



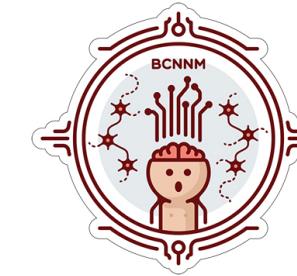
Computational Neuroscience

Lecture 11: Neural system regulation

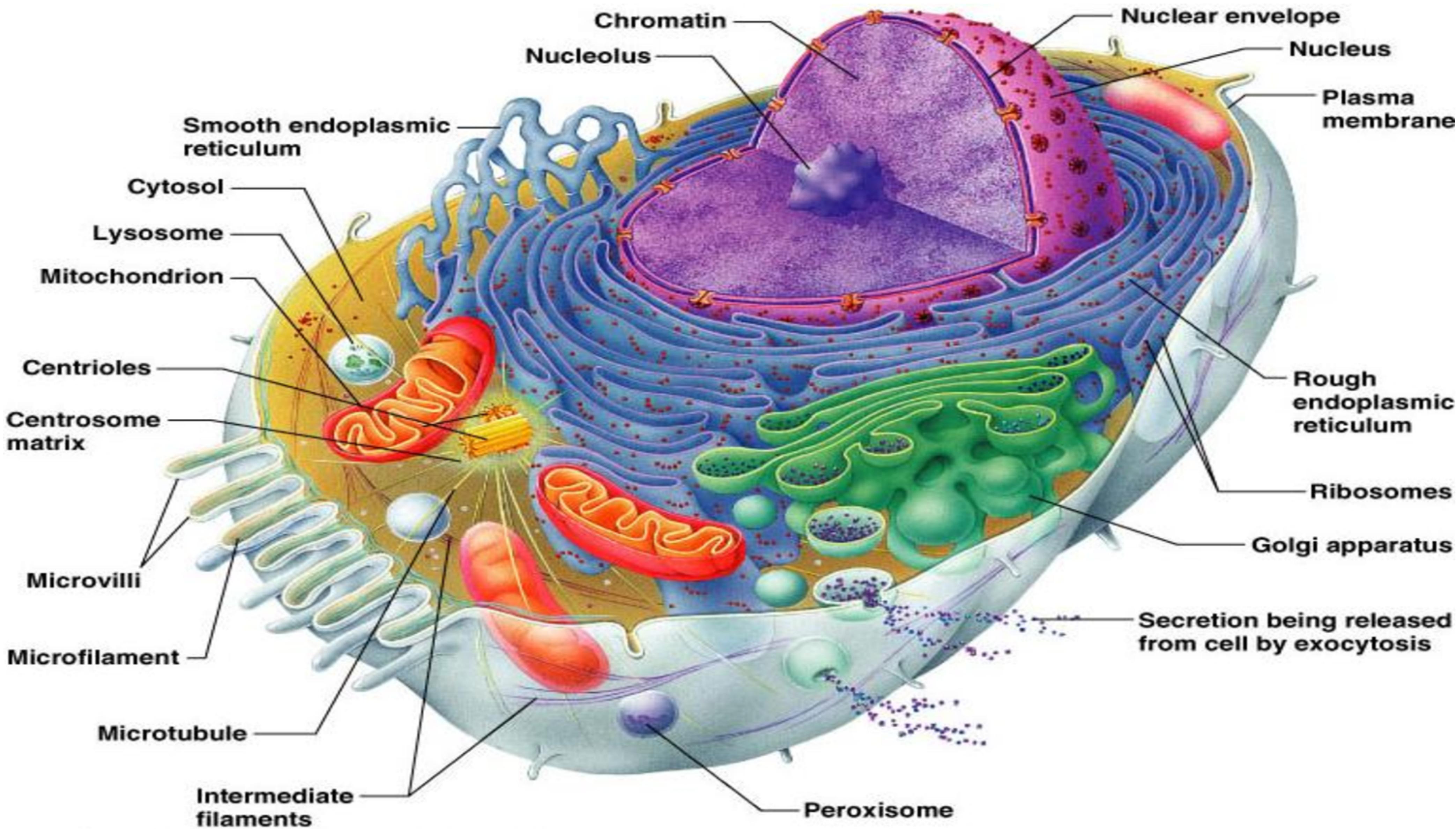
| Dmitry Bozhko | Georgy Galumov | Sofia Kolchanova | Vladislav Myrov |

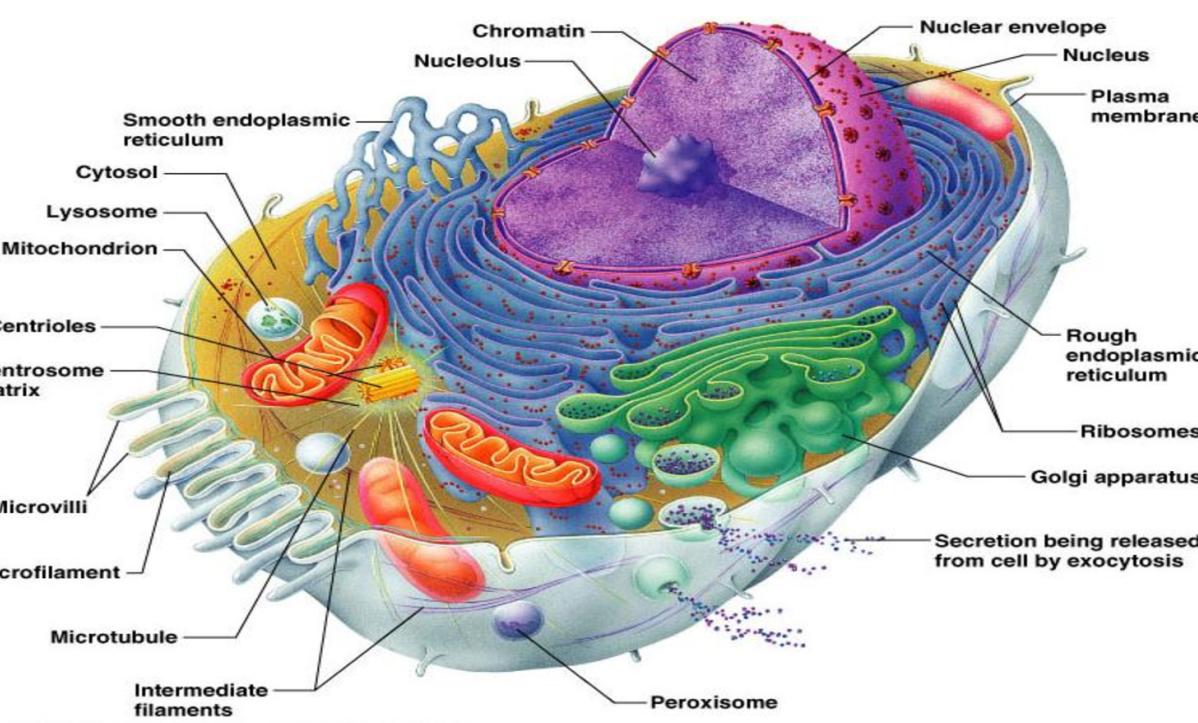
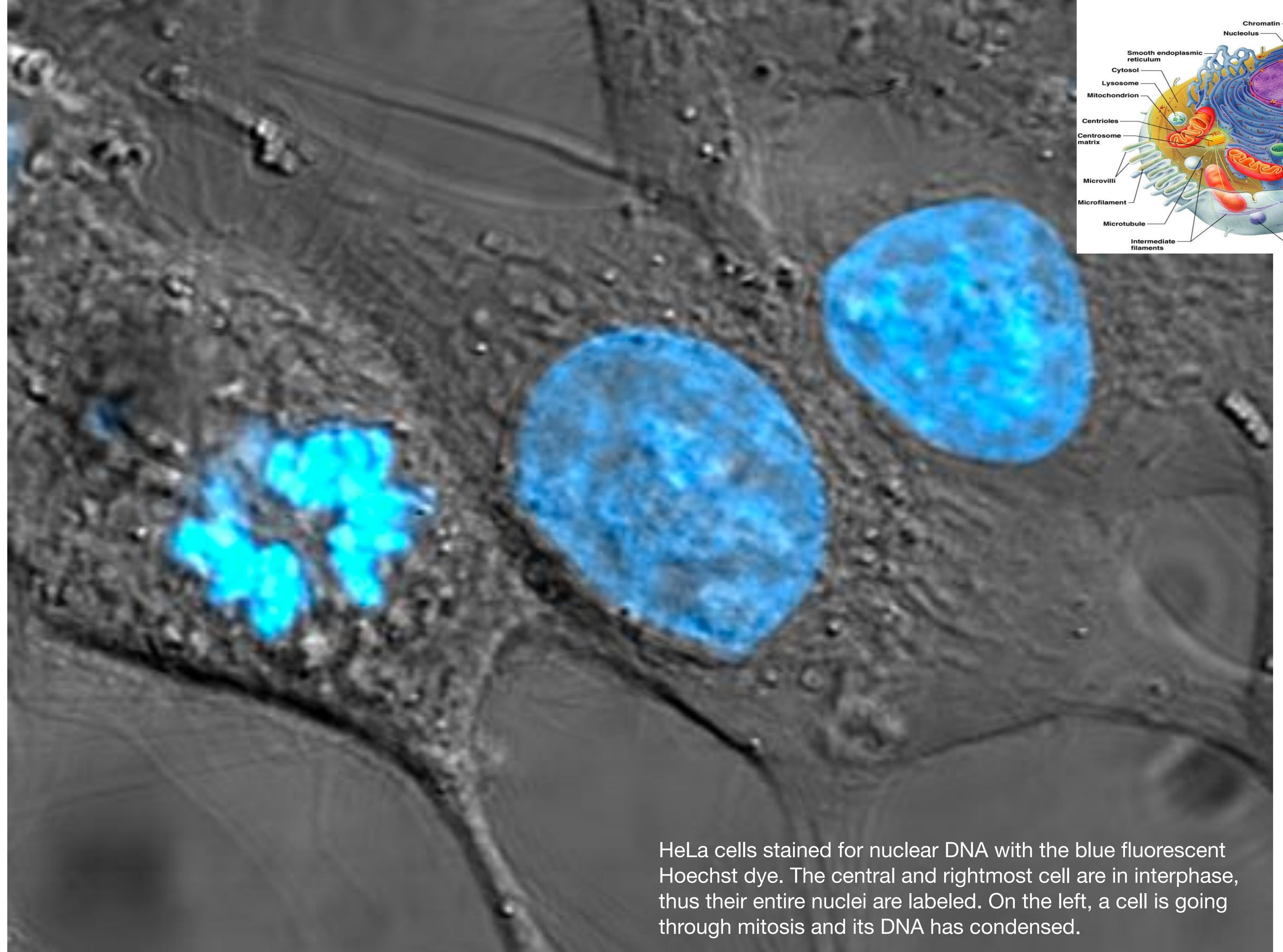
Agenda

- Regulation of a neuron
- Regulation of a system

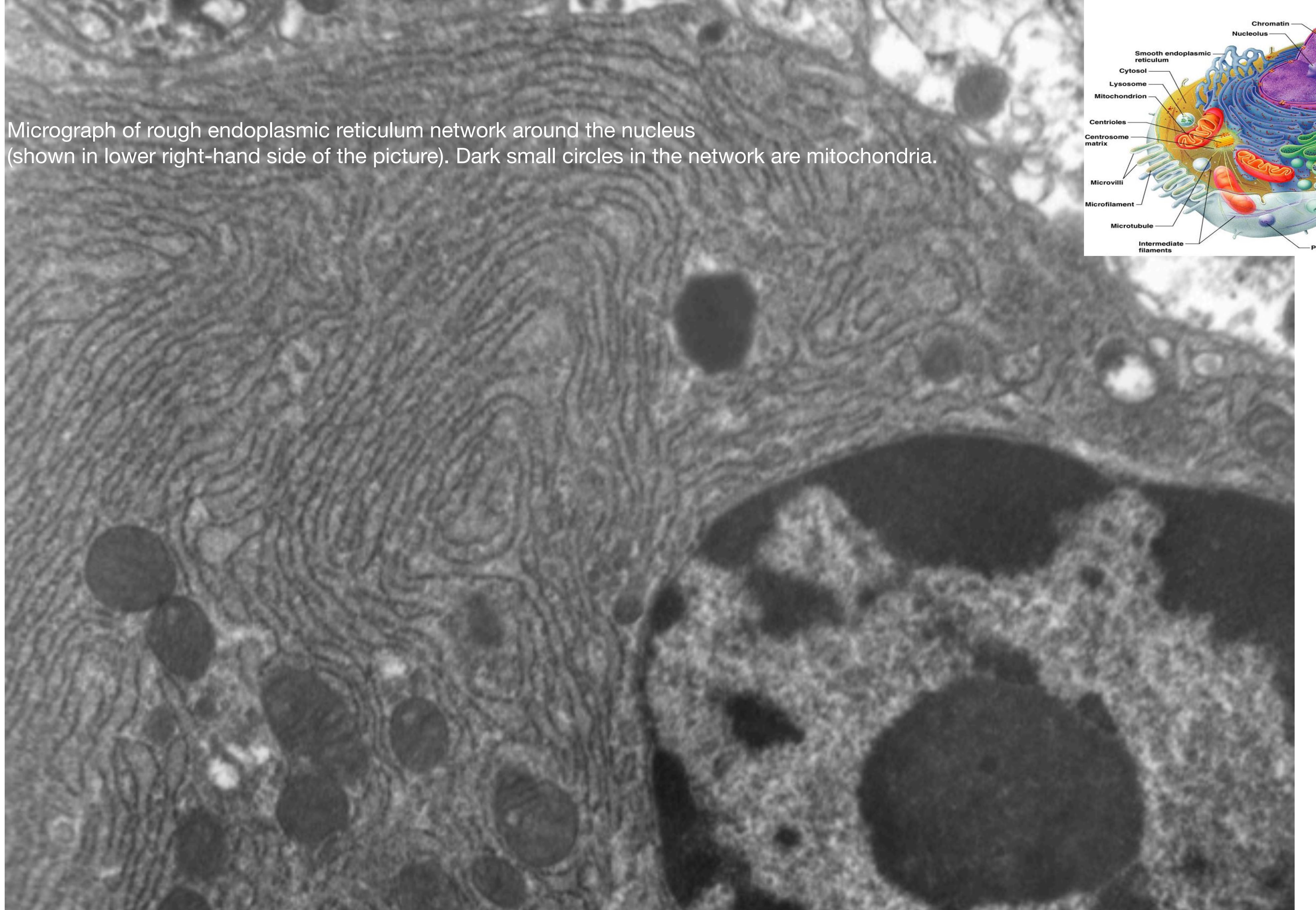


Structure of a Generalized Cell

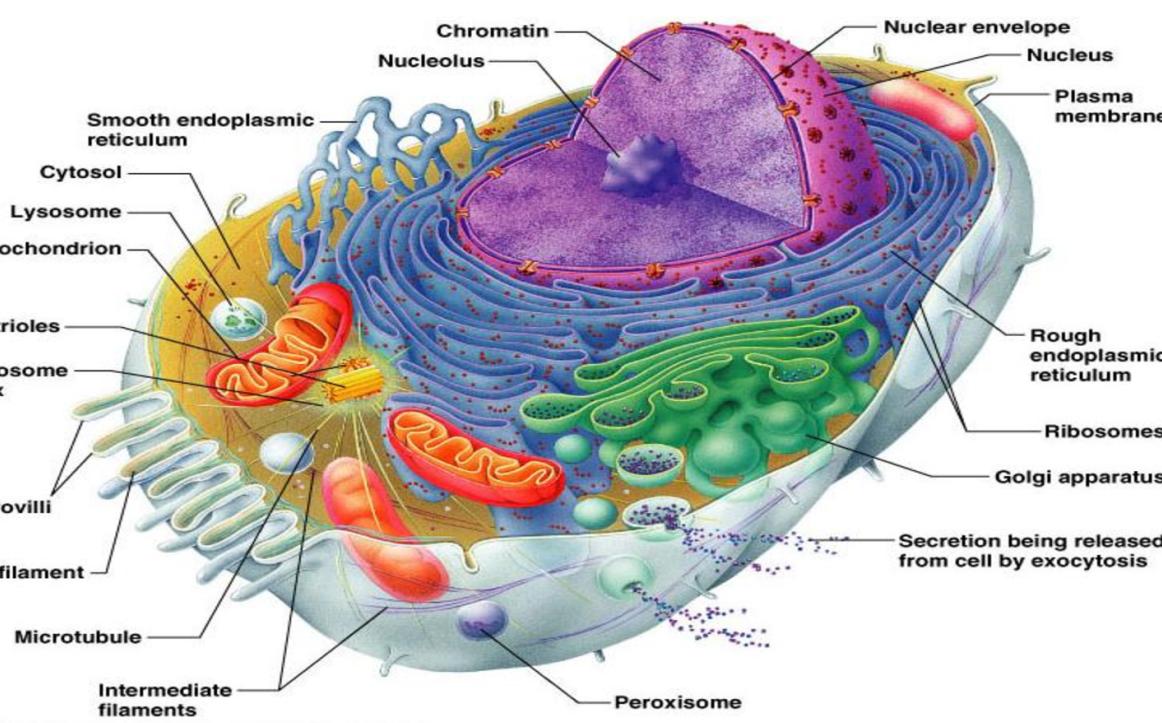


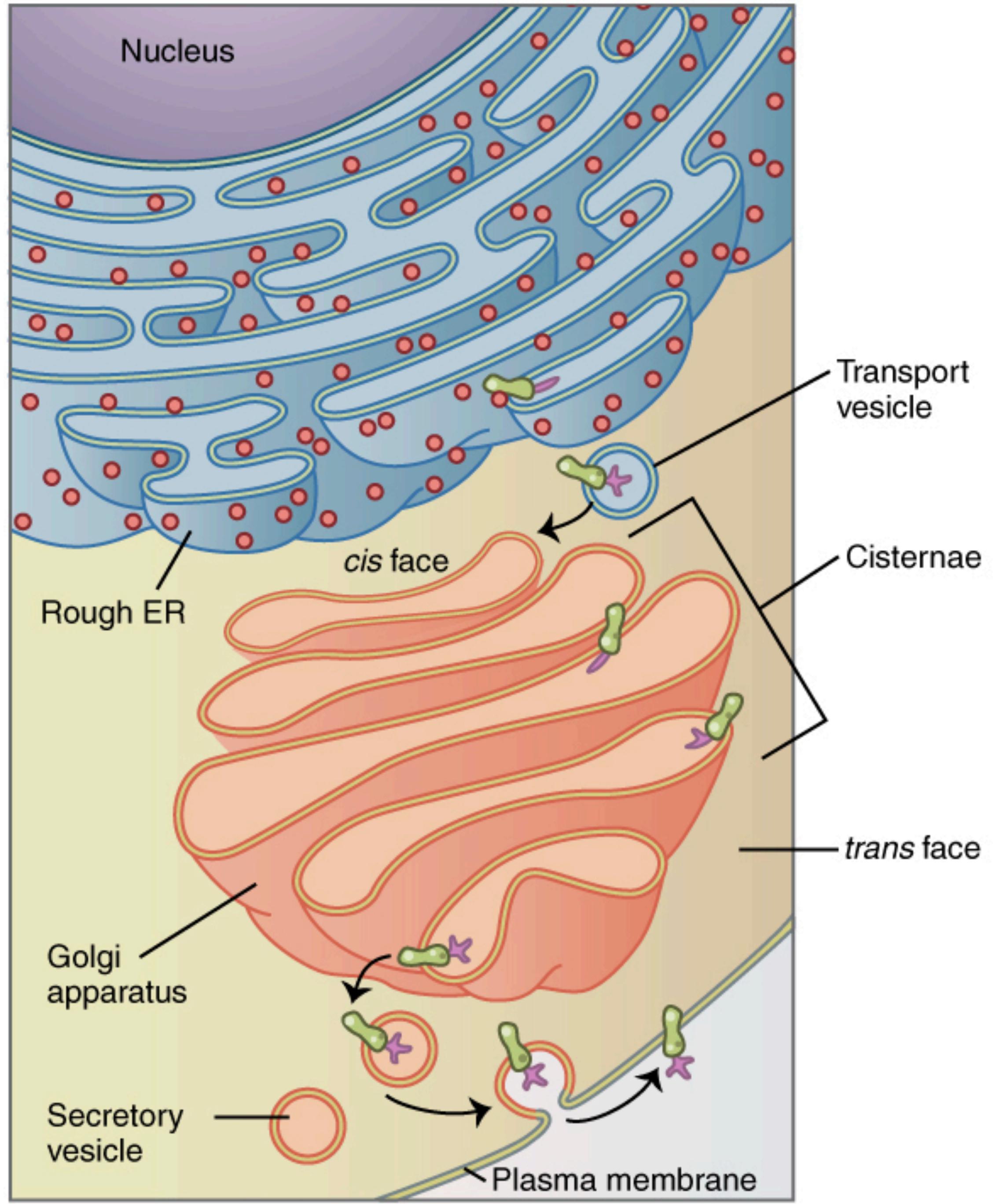


HeLa cells stained for nuclear DNA with the blue fluorescent Hoechst dye. The central and rightmost cell are in interphase, thus their entire nuclei are labeled. On the left, a cell is going through mitosis and its DNA has condensed.

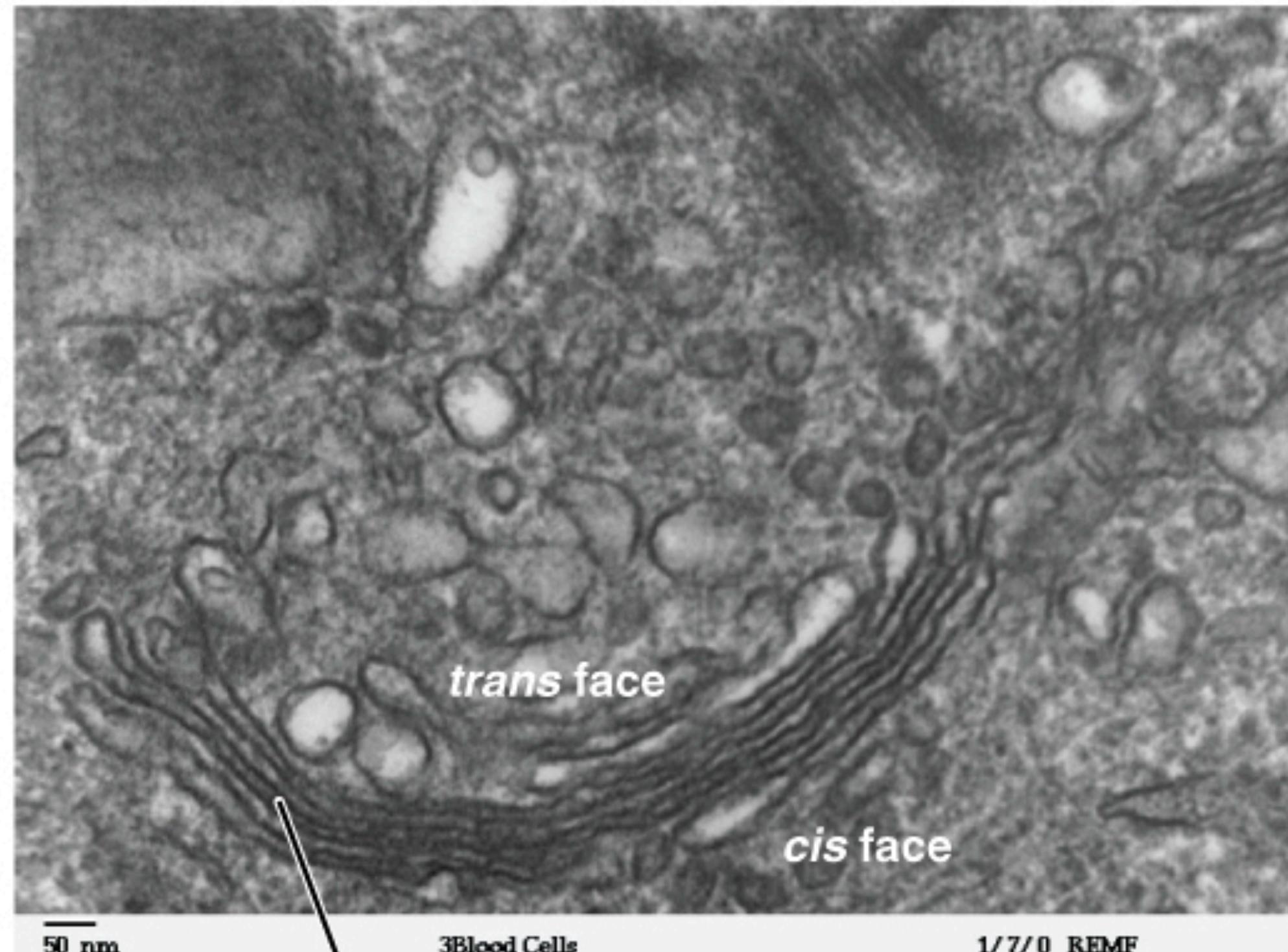


Micrograph of rough endoplasmic reticulum network around the nucleus
(shown in lower right-hand side of the picture). Dark small circles in the network are mitochondria.



