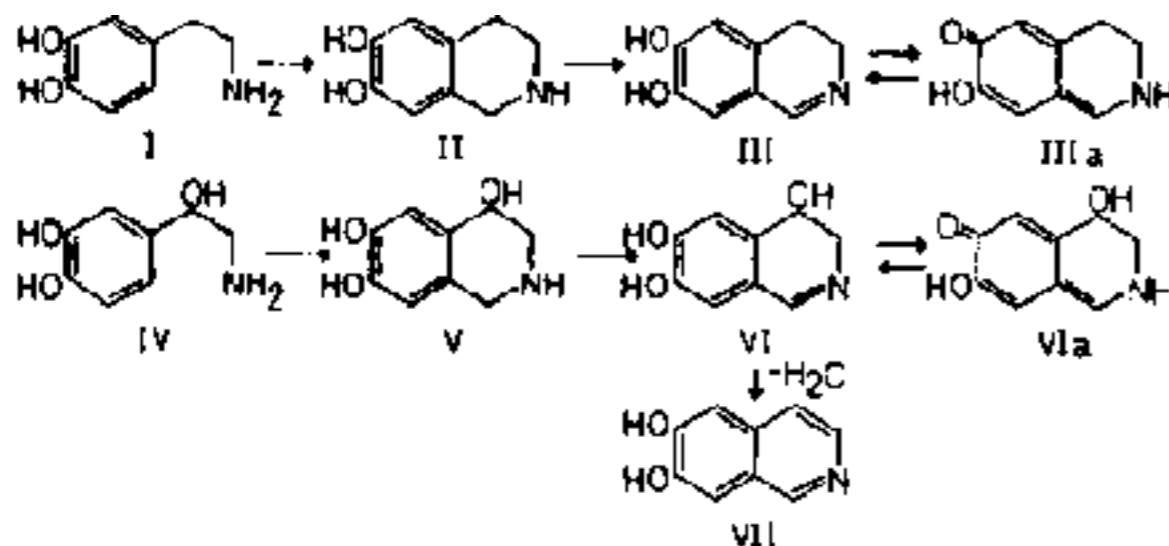
diminished central **serotonin** activity (achieved by tryptophan **depletion**) upon the accuracy of 52 healthy (non-clinical) adults' discriminations of personality from fa ...

Where in the brain?

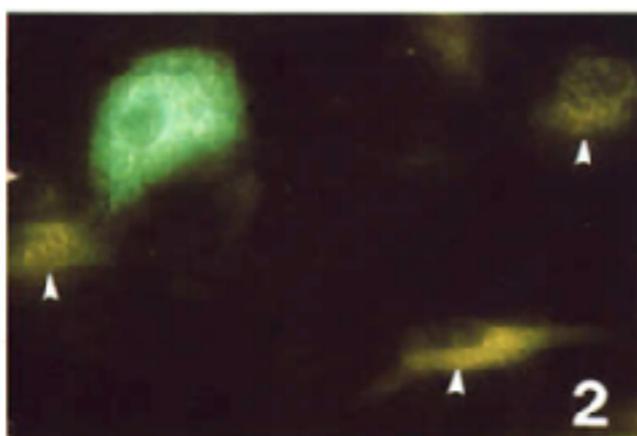


Development of a visualization method

Aldehyde fluorescence method



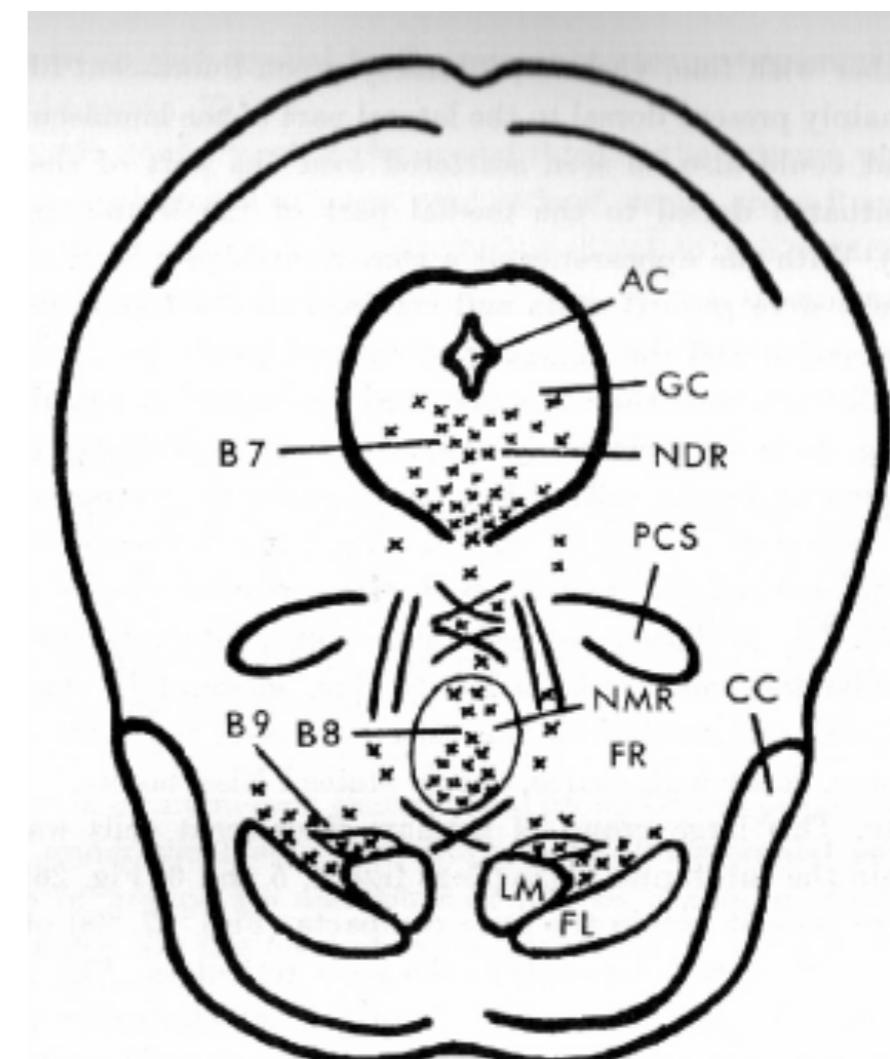
Green (NE/DA)



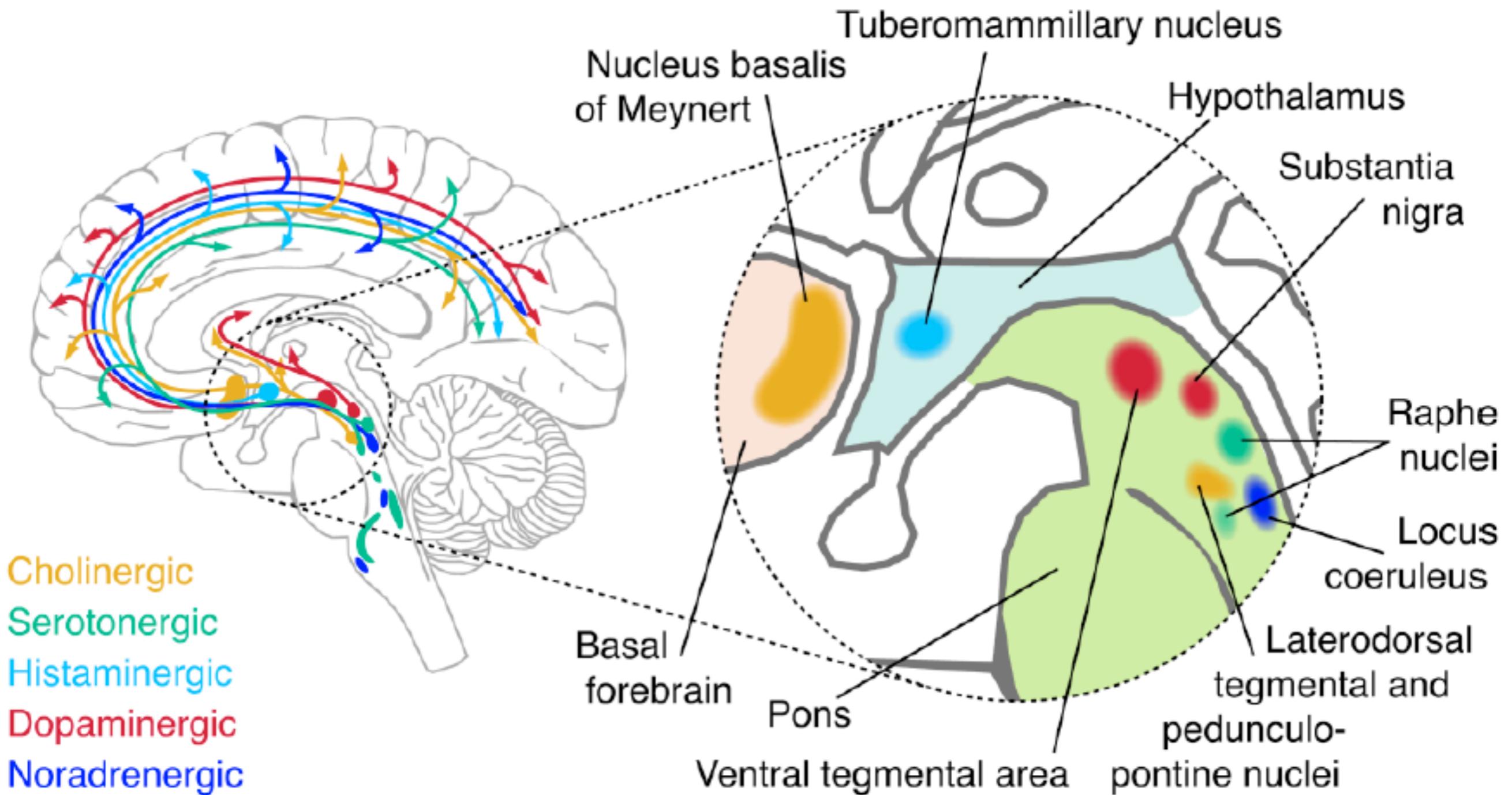
Yellow (HT)

(Falck & Hillarp, 1961)

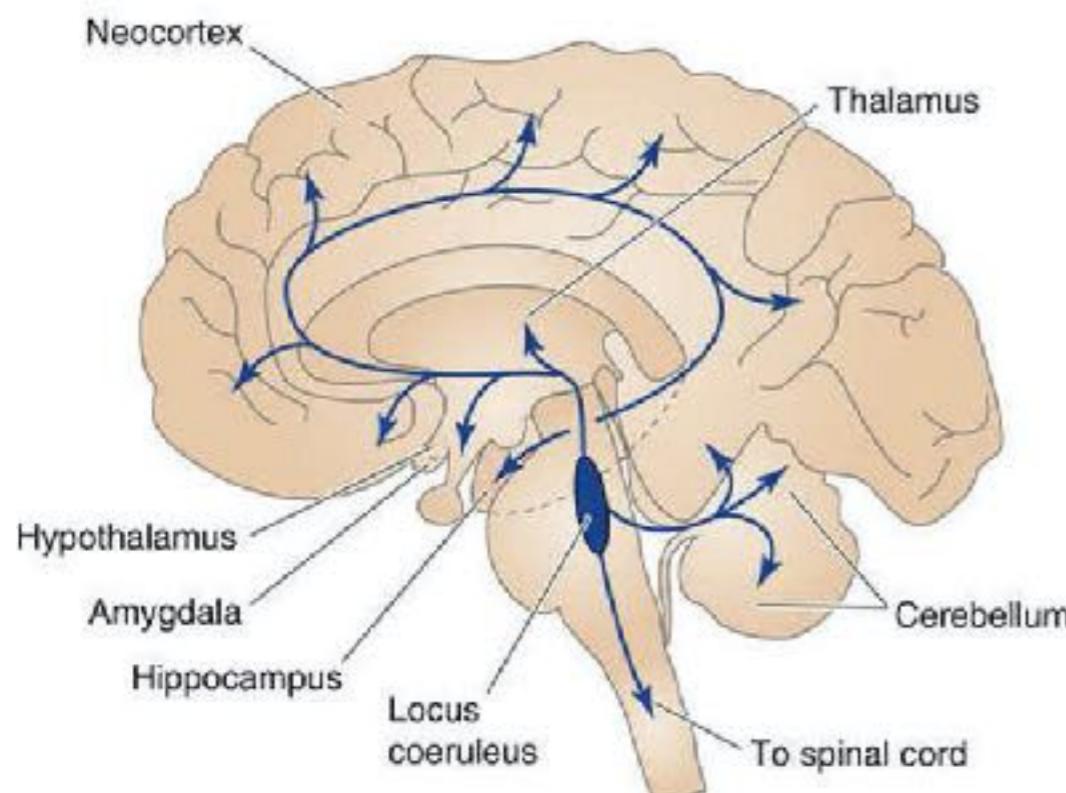
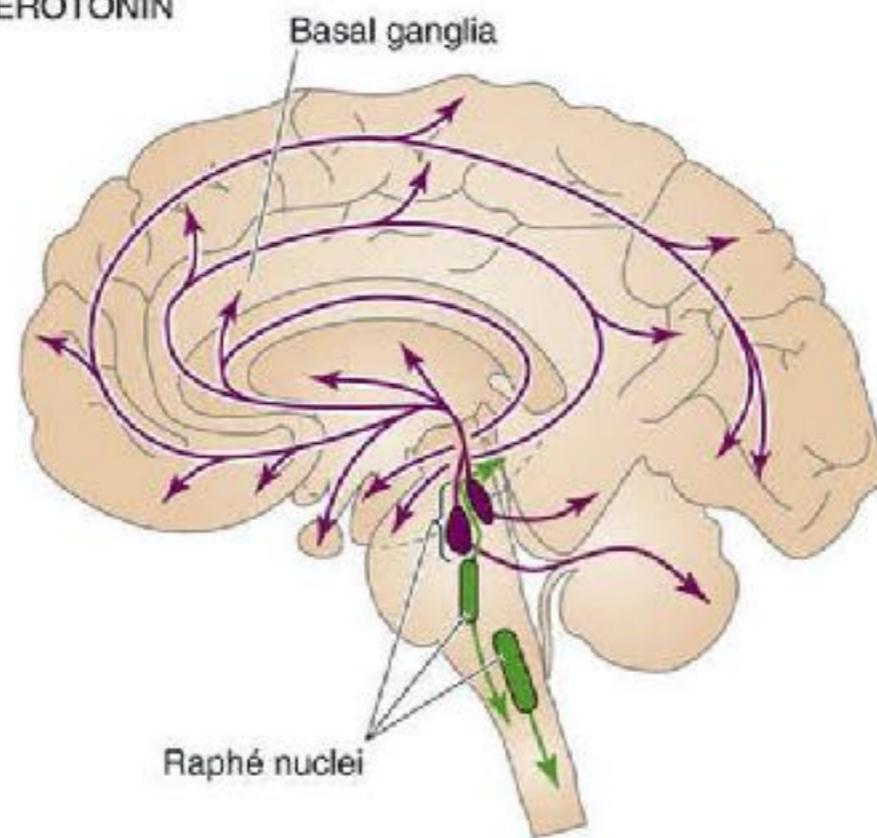
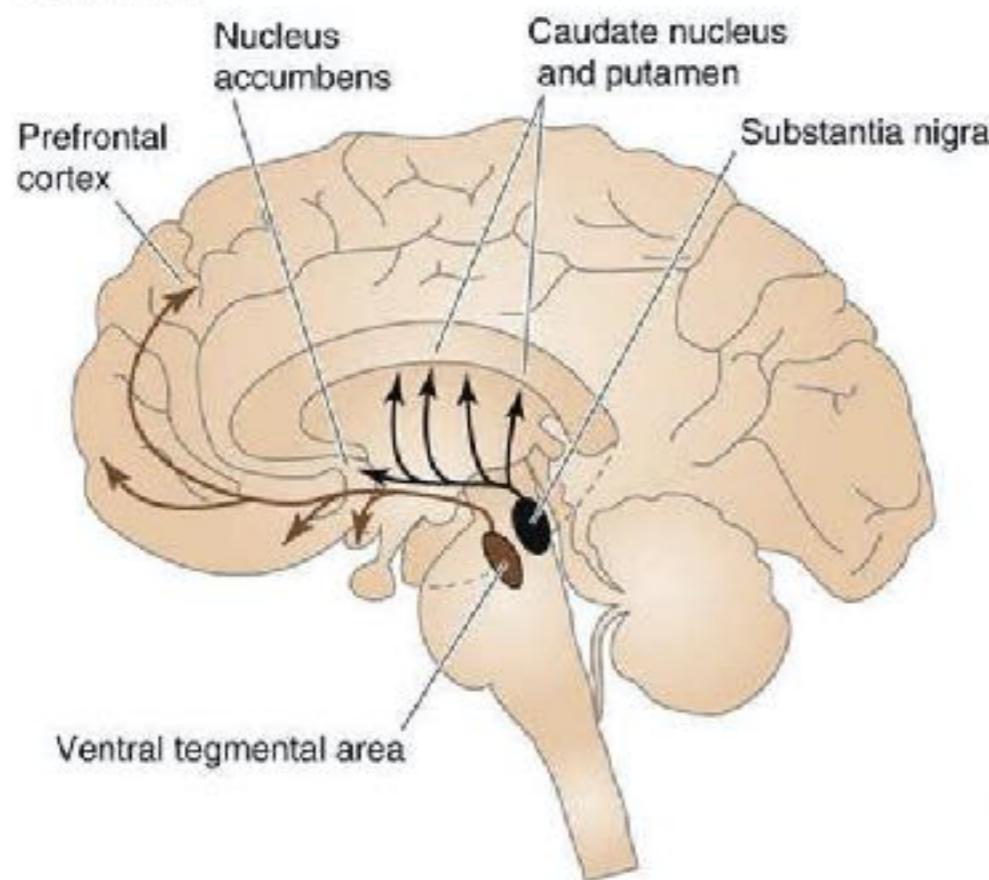
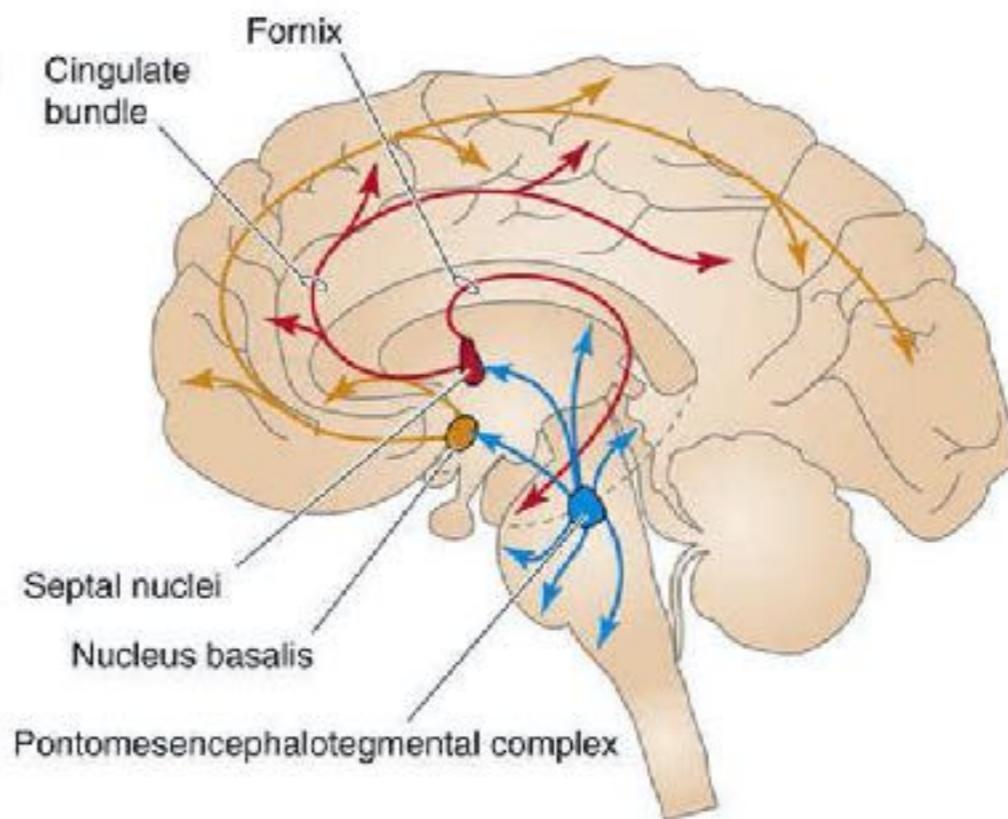
Application to the tissue



