

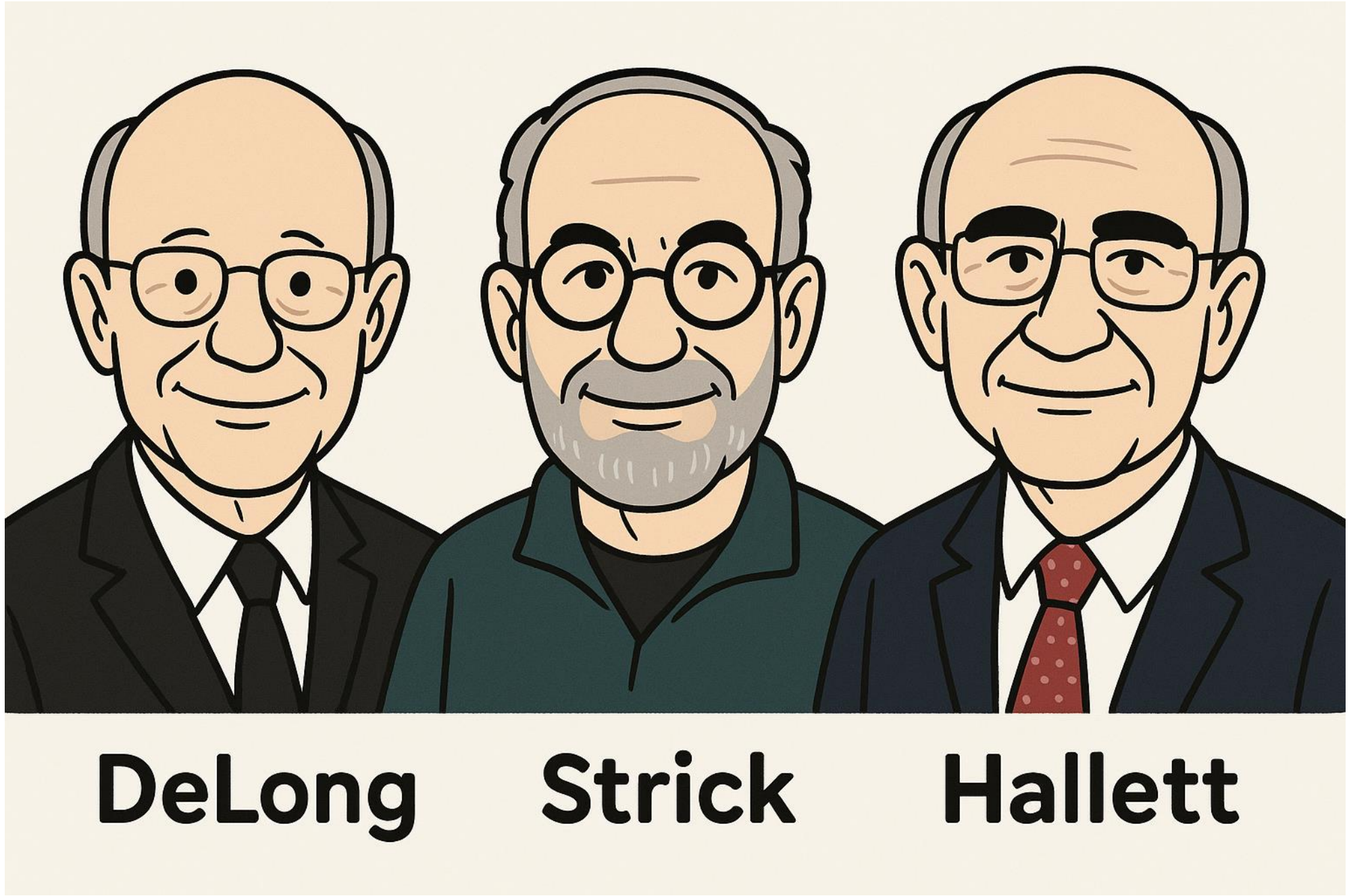
Motor Control and the Basal Ganglia: Anatomy, Physiology and Pathophysiology

