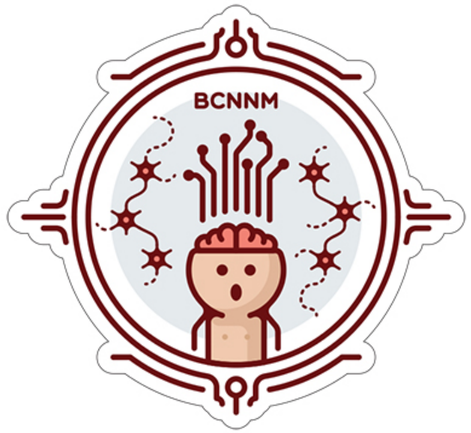


Computational Neuroscience

Lecture 9: Plasticity and learning

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

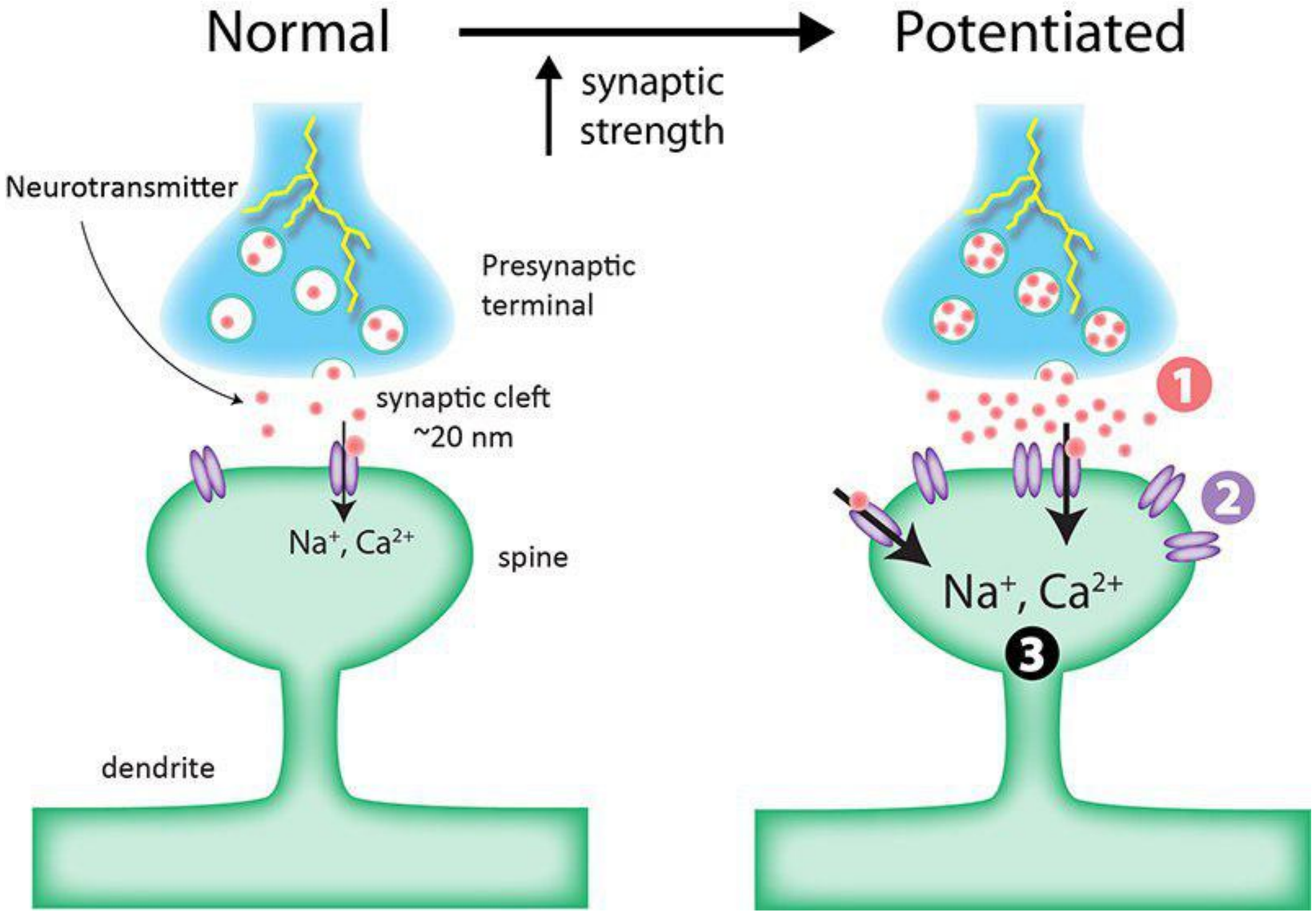
Agenda

- Synaptic plasticity
- Learning mechanisms

Synaptic plasticity

- Hebbian theory
- Biological mechanisms
- Spike-timing dependent plasticity
- Synaptic homeostasis

Synaptic plasticity



Hebbian theory

Postulate: **Cells that fire together, wire together**

- When two joining cells fire simultaneously, the connection between them strengthens (Hebb, 1949)
- Discovered at a biomolecular level by Lomo (1966, long-term potentiation)

Short-term synaptic plasticity

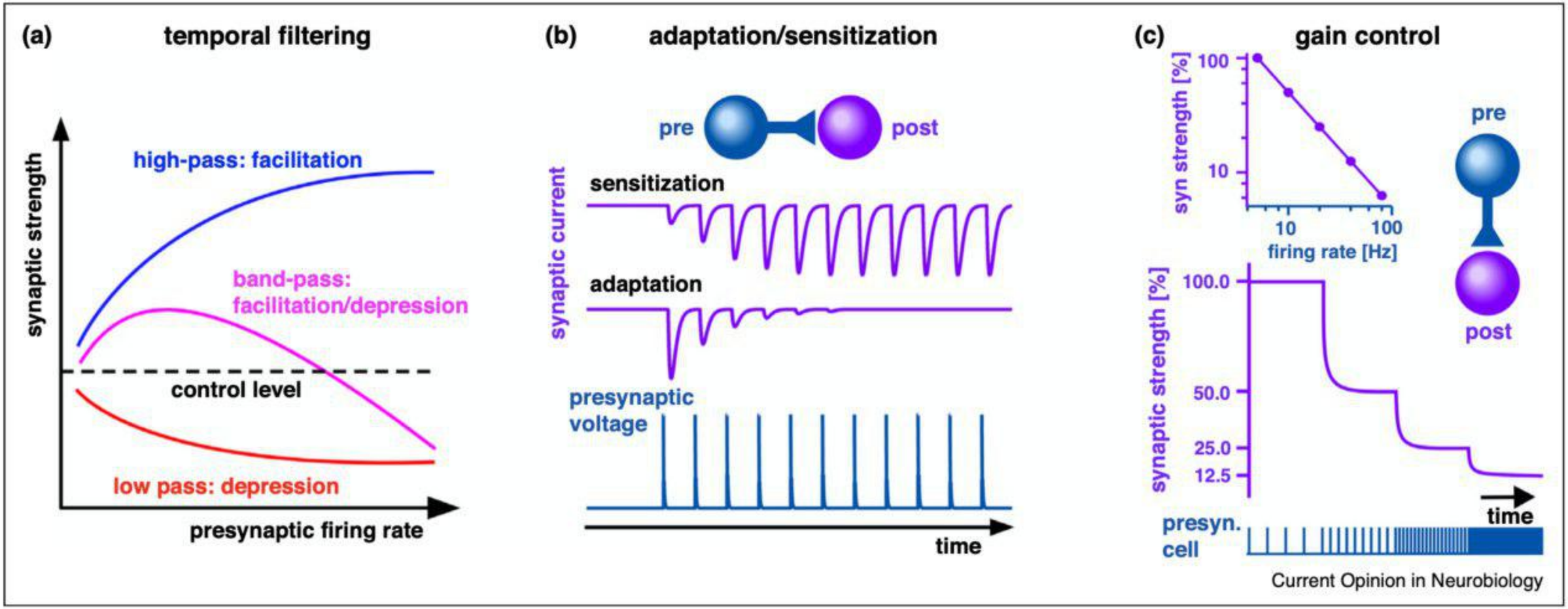
Timescale: tens of ms - a few minutes

- **Potentiation (STP)**: increased probability of synaptic terminals releasing transmitters in response to pre-synaptic action potentials; increase in the amount of packaged transmitter released in response to each action potential.

- **Depression (STD)**: depletion of the readily releasable vesicles; post-synaptic processes; feedback activation of presynaptic receptors.

STP and STD act as dynamic control mechanisms through which a sensory system produces adaptation or sensitisation.