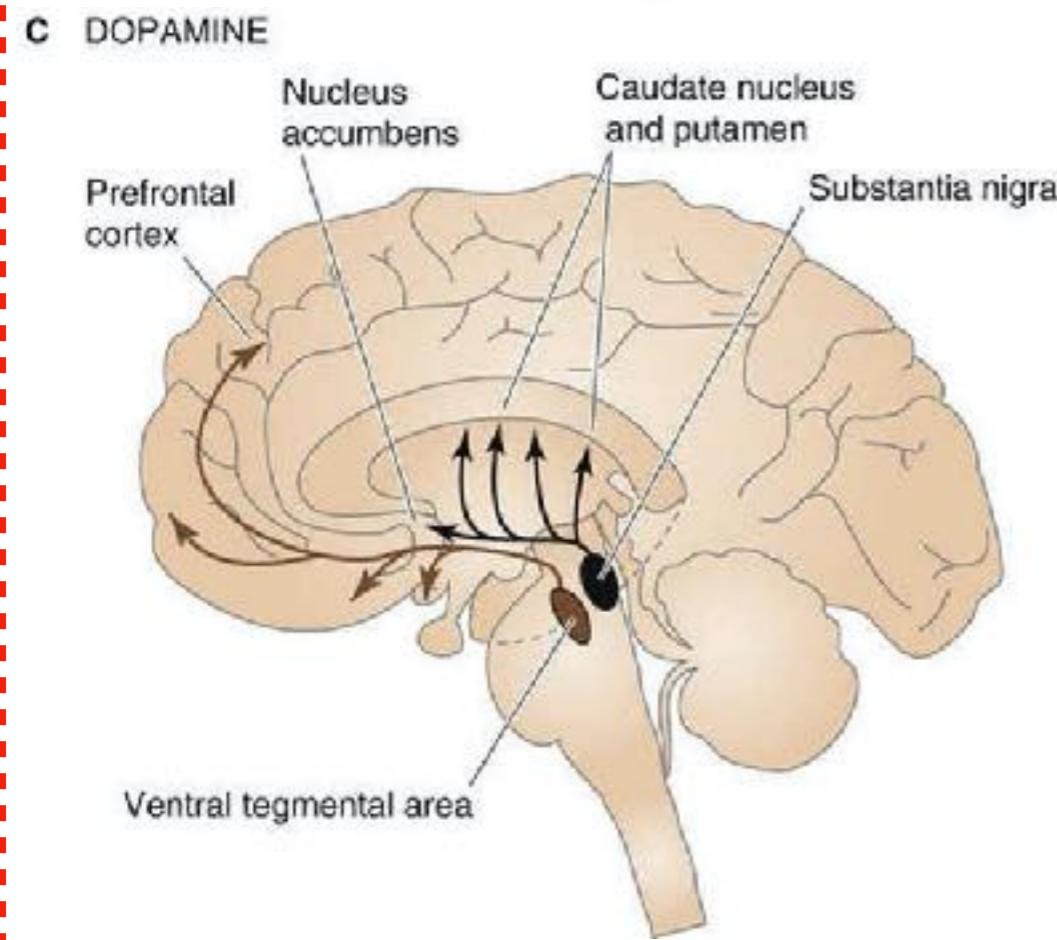
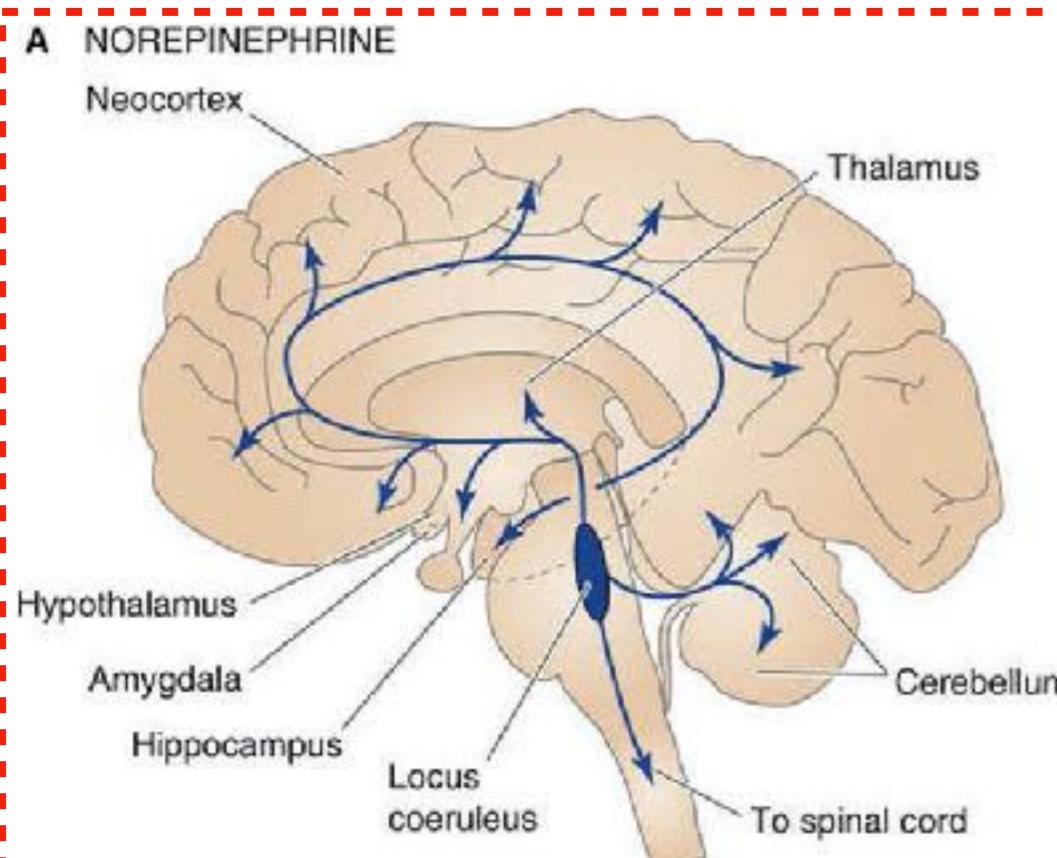
(Dahlstrom & Fuxe, 1964)



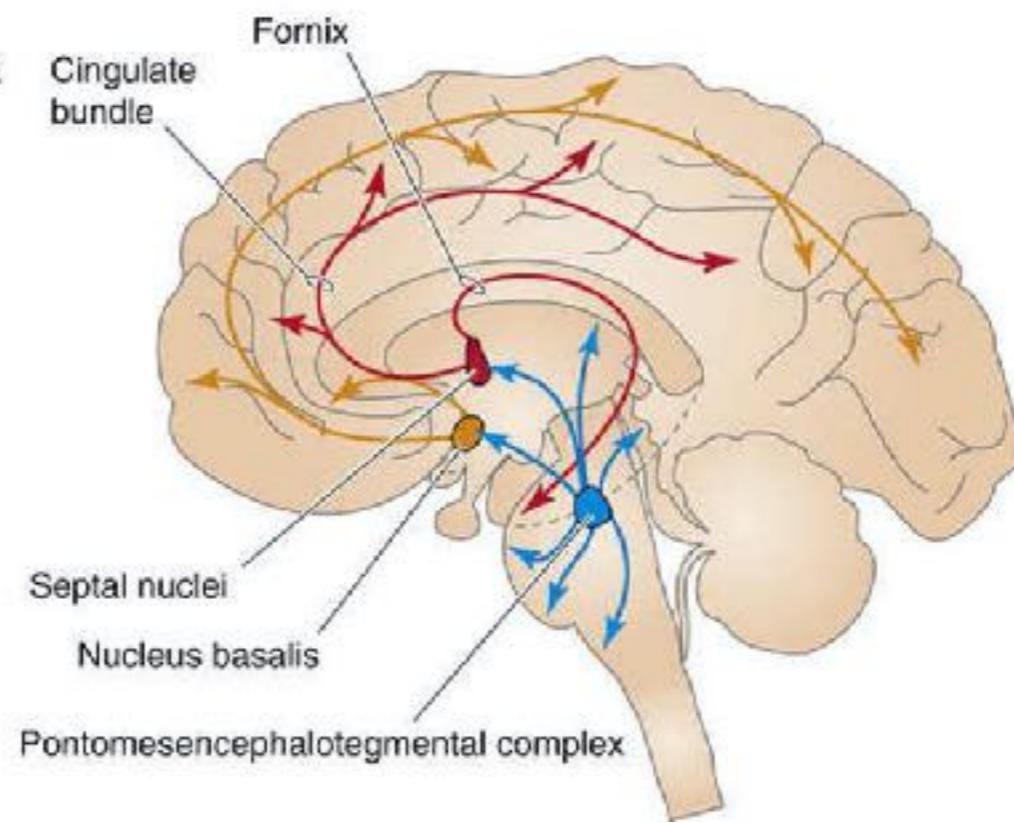
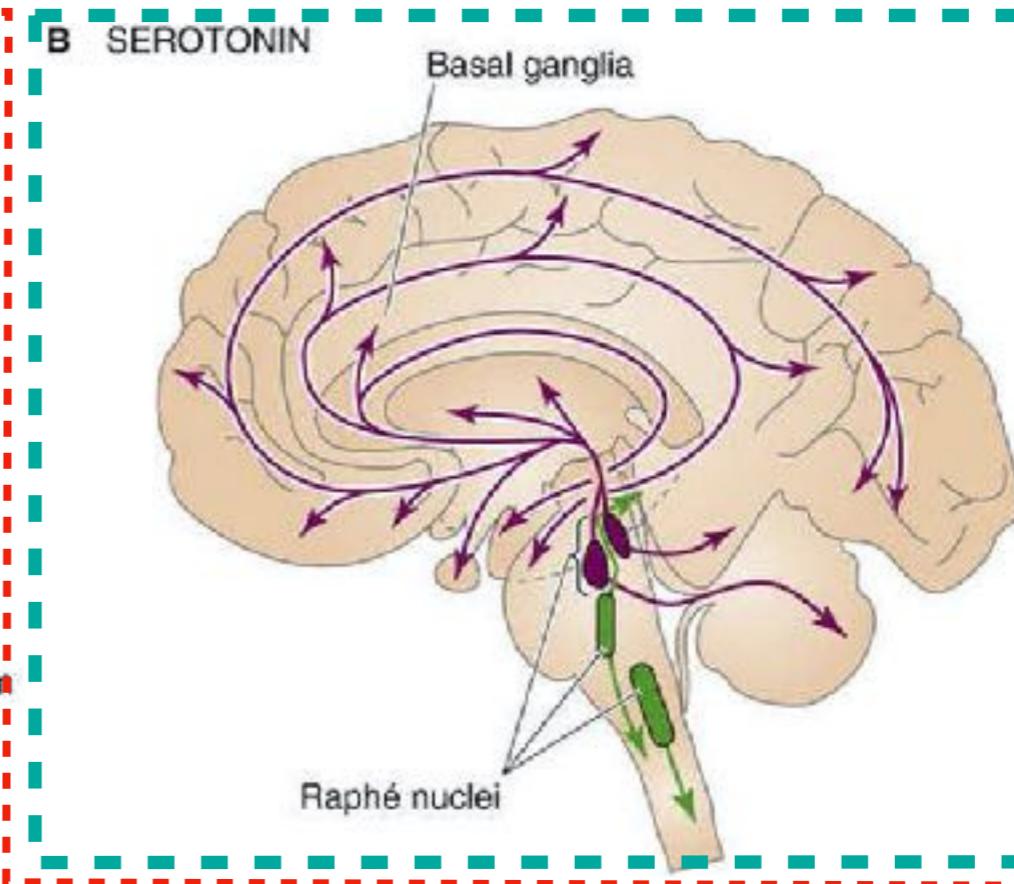
(van den Brink *et al*, 2019)

A NOREPINEPHRINE**B SEROTONIN****C DOPAMINE****D ACETYLCHOLINE**

Bilateral



Midline



Break time



The goal of this lecture

- (1) Basics of neuromodulators**
- (2) How they work at mechanistic levels**
- (3) How mechanisms generalize across functions**

Glutamate, GABA

Neuromodulator

Function

General

More specific??

