Brain Inhibition: Function, Disorders, and Therapeutic Targeting

By Kirill Zavalin, PhD Candidate

Vanderbilt Brain Institute

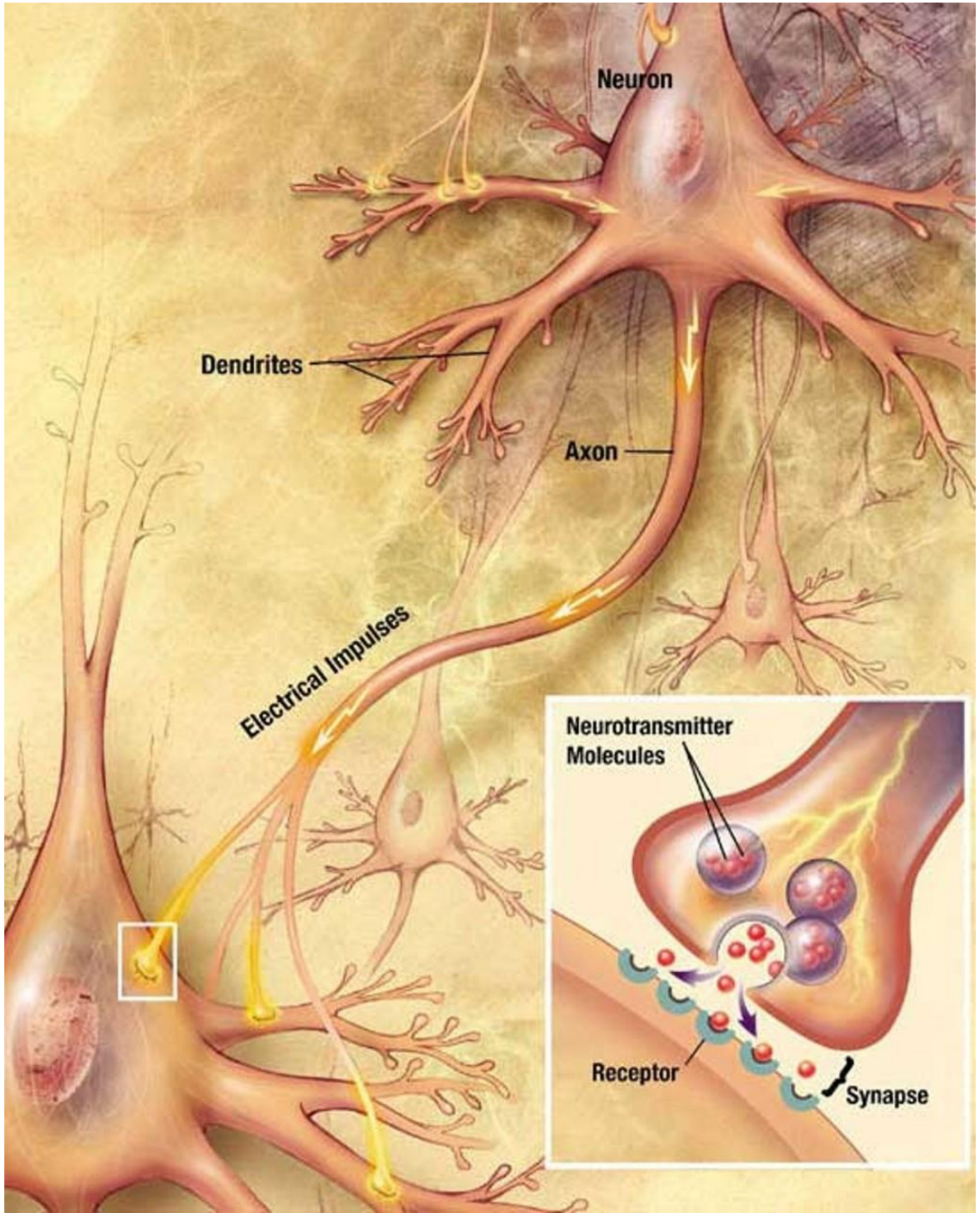
Objectives

- Understand the role inhibition plays in our brain
- Understand how inhibition works on the level of cells and synapses
- Learn of disorders that arise from improper inhibition
- Learn which drugs target the inhibitory system

Neurons Compose Our Brain

Lizzie Renck, 2015, https://dancingastronaut.com/2015/05/music-improves-cognitive-function-productivity-heres/

Neurons Communicate by Releasing Chemical Signals onto One Another



US National Institutes of Health, National Institute on Aging Brochure

Circuits of Neurons in Our Brain Comprise a Complex, Interconnected System

Solari and Stoner et al, 2011

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- Many different types of neurons

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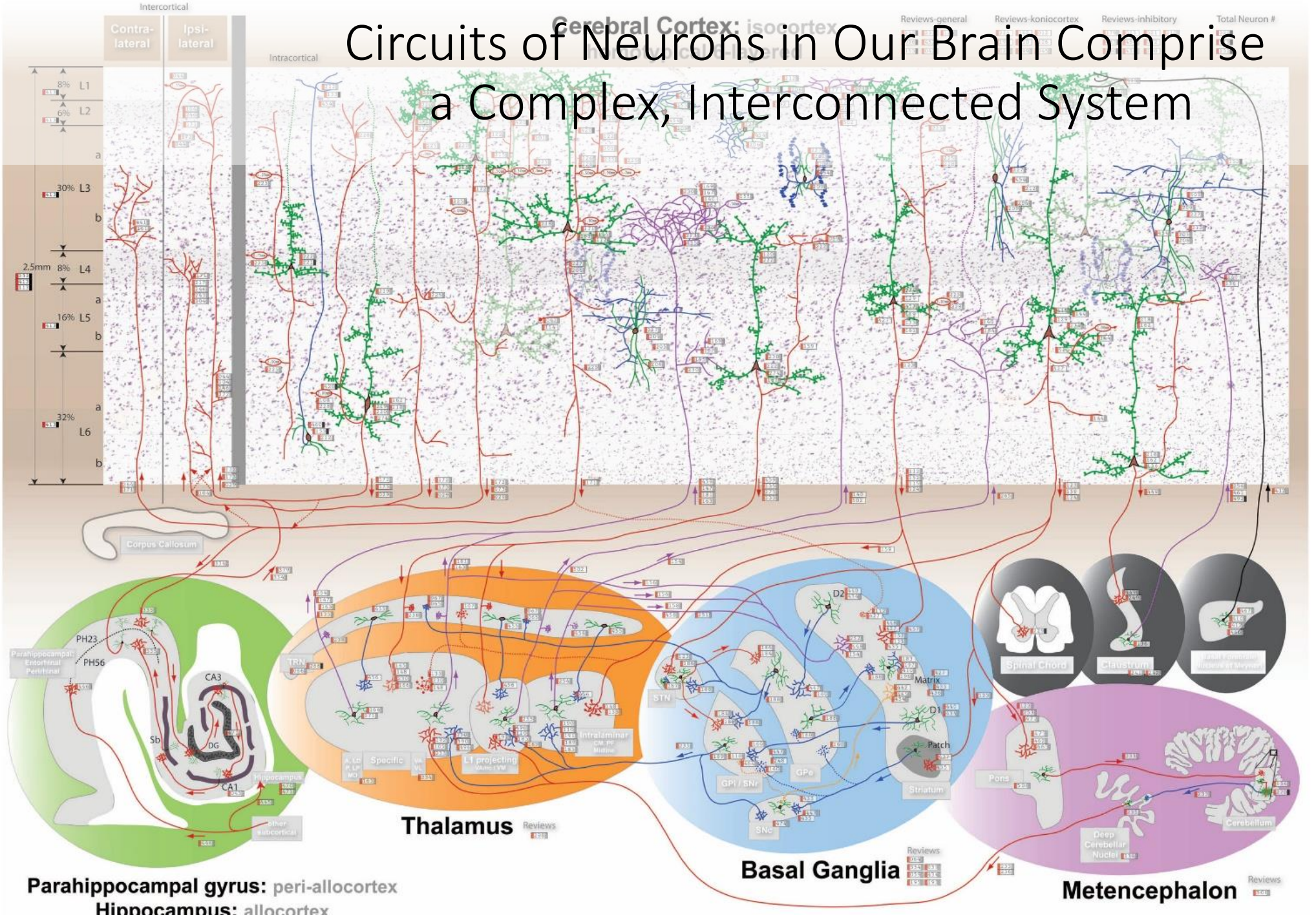
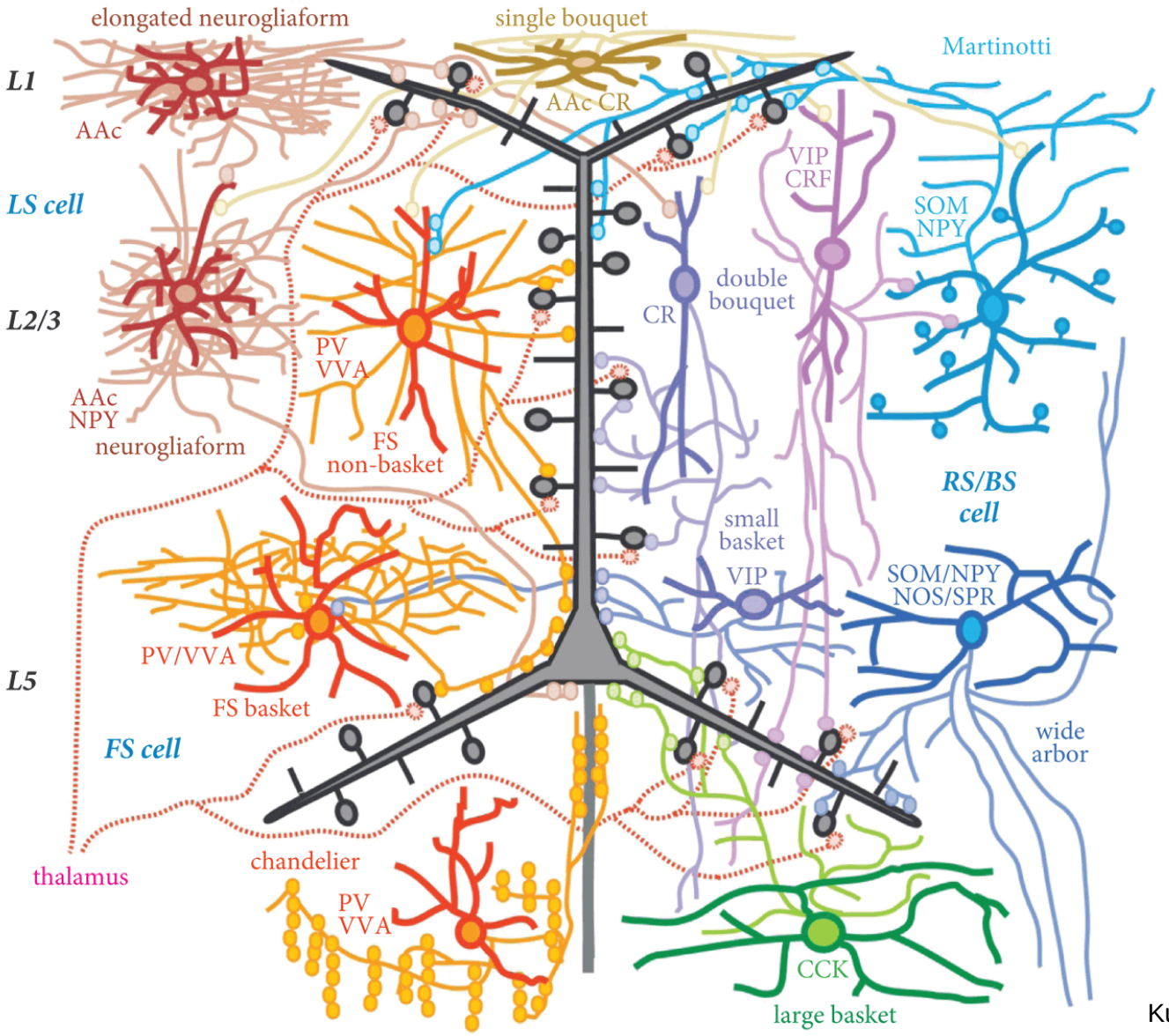


- Many different types of neurons
- Many different brain regions

Solari and Stoner et al, 2011

Inhibitory Cells Control Signal Transduction of Other Neurons



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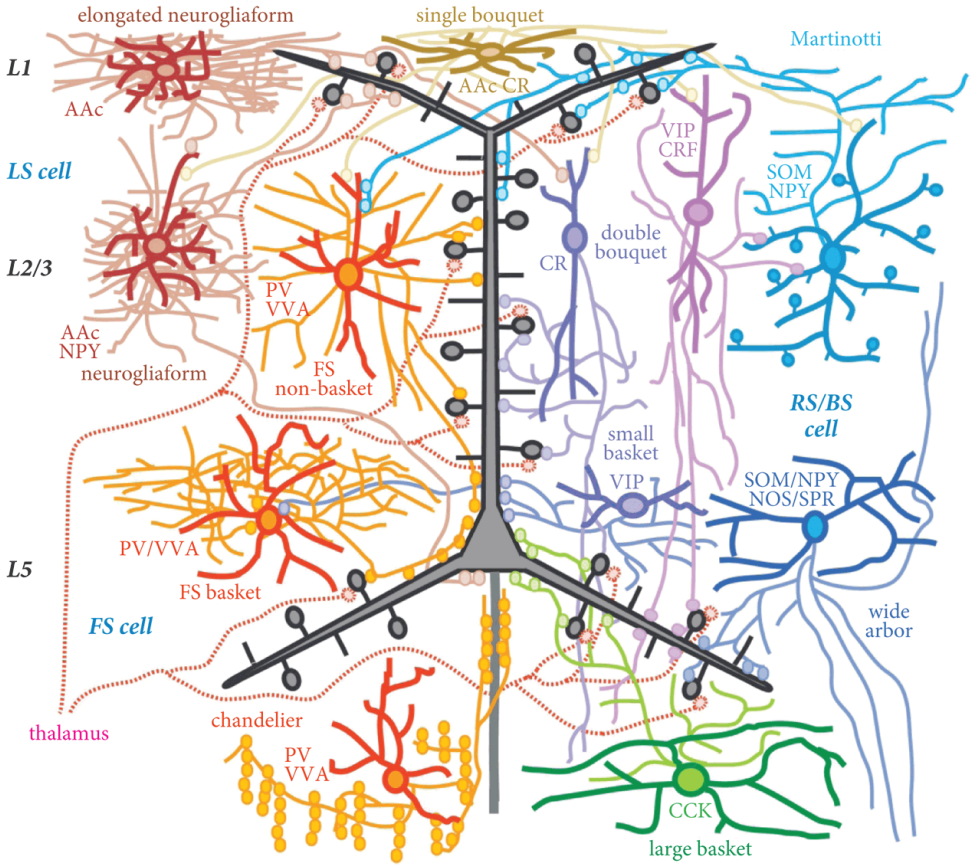
Local “Interneurons” Control Long-Range Signals Sent by Excitatory Cells



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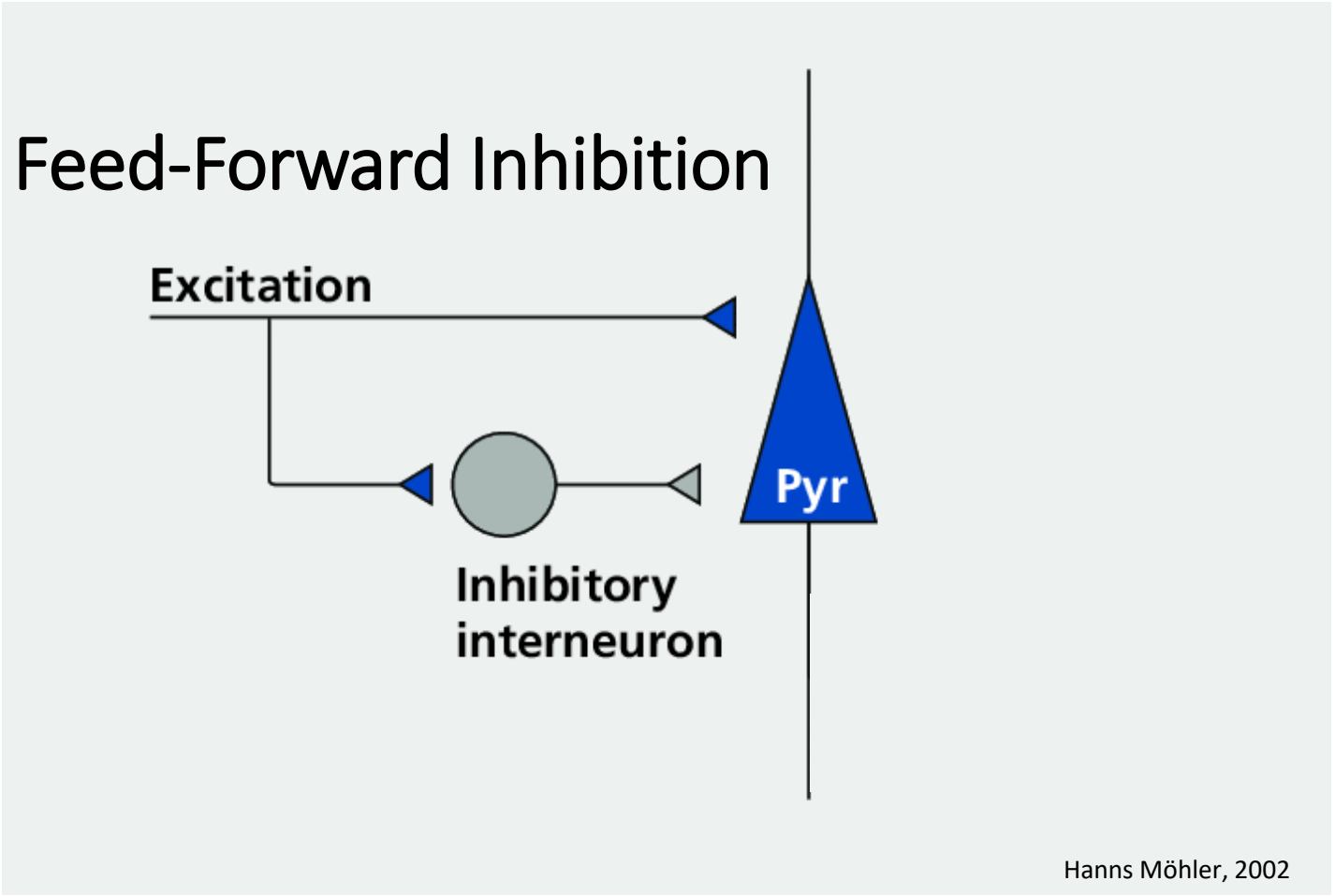

Hanns Möhler, 2002

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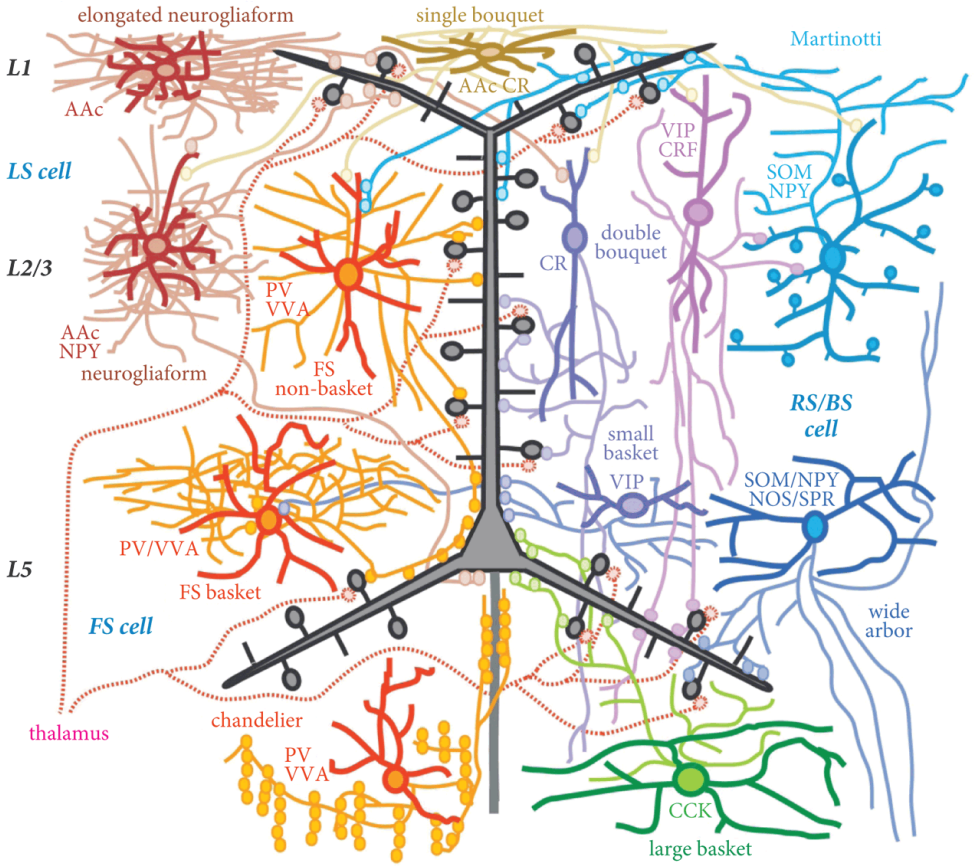

