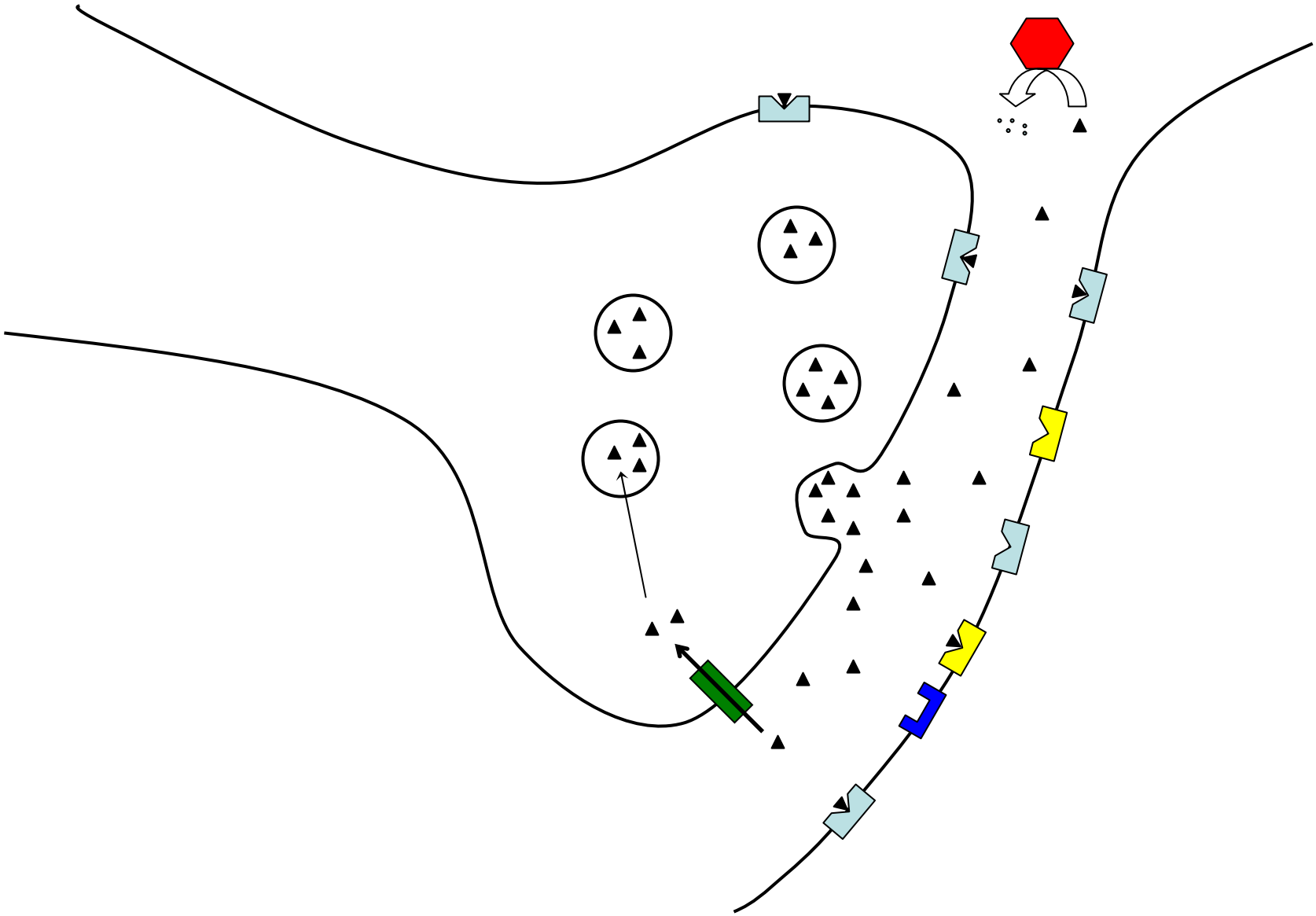
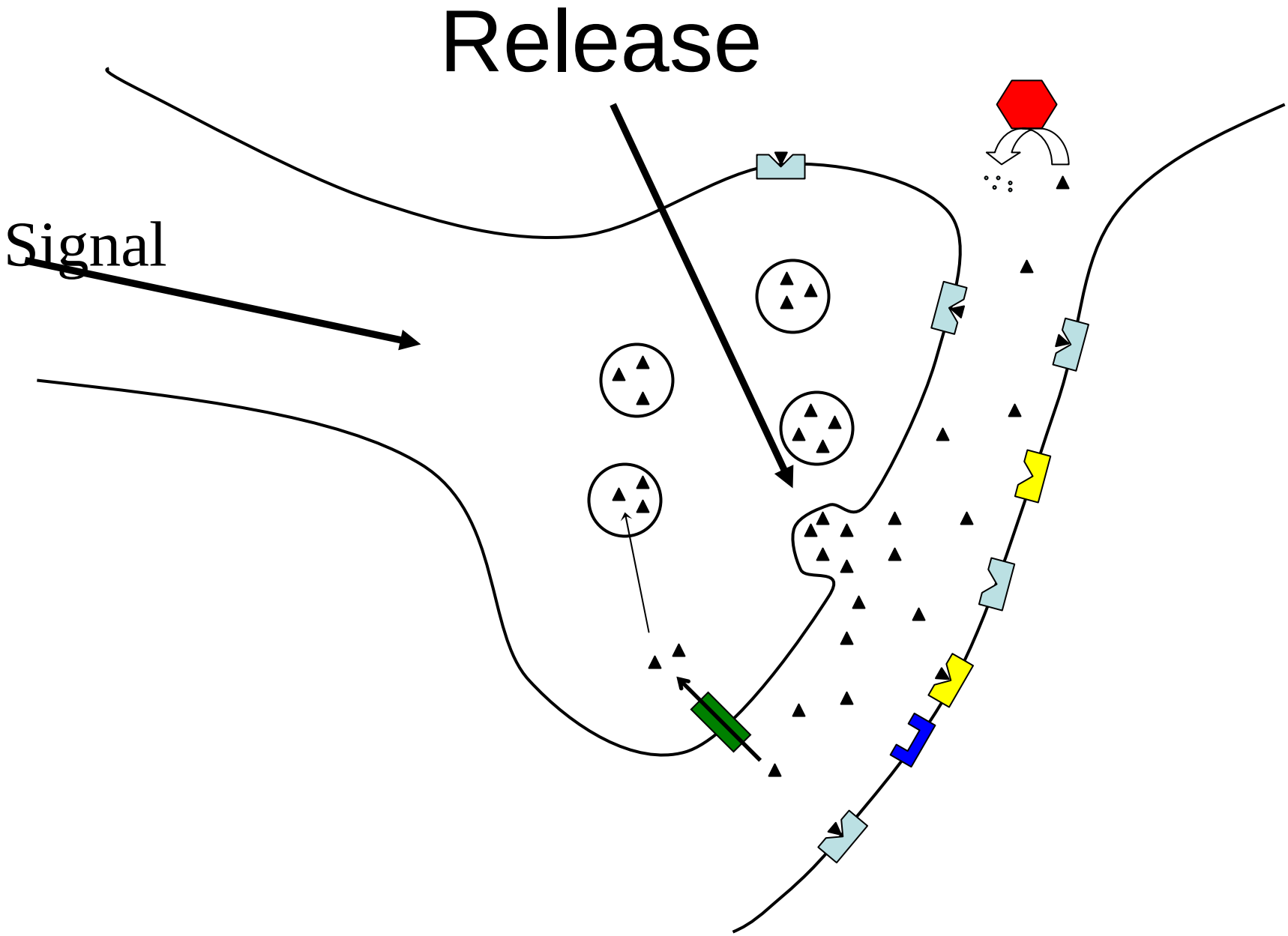
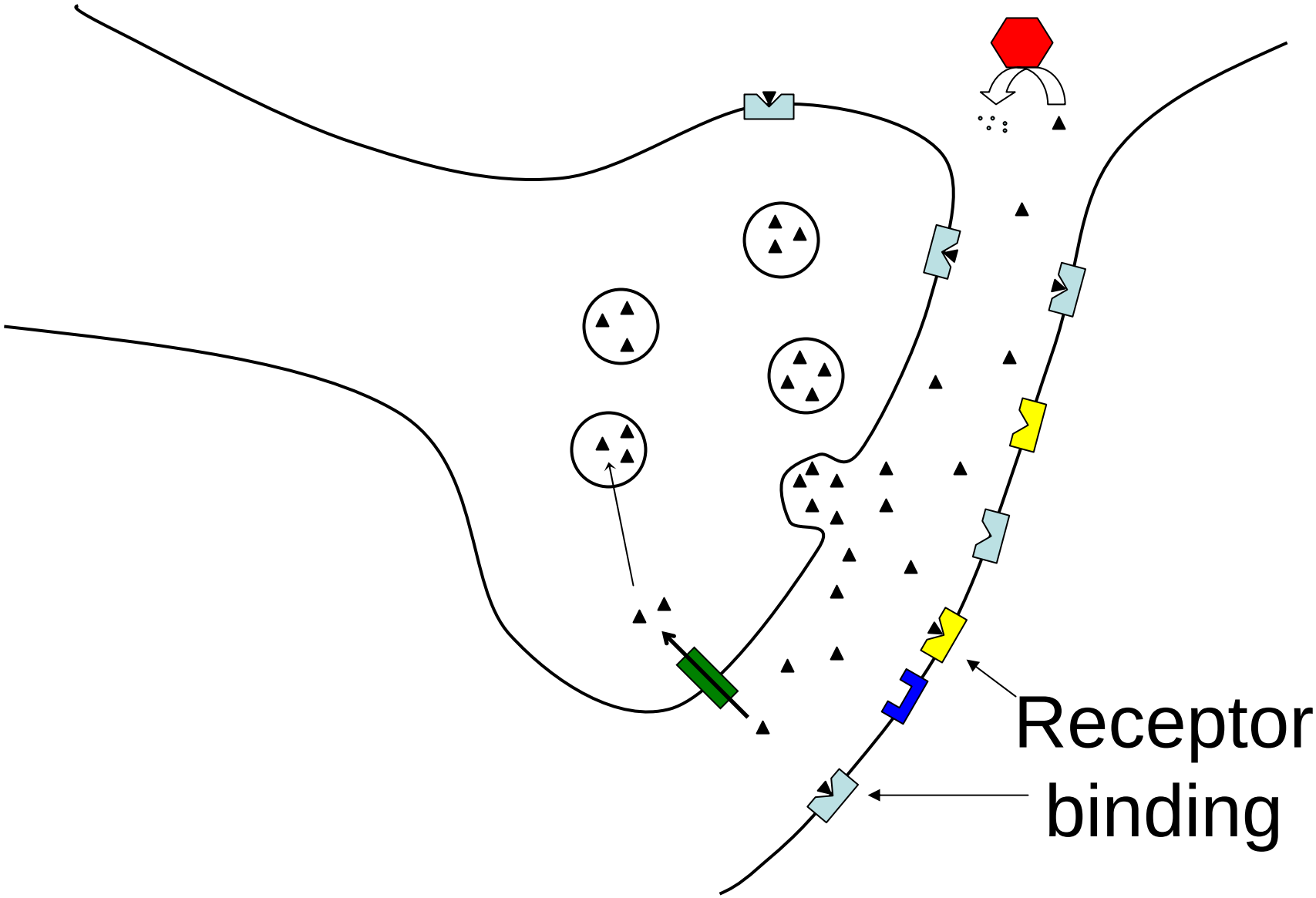
SP.236 / ESG.SP236 Exploring Pharmacology
Spring 2009

Introducing Dopamine and Serotonin

Background: The Synapse



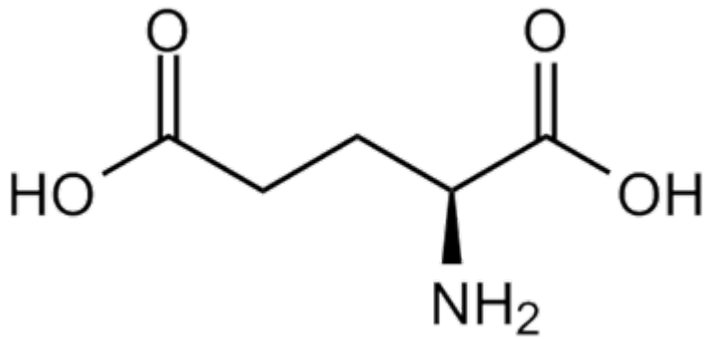

Release
Signal


Receptor
binding

DA and 5-HT

- One thousand times less common than the major neurotransmitters
- Mainly modulatory, slow
- Originate in brainstem, but released throughout the entire brain and spine

Glutamate

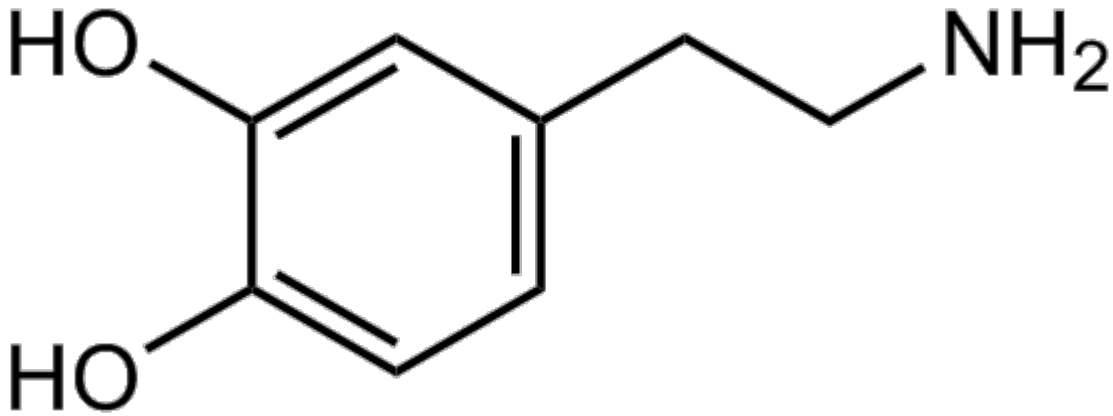


The most common excitatory neurotransmitter Glutamate is releasd by 80% of neurons