Synaptic?

Mostly synaptic

Synaptic / diffusive

Communication mode

One-to-one

One-to-many

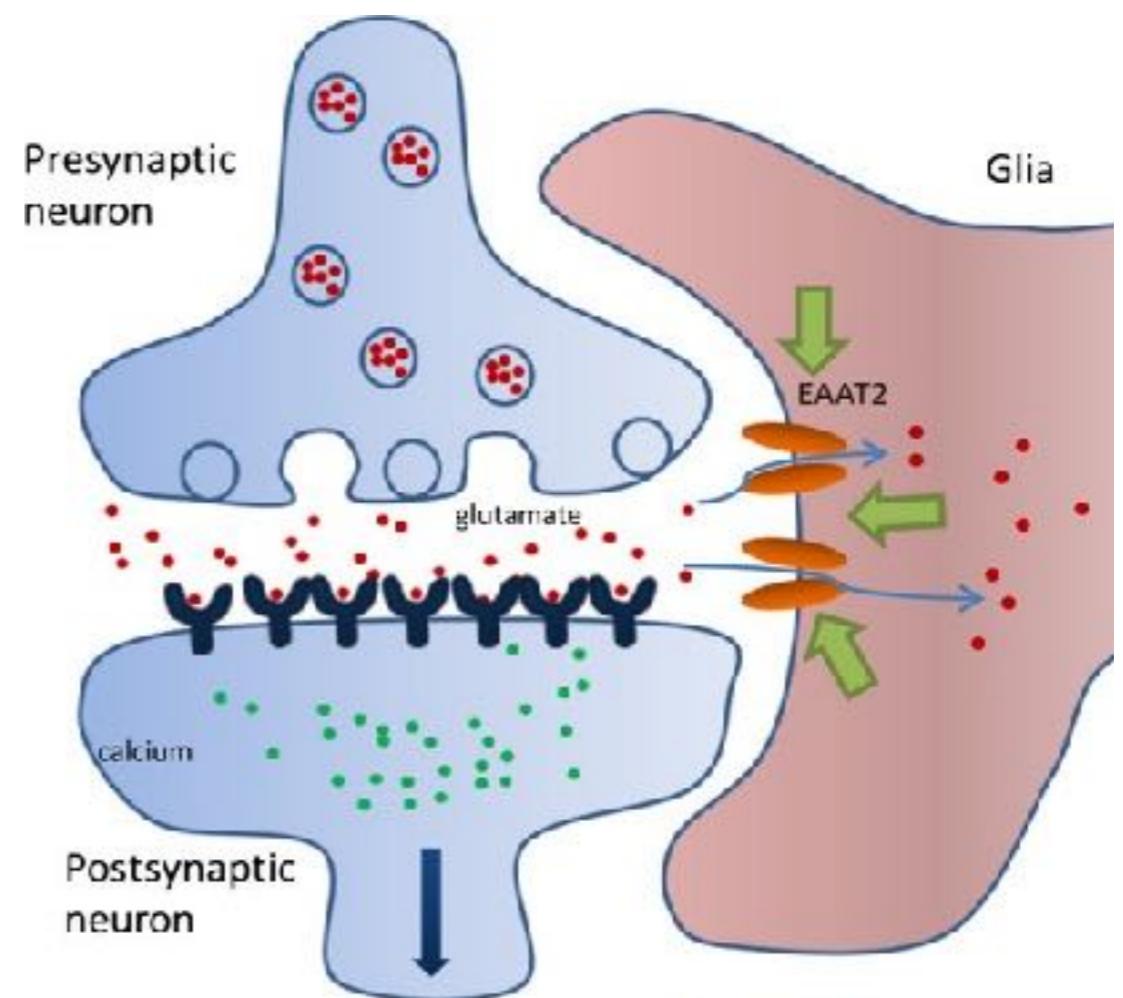
Receptor action

(typically)
Ionic, fast

(typically)
GPCRs, slow

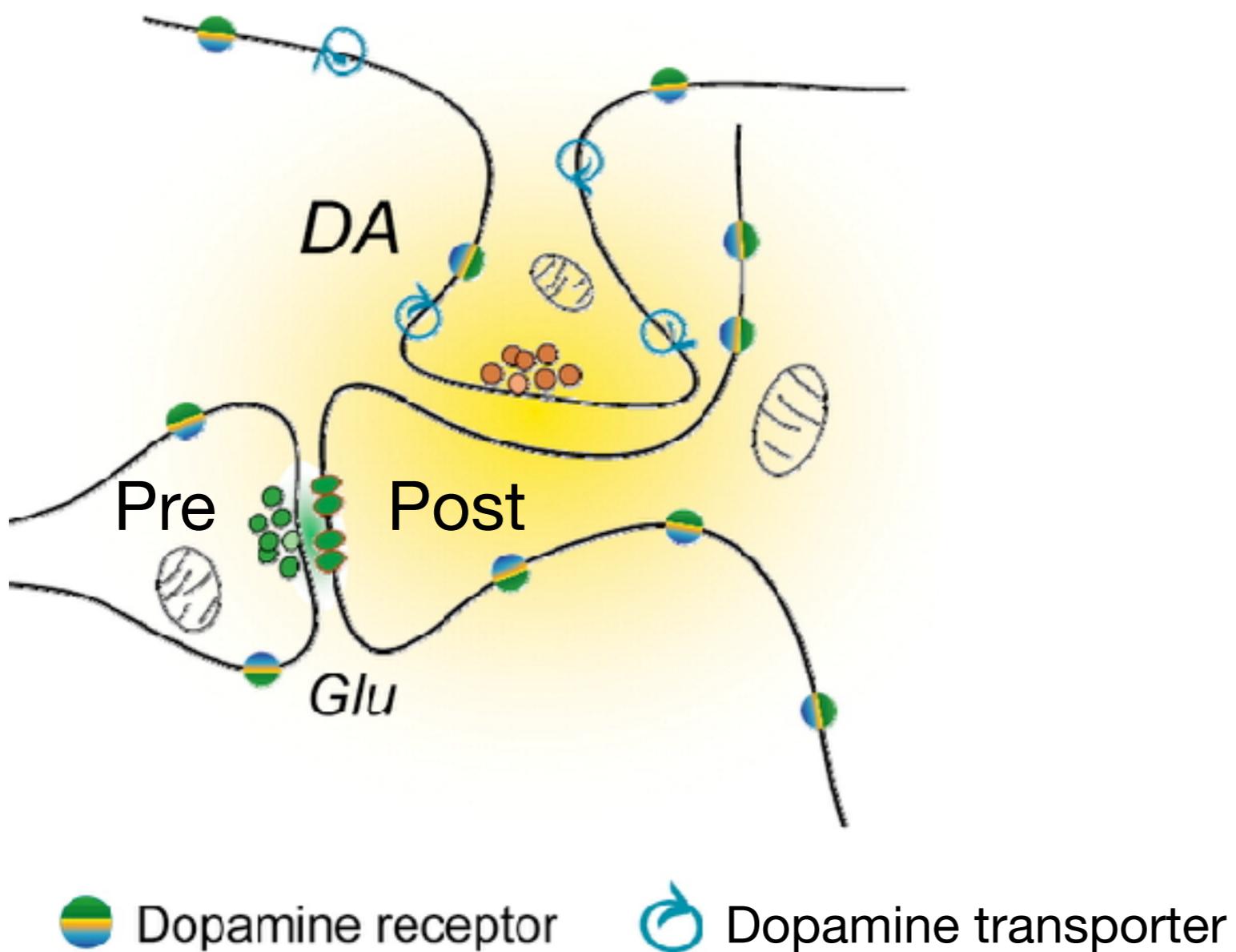
Glutamate synapse

- Receptor at the synaptic cleft
- Rapid reuptake by glia
- Glial enclosure



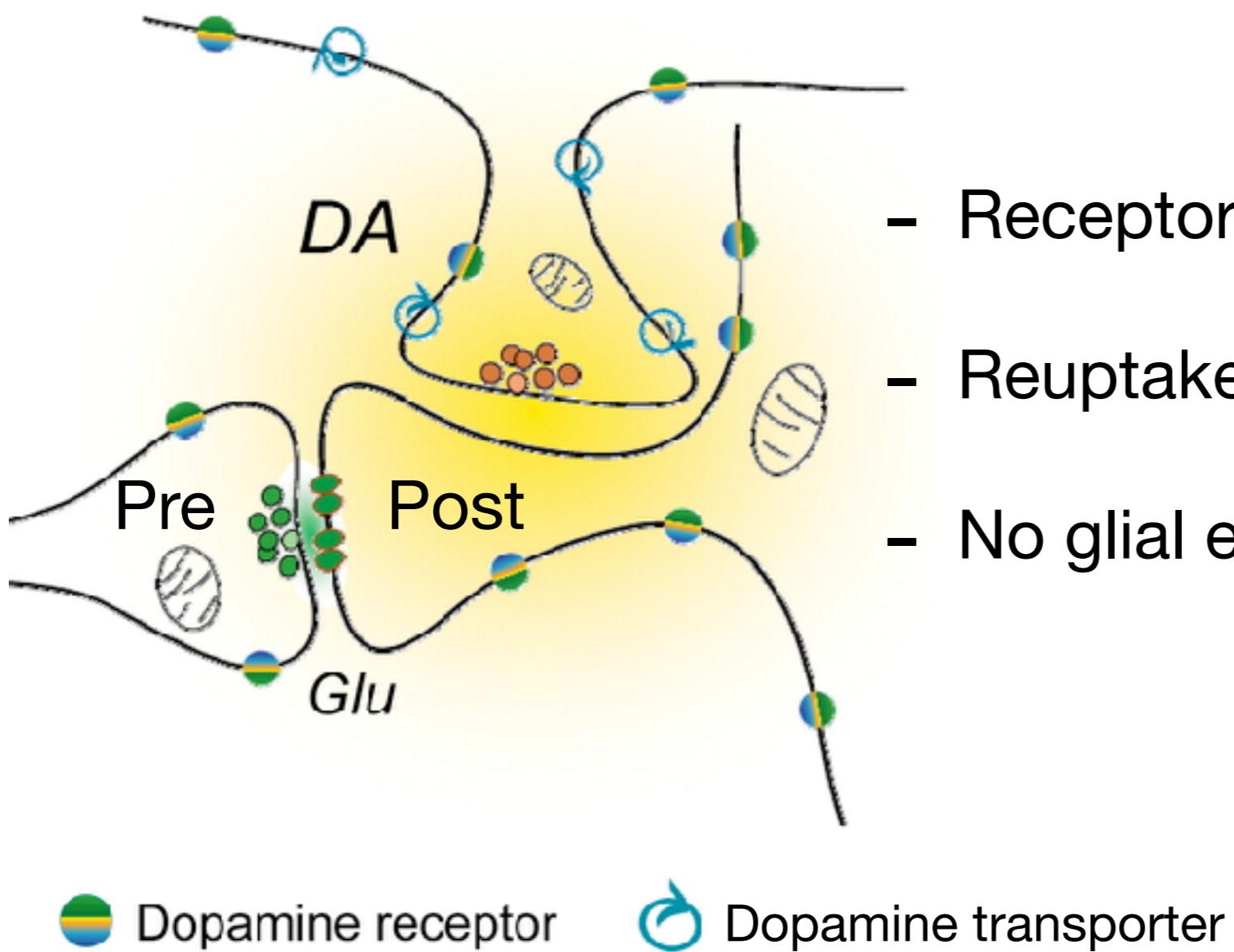
(Fontana, 2015)

Monoamine synapse



(Rice & Cragg, 2008)

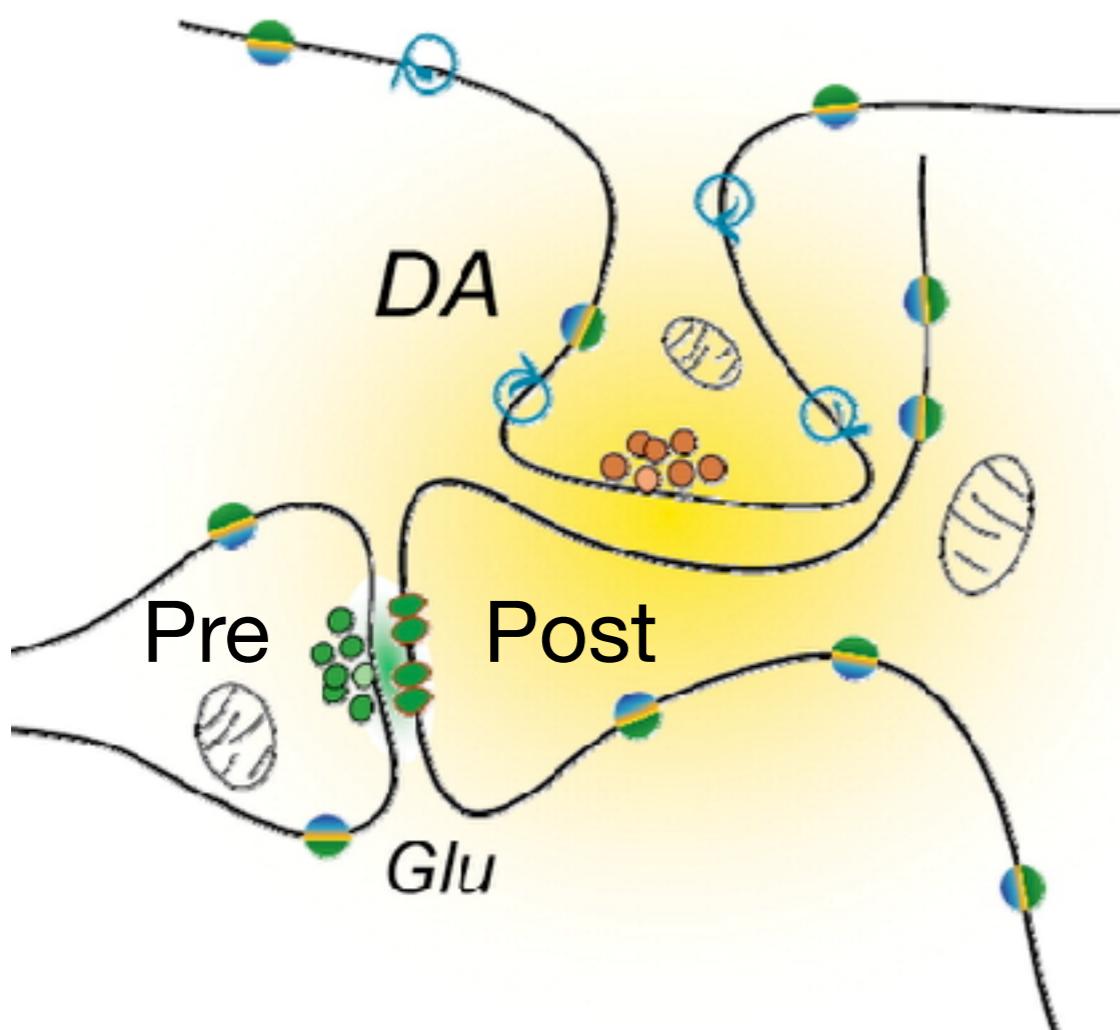
Monoamine synapse



- Receptor NOT at the synaptic cleft
- Reuptake outside the synapse
- No glial enclosure