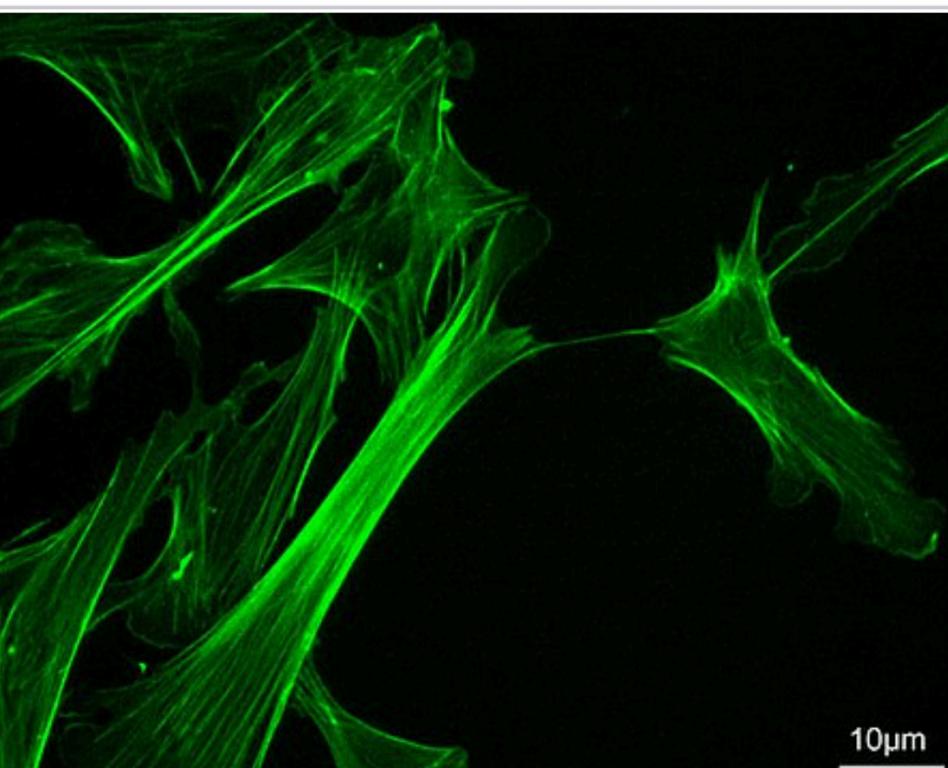
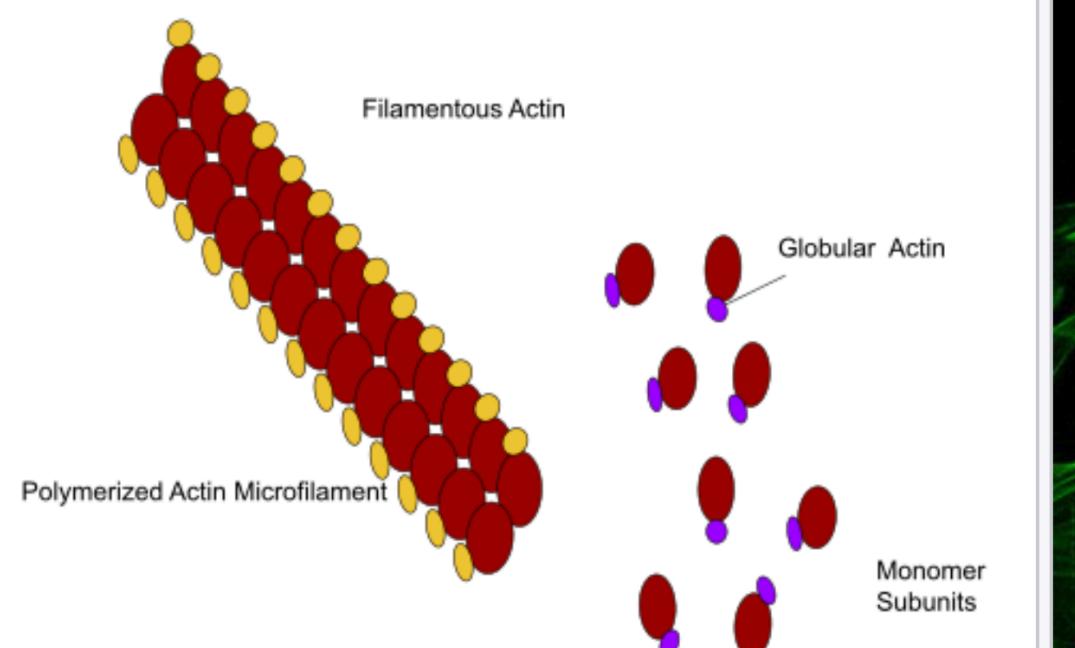


(a)



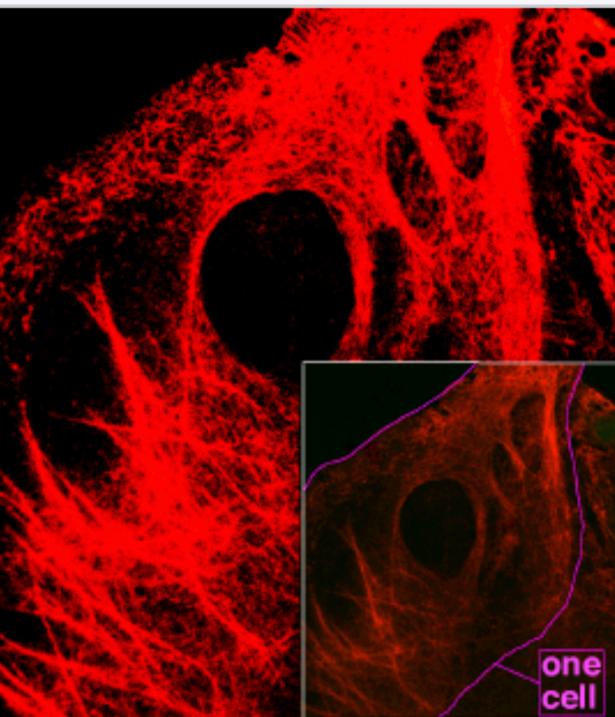
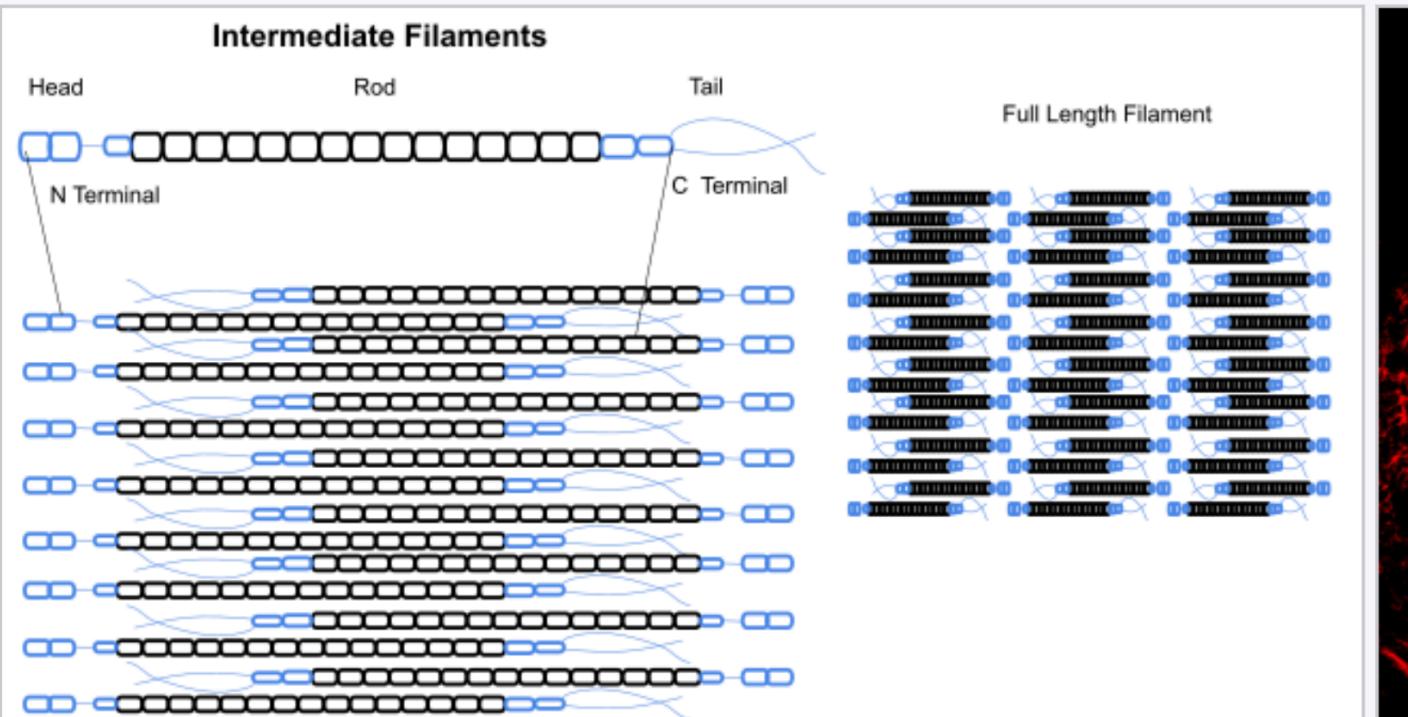
(b)

Microfilament Structure and Assembly



Structure of a microfilament

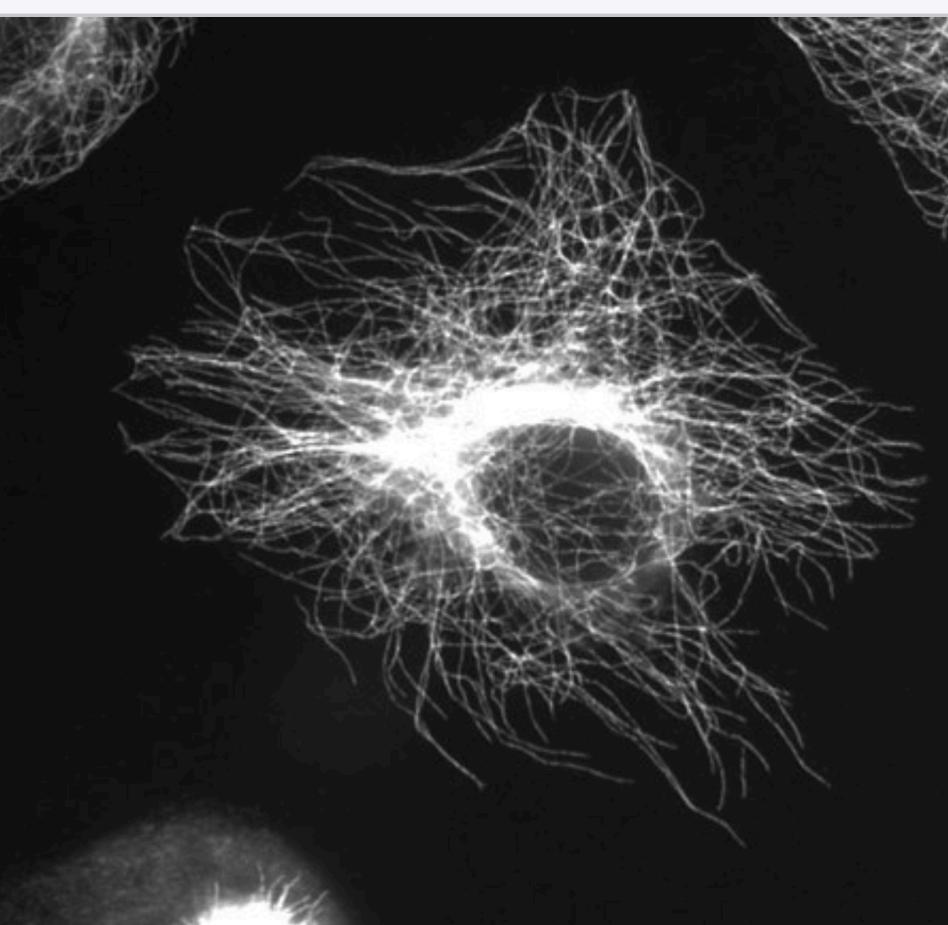
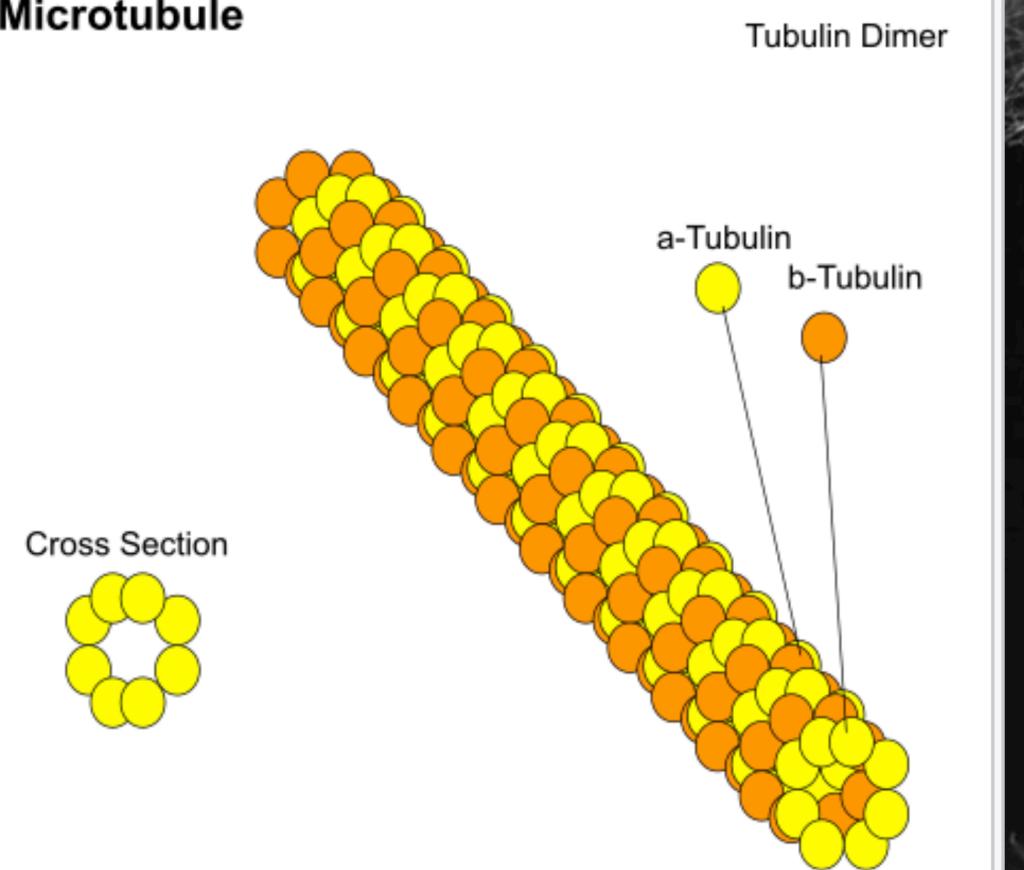
Actin cytoskeleton of mouse embryo fibroblasts, stained with phalloidin



Structure of an intermediate filament

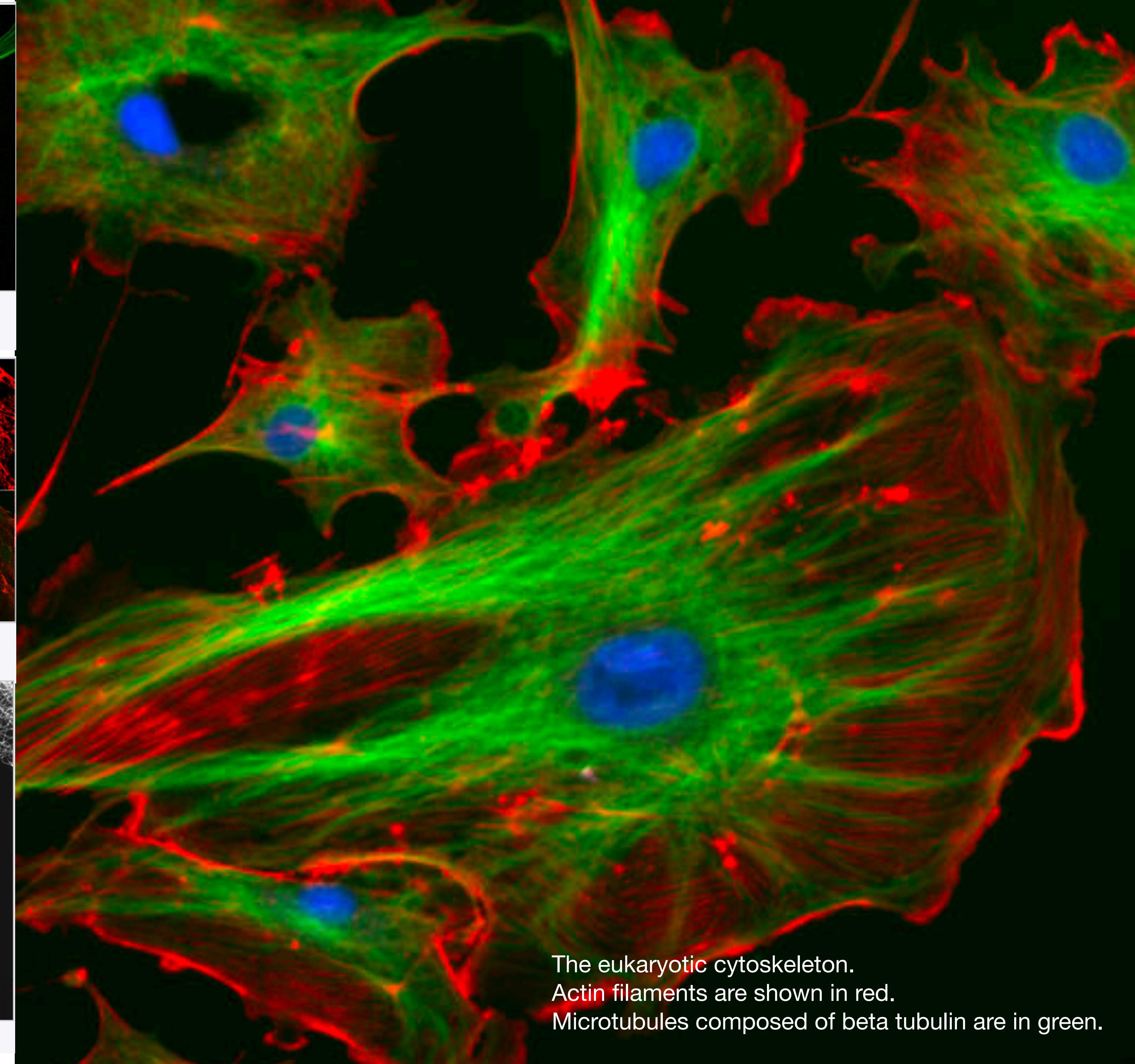
Microscopy of keratin filaments inside cells