Short-term synaptic plasticity

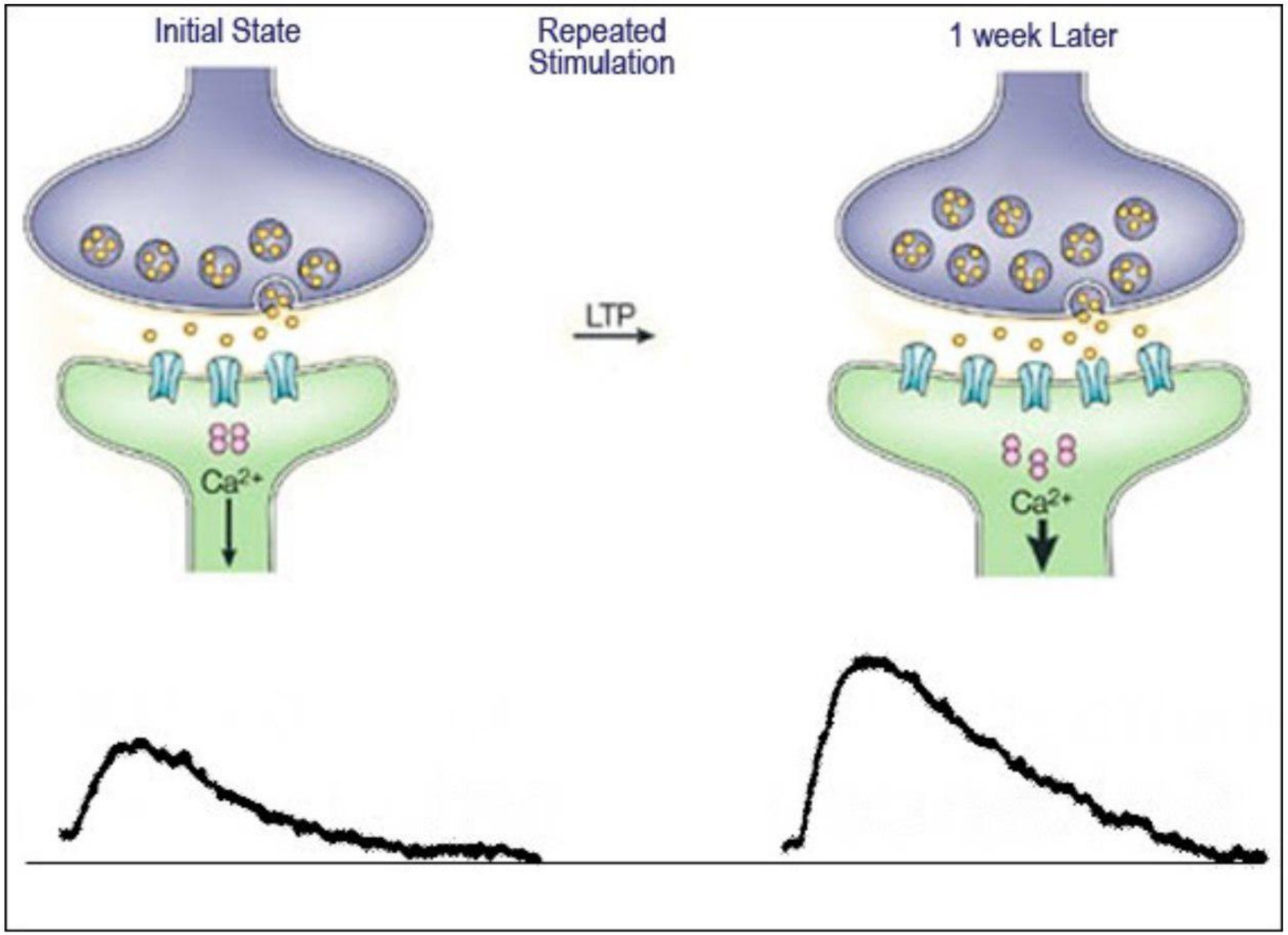


Anwar H, Li X, Bucher D1, Nadim F1
Current Opinion in Neurobiology, 22 Jan 2017, 43:71-78
DOI: 10.1016/j.conb.2017.01.002

Long-term synaptic plasticity

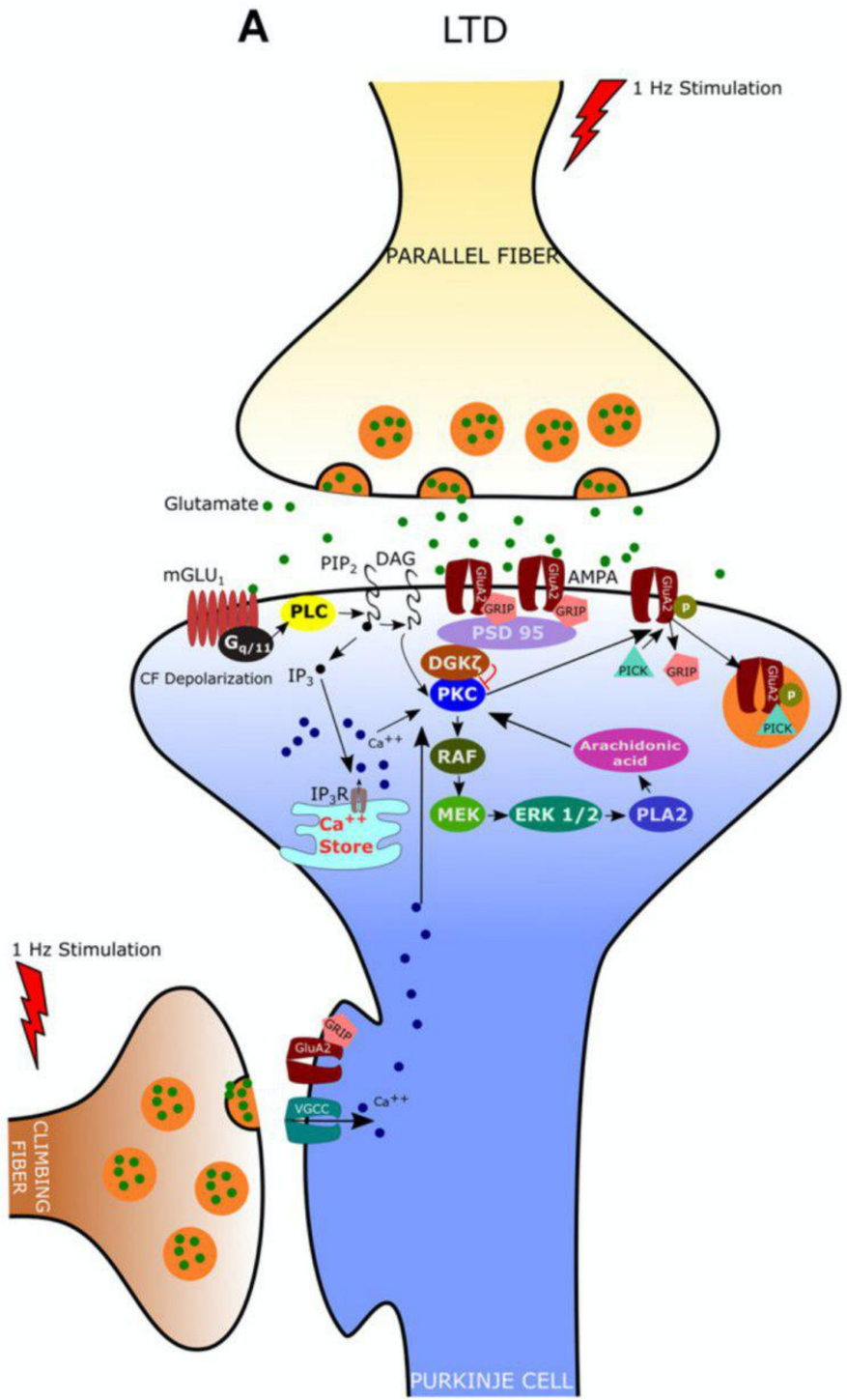
- Long-term depression (LTD) and long-term potentiation (LTP) are two forms of long-term plasticity, lasting minutes or more. Occur in excitatory synapses.

- Synaptic plasticity can change either the amount of neurotransmitter released or the number of postsynaptic receptors available. Both have the effect of altering how much electrical current flows through the ion channels.



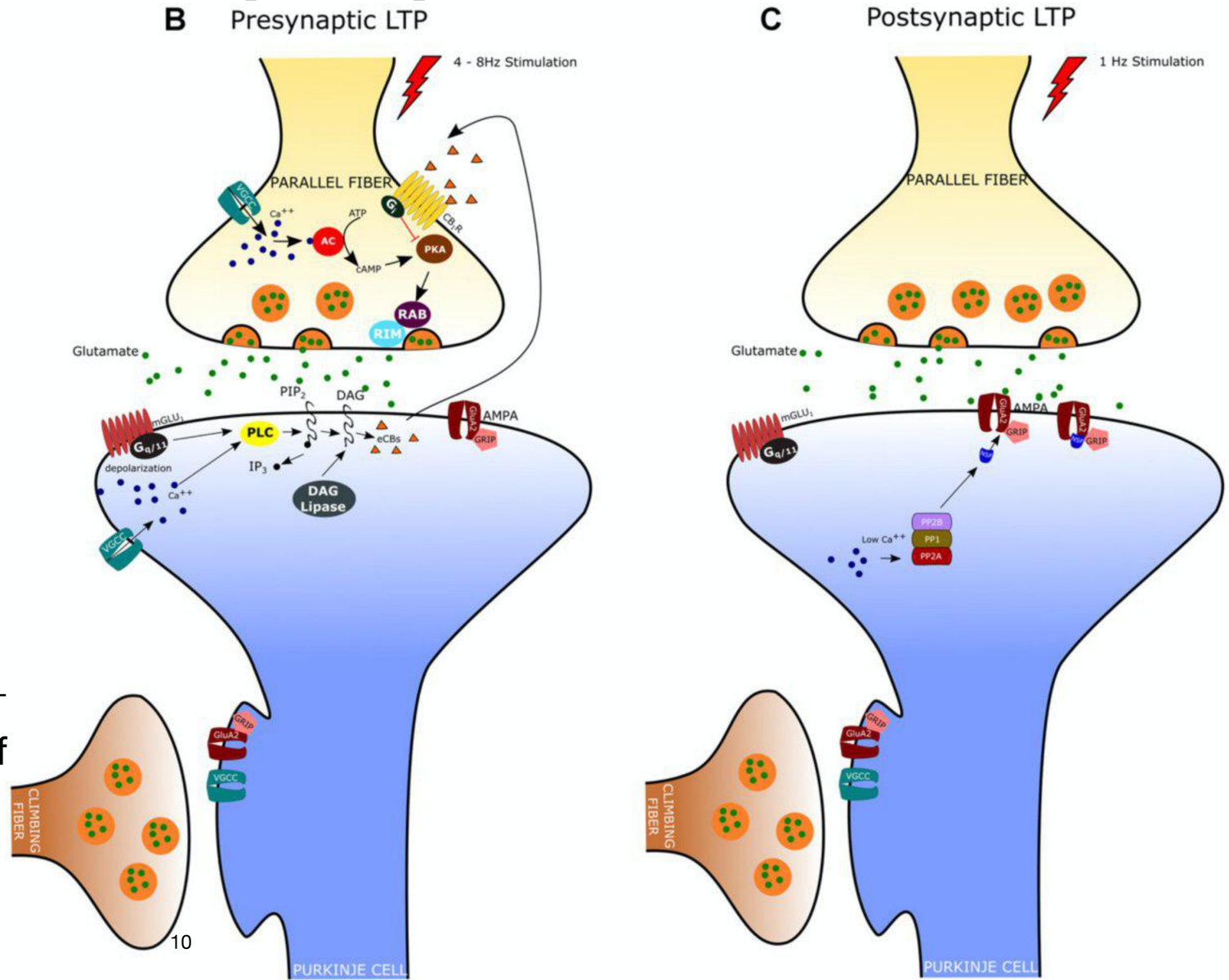
Long-term depression (LTD)