(Rice & Cragg, 2008)

Monoamine synapse



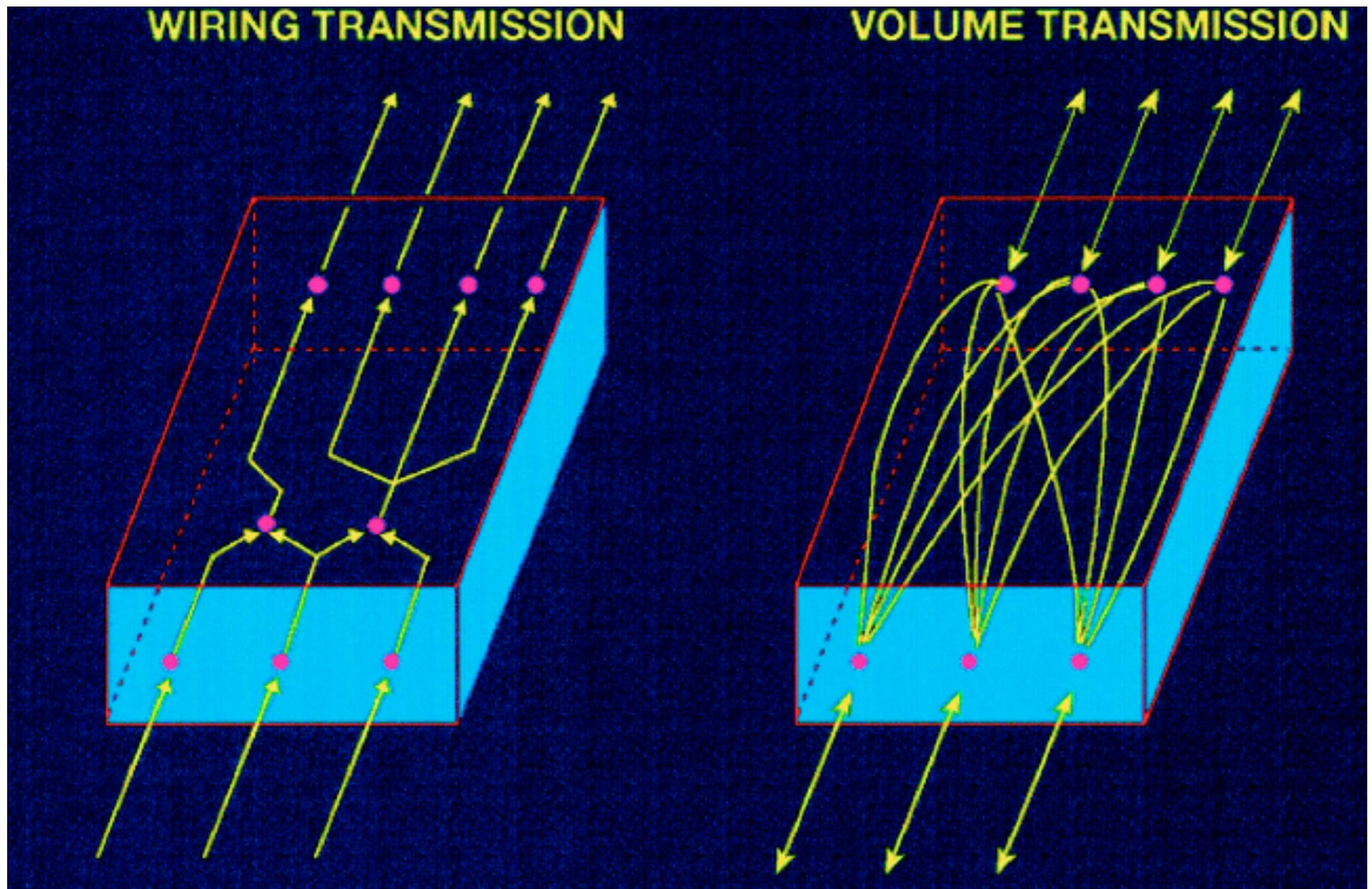
- **UNFIT for precise transmission**
- **Designed for diffusion**
- **Optimized for multi-synapse / multi-cell communication**

Dopamine receptor

Dopamine transporter

(Rice & Cragg, 2008)

“Volume transmission” concept

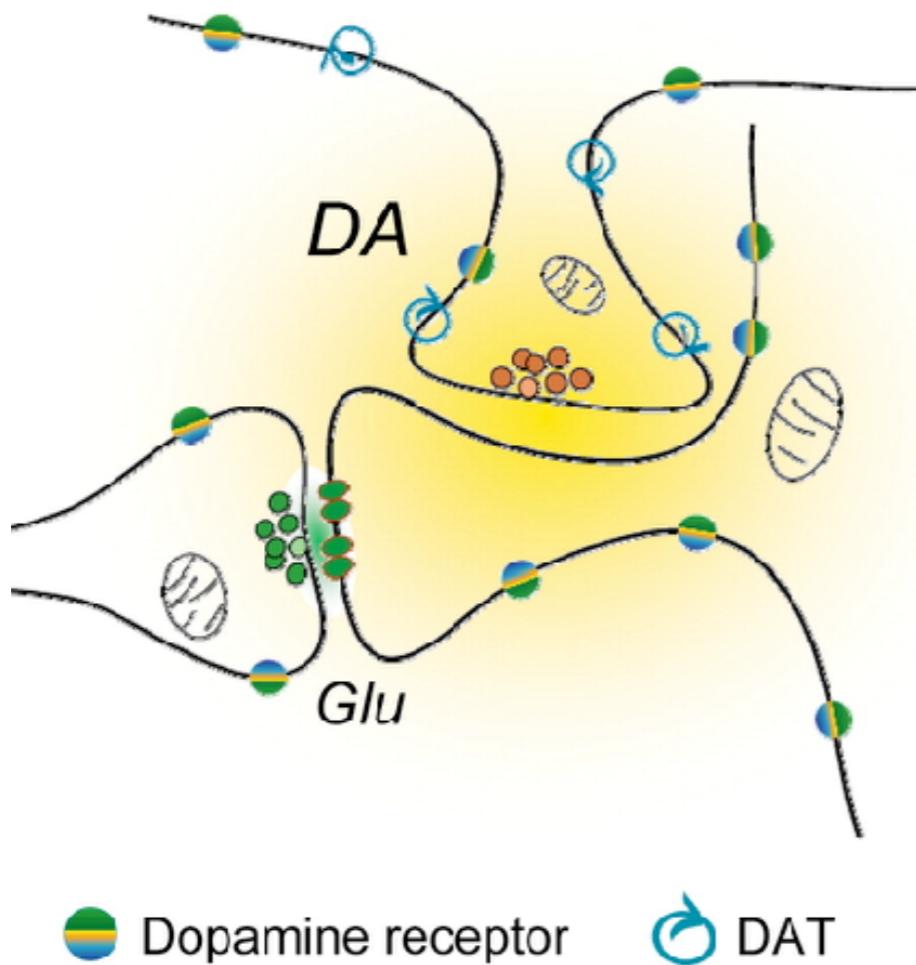


(Zoli *et al.*, 1998)

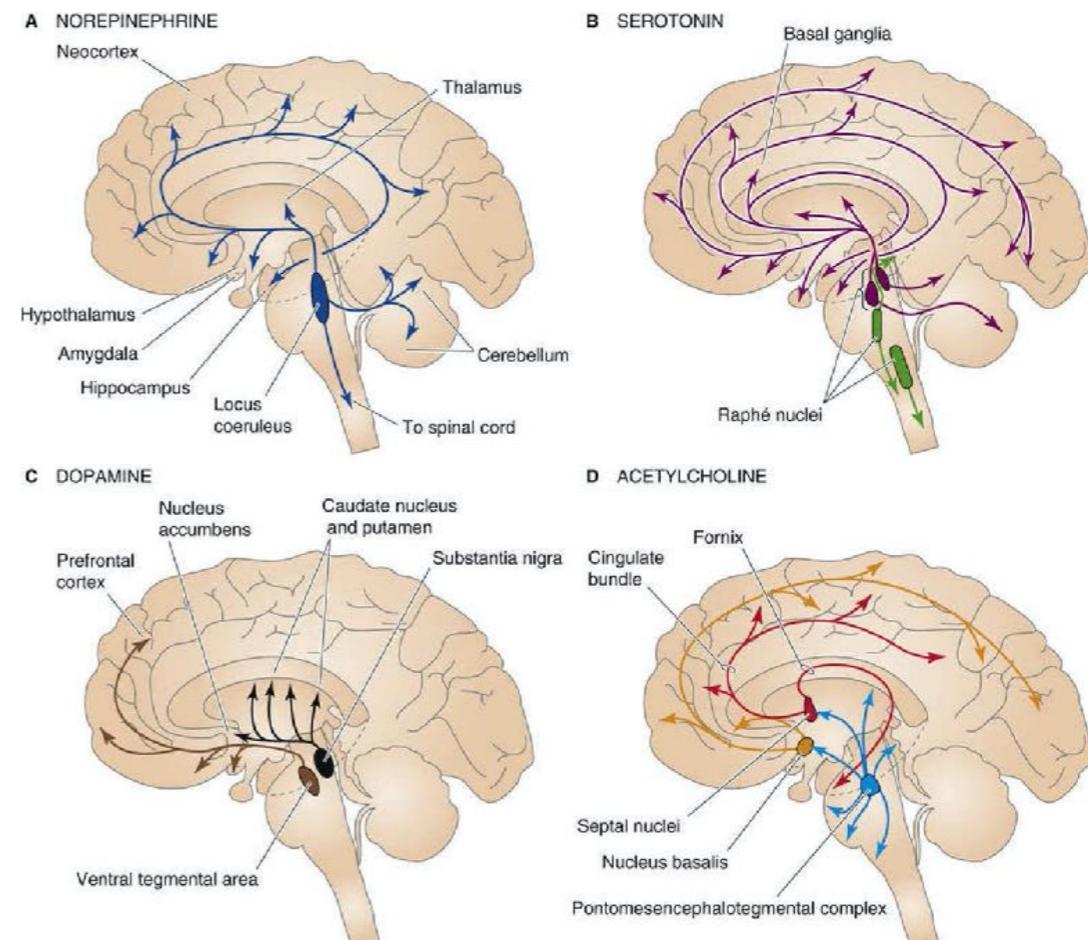
Breakout room discussion: Why do you need such volume transmission?

“Volume transmission” at multiple scale

Synaptic level



Brain-wide level

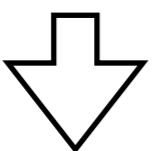


Dimensionality mismatch between external interface and internal objectives

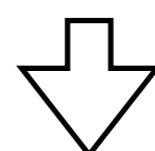
Real-time control

Learning

Many inputs & potential outputs



Many inputs & potential outputs

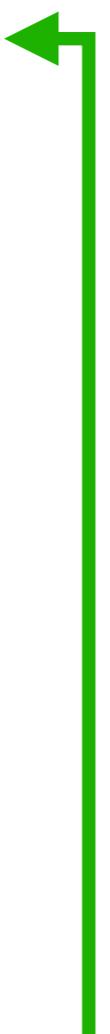


“So exhausted”

VT

“I wanna win”