Microtubule

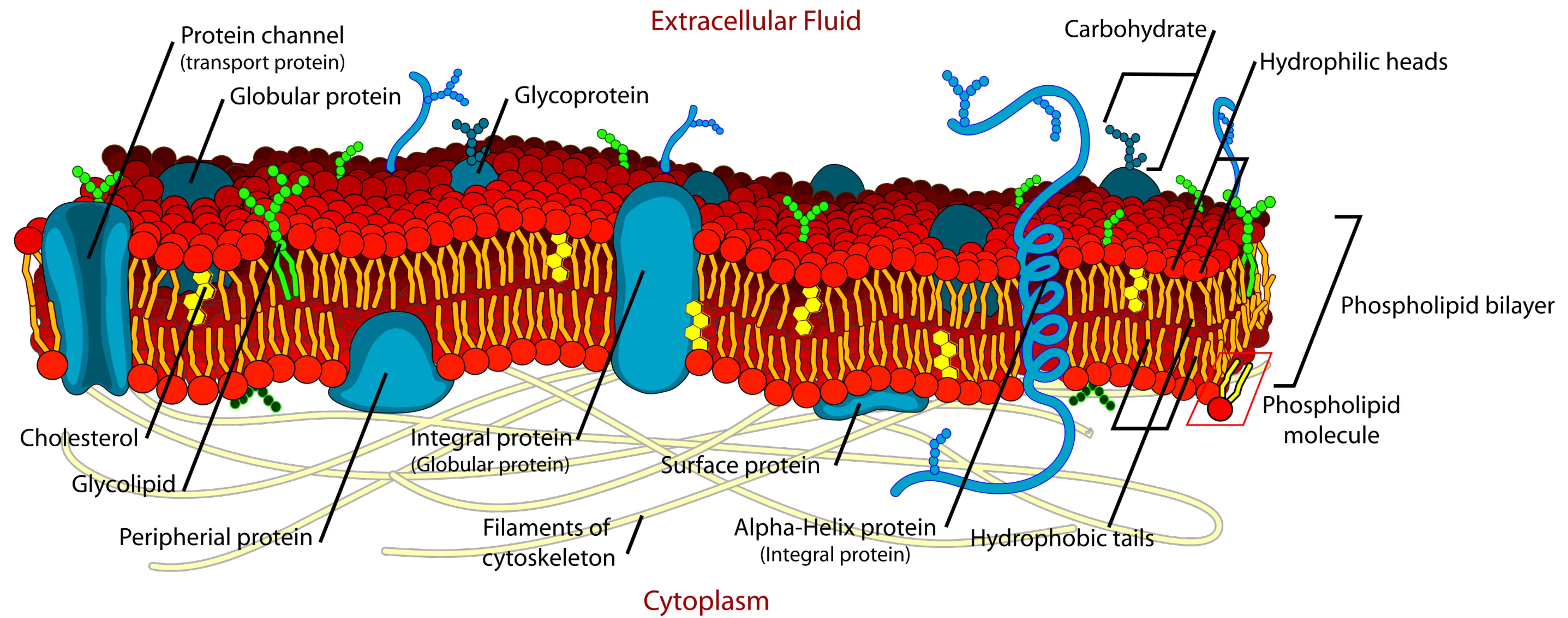


Structure of a microtubule

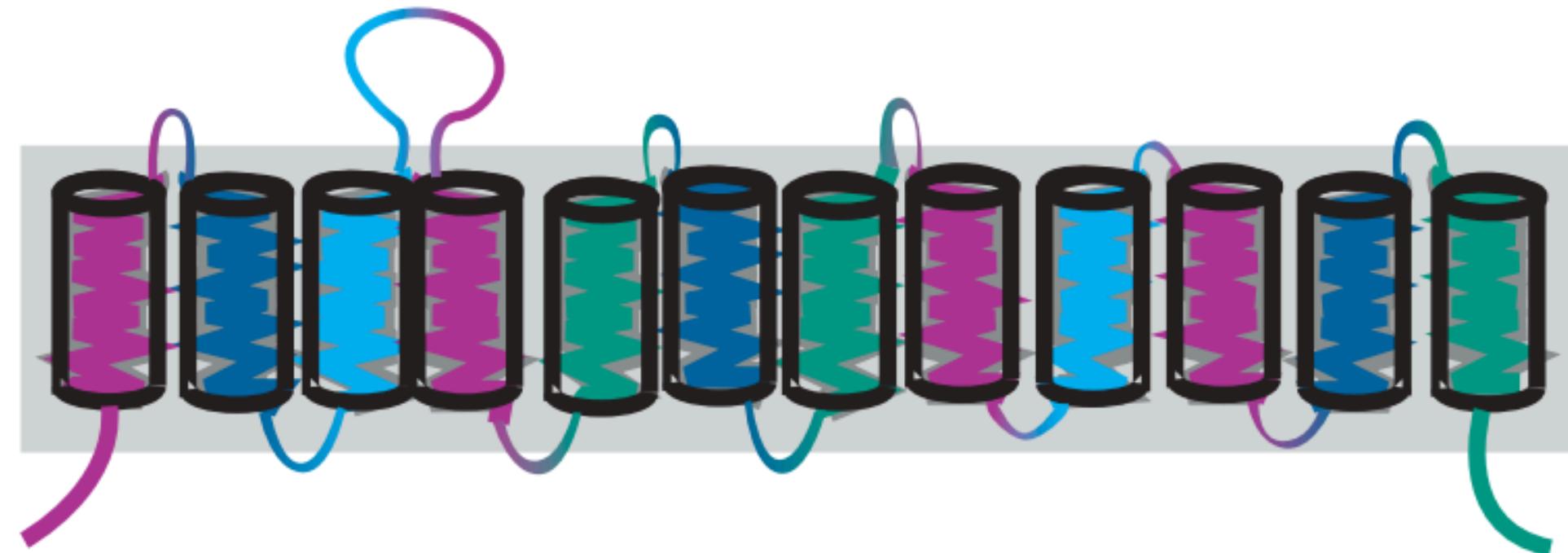
Microtubules in a gel-fixed cell



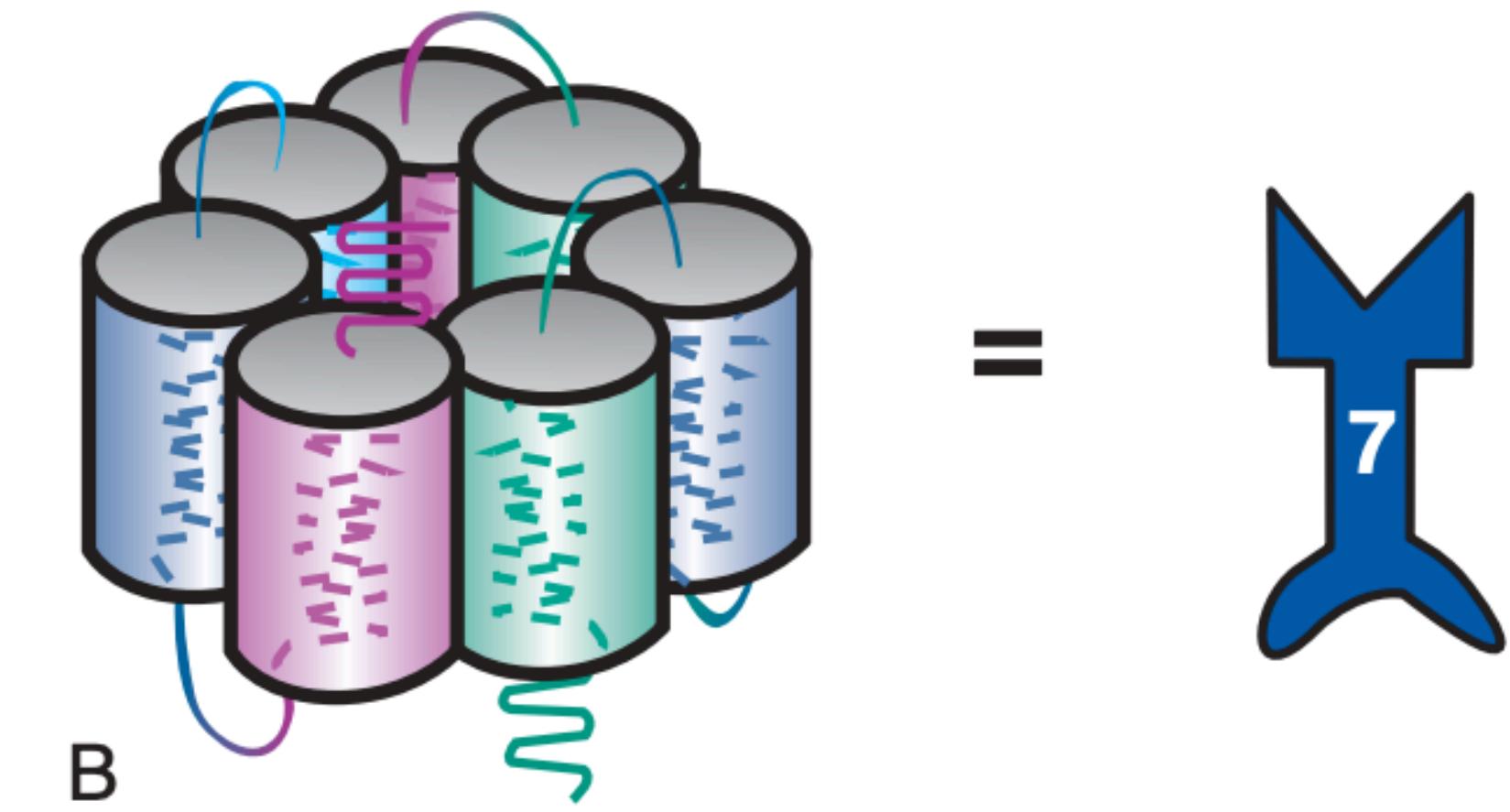
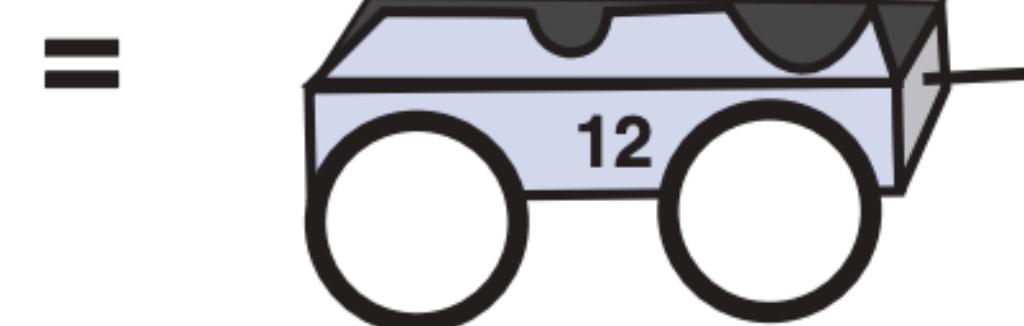
The eukaryotic cytoskeleton.
Actin filaments are shown in red.
Microtubules composed of beta tubulin are in green.



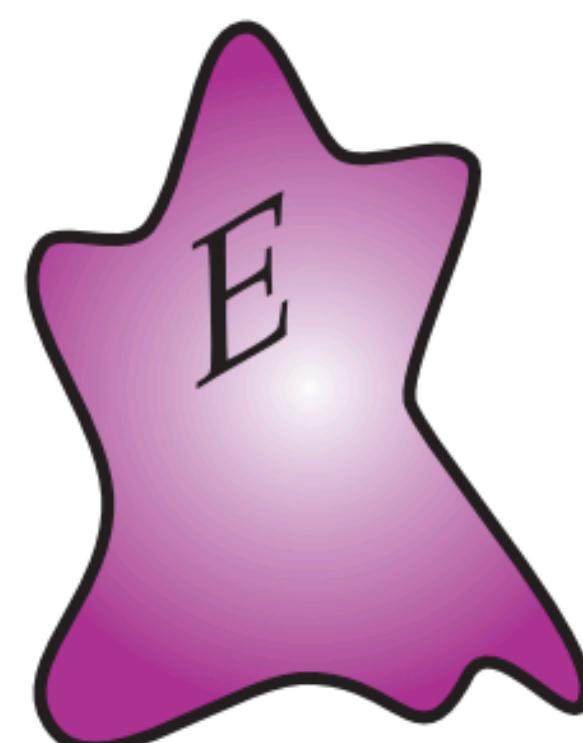
The Five Molecular Targets of Psychotropic Drugs



A
12-transmembrane-
region transporter
~ 30% of psychotropic drugs



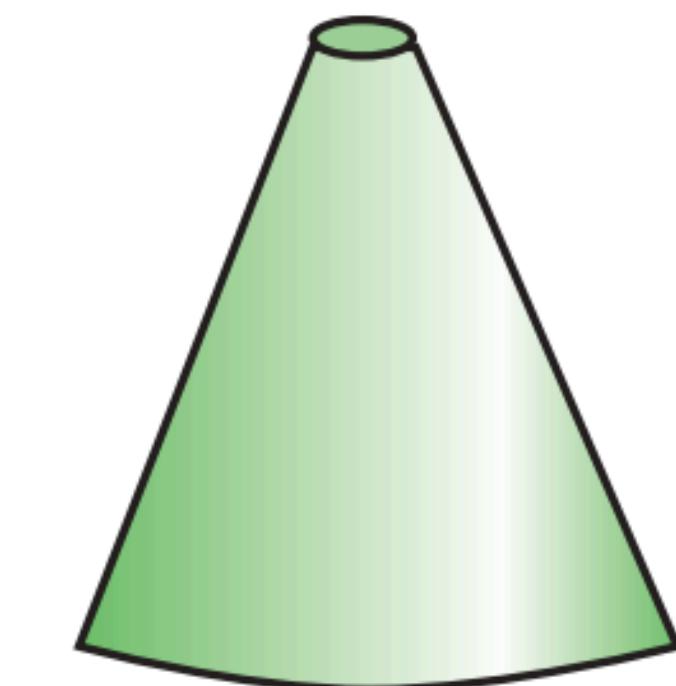
B
7-transmembrane-region
G-protein-linked
~ 30% of psychotropic drugs



C
Enzyme
~ 10% of psychotropic drugs



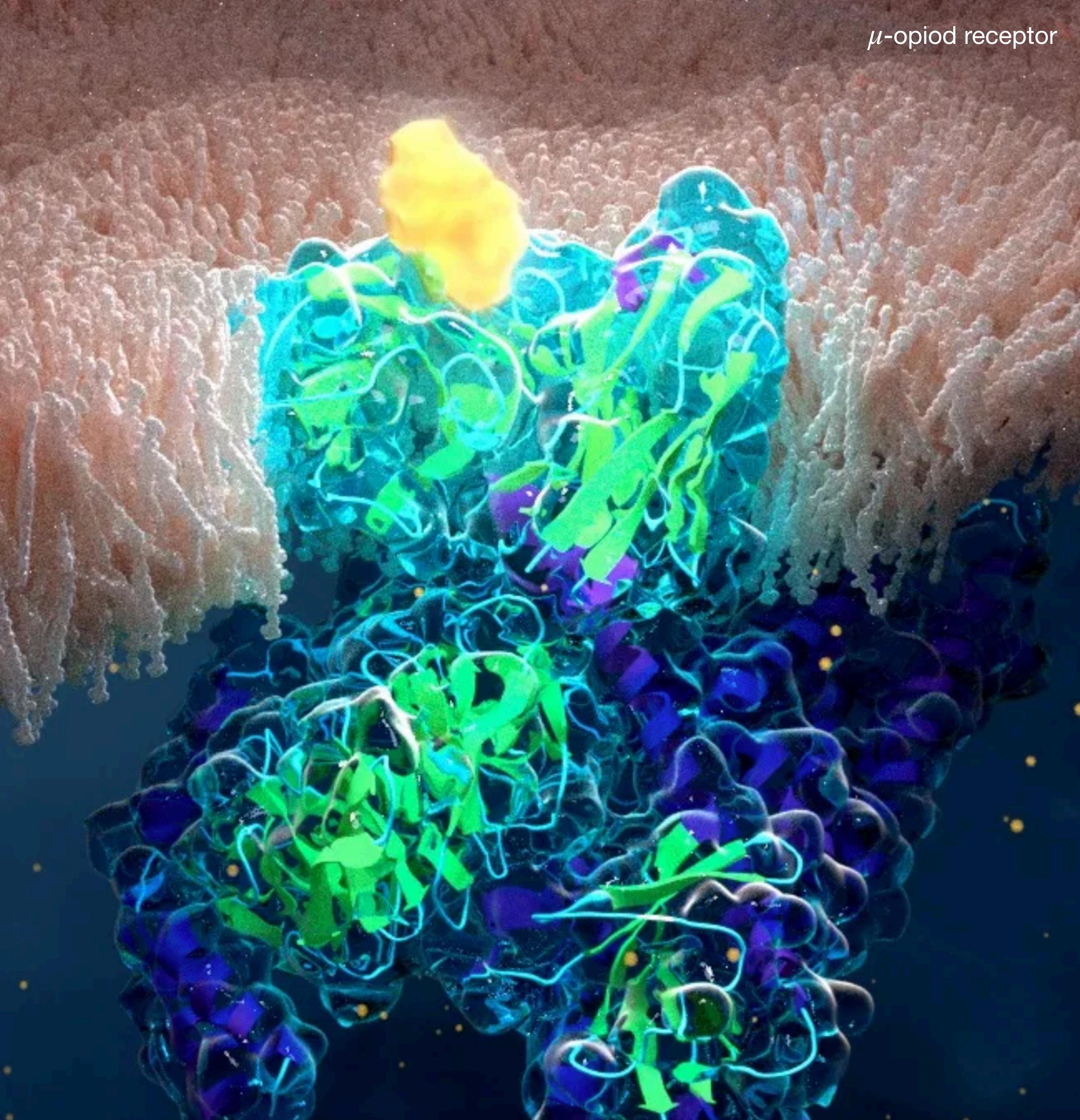
D
4-transmembrane-region
ligand-gated ion channel
~ 20% of psychotropic drugs



E
6-transmembrane-region
voltage-gated ion channel
~ 10% of psychotropic drugs

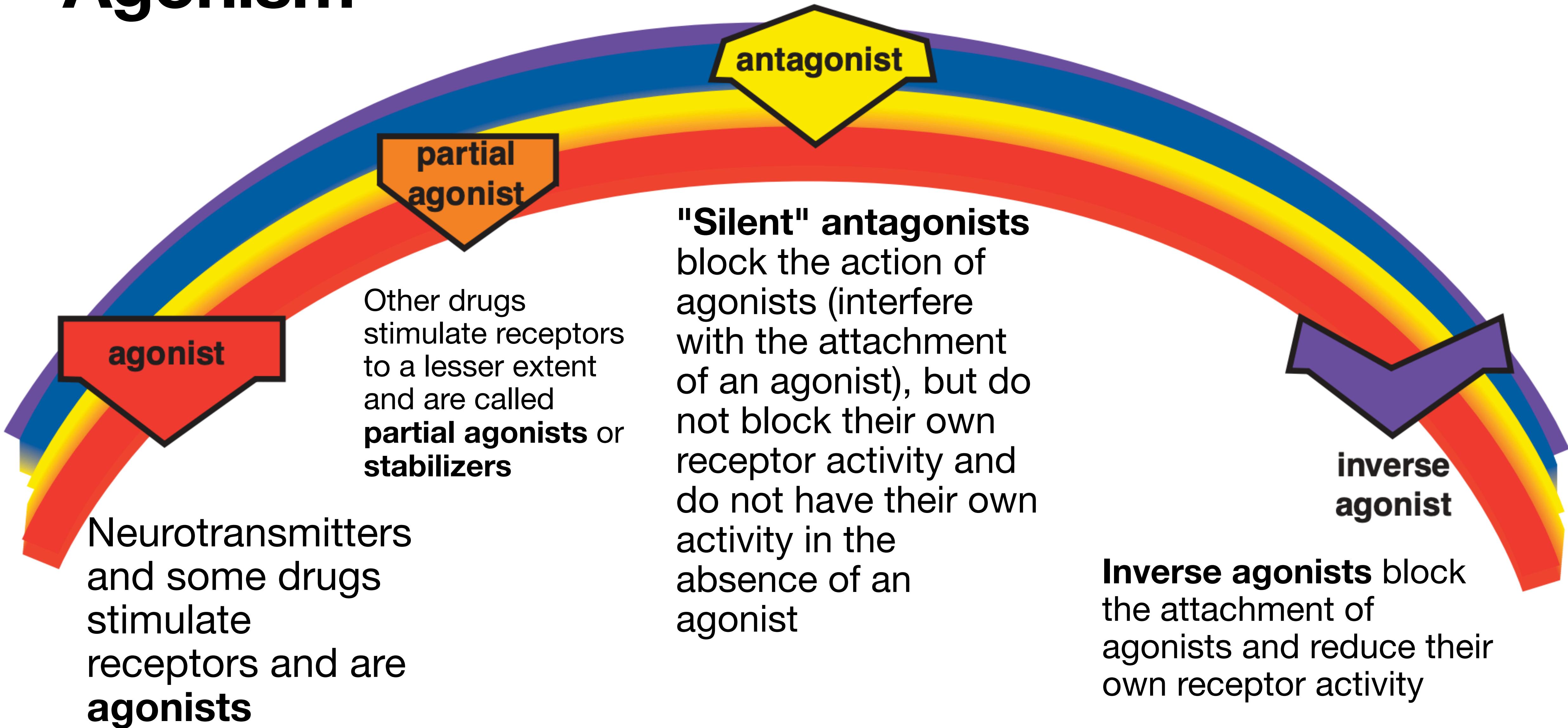
Membrane receptor

- The membrane receptor is a protein complex
- Consists of transmembrane domains
- Complexes of transmembrane domains form ligand binding sites
- There are endogenous and exogenous receptor ligands
- The attached ligand can cause reversible or irreversible changes in the receptor conformation
- Receptors have their own activity
- Can be blocked by inverse agonists (blockers)
- Are subject to allosteric modifications (reversible or irreversible)
- Can break, internalize, desensitize
- Receptors interface with: ion channel (ionotropic); **G protein (metabotropic)**; enzyme (enzyme-coupled)

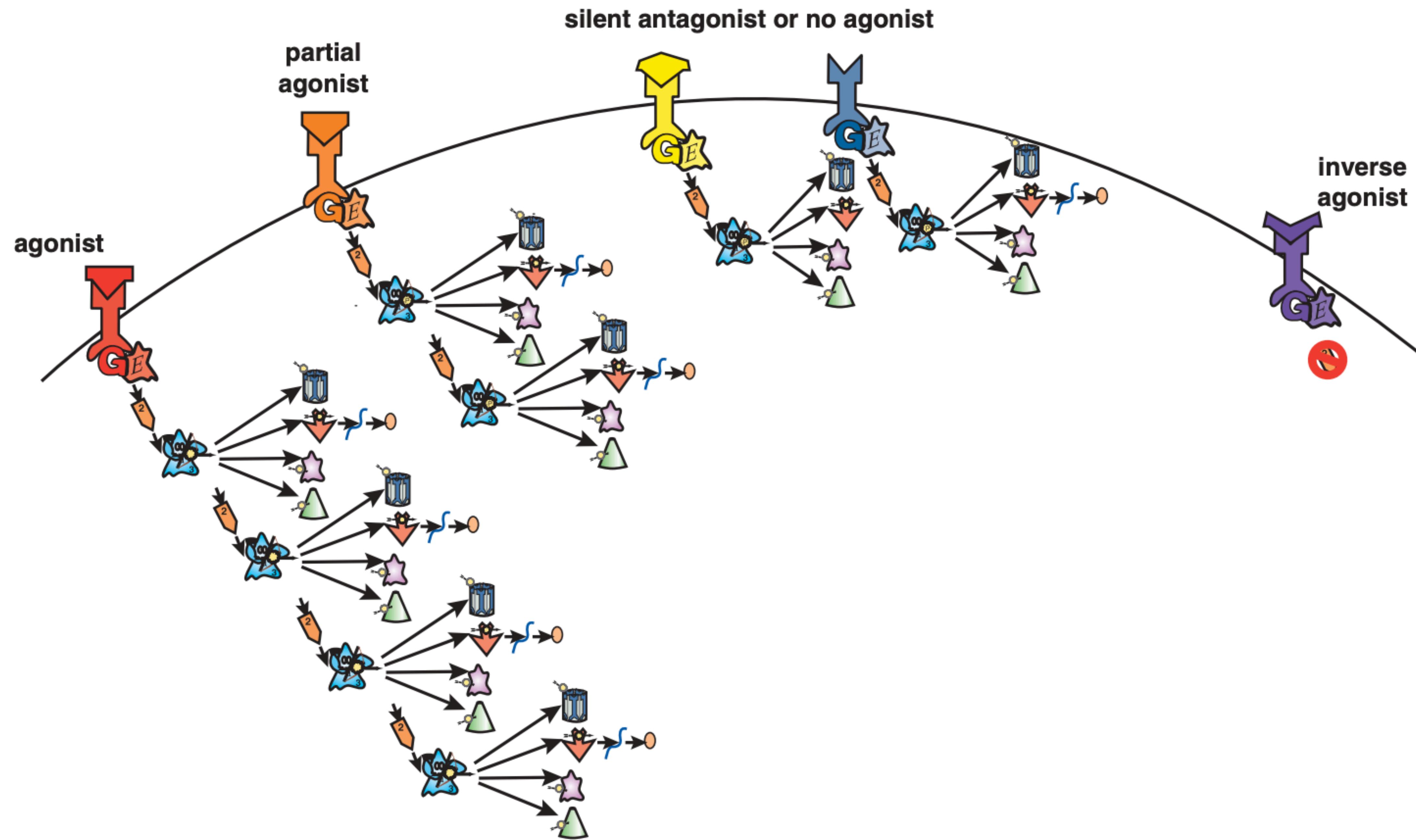


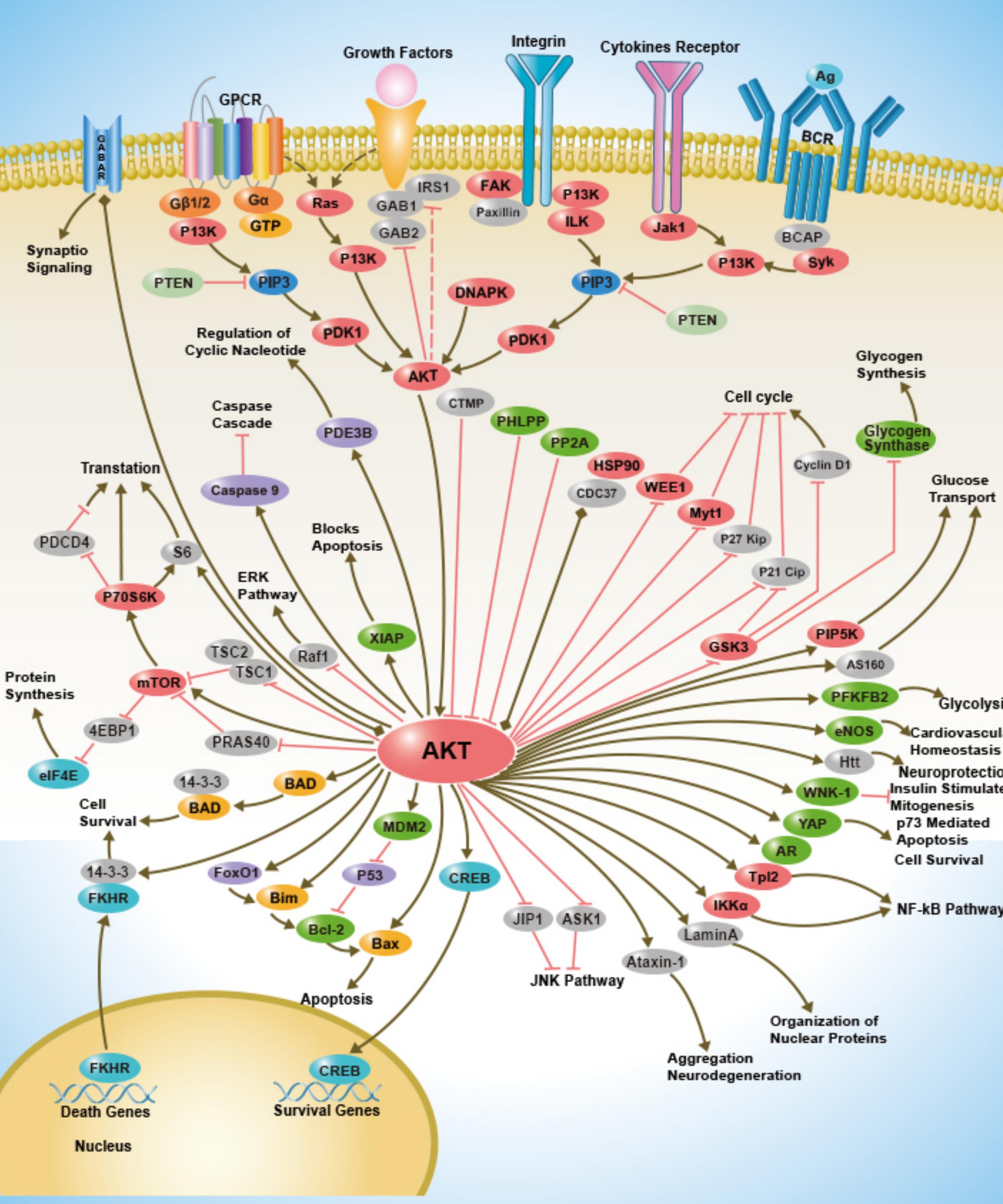
Agonism

The Agonist Spectrum



Agonist Spectrum





Signaling pathway

- Set of sequential reactions
- The probability of interruption at any stage of execution
- Possibility to loop the reaction cycle
- Providing a fast and delayed response
 - milliseconds to activate ion channels
 - minutes to activate secondary and tertiary intermediaries
 - hours or days to change gene expression
- Amplification or reduction of a signal