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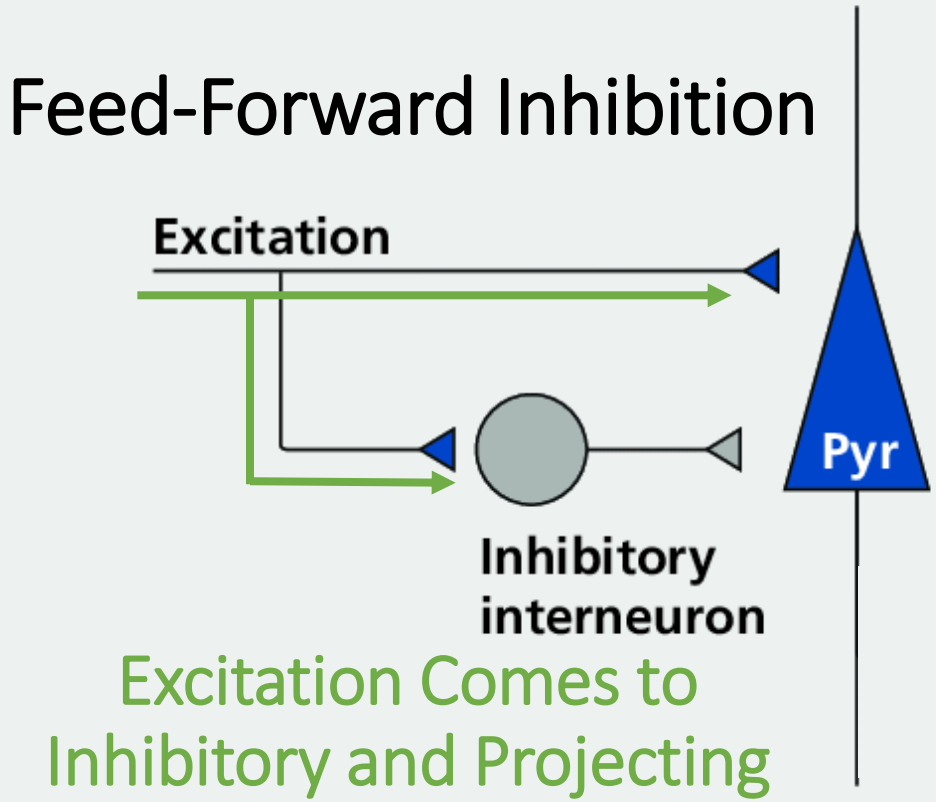

Excitation Comes to Inhibitory and Projecting Neuron

Hanns Möhler, 2002

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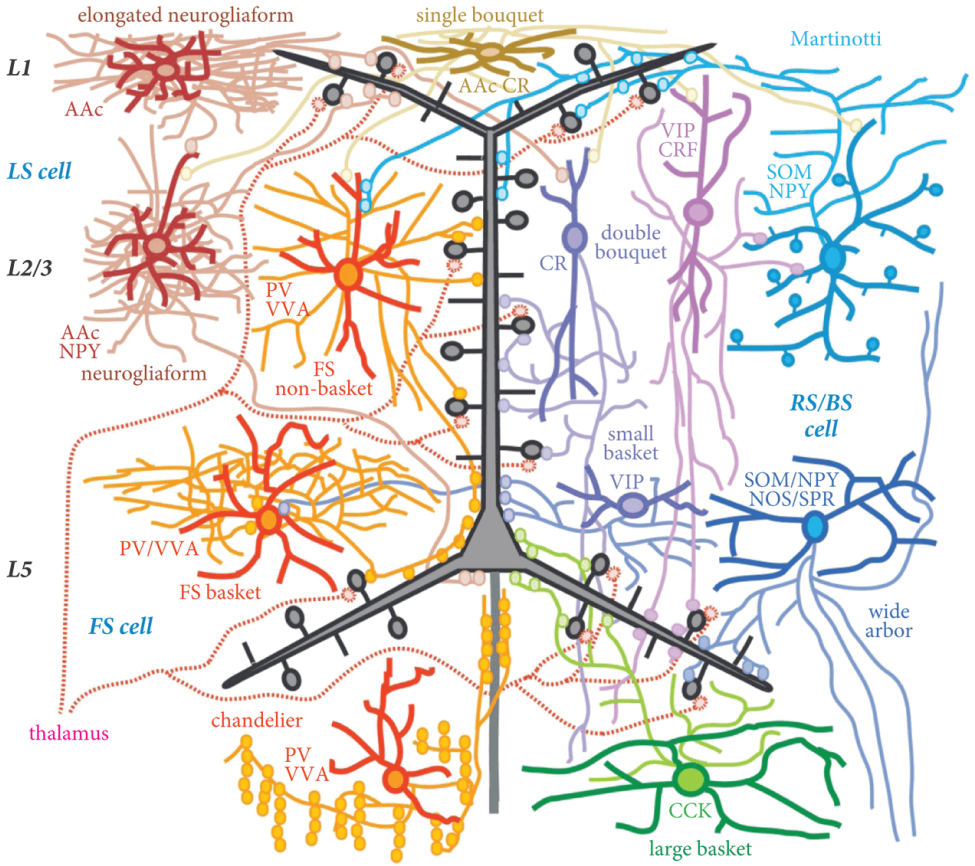

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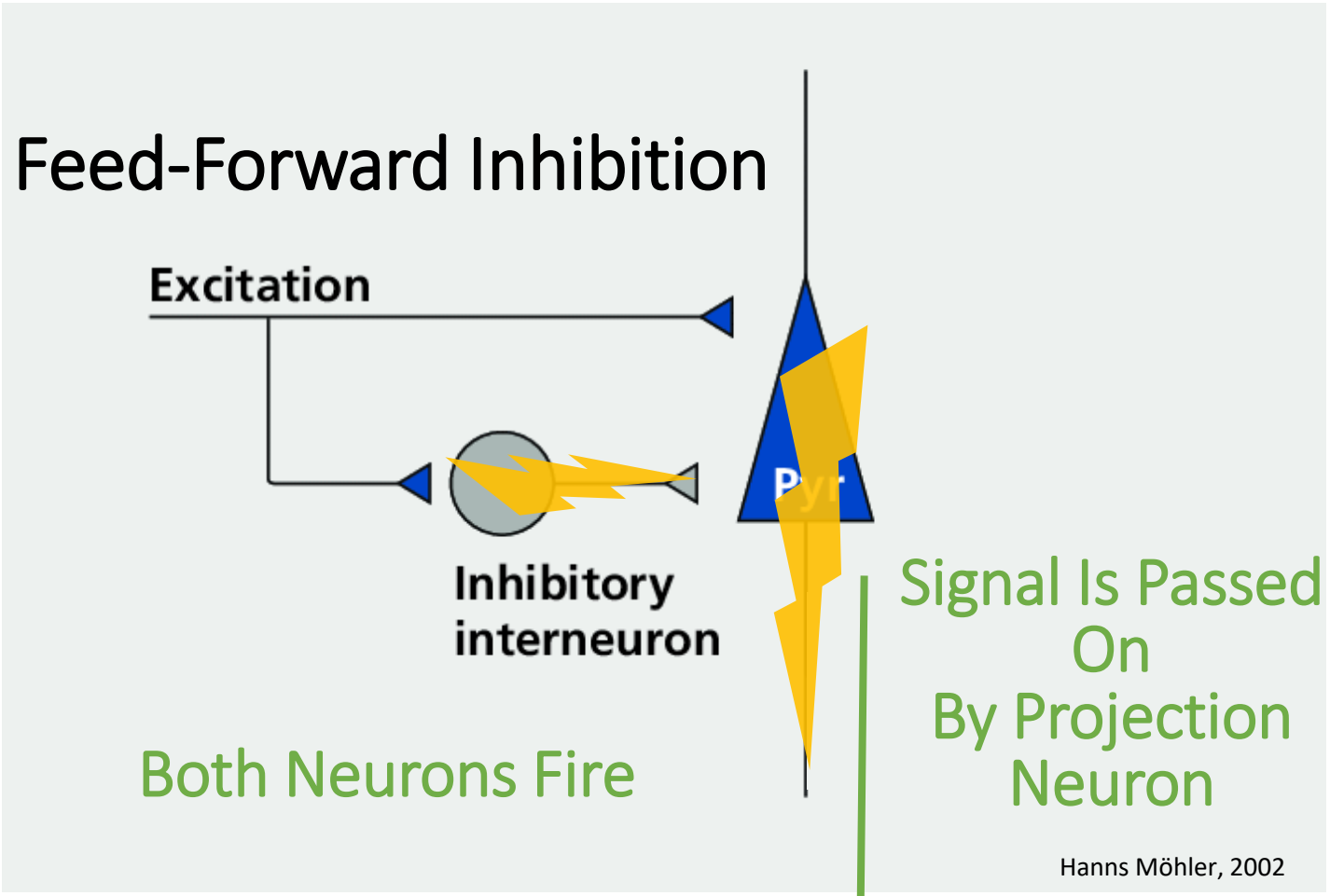

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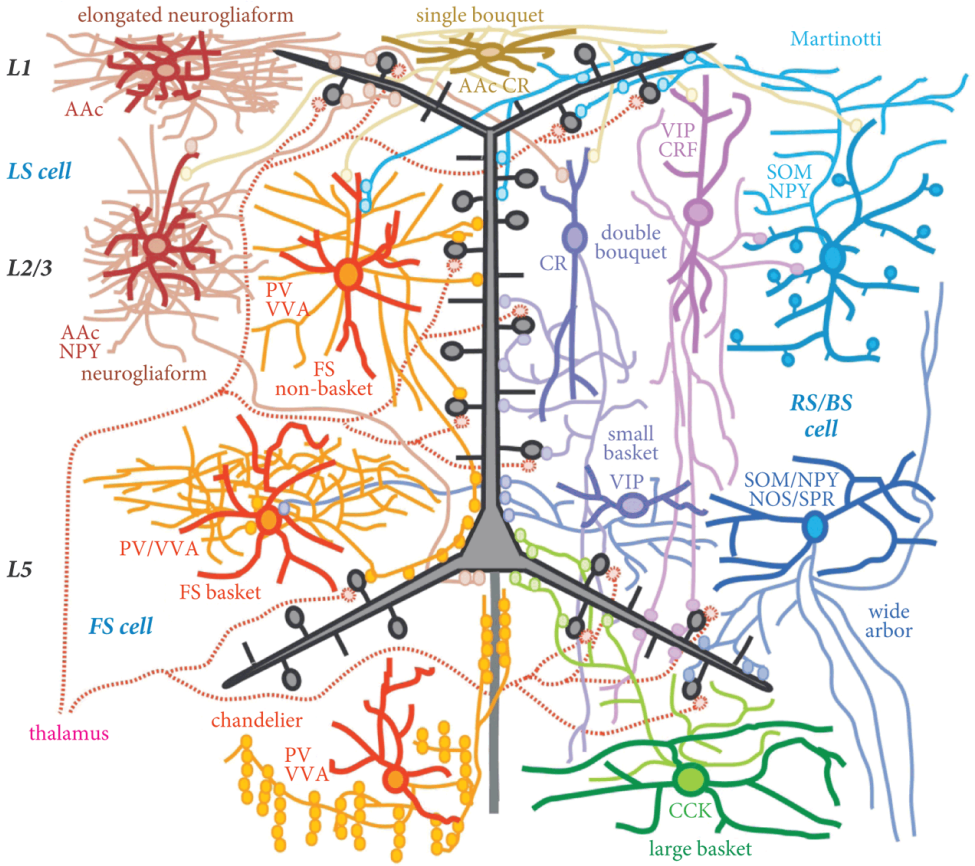

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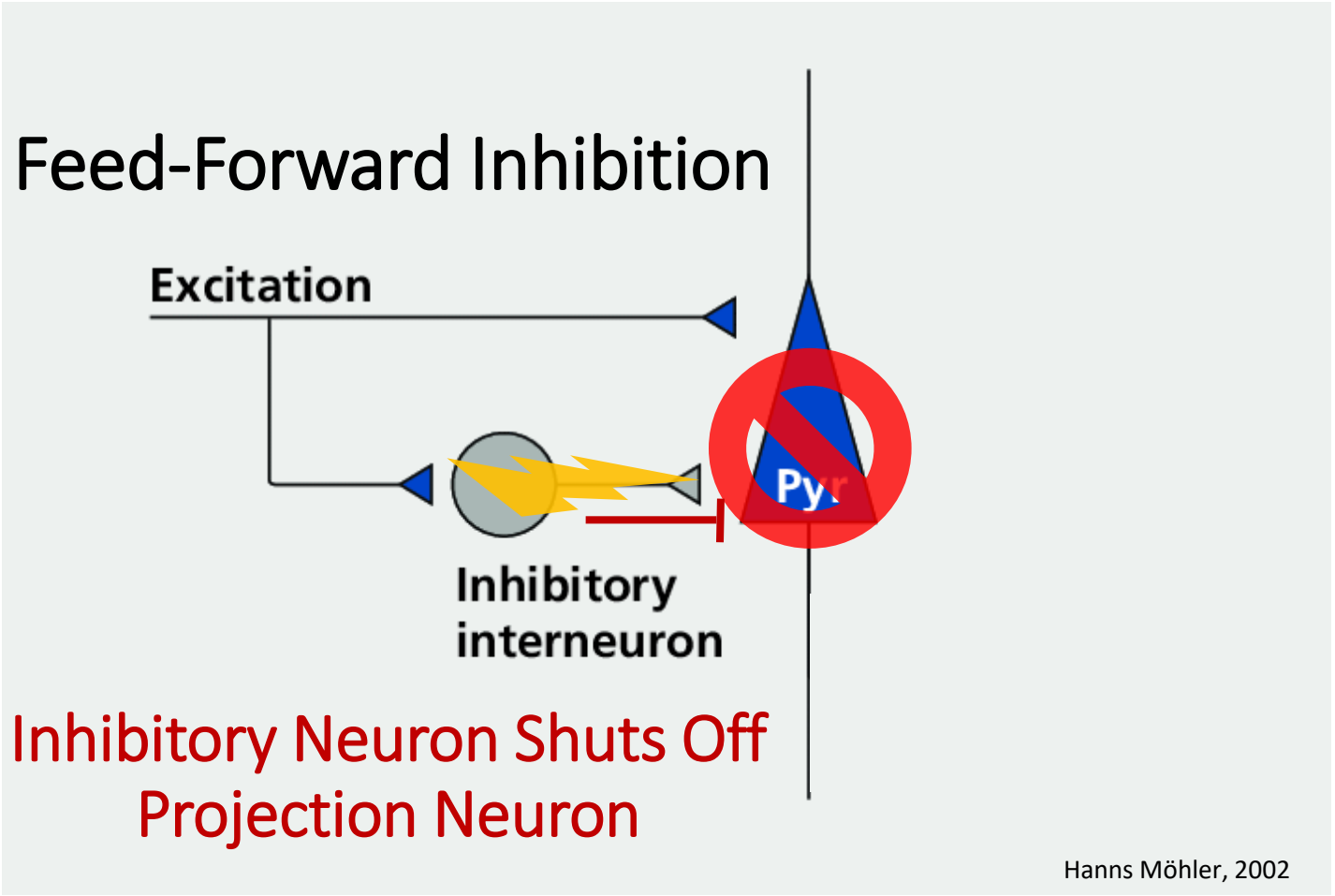

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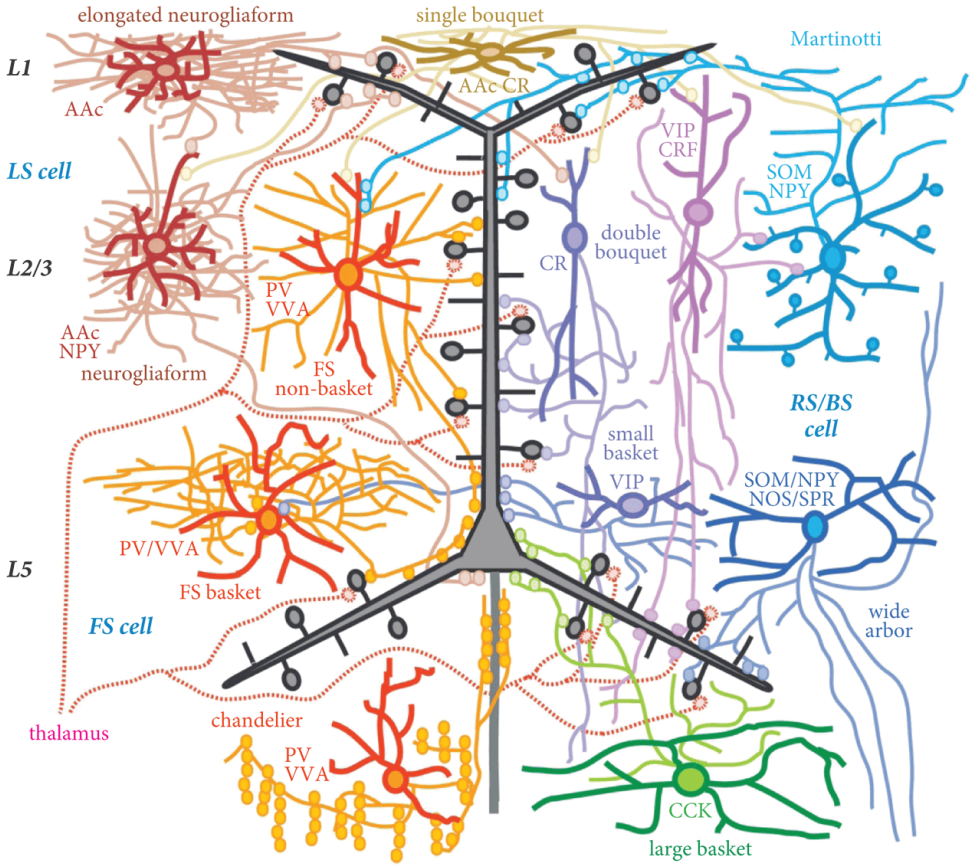

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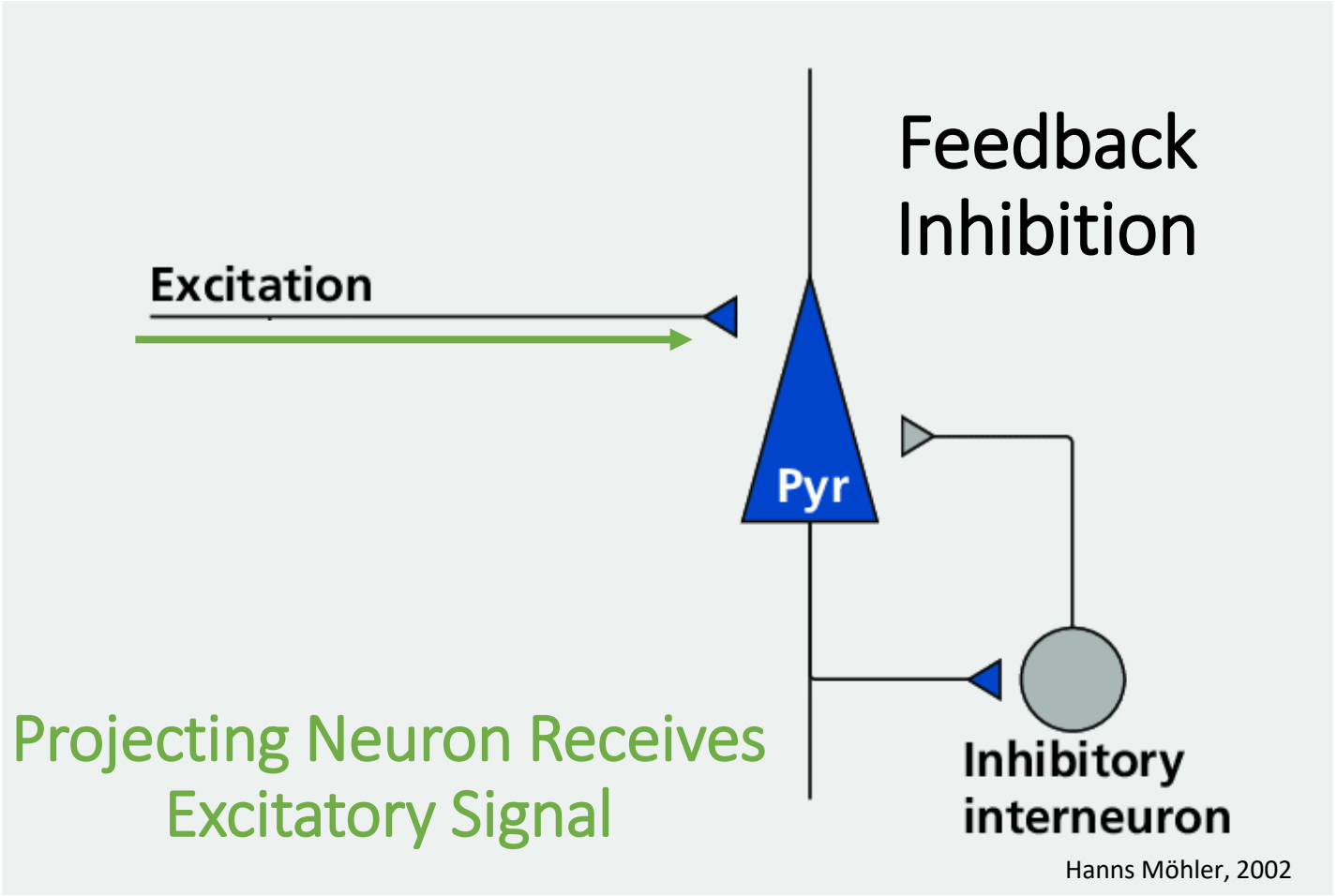

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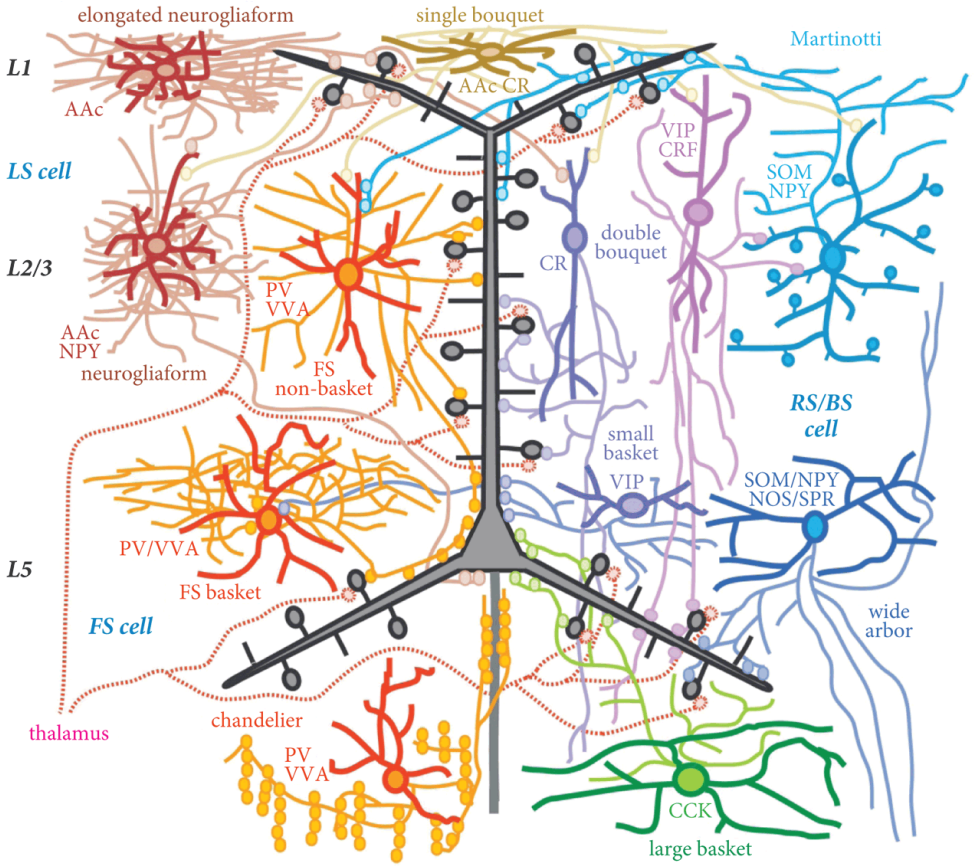