VT



Two perspectives for volume transmission

Control of ongoing functions



Activity modulation

Control of learning mechanisms



Plasticity modulation

Two perspectives for volume transmission

Control of ongoing functions



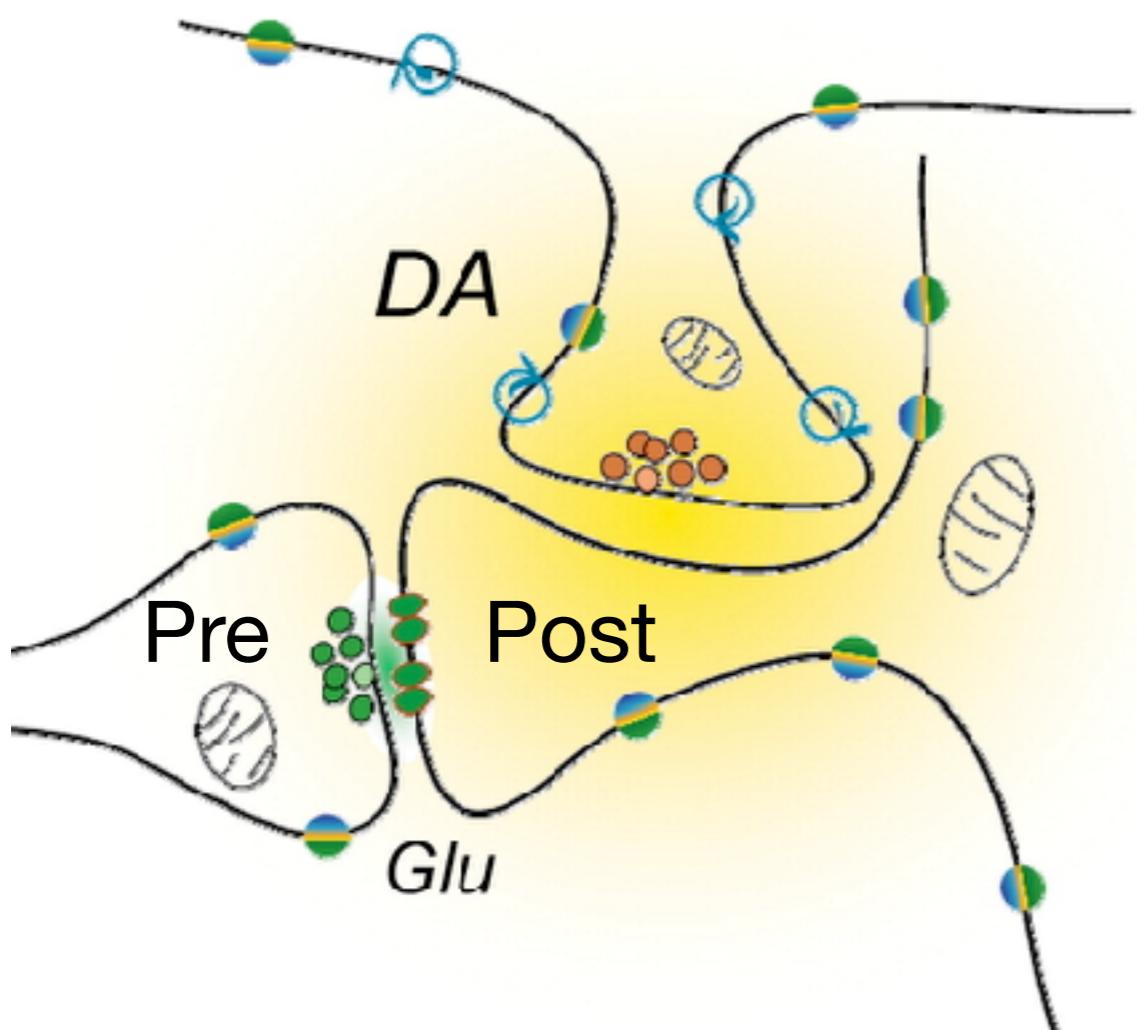
Activity modulation

Control of learning mechanisms



Plasticity modulation

Monoamine synapse



Dopamine receptor

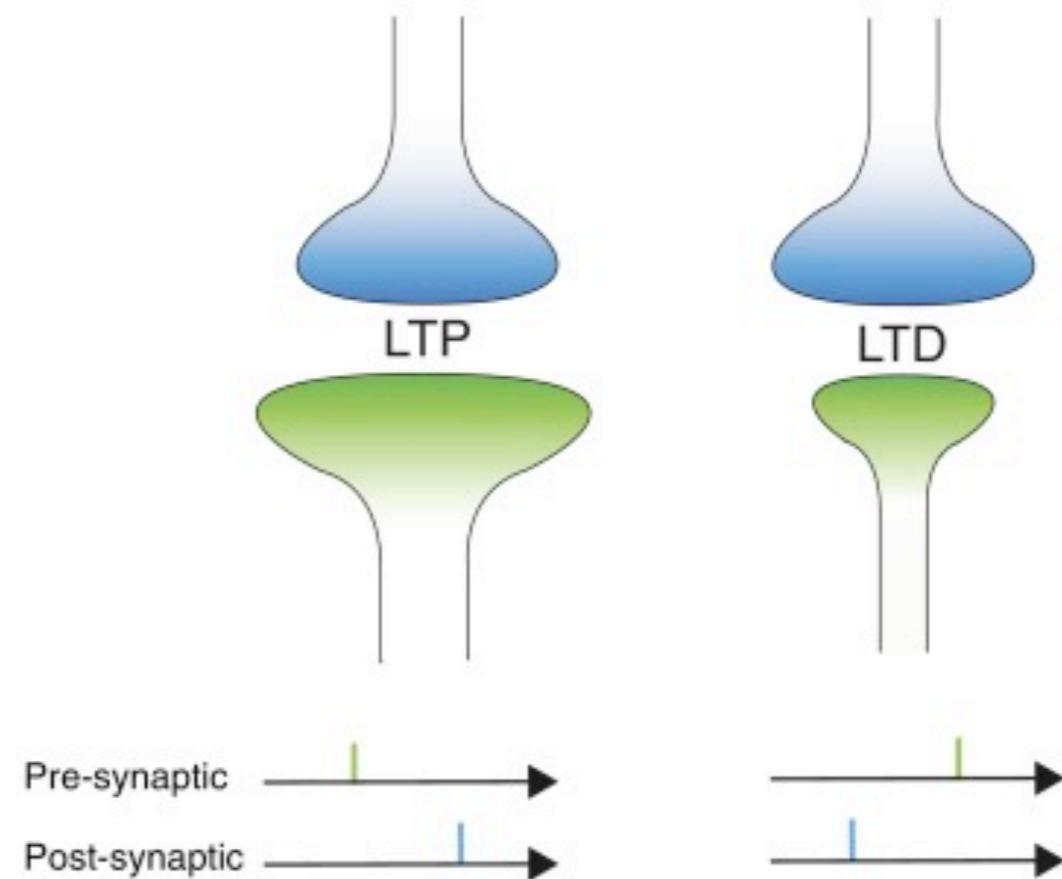
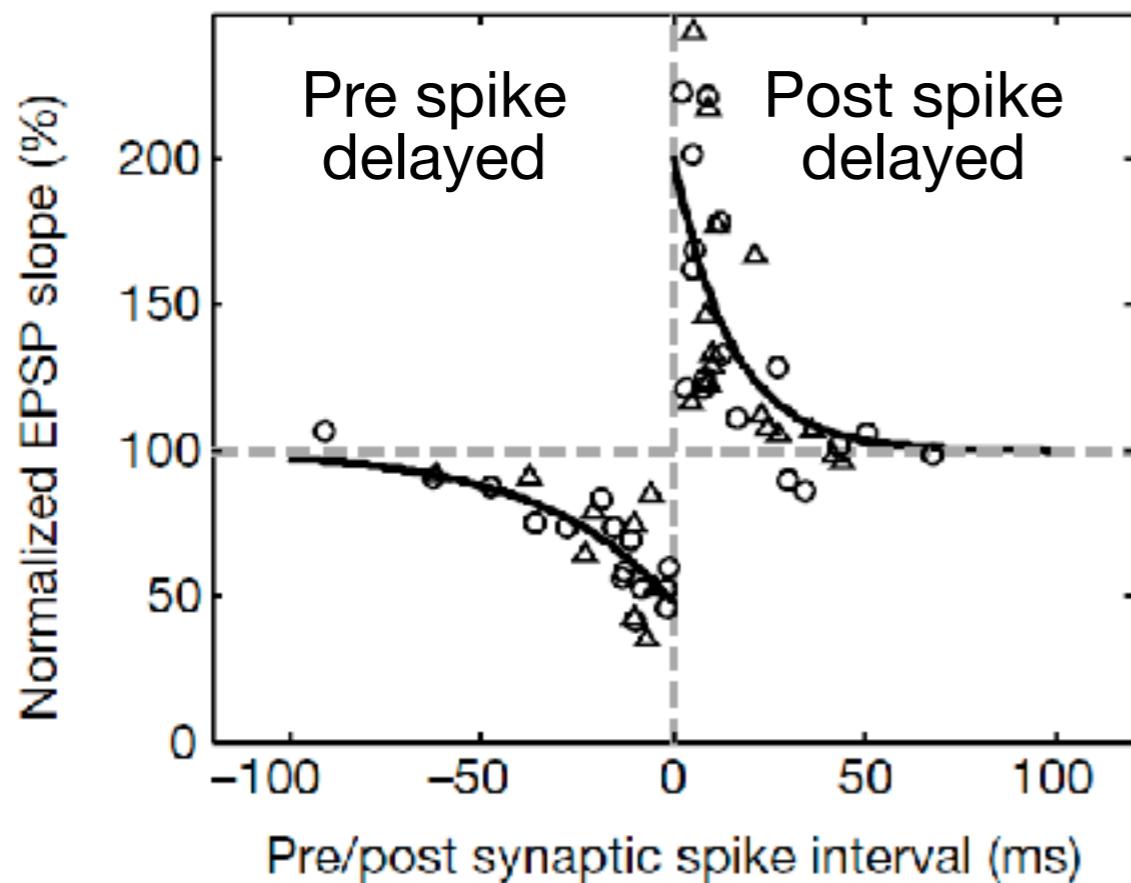
DAT

Three-factor plasticity

Two-factor plasticity: Spike-timing dependent plasticity (STDP)

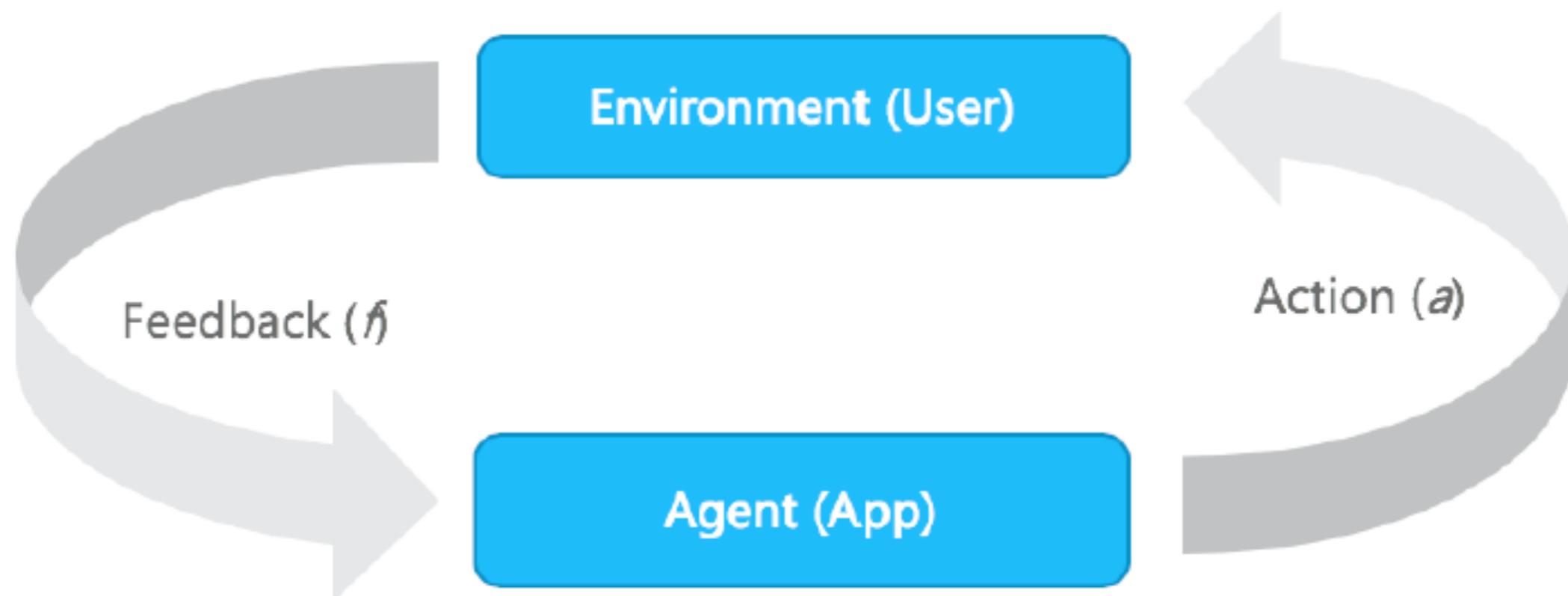
Synaptic model of associative learning

Limitation: all events have to happen at once!