Learning

Memory

Dopamine

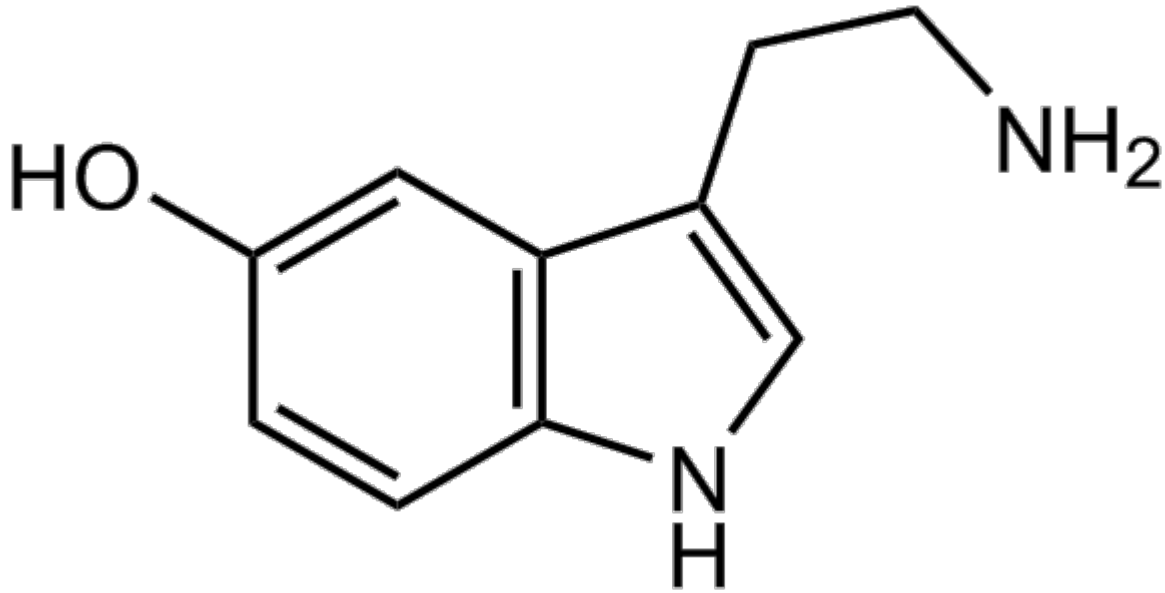


The Salience Neurotransmitter

Rewards sex, eating

Increases alertness, happiness

Serotonin (5-HT)



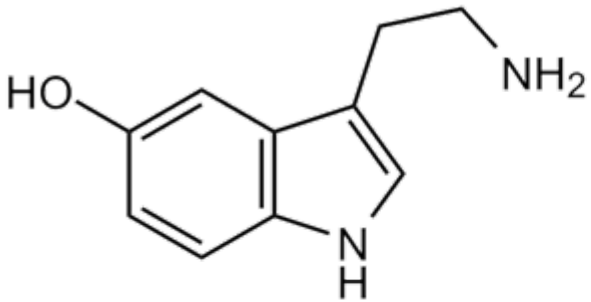
The Satiety Neurotransmitter

Feelings of fullness, contentment

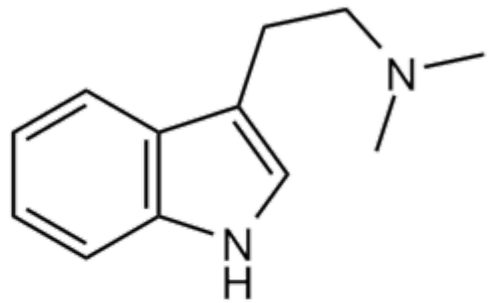
Relieves depression

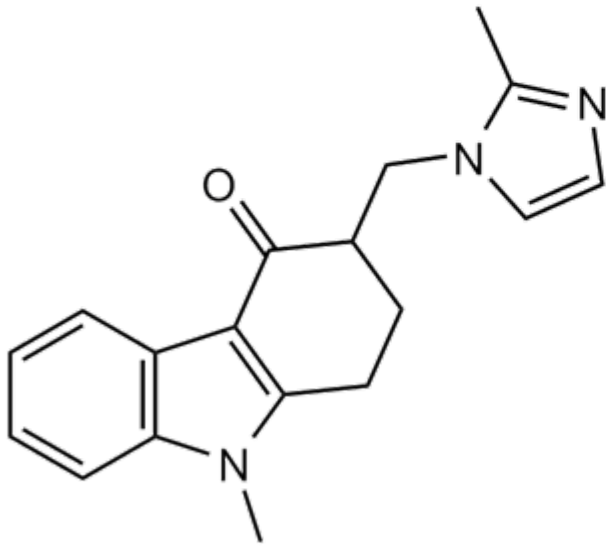
Serotonergic drugs I

Serotonin

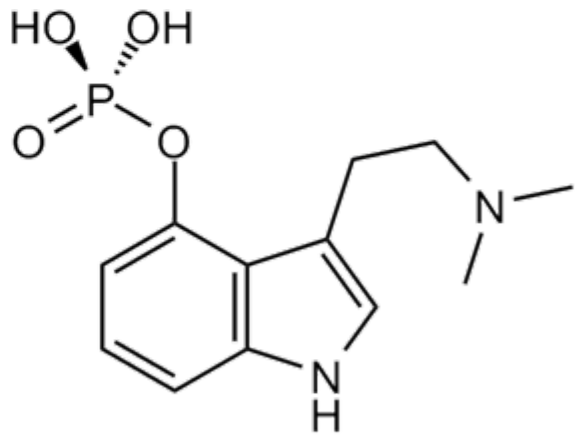


Dimethyltryptamine
DMT



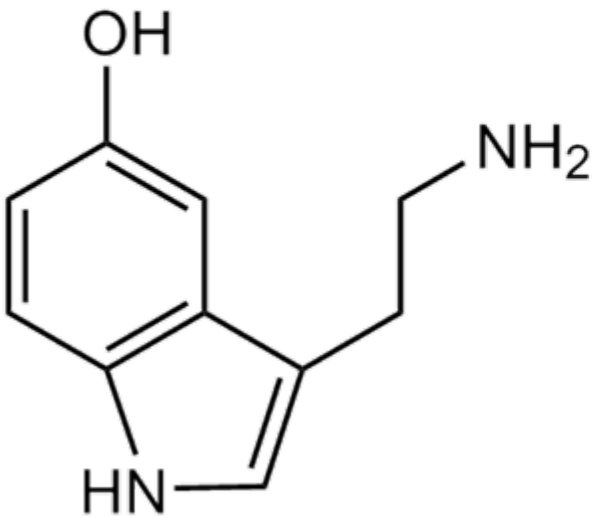


Ondansetron
Zofran

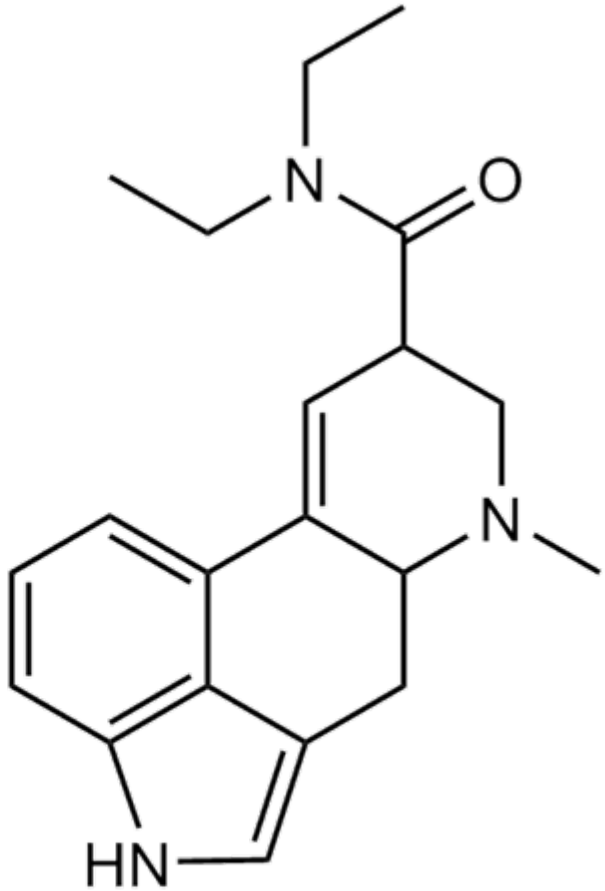


Psilocybin

Serotonergic drugs II



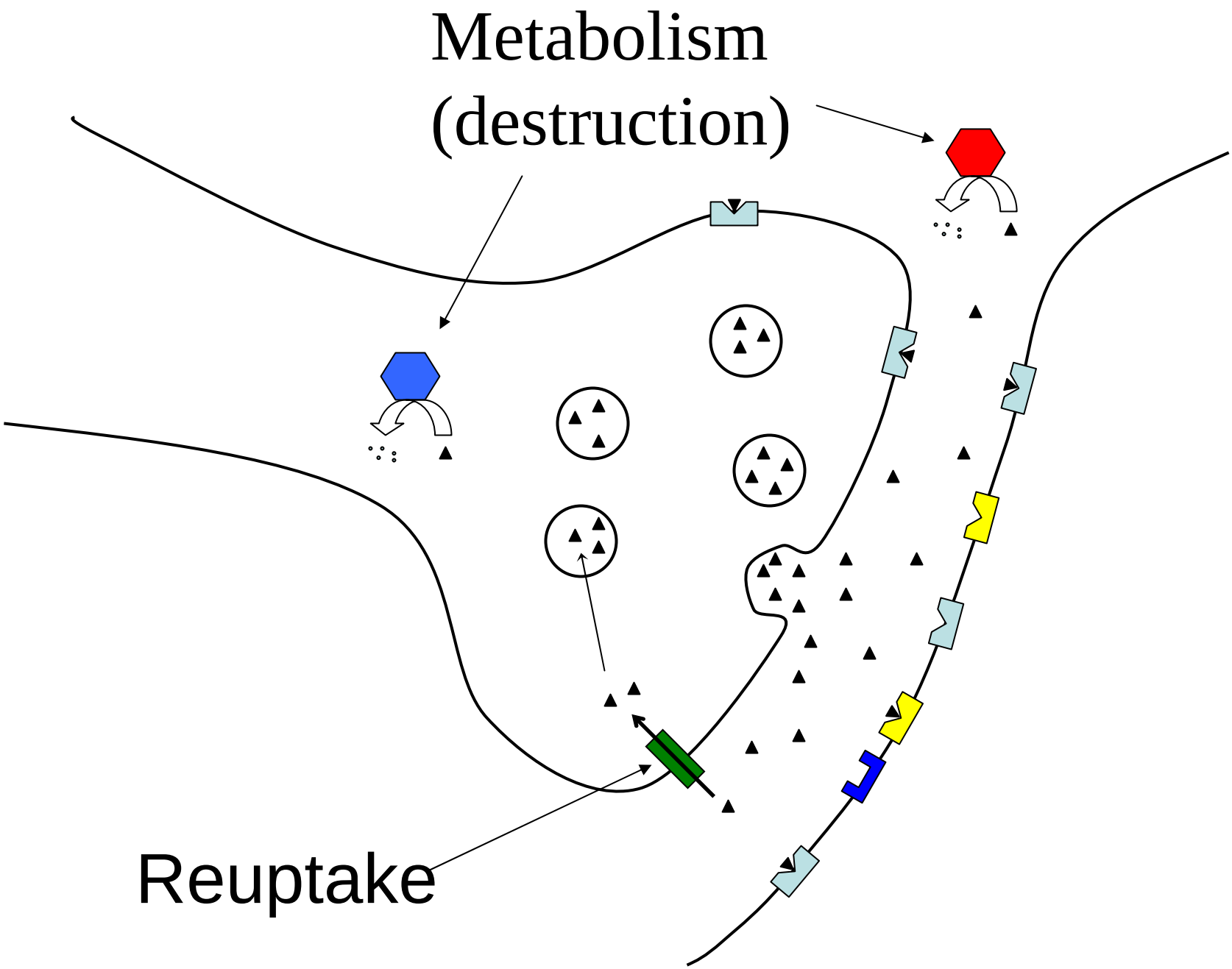
Serotonin



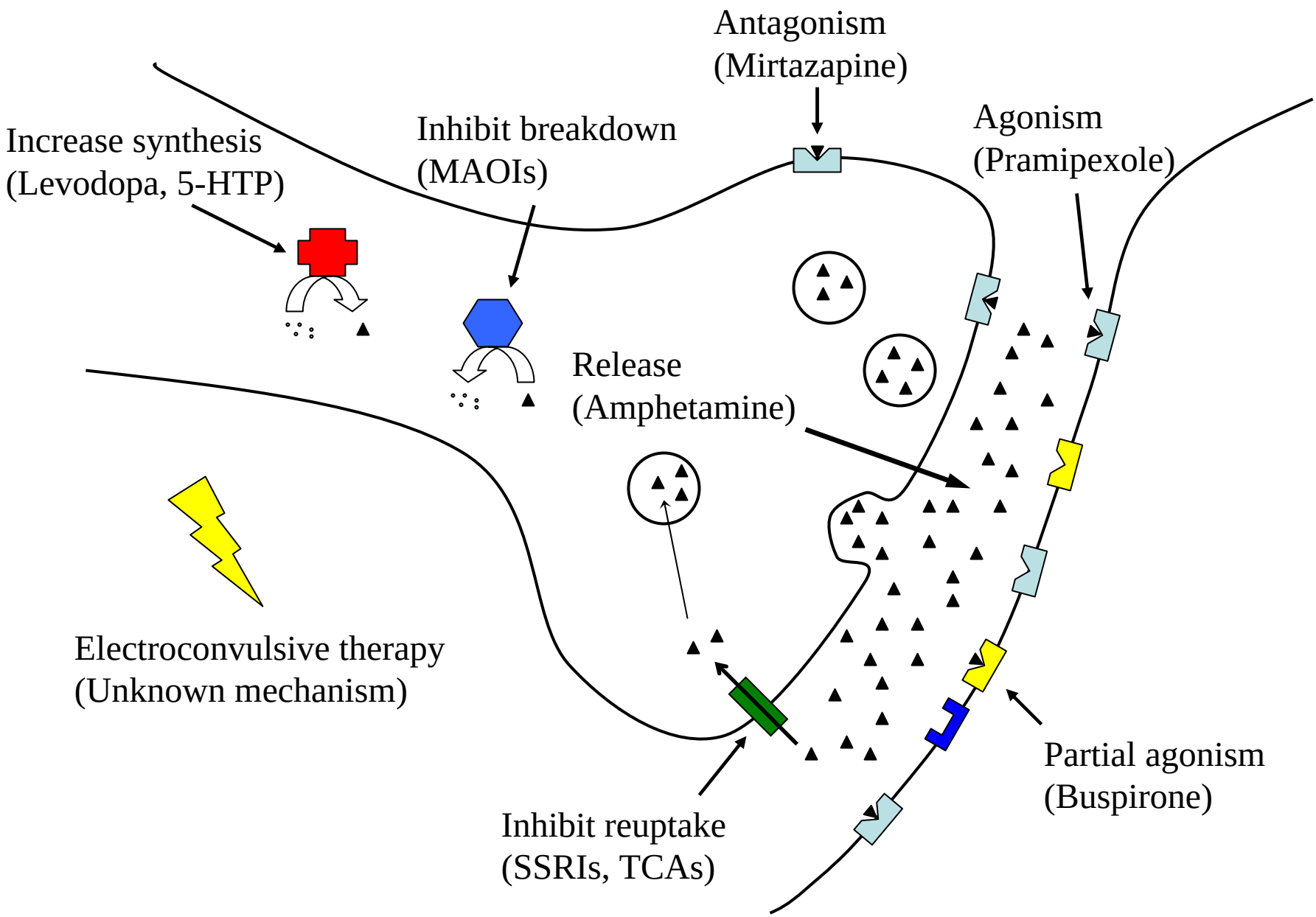
Lysergic Acid Diethylamide

Topics to choose from:

- Appetite and obesity
- Parkinson's disease *see psychosis
- OCD (Obsessive-Compulsive Disorder)
- Schizophrenia and psychedelic drugs
- Addiction
- Depression
- ADHD *see addiction
- Pain


Metabolism
(destruction)
Reuptake

Antidepressant Mechanisms



Key

Increases/causes OR excitatory (synapse)

Note: An arrow from one brain region to another is glutamate, unless otherwise noted

Decreases/blocks OR inhibitory (synapse)

Note: A T-headed arrow from one brain region to another is GABA, unless otherwise noted

Modulates

The relationship may be complex and/or poorly understood

Entity

A brain region, cell, protein, or other entity

Entity

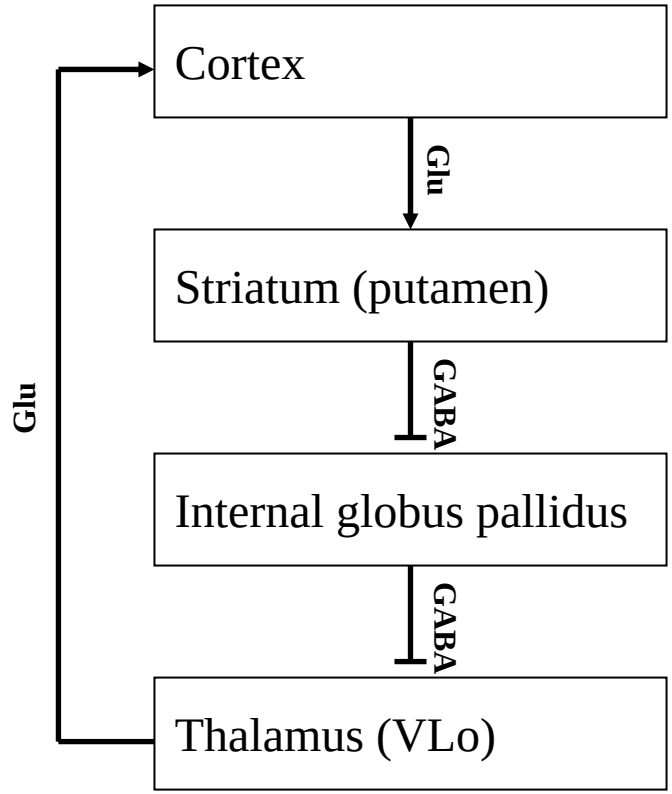
Hypoactive, decreased, or dead

Entity

Hyperactive, increased

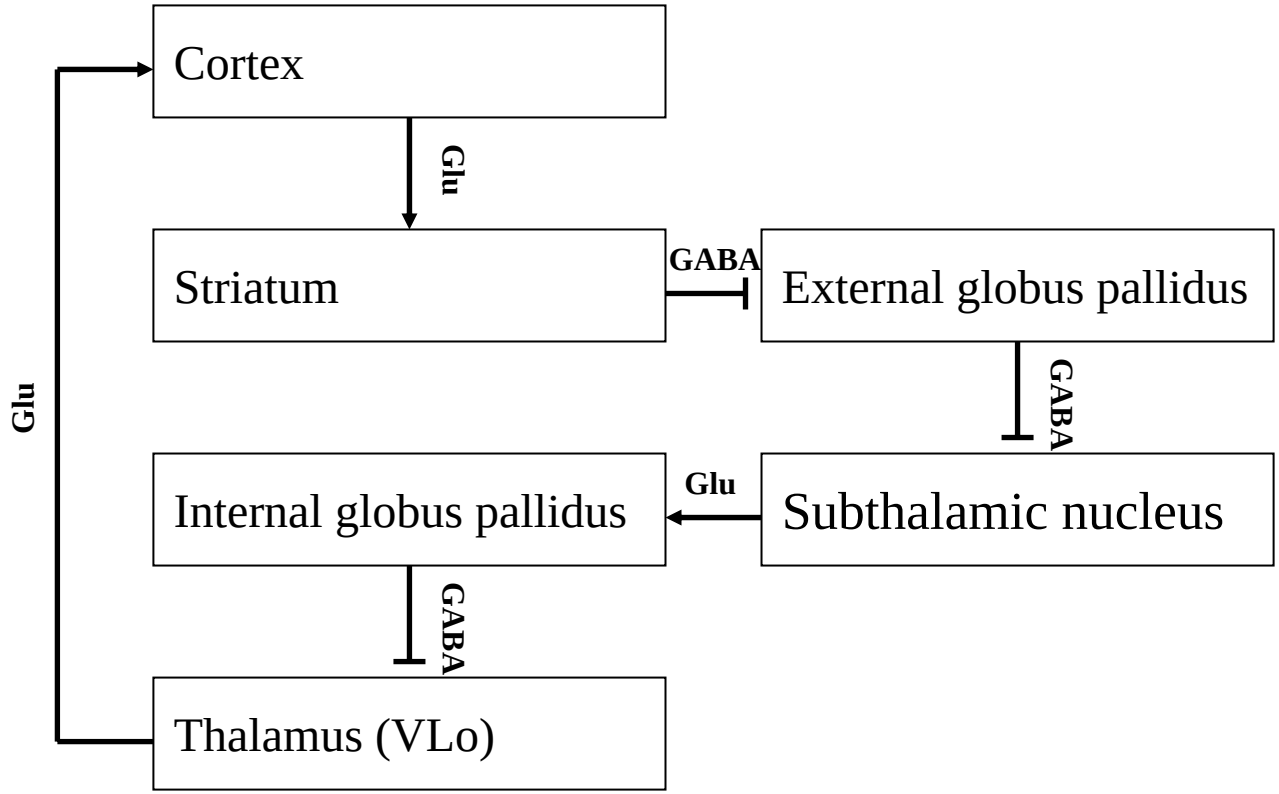
The direct pathway

Amplifies activity in the cortex. It is thought that a plan for movement is a small flurry of activity in the cortex, and that neural activity (plan) is amplified by going through this loop several times until finally enough activity builds up and the movement is performed.



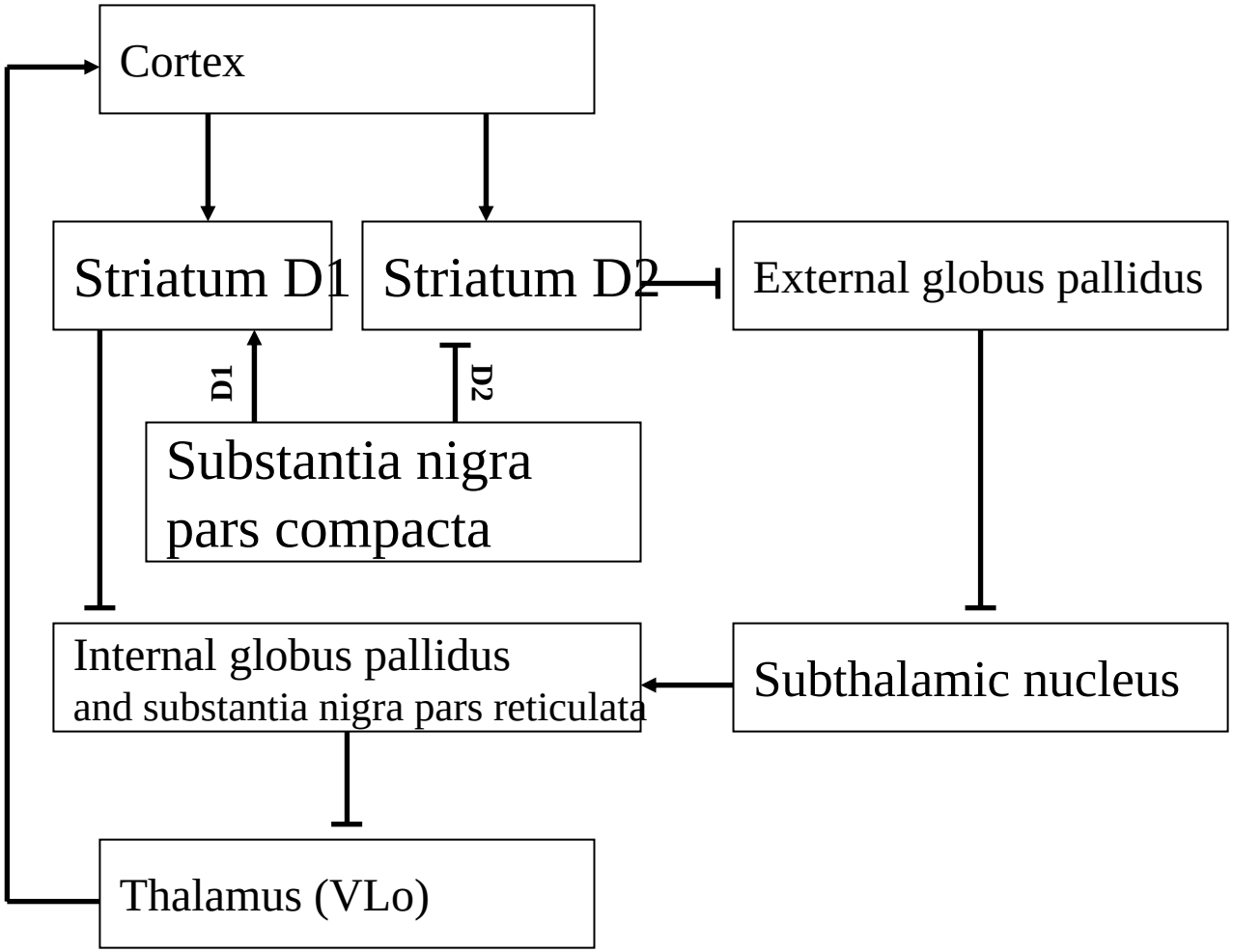
The indirect pathway

This inhibits activity in the cortex, rather than amplifying it like the direct pathway. This inhibitory loop may be important for eliminating plans that we do not carry out, so that only certain movements are chosen and executed.



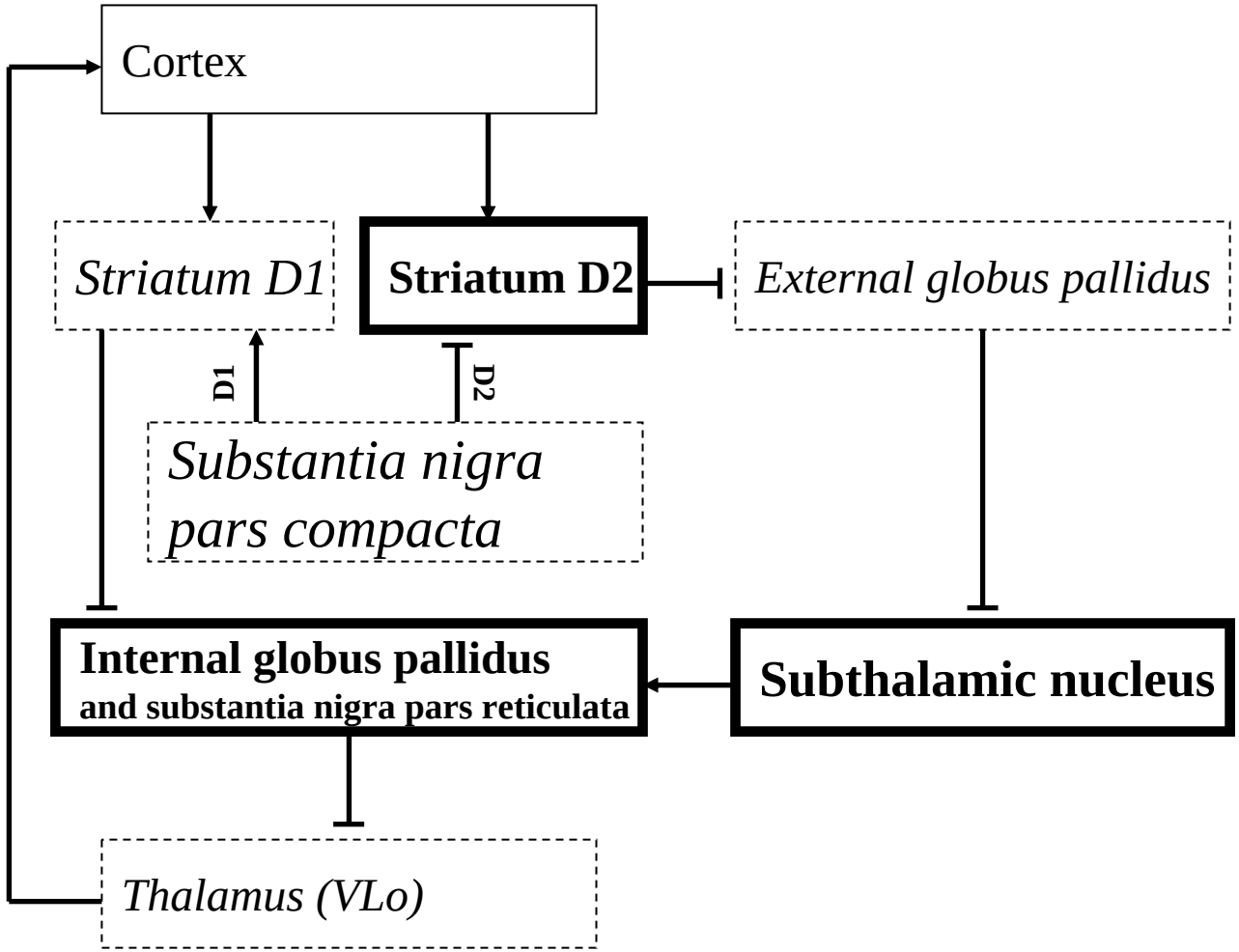
Adding the substantia nigra

Dopamine from the substantia nigra pars compacta activates the direct pathway and inhibits the indirect pathway, both of which have the net result of reinforcing cortical activity.