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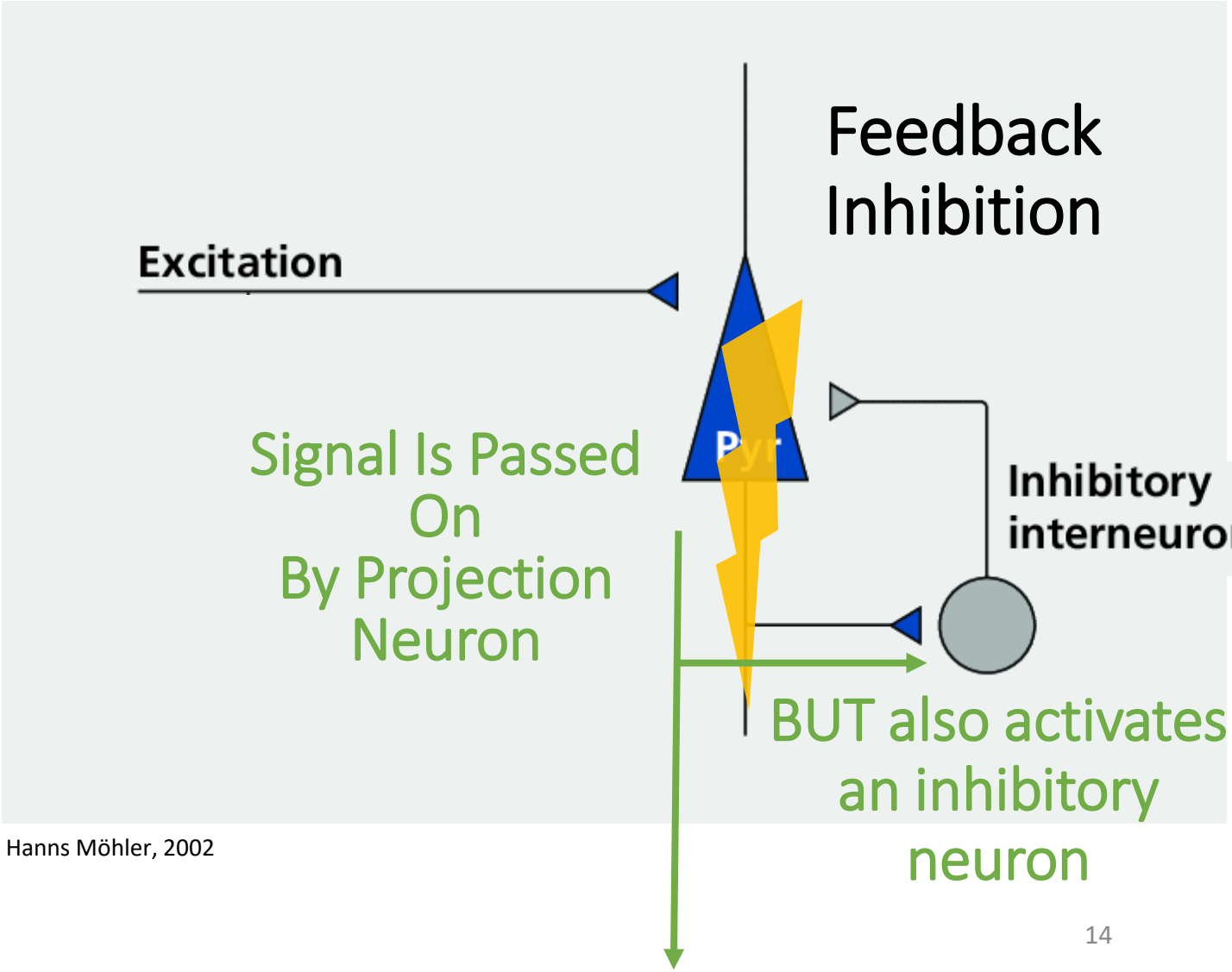

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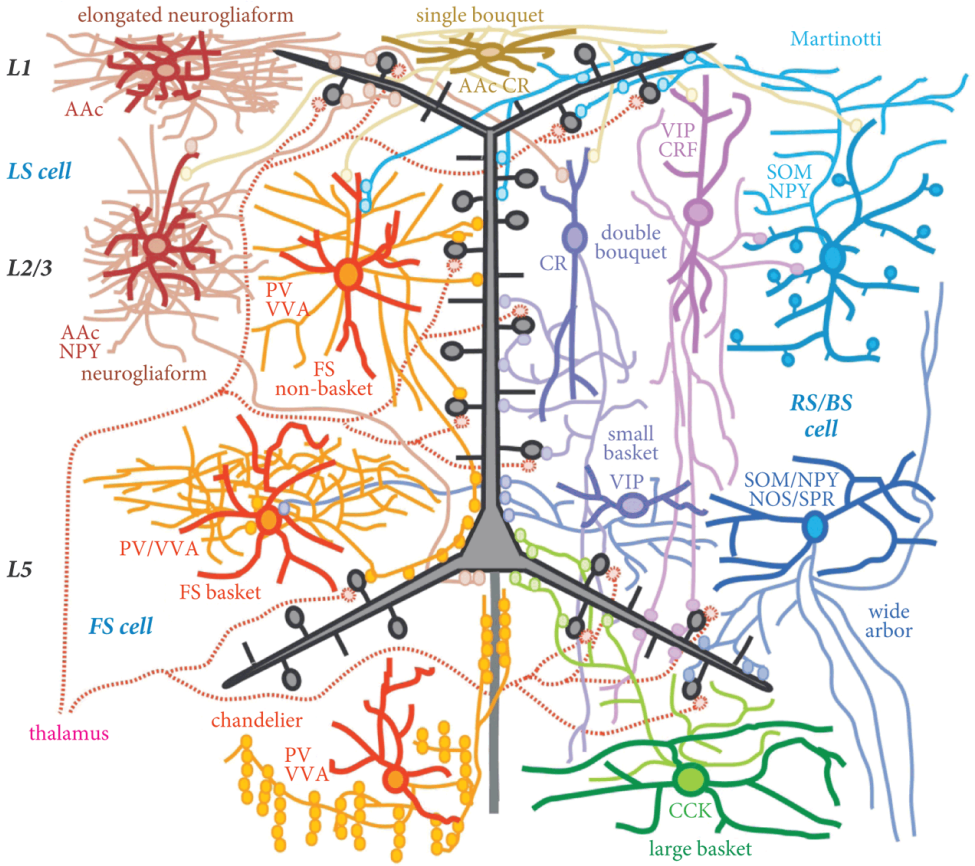

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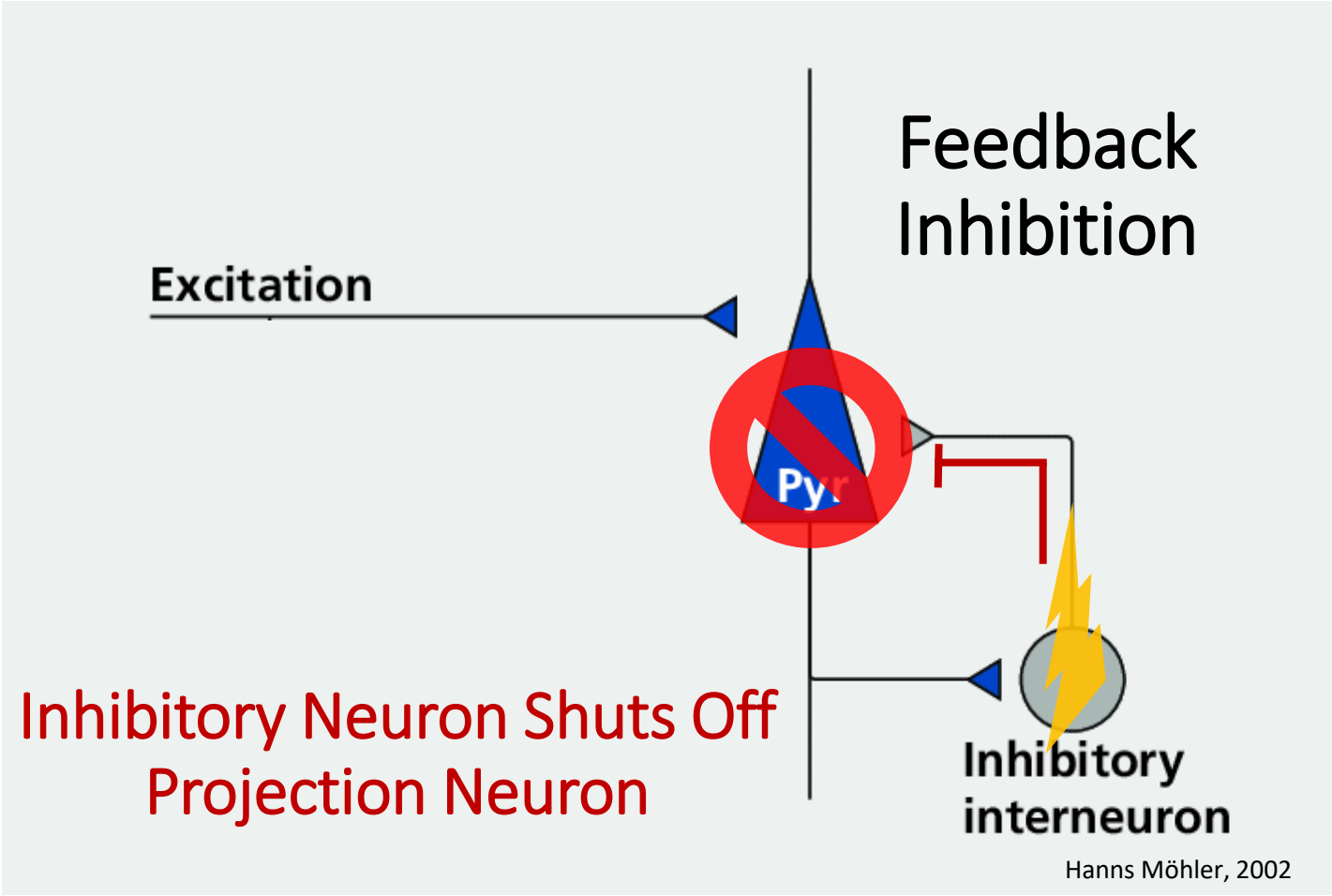
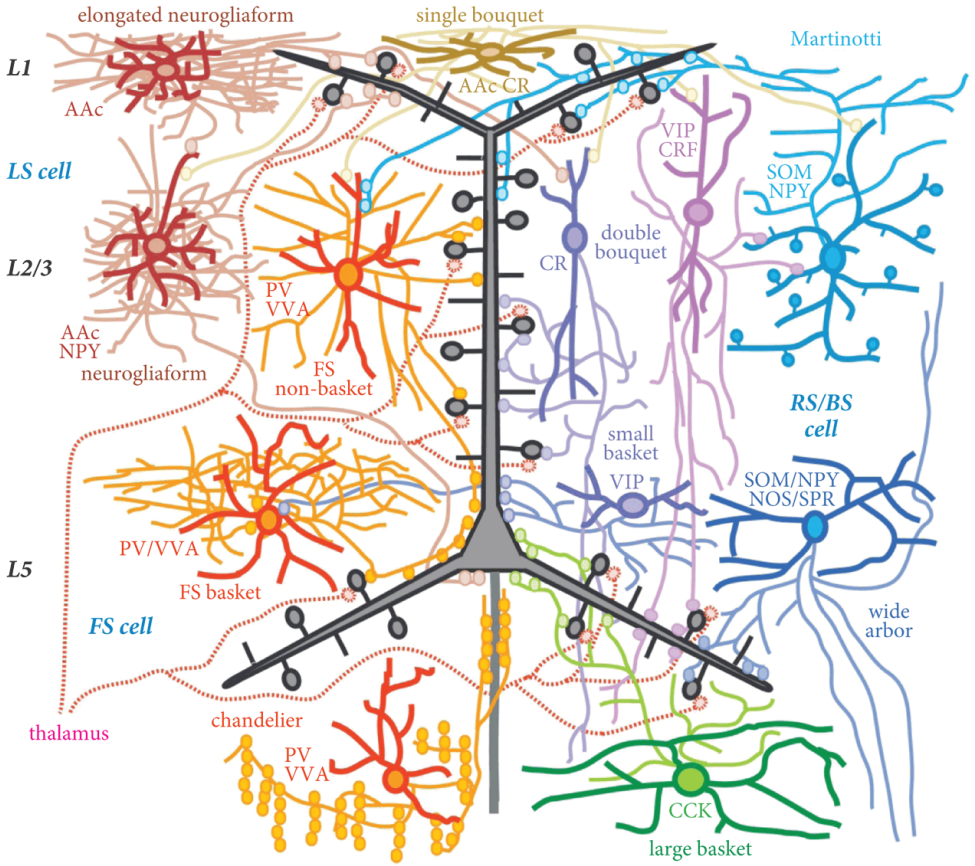


Feed-Forward and Feedback Inhibition Are Common Motifs Used to Regulate Circuits of Neurons



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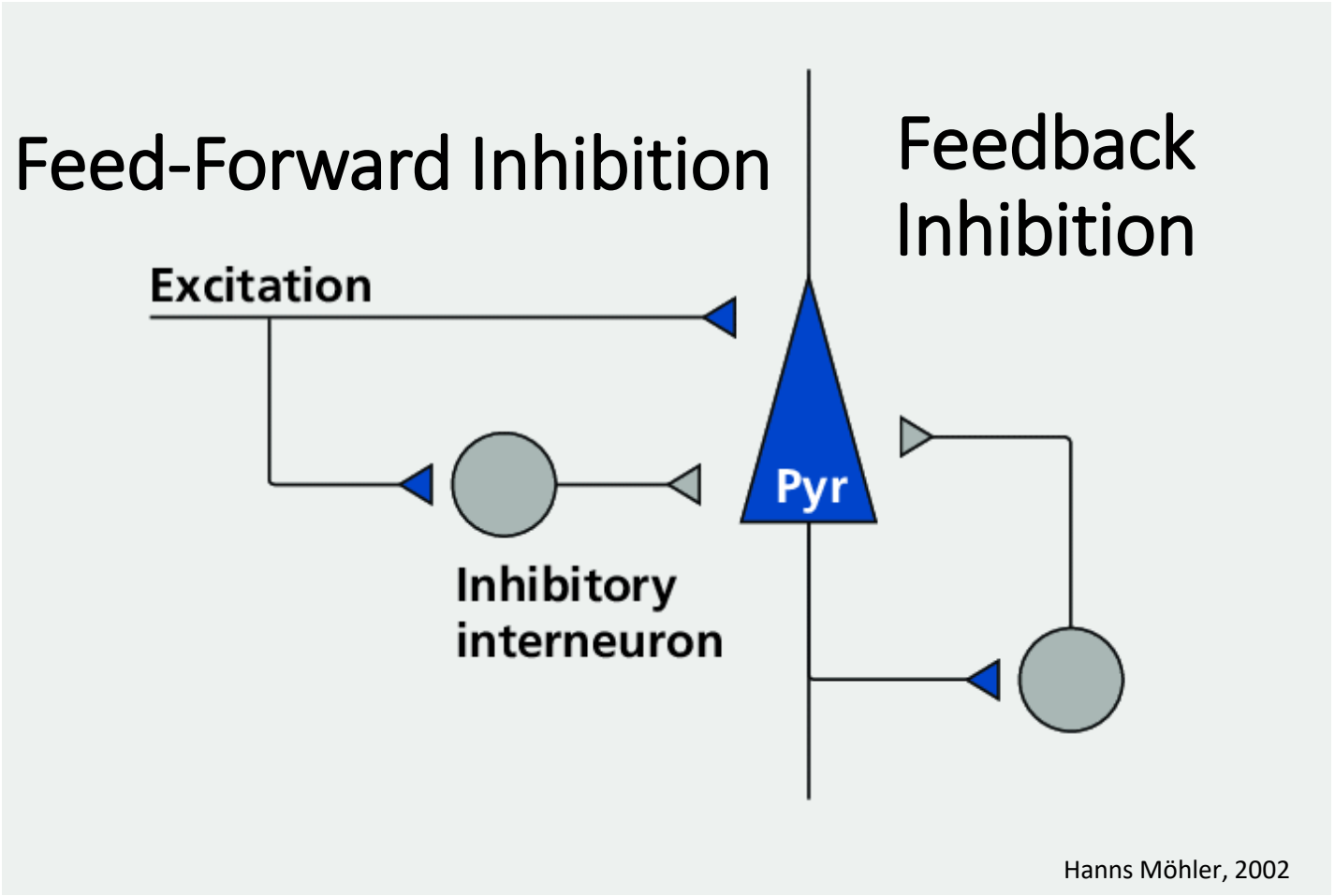

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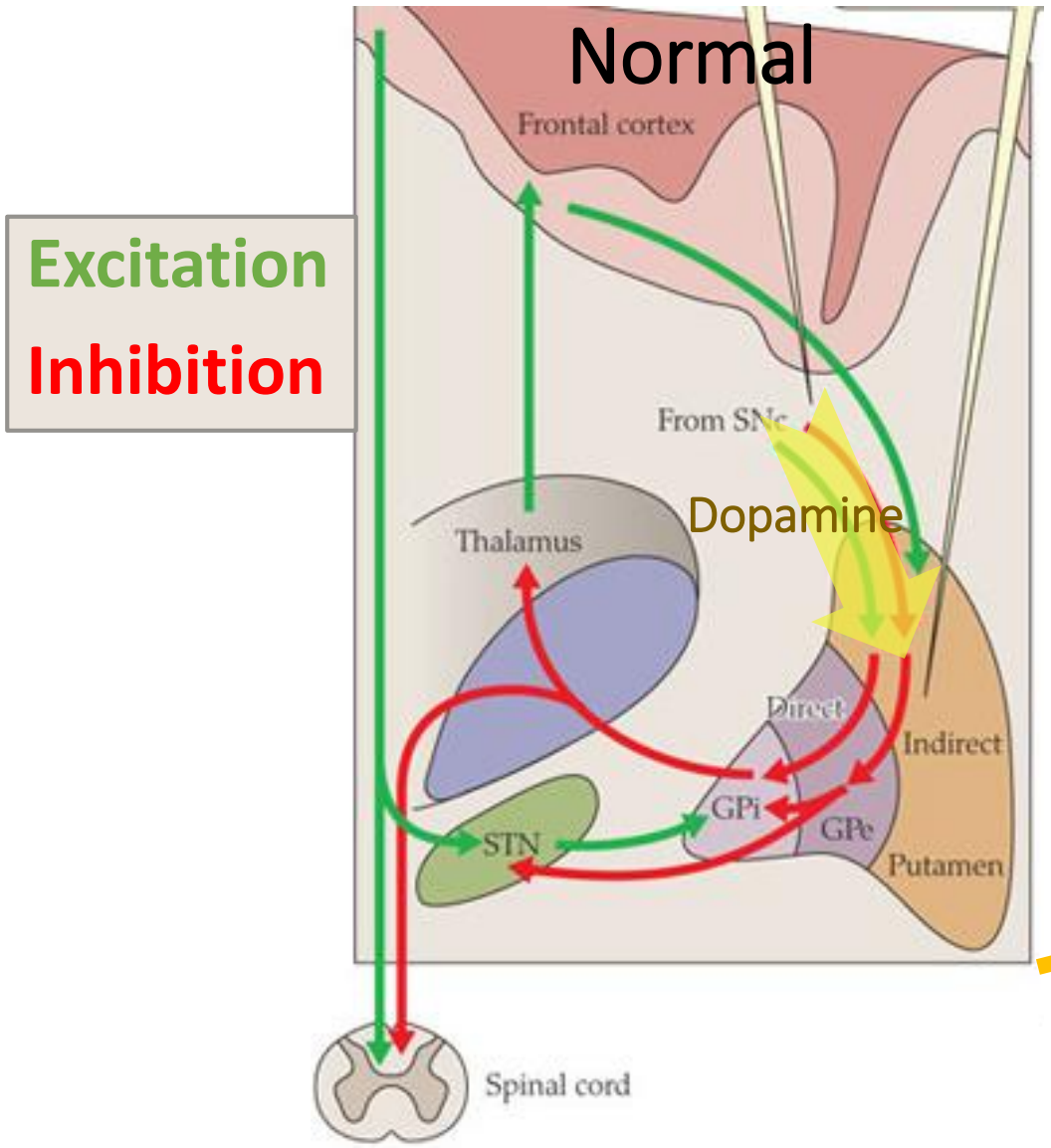
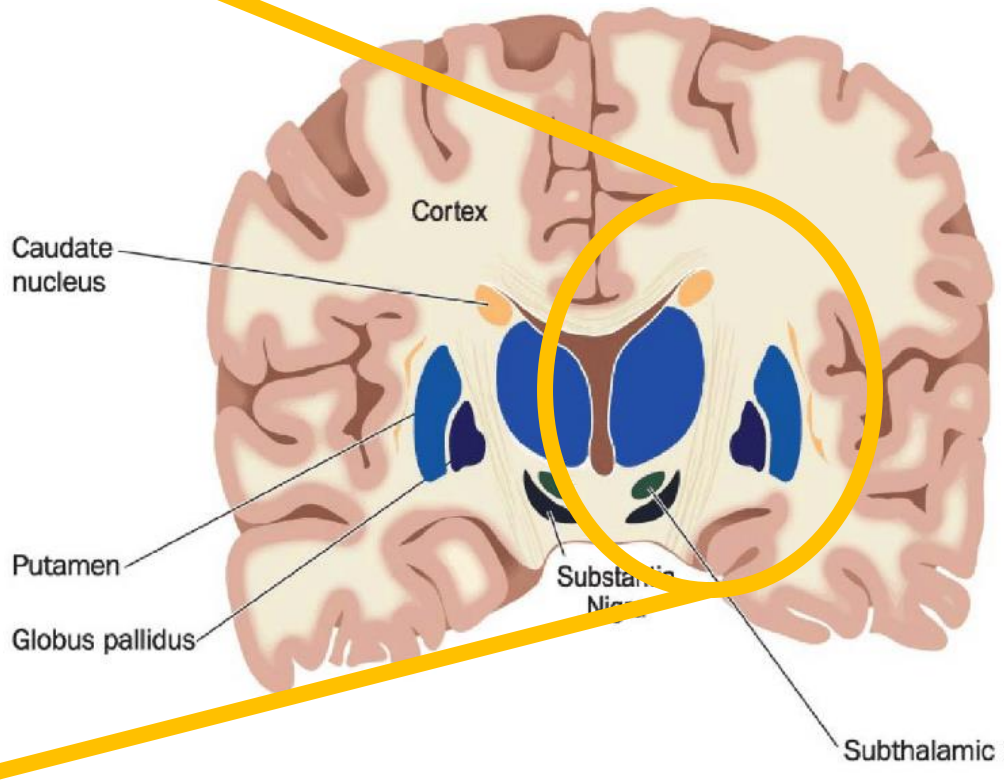
Regions Outside of Cortex Can Send Long-Range Inhibitory Signals