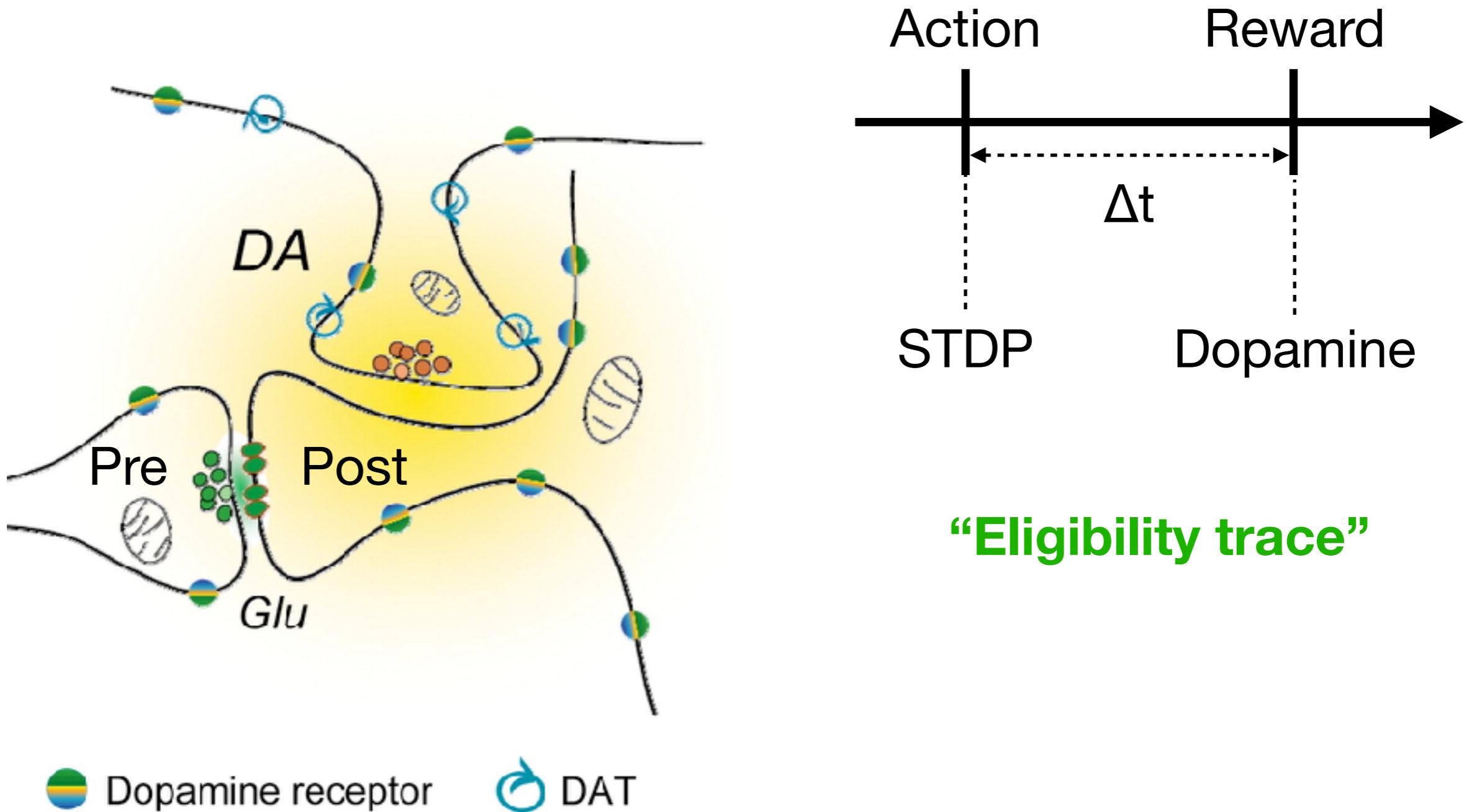
Froemke *et al.*, 2002

Usually, there is a delay between events that you want to associate

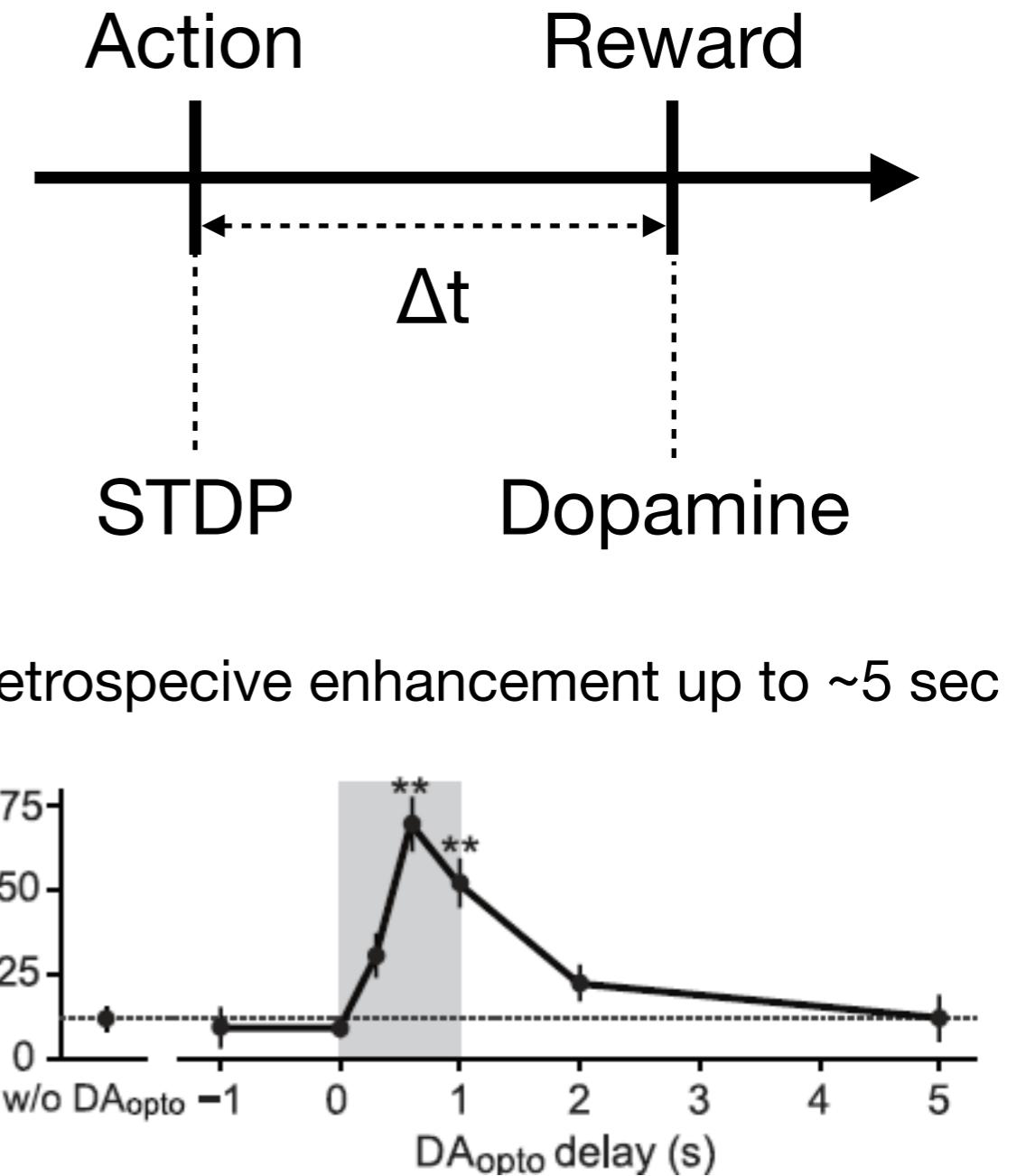
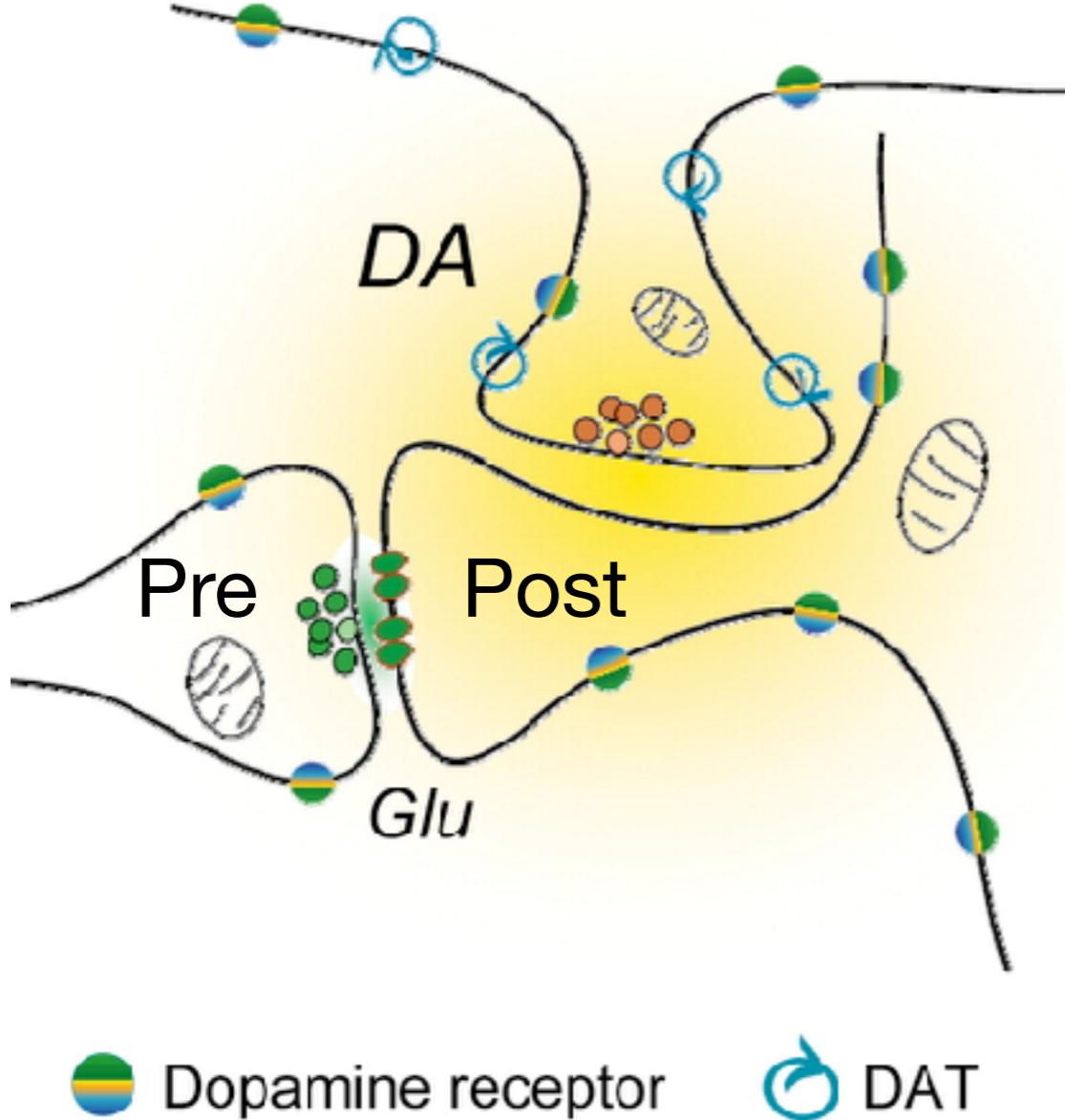


(Biswas, 2020)

Three-factor plasticity: Retrospective enhancement of STDP



Three-factor plasticity: Retrospective enhancement of STDP



(Yagishita *et al.*, 2014)

Two perspectives for volume transmission

Control of ongoing functions



Activity modulation

Control of learning mechanisms



Plasticity modulation

Modulation of neural activity: difficulty

These can co-express
in the same cell



**Excitation/inhibition
depends on**
(1) receptor balance
(2) firing patterns

Receptor family	Subtypes	Function
5-HT ₁	5-HT _{1A} 5-HT _{1B} 5-HT _{1D} 5-HT _{1E} 5-HT _{1F}	Inhibitory auto- and hetero-receptor
5-HT ₂	5-HT _{2A} 5-HT _{2B} 5-HT _{2C}	Excitatory heteroreceptor
5-HT ₃		Excitatory heteroreceptor
5-HT ₄		Excitatory heteroreceptor
5-HT ₅	5-HT _{5A} 5-HT _{5B} ^a	Inhibitory
5-HT ₆		Excitatory
5-HT ₇		Excitatory

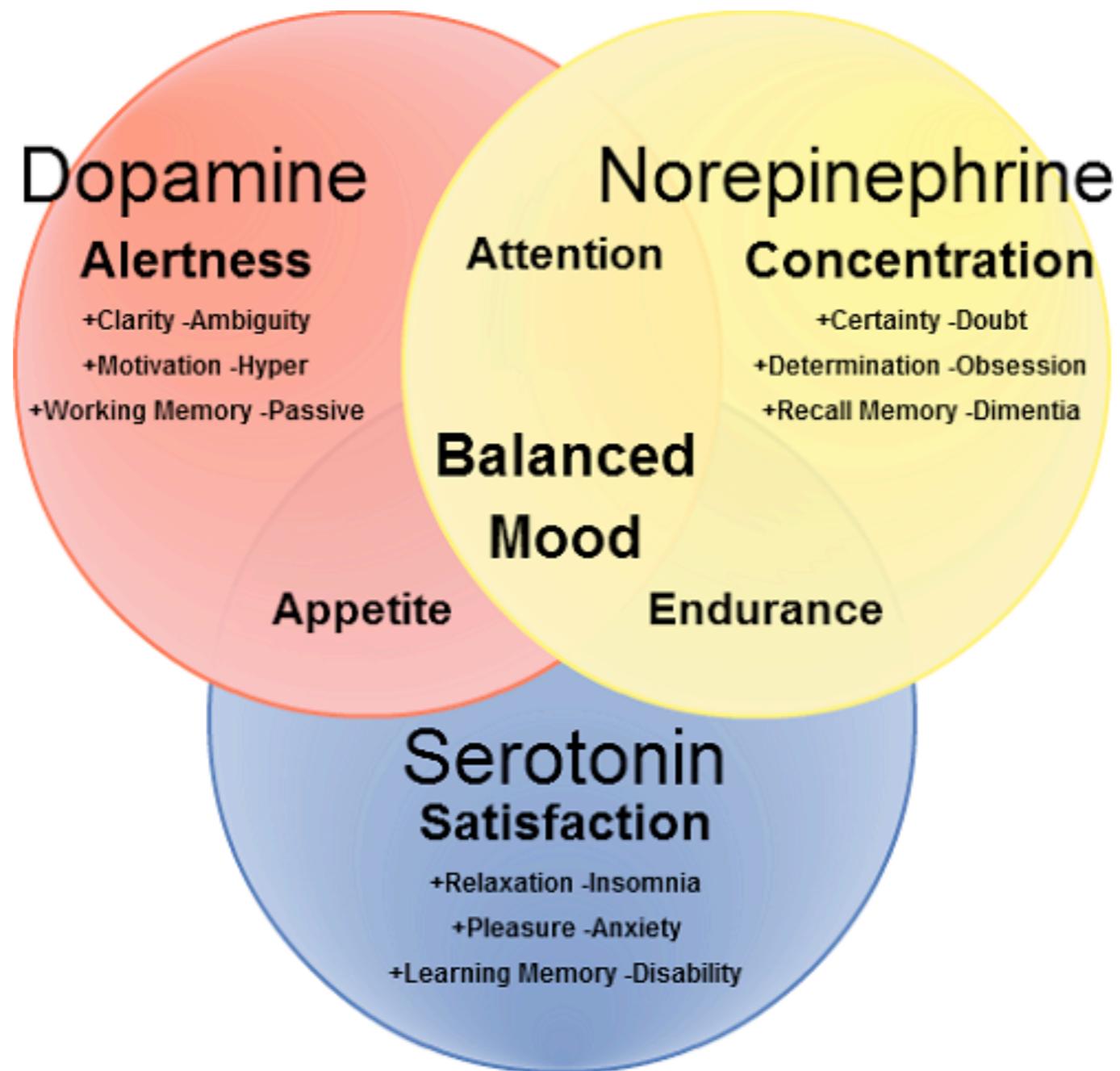
^aNot expressed in humans.

Can we use large-scale neural activity recording?

The goal of this lecture

- (1) Basics of neuromodulators**
- (2) How they work at mechanistic levels**
- (3) How mechanisms generalize across functions**

Does a neuromodulator have a specific function ?



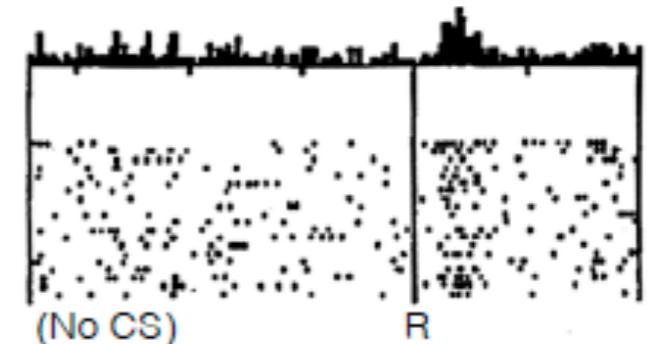
Dopamine encodes rewards prediction error in learning contexts

TD(0) learning theory

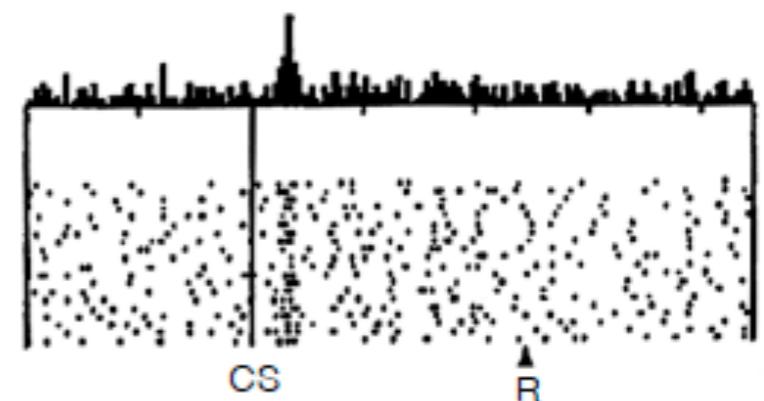
$$V(s_t) \leftarrow V(s_t) + \alpha [r_{t+1} + \gamma V(s_{t+1}) - V(s_t)]$$

Neuron in the VTA

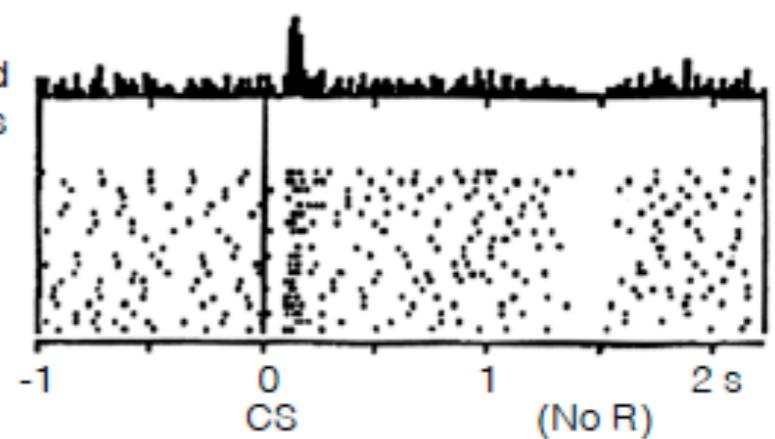
No prediction
Reward occurs



Reward predicted
Reward occurs



Reward predicted
No reward occurs



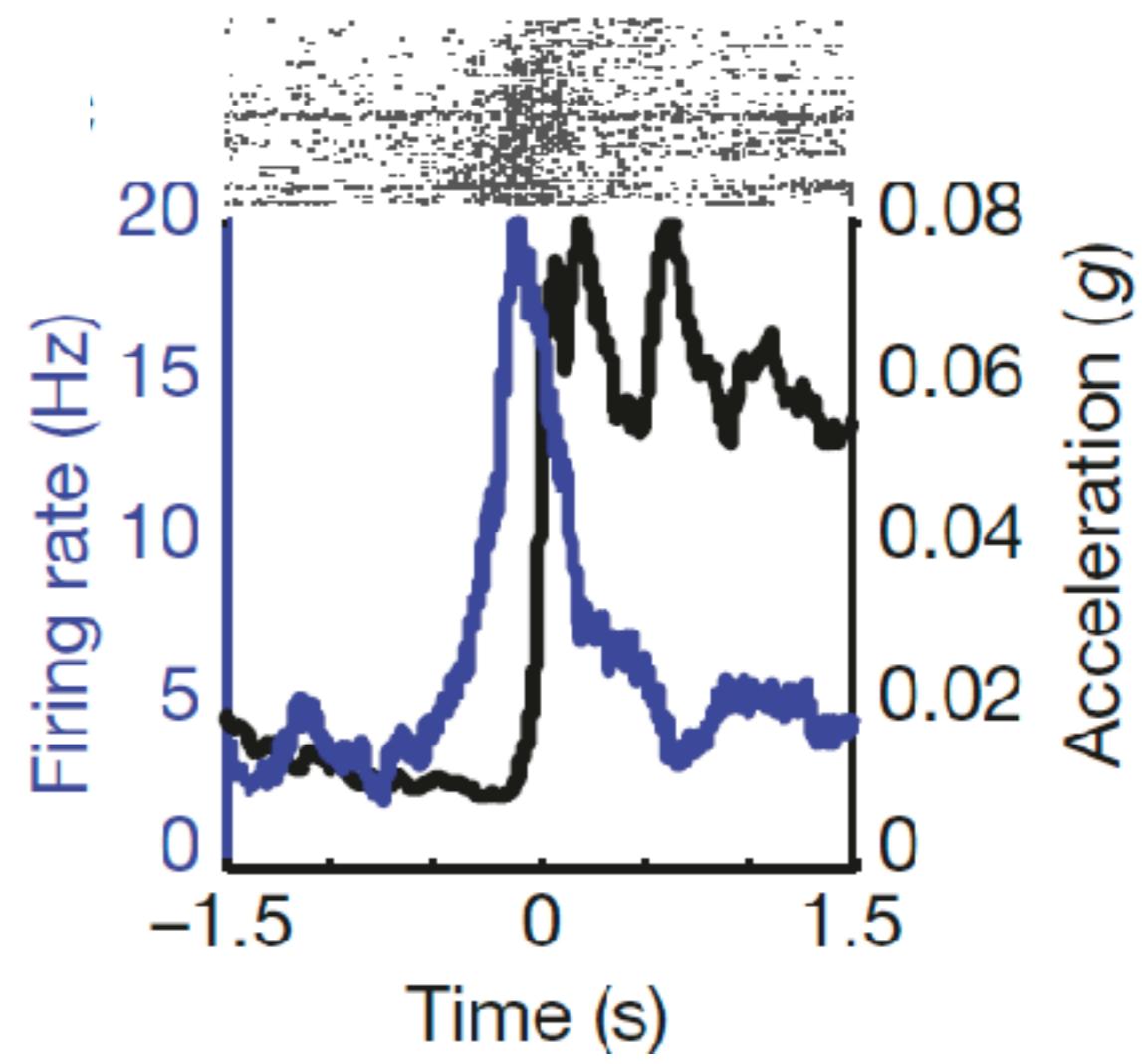
(Schultz, 1998)