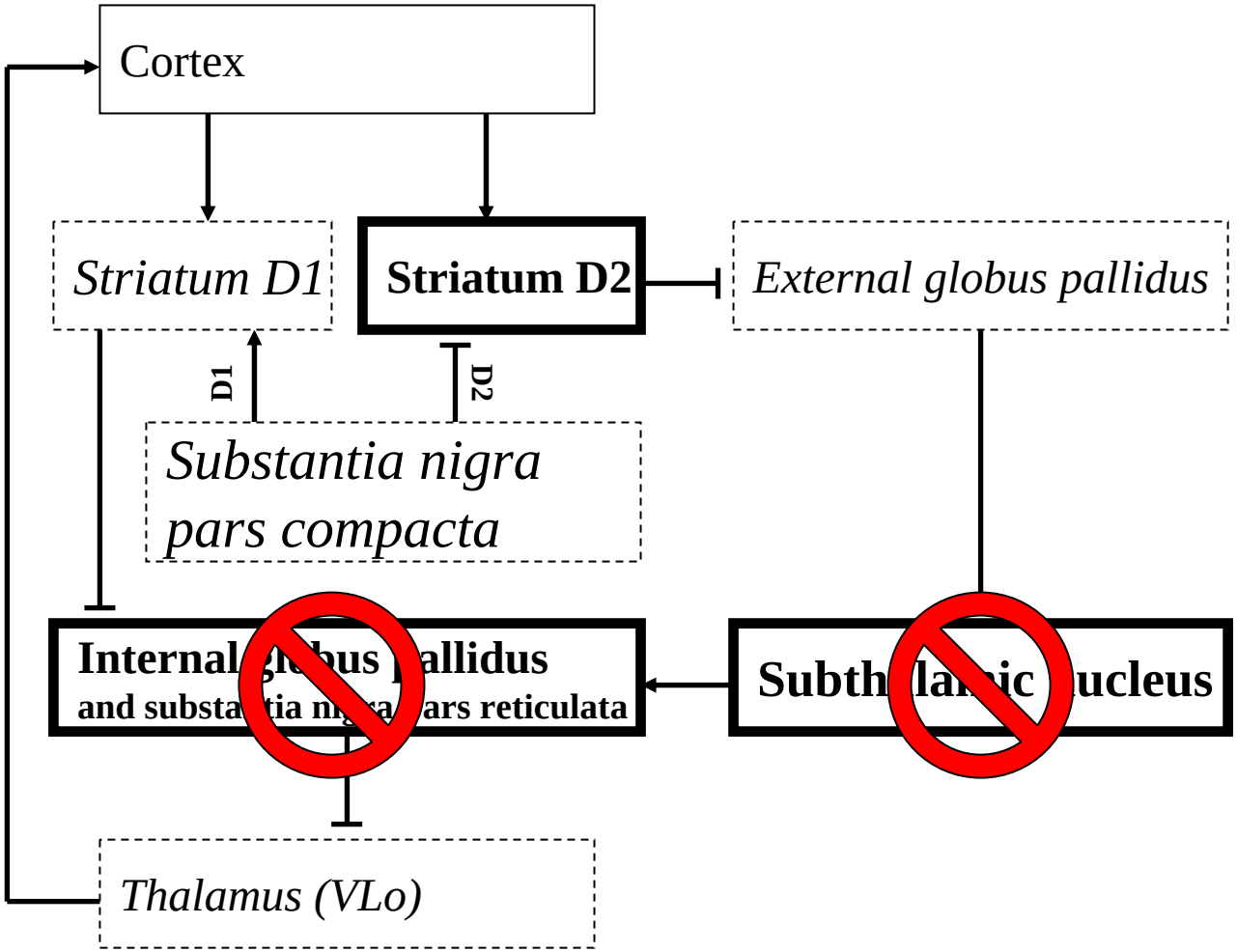
Parkinson's Disease

The substantia nigra pars compacta dopaminergic neurons die, leading to the pattern of hyper- and hypoactivity shown here, which ultimately leads to decreased activity in the areas of cortex necessary to initiate movement.



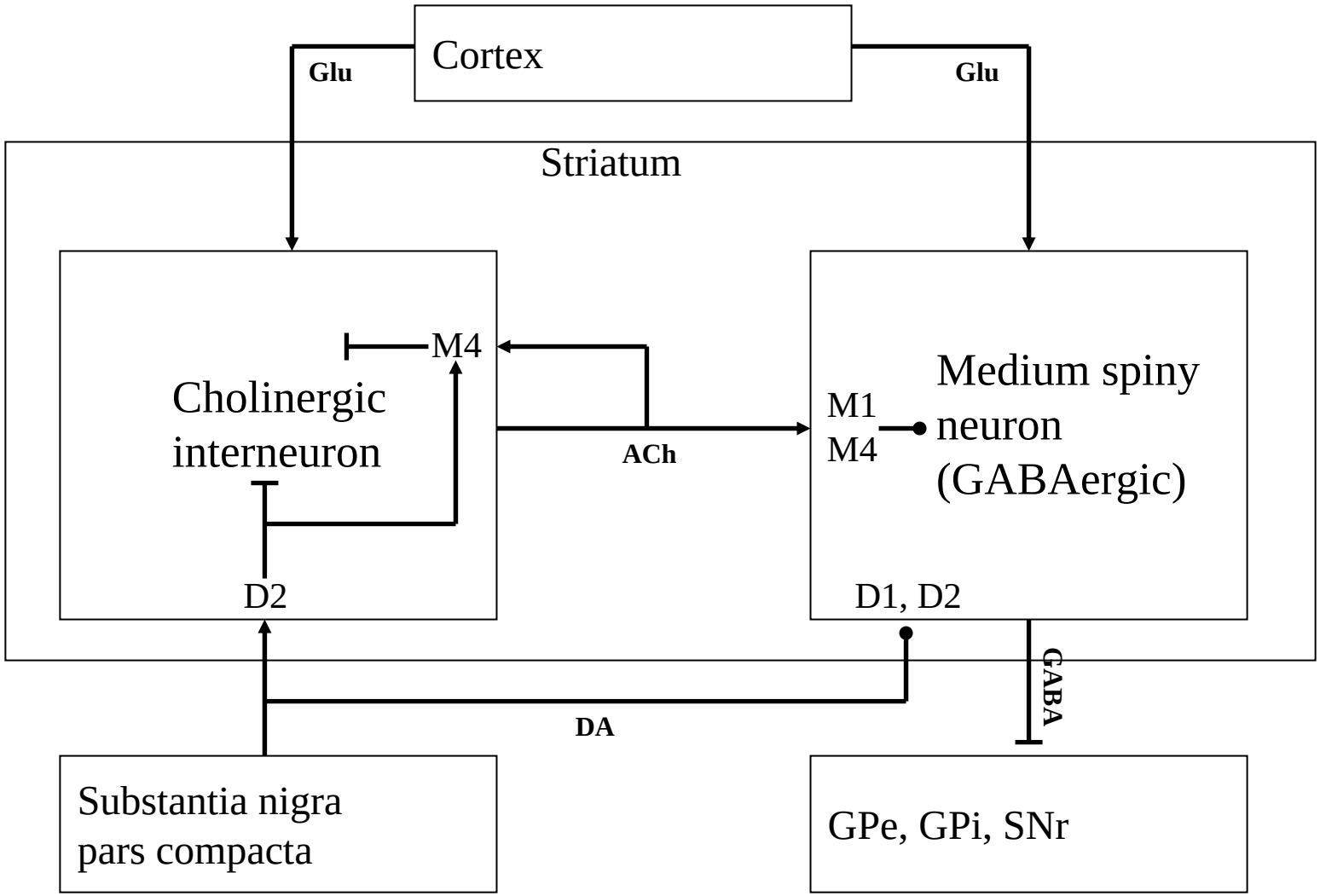
Treatments for PD

Surgical lesions or deep brain stimulation can inhibit the globus pallidus or subthalamic nucleus, hopefully reversing their pathological overactivity.



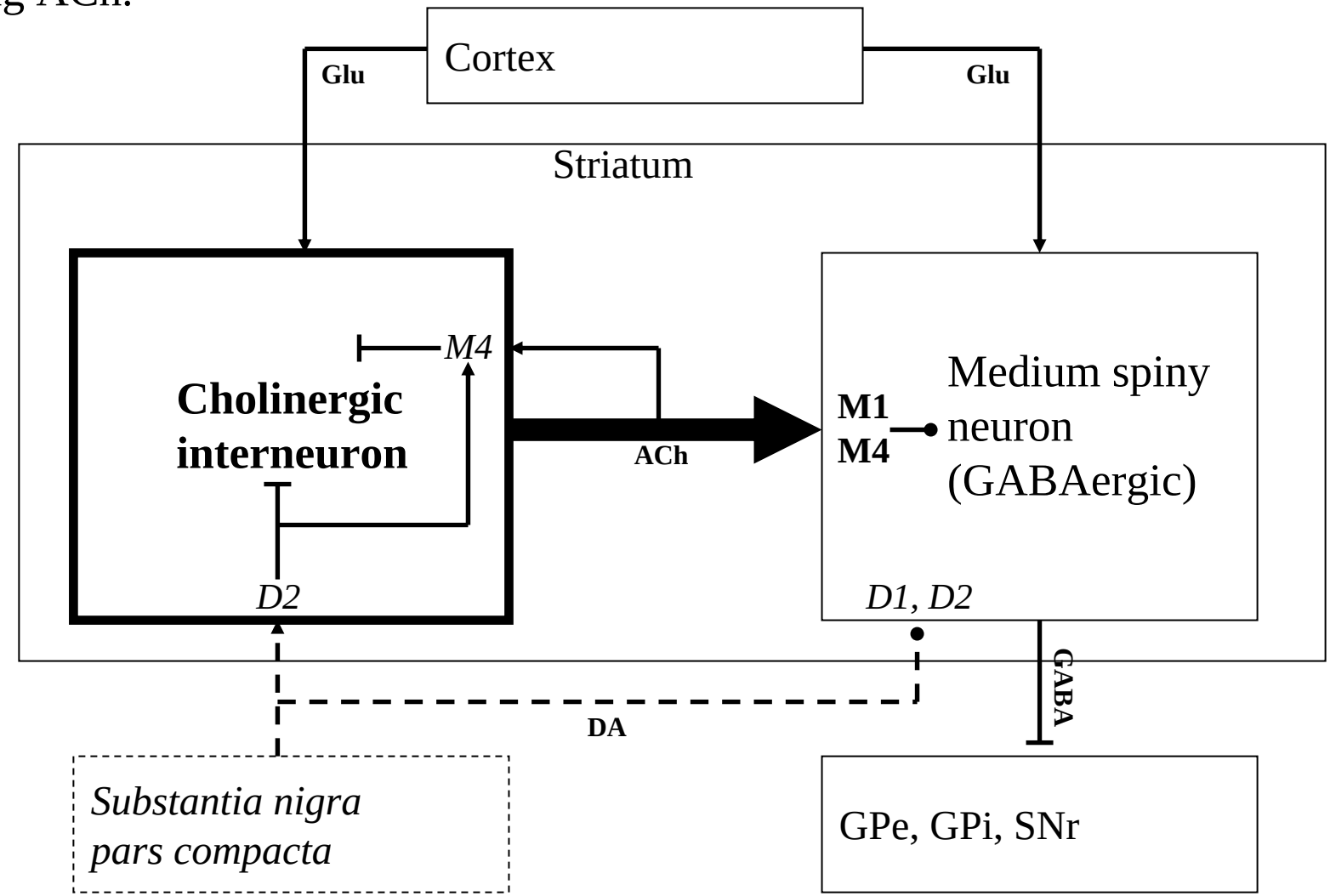
Synaptic structure

Dopamine from the substantia nigra pars compacta activates the direct pathway and inhibits the indirect pathway, both of which have the net result of reinforcing cortical activity.



