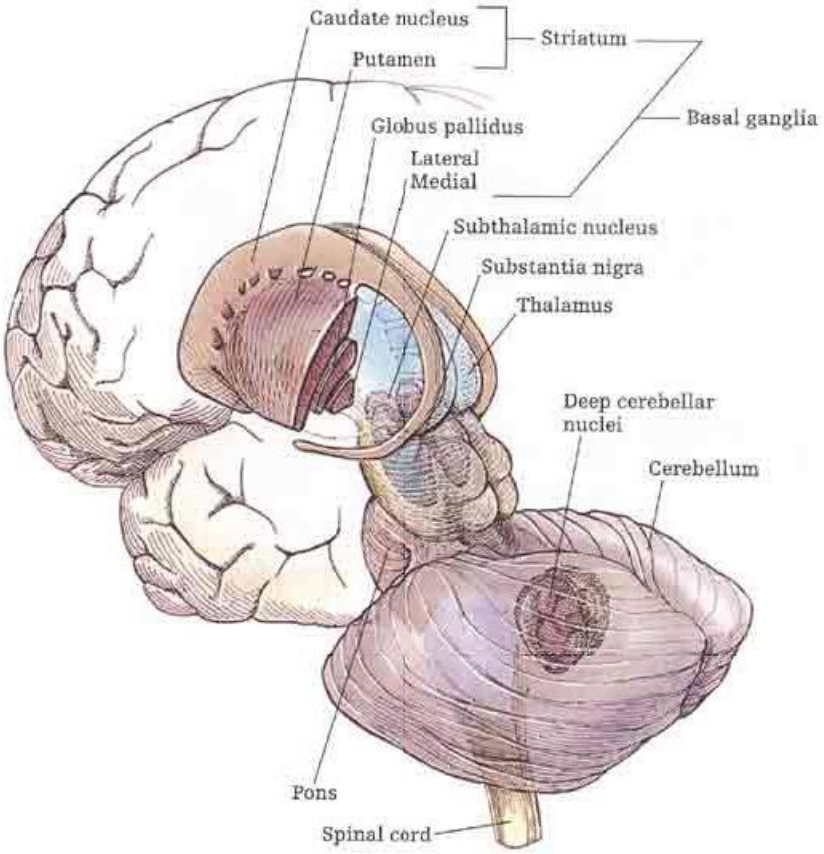
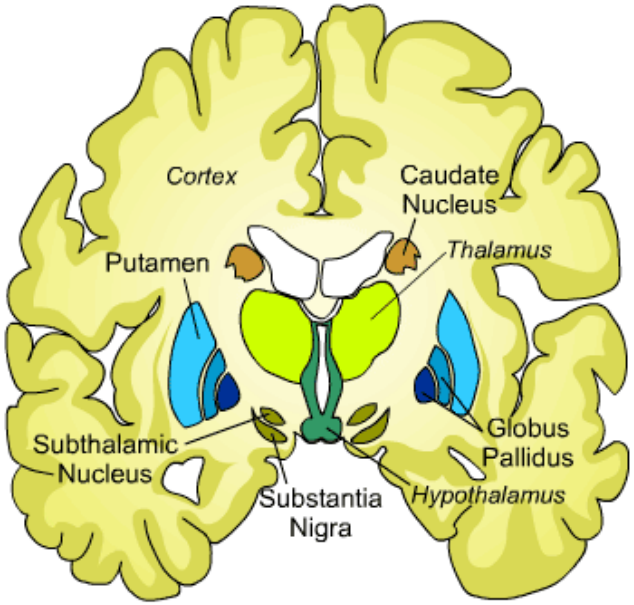
Basal Ganglia Anatomy, Physiology, and Function

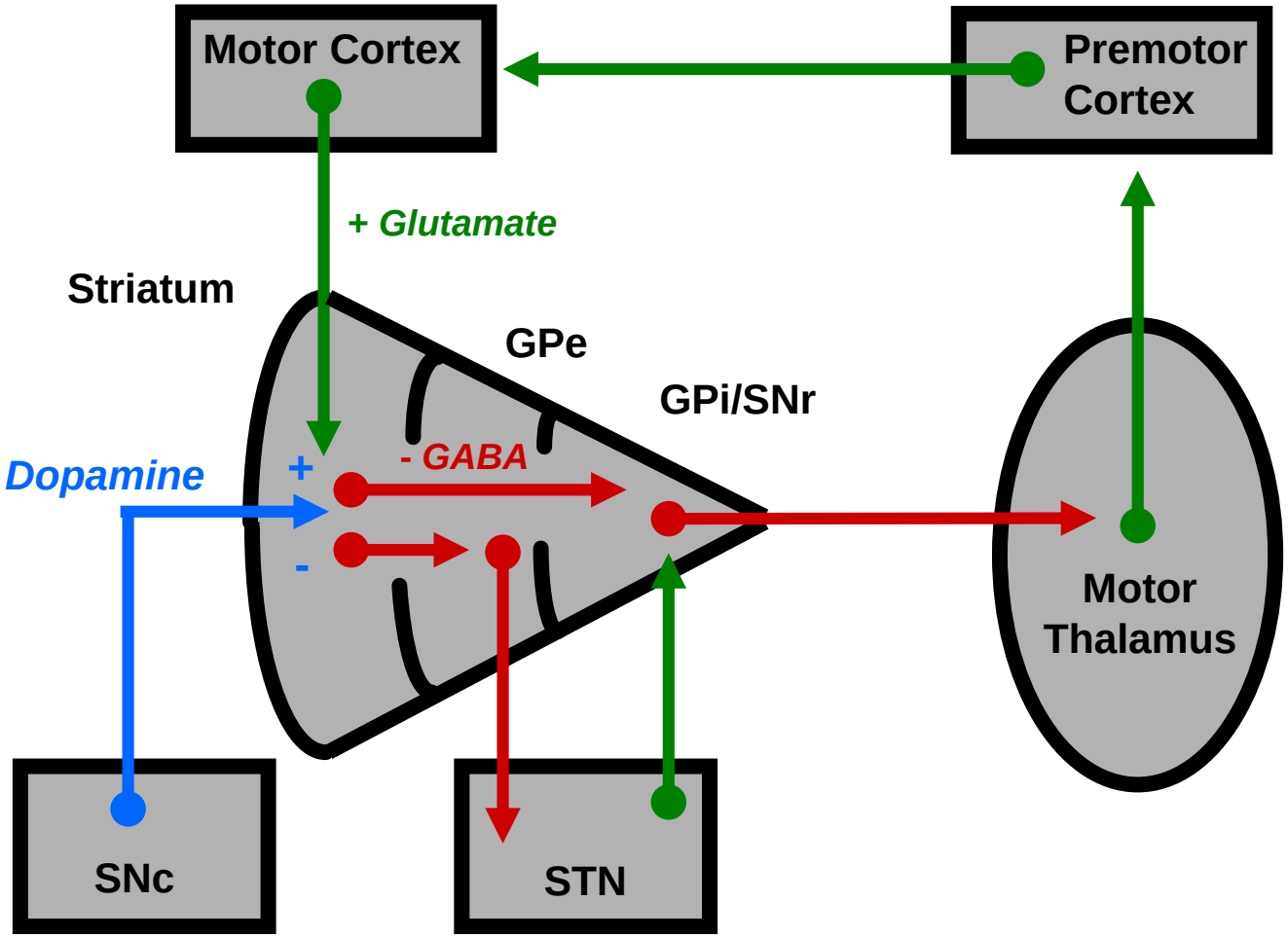
NS201c

Human Basal Ganglia Anatomy

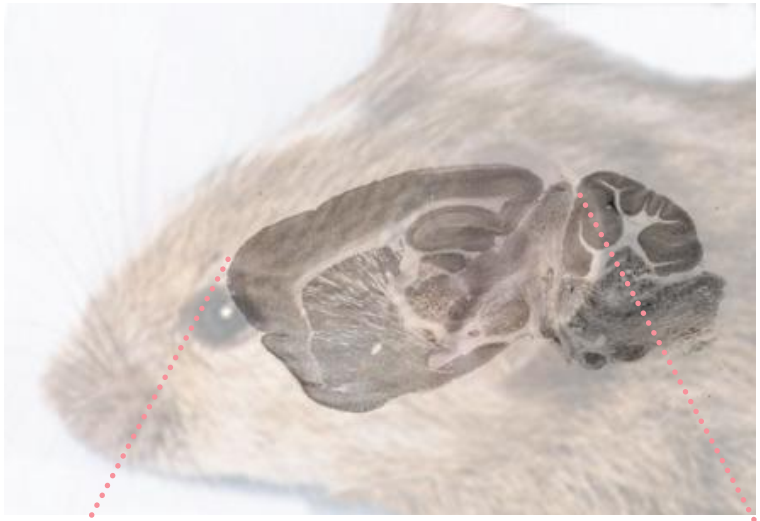


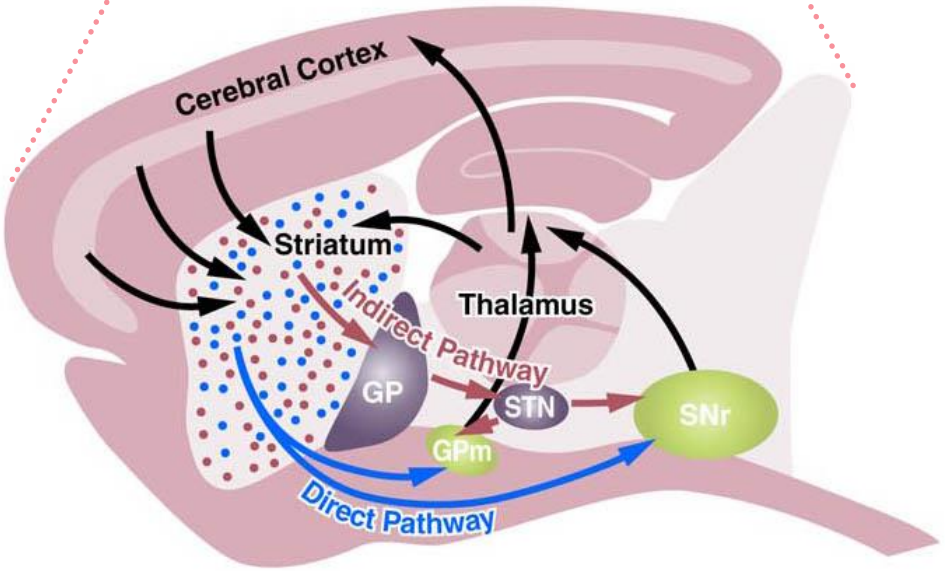


Basal Ganglia Circuits: The 'Classical' Model of Direct and Indirect Pathway Function



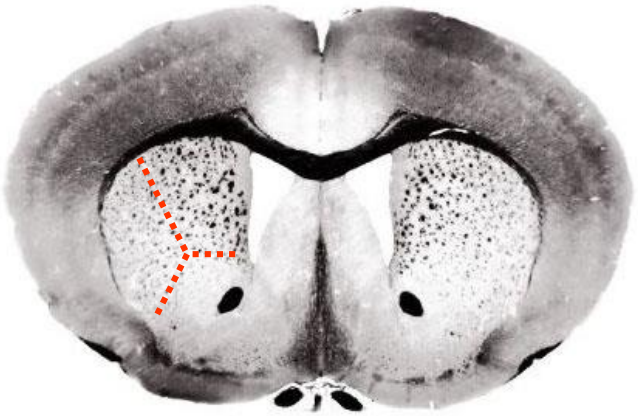
Analagous rodent basal ganglia nuclei





Gross anatomy of the striatum: gateway to the basal ganglia

rodent



<u>Striatal subregions:</u>
Dorsomedial (caudate)
Dorsolateral (putamen)
Ventral (nucleus accumbens)

Dorsomedial striatum:

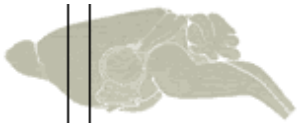
-Inputs predominantly from mPFC, thalamus, VTA

Dorsolateral striatum:

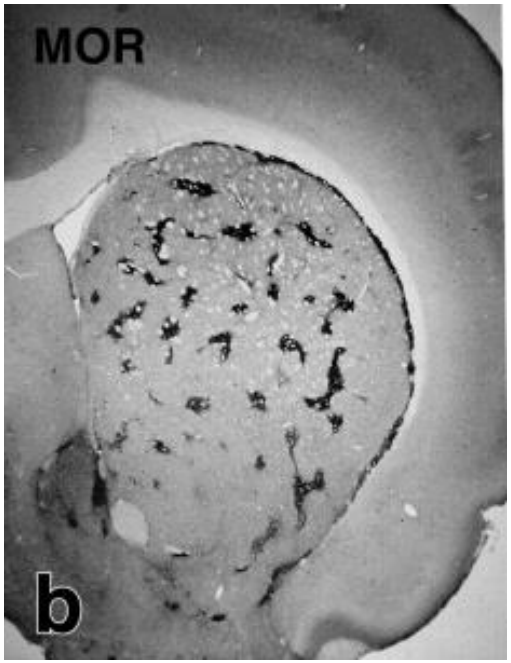
-Inputs from sensorimotor cortex, thalamus, SNc

Ventral striatum:

-Inputs from vPFC, hippocampus, amygdala, thalamus, VTA



Gross anatomy of the striatum: patch and matrix compartments



Patch/Striosome:

-substance P

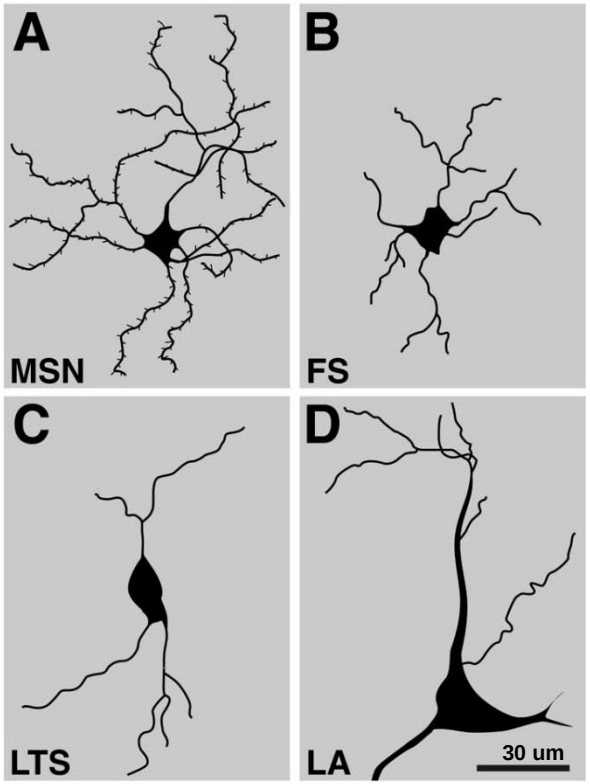
-mu-opioid receptor

Matrix:

-ChAT and AChE

-somatostatin

Microanatomy of the striatum: cell types



Projection neurons:

MSN: medium spiny neuron (GABA)

- striatonigral projecting – 'direct pathway'
- striatopallidal projecting – 'indirect pathway'

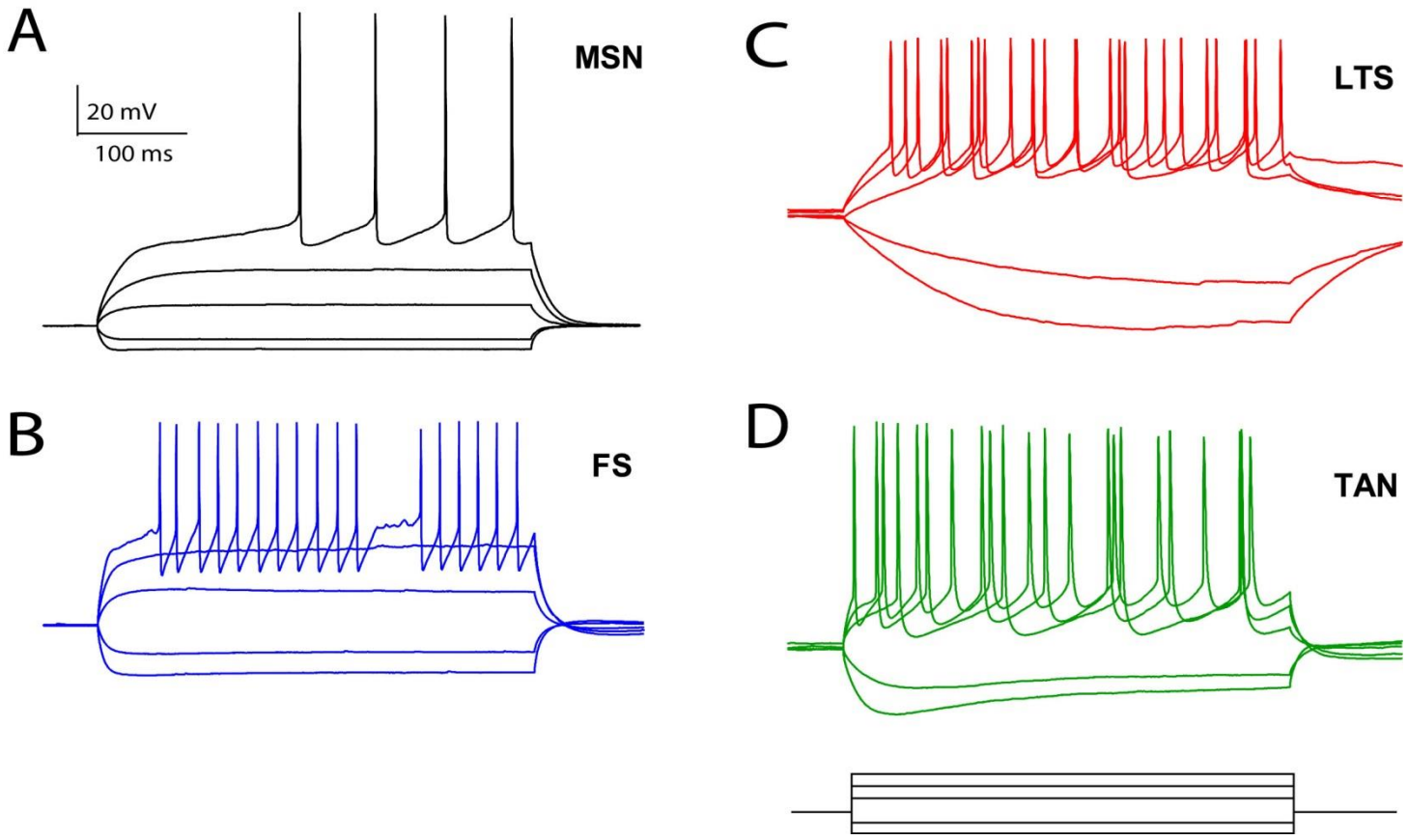
Interneurons:

FS: fast-spiking interneuron (GABA)

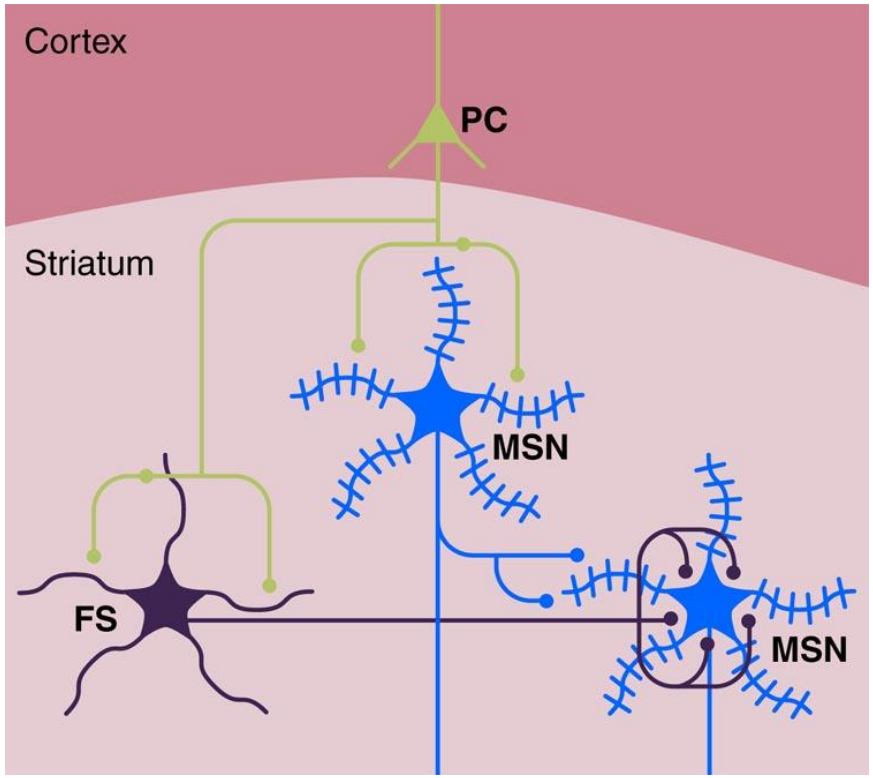
LTS: low-threshold spiking interneuron (GABA)

LA: large aspiny neuron (ACh)

Cellular properties of striatal neurons



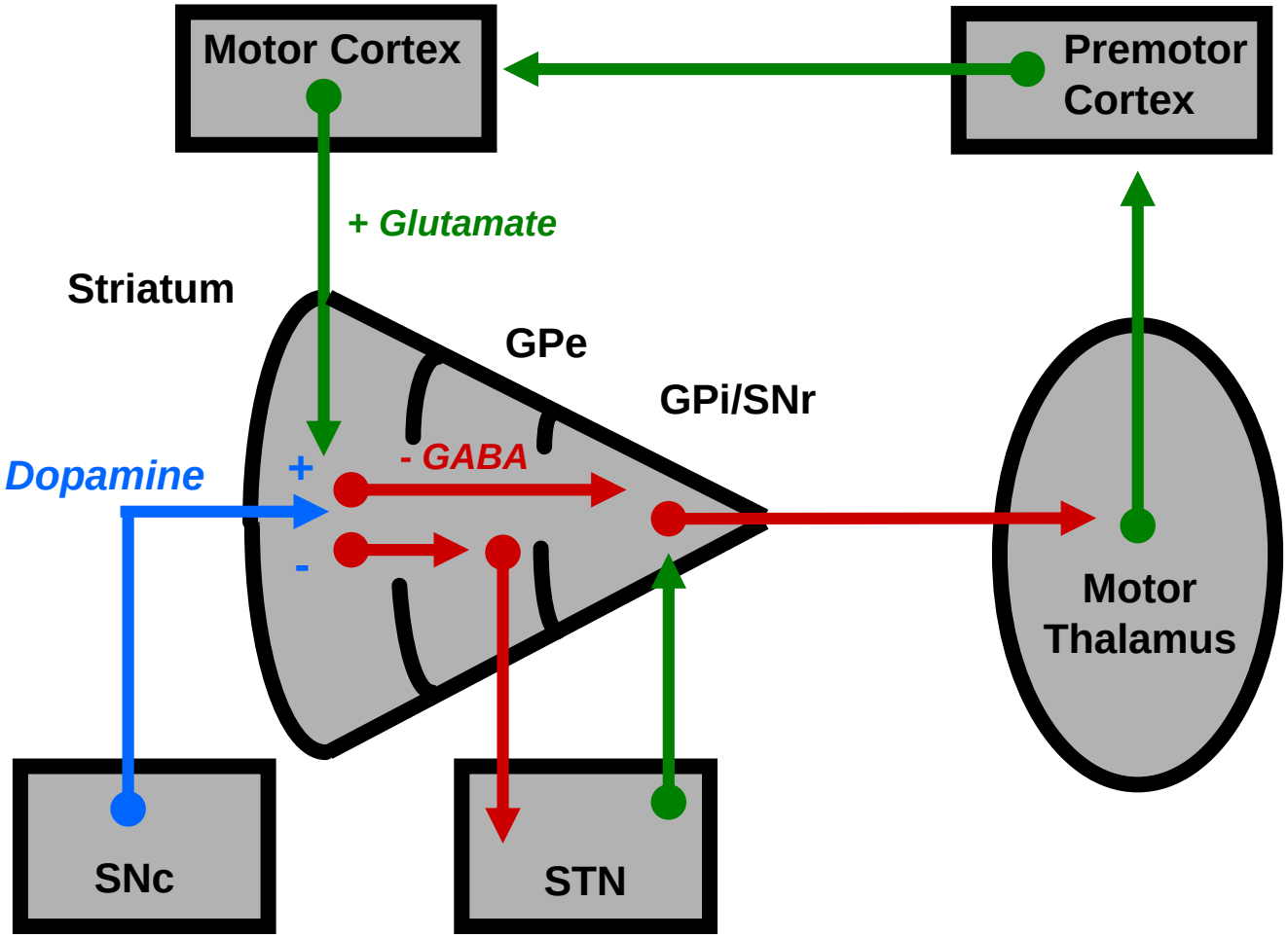
Microanatomy of the striatum: striatal microcircuits



- Feedforward inhibition (mediated by fast-spiking interneurons)

- Lateral feedback inhibition (mediated by MSN collaterals)

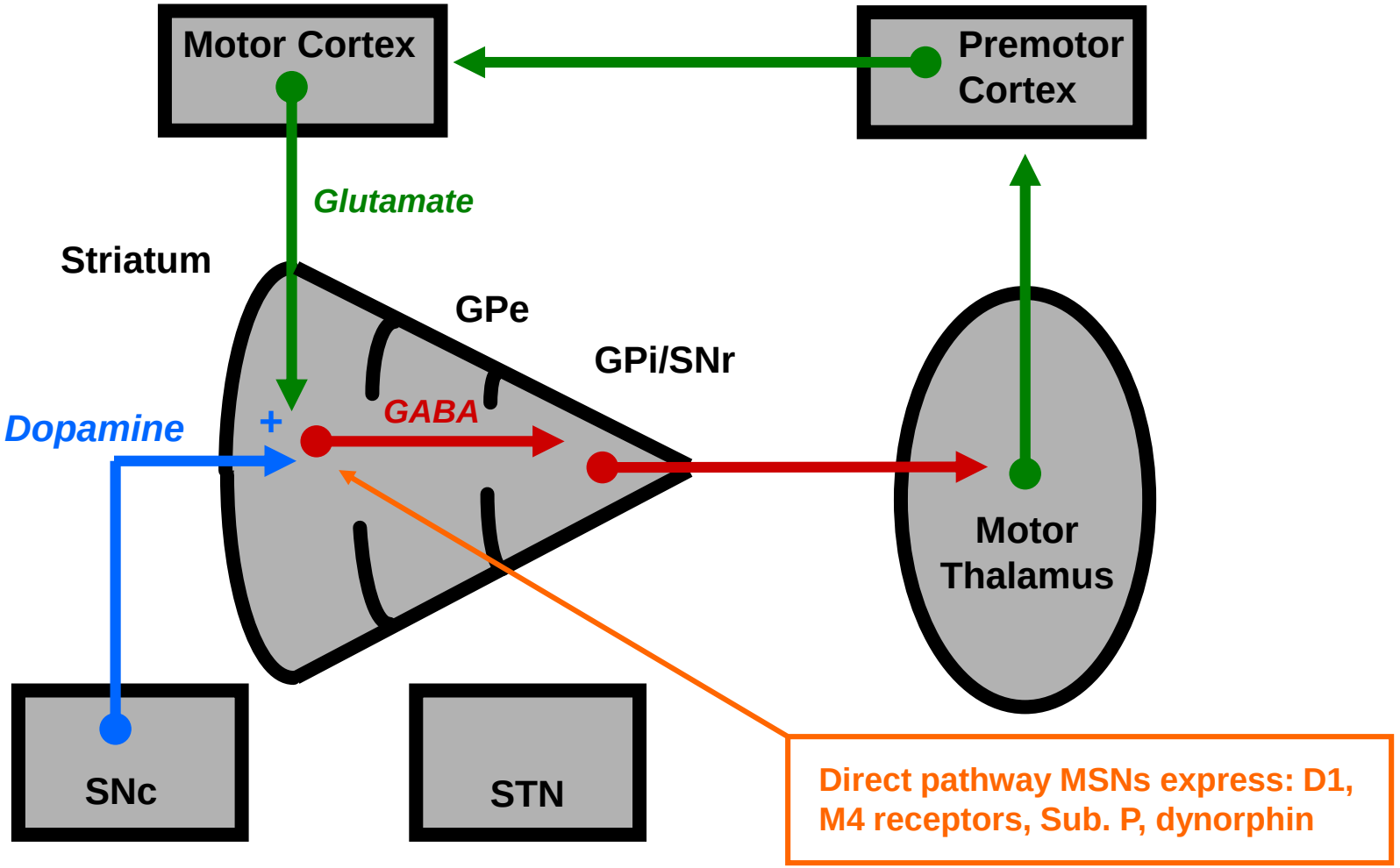
Basal Ganglia Circuits: The 'Classical' Model of Direct and Indirect Pathway Function



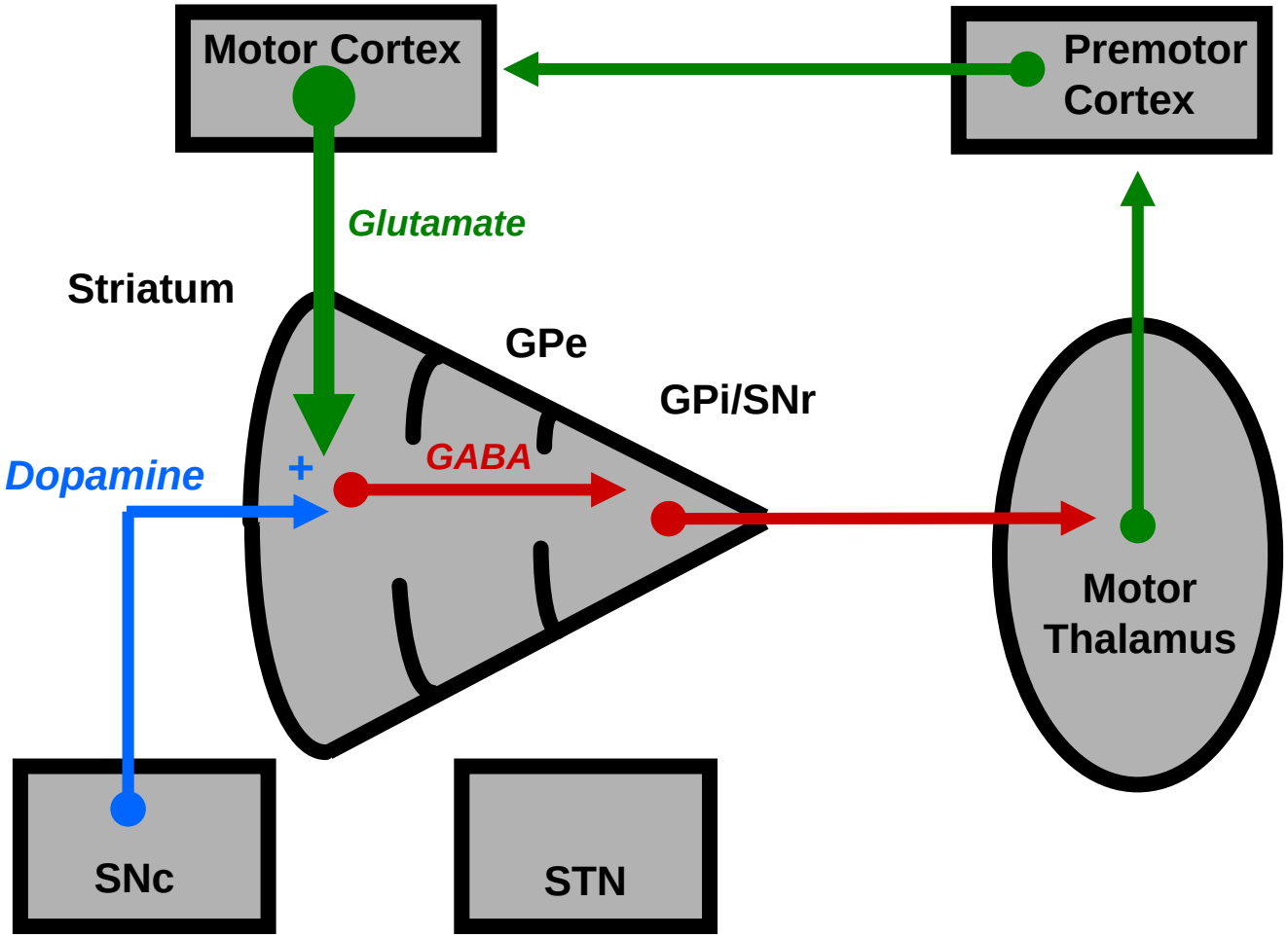
The simplified ‘classical’ model of basal ganglia circuit function

- Information encoded as firing rate
- Basal ganglia circuit is linear and unidirectional
- Dopamine exerts opposing effects on ***direct*** and ***indirect*** pathway MSNs