- Ca^{2+} entry (from EPR or from the outside) and other secondary messengers activate PKC
- PKC induces the phosphorylation of AMPA receptors, which results in the elimination of the receptor from the dendritic spines via clathrin-mediated endocytosis
- This is the key change for LTD expression since it is responsible for the reduced responsiveness to glutamate

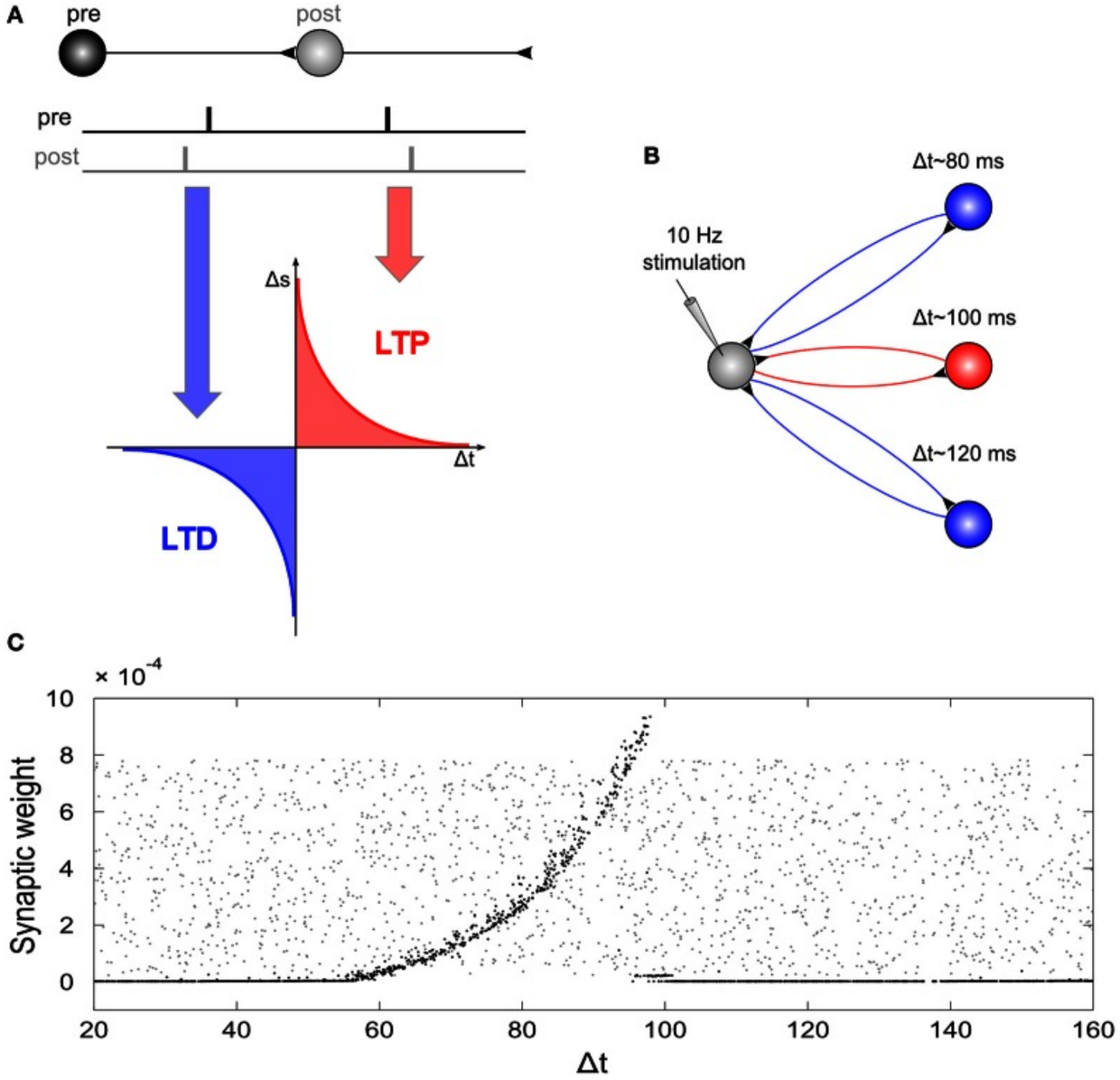


Long-term potentiaton (LTP)

- Both pre- and postsynaptic LTP can be induced by presynaptic cell stimulation at different frequencies (high vs low, respectively)
- A retrograde signaling mechanism mediated by cannabinoids regulates **presynaptic LTP**. Ca^{2+} and other secondary messengers also involved. Increased glutamate release is the result
- **Postsynaptic LTP**: induced by lower-freq. stimulation, depends on lower Ca^{2+} transients than LTD, requires activation of protein phosphatases which stabilize the AMPA receptors to the membrane



Spike-timing dependent plasticity (STDP)



Basic STDP model

Presynaptic firing times at synapse j is t_j^f with $f = 1, 2, 3 \ldots$

Postsynaptic firing times is t_i^n with $f = 1, 2, 3 \ldots$

The total weight change Δw_j induced by a stimulation protocol with pairs of pre- and postsynaptic spikes is then (Gerstner and al. 1996, Kempter et al. 1999)

$\Delta w_j = \sum_{f=1}^{N} \sum_{n=1}^{N} W(t_i^n - t_j^f)$, where $W(x)$ denotes one of the STDP functions

$W(x) = A_+ exp(-x/\tau_+) \qquad \text{for } x > 0$
$W(x) = -A\_exp(x/\tau\_) \qquad \text{for } x < 0$

$W(x)$ fits to experimental data (Zhang et al. 1998) and models (e.g, Song et al. 2000). The parameters A_+ and $A\_$ may depend on the current value of the synaptic weight w_j. The time constants are on the order of $\tau_+ = 10\ ms$ and $\tau\_ = 10\ ms$

Synaptic homeostasis

- Motivation for studies of homeostatic plasticity is the concern that Hebbian networks are potentially unstable because of positive feedback loops

→ There are probably additional types of plasticity, complementary to STDP, that may serve to constrain synaptic weights and/or neuronal firing

- These are collectively known as “homeostatic plasticity”
- Include schemes that control the total synaptic strength of a neuron, modulate its intrinsic excitability as a function of average activity, or make the ability of synapses to undergo Hebbian modification depend upon their history of use.

Synaptic homeostasis:

- Operates at a much slower time scale than more acute forms of plasticity, such as LTP and LTD
- Is a critical mechanism by which the cell tunes the strength of its synaptic inputs up or down
- Counteracts normal or pathological activity perturbations
- Contributes to the restoration of baseline neuronal output

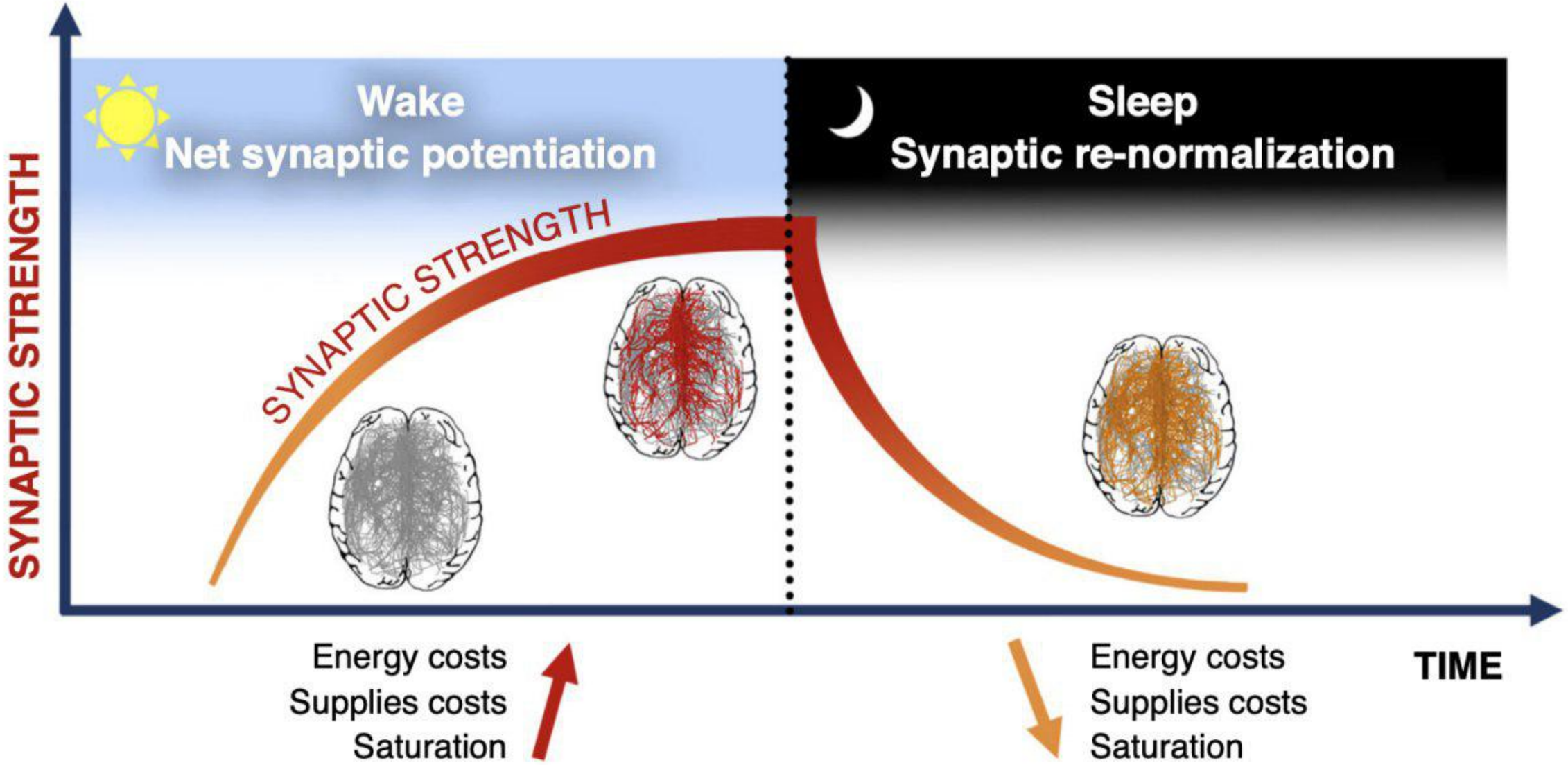
Possible mechanisms of synaptic homeostasis