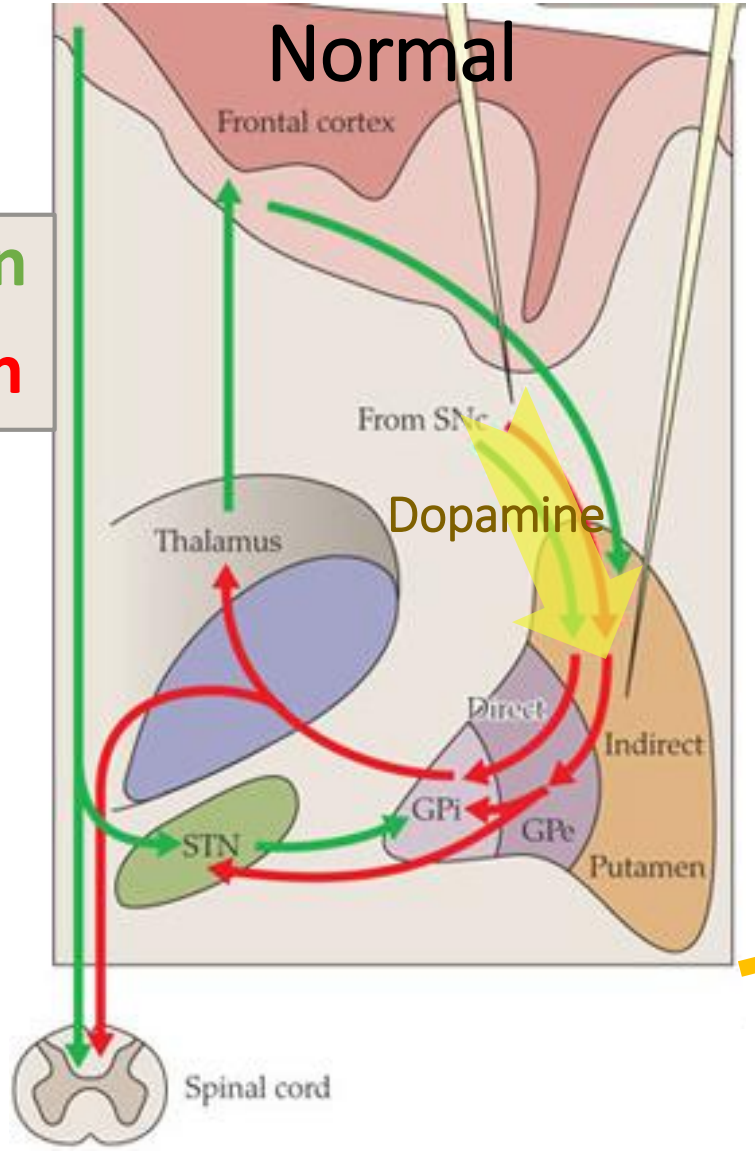
Hanjing Emily Wu et al, 2018

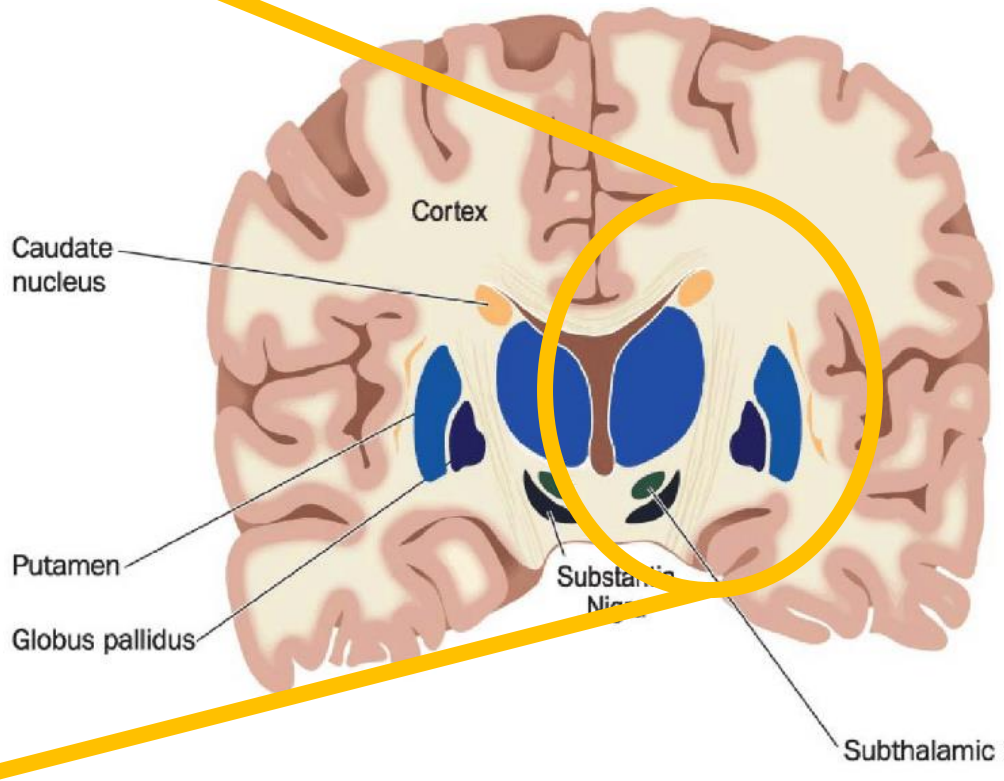
https://scienceofpd.files.wordpress.com/2016/02/pathways.jpg?w\u003d830

Basal Ganglia Controls Movement Initiation Through Inhibition

Excitation

Inhibition





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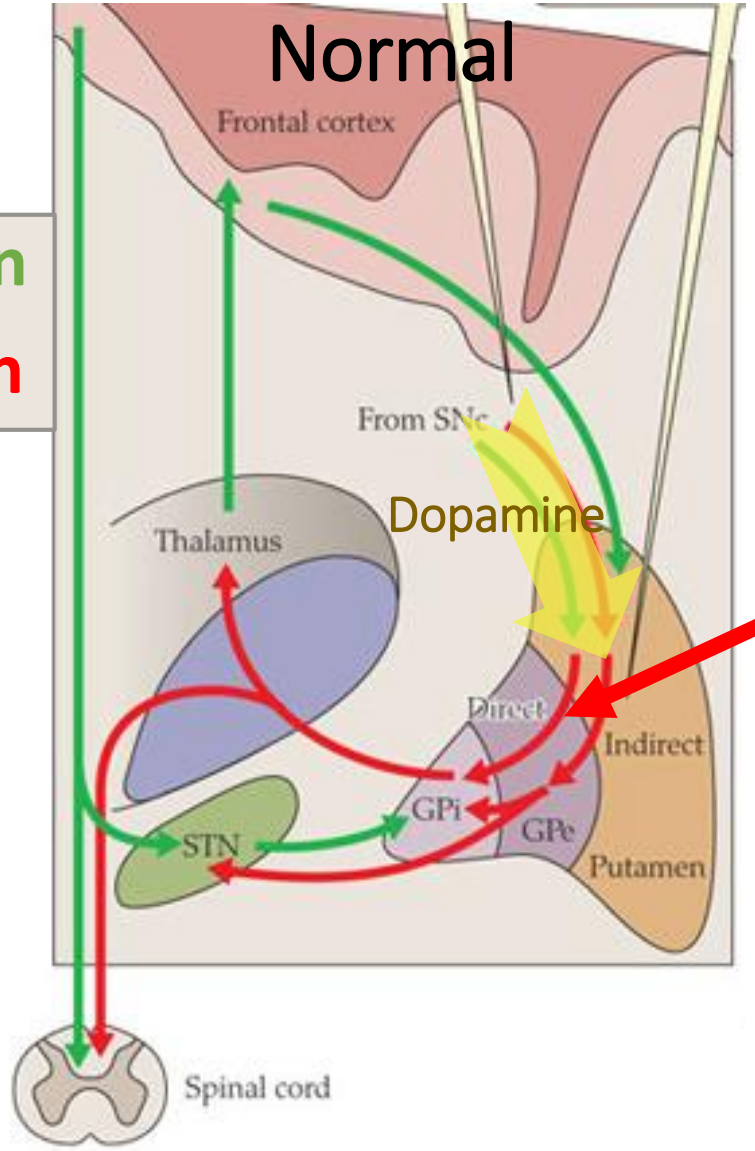

Regions of basal ganglia communicate with inhibitory cues to initiate movement

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Parkinson's Disease: Movement Initiation is Prevented by Increased Inhibition of Thalamus by Basal Ganglia

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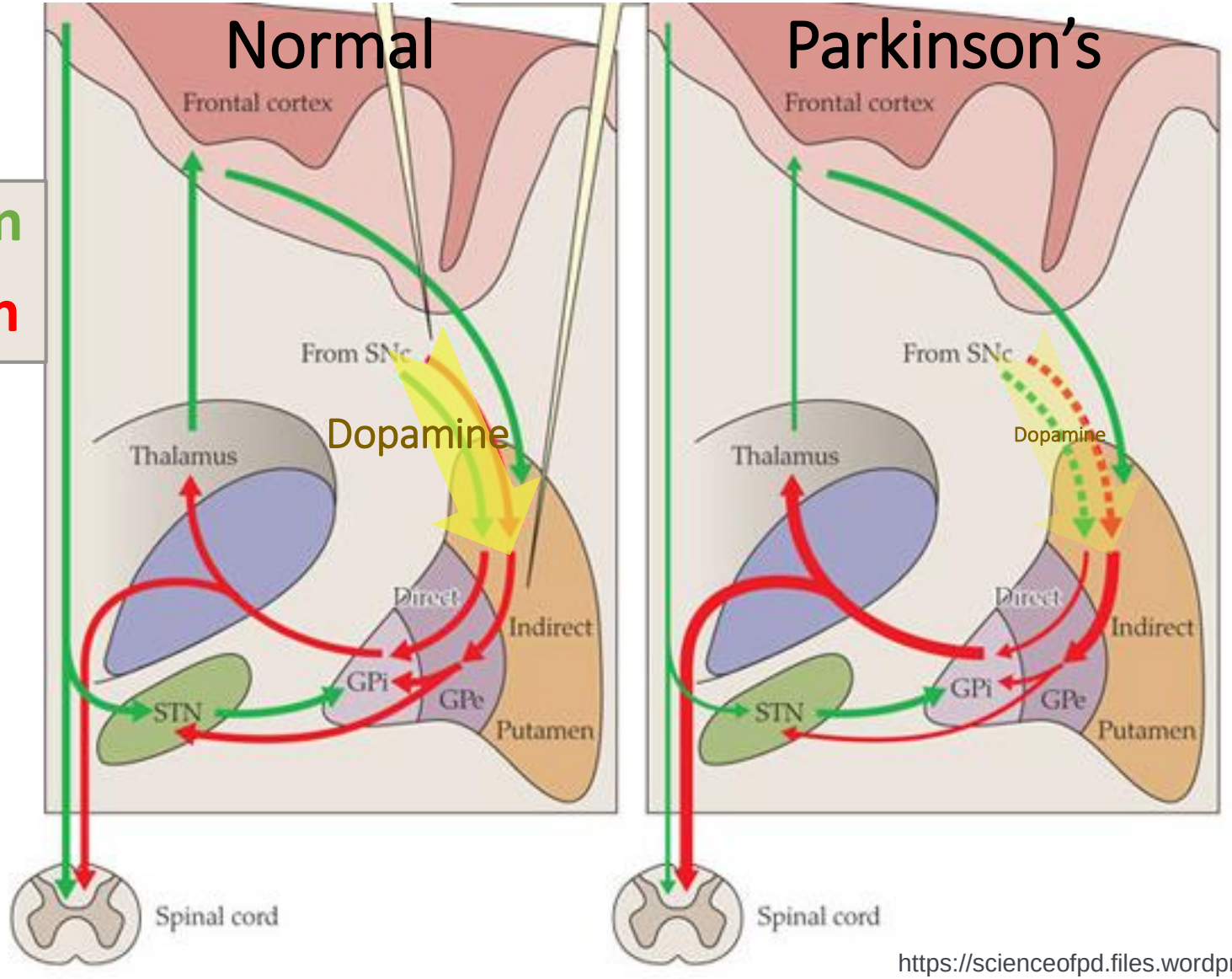

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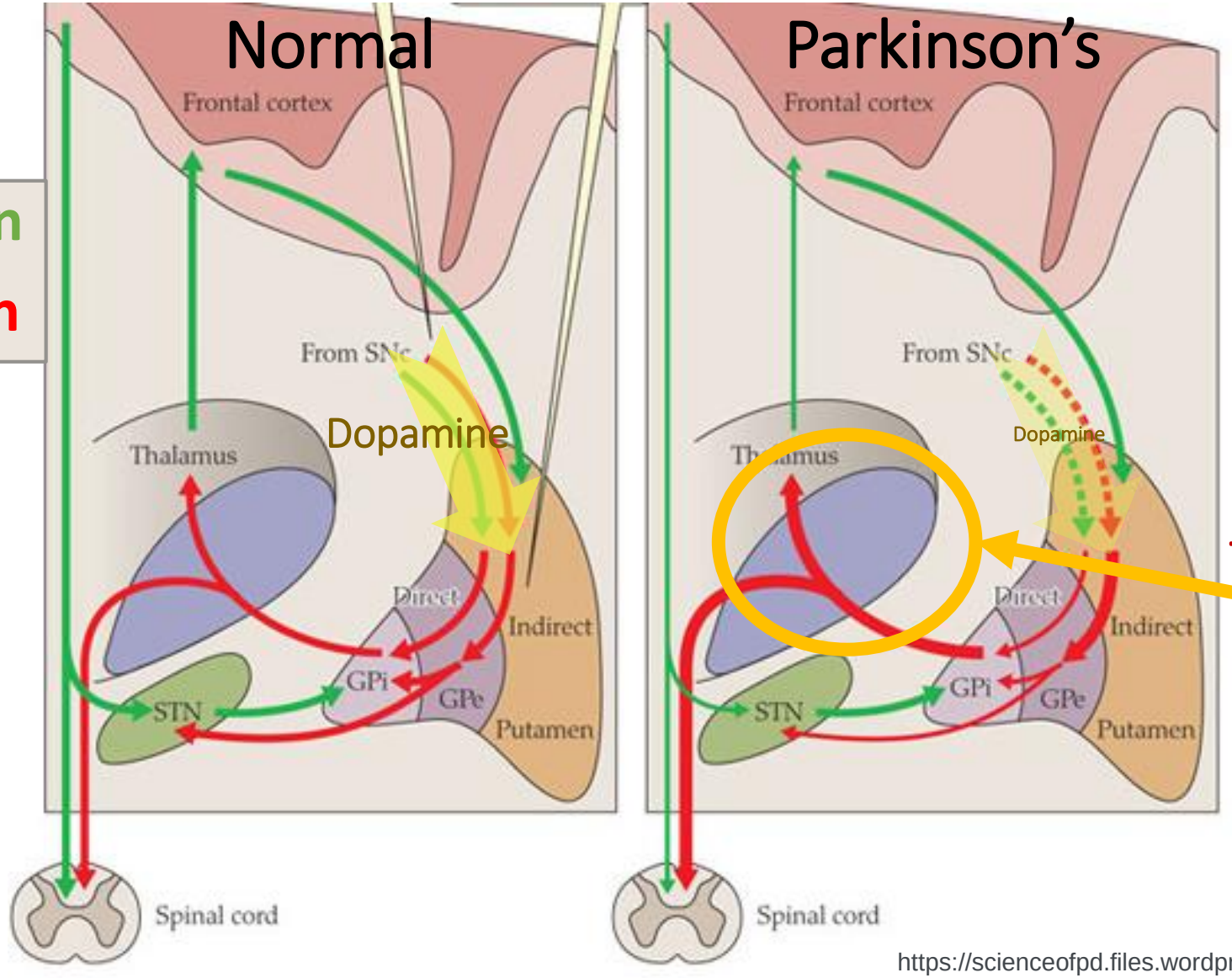

Inhibition of thalamus too strong!

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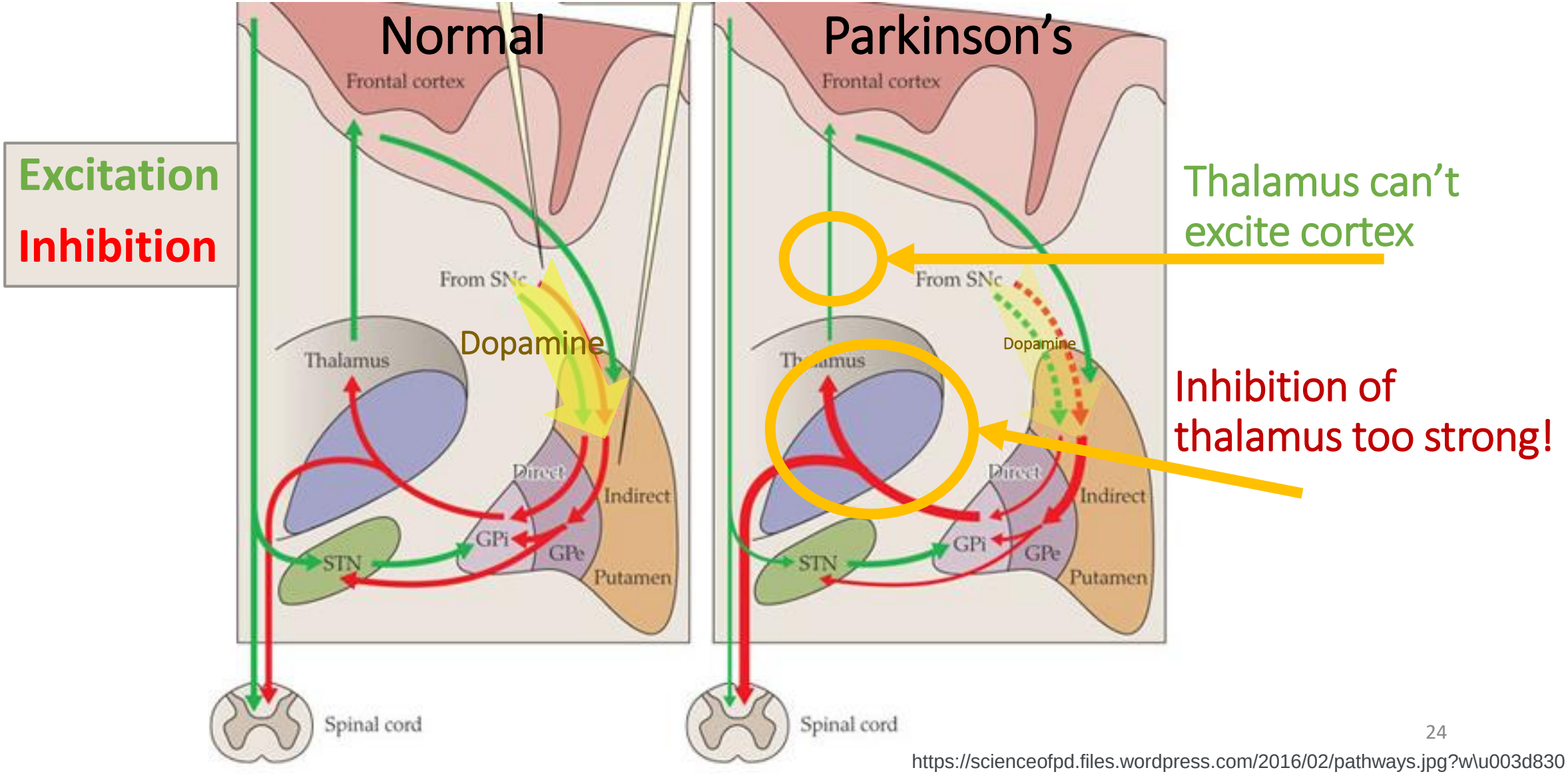