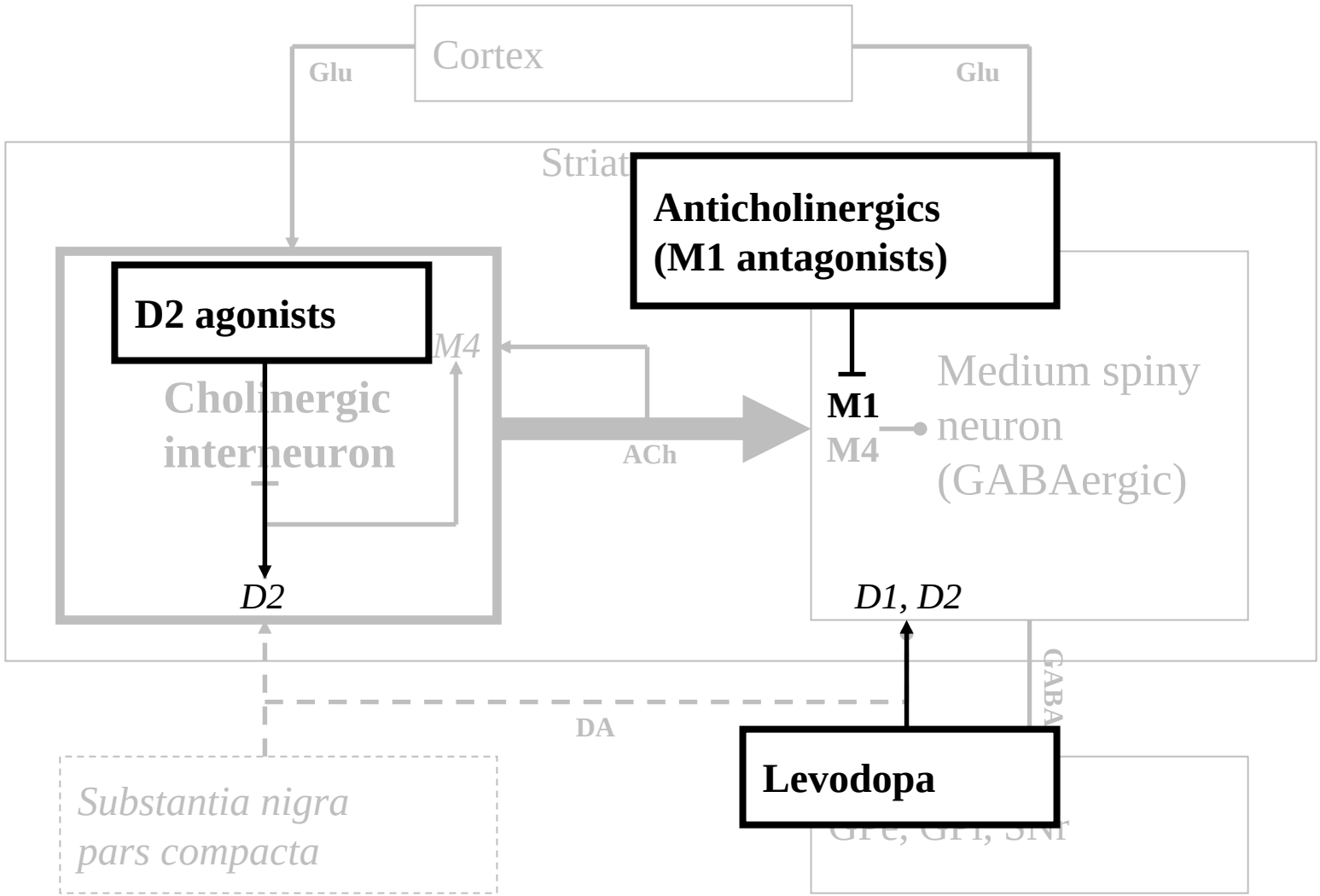
ACh/DA balance in PD

There is too little DA in Parkinson's Disease (PD). This causes symptoms directly through D1 and D2 receptors on the MSNs, but it also causes symptoms indirectly by elevating ACh.



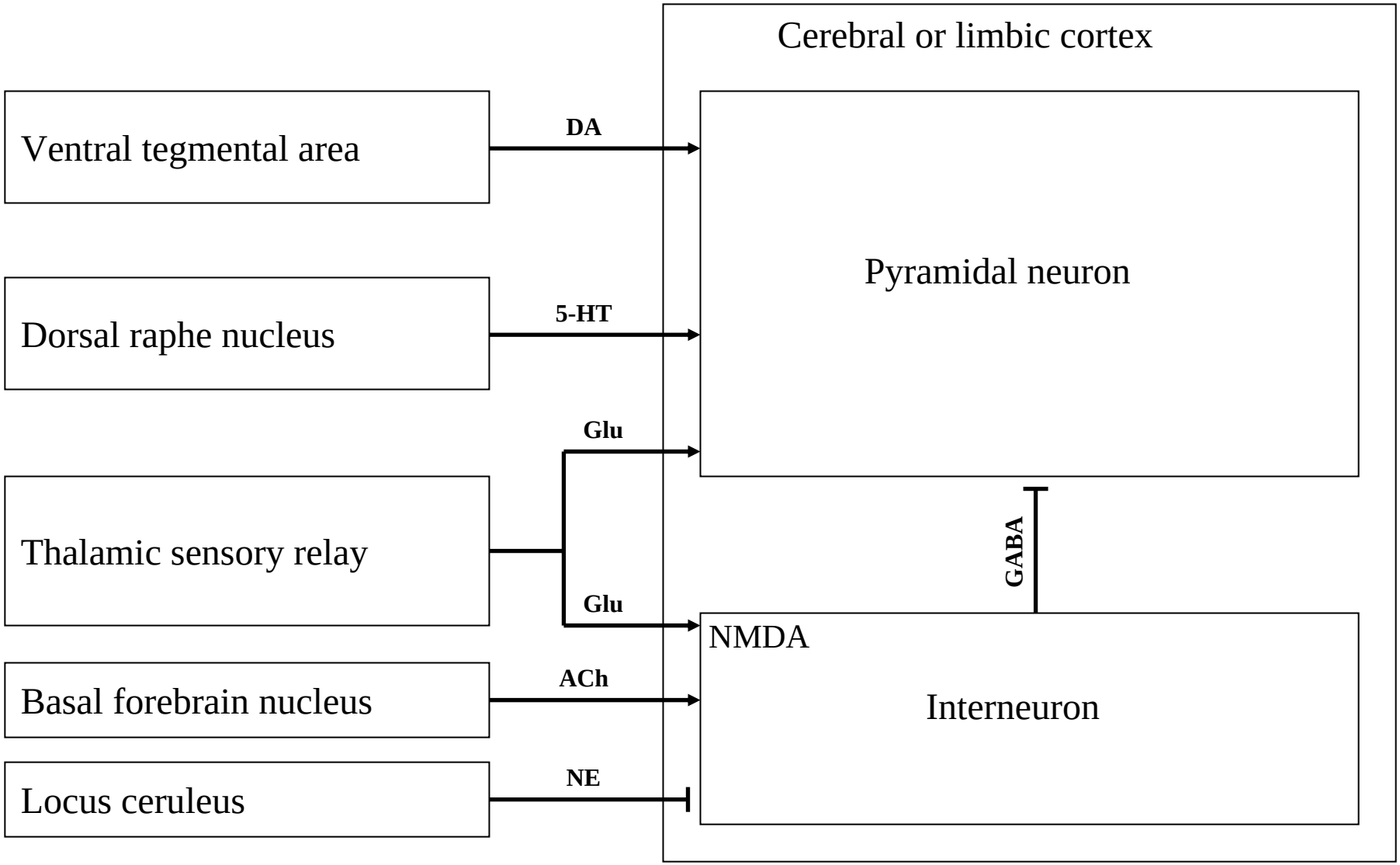
ACh and DA drugs for PD

Drugs that increase DA or decrease ACh can help alleviate the symptoms of PD.



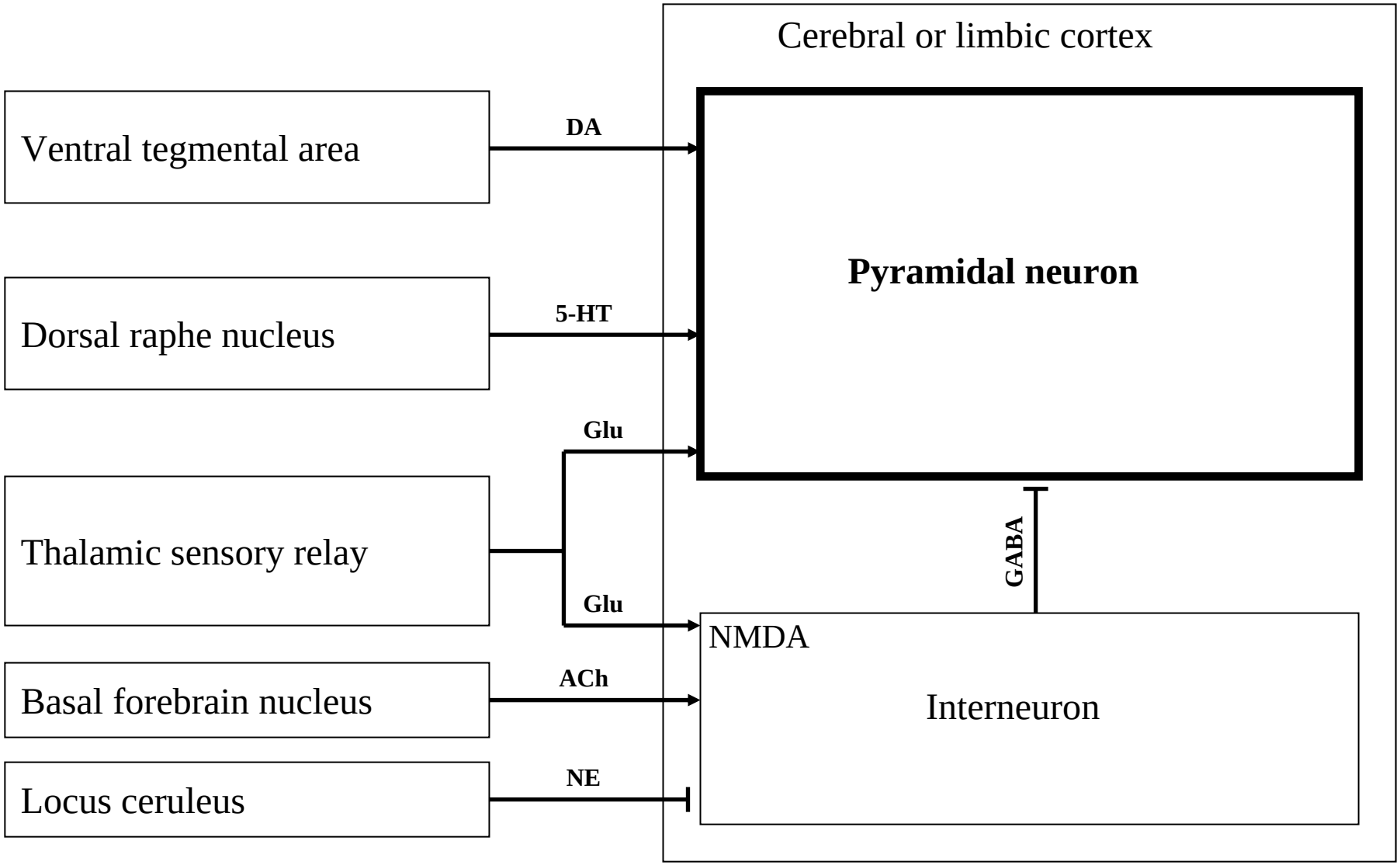
Schizophrenia

This diagram shows the pathways that may be involved in schizophrenia.



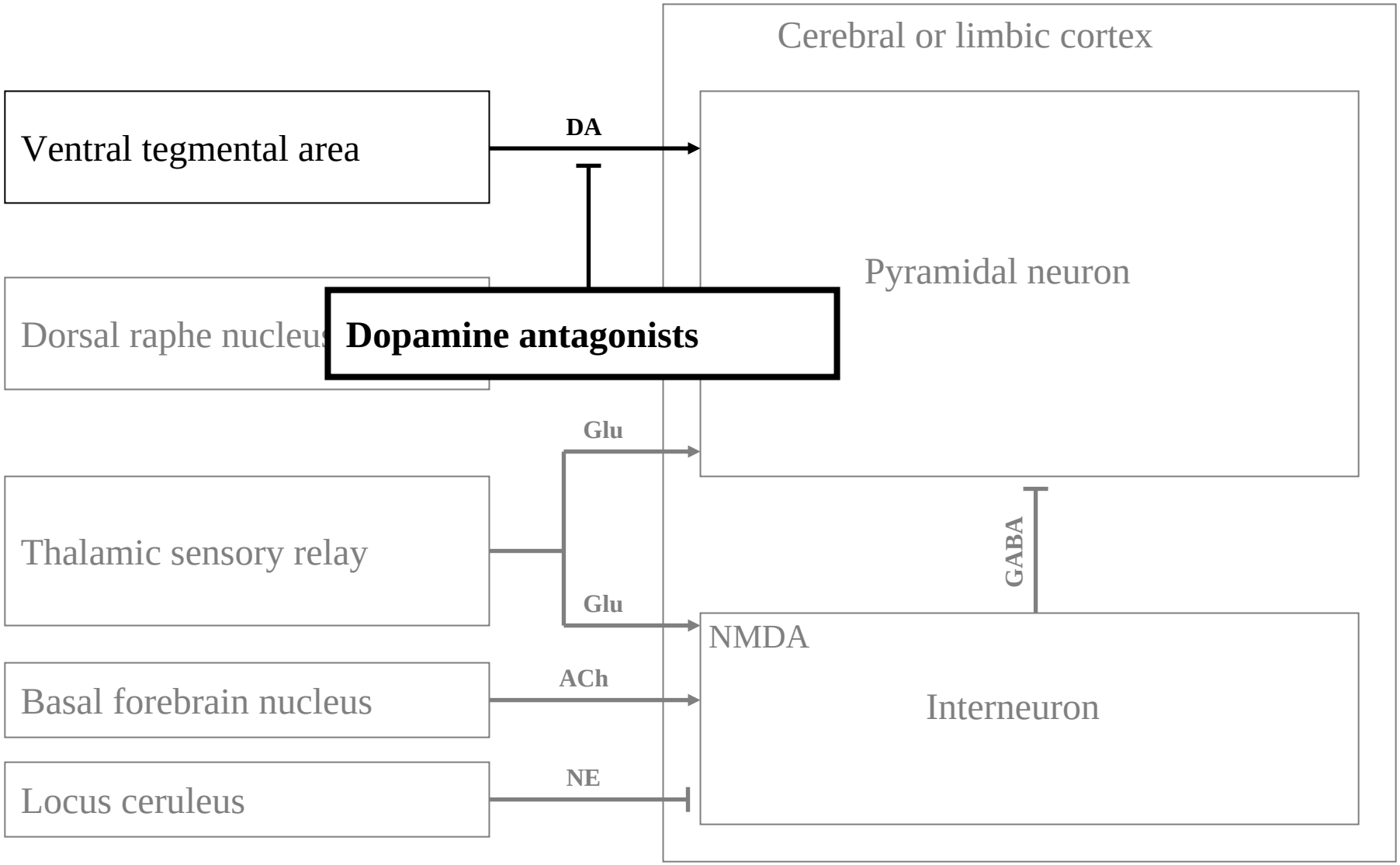
Schizophrenia

Psychosis results when the pyramidal neurons are overly excited and fire too often.