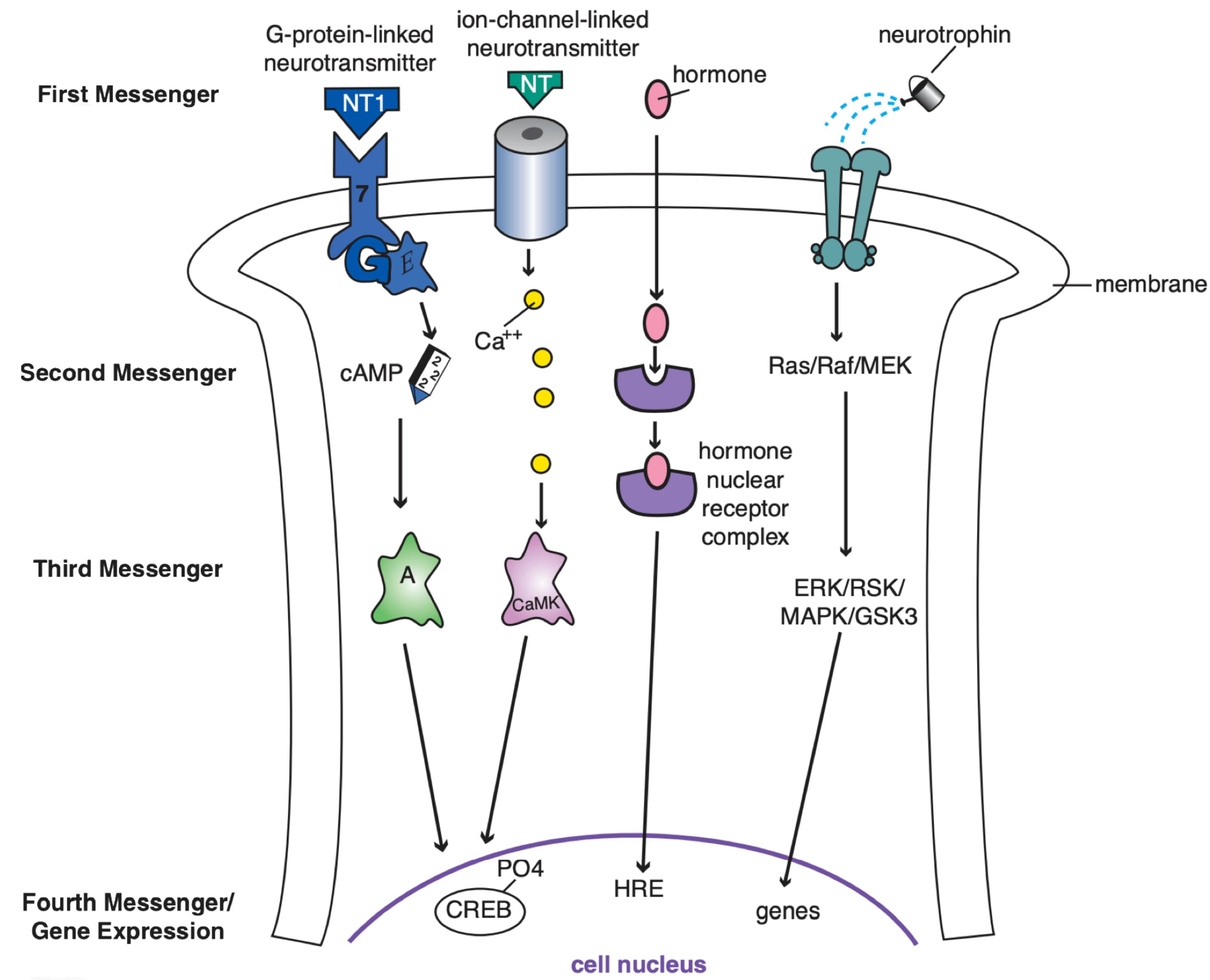
Various cascades

Each cascade begins with a primary messenger that binds to its specific receptor

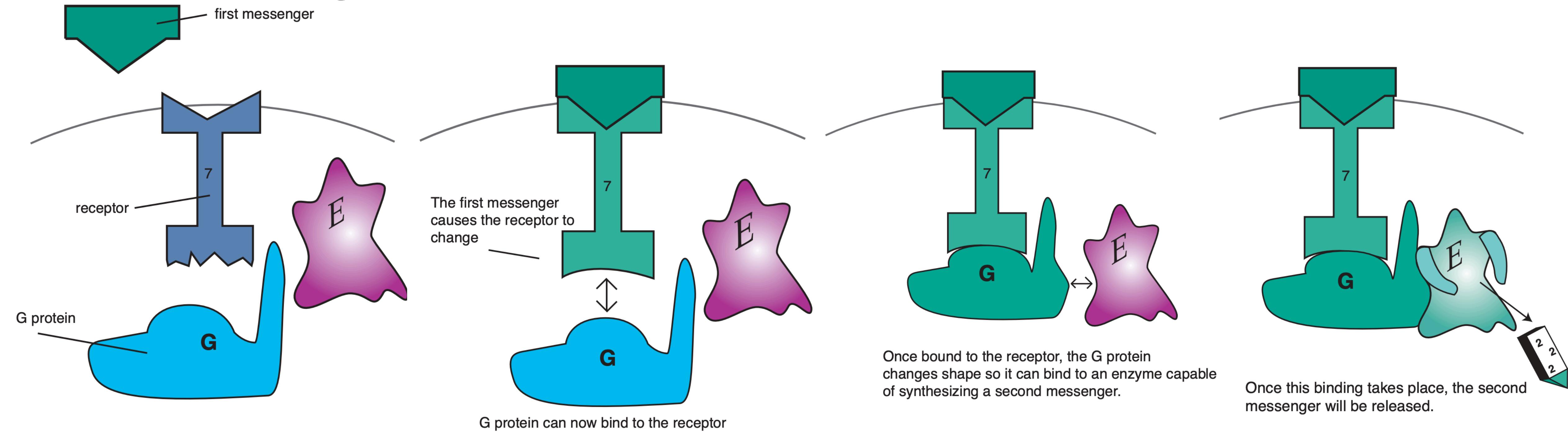
- Activation by NEUROMEDIATORS of ion channels and receptors associated with the G-protein leads to the activation of genes in the nucleus by phosphorylation of the transcription factor CREB (*)
- Certain HORMONES (estrogen and other steroids) can enter the neuron and bind to the nuclear receptor. The associated complex enters the nucleus and interacts with the HRE (**), causing the activation of certain genes.
- The system associated with NEUROTROPHINS activates a number of kinase enzymes to trigger the expression of genes that can control synaptogenesis and neuron survival

(*) CREB (cAMP response element-binding protein) binds to certain DNA sequences called CRE (cAMP response elements), regulating (enhancing or weakening) the transcription of the corresponding genes.

(**) HRE (hormon response elements) is a short DNA sequence inside a gene promoter capable of binding a specific hormone receptor into a complex and regulating transcription. A gene can have many different response elements, allowing complex control of the level and rate of transcription



Enabling GPCR



Binding model:

1. The ligand binds to the GPCR on the cell membrane. As a result of ligand binding, the conformation of the entire receptor changes and the receptor-coupled intracellular G-protein is activated.
2. In an inactive state, the G-protein is bound to the GDP molecule. After activation, GDP is replaced by GTP, and the G-protein is divided into two parts (into α - and $\beta\gamma$ -subunits).
3. The active part of the G-protein (α -subunit) attaches to the enzyme adenylate cyclase and activates it. Adenylate cyclase catalyzes the conversion of ATP to cAMP.
4. cAMP is a **secondary messenger** of this signaling chain in the cell. Then cAMP spreads throughout the cell and binds to cAMP-dependent protein kinase A, and 4 cAMP molecules bind to one protein kinase molecule.

*GDP - guanosine diphosphate, GTP - guanosine triphosphate, ATP - adenosine triphosphate, cAMP - cyclic adenosine monophosphate.

[de]Phosphorylation

Phosphorylation is one of the most common types of post-translational protein modification.

Phosphorylation - the process of transfer of the phosphoric acid residue from the phosphorylating donor agent to the substrate, usually catalyzed by enzymes.



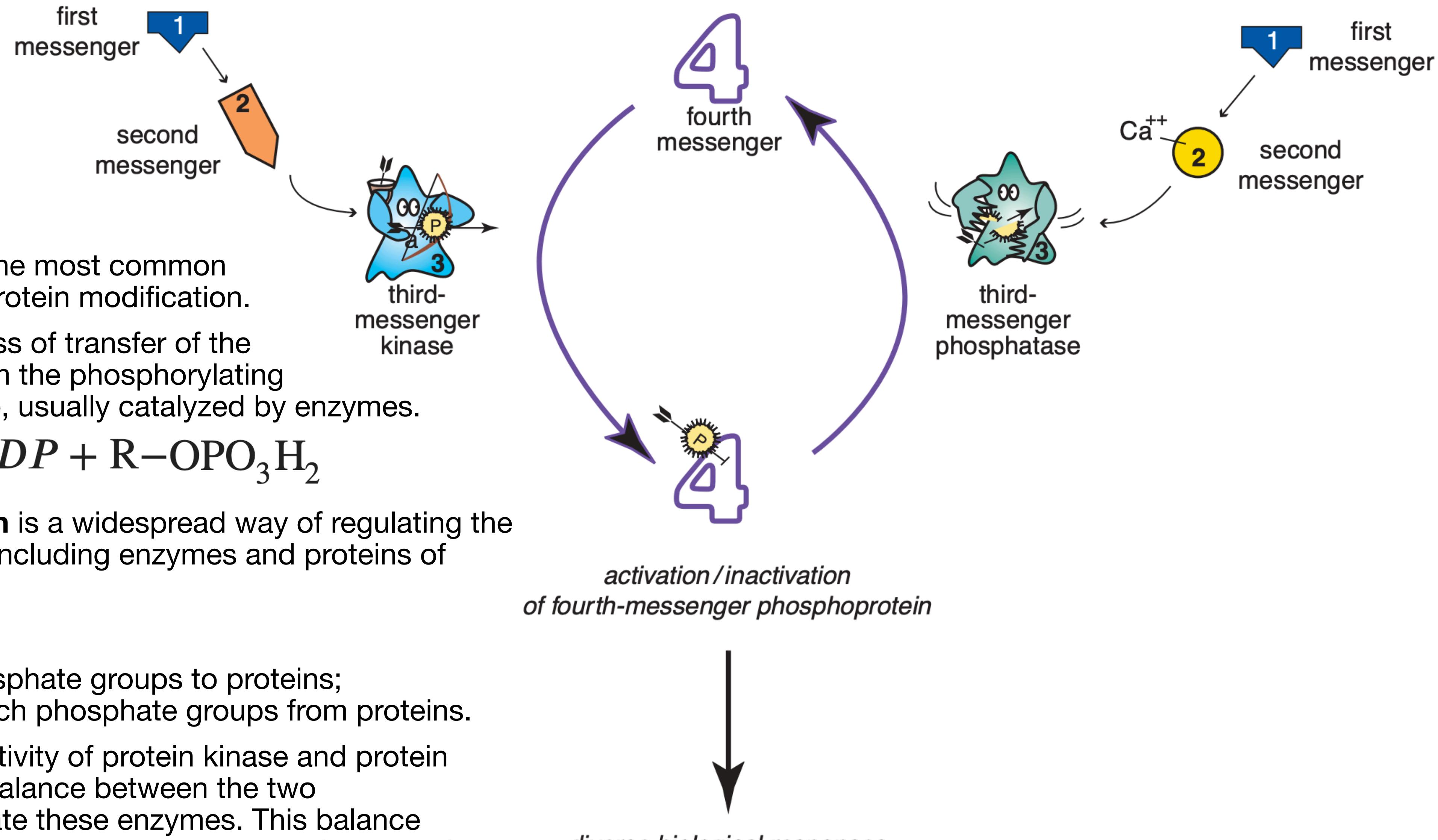
Reversible phosphorylation is a widespread way of regulating the activity of key cell proteins, including enzymes and proteins of signaling pathways.

Tertiary messengers:

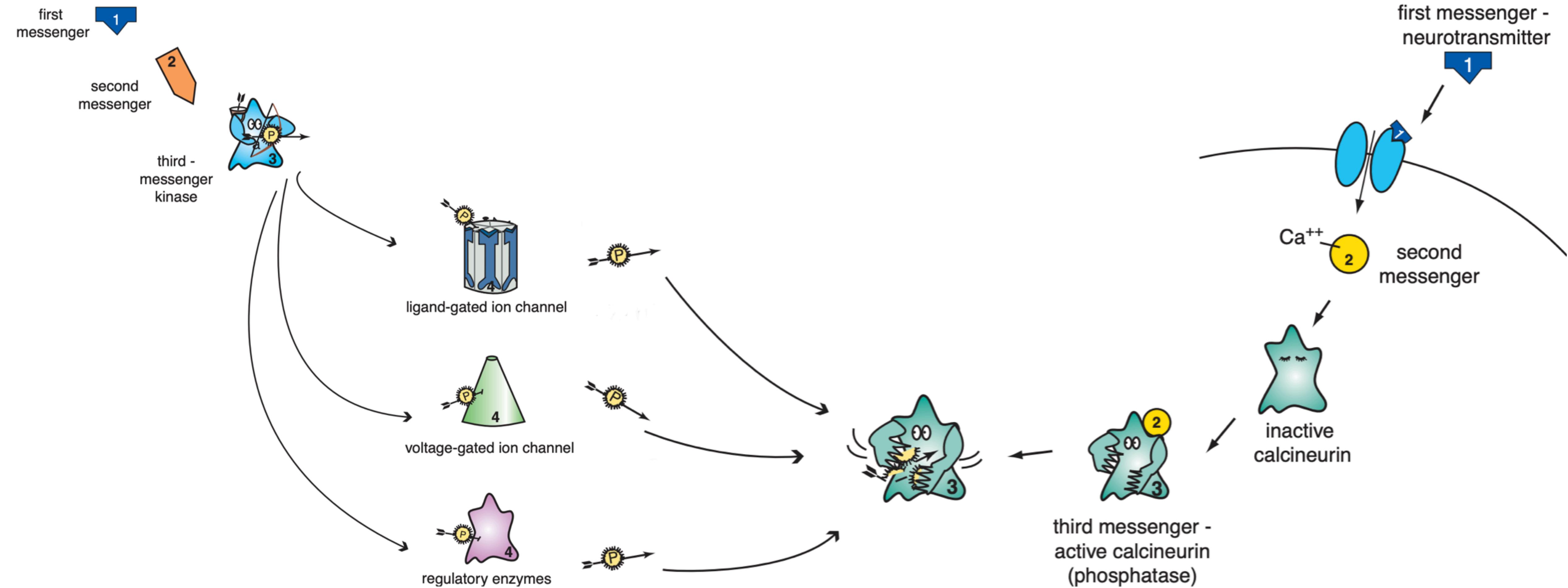
protein kinases - attach phosphate groups to proteins;

protein phosphatases - detach phosphate groups from proteins.

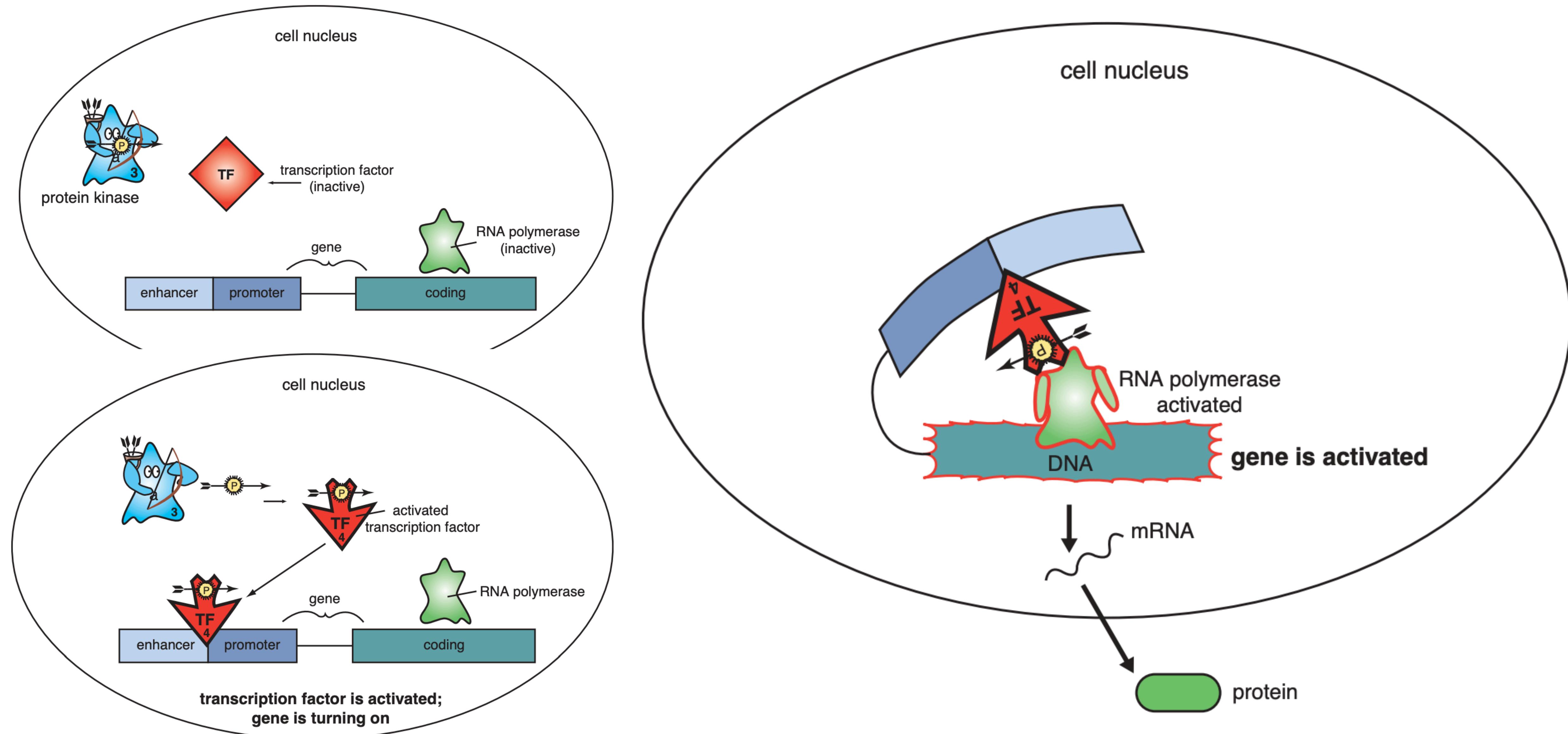
The balance between the activity of protein kinase and protein phosphatase indicates the balance between the two neurotransmitters that activate these enzymes. This balance determines the degree of chemical activity that manifests itself in various biological responses (gene expression, synaptogenesis).



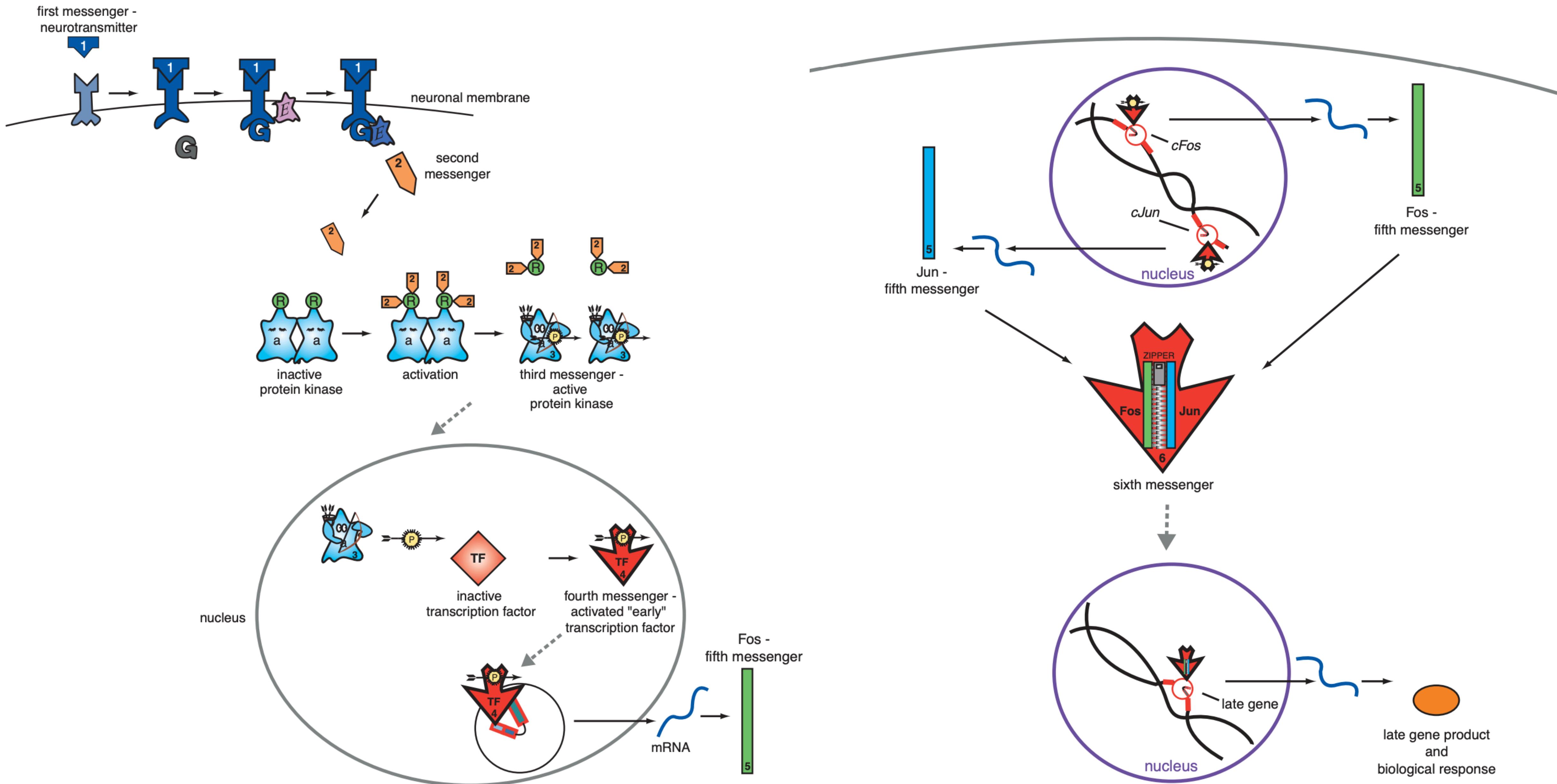
[de]Phosphorylation



Gene activation



Gene activation how to

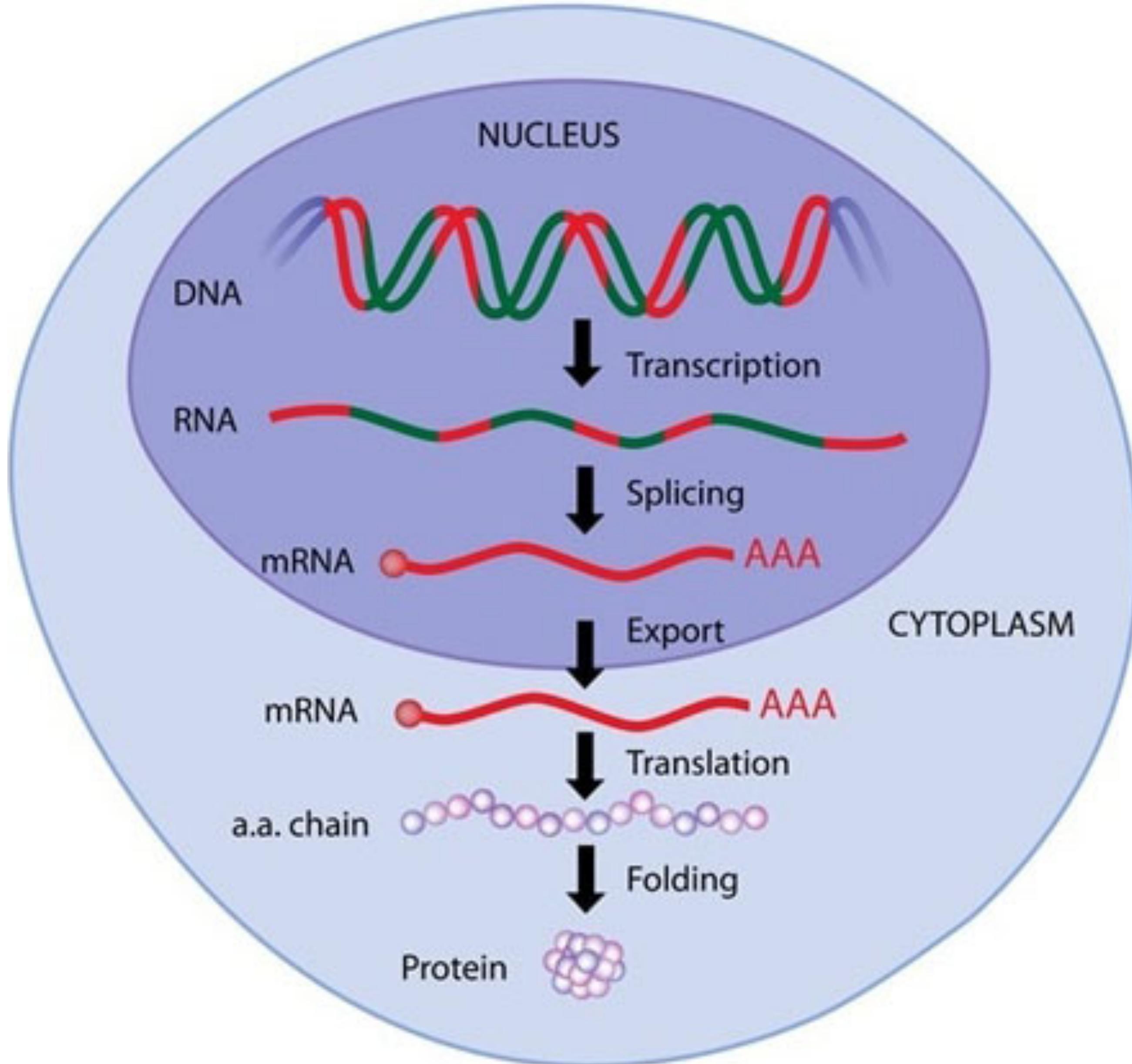


Gene expression

Gene expression is the process by which information from a DNA nucleotide sequence (gene) is converted into a functional product: RNA or protein.