- **Synaptic scaling**: directly regulates the strength of synapses
- **Homeostatic Intrinsic Plasticity**: neurons and circuits maintain appropriate levels of electrical activity through overall shifts in cellular excitability. Activity manipulation affects channel density, but also localization and gating characteristics.
- **Metaplasticity**: the capacity of synapses to undergo Hebbian modification depend upon their history of use or upon the history of neuronal activity

Synaptic scaling

- One of the best-studied homeostatic plasticity mechanisms
- It directly regulates the strength of synapses (the same synapses that, undergoing synaptic plasticity like STDP, are likely to be among the sources of destabilisation of a neuron's firing rate)
- With scaling, a neuron can keep its synapses within some optimal size range: energetically advantageous
- Like in LTP, **calcium** acts as the signal that affects a change in AMPA receptors at synapses. Other signaling molecules also appear to be involved.
- How these signaling mechanisms interact remains to be determined

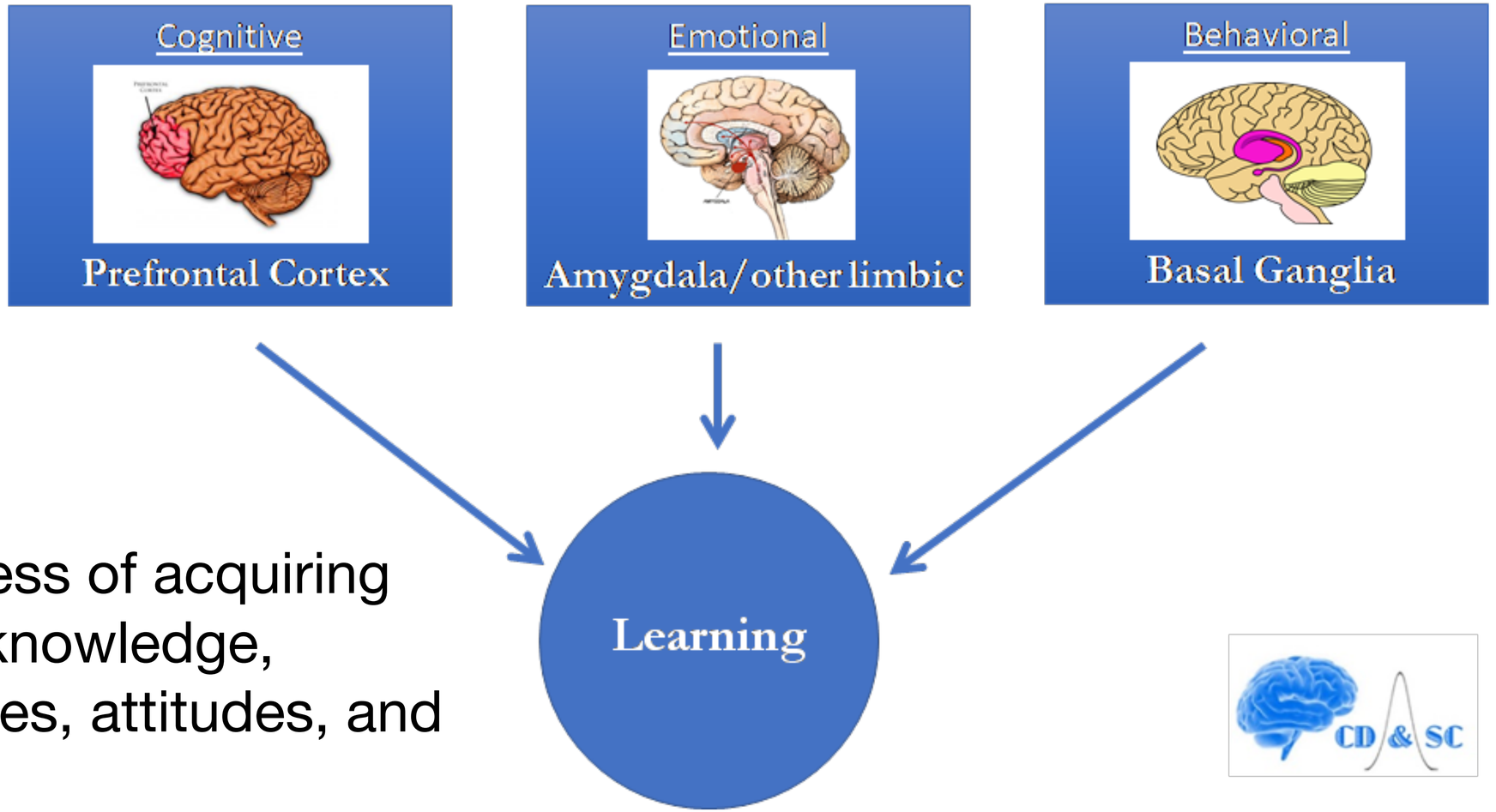
Sleep?


Wake
Net synaptic potentiation
Sleep
Synaptic re-normalization
SYNAPTIC STRENGTH
SYNAPTIC STRENGTH
Energy costs
Supplies costs
Saturation
Energy costs
Supplies costs
Saturation
TIME

Learning mechanisms

- Types of learning
- Associative learning
- Reward system
- Dopaminergic modulation
- Pathologies

Learning in living systems

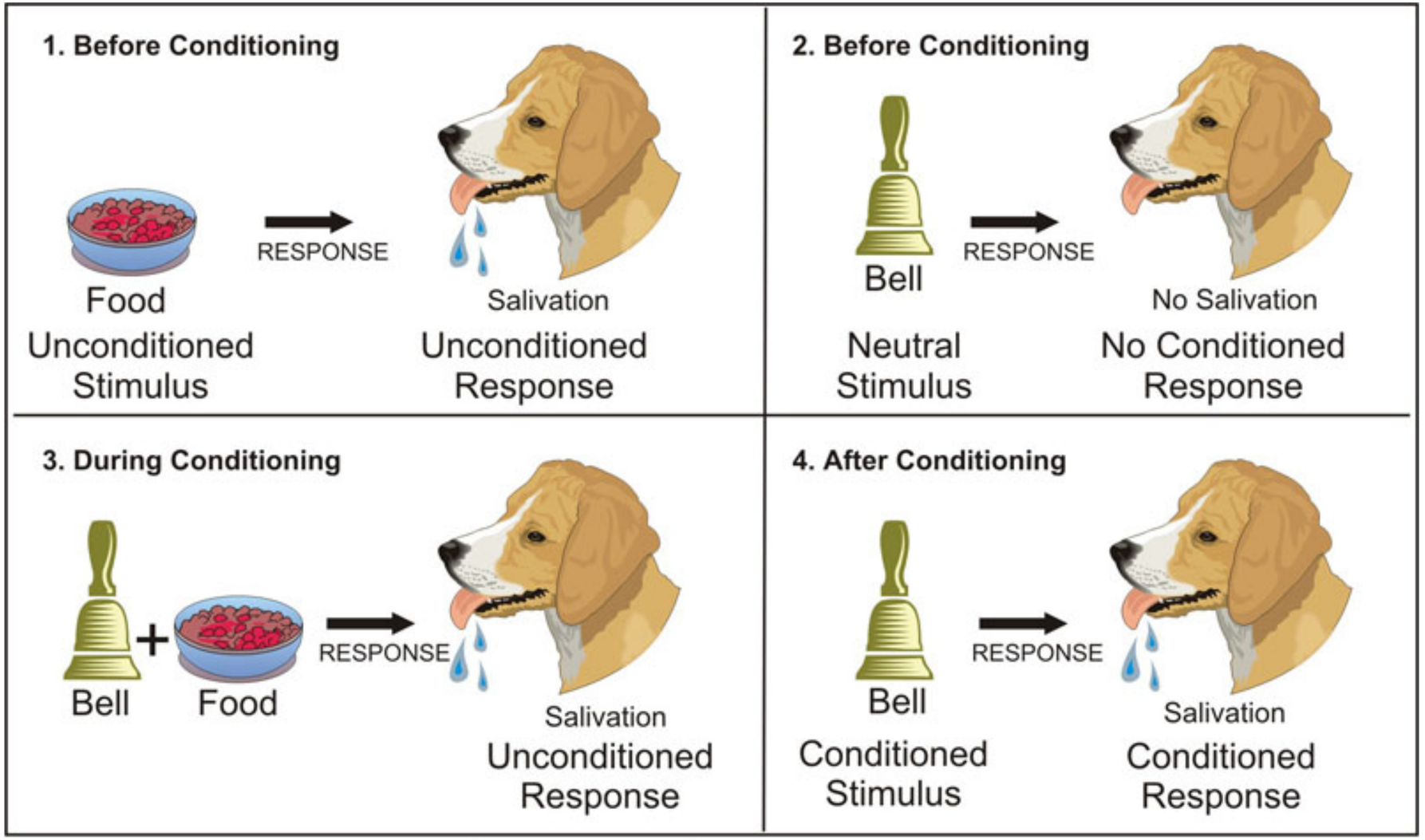


Learning is the process of acquiring new understanding, knowledge, behaviors, skills, values, attitudes, and preferences.