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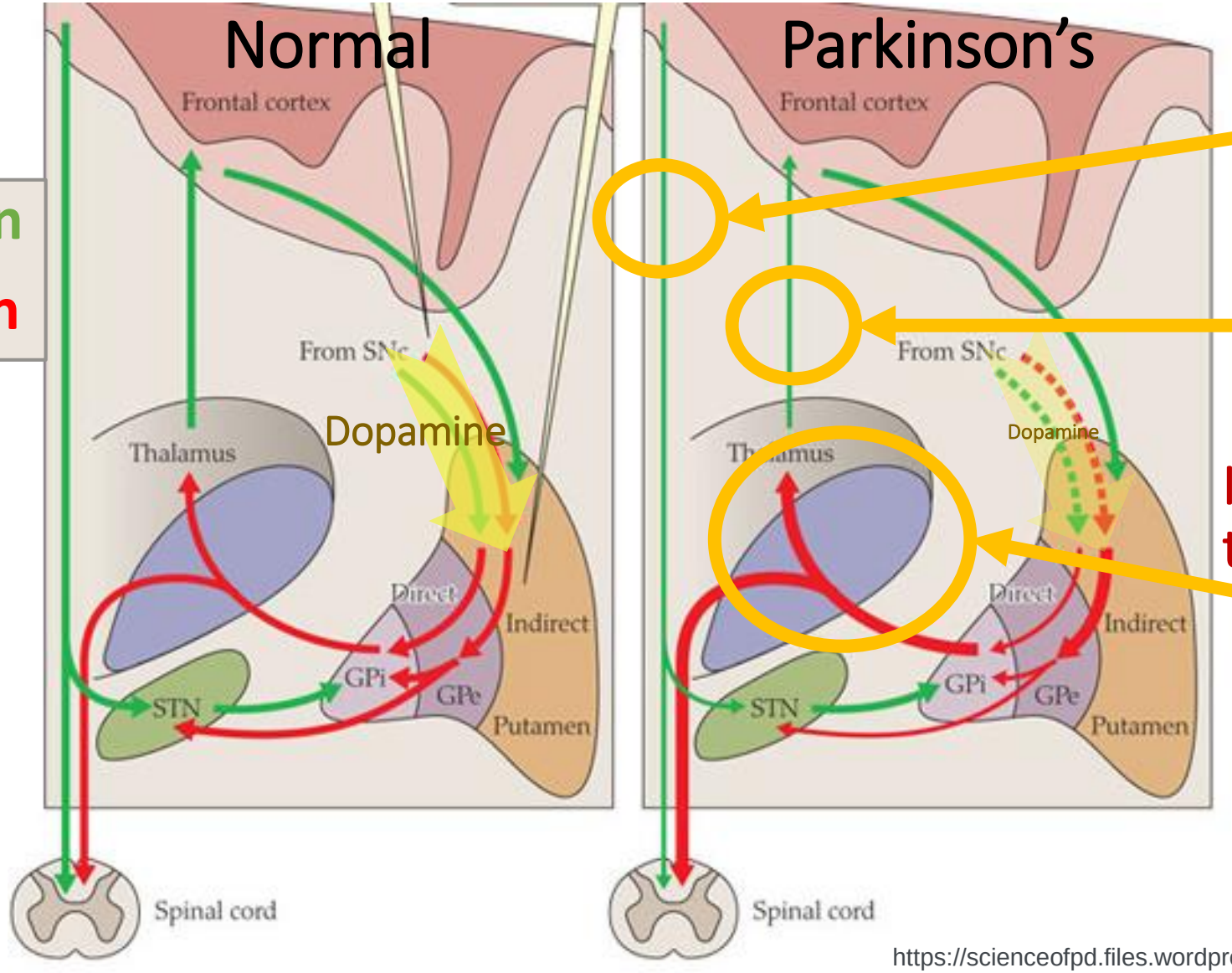

Cortex can't tell muscle to contract

Thalamus can't excite cortex

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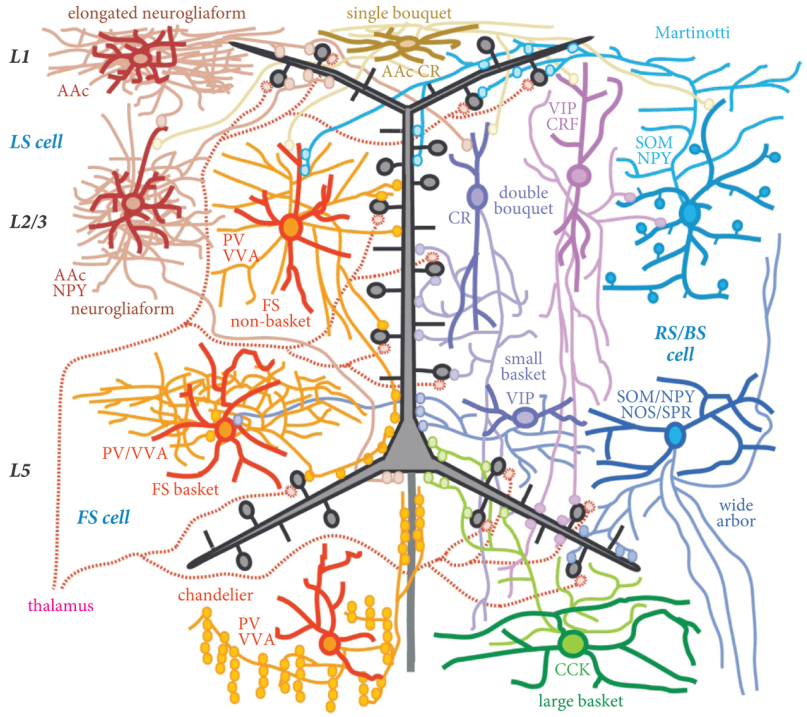

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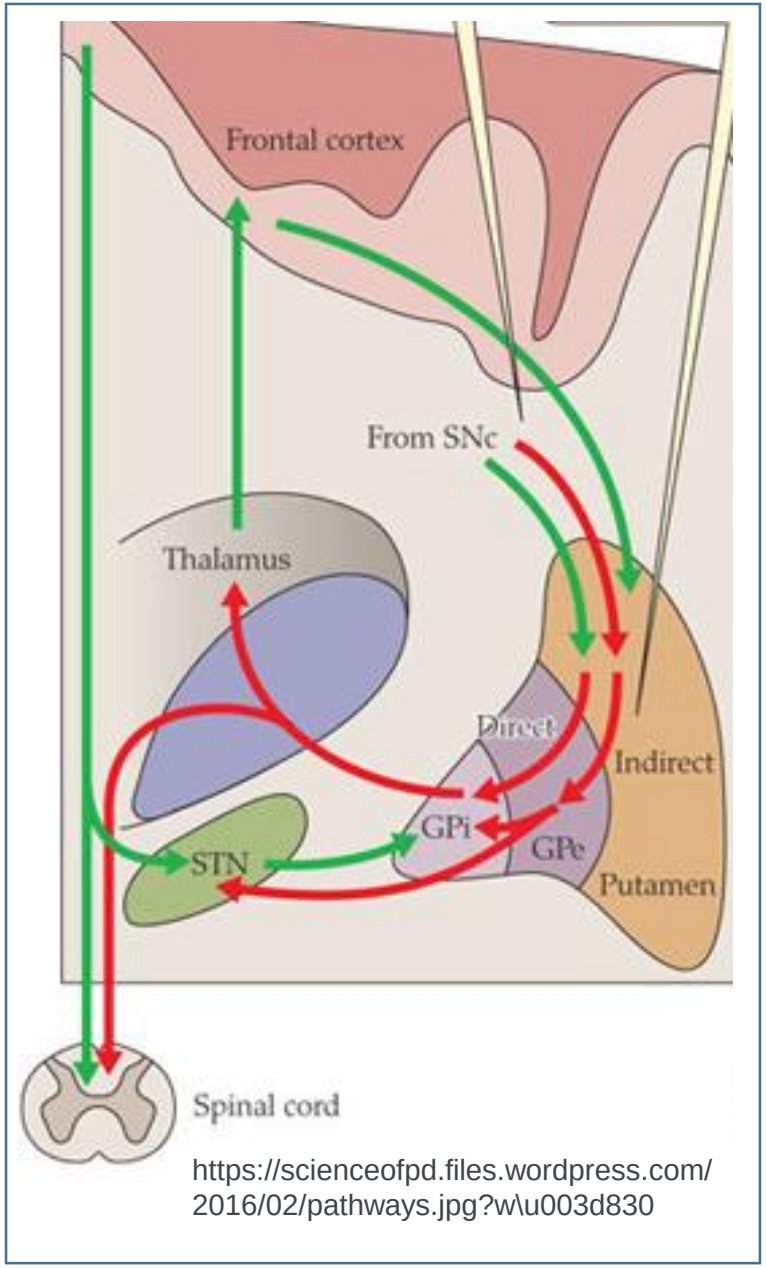

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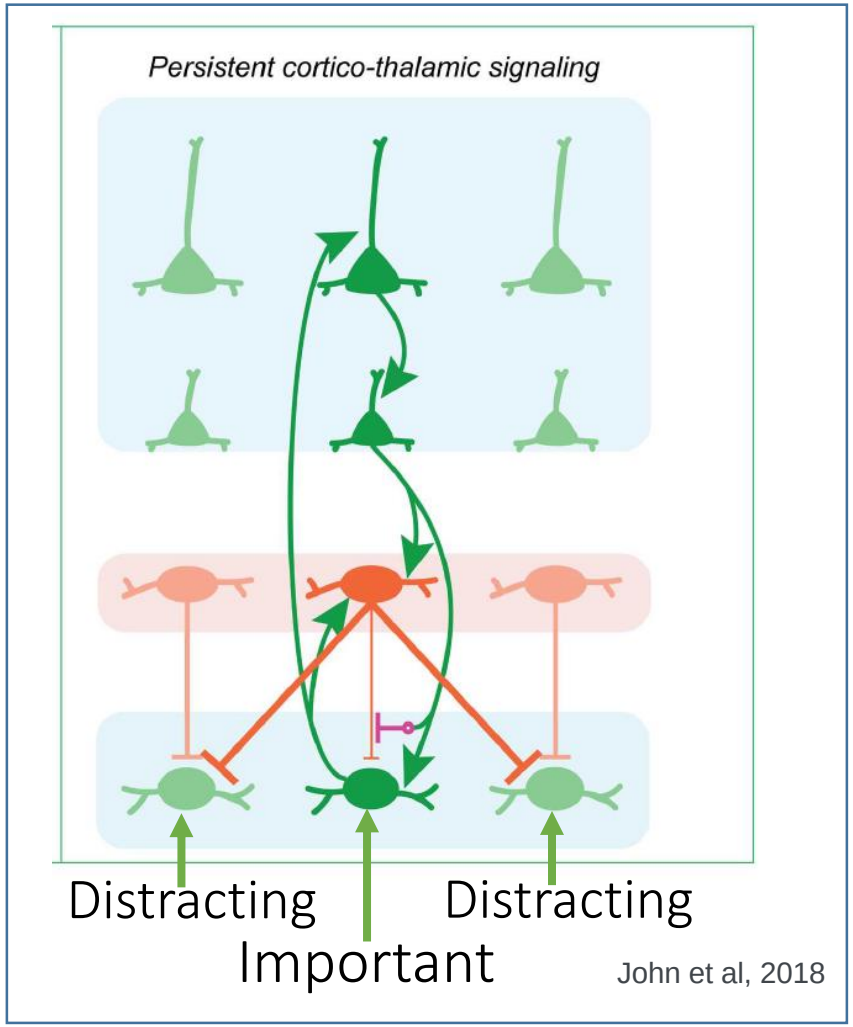

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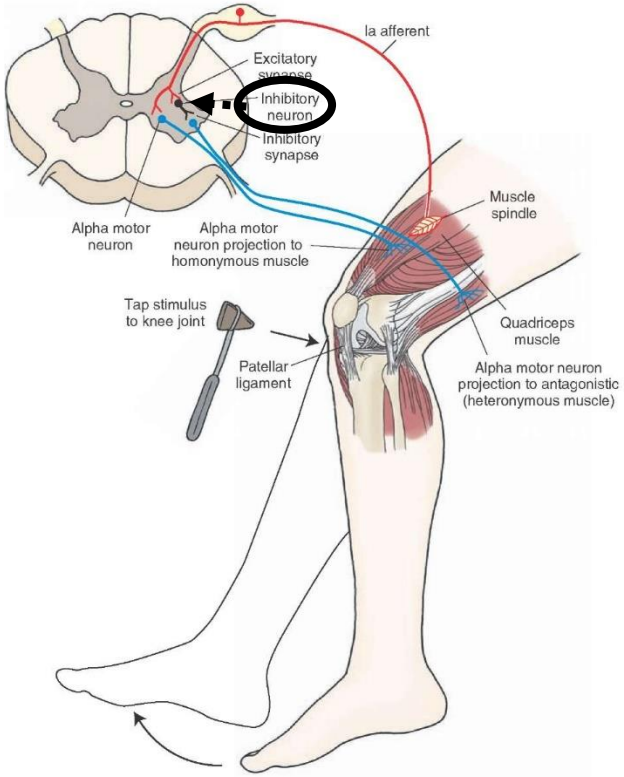

http://what-when-how.com/neuroscience/the-spinal-cord-organization-of-the-central-nervous-system-part-5/

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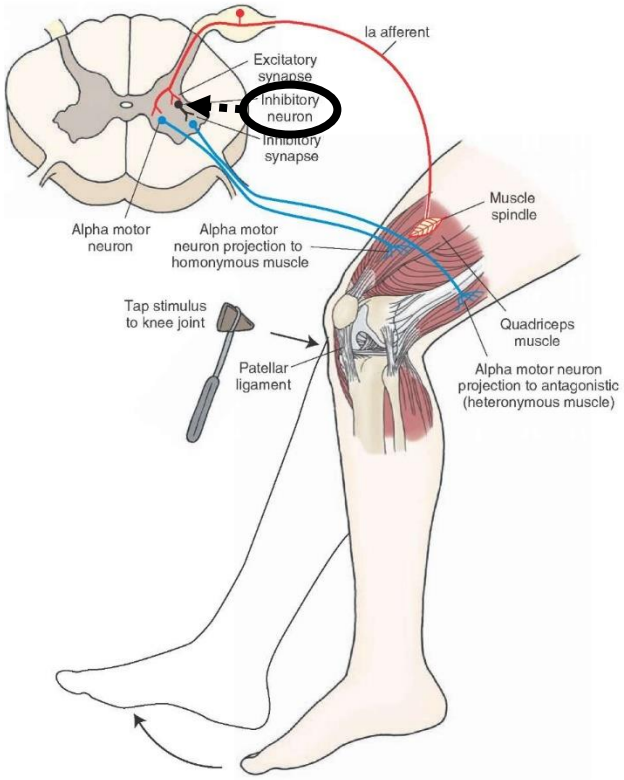

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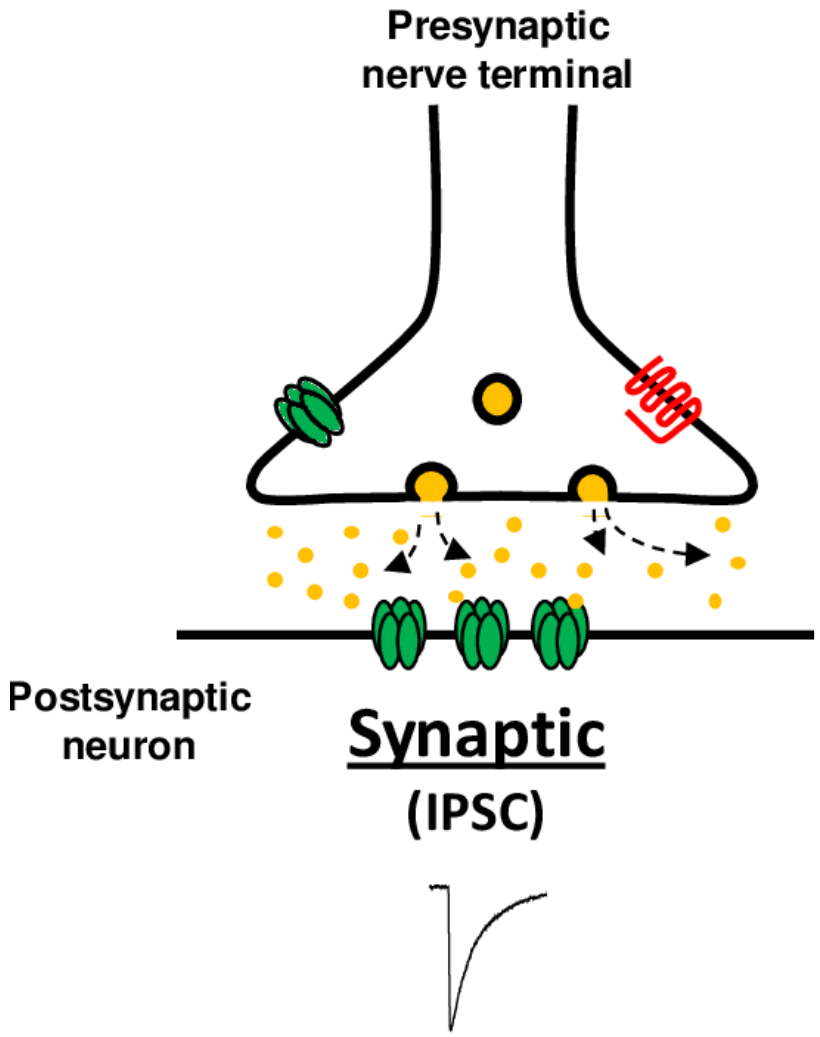
Many Diseases and Disorders Occur Because of Disrupted Inhibition

- Epilepsy
- Anxiety Disorders
- Sleep Disorders
- Schizophrenia
- Autism Spectrum Disorders

How Inhibitory Signaling Occurs: Neurotransmitter GABA Activates GABA Receptors



Bg Patel, 2015

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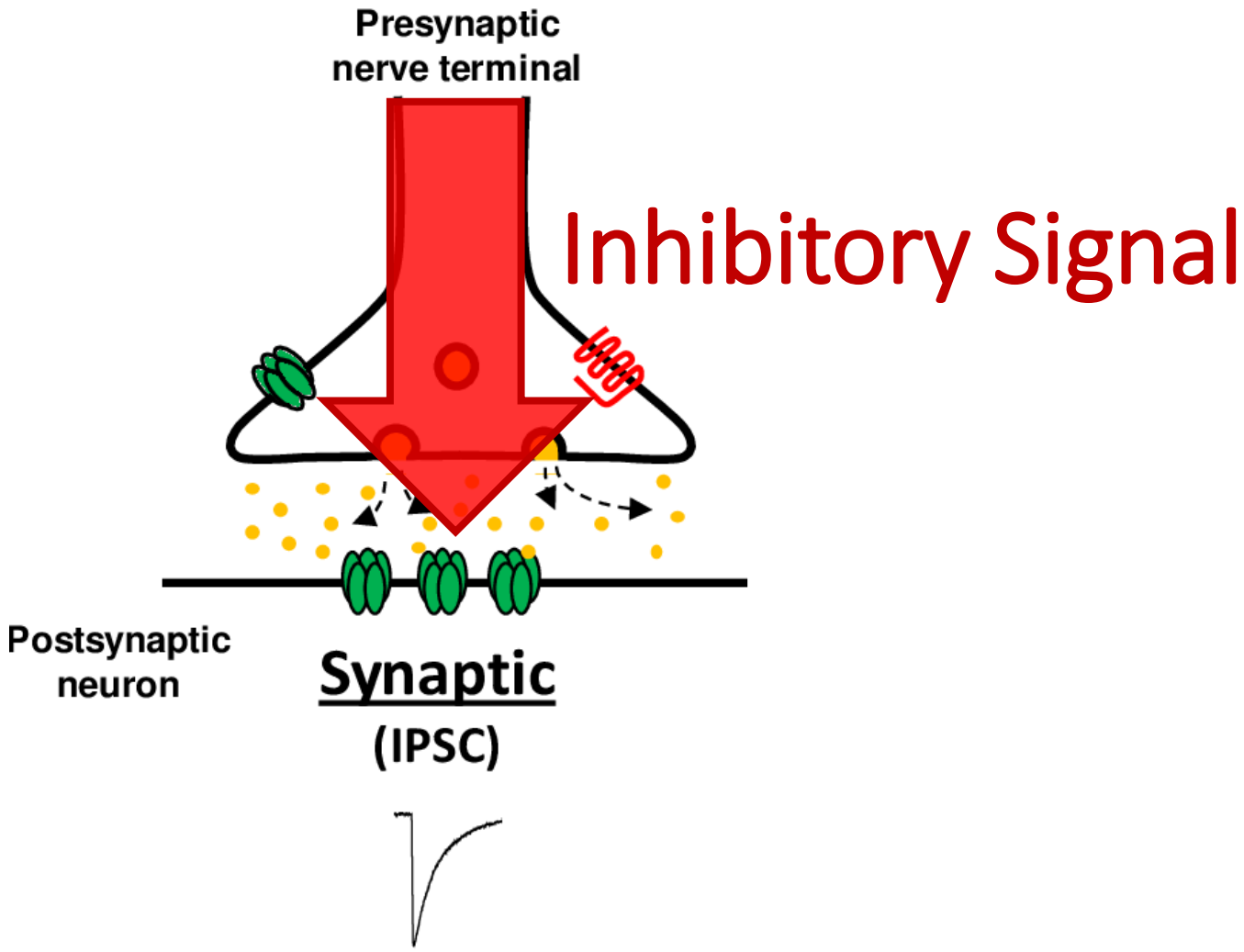