Stages:

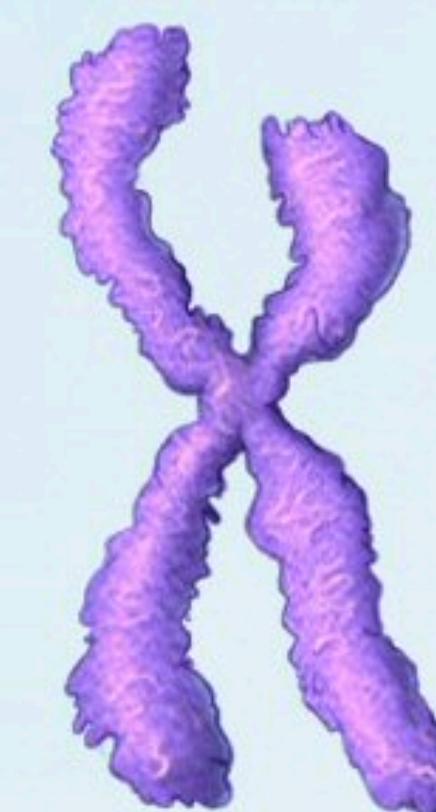
- DNA transcription - the process of RNA synthesis taking place in all living cells using DNA as a template
- RNA splicing - the process of cutting out certain nucleotide sequences from RNA molecules and joining sequences that are stored in a "mature" molecule during RNA processing
- RNA translation - a ribosome process of protein synthesis from amino acids
- Post-translational modifications - chemical modification of a protein after its synthesis on the ribosome. PM increase the variety of proteins in the cell.



EPIGENETIC MECHANISMS

are affected by these factors and processes:

- **Development** (in utero, childhood)
- **Environmental chemicals**
- **Drugs/Pharmaceuticals**
- **Aging**
- **Diet**



CHROMOSOME

DNA

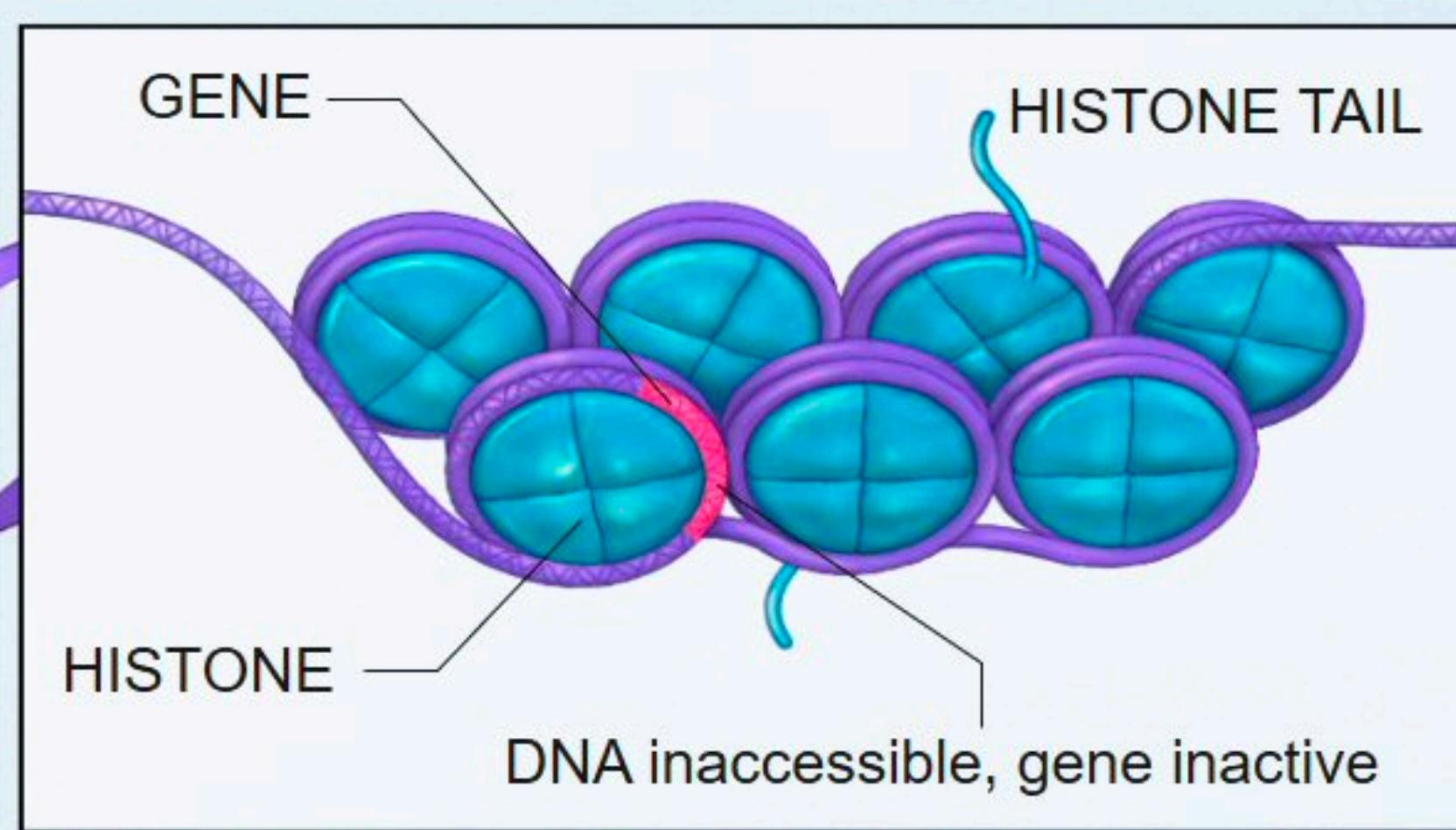
METHYL GROUP

CHROMATIN

DNA methylation

Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.



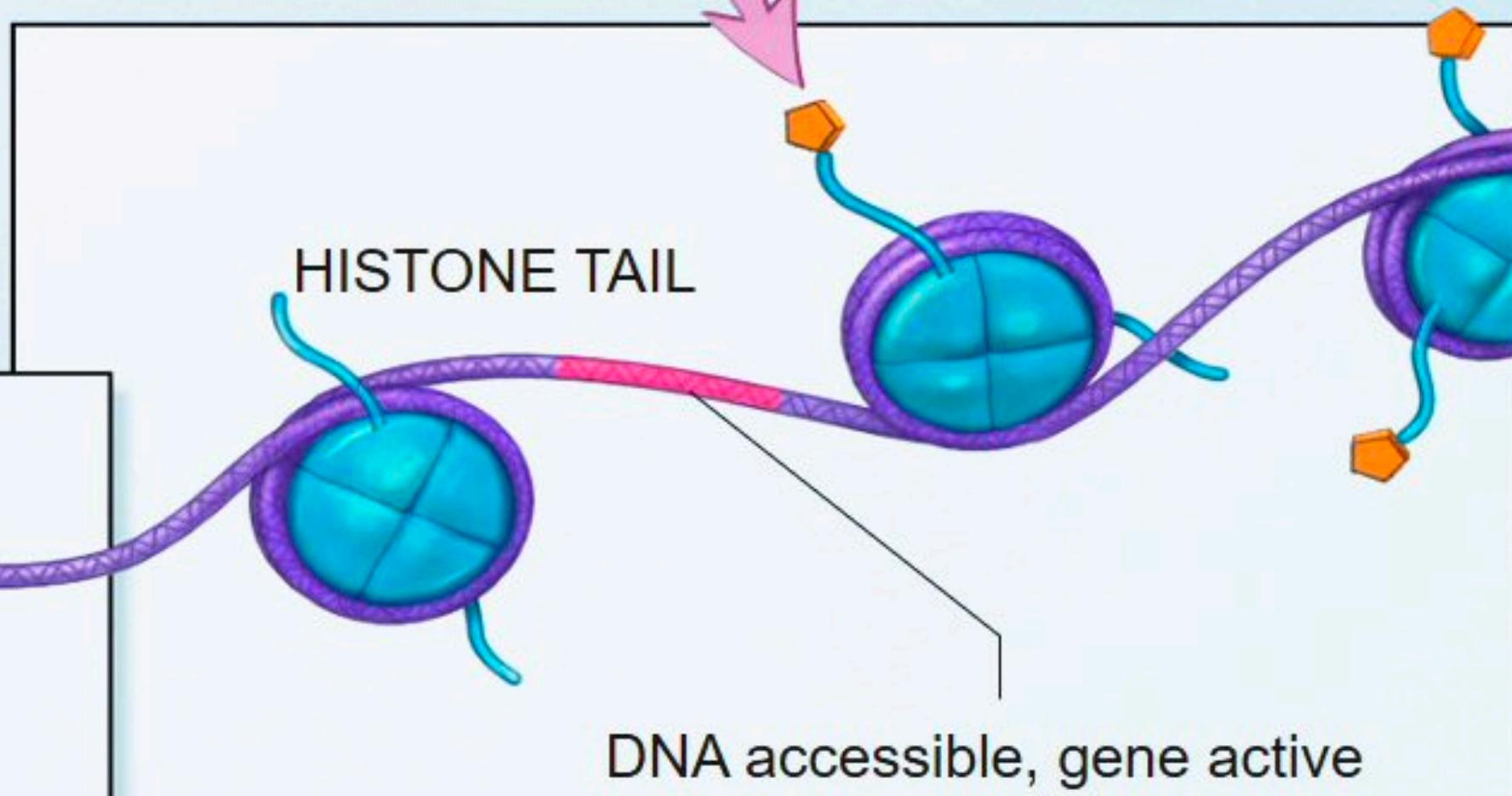
Histone modification

The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

HEALTH ENDPOINTS

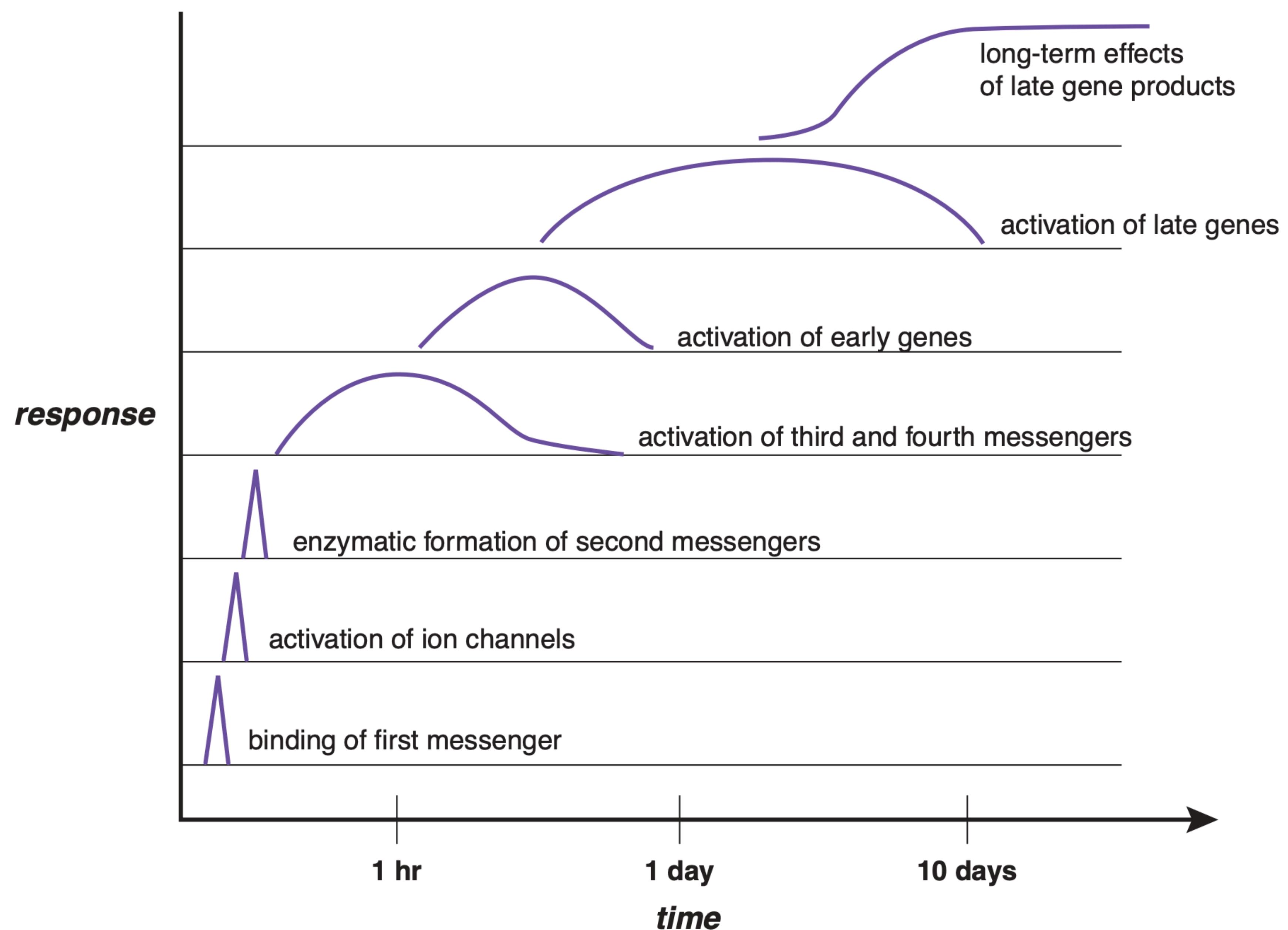
- **Cancer**
- **Autoimmune disease**
- **Mental disorders**
- **Diabetes**

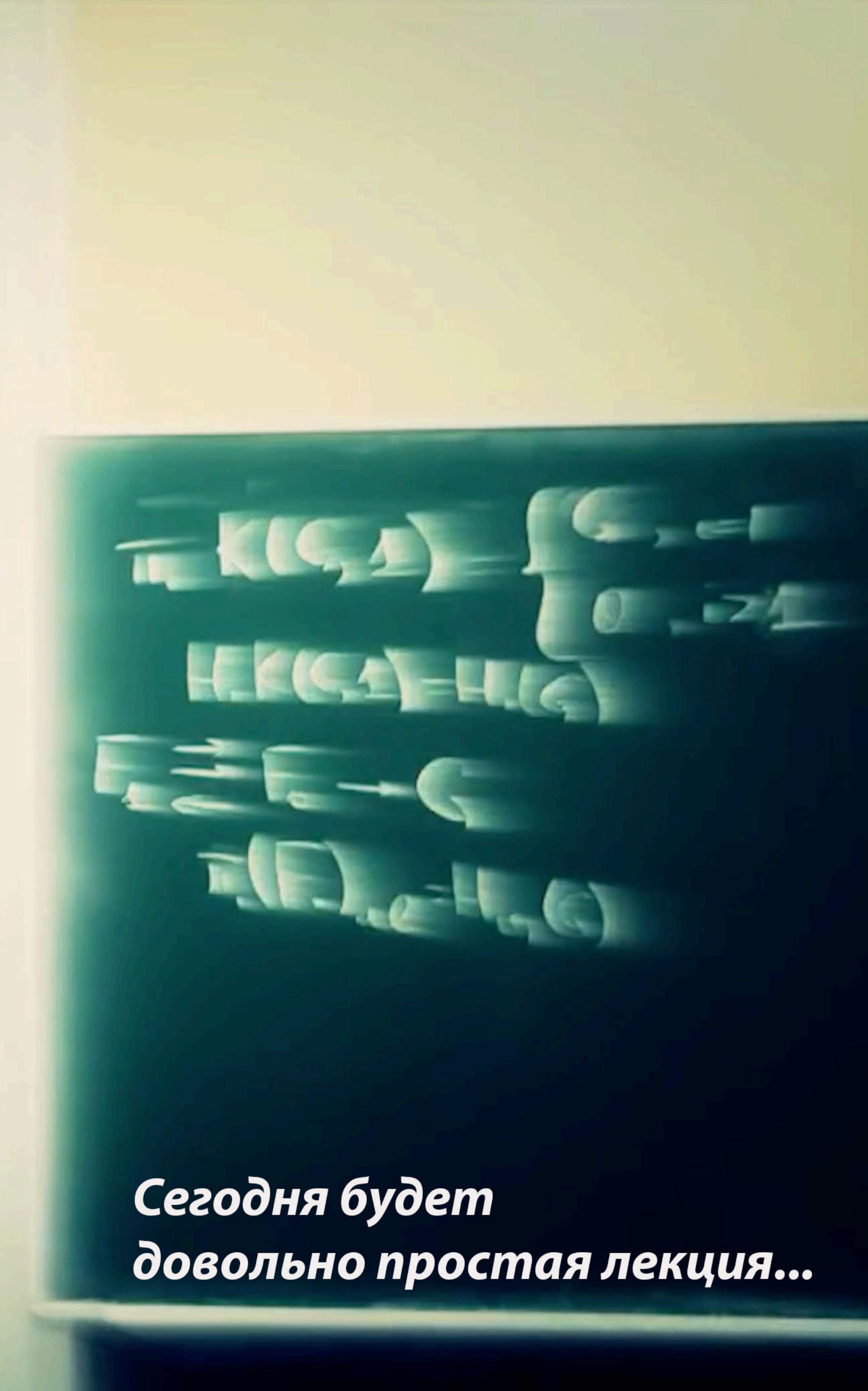
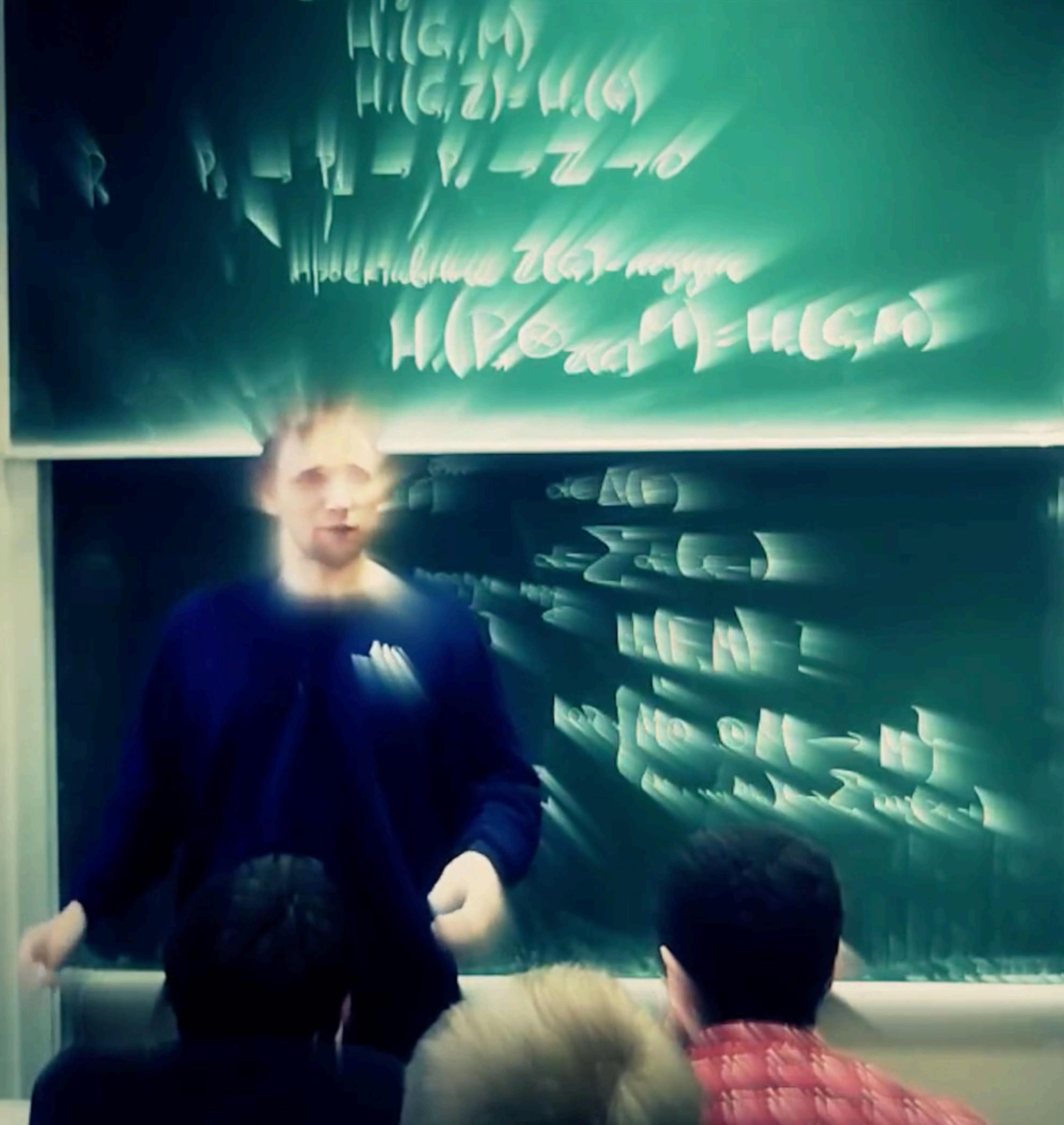
EPIGENETIC FACTOR