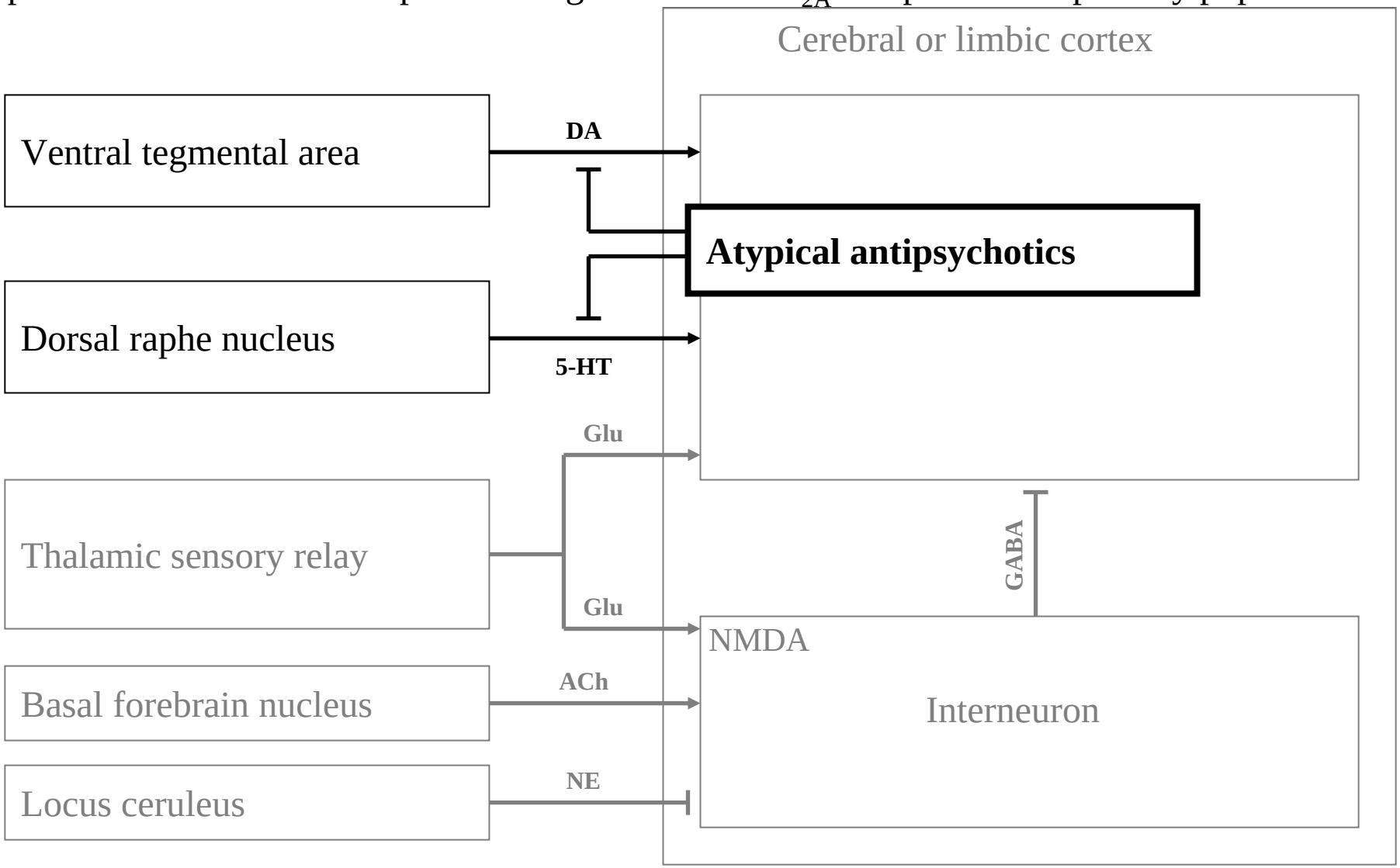
Antipsychotics

Typical antipsychotics, also called neuroleptics, are antagonists at dopamine receptors



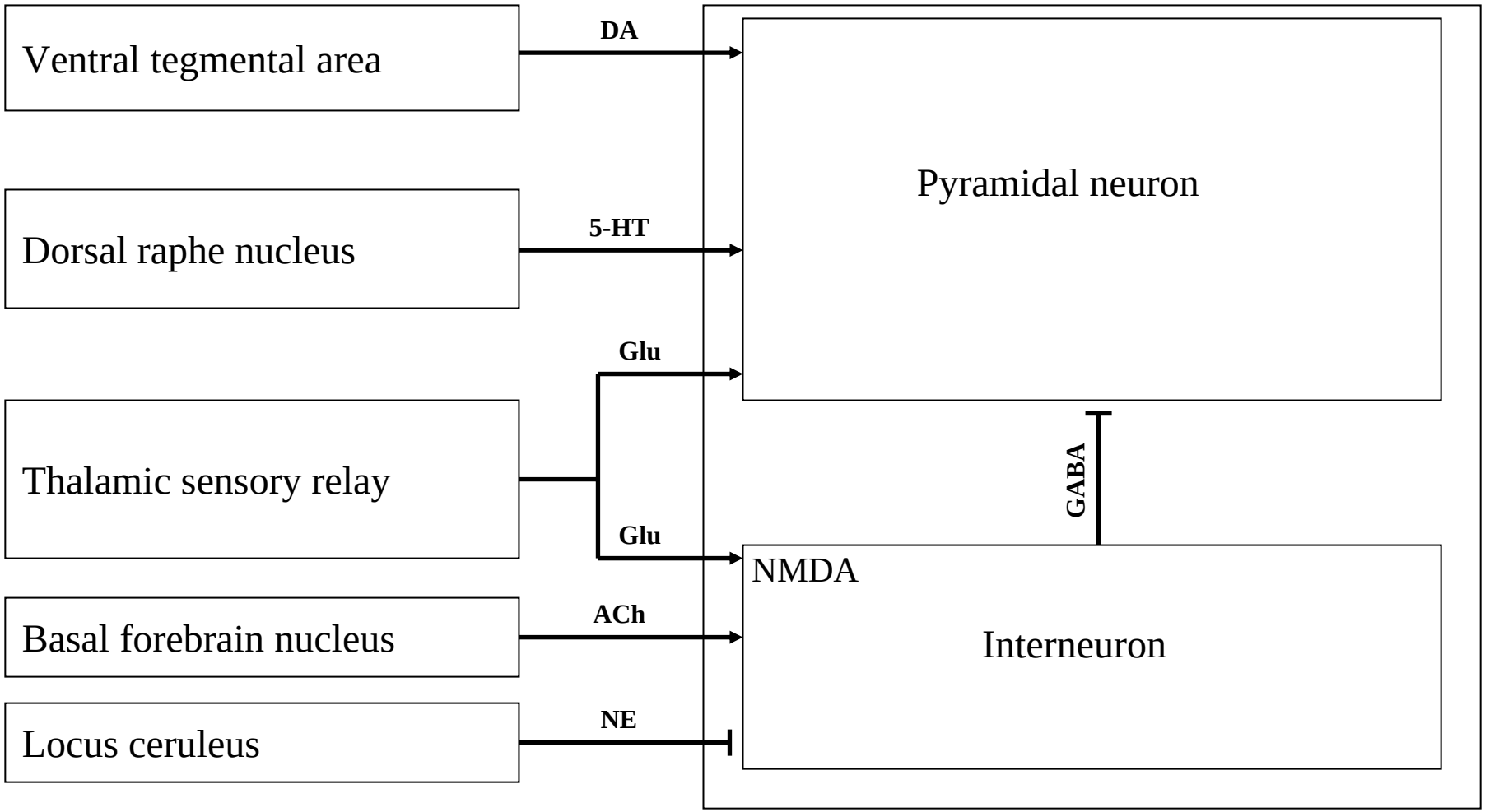
Atypical antipsychotics

Atypical antipsychotics (second-generation antipsychotics) are often antagonists at both dopamine and serotonin receptors. Antagonists of 5-HT_{2A} receptors are especially popular.



Psychotomimetics

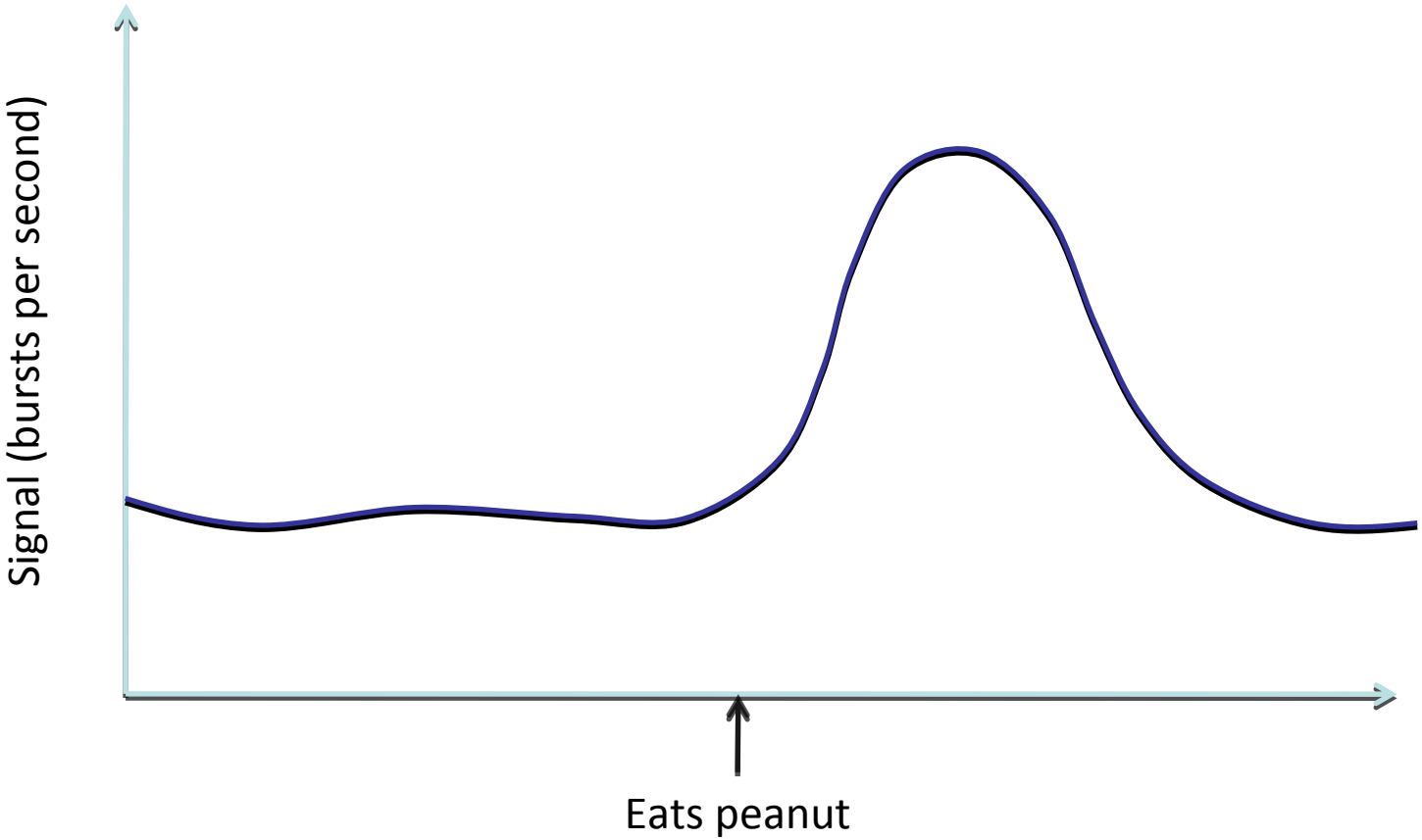
Psychotomimetics are drugs that cause psychosis. Drugs that increase 5-HT, DA, and/or NE are all psychotomimetics (amphetamine, cocaine, psychedelics). Drugs that block NMDA receptors (ketamine, PCP, dextromethorphan) and drugs that block muscarinic ACh receptors (anticholinergics) are also psychotomimetic.