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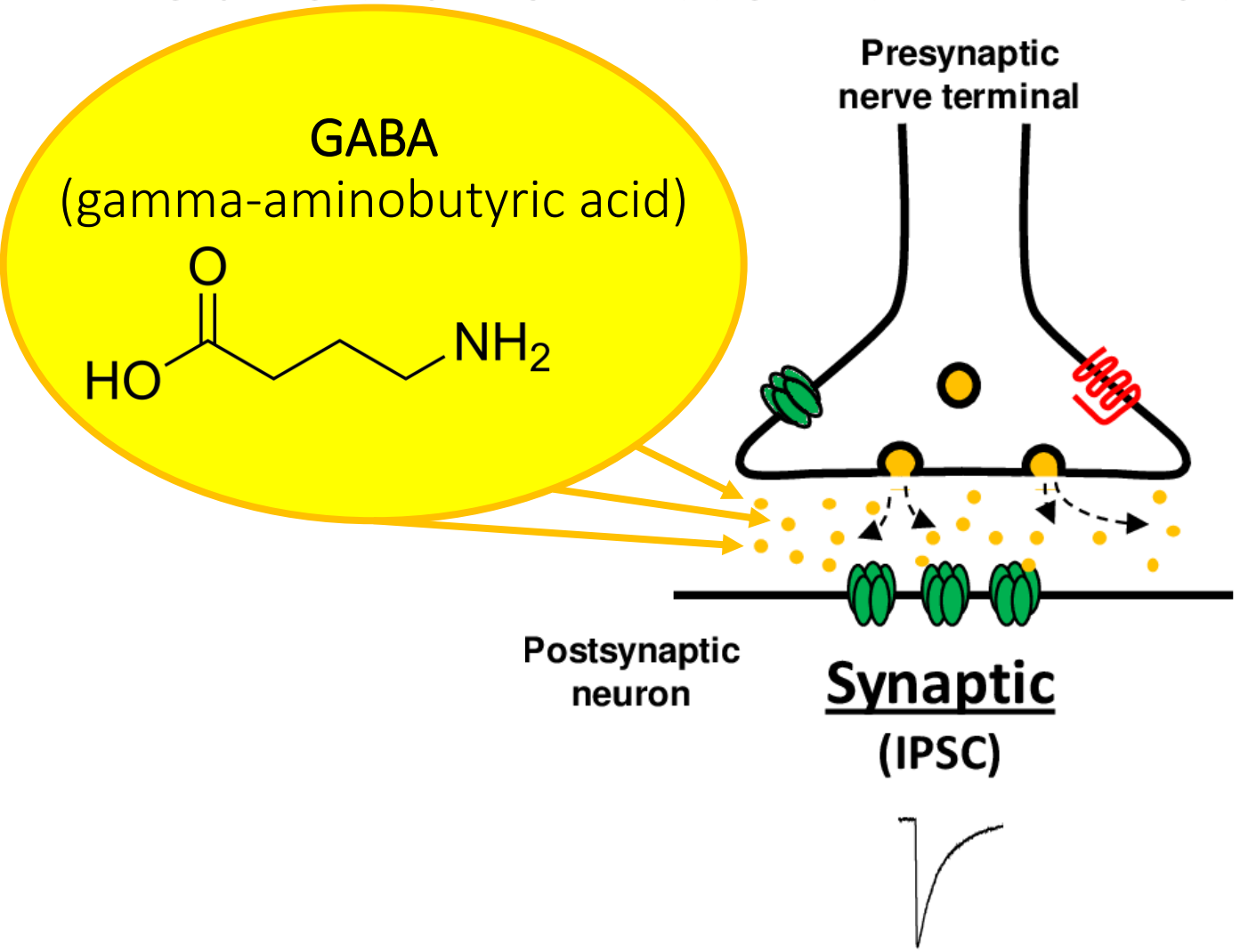

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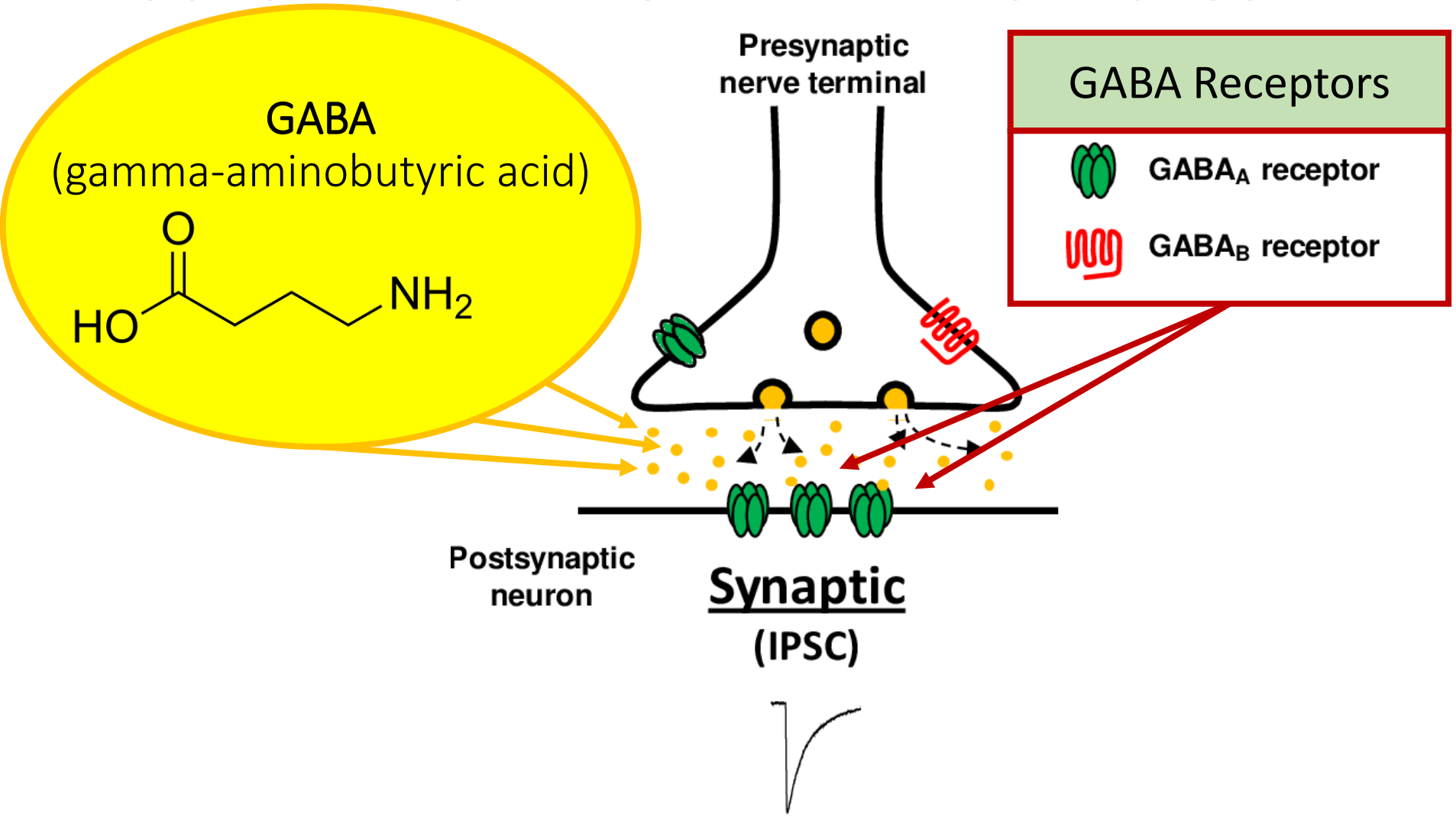

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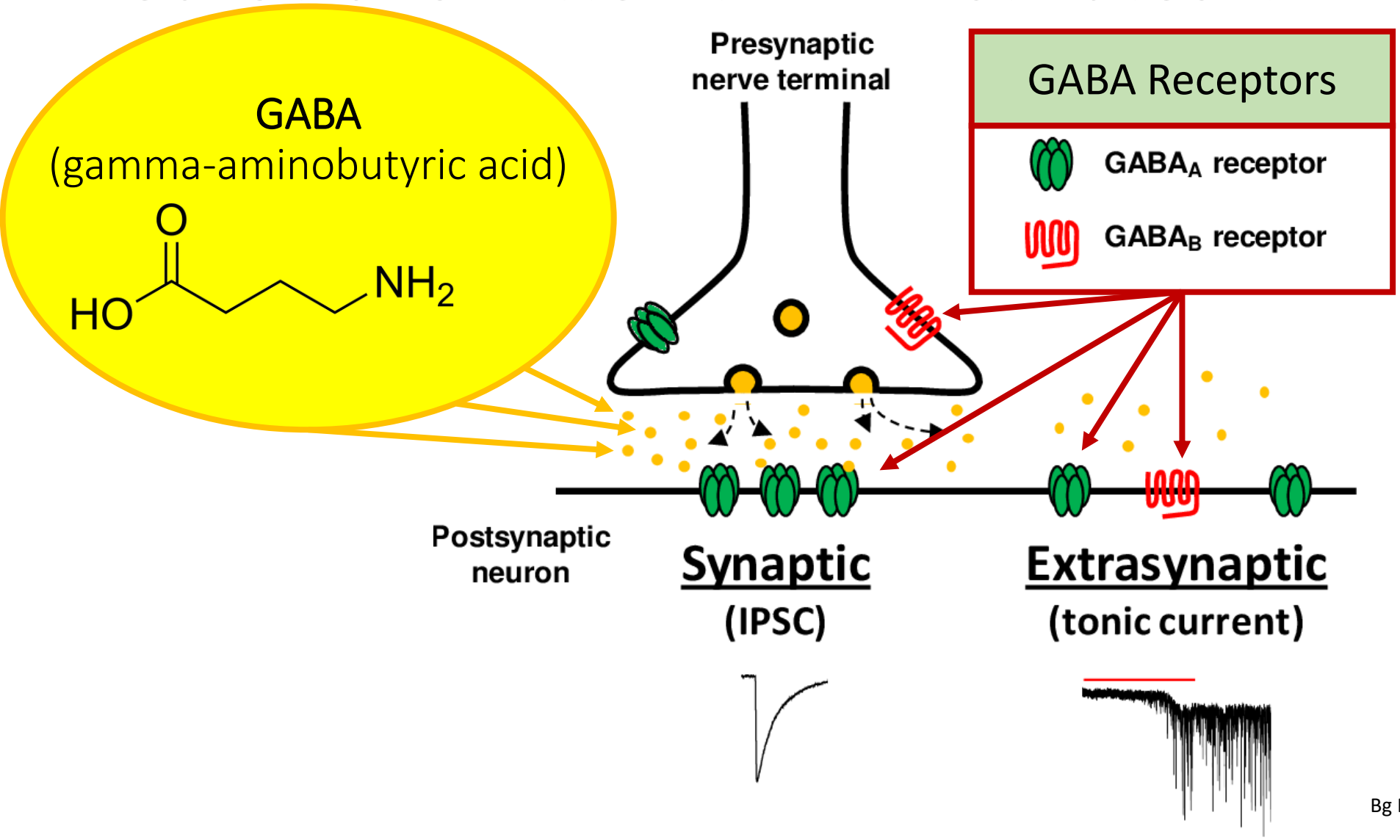

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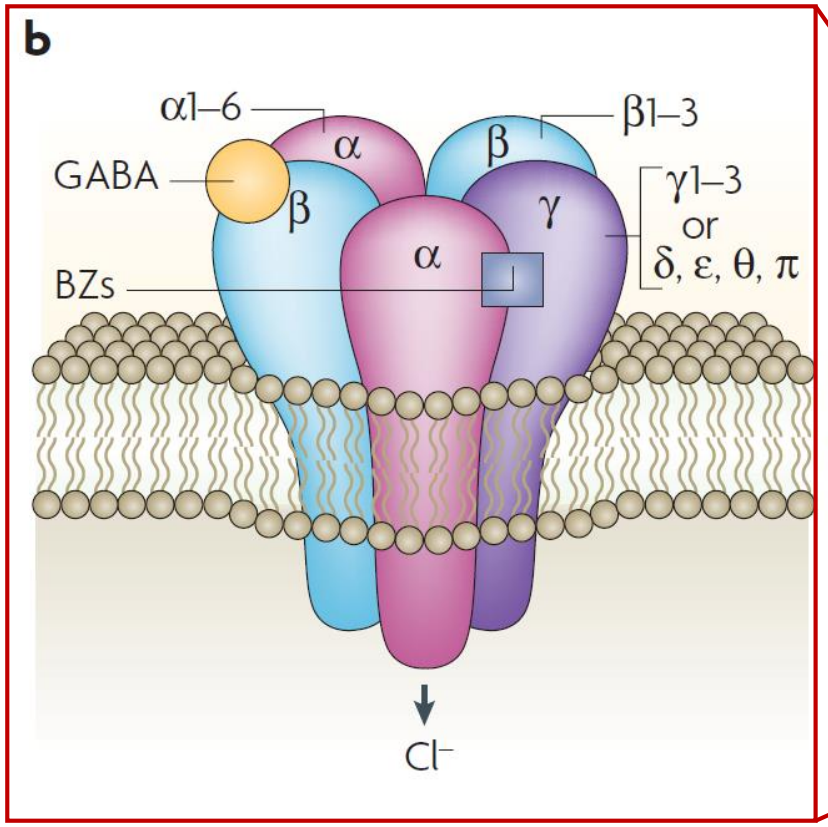
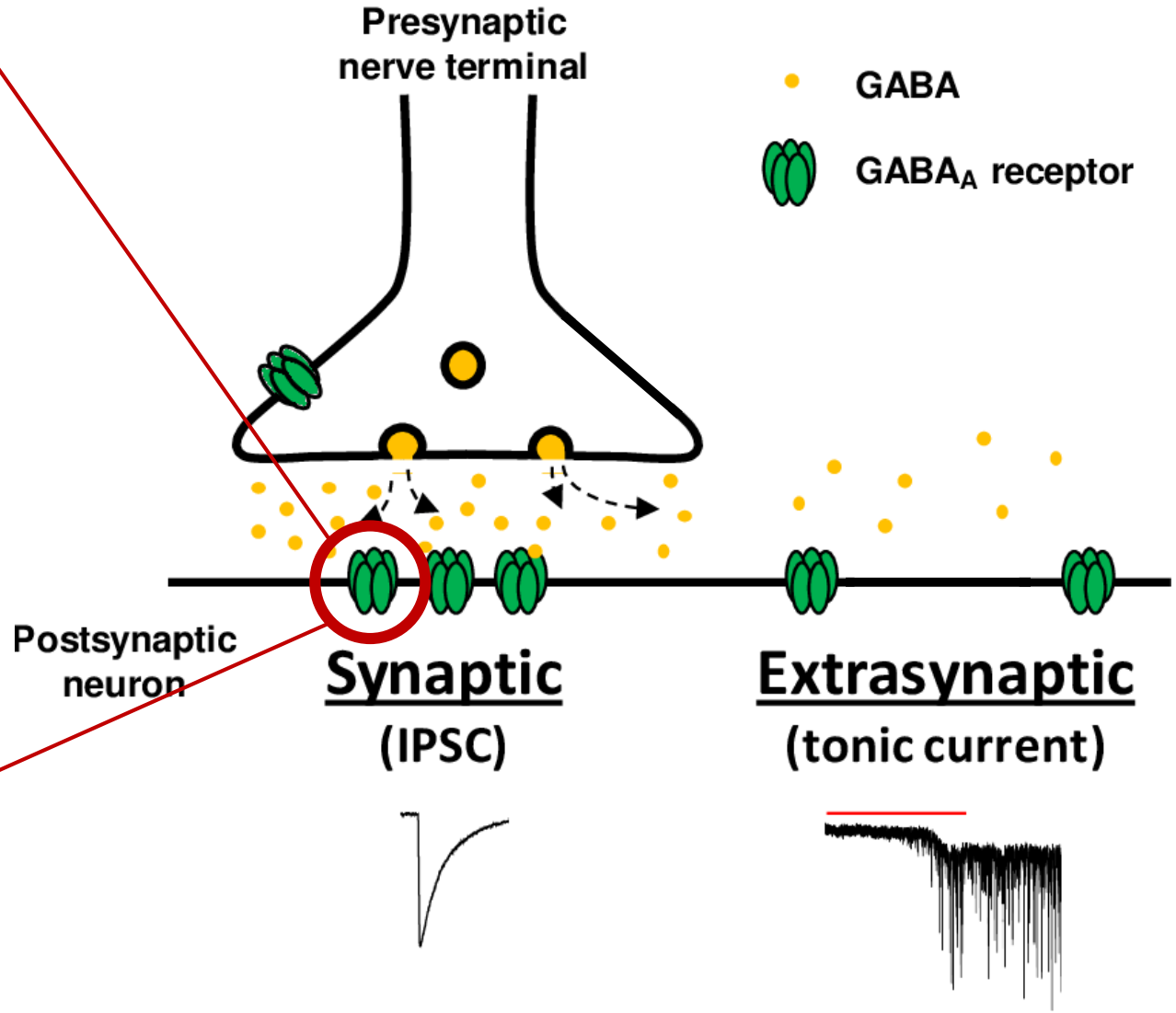
$GABA_A$ Receptors Mediate Quick Inhibitory Signals

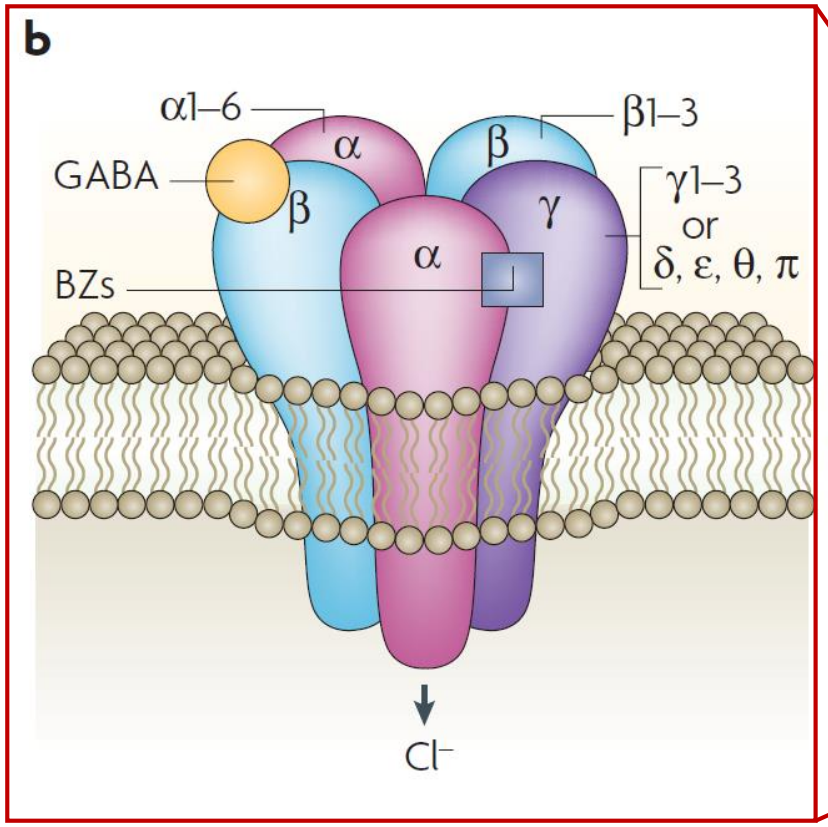


Jacob et al, 2008



Bg Patel, 2015

$GABA_A$ Receptors Mediate Quick Inhibitory Signals



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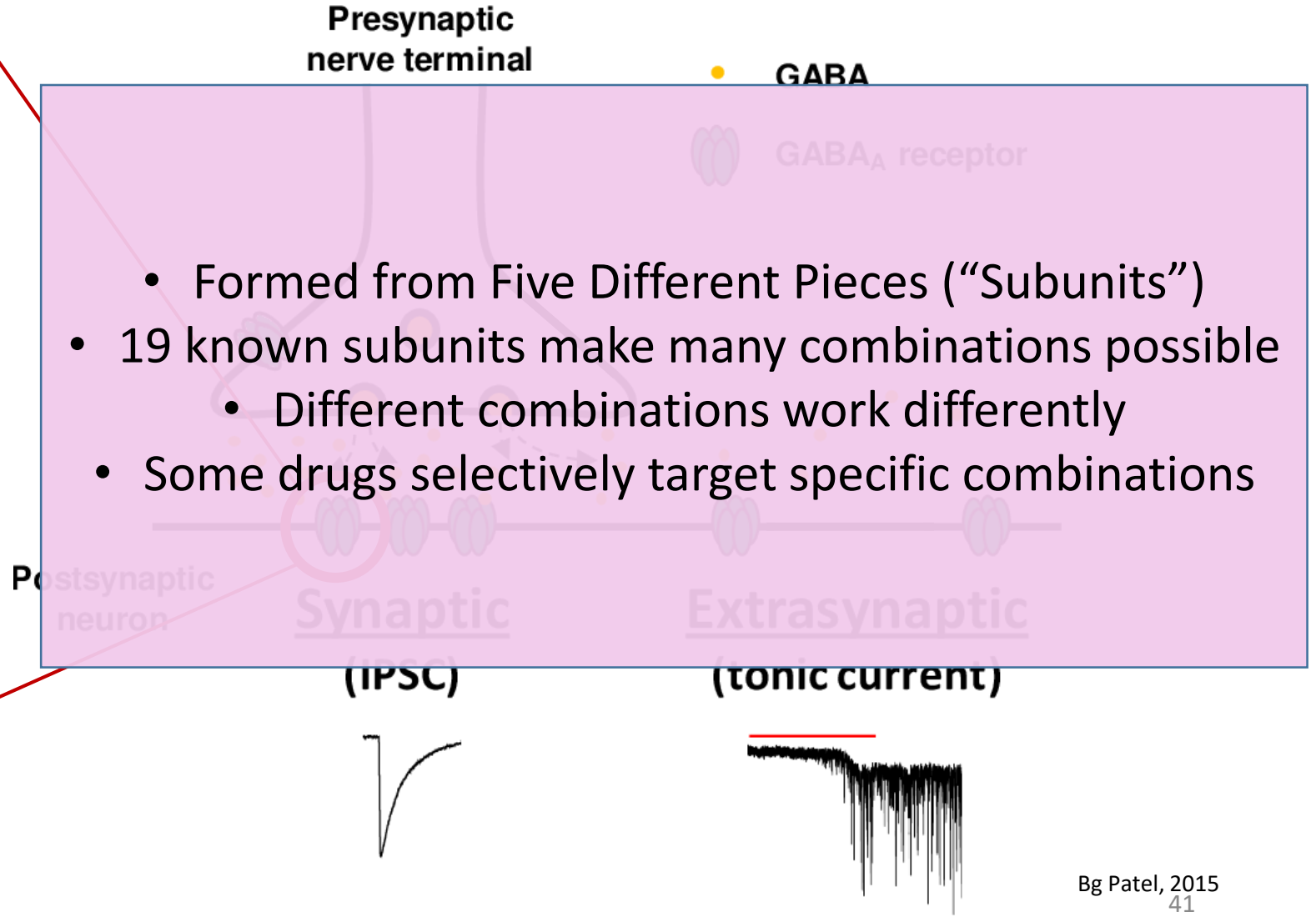