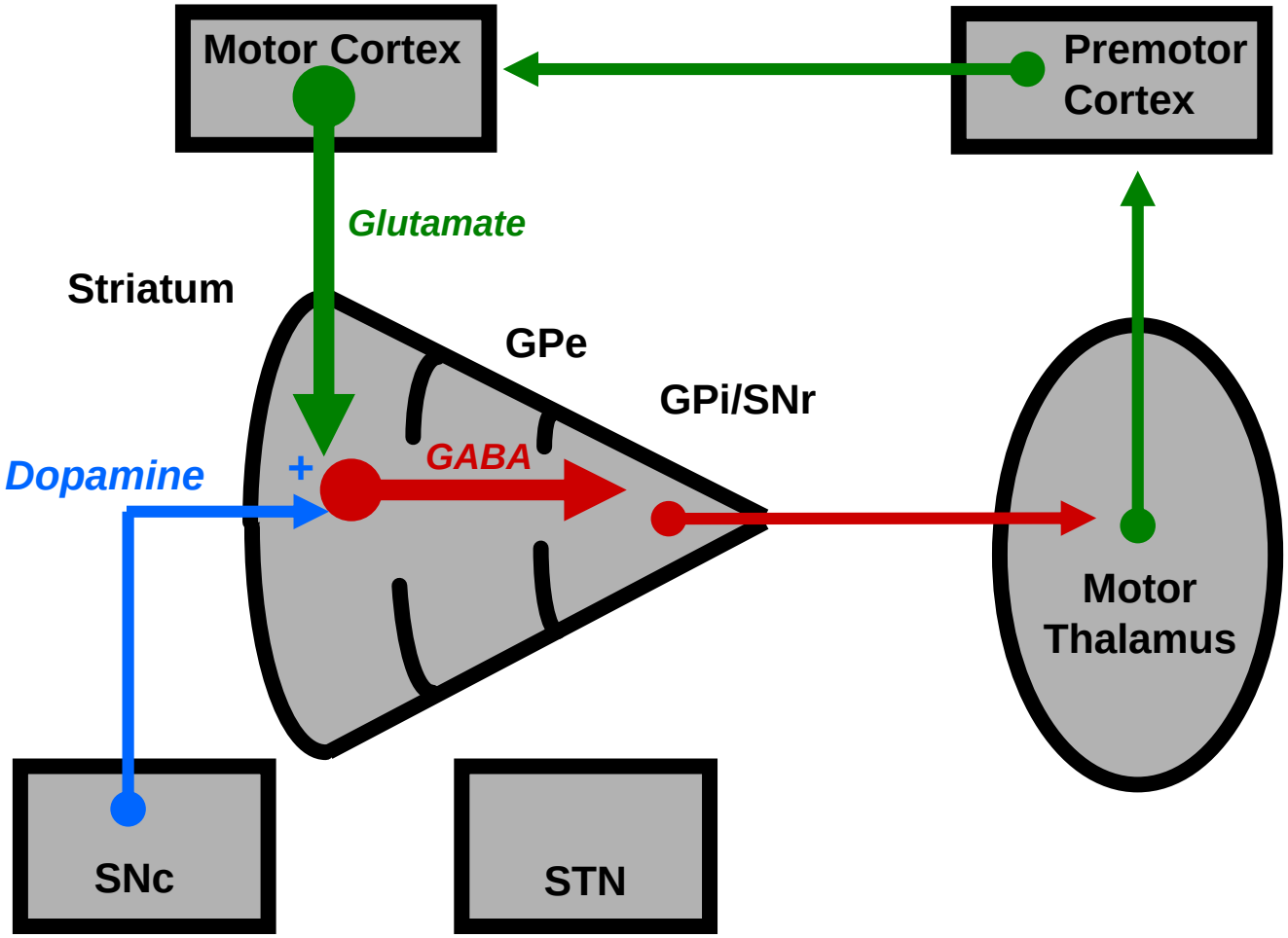
Basal ganglia motor circuit: direct pathway



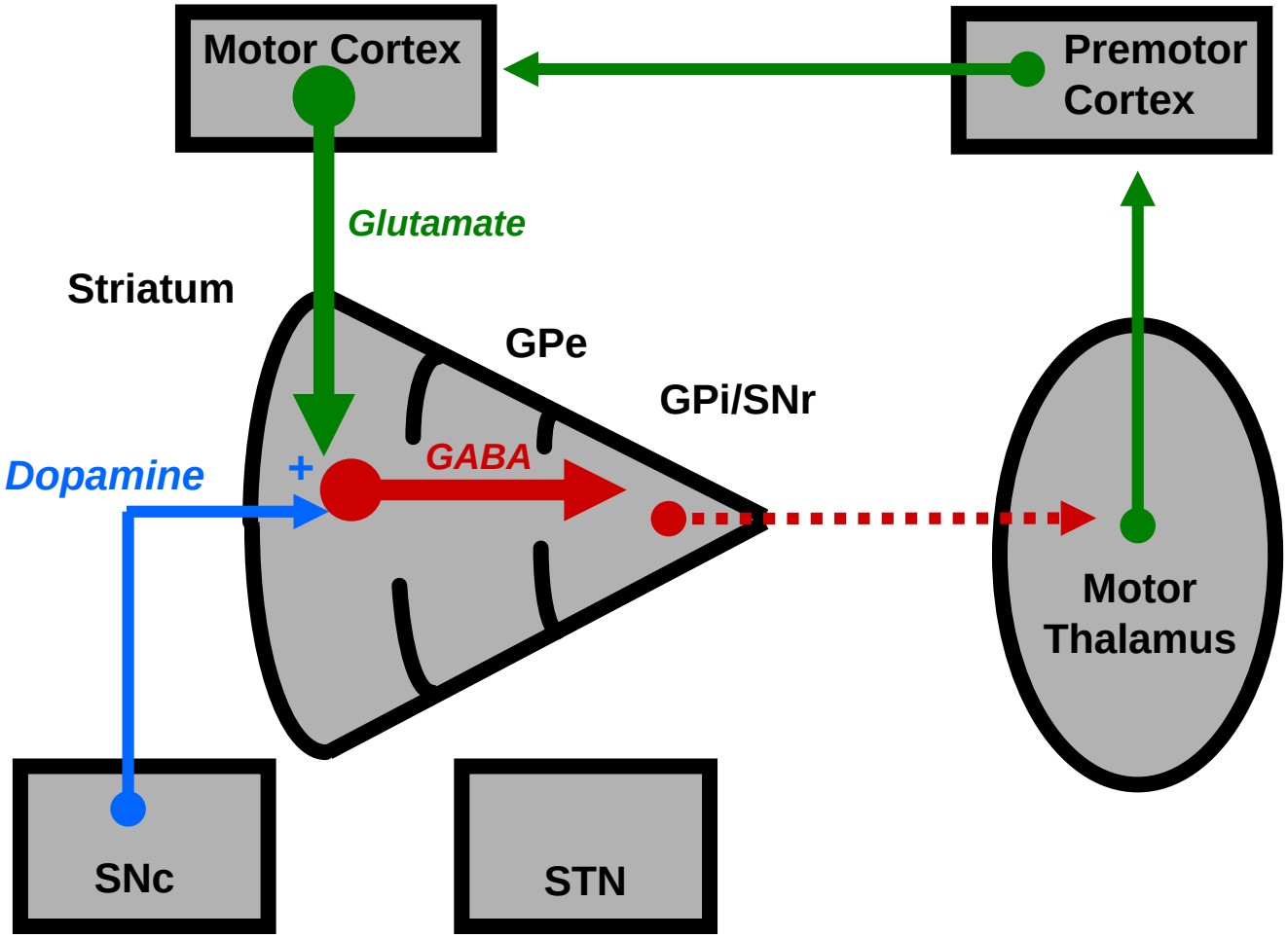
Basal ganglia motor circuit: direct pathway



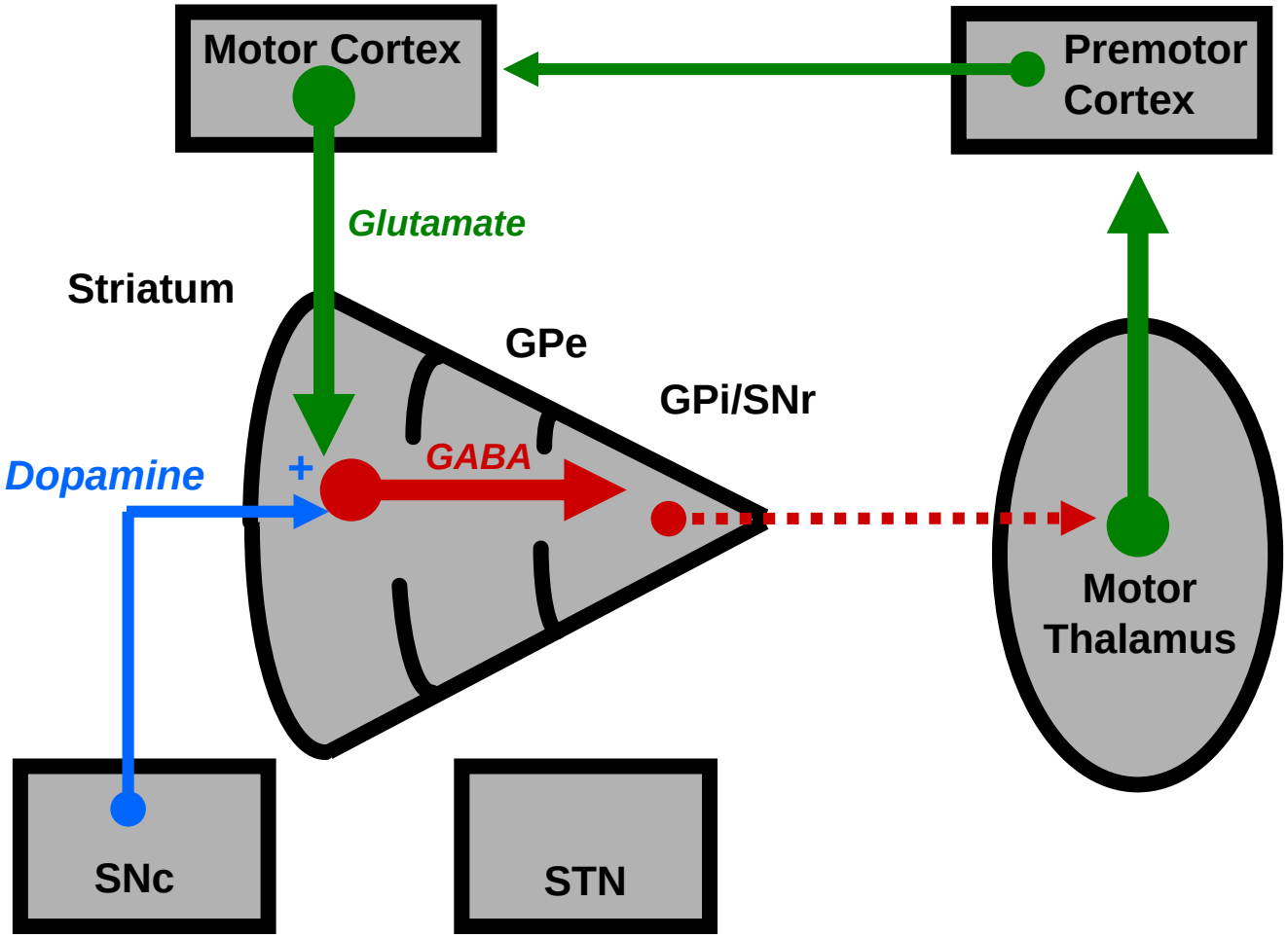
Basal ganglia motor circuit: direct pathway



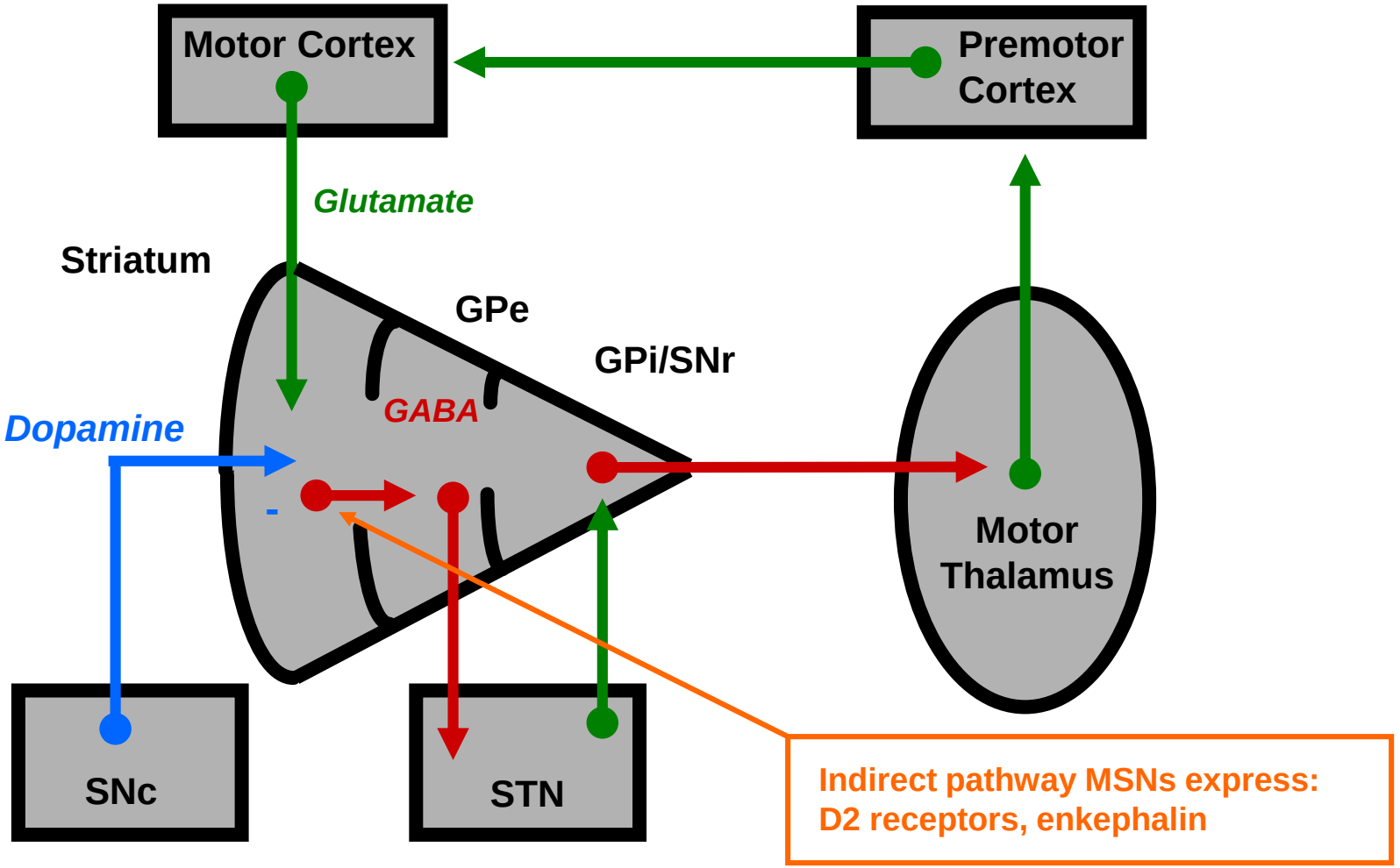
Basal ganglia motor circuit: direct pathway



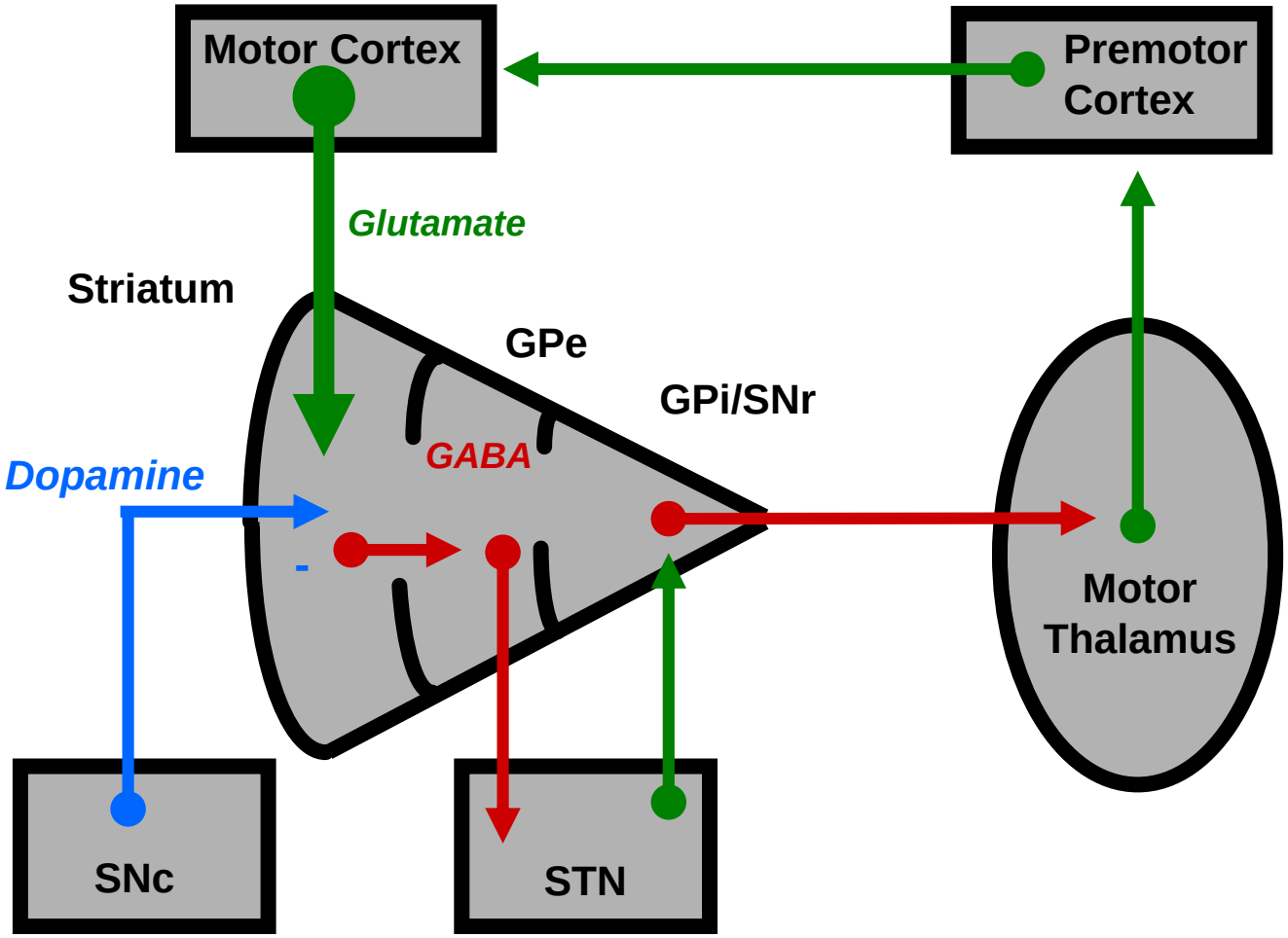
Basal ganglia motor circuit: direct pathway