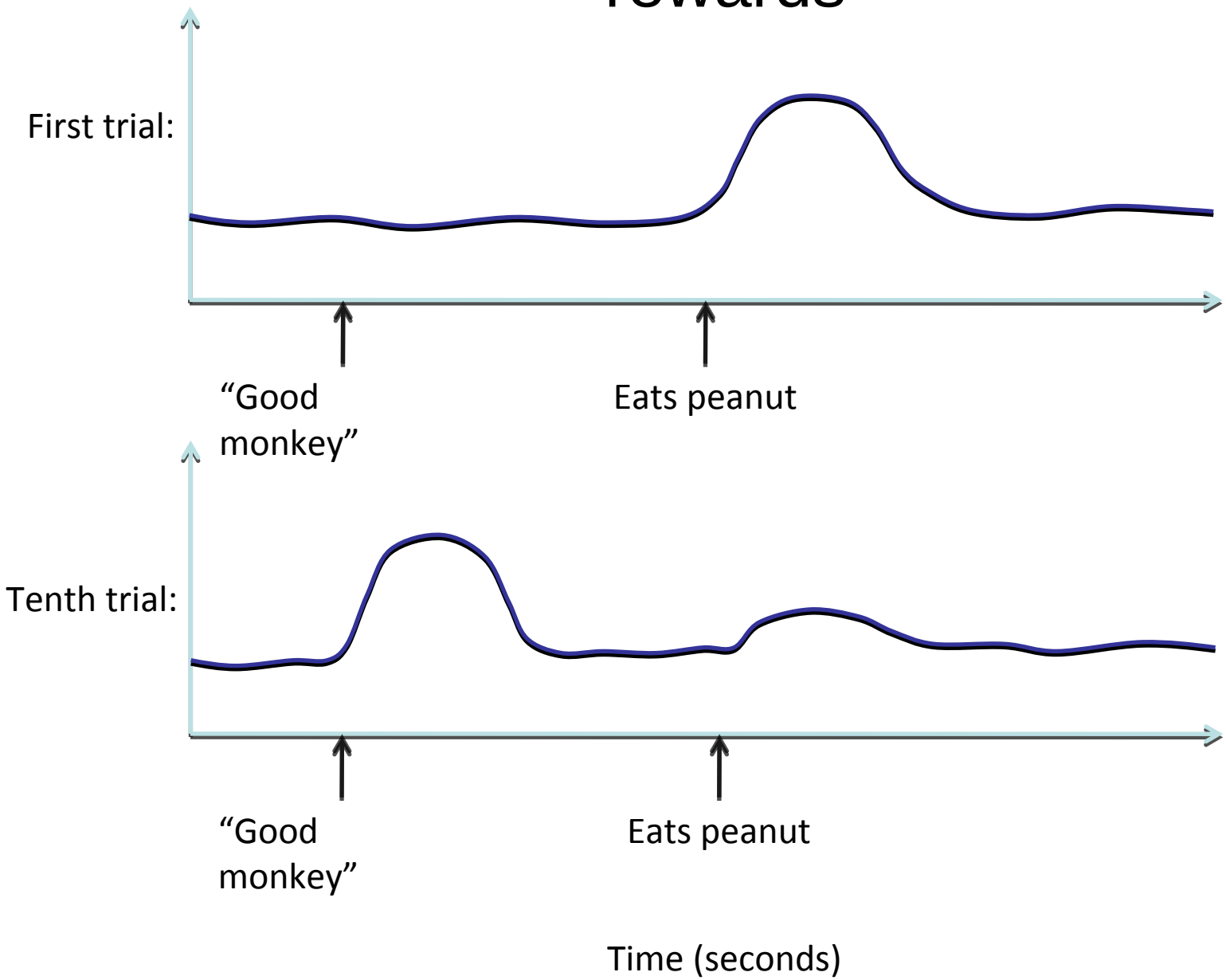
Other psychosis treatments

- Benzodiazepines, which boost the inhibitory effect of GABA, can effectively suppress psychosis. (This was predicted by the diagram.)
- Clozapine increases ACh release, which helps alleviate psychosis (as predicted).
- Many antipsychotics block NE, which further helps treat psychosis.

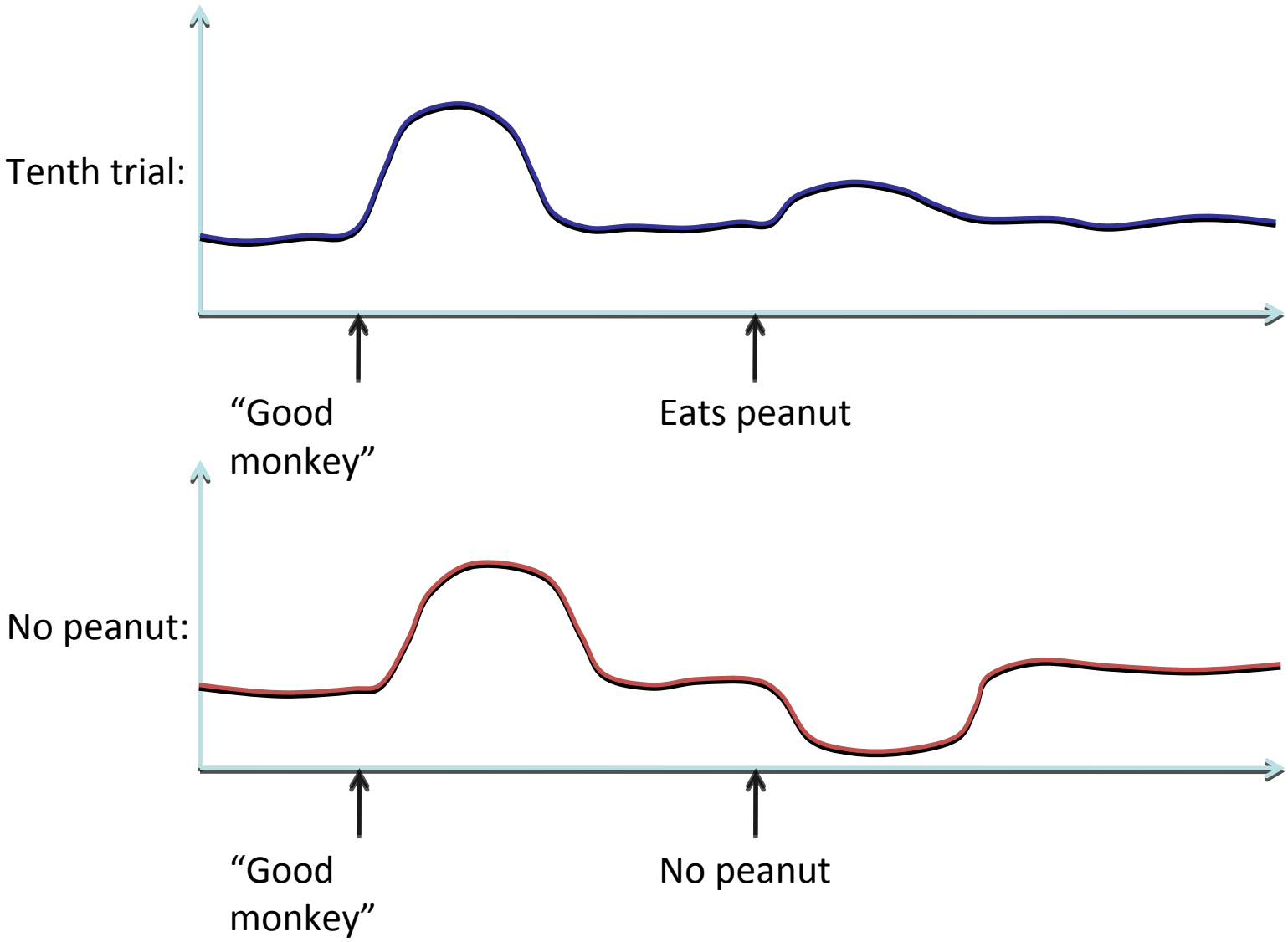
Dopamine signals unexpected rewards



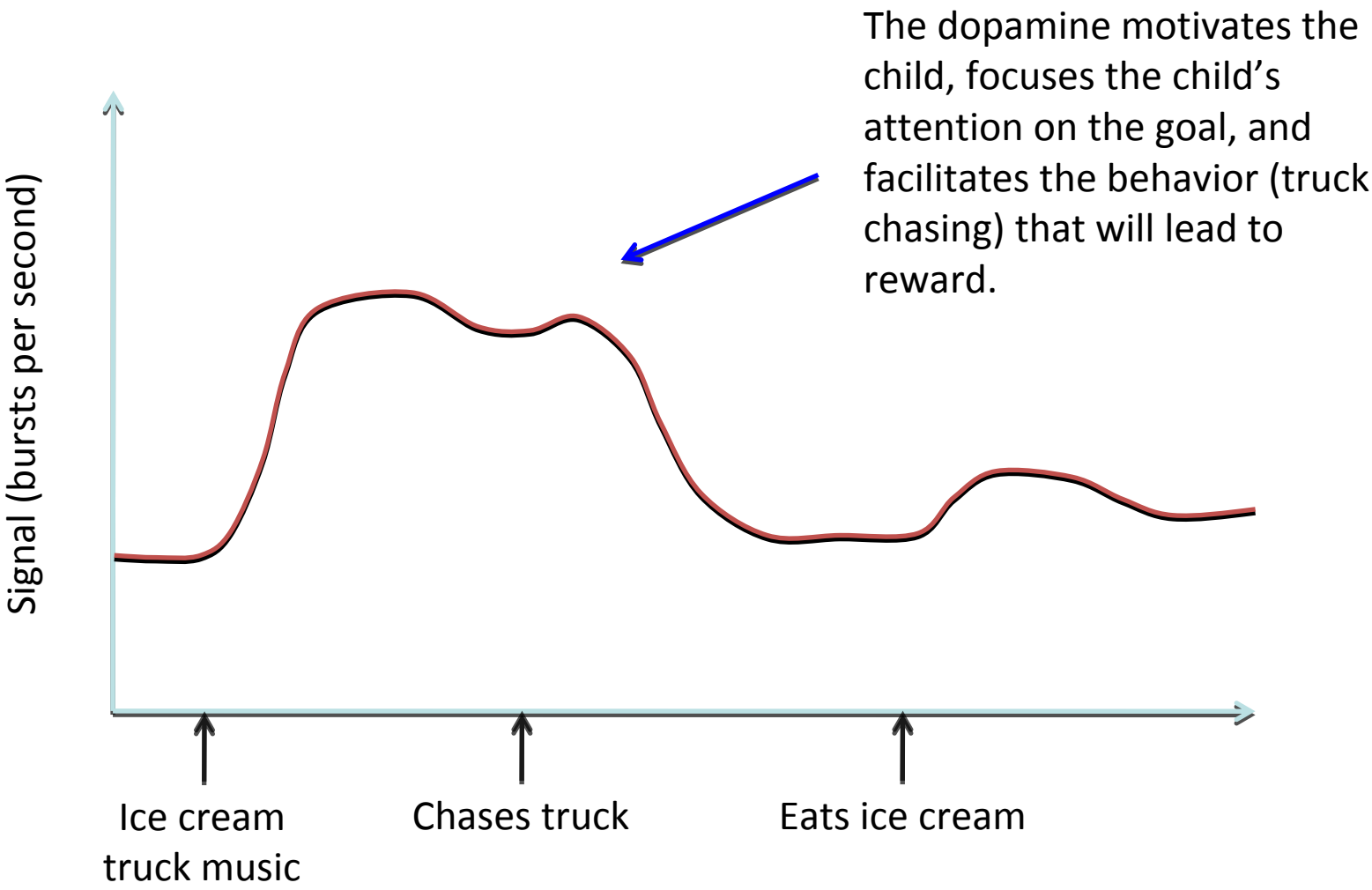
Dopamine signals predicted/expected rewards