Types of learning

- Non-associative learning
- Associative learning
- Cognitive learning

Associative learning

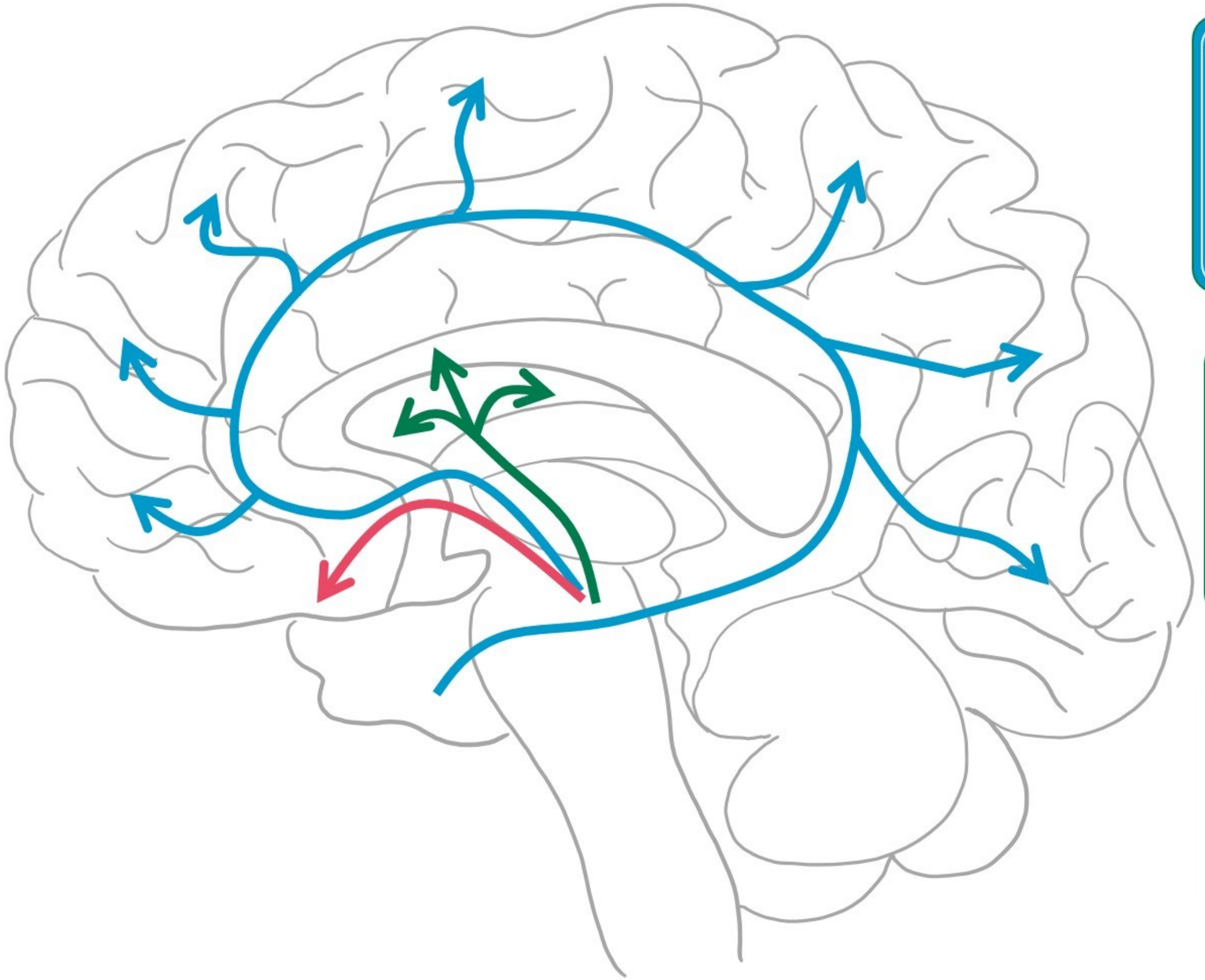


Classical Conditioning

Reward system

The **reward system** (the mesocorticolimbic circuit) is a group of neural structures responsible for incentive salience (i.e., motivation and "wanting"; desire or craving for a reward), associative learning (primarily positive reinforcement and classical conditioning), and positively-valenced emotions, particularly ones involving pleasure as a core component (e.g., joy, euphoria and ecstasy).

Mesolimbic and mesocortical pathways



MESOCORTICAL

Cognition, Memory, Attention, Emotional Behavior, & Learning

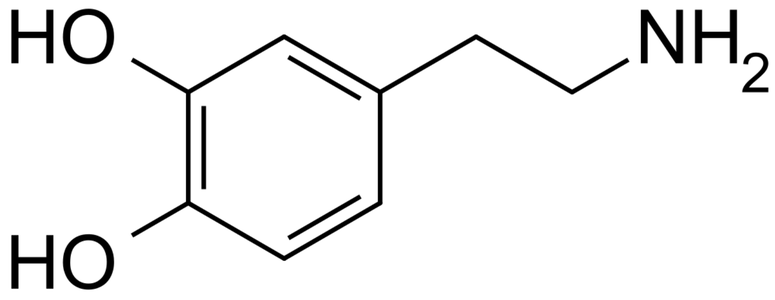
NIGROSTRIATAL

Movement & Sensory Stimuli

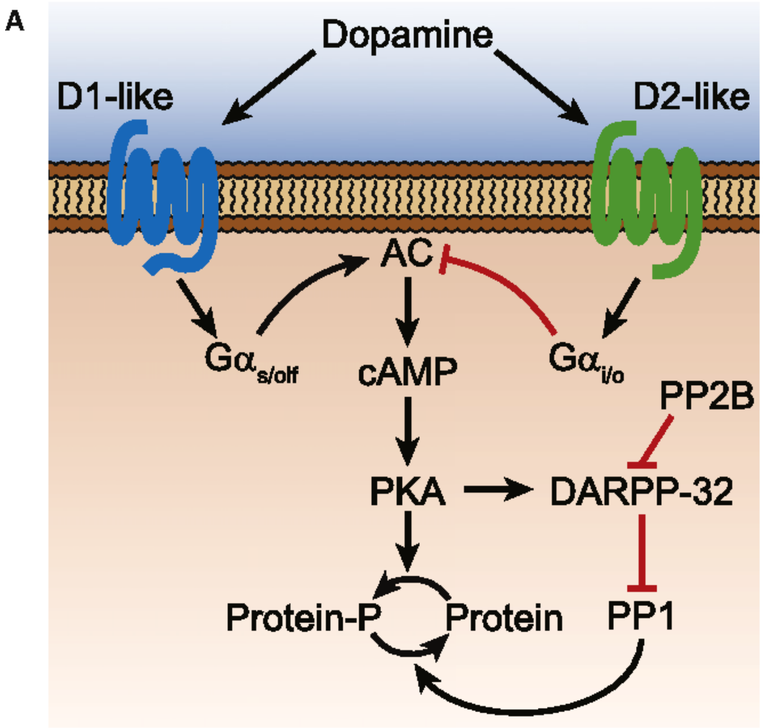
MESOLIMBIC

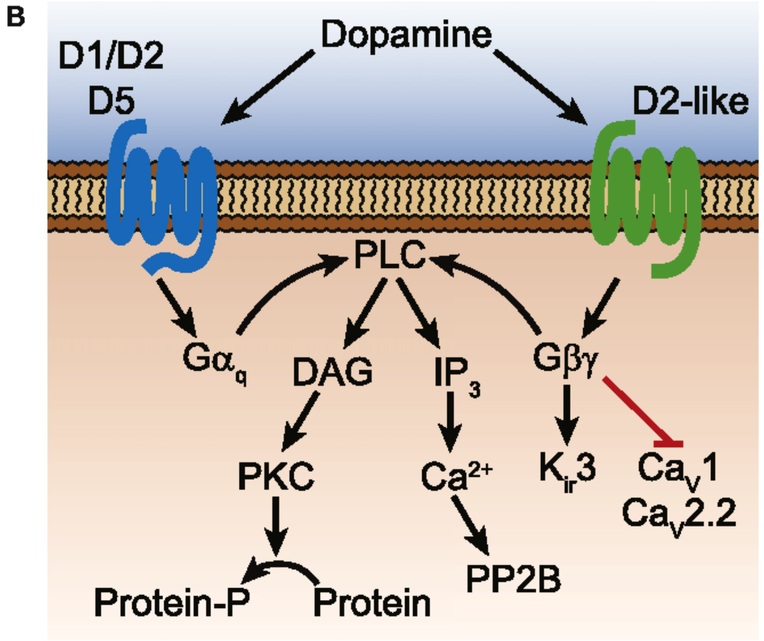
Pleasure & Reward Seeking Behaviors; Addiction, Emotion, Perception

Dopamine



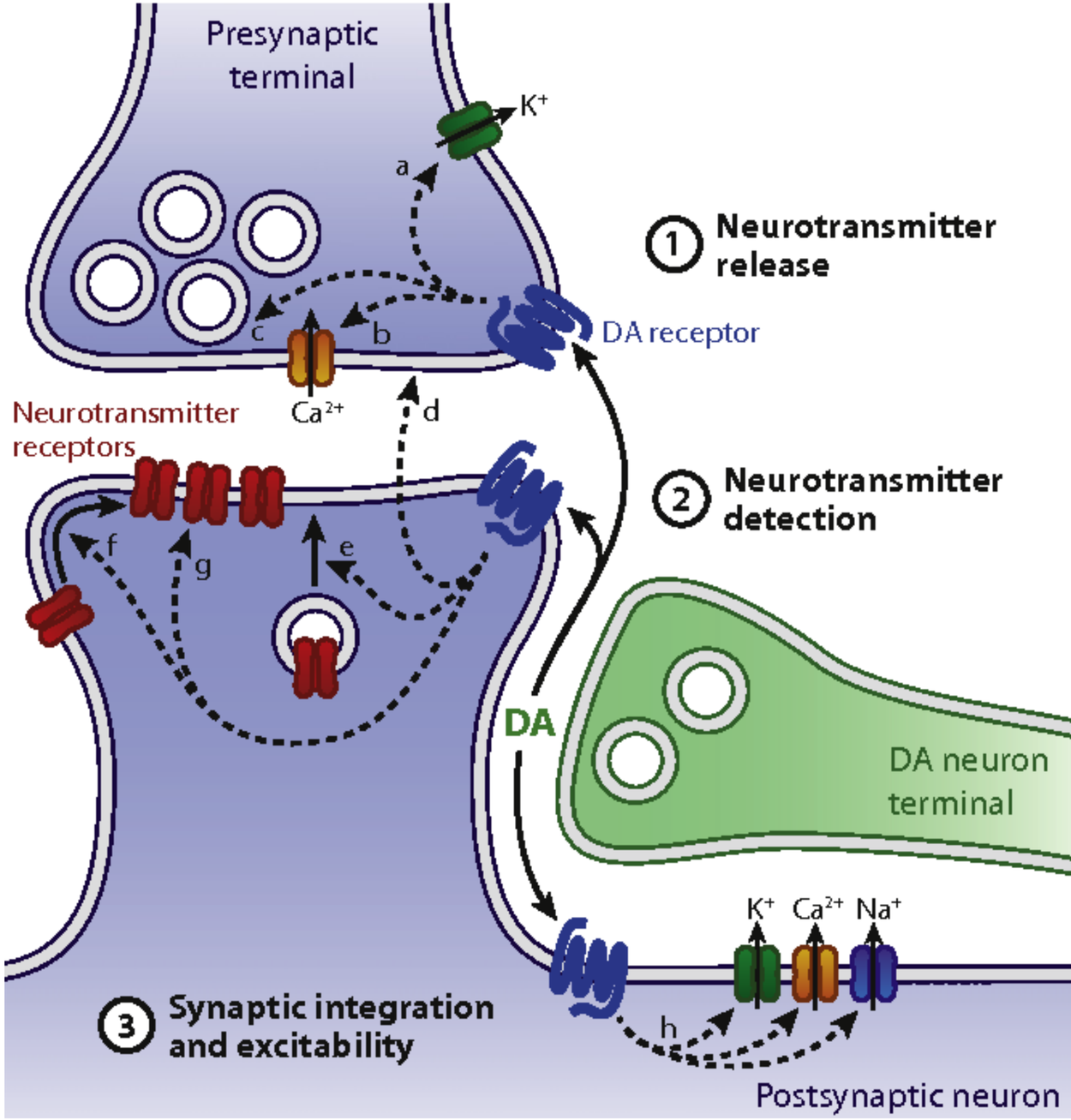
- Plays important roles in executive functions, motor control, motivation, arousal, reinforcement, and reward, as well as lower-level functions including lactation, sexual gratification, and nausea
- The dopaminergic cell groups and pathways make up the dopamine system which is neuromodulatory
- A total of around 400,000 in the human brain