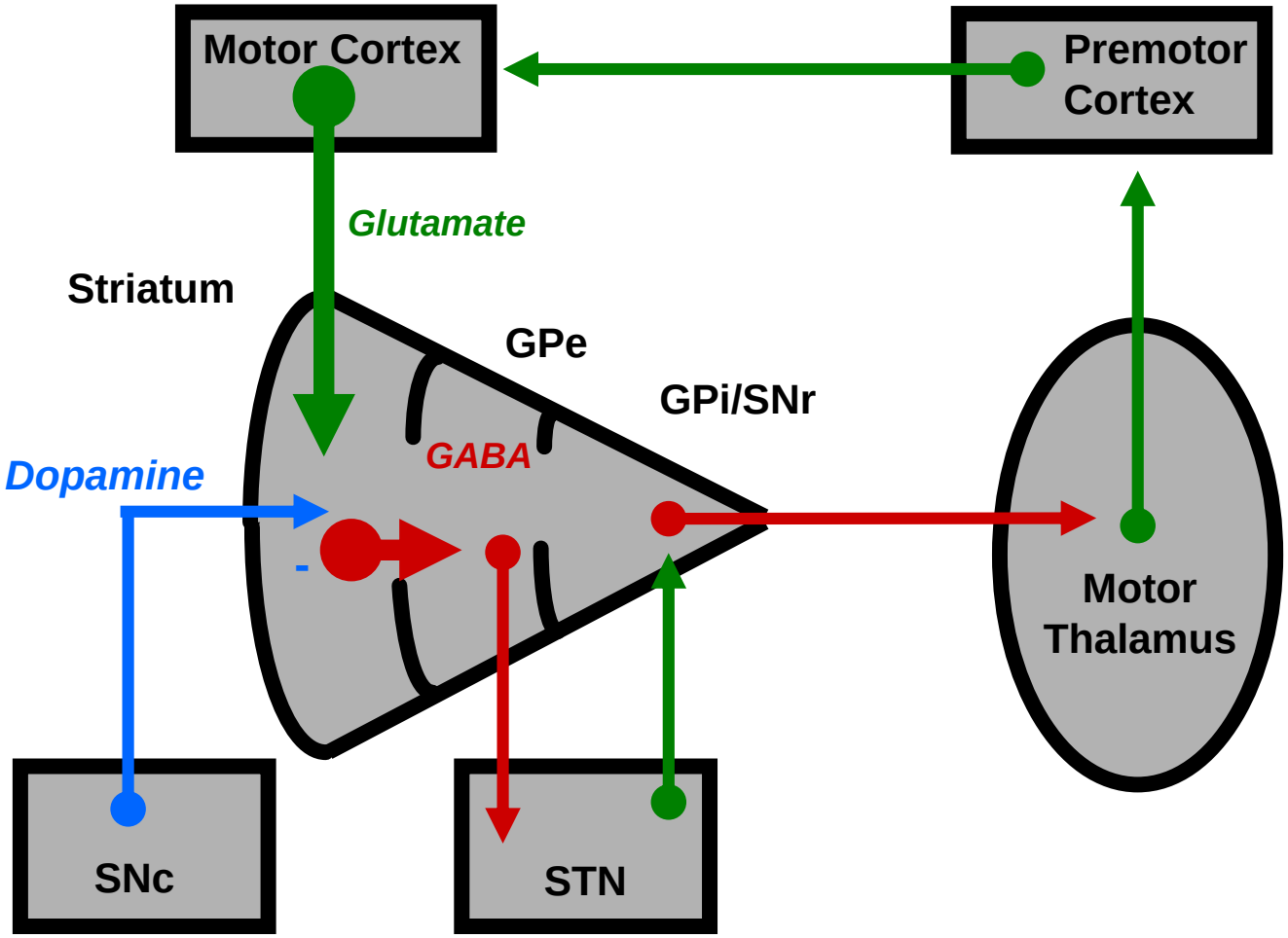
Basal ganglia motor circuit: indirect pathway



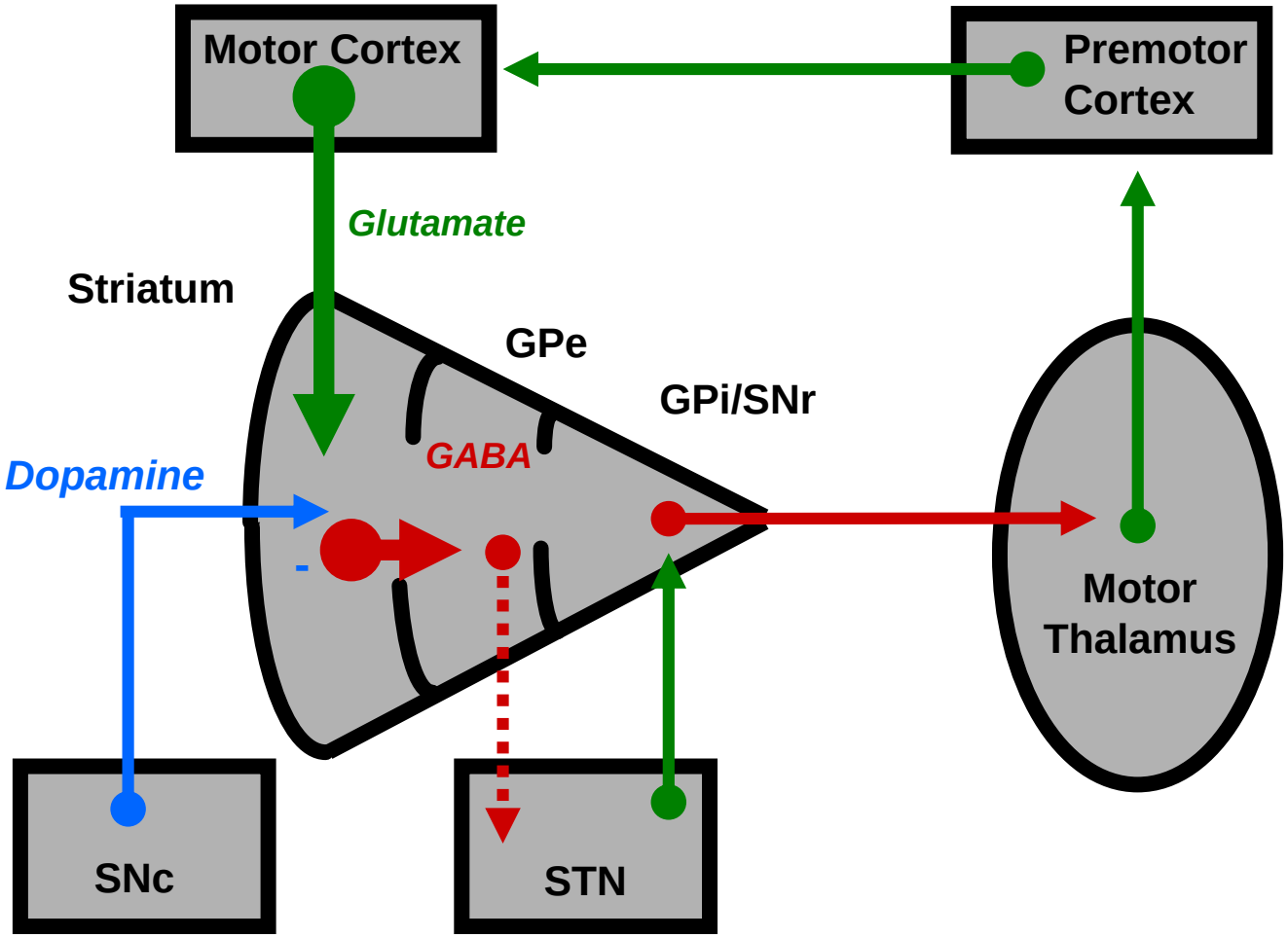
Basal ganglia motor circuit: indirect pathway



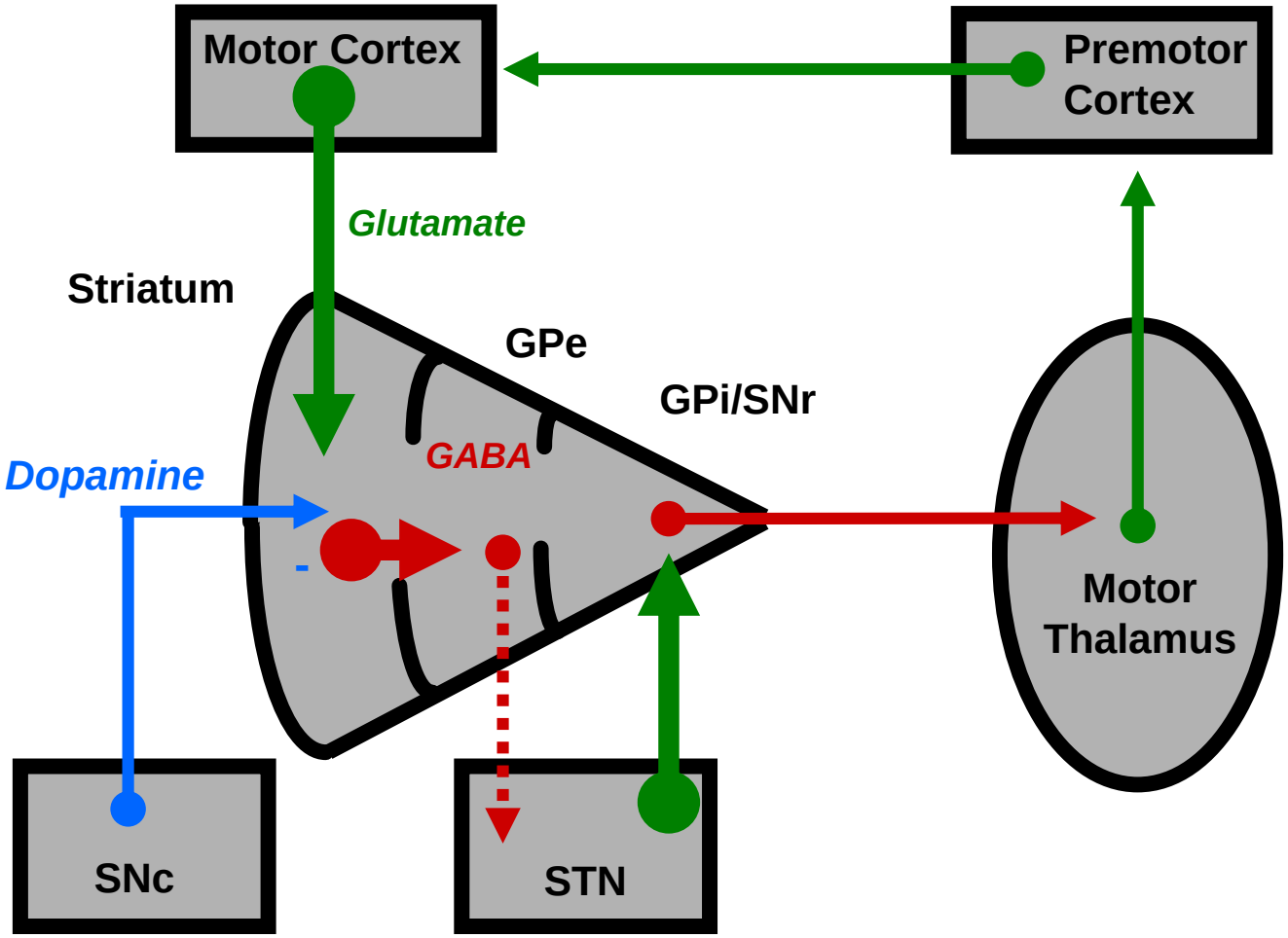
Basal ganglia motor circuit: indirect pathway



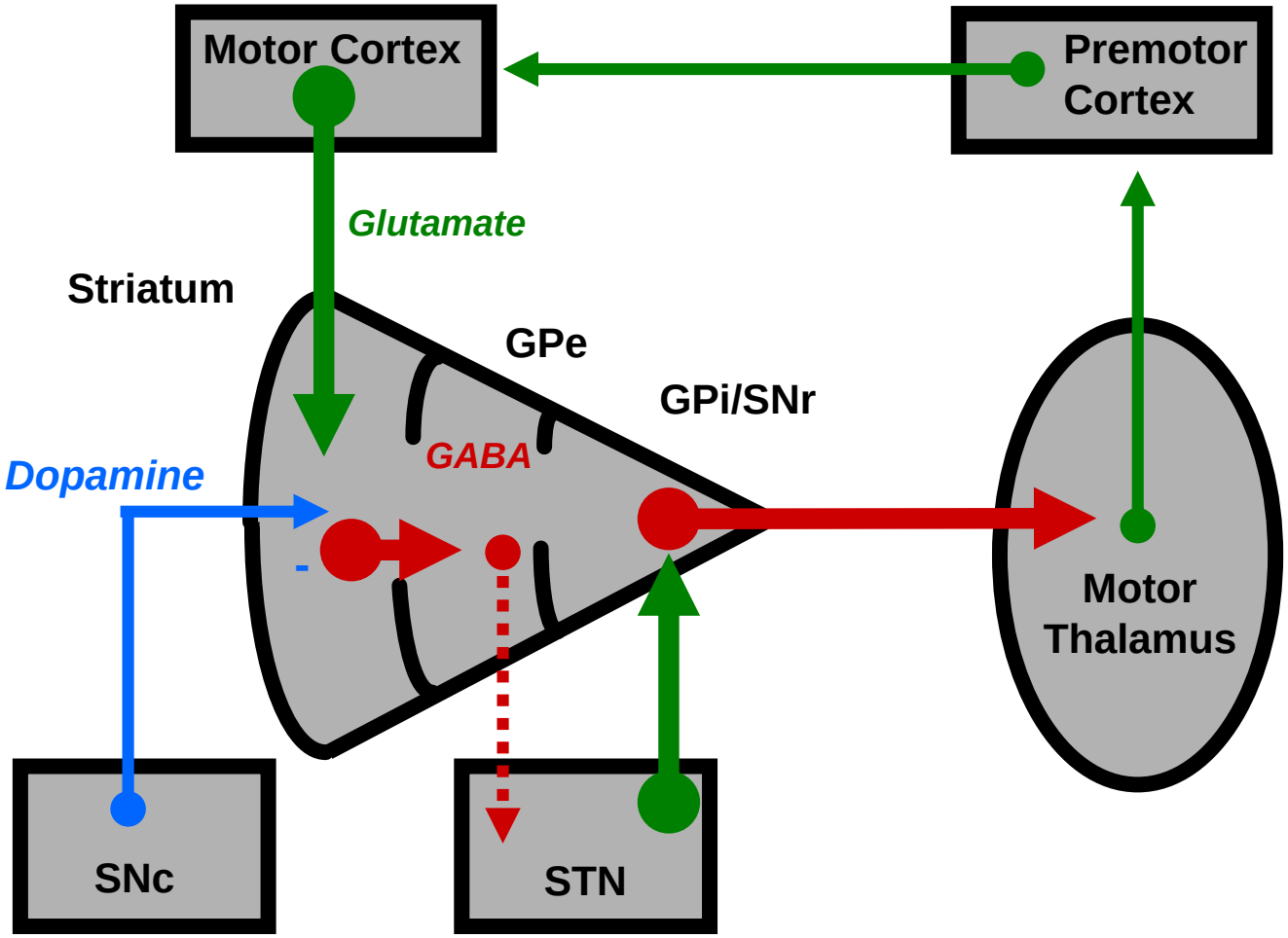
Basal ganglia motor circuit: indirect pathway