Time Course of Signal Transduction

Time scale





Memory as experience

- The vast majority of animal species are able to adapt to the circumstances of life
- The body's reaction to circumstances when they reappear is often different than when it first meets them.
- The ability of a living system to learn determines the individuality of the animal's behavior, due to personal experience (MEMORY)
- One of the forms of memory is immune memory, due to which information about a foreign antigen that has once entered it is retained in the body for a long time
- A more complex form of memory is neurological memory associated with the functioning of the central nervous system and determining various forms of animal behavior.
- In the process of learning, remembering or adapting to any effect (molecular and / or cytological) changes occur in the cells of the central nervous system, which can persist for a certain period of time
- In the process of learning and developing skills, changes occur in the structure of neurons and synapses

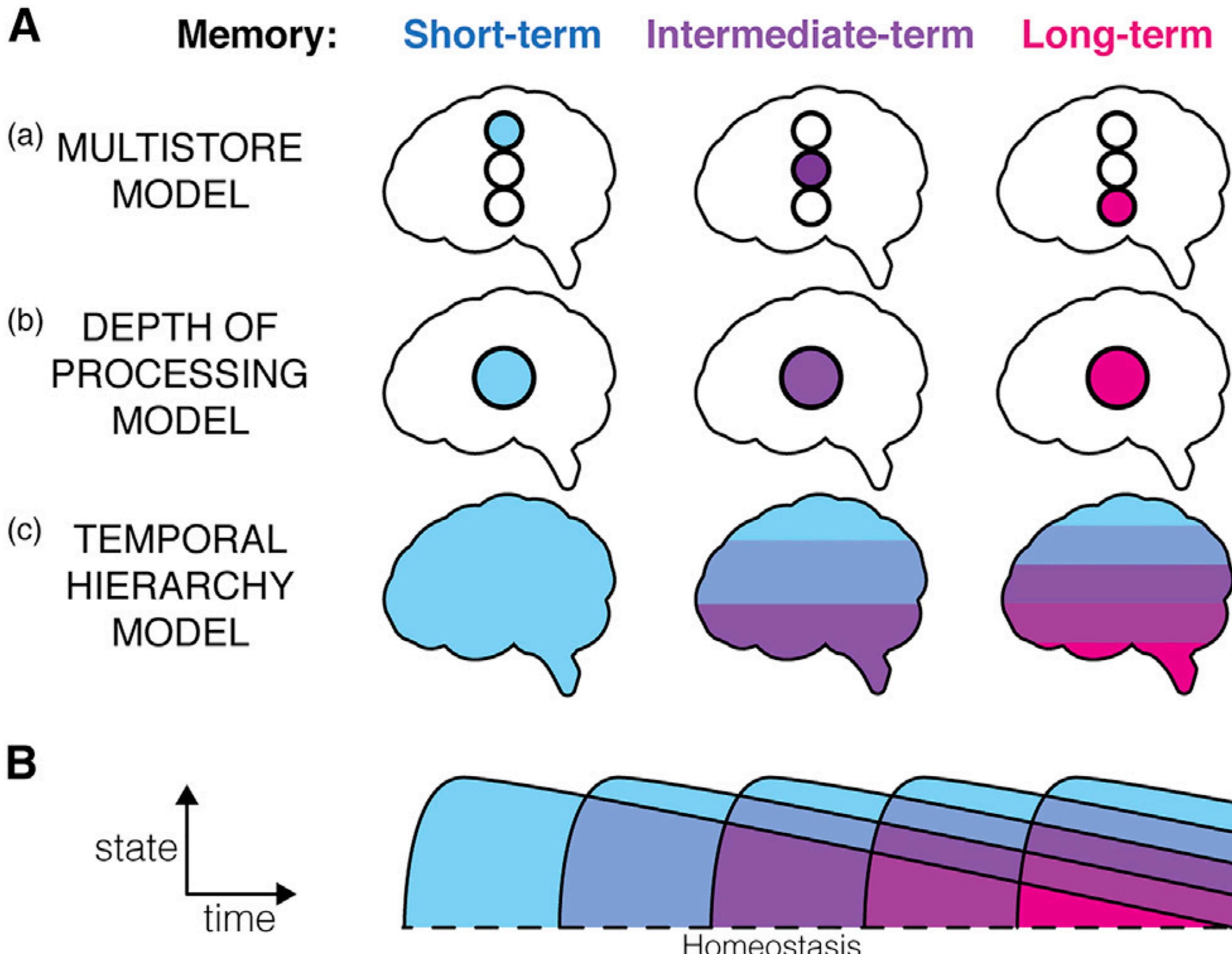


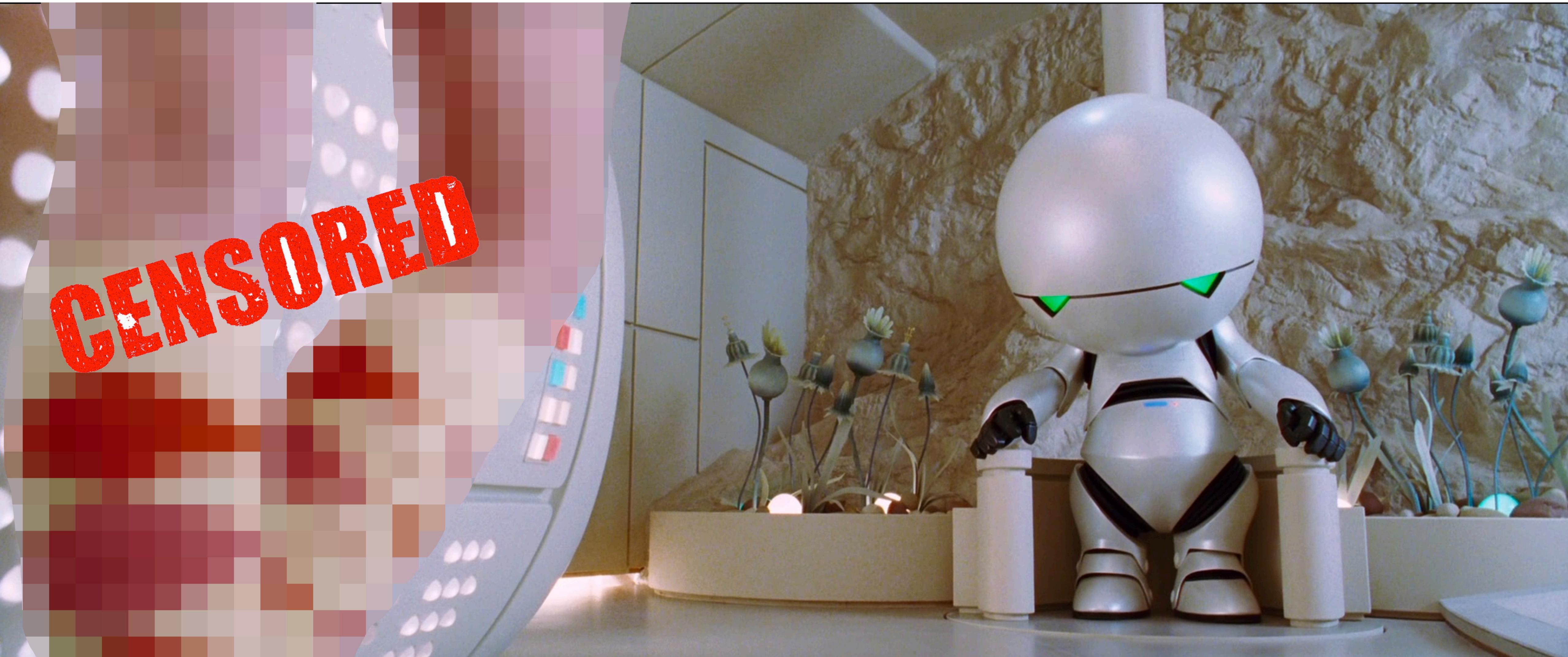
Frameworks for memory

(B) The experience can be seen as a series of time-limited changes in homeostasis.

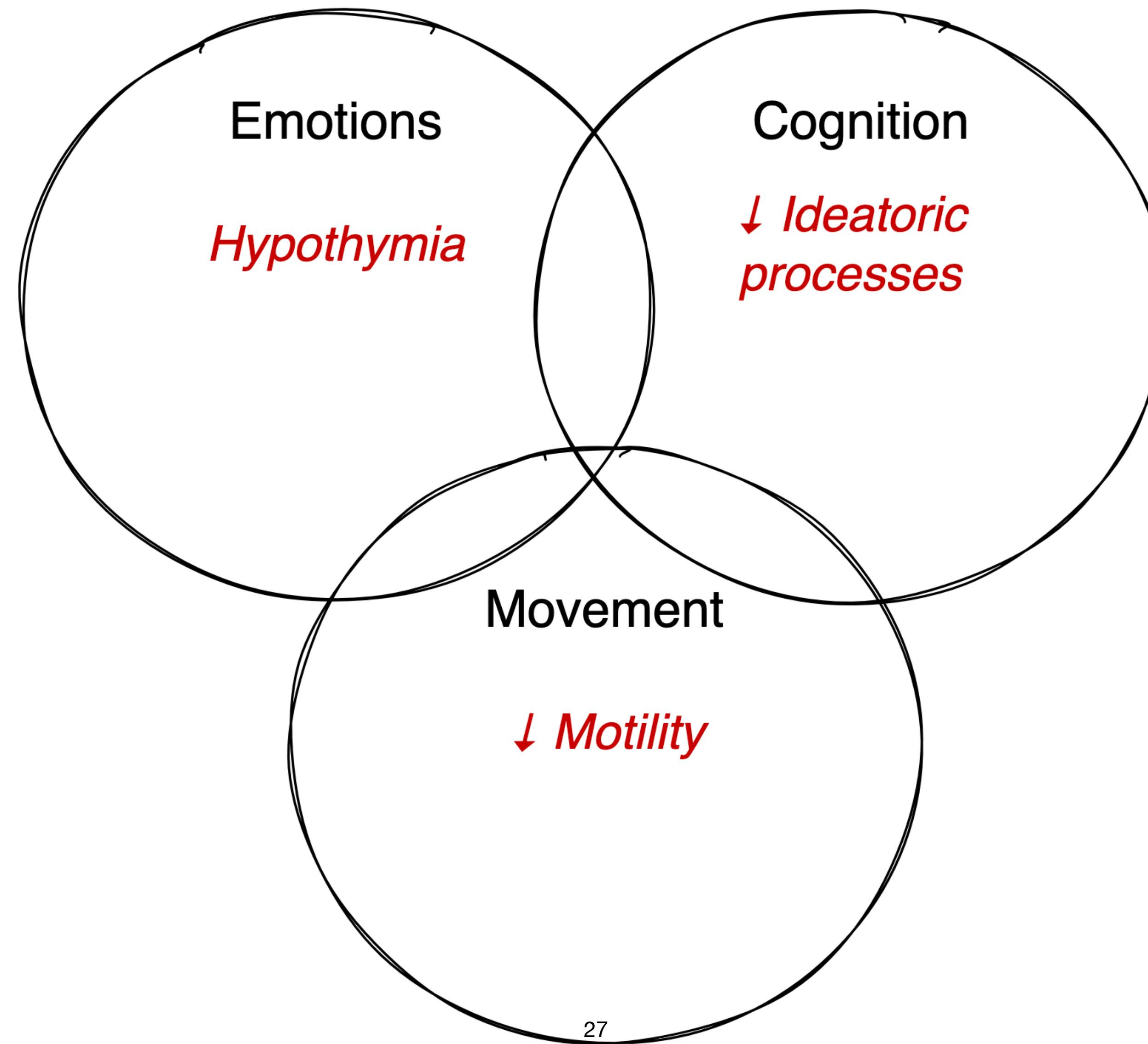
The temporal structure of experience, illustrated in different colors, defines the temporal structure of memory shown in (A).

For example, retrying attempts to learn simultaneously retain information from recent attempts as well as information from all combinations of previous attempts.





Depressive triad



Depression

Cause

Endogenous

Psychogenic

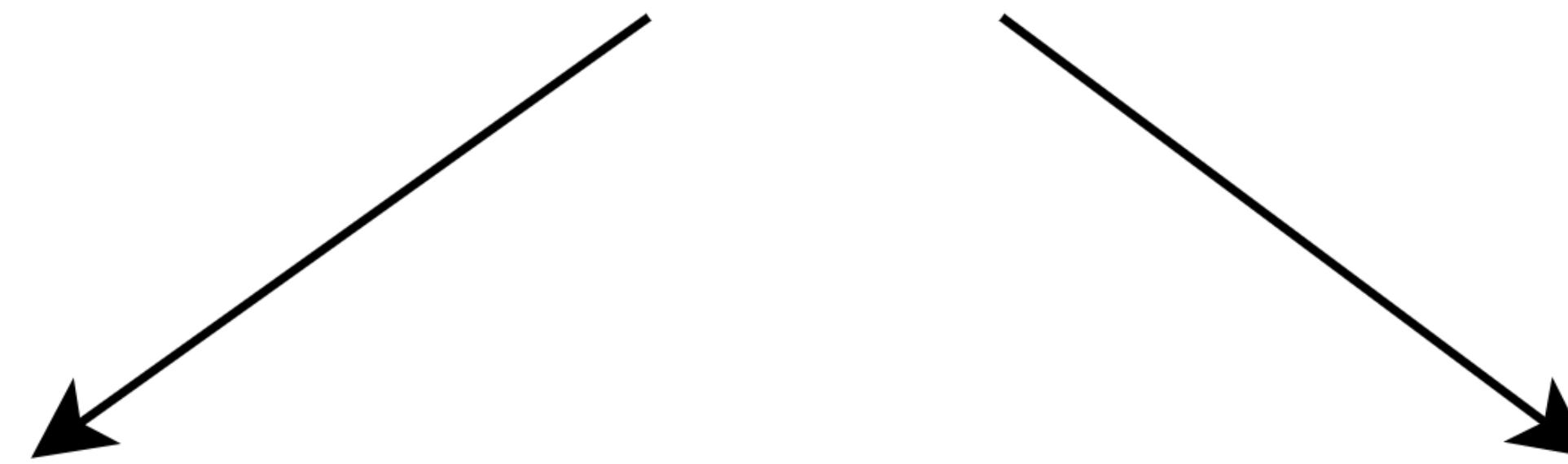
Somatogenic

Primary
symptoms

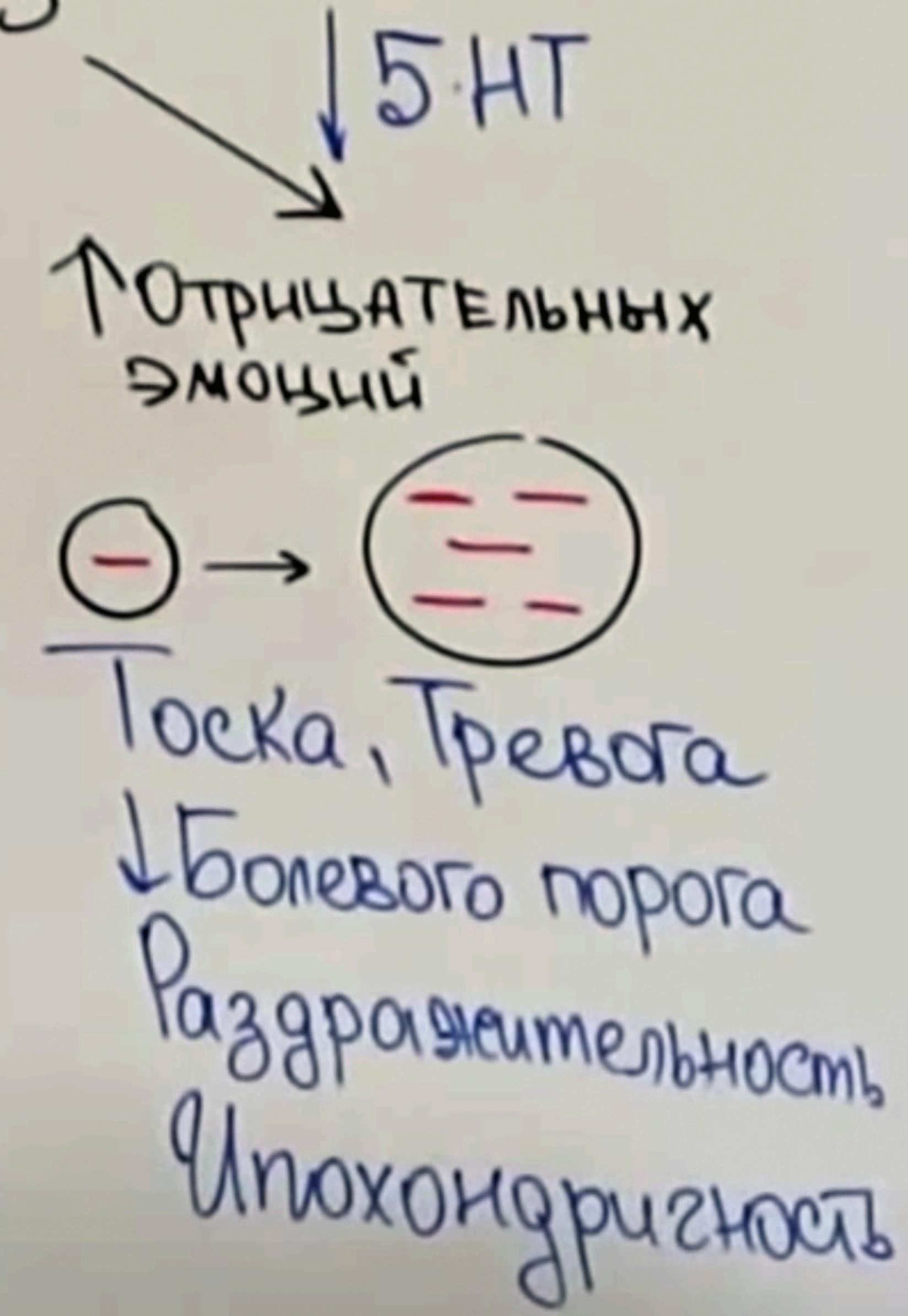
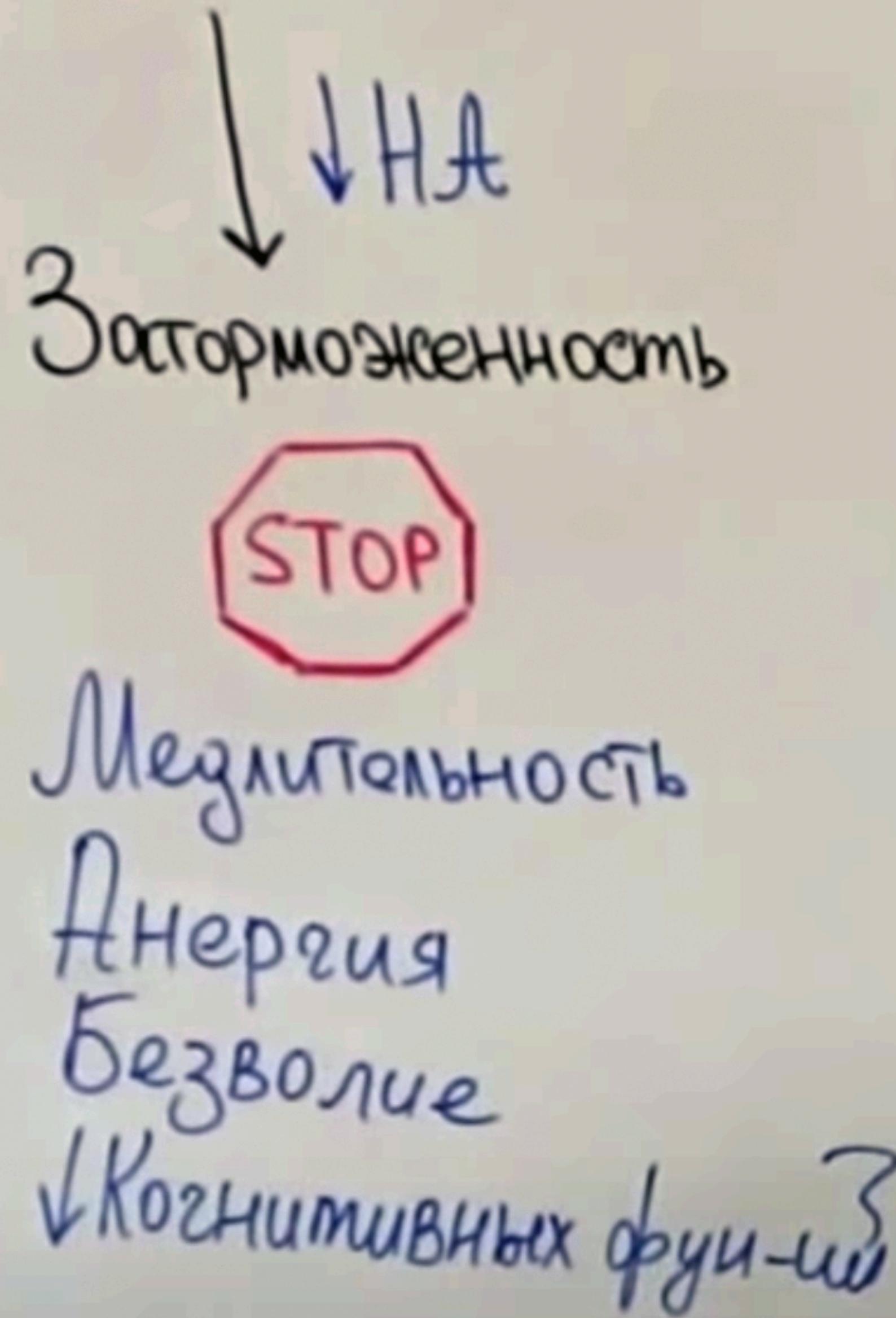
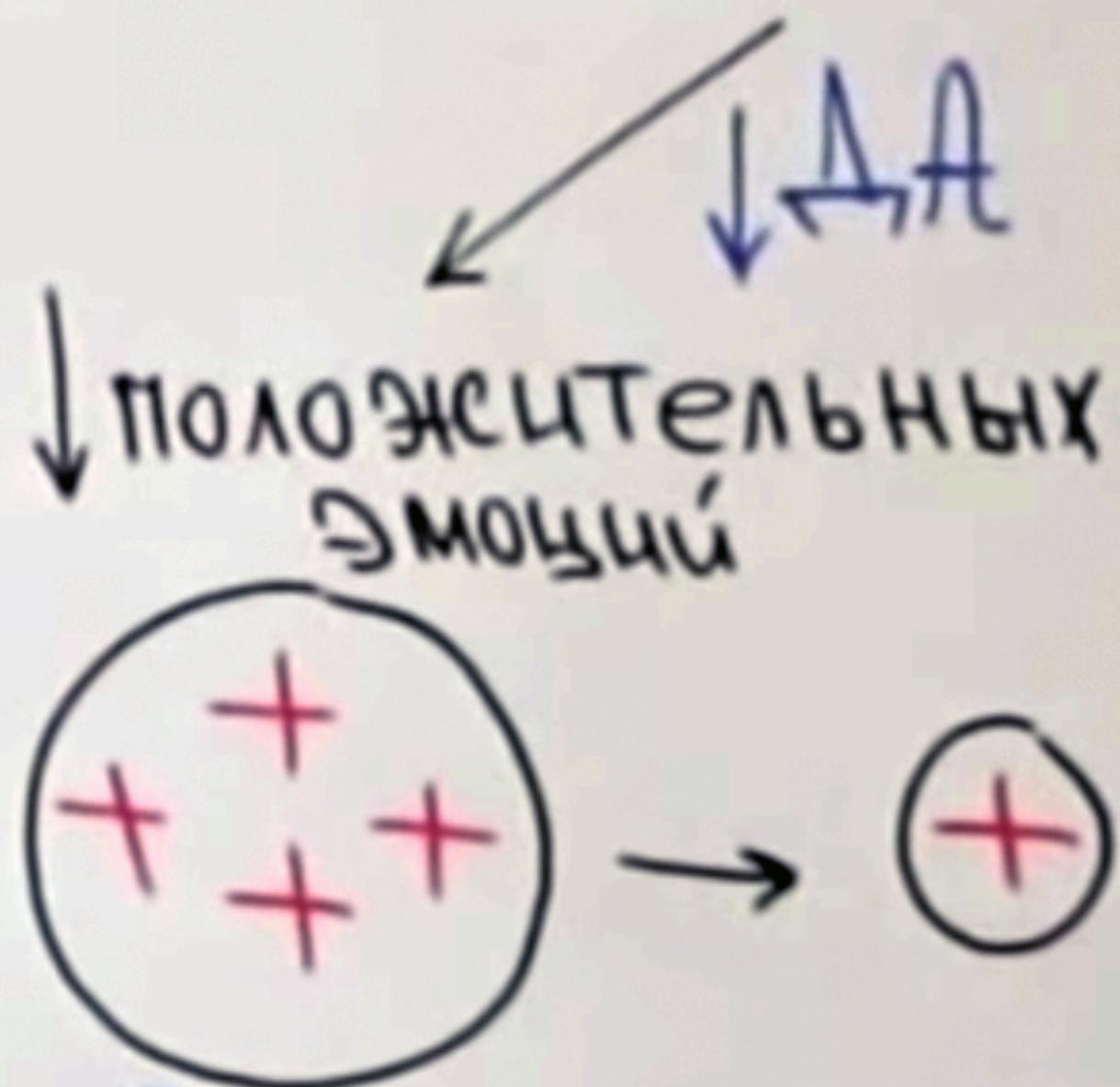
Melancholy