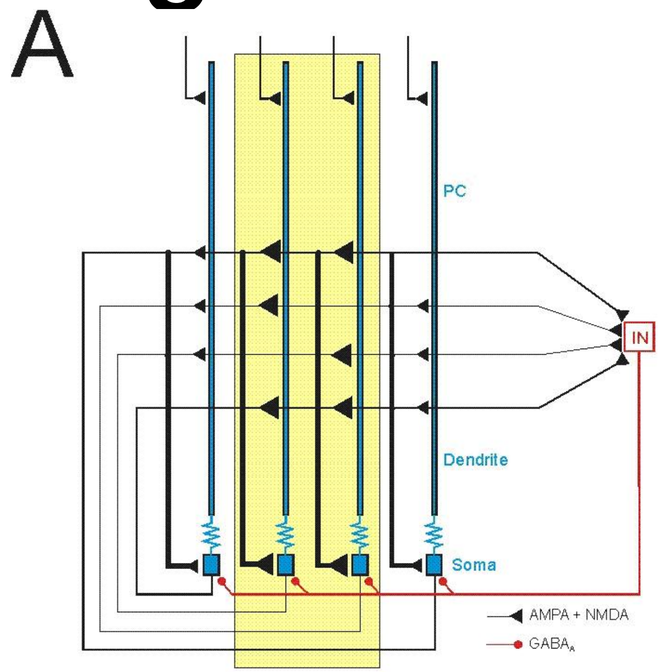
Dopamine modulation

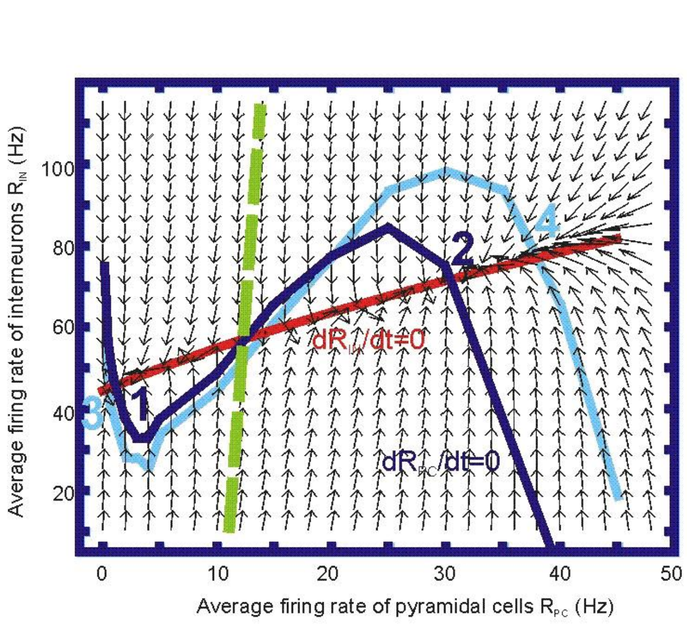
- DA neurons show two predominant patterns of firing activity termed tonic and phasic
- DA can potently modulate fast events in the striatum that are associated with learning
- Dopamine modulation appears to be input selective

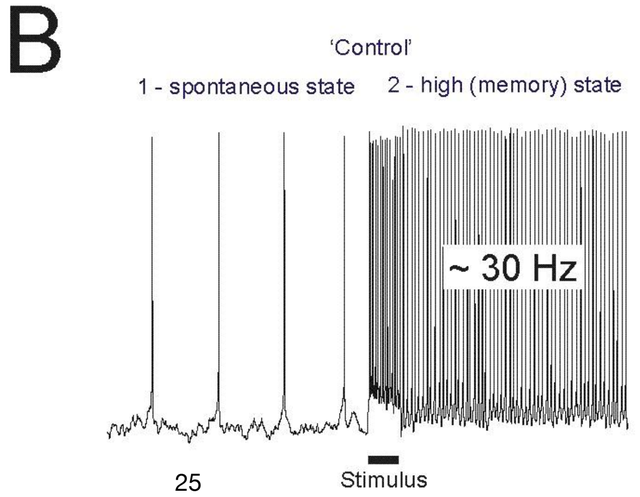


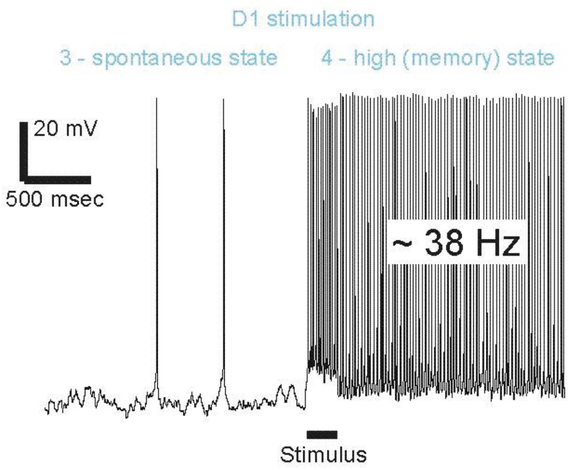
Models of dopaminergic modulation

- Support of cellular bistability
- HH-type -> DA effects can be implemented quite directly
- Abstract models -> net effects of DA
- How the balance between the D1 and D2 state is regulated?









Reward system models

- Schultz et al., A Neural Substrate of Prediction and Reward; Science 14 Mar 1997, DOI: 10.1126/science.275.5306.1593
- Frank and Claus, Anatomy of a Decision: Striato-Orbitofrontal Interactions in Reinforcement Learning, Decision Making, and Reversal; Psychol Rev 2006 Apr; 113(2):300-326. doi: 10.1037/0033-295X.113.2.300.
- Grossberg, S., Schmajuk, N. A., 1989. Neural dynamics of adaptive timing and temporal discrimination during associative learning. Neural Networks 2, 79–102. https://doi.org/10.1016/0893-6080(89)90026-9

Frank and Claus, 2006

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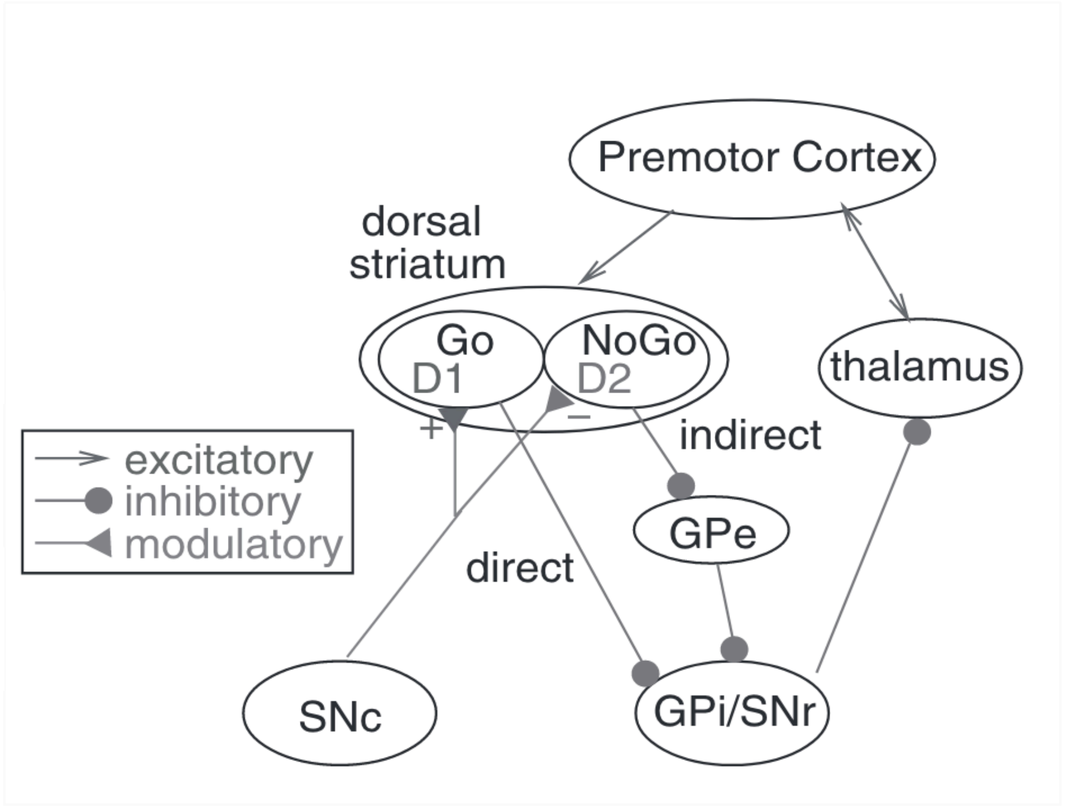