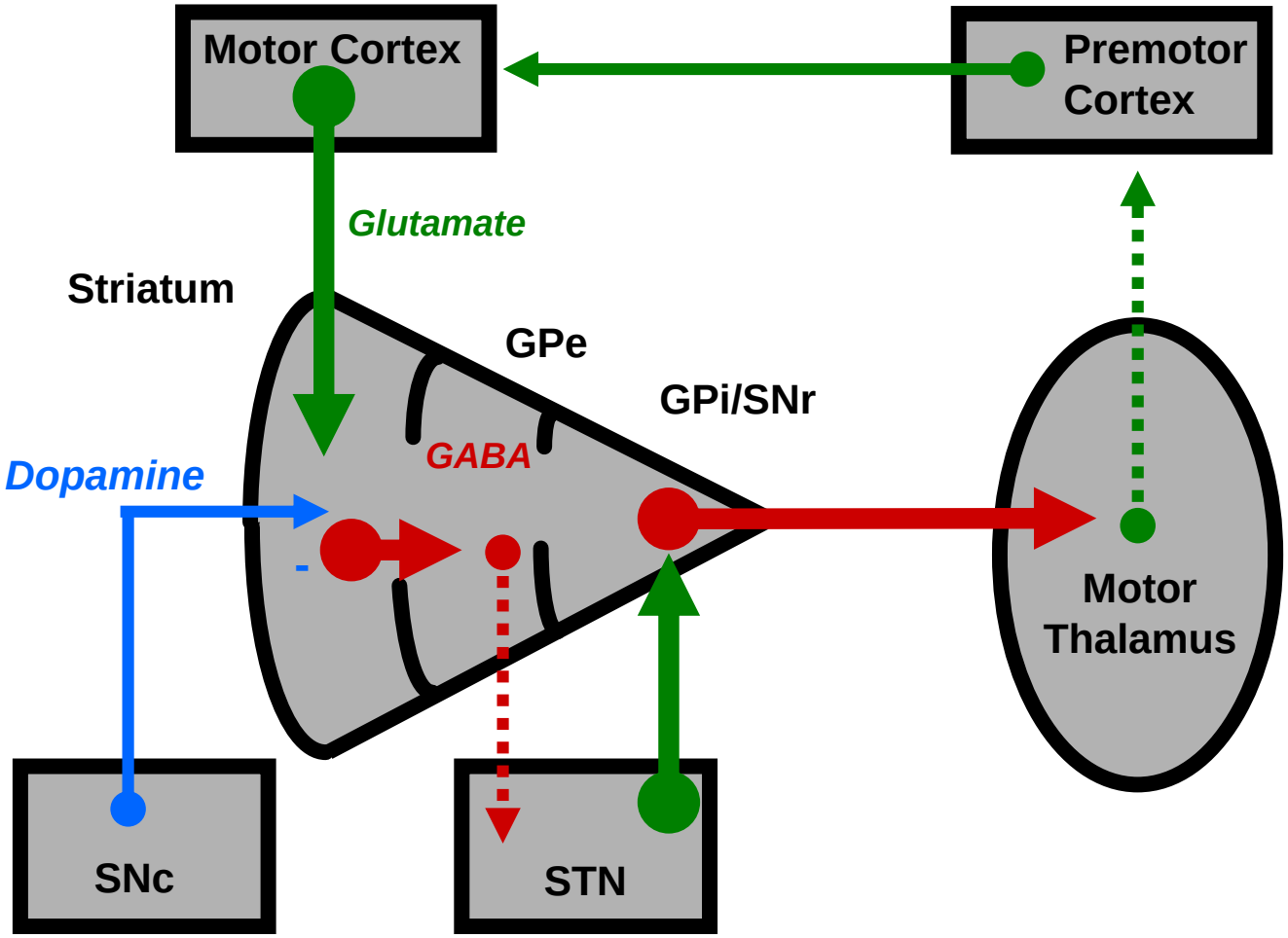
Basal ganglia motor circuit: indirect pathway



Basal ganglia motor circuit: indirect pathway



Basal ganglia motor circuit: indirect pathway



Summary of the ‘classical’ model of basal ganglia circuit function

- Activation of the direct pathway facilitates/selects/initiates proper movements

- Activation of the indirect pathway inhibits/terminates unwanted movements

- Dopamine normally inhibits the indirect pathway and potentiates the direct pathway

Physiology of Basal Ganglia: Striatal Synaptic Plasticity Regulates Circuitry

- **Striatum is the major input nucleus to the basal ganglia**
- **Striatal MSNs exhibit very negative resting potentials (-85 mV), due to high Kir expression**
- **Striatal MSNs require coordinated presynaptic excitatory activity in order to depolarize sufficiently to fire action potentials**
- **Changes in excitatory synaptic strength have a major impact on MSN firing patterns and downstream circuit activity**

Long-term synaptic plasticity at excitatory striatal afferents

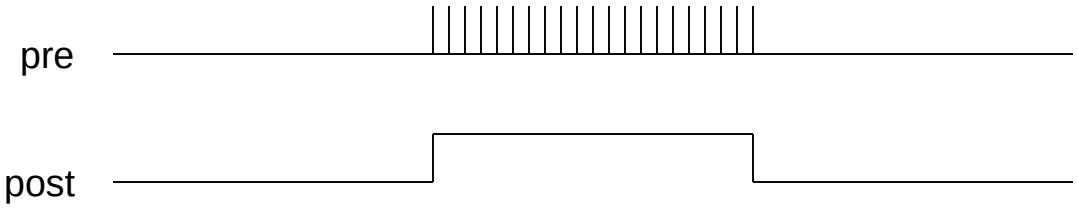
- **Long-term potentiation (LTP)**
  - **Direct-pathway MSNs**
  - **Indirect-pathway MSNs**

- Long-term depression (LTD)
  - Direct-pathway MSNs
  - Indirect-pathway MSNs

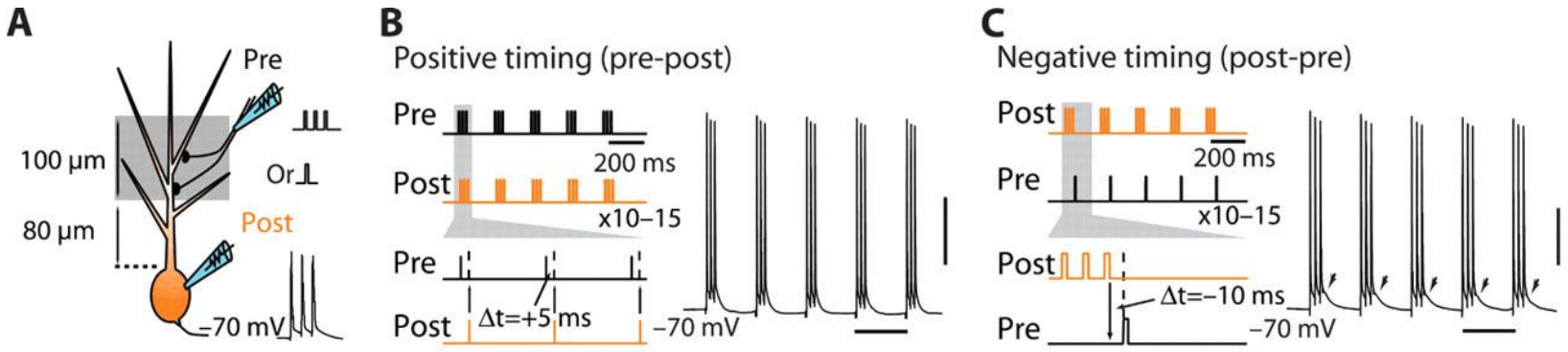
Induction of LTP or LTD: methods

High-frequency stimulation (HFS)

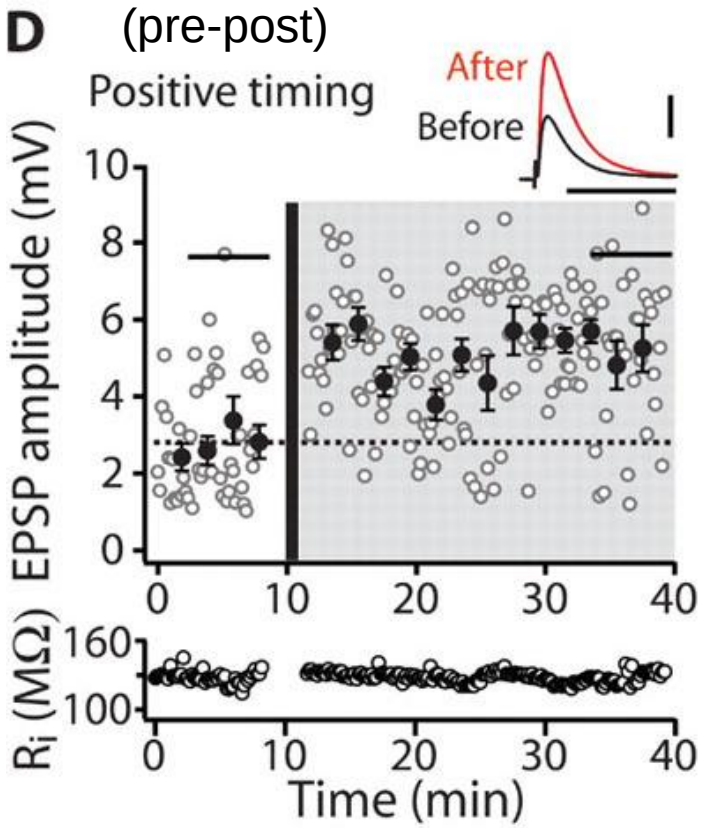
- 100 Hz for 1 second, repeated 4 times at 10 second intervals
- Paired with postsynaptic depolarization from -70 to 0 mV



Spike-timing-dependent plasticity (STDP)

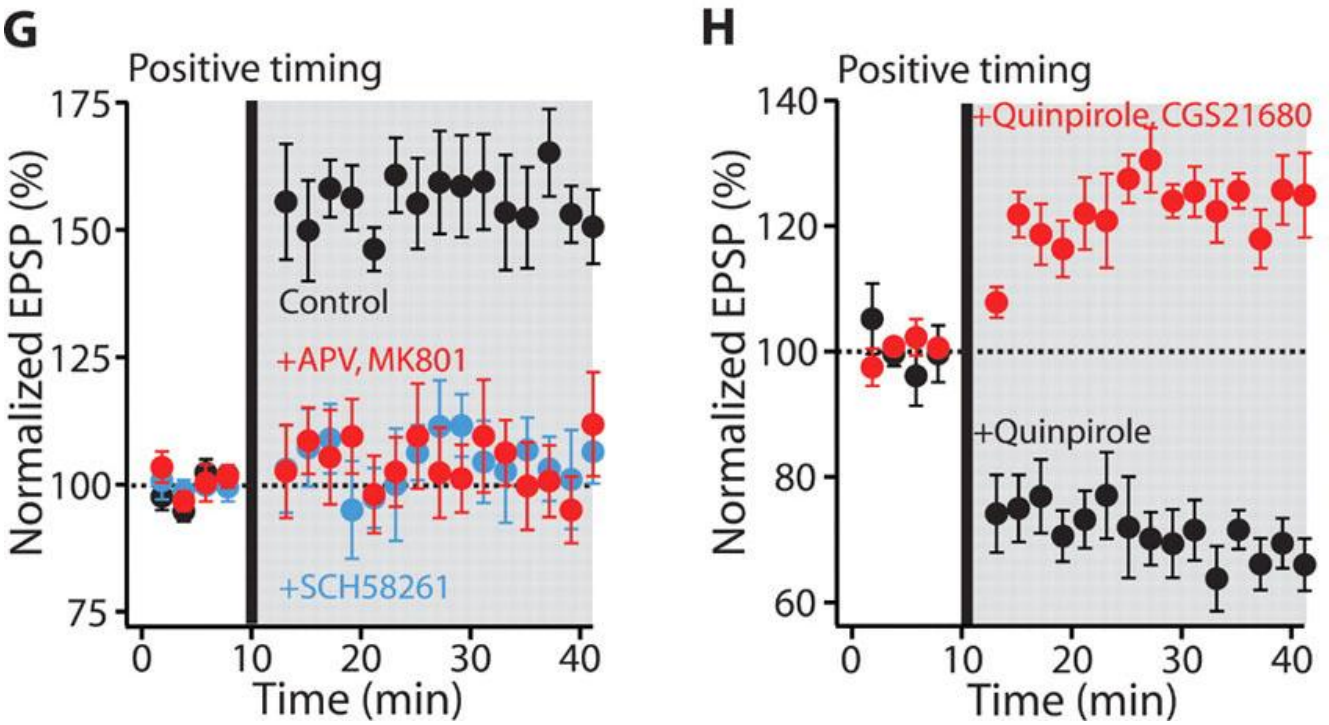


STDP-LTP in striatal indirect-pathway MSNs



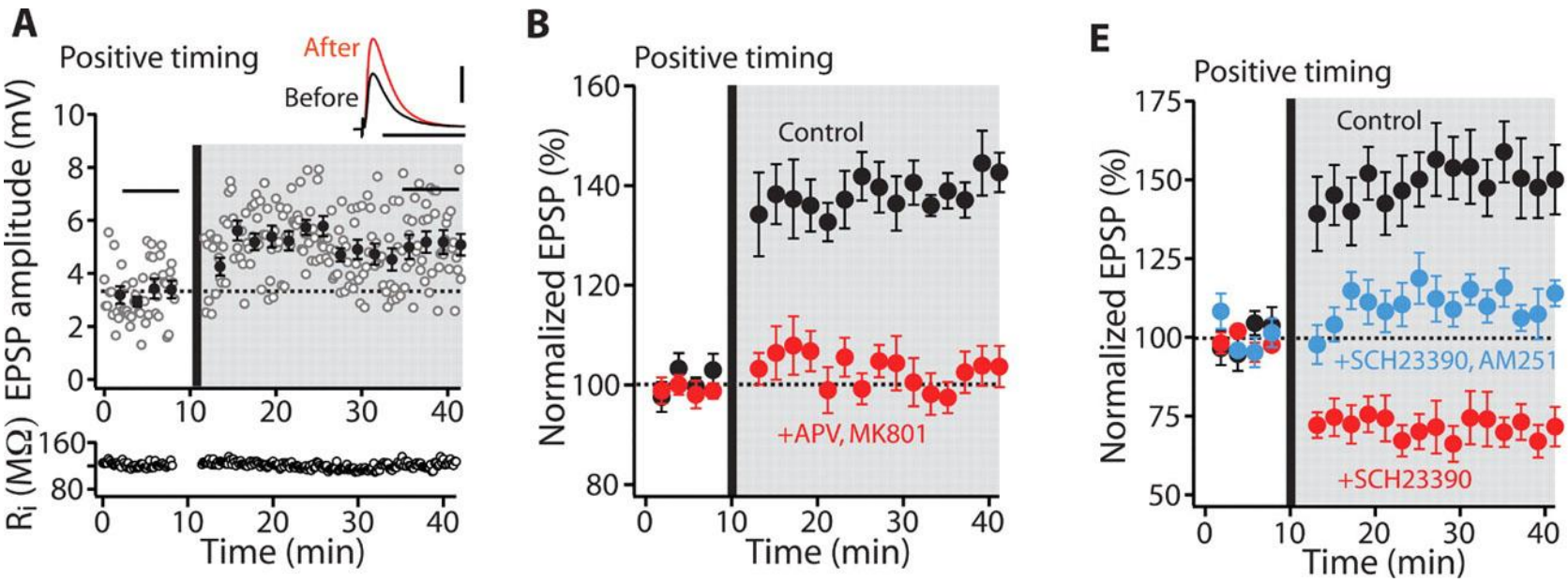
Shen et al, Science 2008

Indirect-pathway LTP requires adenosine A2A and NMDA receptors



APV: NMDA antagonist
SCH58261: adenosine A2A antagonist
CGS21680: adenosine A2A agonist
Quinpirole: D2 agonist

Direct-pathway LTP requires NMDA, dopamine D1 receptors



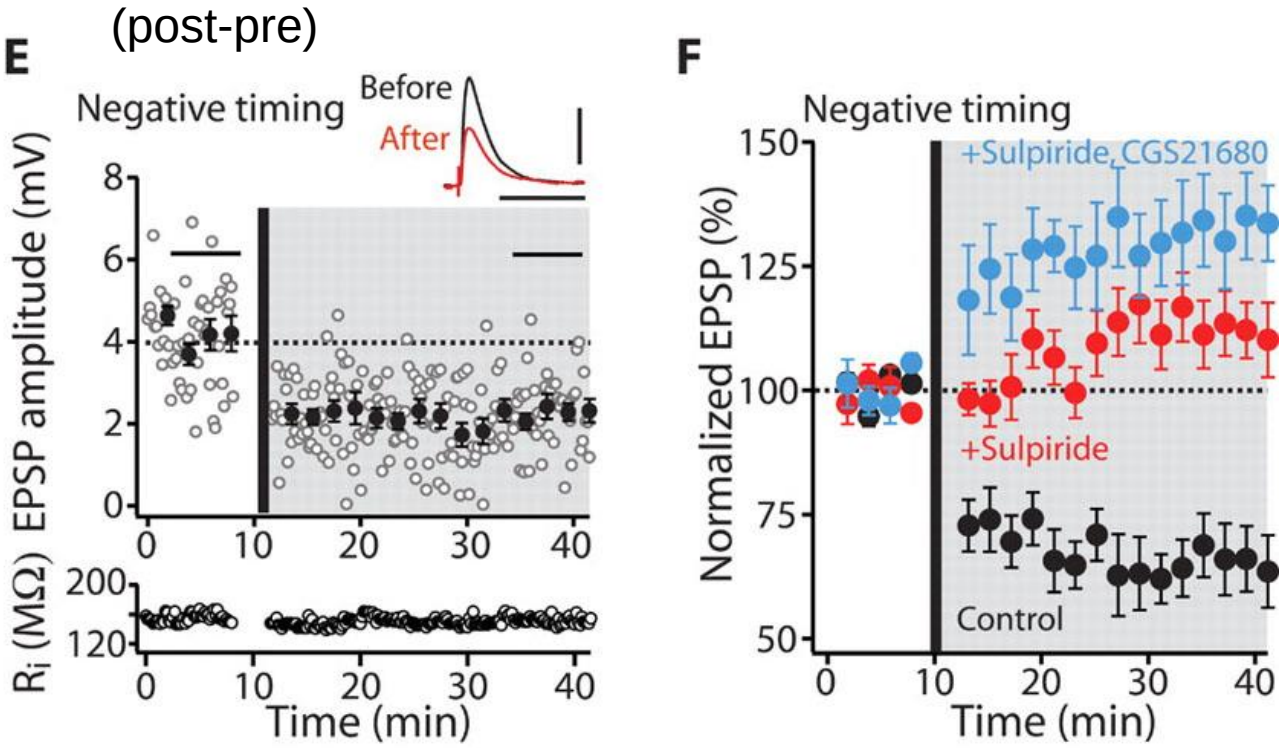
APV: NMDA antagonist
SCH23390: D1 antagonist
AM251: CB1 antagonist