Dopamine triggers the initiation of voluntary movements

Parkinson's disease



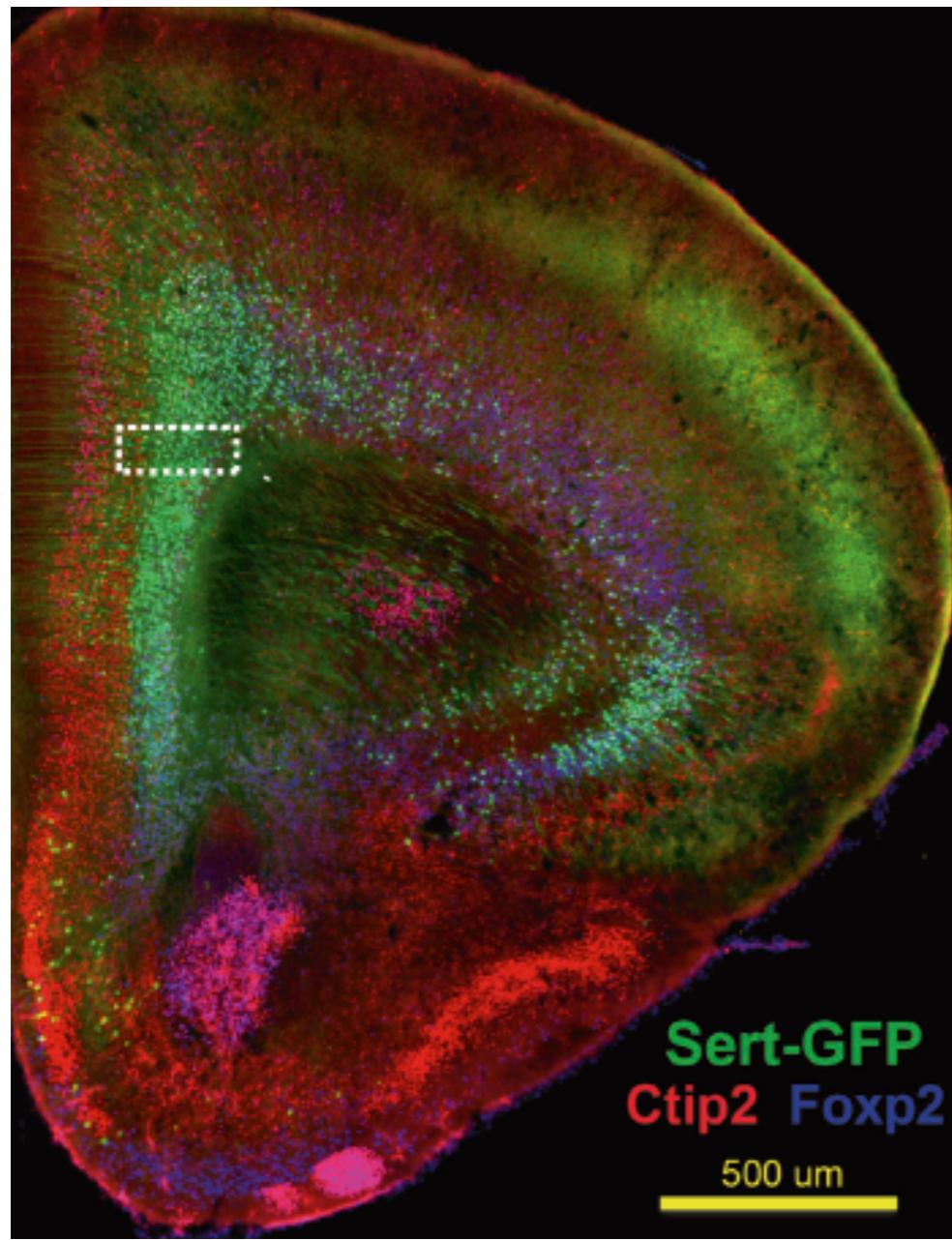
Neuron in the SNc



(Alves da Silva *et al.*, 2018)

Serotonin mediates mood control

Serotonin transporter in PFC



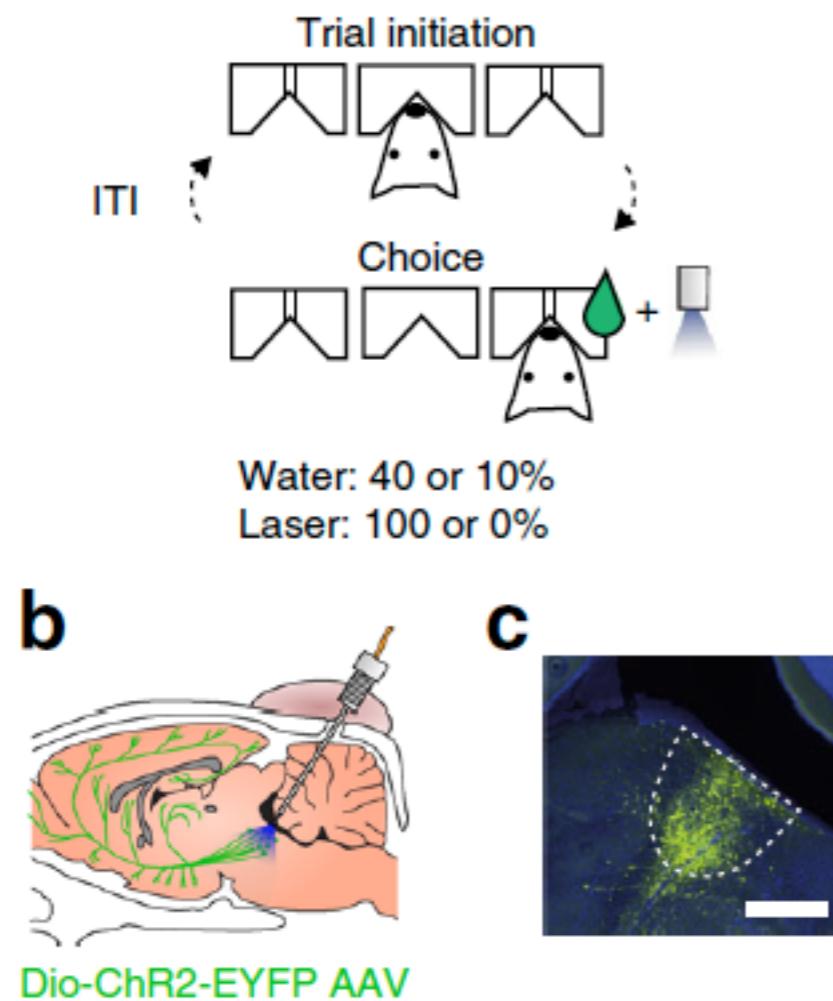
(Soiza-Reilly *et al.*, 2019)

SSRI: Anti-depressant



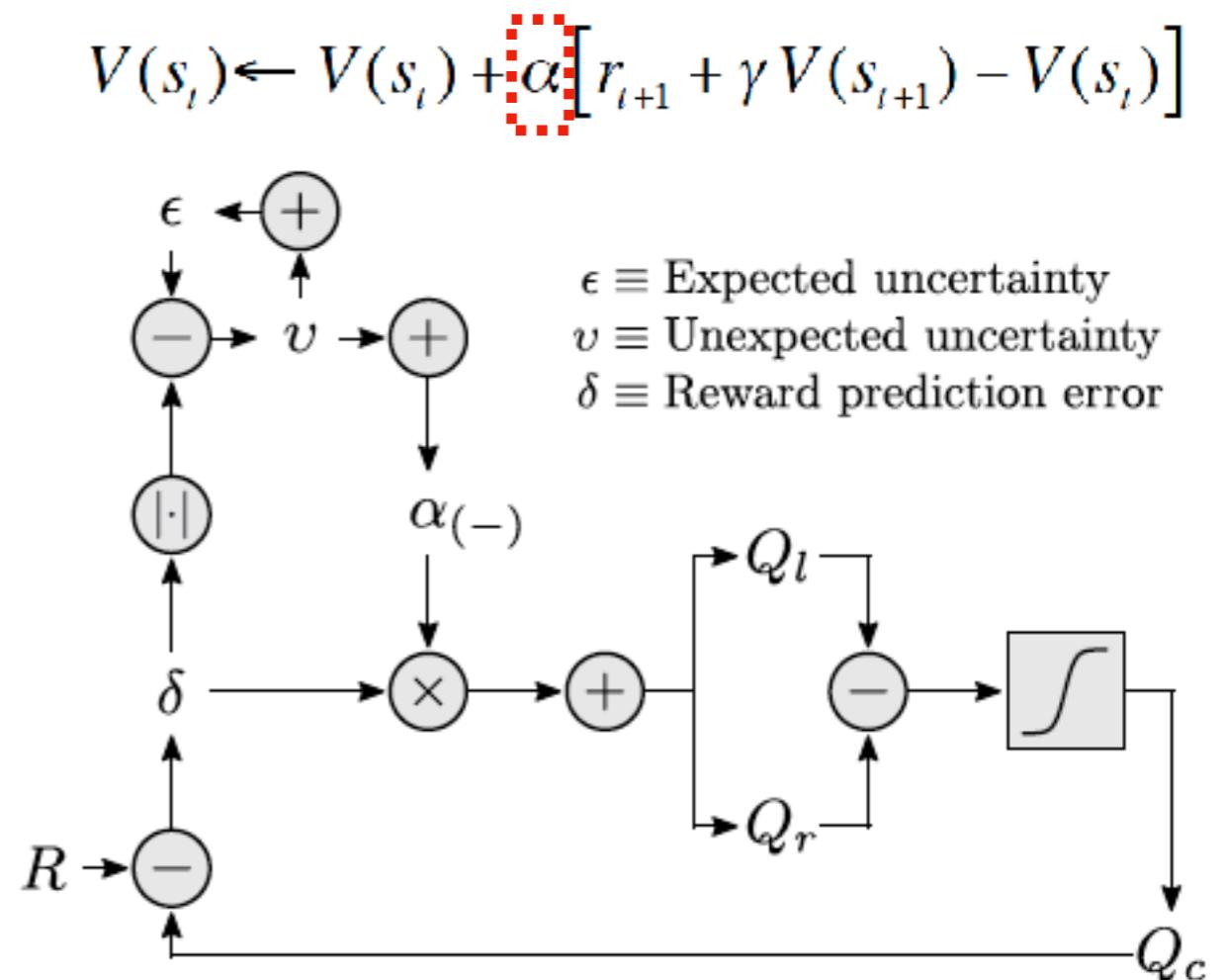
Serotonin mediates meta-learning

Enhancing learning rate
by photostimulation



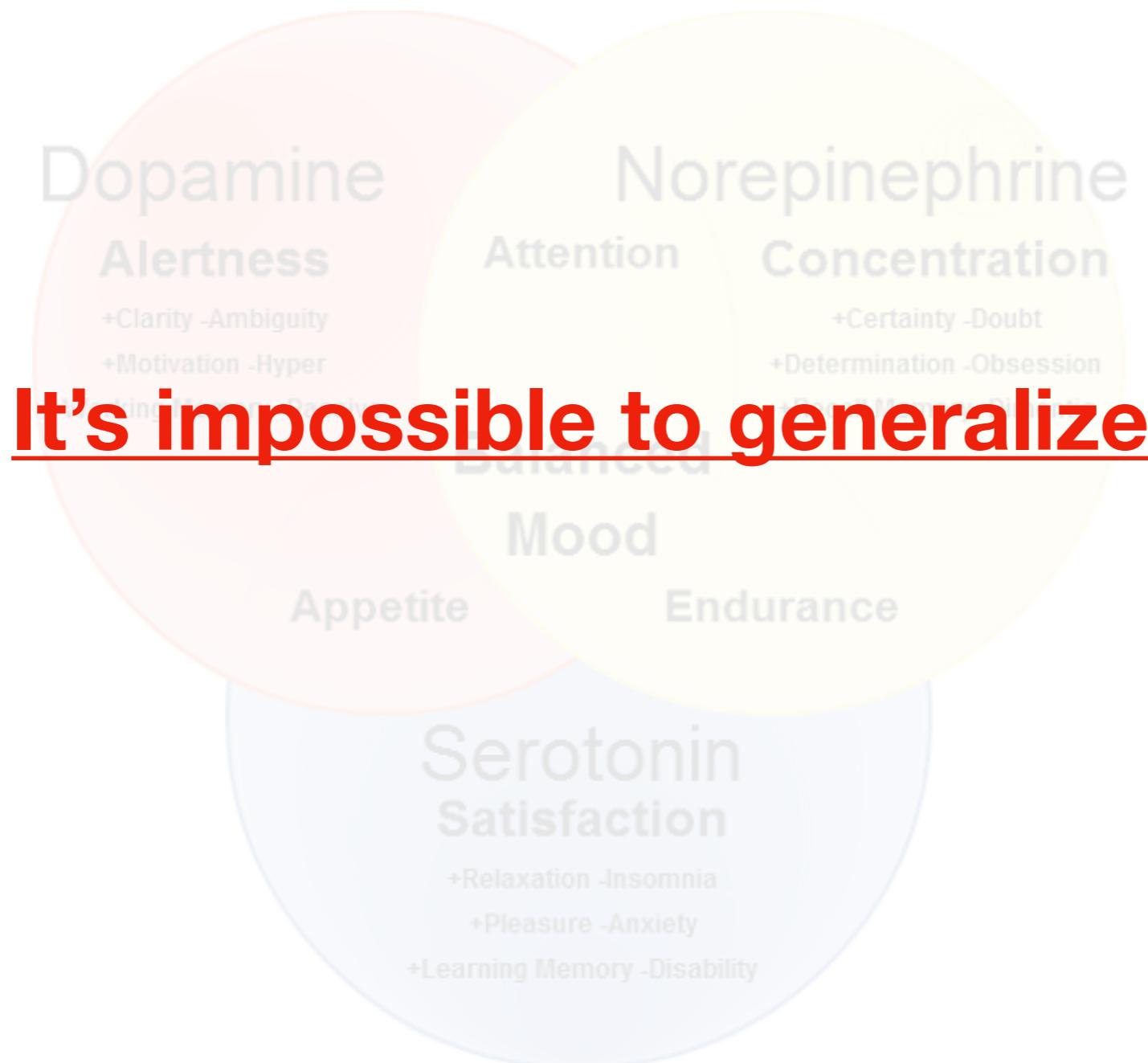
(Iigaya *et al.*, 2018)

Adjusting learning rate
based on uncertainty



(Grossman *et al.*, 2020)

Does a neuromodulator have a specific function ?