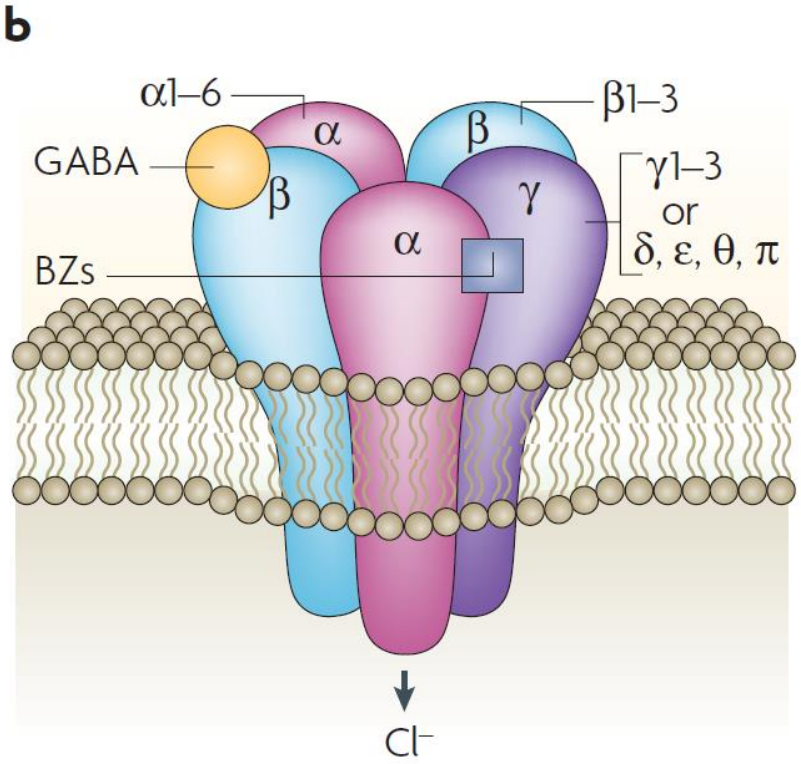
- Formed from Five Different Pieces ("Subunits")
- 19 known subunits make many combinations possible
  - Different combinations work differently
- Some drugs selectively target specific combinations

Bg Patel, 2015

Many Diseases and Disorders Occur Because of Disrupted Inhibition

- Epilepsy
- Anxiety Disorders
- Sleep Disorders
- Schizophrenia
- Autism Spectrum Disorders

Mutations in $GABA_A$ Receptor Subunits Are Often Causes of Genetic Epilepsies



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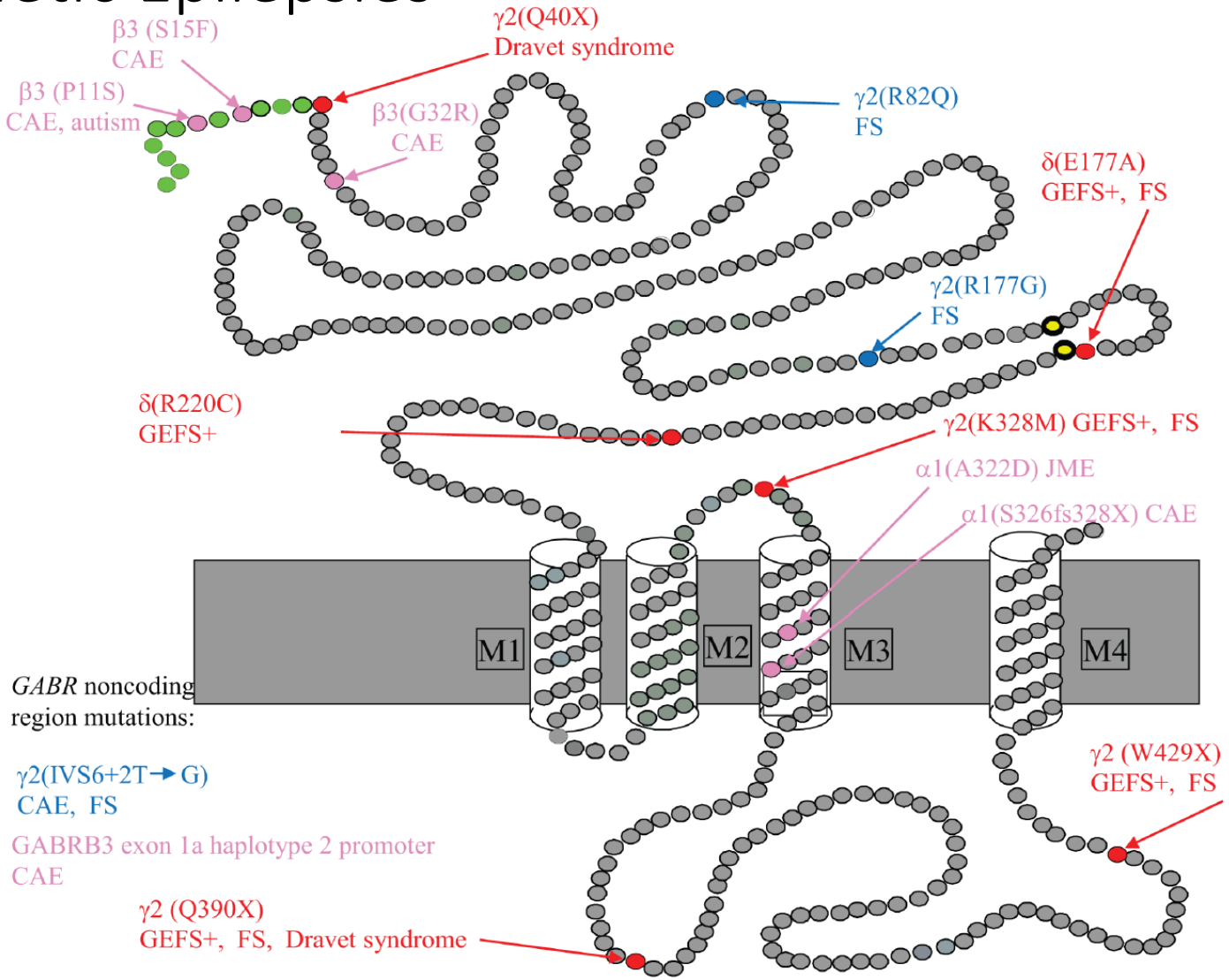
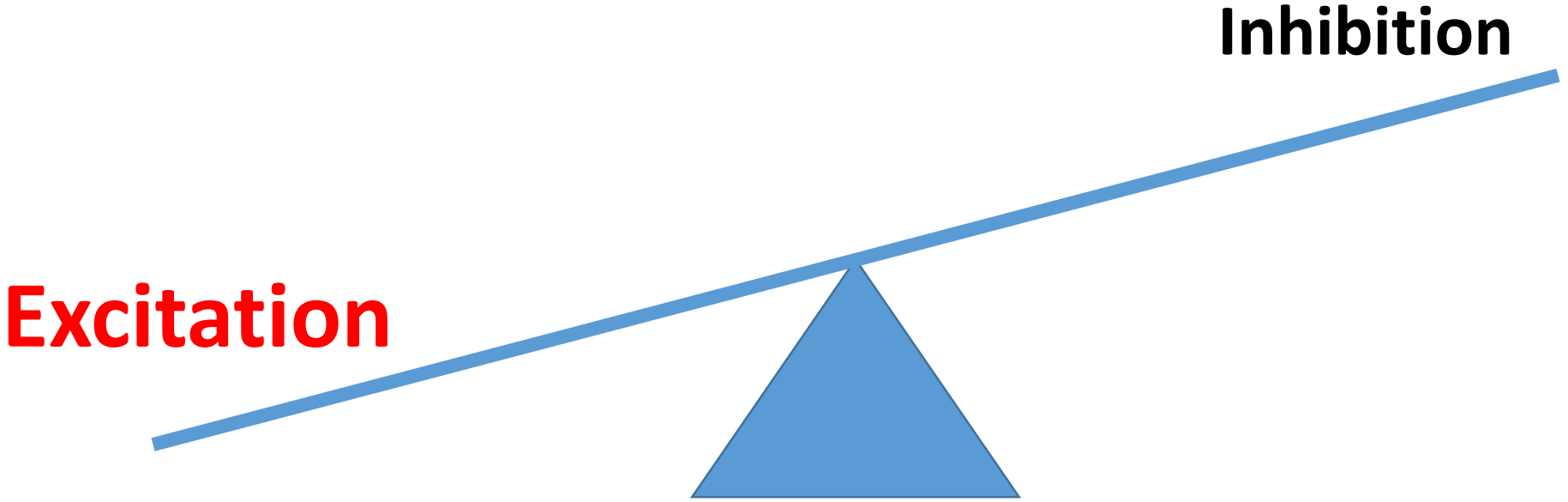
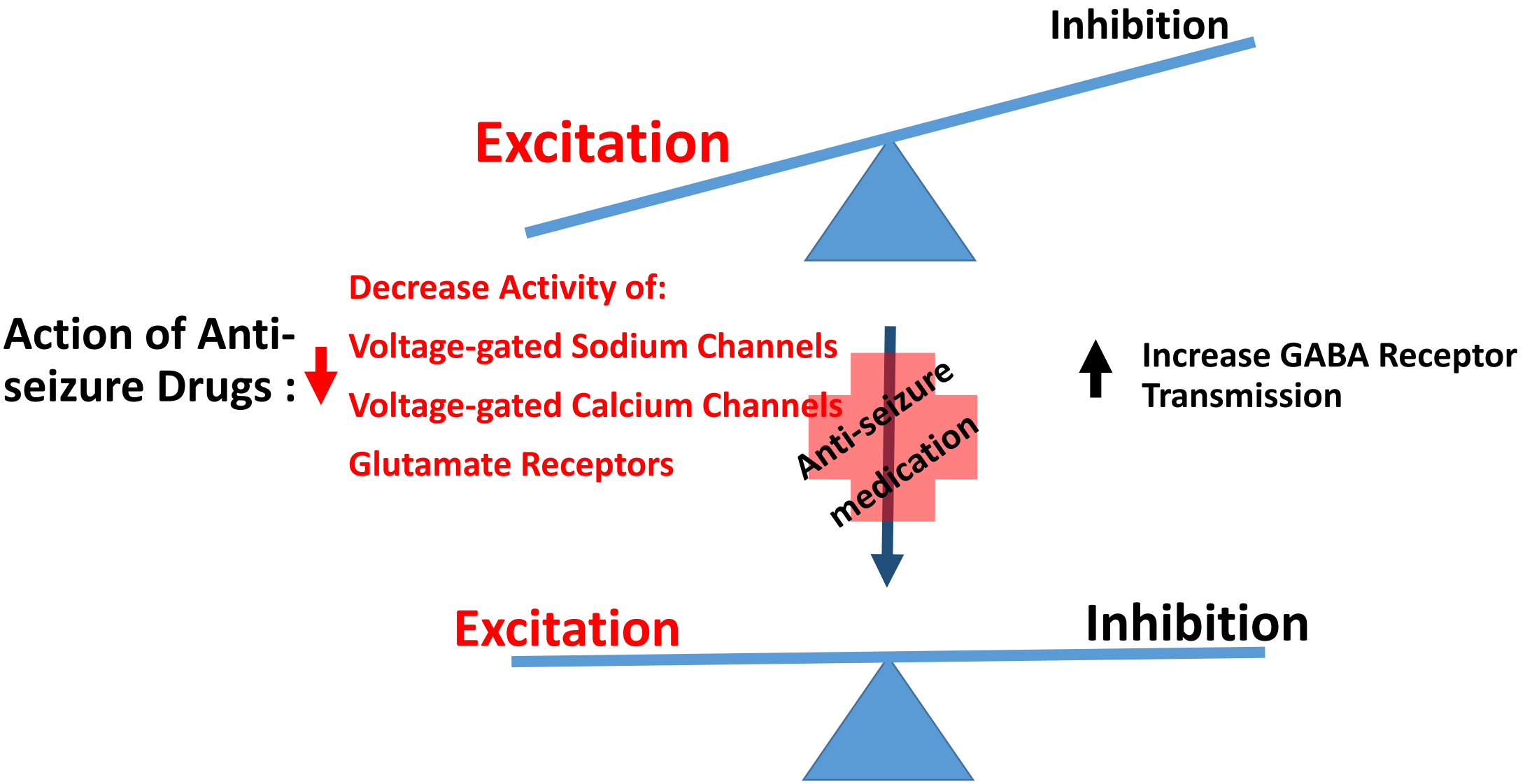


Modified from Macdonald et al., J Physiol, 2010

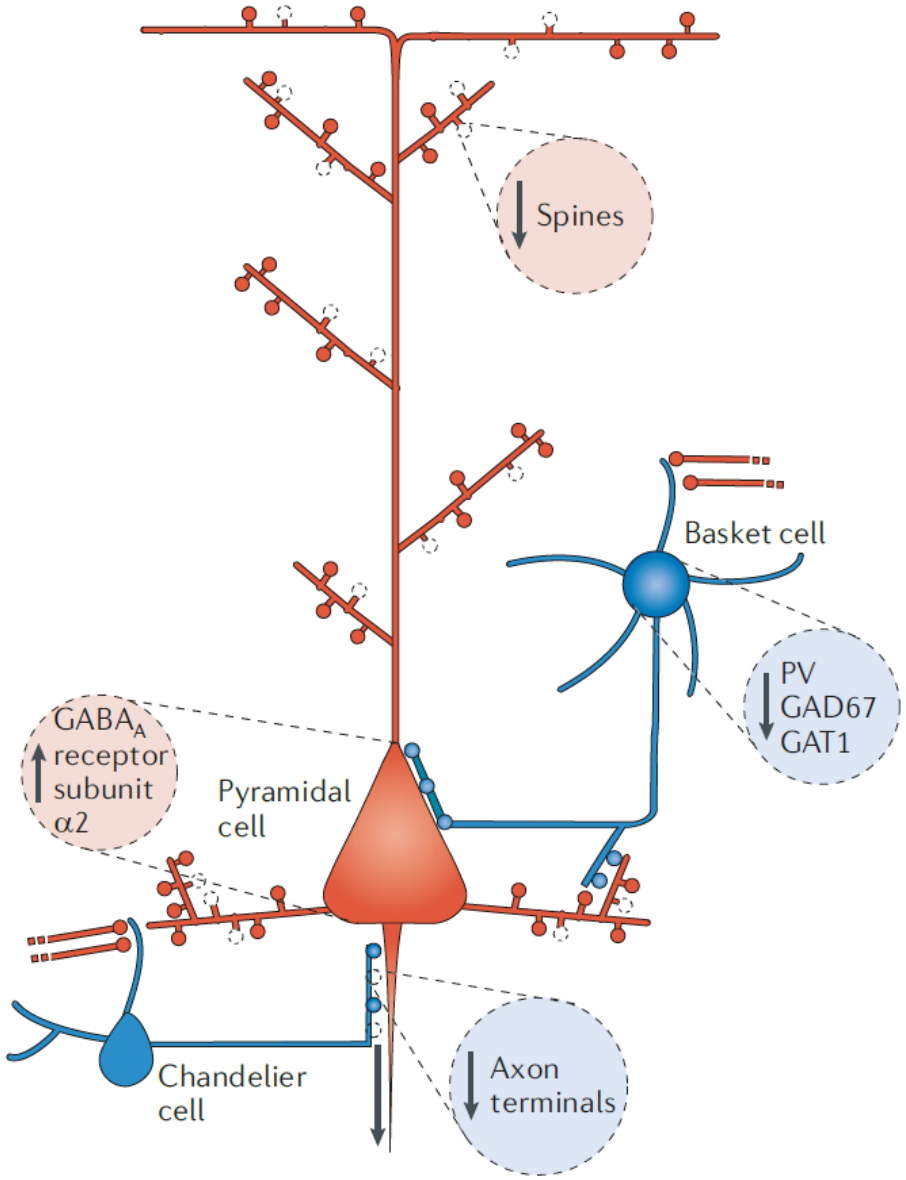
Defective GABA Receptors Can Create Too Little Inhibition, Causing an Imbalance in Neural Circuits That Can Cause Seizures



Seizure Medication Restores Balance By Decreasing Excitation or Increasing Inhibition



Abnormal Inhibitory Function in Prefrontal Cortex Might Cause the Cognitive Disturbances in Schizophrenia



Oscar Marin, 2012

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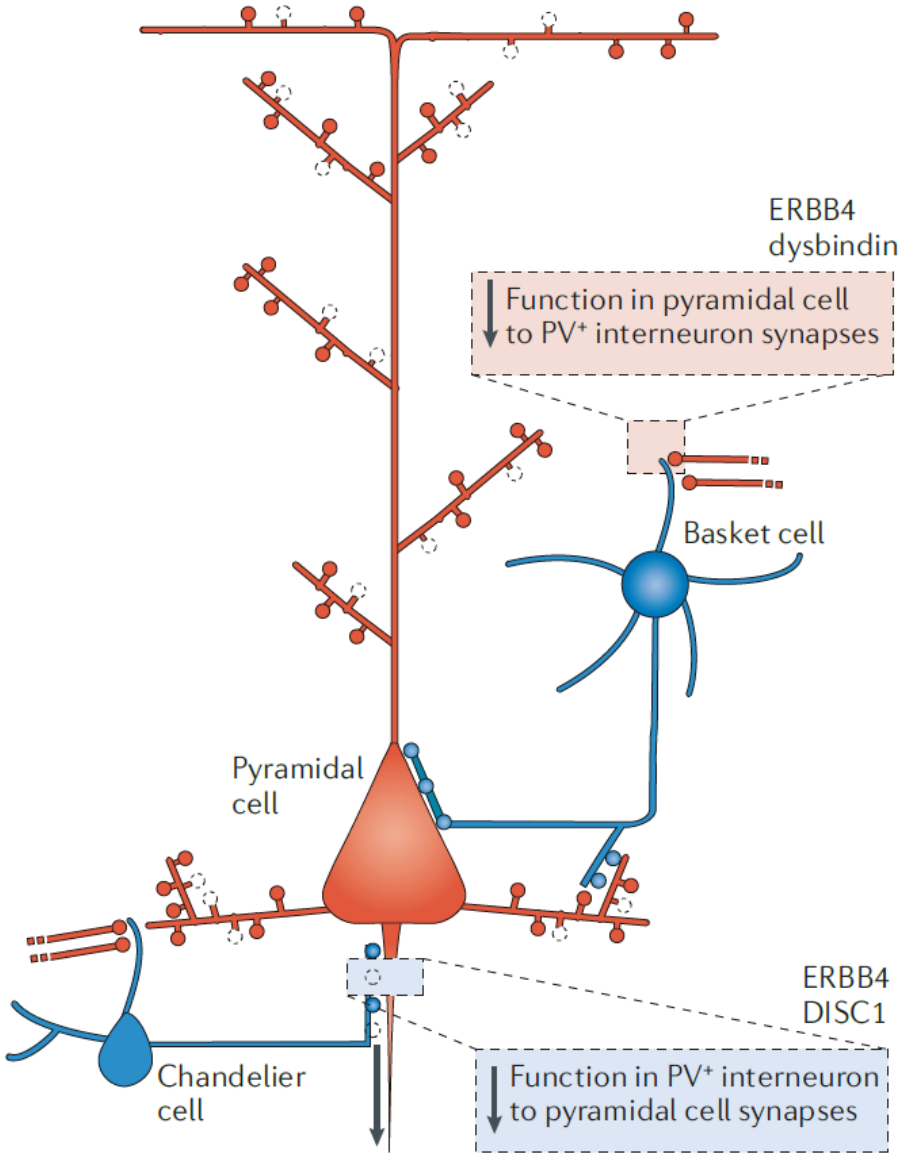
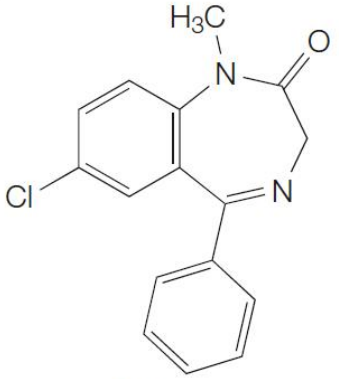
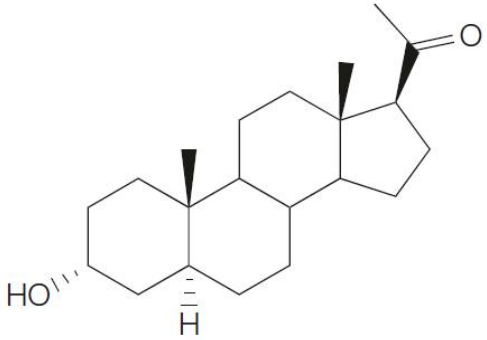


Oscar Marin, 2012

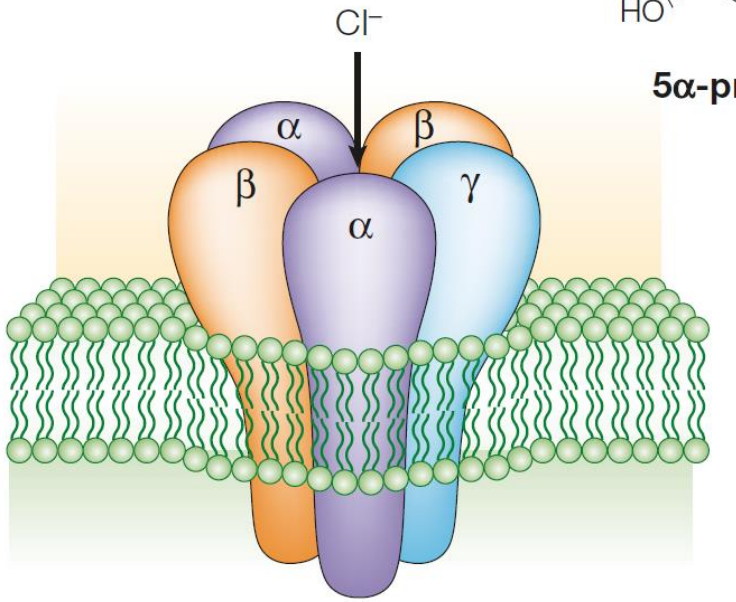
$GABA_A$ receptors
Target of Many of Our Most Useful Medications