Anxiety

Anergia



Моноаминовая гипотеза



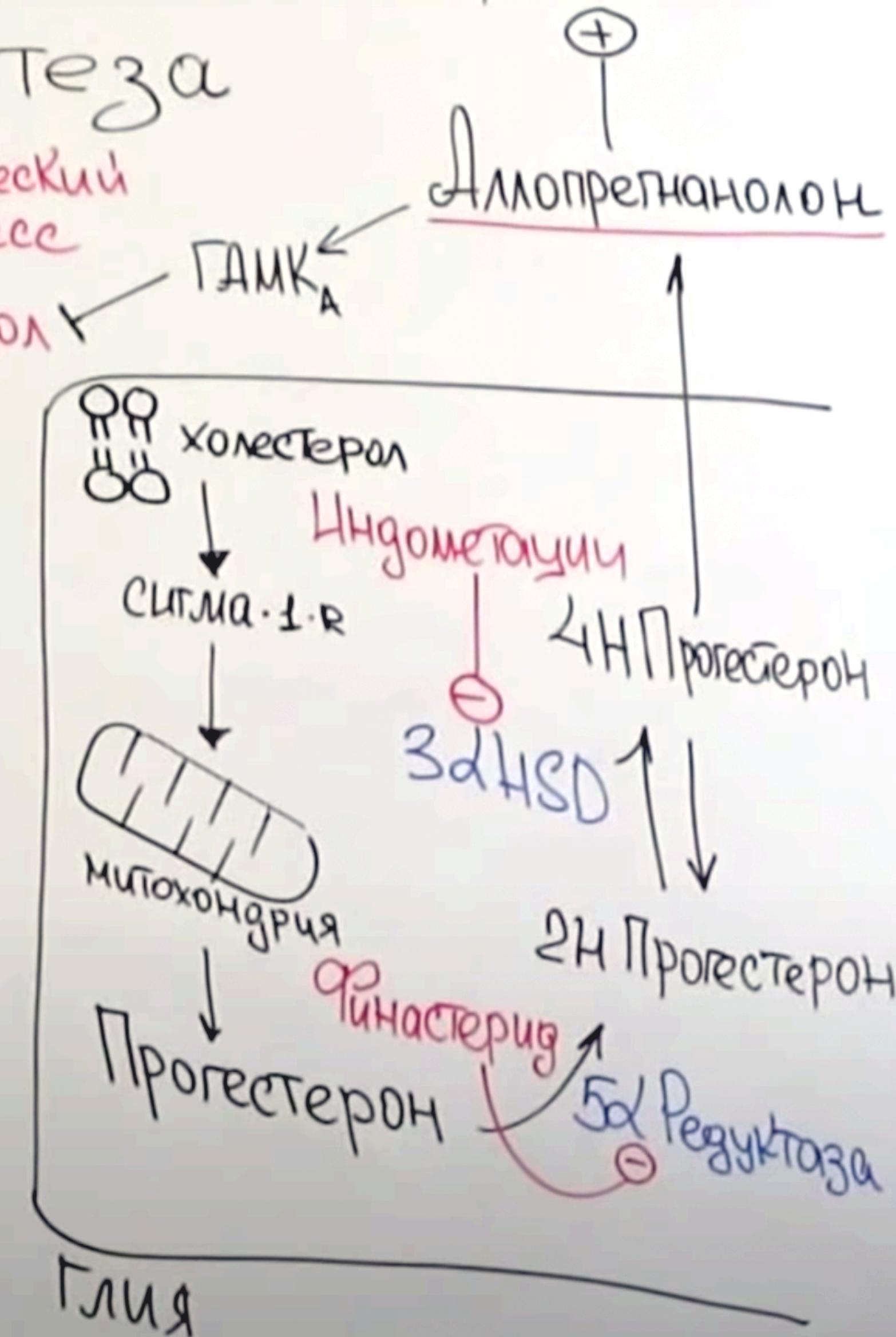
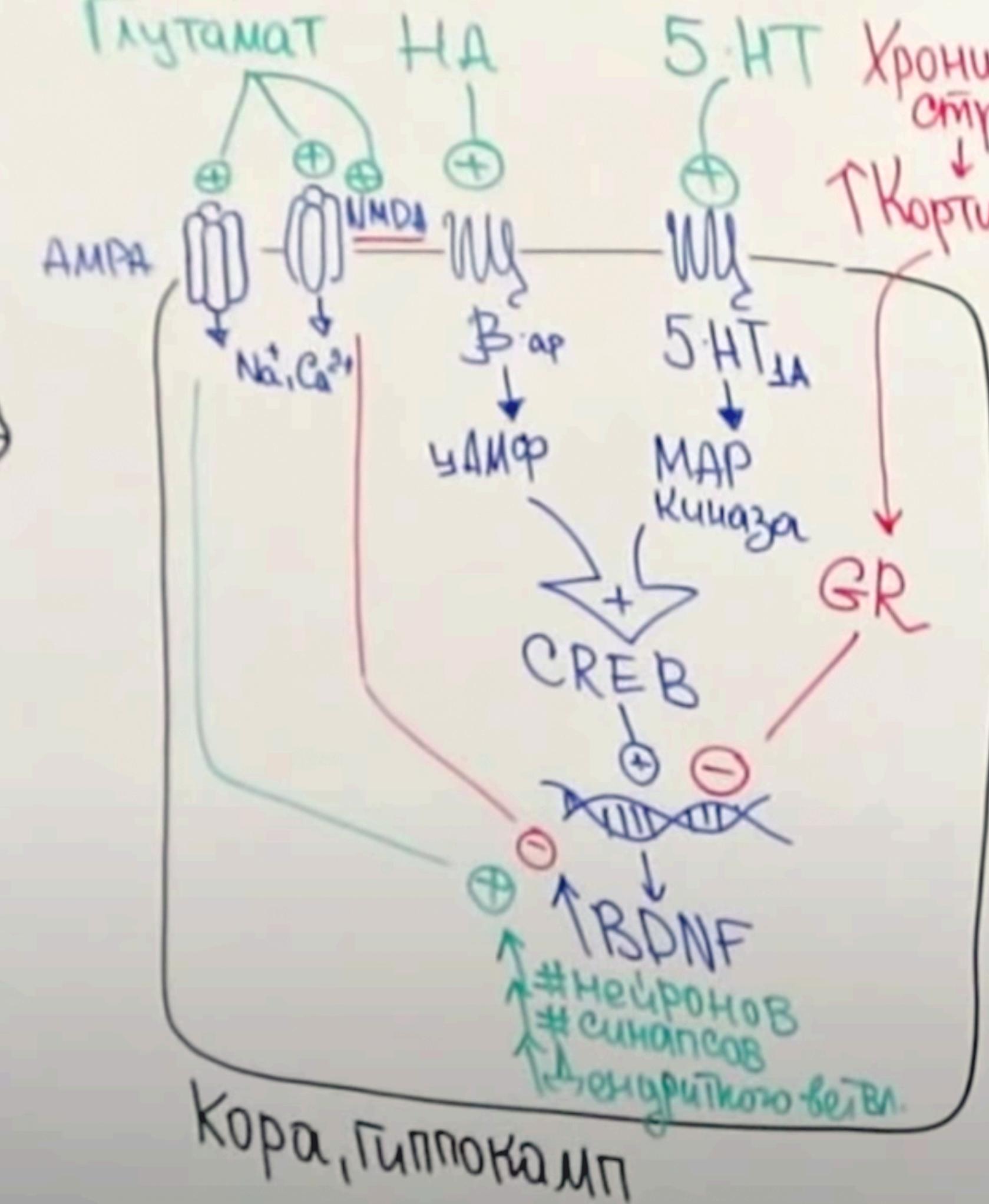
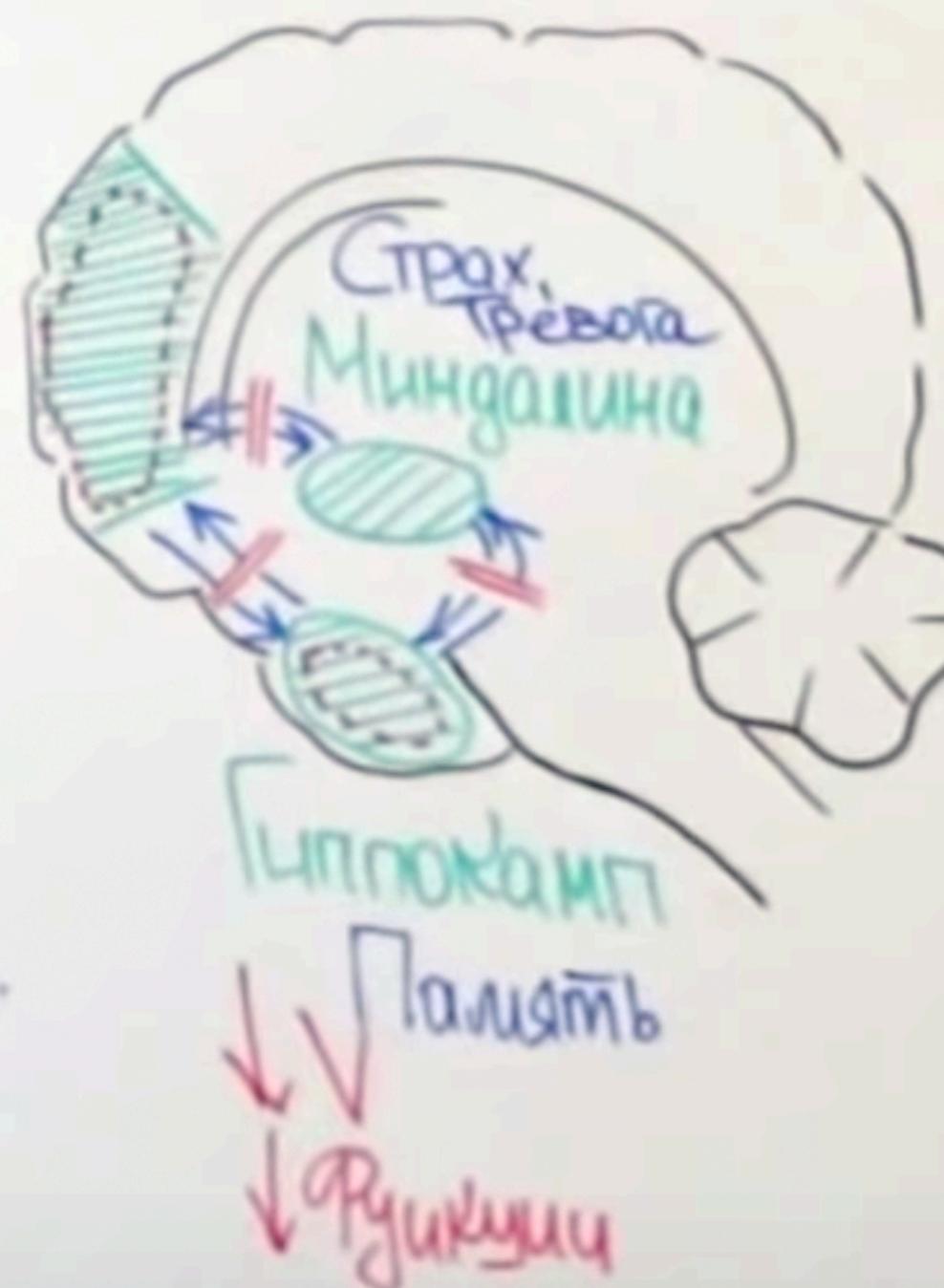
Нейропластичность