Synaptic plasticity in striatal MSNs

- Long-term potentiation (LTP)
  - Direct-pathway MSNs
  - Indirect-pathway MSNs

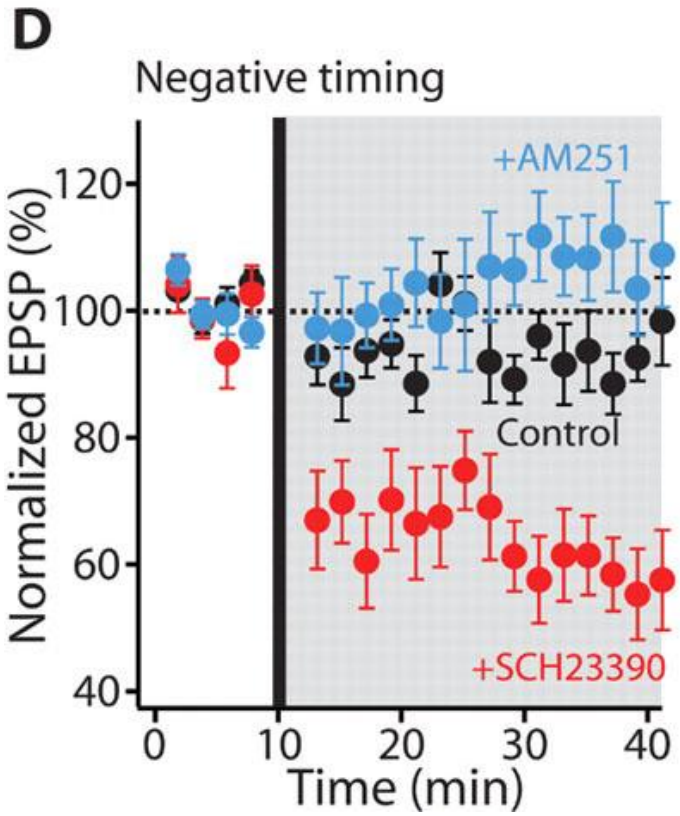
- **Long-term depression (LTD)**
  - **Direct-pathway MSNs**
  - **Indirect-pathway MSNs**

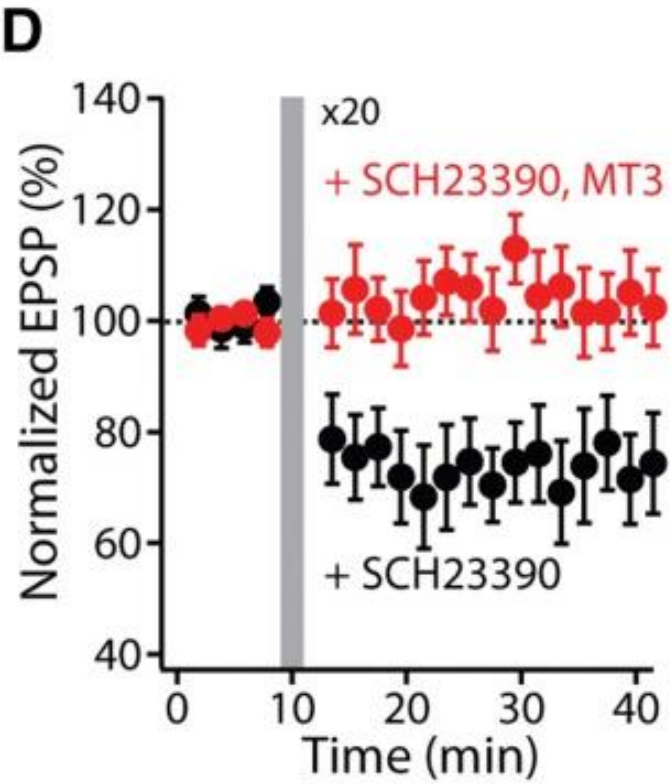
Indirect-pathway STDP-LTD requires eCBs, activation of D2 receptors



Sulpiride: D2 antagonist
CGS21680: A2A agonist

Direct-pathway STDP-LTD requires eCBs, *inhibition* of D1 receptors, activation of M4 receptors





SCH23390: D1 antagonist
AM251: CB1 antagonist
MT3: M4 antagonist

Striatal Plasticity: Summary

Direct Pathway: LTP requires NMDA, D1 activation

LTD requires eCBs and M4 activation

blocked by D1 activation

Indirect Pathway: LTP requires NMDA, A2A activation

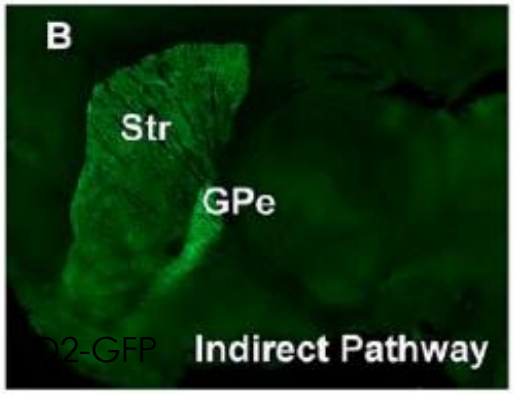
LTD requires eCBs and D2 activation

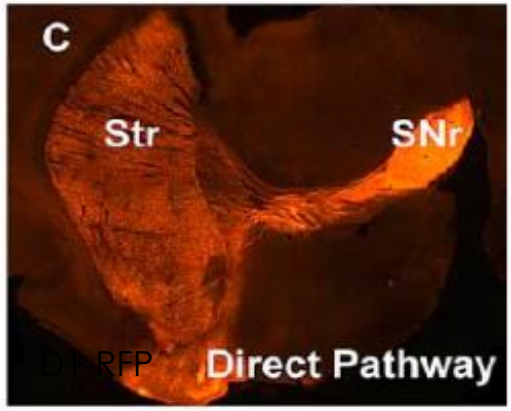
blocked by A2A activation

Striatal dopamine predicted to facilitate direct-pathway LTP, indirect-pathway LTD

Testing Function of Basal Ganglia Circuits: Recording, Optogenetics, and Behavior

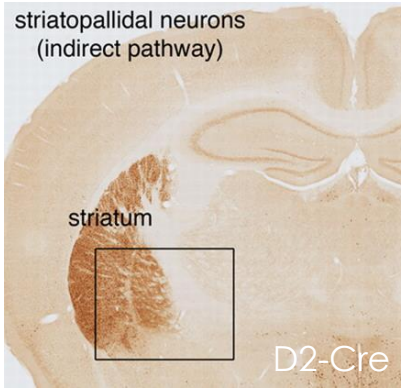
Fluorophores

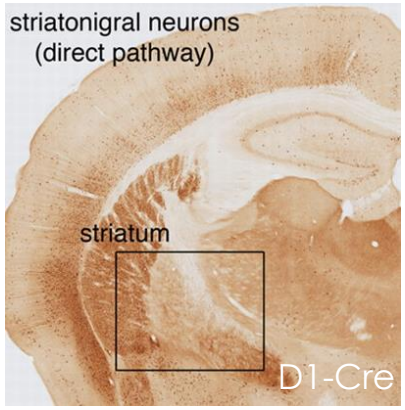




Shuen et al, 2008

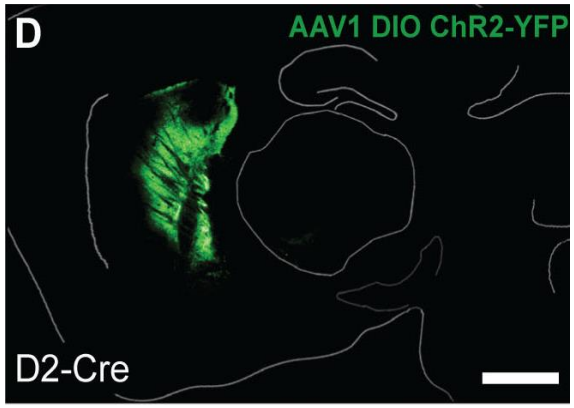
Cre Recombinase

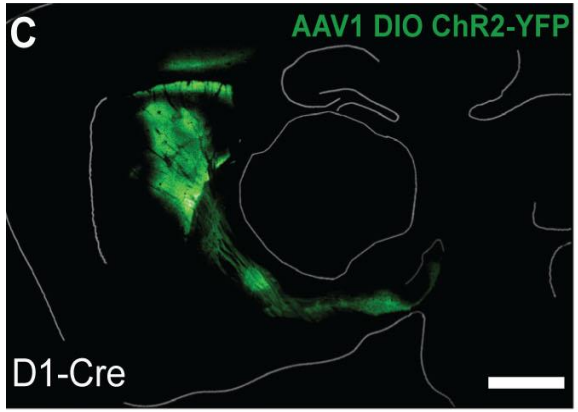




Gong et al, 2007

Channelrhodopsin-2

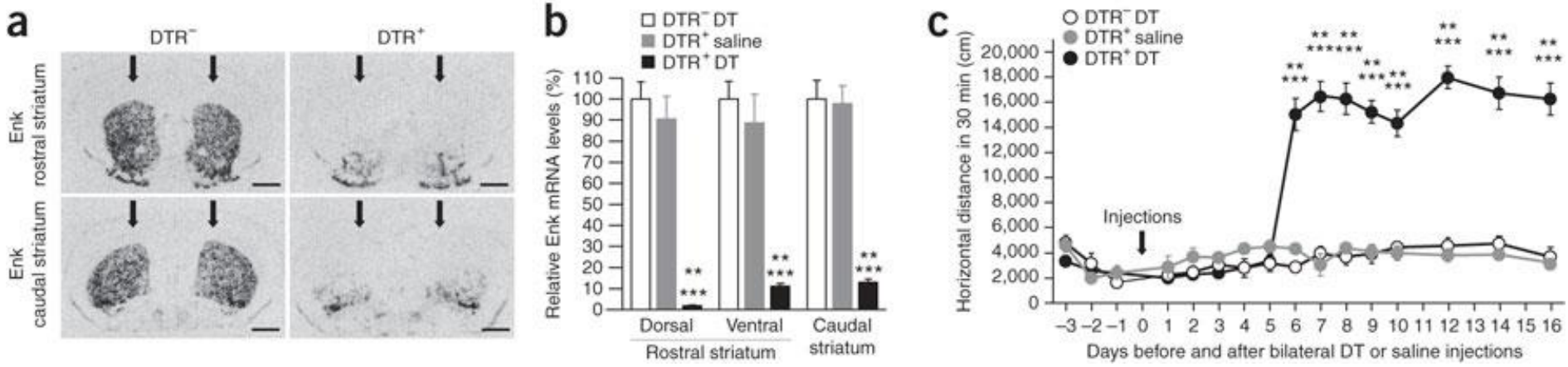




Kravitz et al, 2010

Also see http://www.gensat.org

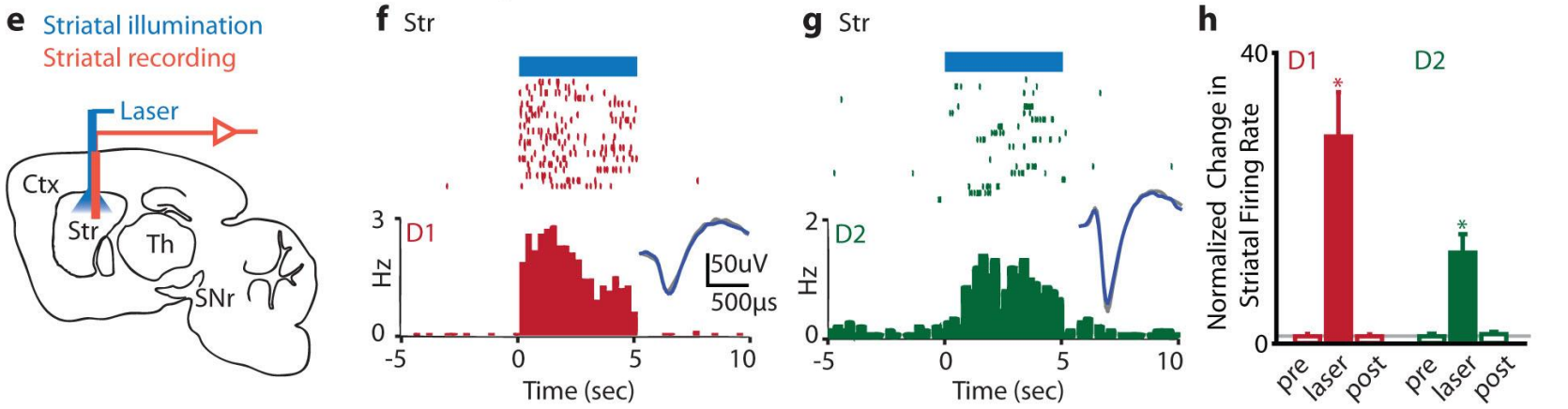
Cell-Type Specific Lesions of Basal Ganglia Circuitry



Durieux et al 2009, Nat Neurosci

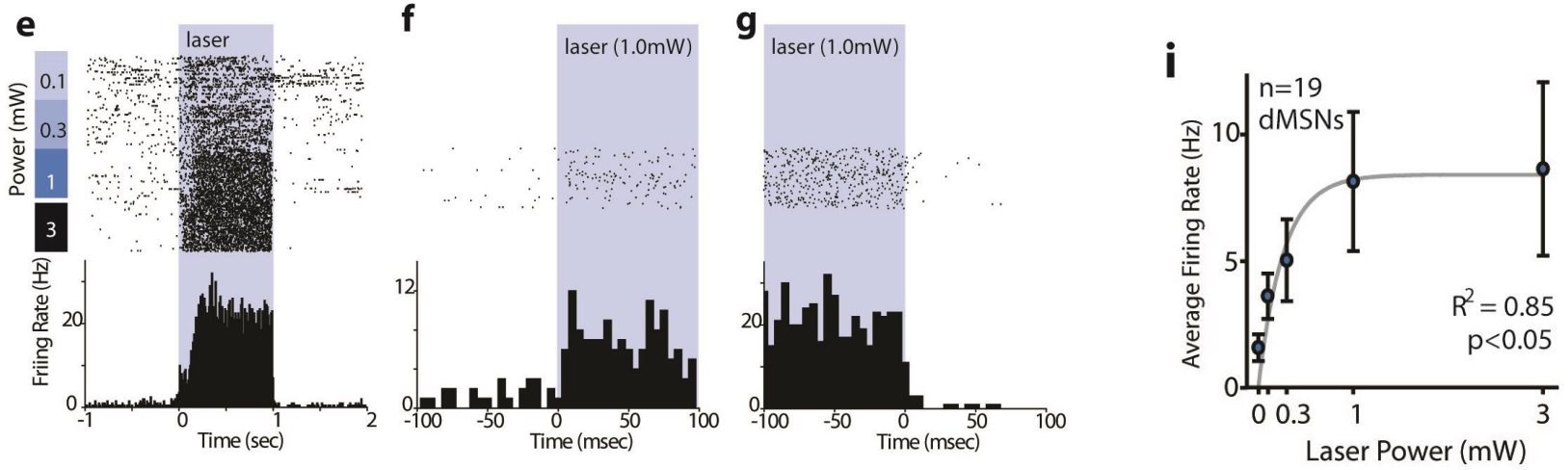
ChR2-Mediated Activation of Striatal MSNs *In Vivo*