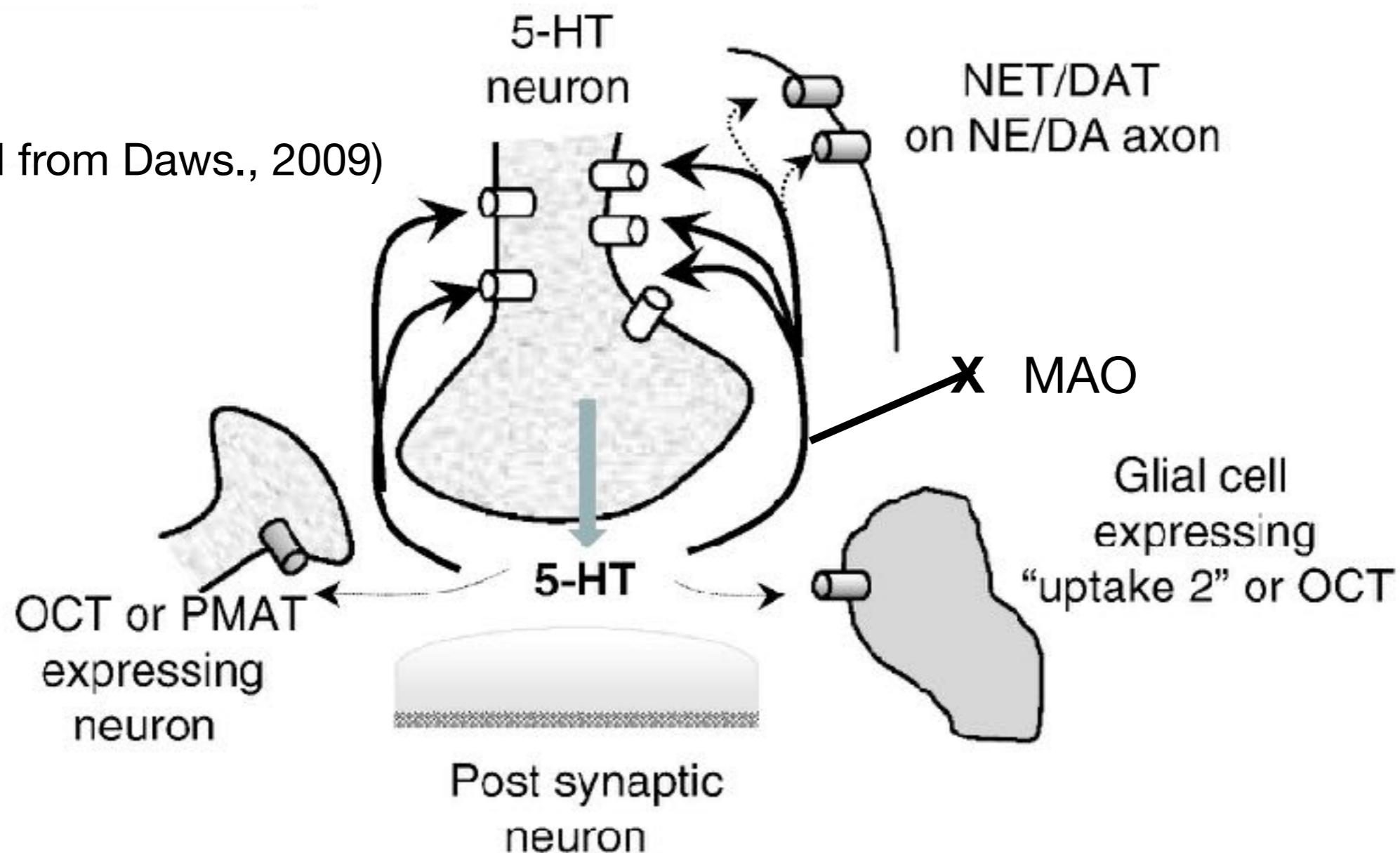
Does a neuromodulator have a specific function ?

Alternative hypothesis

Neuromodulators have different basic properties from each other and evolved to fit wherever useful

Neuromodulator: synthesis and reuptake

(modified from Daws., 2009)



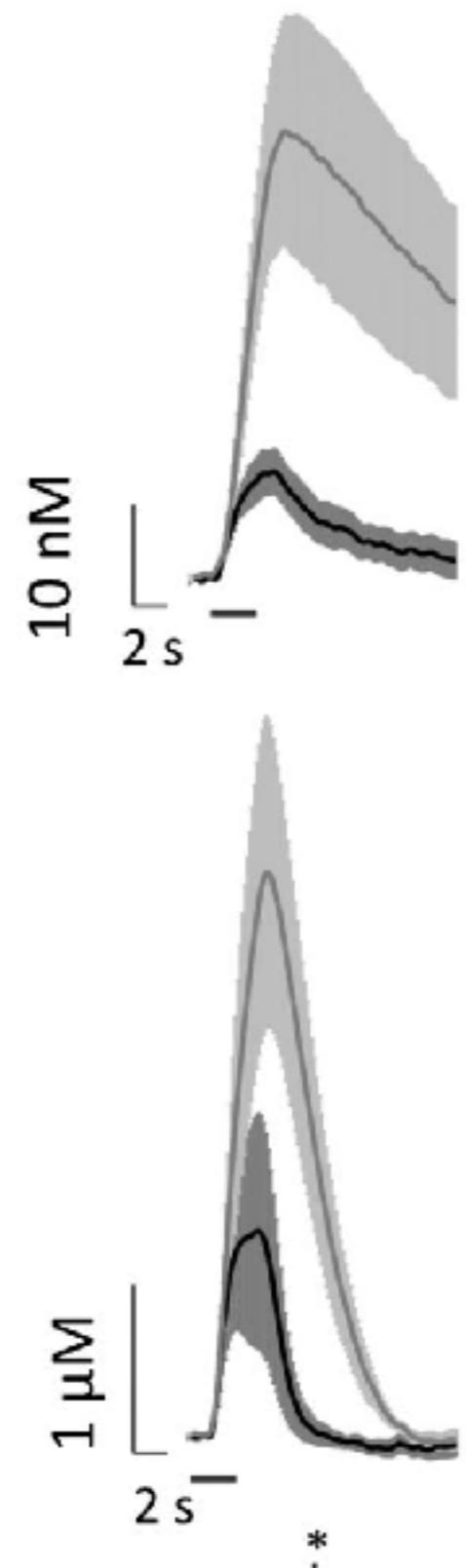
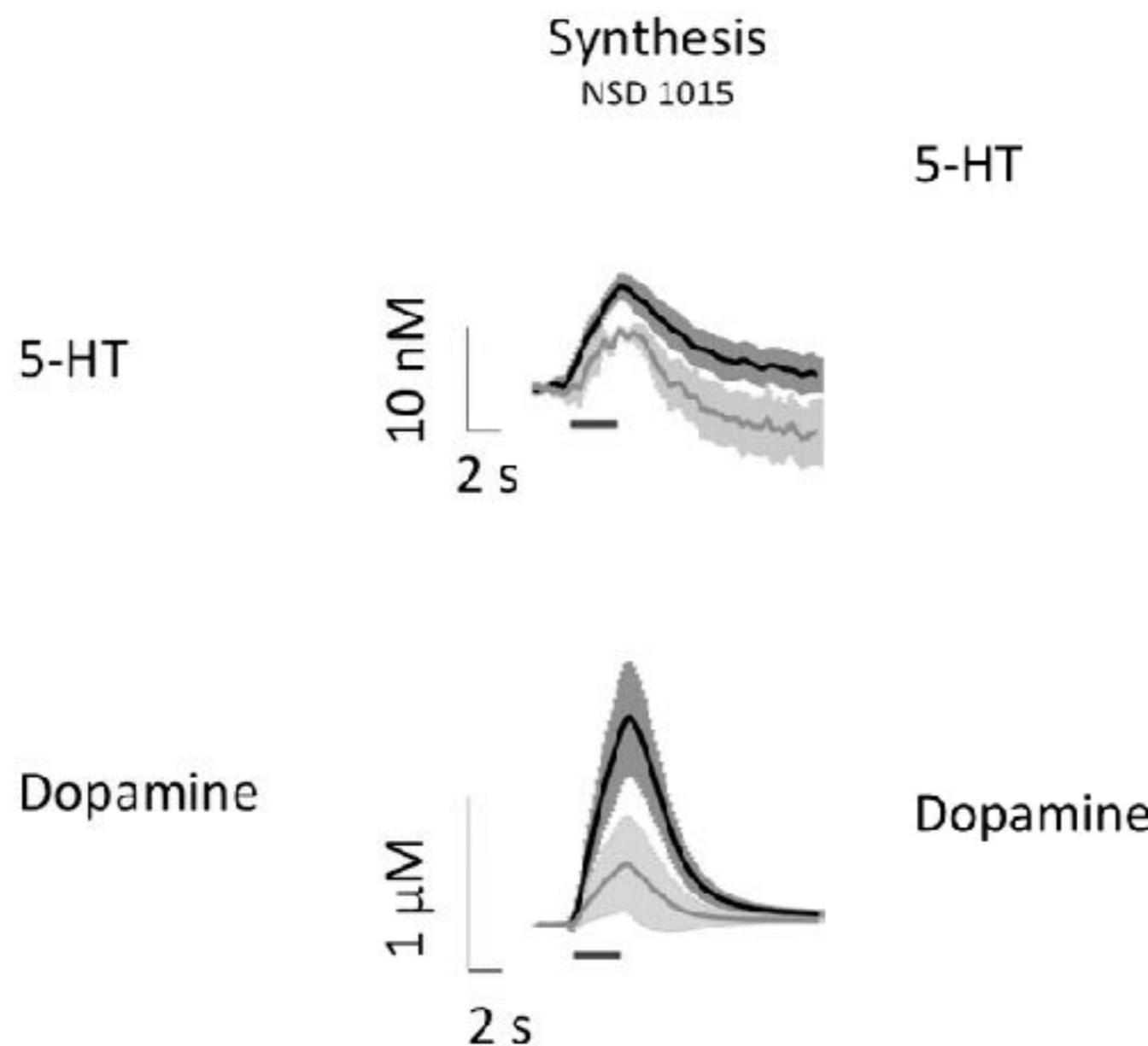
Synthesis depends on the presynaptic cells

Reuptake depends on the surroundings

Uptake
Citalopram (5-HT)
GBR 12909 (Dopamine)

Dopamine depends on synthesis Serotonin depends on reuptake

(Hashemi *et al.*, 2012)



Radical analogy would be...

Dopamine



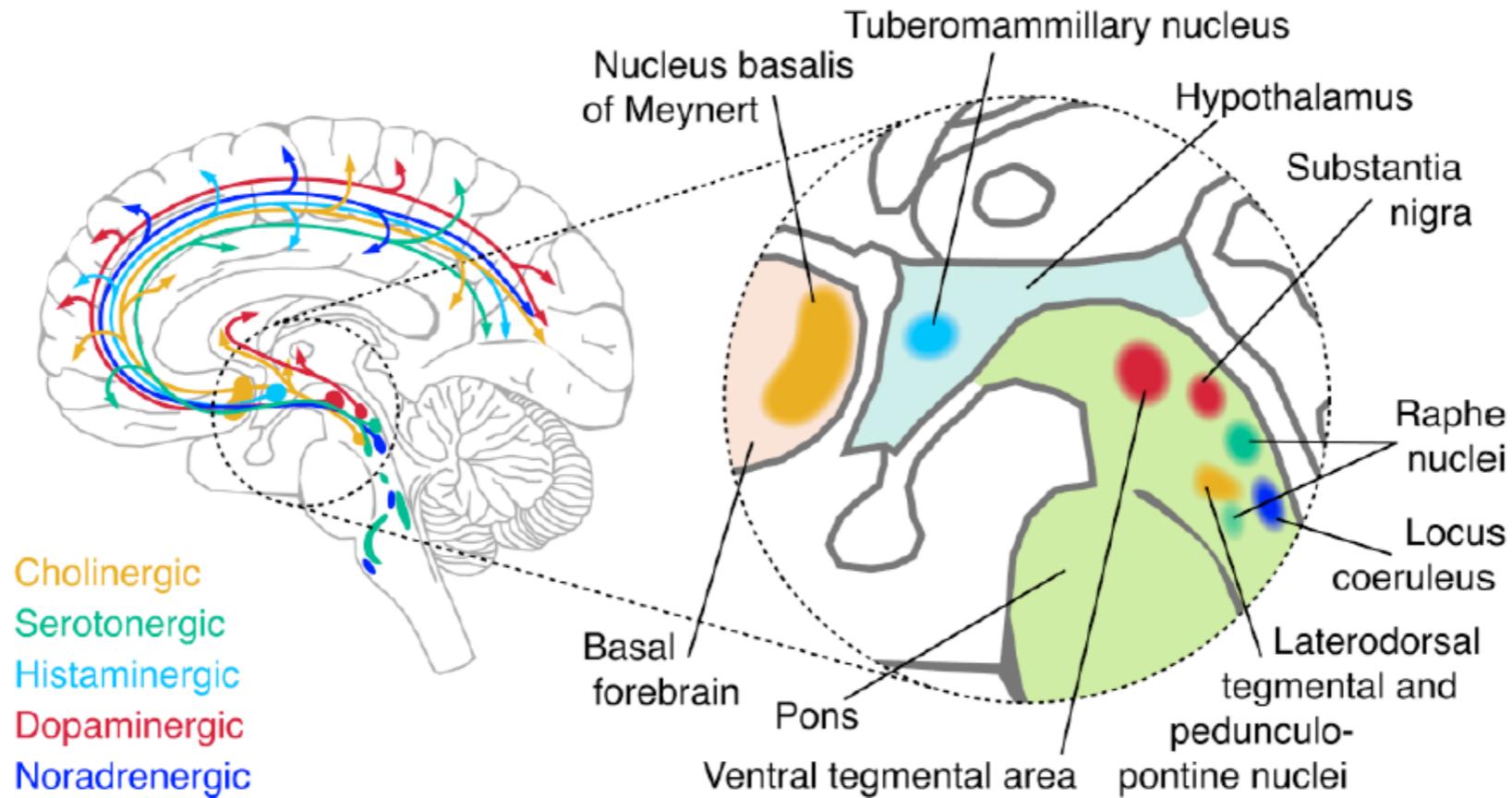
Top-down paycheck
from the central system

Serotonin

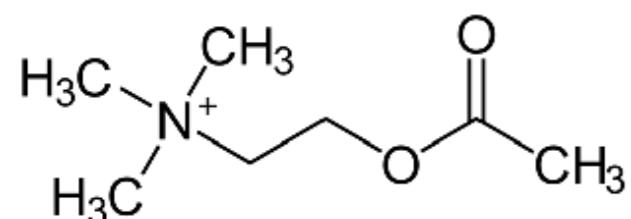


On-demand bank
for various brain regions

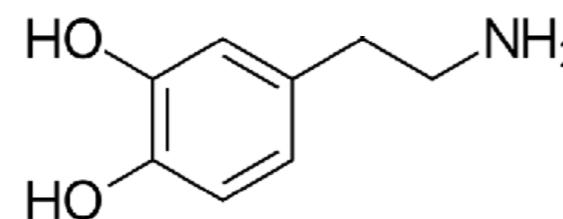
Neuromodulatory system evolved from their basic properties



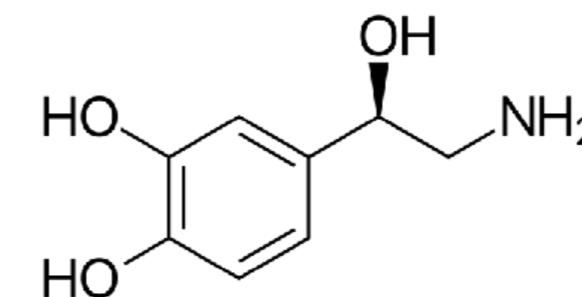
Acetylcholine



Norepinephrine



Dopamine



Serotonin