Norman Fixel Institute Campus

Michael S. Okun MD

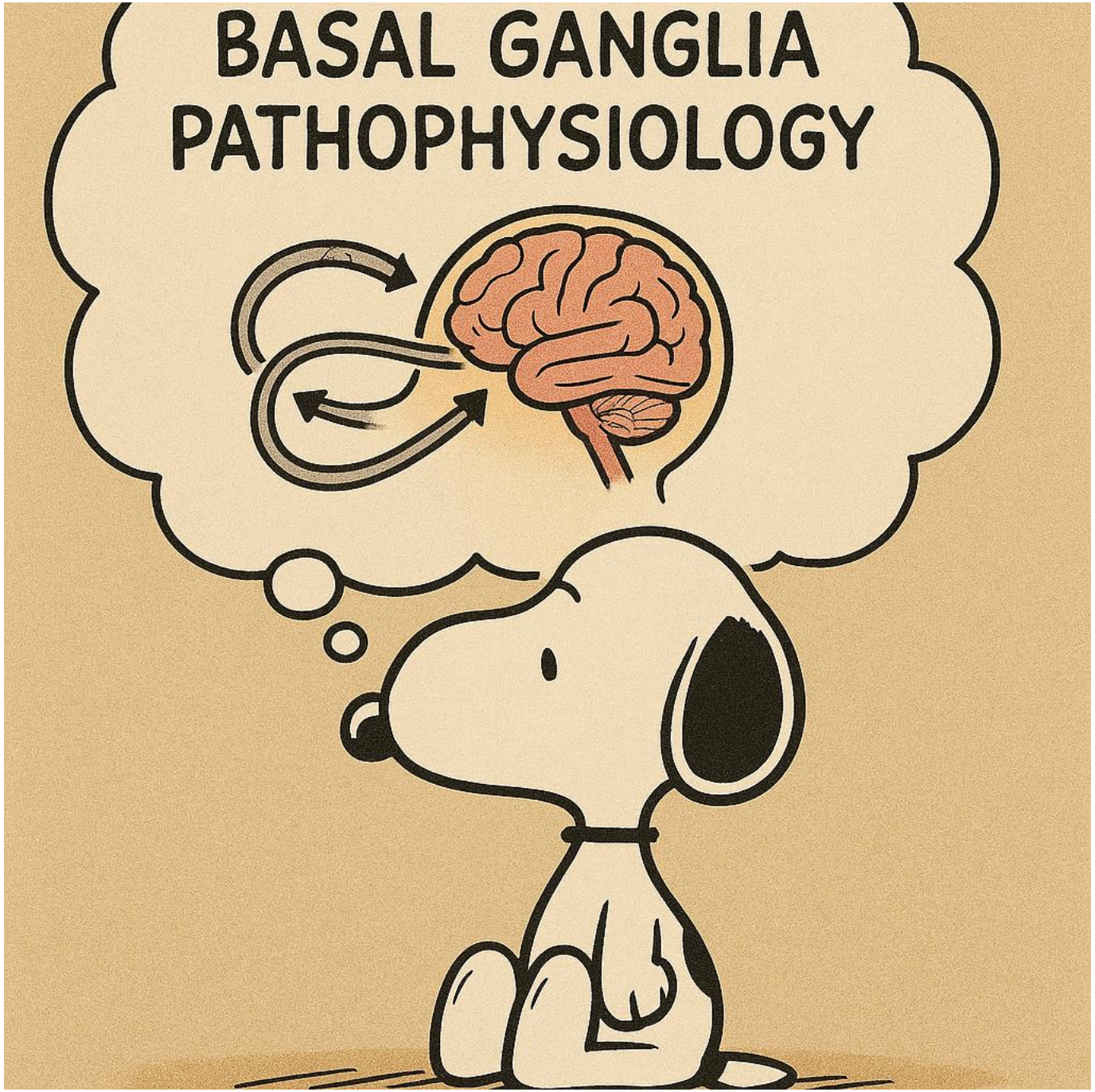





DeLong
Strick
Hallett

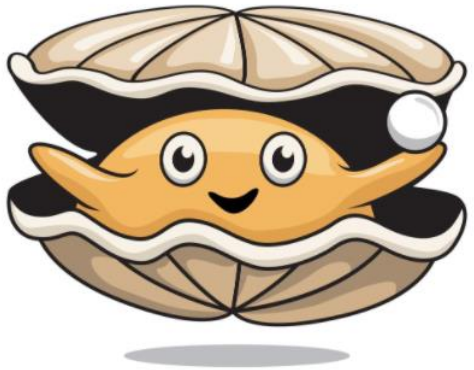
Social Media:
@MichaelOkun
@FixelInstitute

Blog: www.PDplan.com



- UH3 NS18-023 Defining Targets for Tic Detection and Suppression in Tourette Syndrome Deep Brain Stimulation NS18-023
- R01NS131342 Thalamic DBS and Voice Tremor
- U01 Automated Image Differentiation of Parkinson's
- R25NS108939 University of Florida R25 Early Research Program for Neurology and Neurosurgery Residents
- R01NS096008 The Human Thalamocortical Network in Tourette Syndrome
- R01NR014852 Mobile Decision Support System for Nurse Management of Neuromodulation Therapy
- R21NS072897 Neural Correlates of Tourette Syndrome
- R21NS119849 Balance and Gait in Essential Tremor
- R34MH080764 Scheduled and Responsive Brain Stimulation for the Treatment of Tourette Syndrome