anesthetized

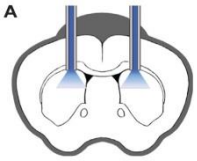


Kravitz et al, *Nature* 2010

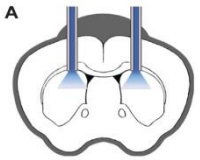
awake



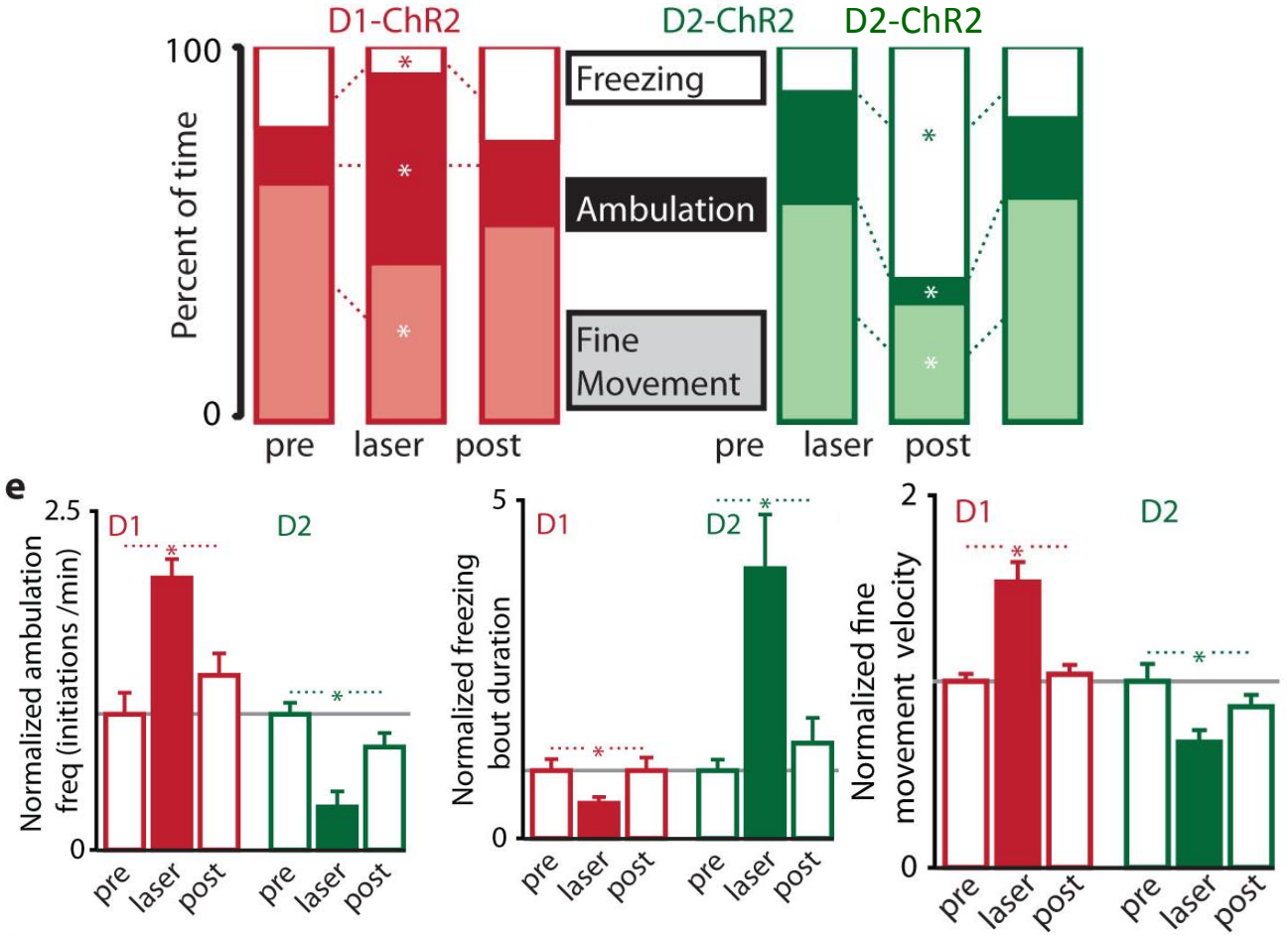
Bilateral Activation of Striatal Direct Pathway MSNs in Freely Moving Mice