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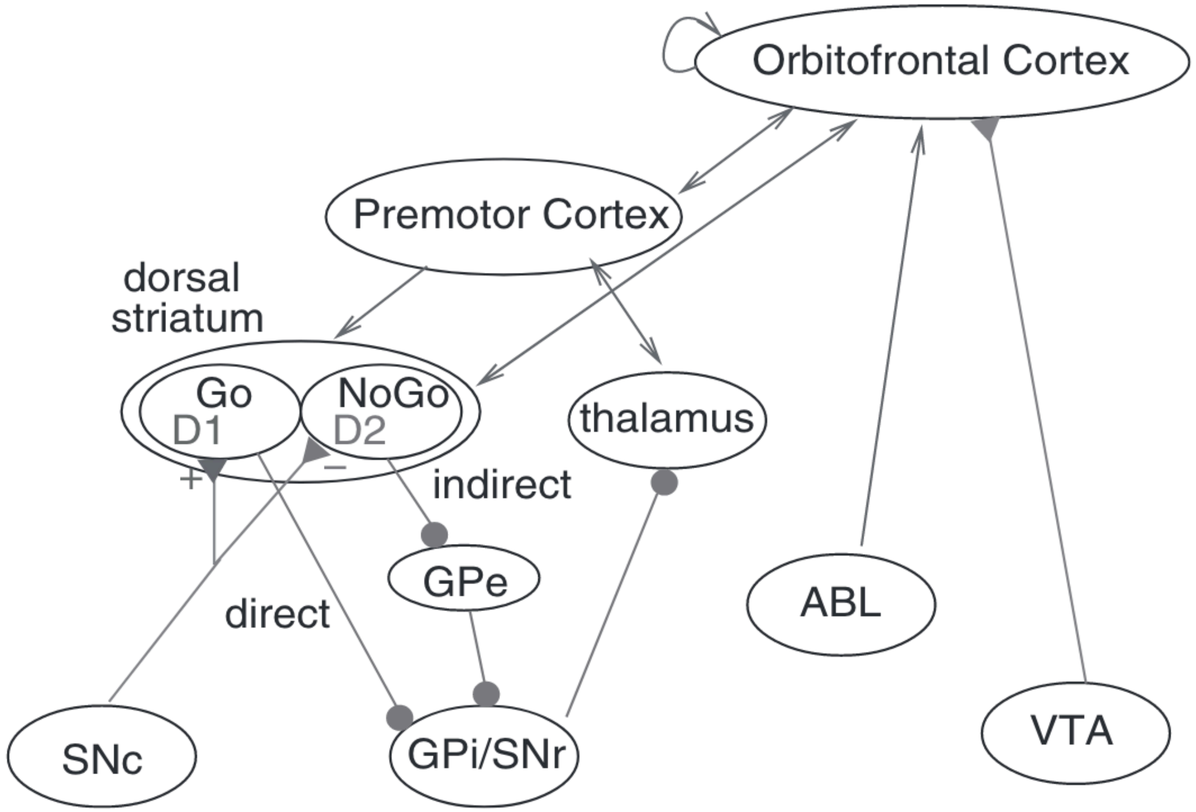
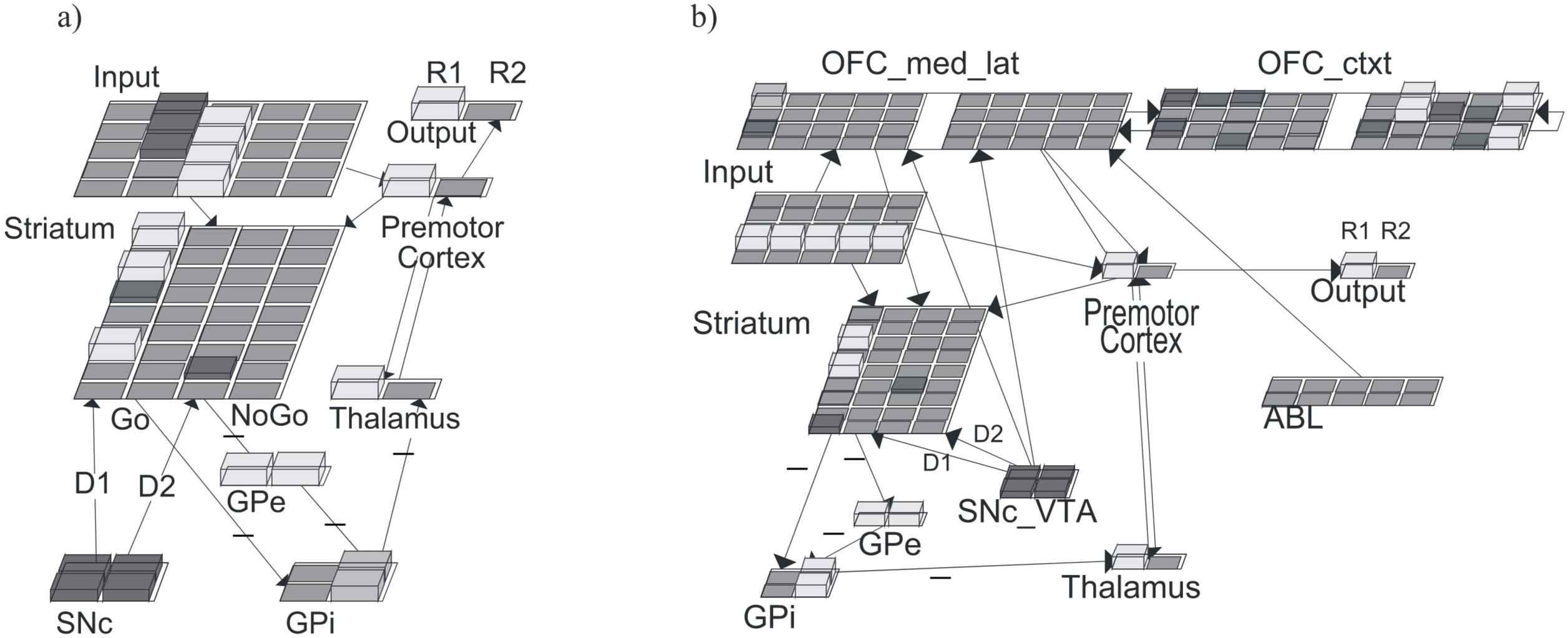


Psychol Rev 2006 Apr;113(2):300-326. doi: 10.1037/0033-295X.113.2.300.

Frank and Claus, 2006

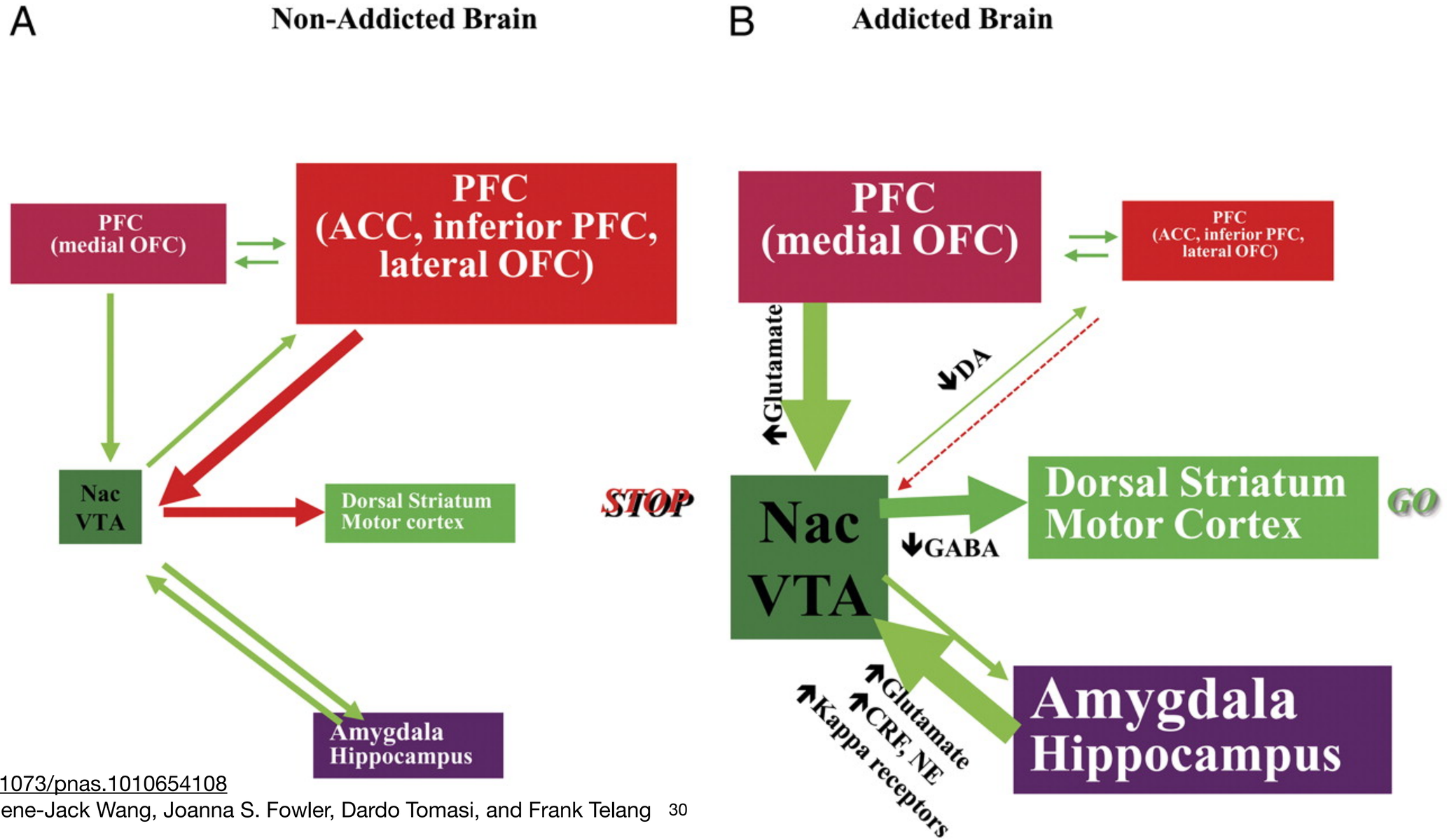


Psychol Rev 2006 Apr;113(2):300-326. doi: 10.1037/0033-295X.113.2.300.