Нейротрофическая Гипотеза

$\downarrow V$
Рукичи

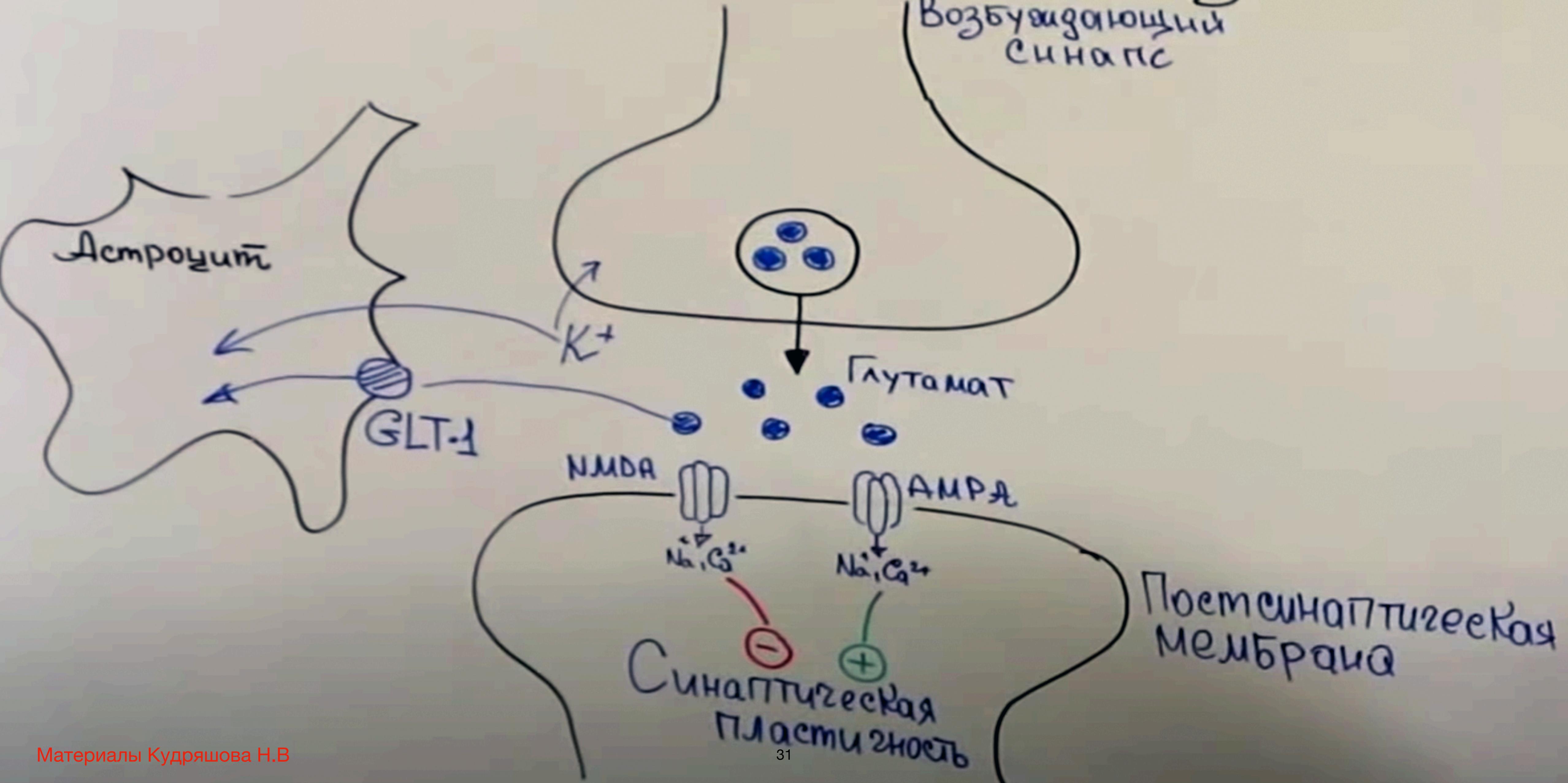
Фронтальная
Кора

1. Обработка информации
2. Регуляция функций внутр. органов

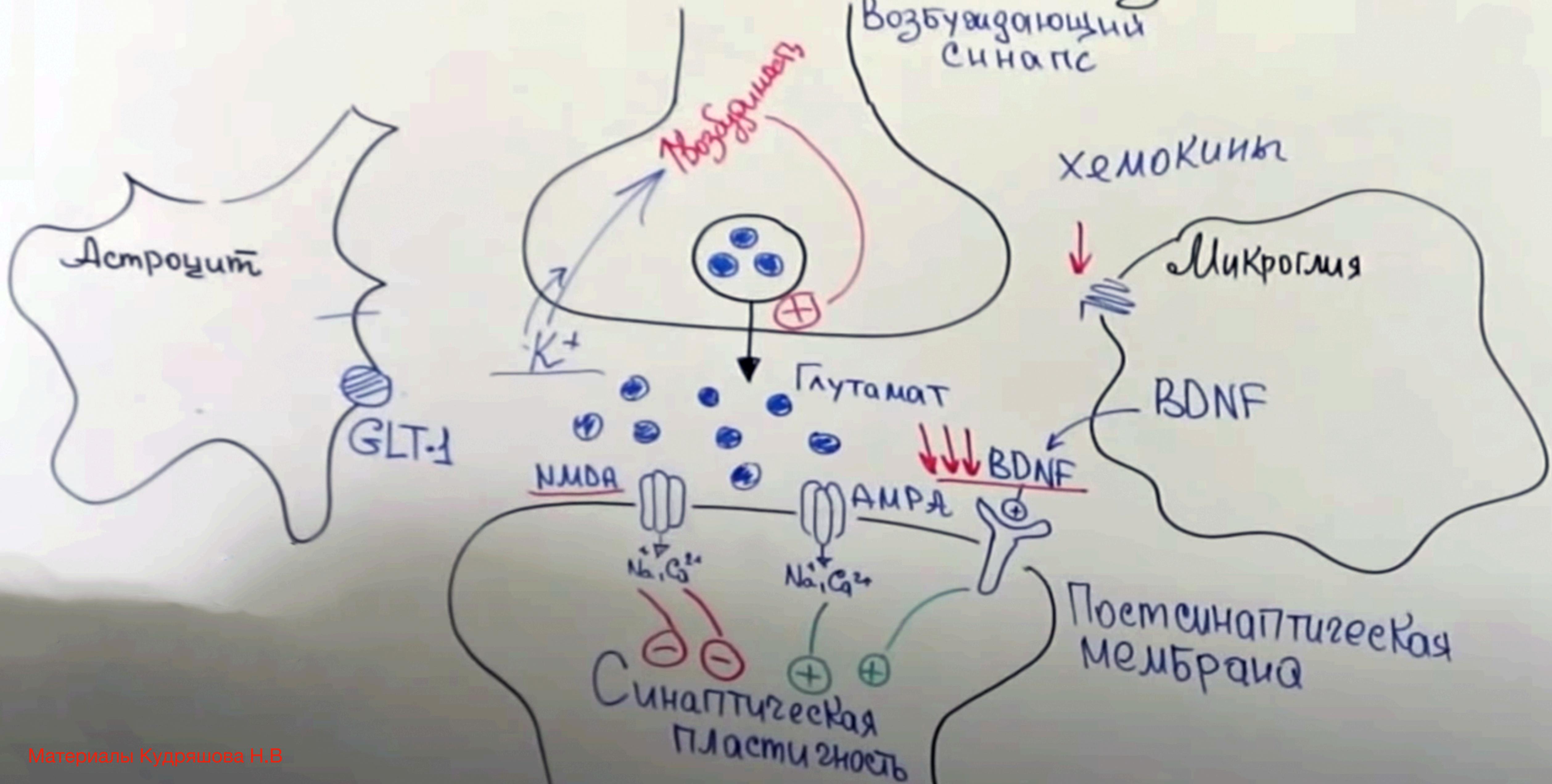


Глиальная гипотеза

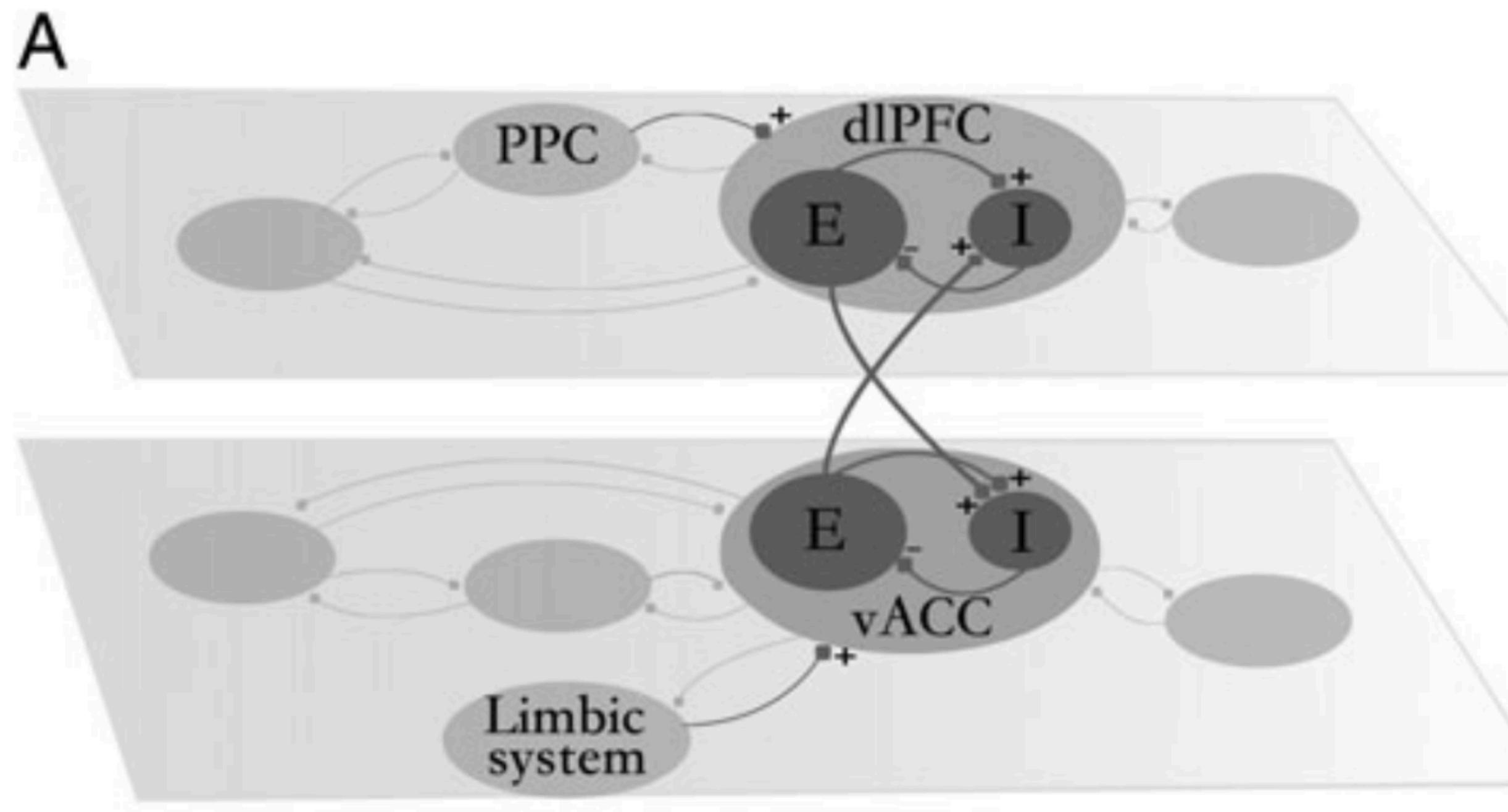
Возбуждающий синапс



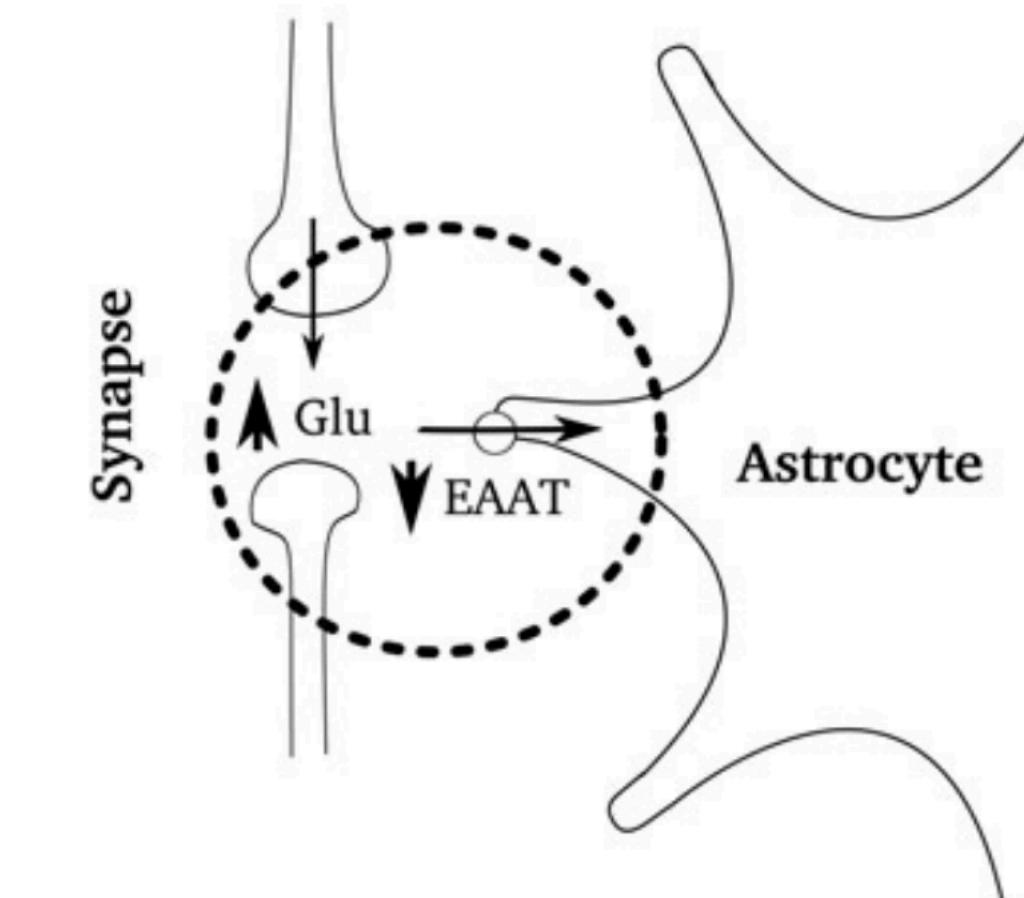
Глиальная Гипотеза



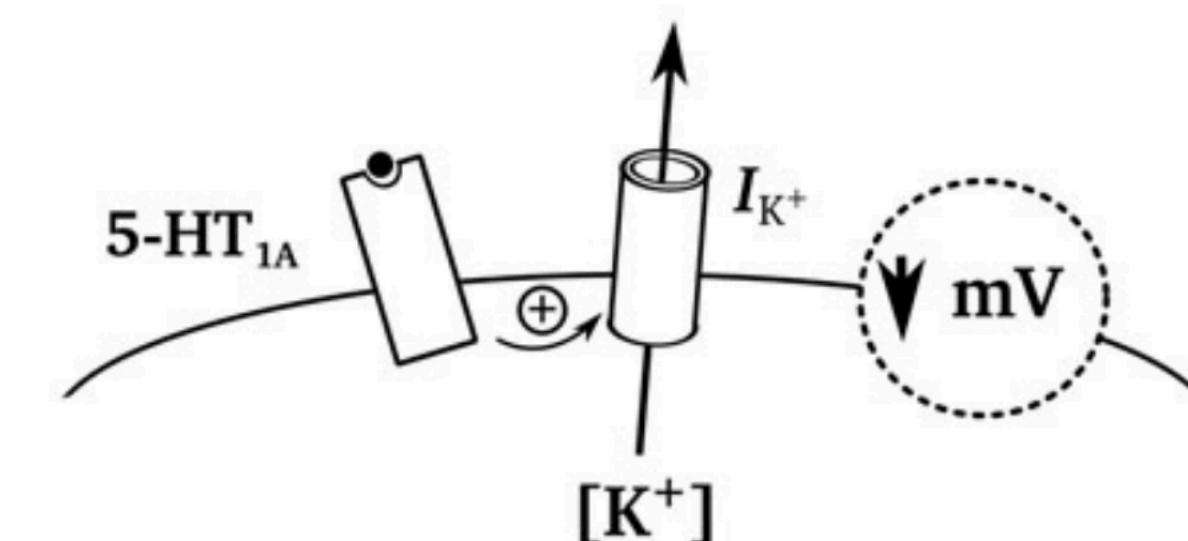
Computational MDD model, 2015



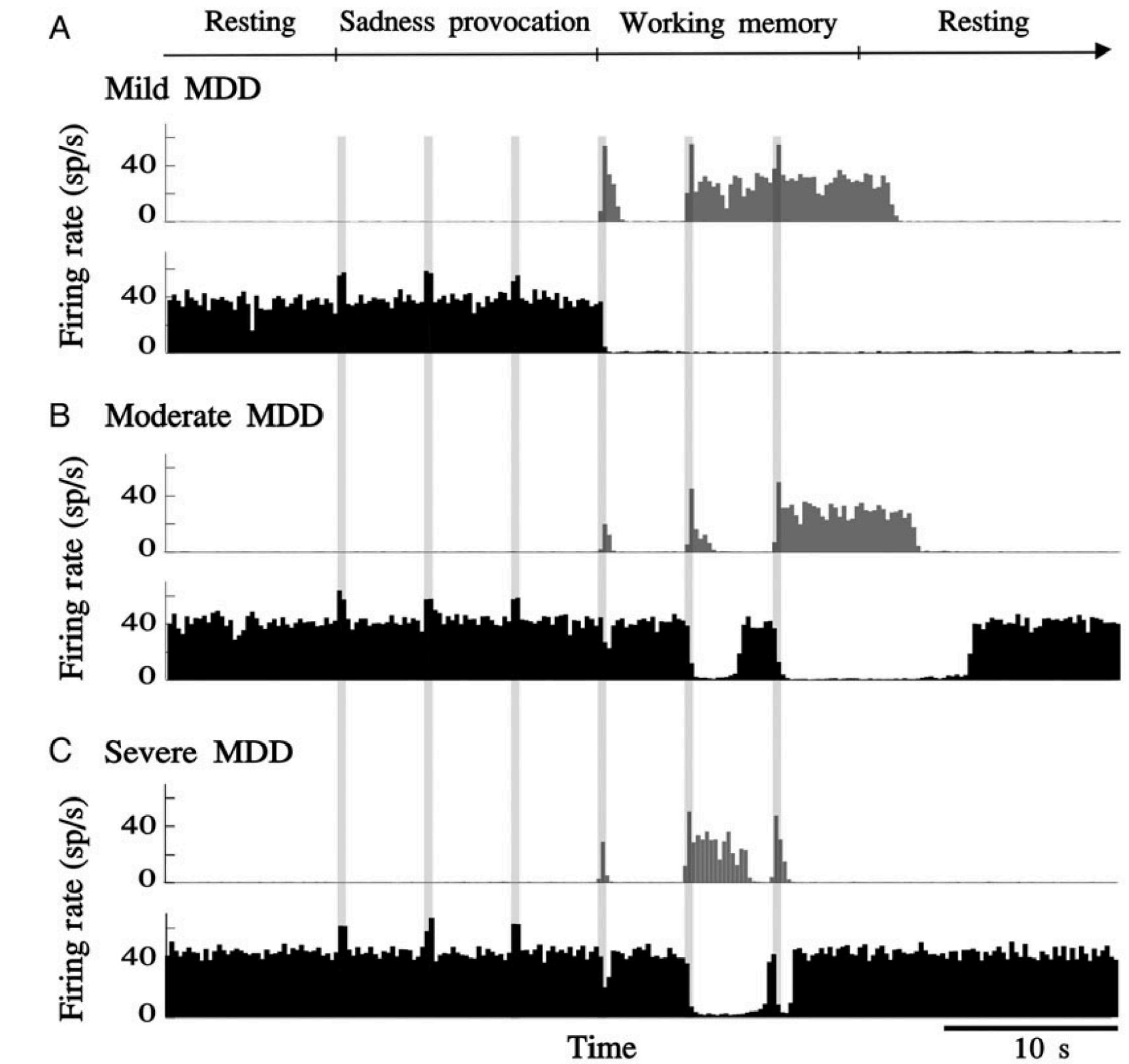
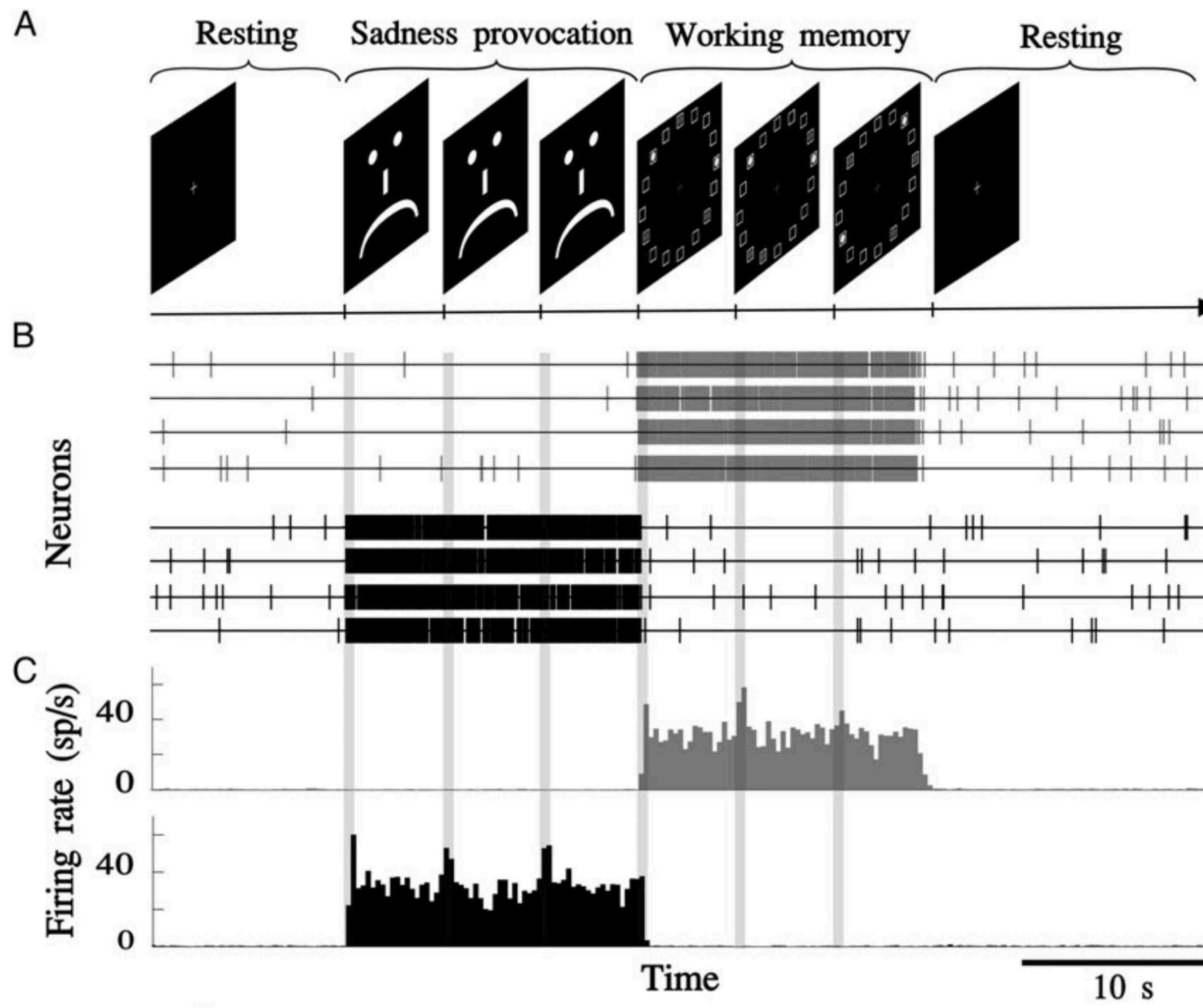
B MDD: slower glutamate decay in vACC



C SSRI: vACC hyperpolarization through 5-HT_{1A}R

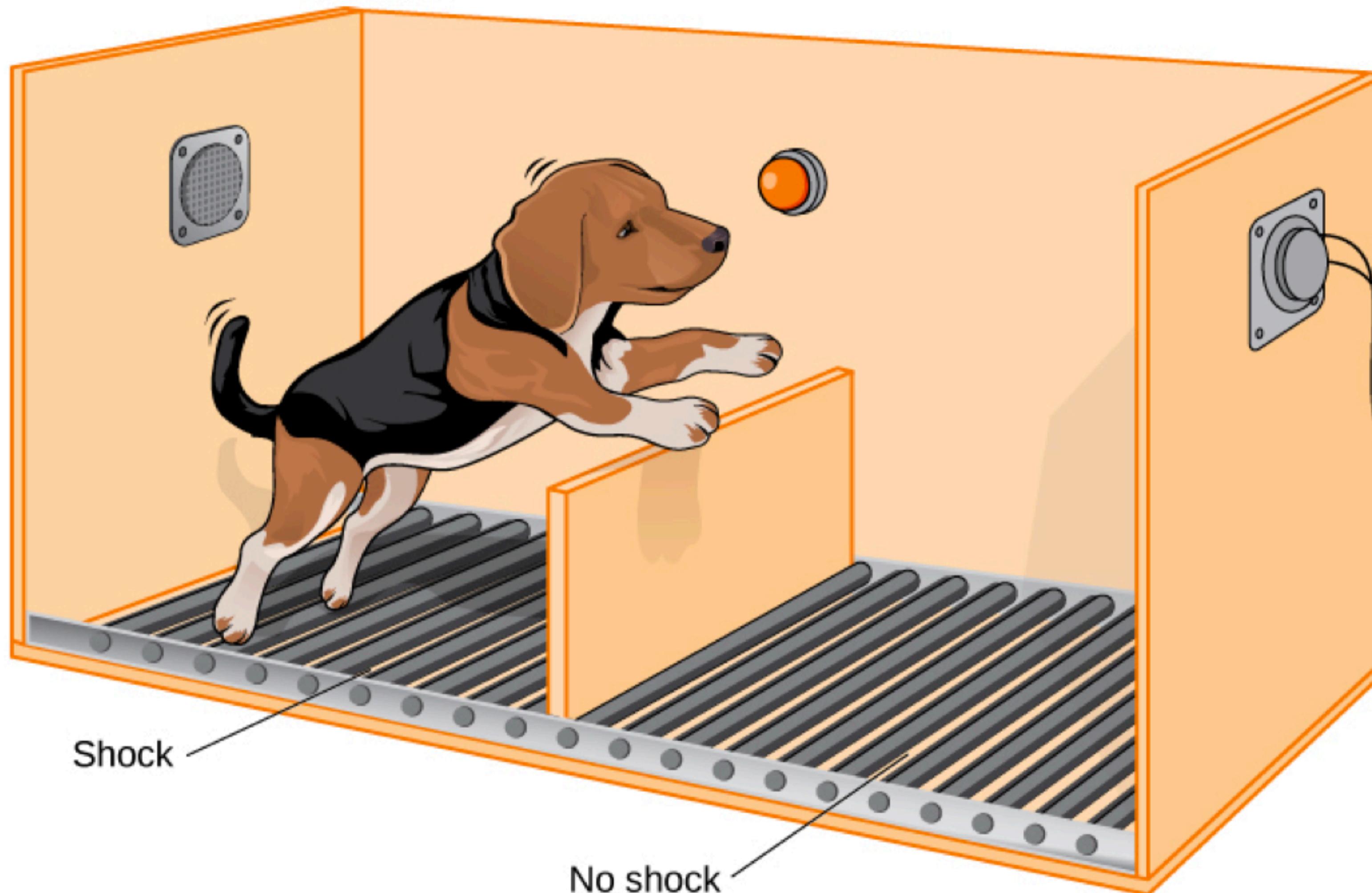


“Healthy” and “depressed” network





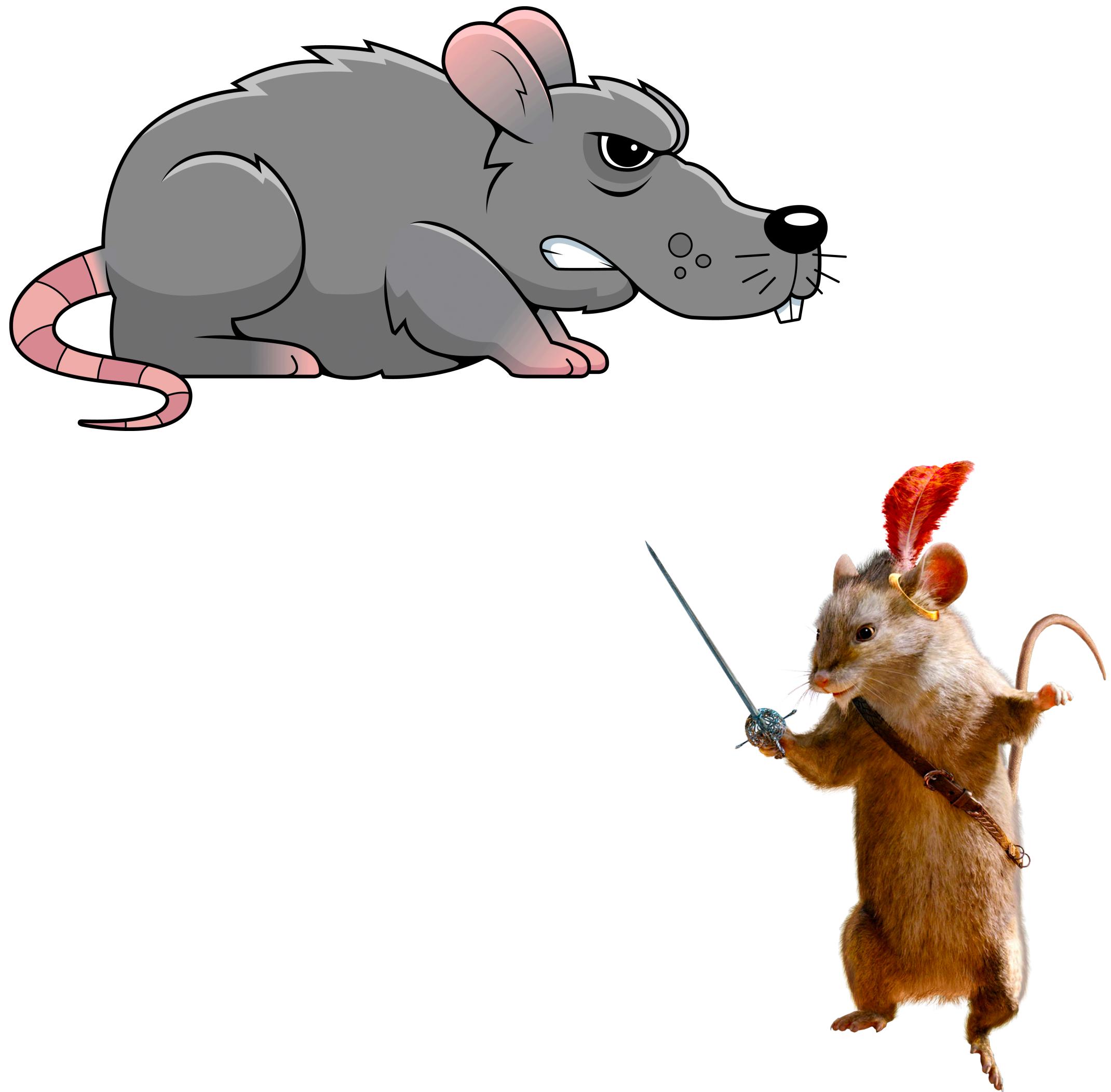
Learned helplessness



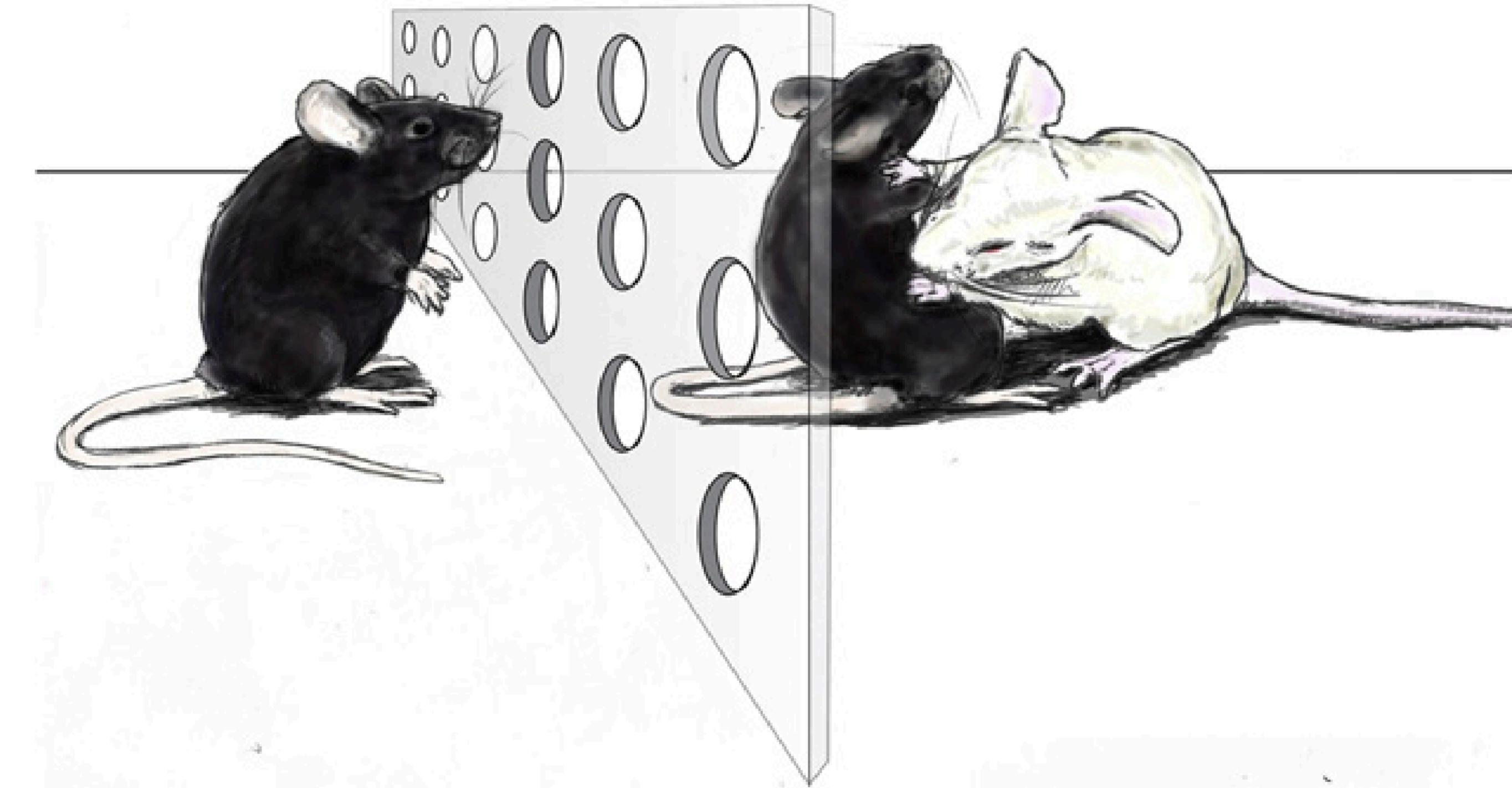
Despair



Stress & social defeat



Vicarious Social Defeat Stress



References

- Основы патофизиологии депрессии <https://youtu.be/5u39L1Yw08c>
- Стивен М. Стал Основы психофармакологии: теория и практика