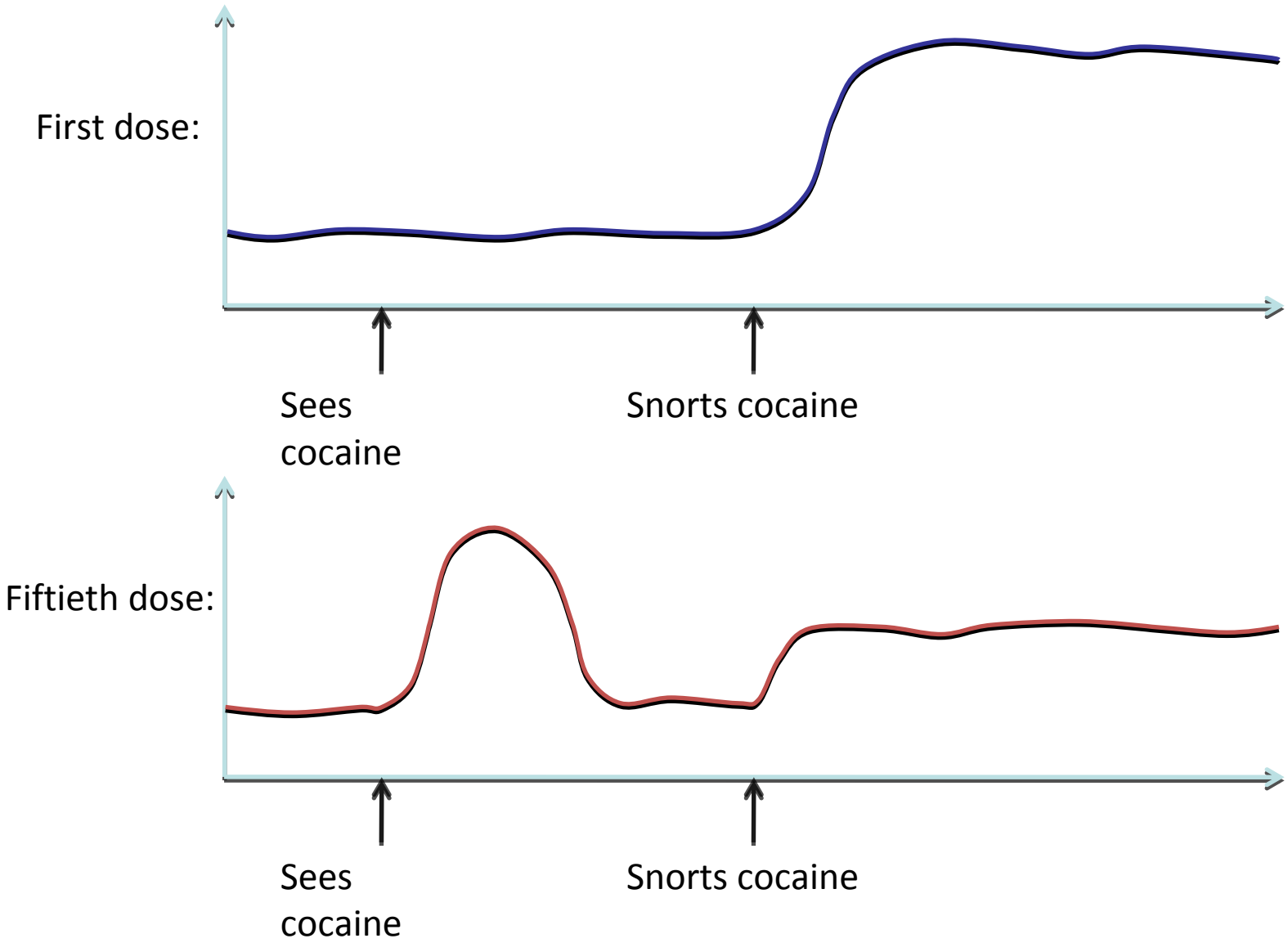
Dopamine signals error in prediction



The dopamine burst motivates the animal

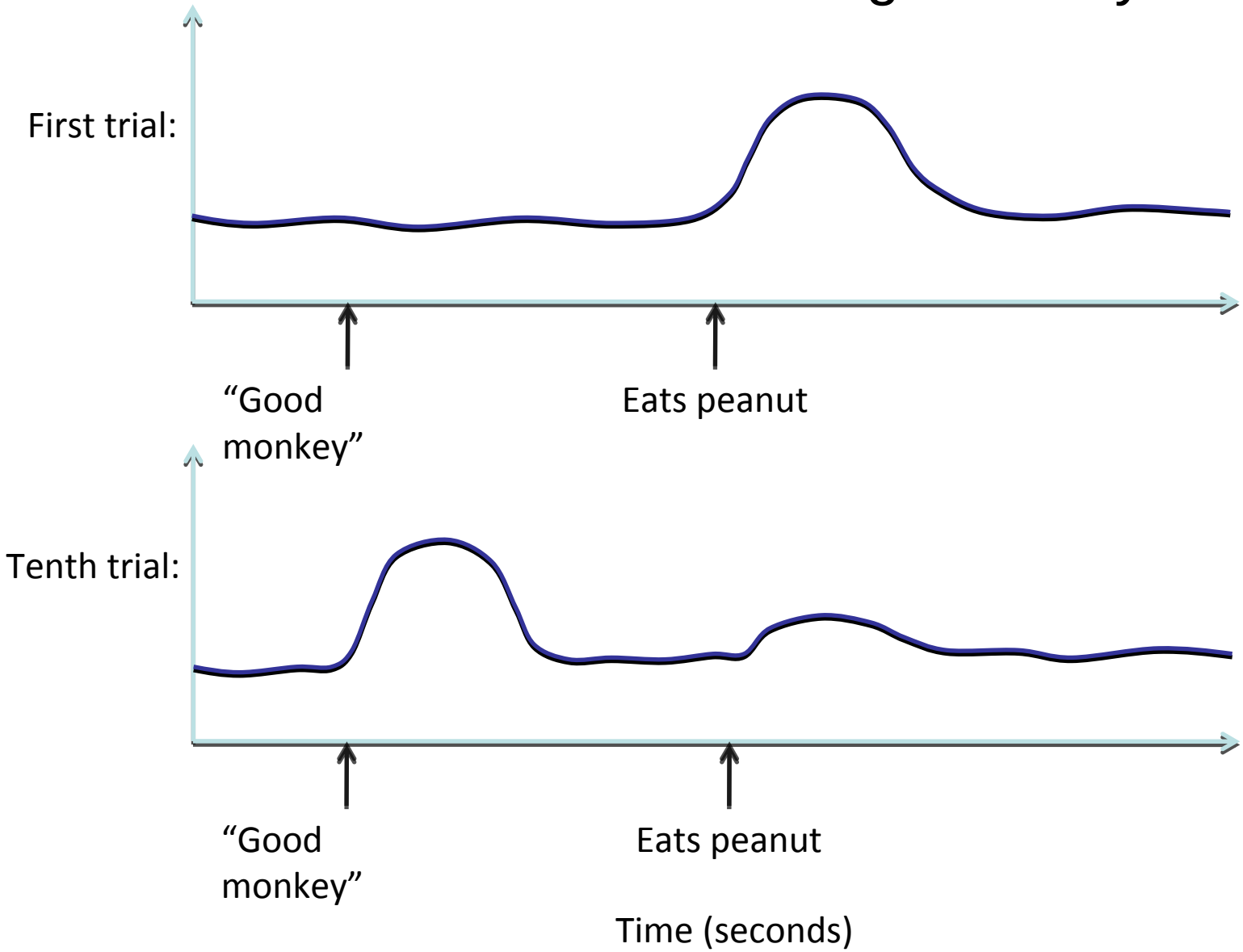


Drugs of abuse mimic natural reward



Why does seeing cocaine cause dopamine release?

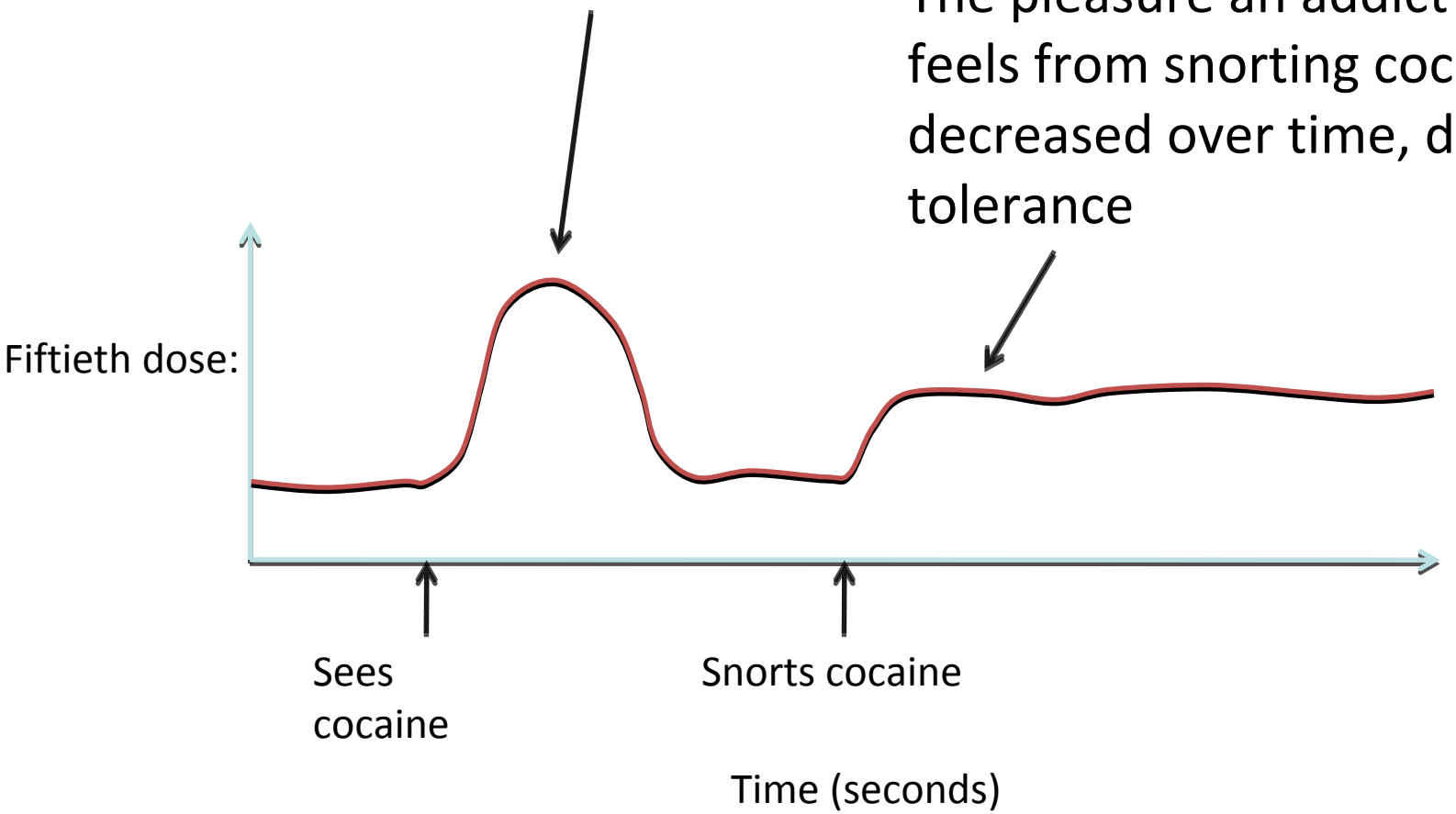
Remember how conditioning normally works:



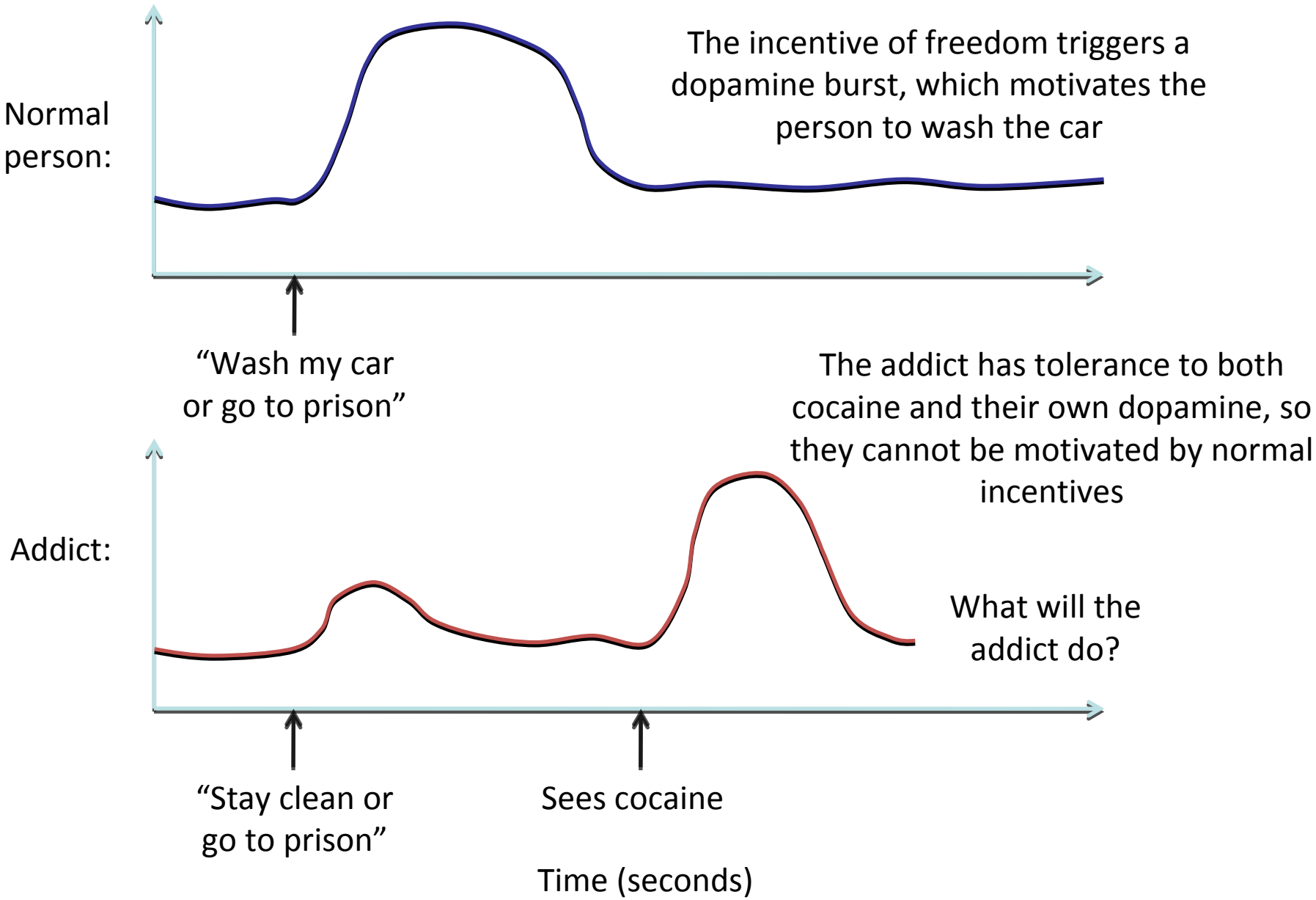
Drugs of abuse mimic natural reward

When an addict sees cocaine, the dopamine burst *produced by his own cells* motivates him to get cocaine and snort it.

The pleasure an addict actually feels from snorting cocaine is decreased over time, due to tolerance



Drug addicts are insensitive to non-drug motivators



Liking versus wanting

Addicts don’t like doing drugs as much as they used to

Addicts want to do drugs

Addicts don’t want to do anything else

Speed of onset and addiction

Drugs which take effect quickly are more addictive, because a fast spike in dopamine more closely mimics natural rewards and the drug-taking behavior is more closely associated with the reward if they come close together

Speed of onset and addiction

Faster onset, more addictive:

Crack cocaine

Injected heroin

Smoked meth (ice)

Slower onset, less addictive:

Powder cocaine (snorted, has an 11 minute absorption half-time)

Snorted heroin (absorbed faster than snorted cocaine. Why?)

Snorted meth (even less addictive: swallowed meth)

Speed of onset and addiction

Faster onset, more addictive:

Xanax (the fast elimination and need for more doses also increases addiction potential. Why do frequent doses lead to stronger addiction? Discuss.)

Slower onset, less addictive:

Klonopin, Librium

Speed of onset and addiction

Faster onset, more addictive:

Snorted Ritalin

Vicodin

Abused (chewed, crushed and snorted) OxyContin

Slower onset, less addictive:

Oral Ritalin

OxyContin

Properly used (intact time-release tablets) OxyContin

ADHD

ADHD is treated with stimulants that boost dopamine (and norepinephrine), why does this work?

Dopamine normally facilitates goal-directed behavior by:

- Increasing motivation
- Focusing attention on the goal
- Providing energy to work towards the goal
- Speeding learning and reinforcing memory

ADHD

Why does dopamine speed learning and reinforce memory?
Discuss