Pathologies of reward system

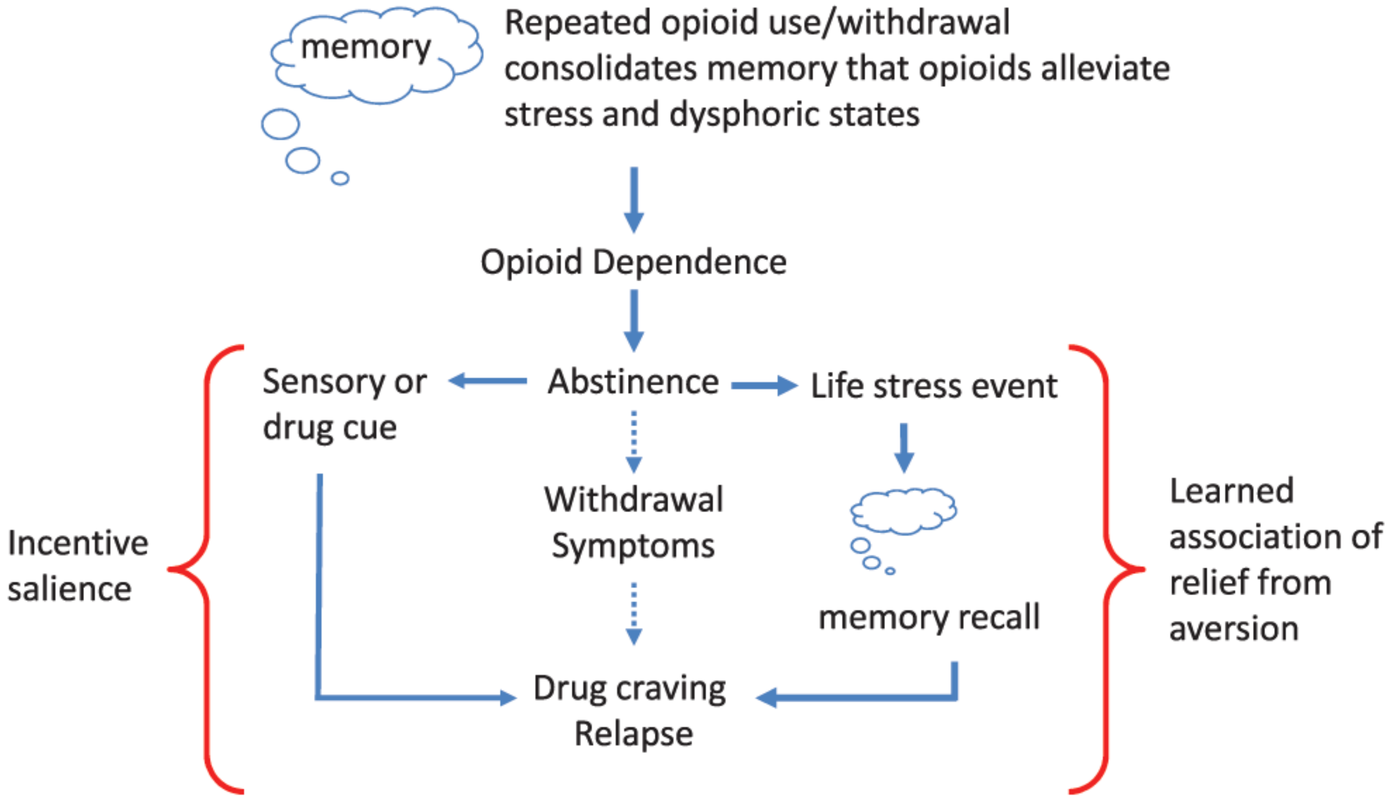
- Addiction
- Motivation salience
- Mood disorders
- Schizophrenia

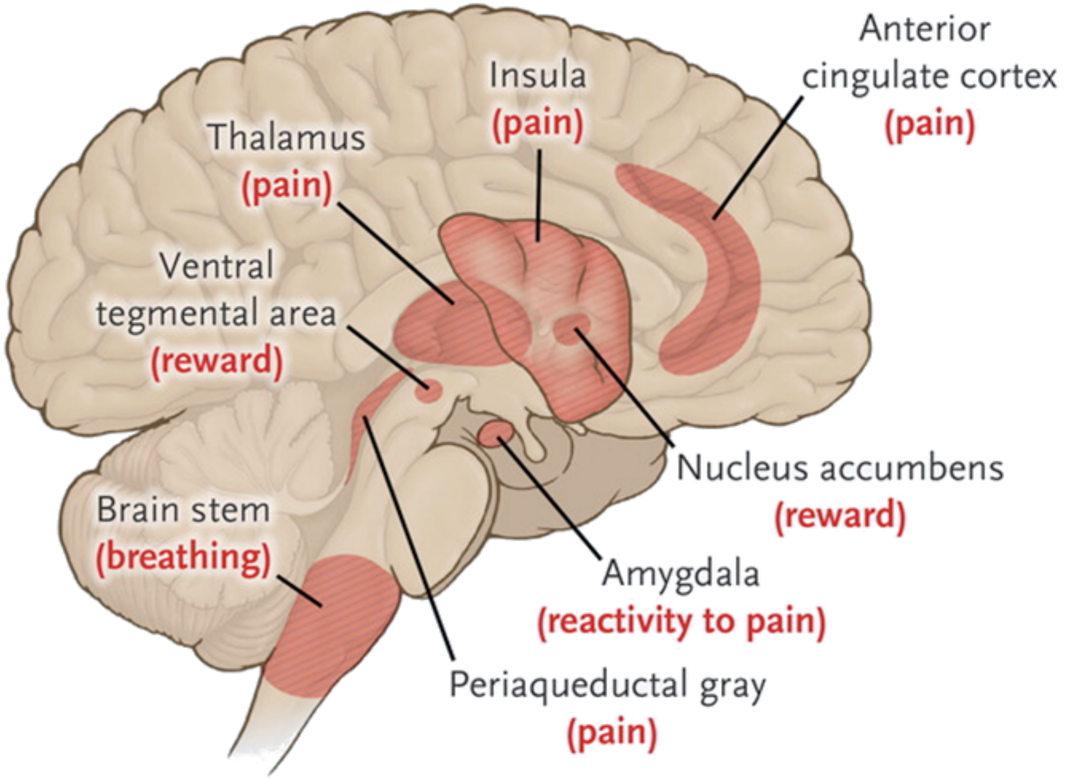
Addiction



https://doi.org/10.1073/pnas.1010654108

Addiction vs pain





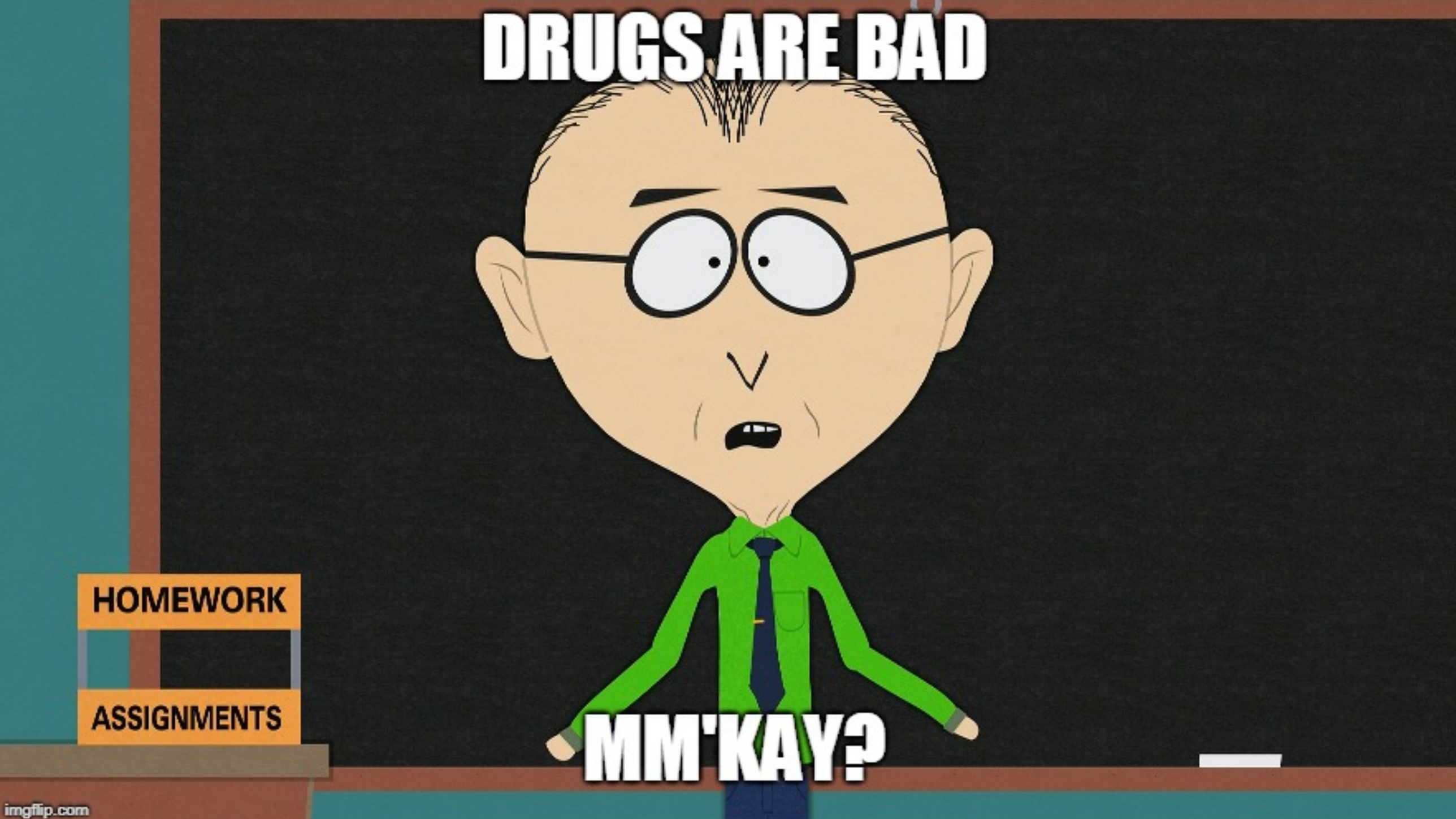
Christopher J. Evans, Catherine M. Cahill, https://doi.org/10.12688/f1000research.8369.1

Nora D. Volkow, M.D., and A. Thomas McLellan, Ph.D. DOI: 10.1056/NEJMra1507771

Conclusions

- Synaptic plasticity is the key to learning processes
- Synaptic homeostasis is crucial
- Learning involves many different brain regions and molecular mechanisms
- Bugs in the reward system lead to complex pathologies

Aaaaaaand…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HOMEWORK
ASSIGNMENTS
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