Bilateral Activation of Striatal Indirect Pathway MSNs in Freely Moving Mice

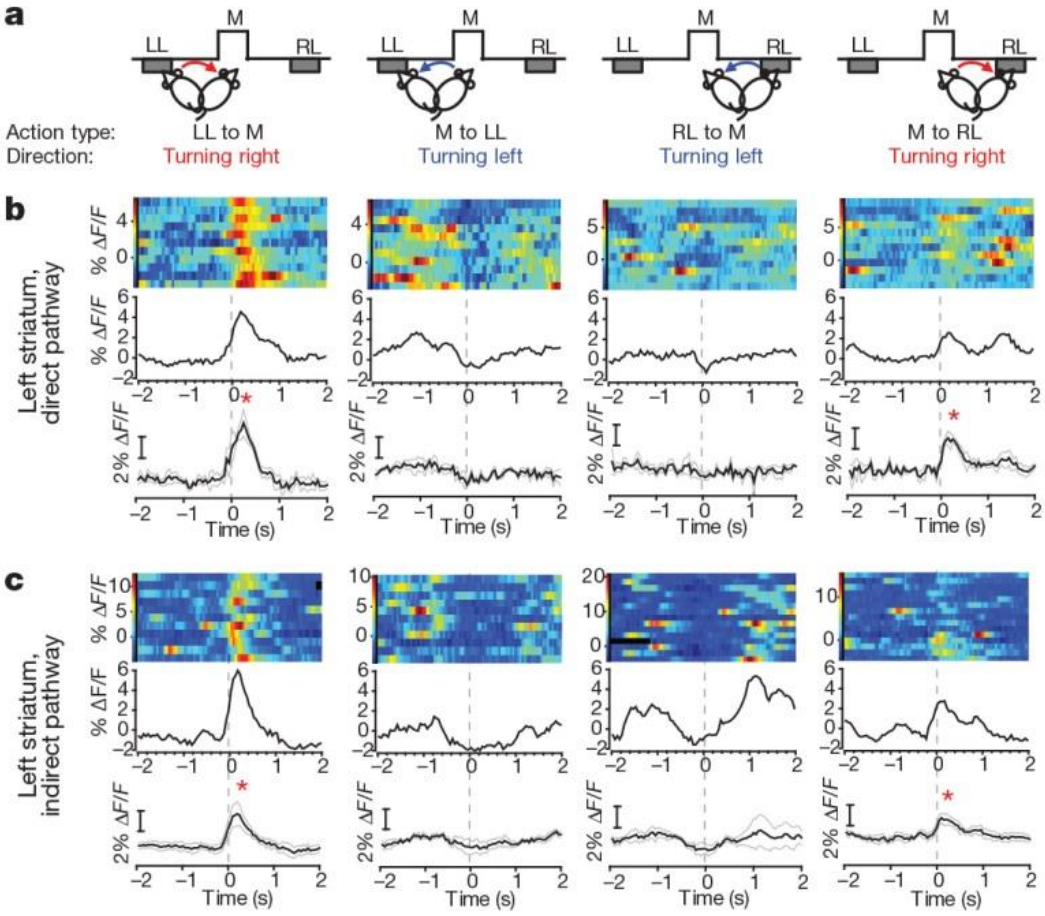


Regulation of Motor Behavior by Optogenetic Activation of Basal Ganglia Circuits



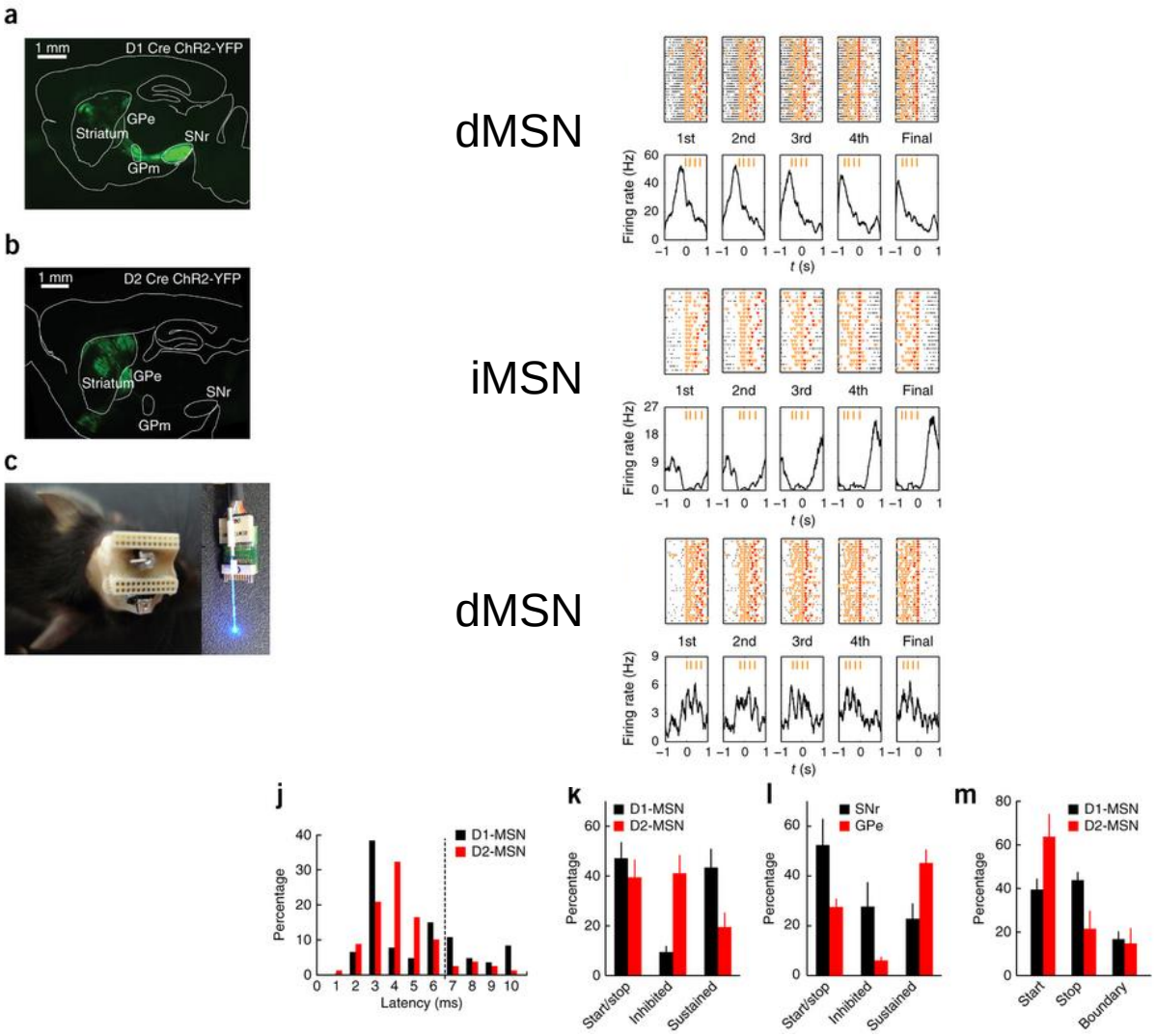
Kravitz et al, *Nature* 2010

Activity of Basal Ganglia Circuits During Motor Behavior



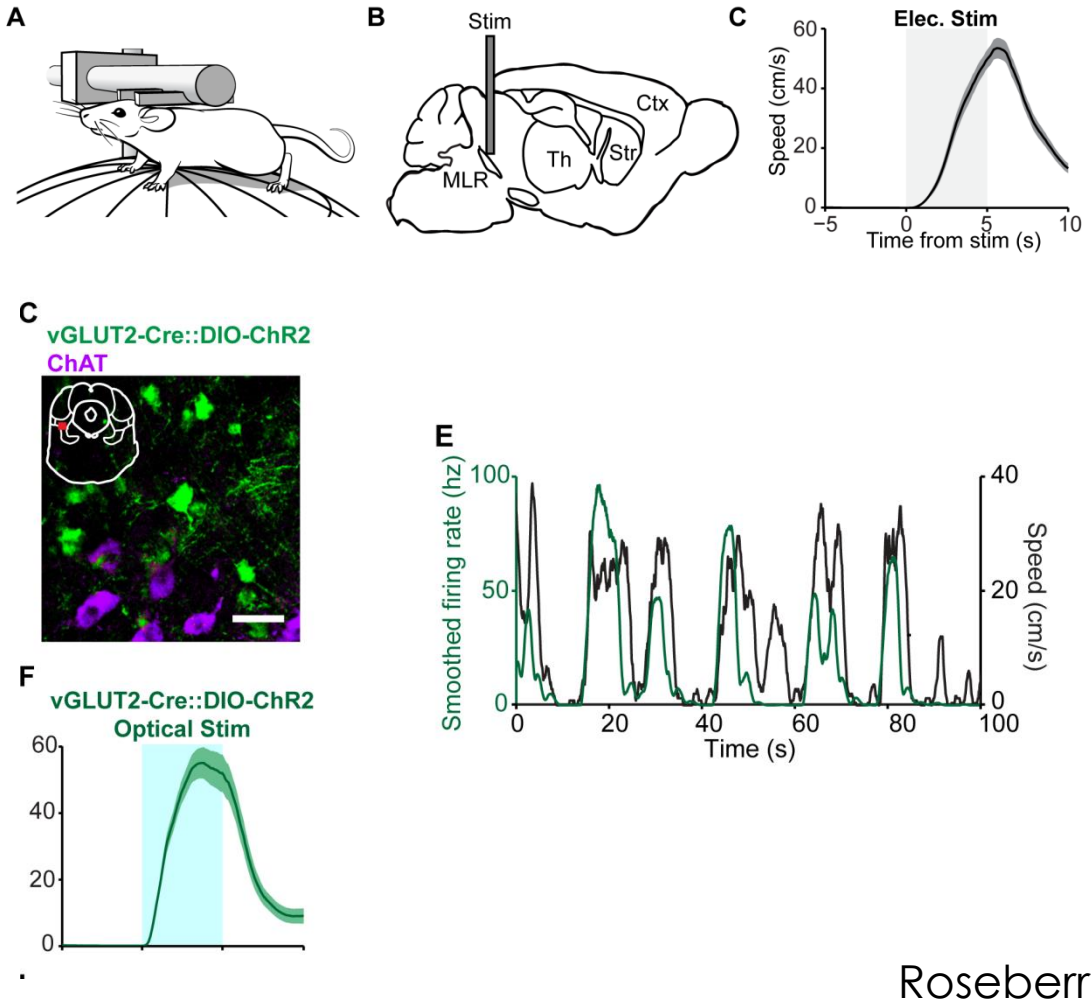
Cui et al, *Nature* 2013

Sequence-Related Activity in dMSNs and iMSNs



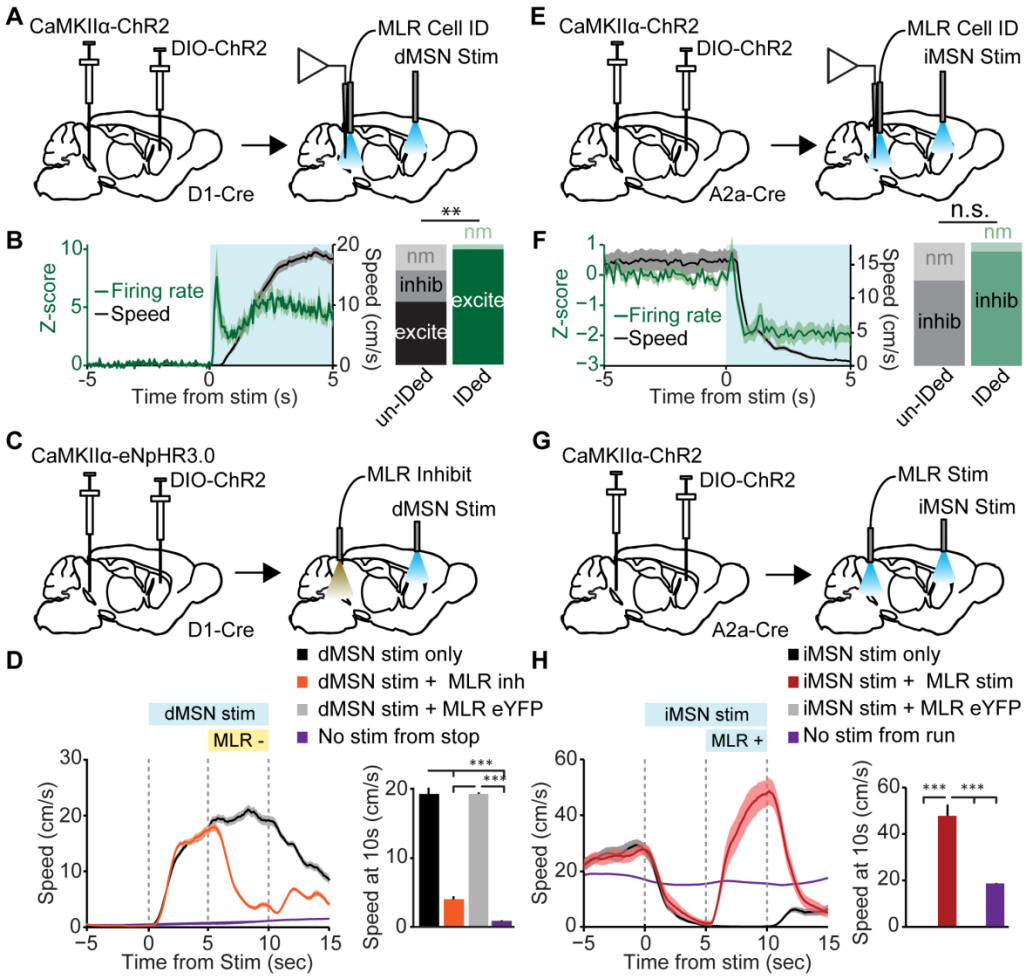
Jin et al, *Nat Neurosci* 2014

Control of Locomotion by Basal Ganglia Output



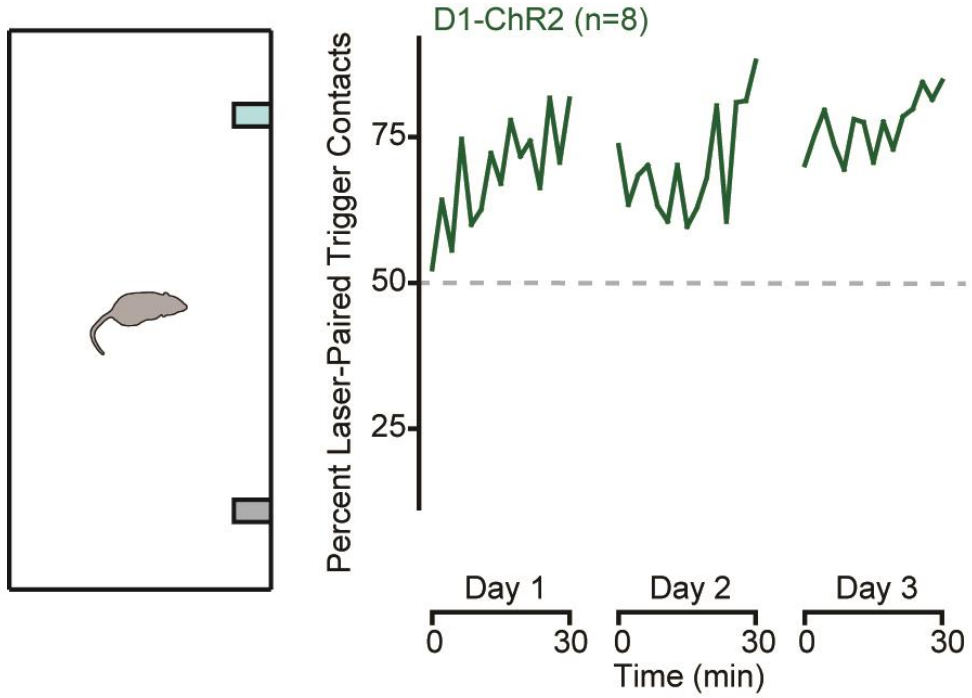
Roseberry et al, *Cell* 2016

Key Role for MLR Glutamate Neurons in Basal Ganglia Driven Locomotion



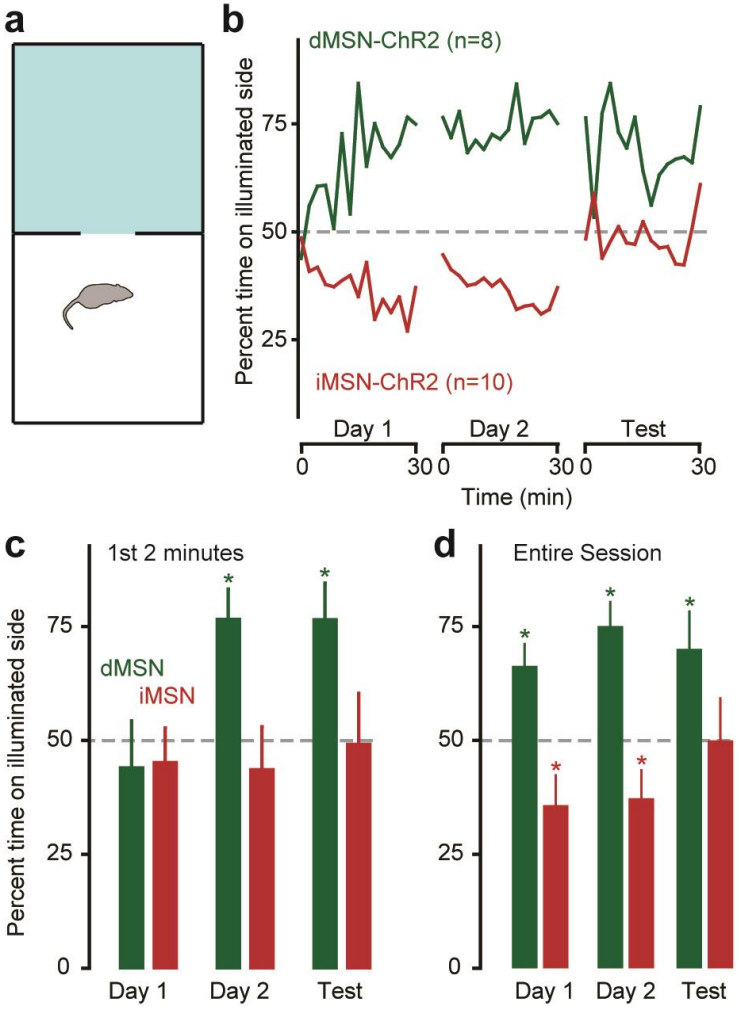
Roseberry et al, *Cell* 2016

Activation of the Direct Pathway is Sufficient for Reinforcement Learning



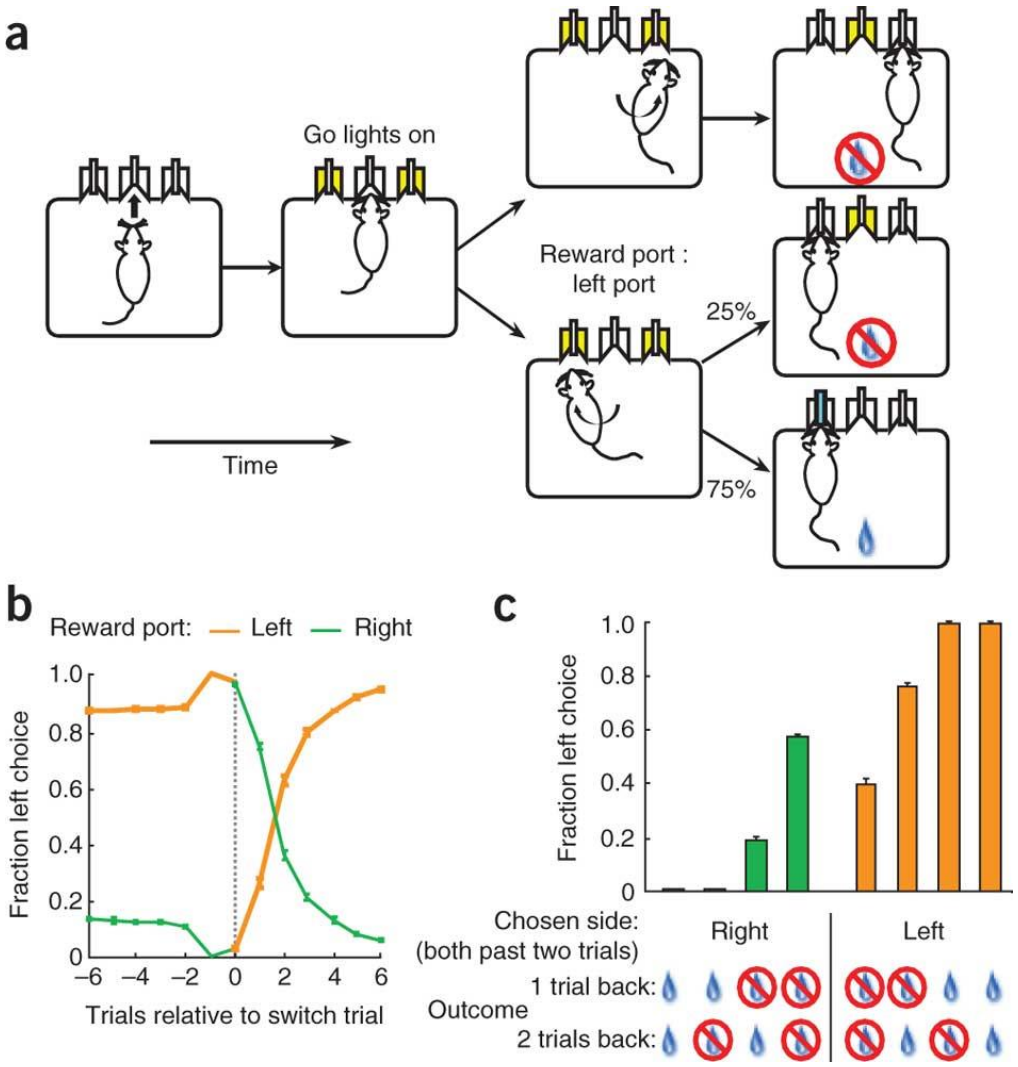
Kravitz et al, *Nat Neurosci* 2012

Direct and Indirect Pathway Activation Regulates Place Preference



Kravitz et al, *Nat Neurosci* 2012

BG Circuits Influence Decision Making



Tai et al, *Nat Neurosci 2012*

BG Circuits Influence Decision Making

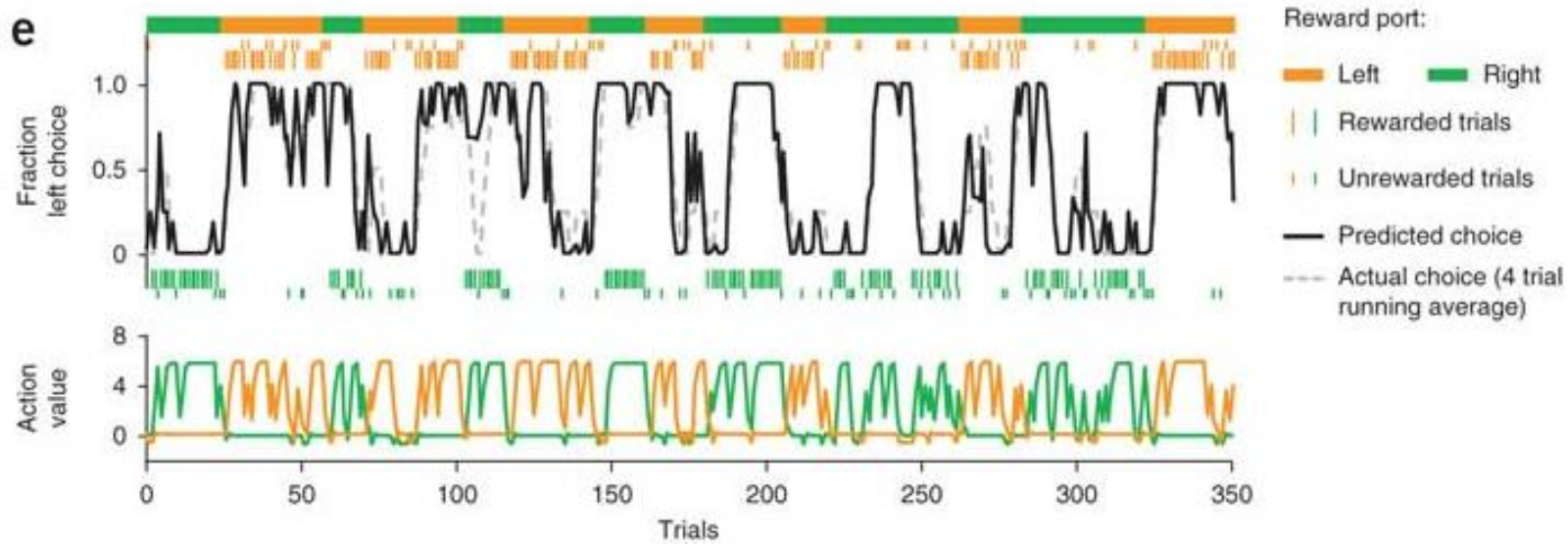
Q-Learning model:

Updated Action Value | Old Value | Reward Prediction Error

$$Q(t+1) = Q(t) + \alpha[R(t) - Q(t)]$$

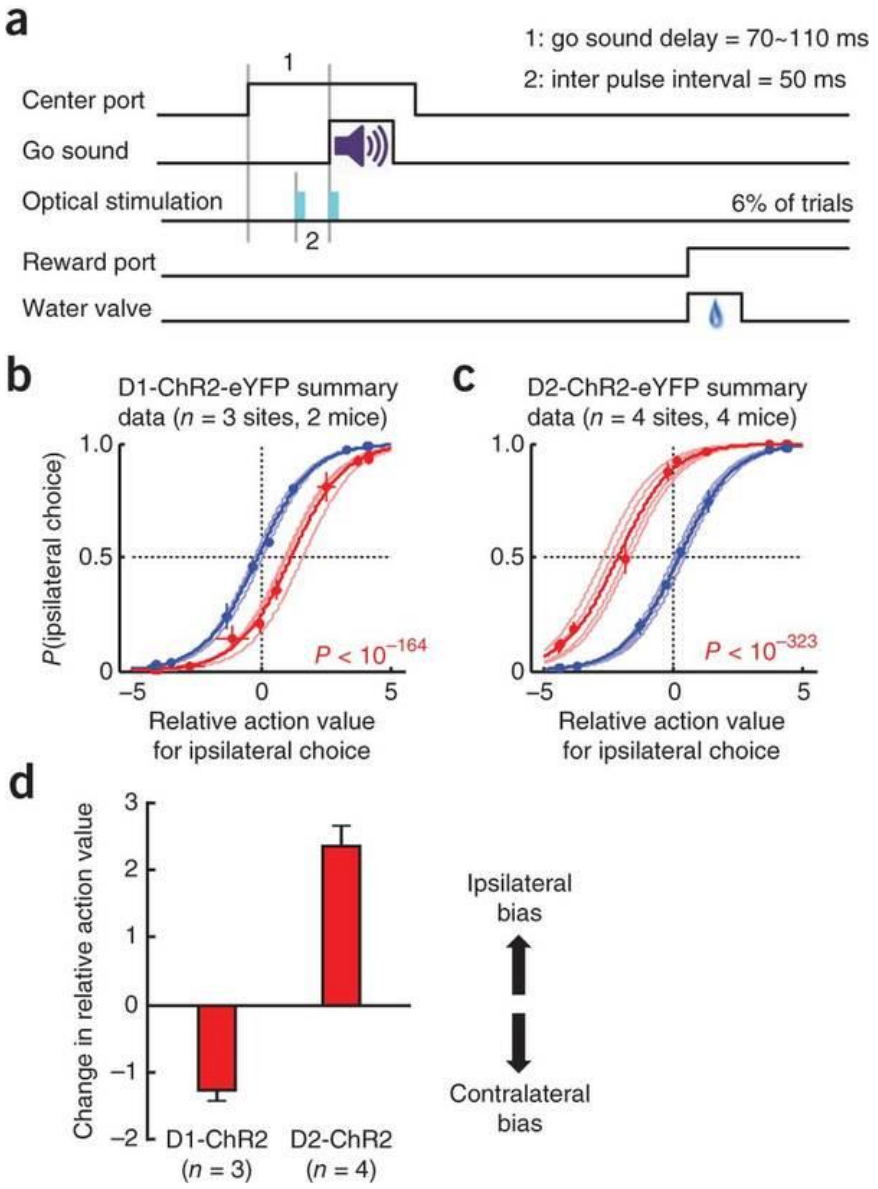
Learning rate

softmax function → choice probability



Tai et al, *Nat Neurosci 2012*

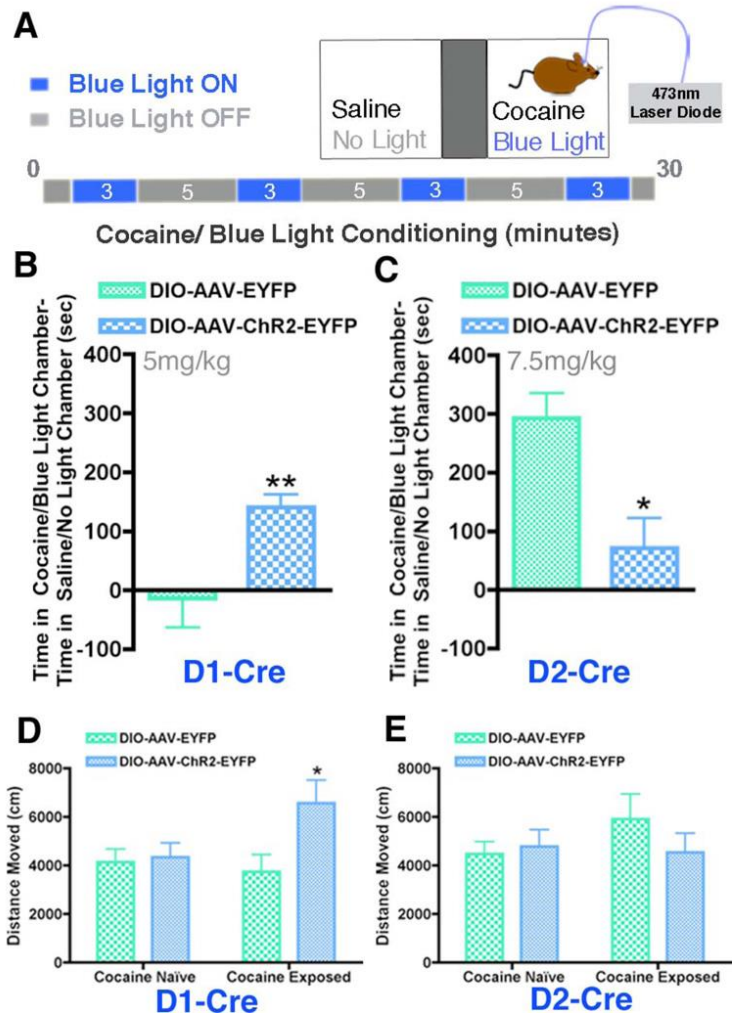
BG Circuits Influence Decision Making



Blue = no stim
red = opto stim

Tai et al, *Nat Neurosci 2012*

A Role for Basal Ganglia Circuits in Addiction



Lobo et al, *Science 2010*