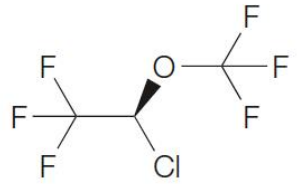
Diazepam



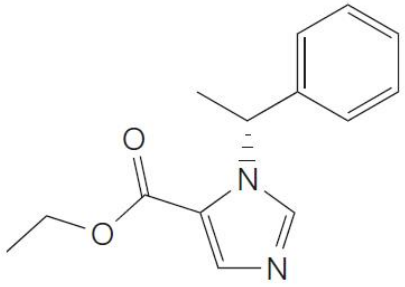
5α-pregnan-3α-ol-20-one



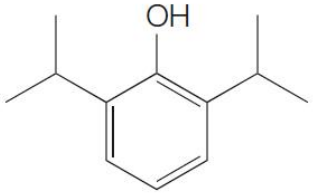
Ethanol



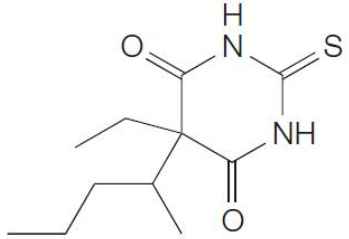
S-Isoflurane



R-(+)-Etomidate



Propofol

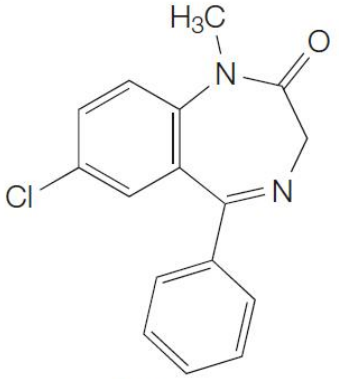


Thiopental

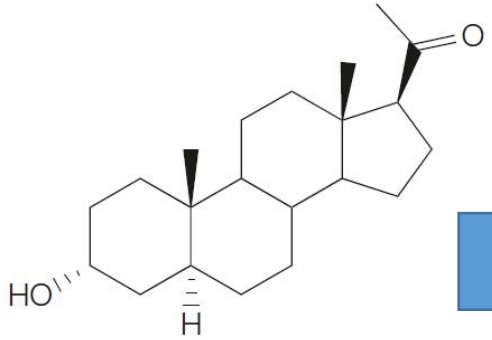
Jacob et al, 2008; Andre Lagrange presentation

$GABA_A$ receptors
Target of Many of Our Most Useful Medications

Valium (anxiolytic, sedative, antiseizure)

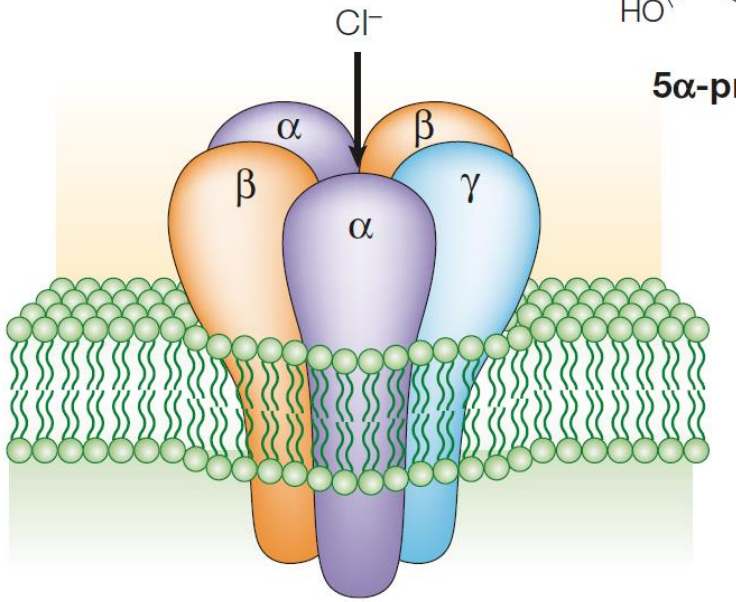


Diazepam

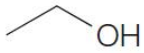


5α-pregnan-3α-ol-20-one

Neurosteroid



Alcohol



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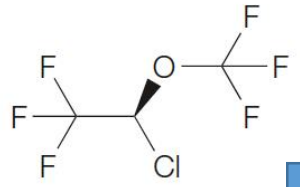
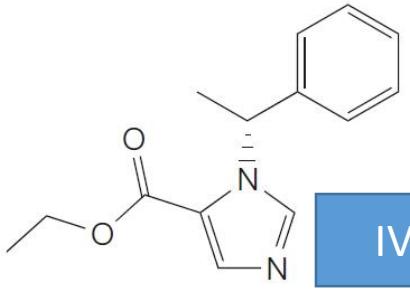


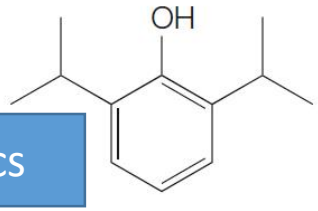
S-Isoflurane

Inhaled Anesthetic

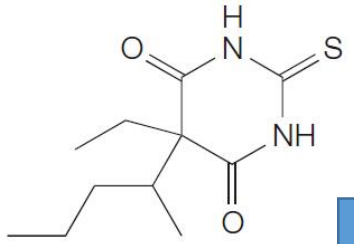


R-(+)-Etomidate

IV Anesthetics



Propofol



Thiopental

Barbiturate Anesthetic

Jacob et al, 2008; Andre Lagrange presentation

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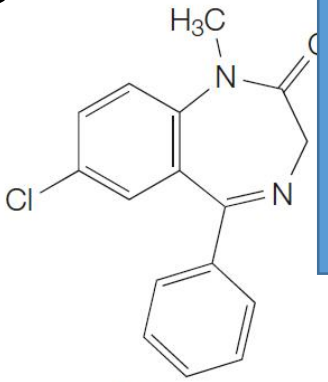
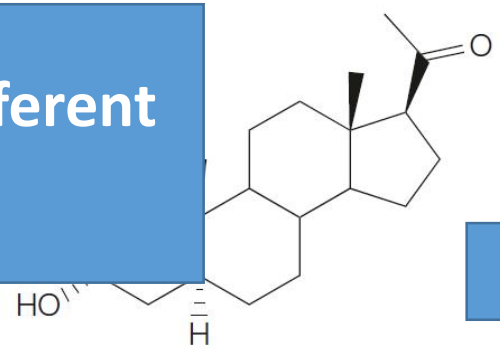


Diazepam

Many of these have different binding sites!



5α-pregnan-3α-ol-20-one

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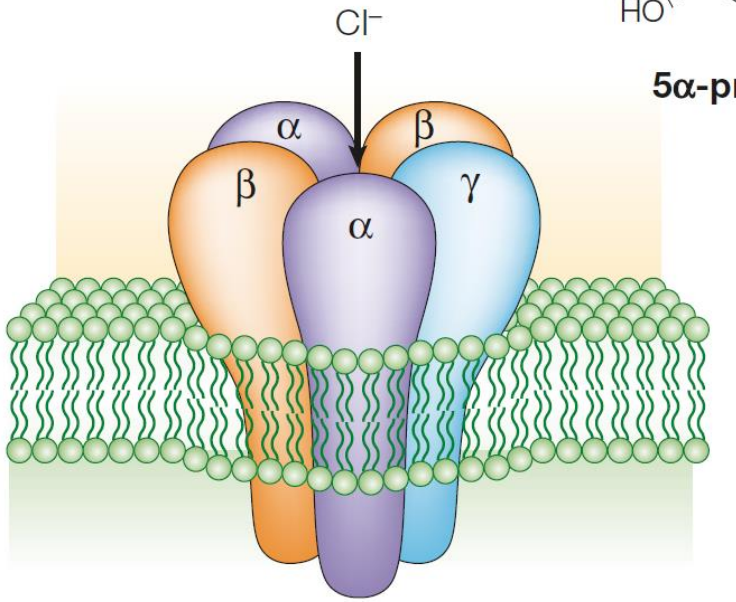
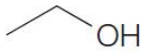
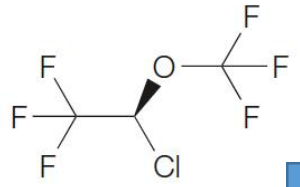


Alcohol

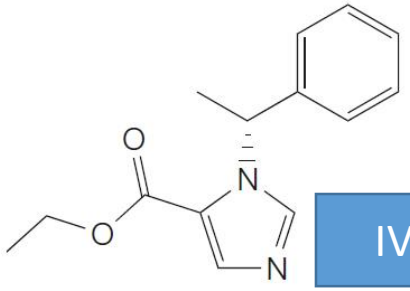


Ethanol



S-Isoflurane

Inhaled Anesthetic



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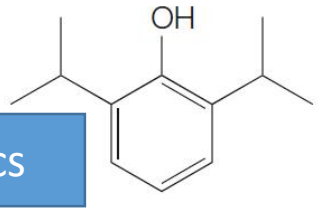
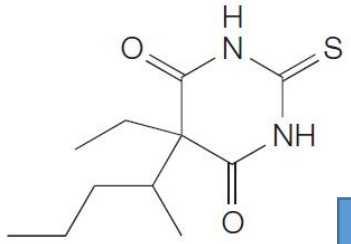


Propofol



Thiopental

Barbiturate Anesthetic

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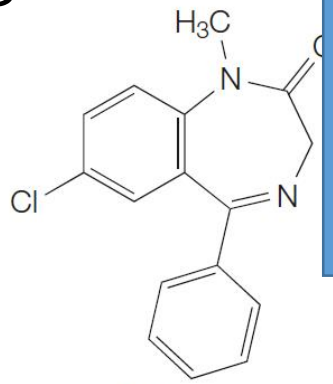
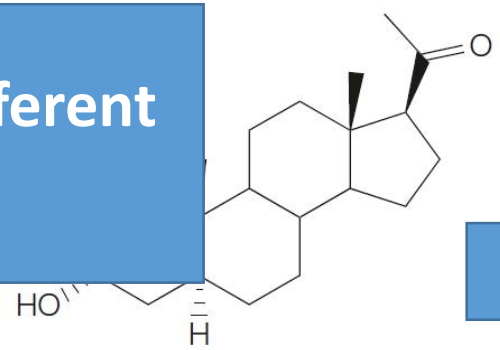


Diazepam



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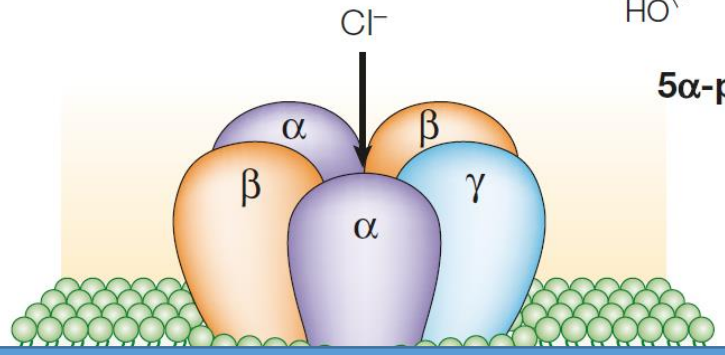

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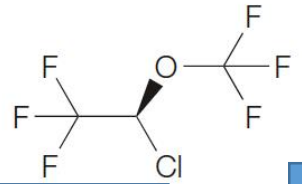
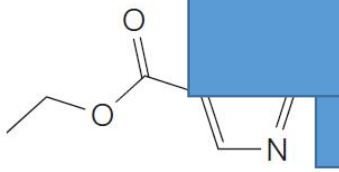


Inhaled Anesthetic

- **Target different subunit combinations**
- **Have different effect (anxiolytic/sedative vs anesthesia).**

IV Anesthetics



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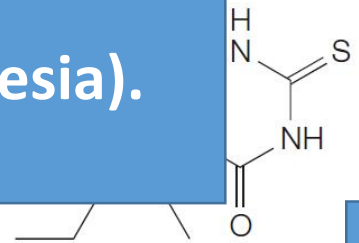
Propofol

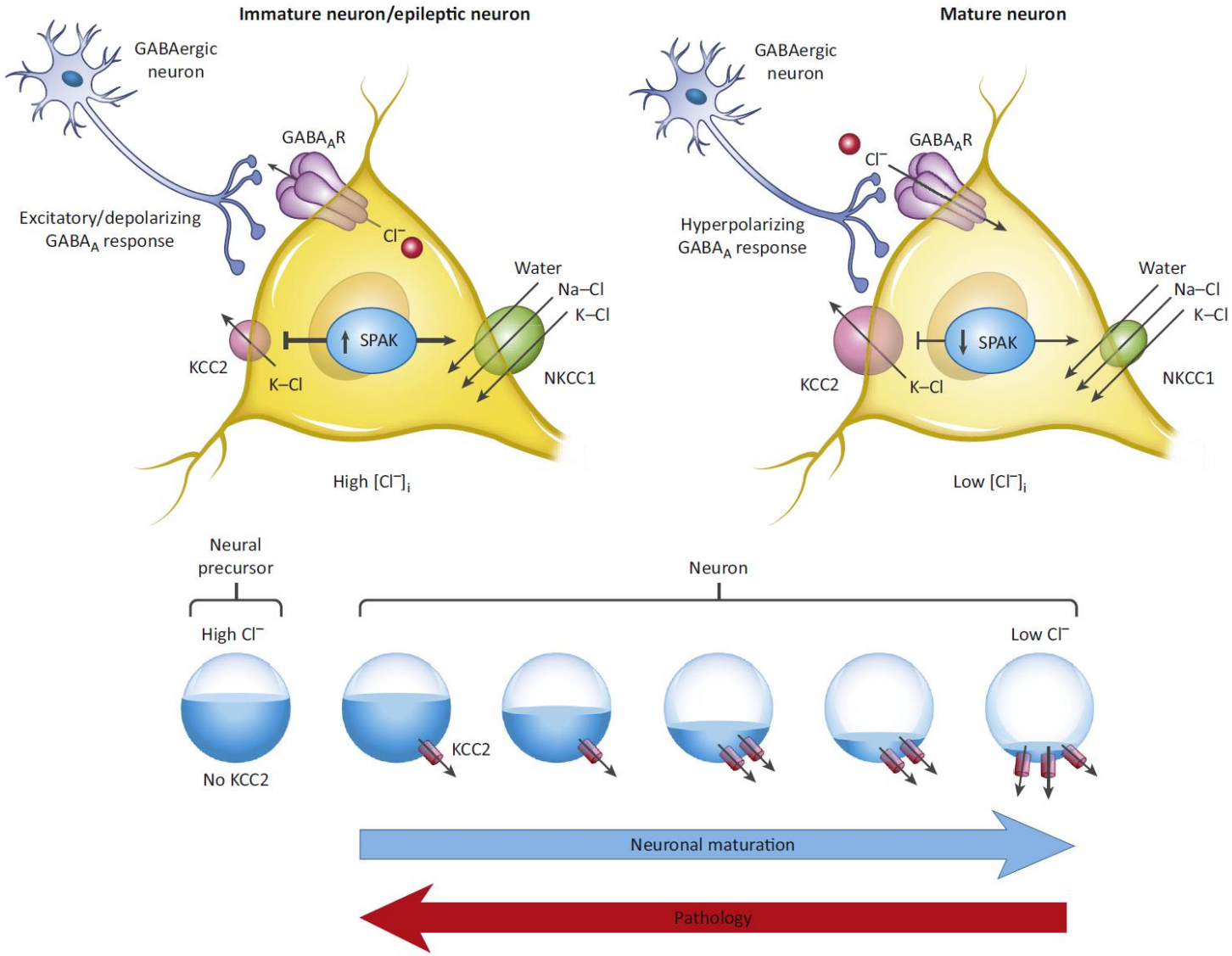


Thiopental

Barbiturate Anesthetic

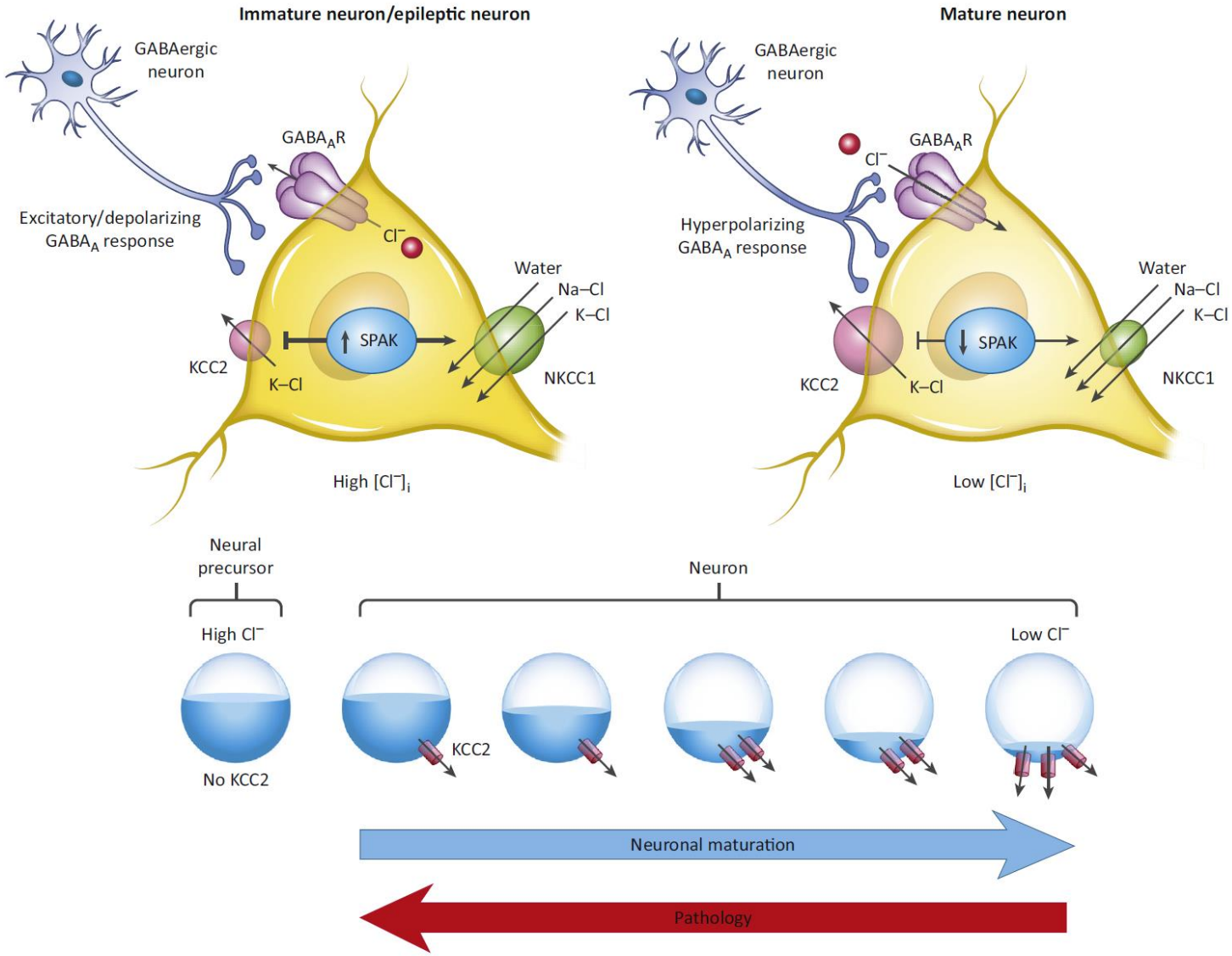
Jacob et al, 2008; Andre Lagrange presentation

During Embryonic Development, $GABA_A$ Receptors Are Actually Excitatory!



Moore et al, 2017

If this condition occurs in the adult brain, it can cause epilepsy (for instance, this contributes to temporal lobe epilepsy)



Moore et al, 2017

Summary

- Specialized neurons inhibit other neurons by releasing neurotransmitter GABA to activate inhibitory GABA receptors
- Inhibition 1) sends signals and 2) regulates other neurons
  - Cortex and throughout CNS: Interneurons regulate signal transmission of projecting neurons
  - Thalamus: controls relay of sensory information (sleep and attention)
  - Basal Ganglia: controls movement initiation
  - Spinal Cord: relaxes muscles
  - Many other examples

Summary

- Specialized neurons inhibit other neurons by releasing neurotransmitter GABA to activate inhibitory GABA receptors
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- If inhibition goes wrong:
  - Anxiety
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  - Schizophrenia
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- Many drugs target $GABA_A$ receptors (sedative, anxiolytic, muscle relaxant, anti-seizure, anesthesia)
  - Alcohol
  - Benzodiazepines (e.g. Valium)
  - Barbiturates
  - Neurosteroids (Progesterone)
  - Anesthetics (Propofol)

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    - Machinery that regulates how much GABA is released by inhibitory cells

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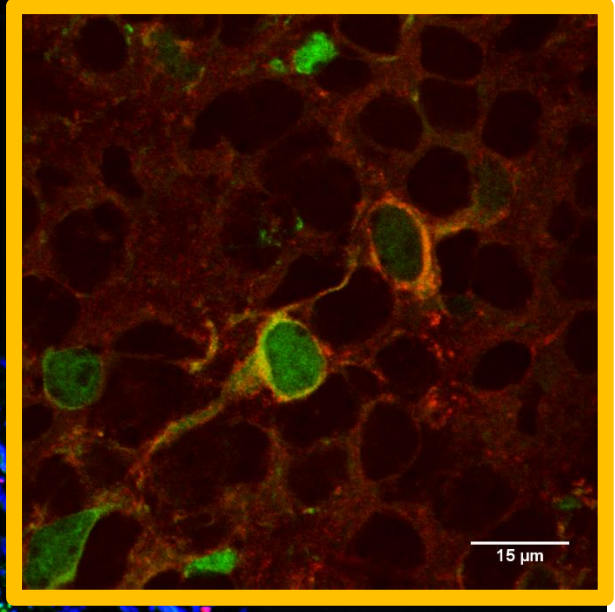
- GABA is excitatory during brain development and in epileptic neurons

Thank you for your time! Questions?