The ‘cypher’ for my talk



Clinical Pearl



New Paper



‘Hot’ Paper

‘Shout out’ to Fellows





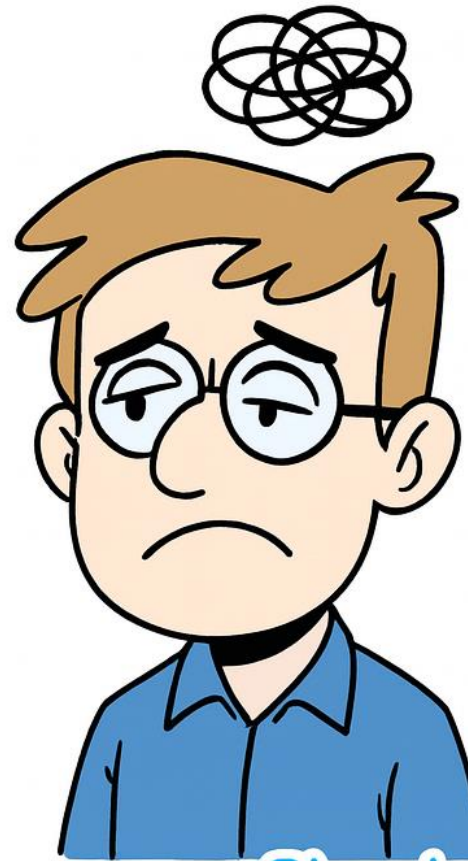




How do you tell the difference between altitude sickness and frustration with understanding the basal ganglia?



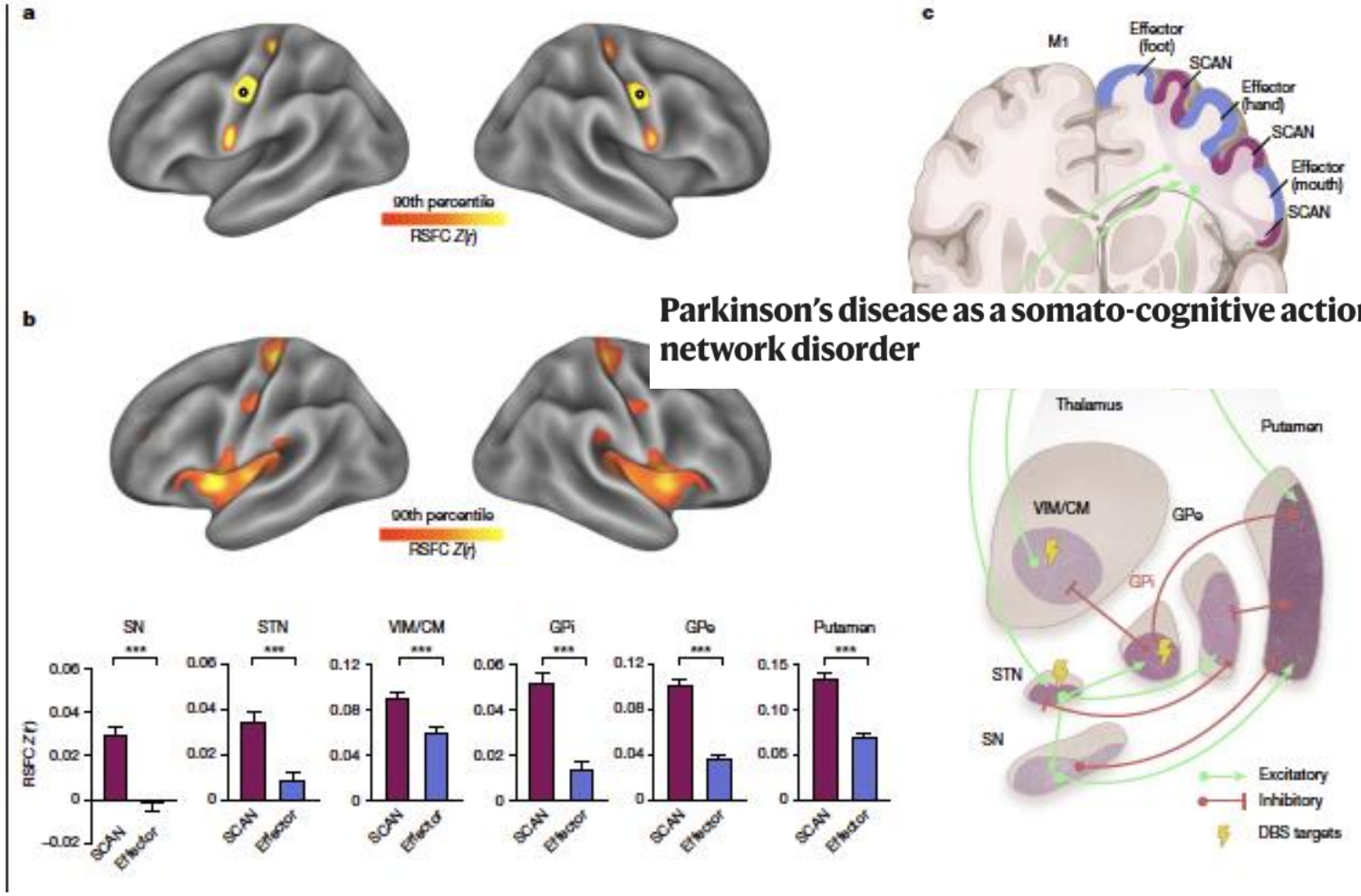
- Nausea
- Vomiting
- Fatigue
- Rapid breathing
- Shortness of breath



Nausea
Vomiting
Fatigue
Rapid breathing
Shortness of breath

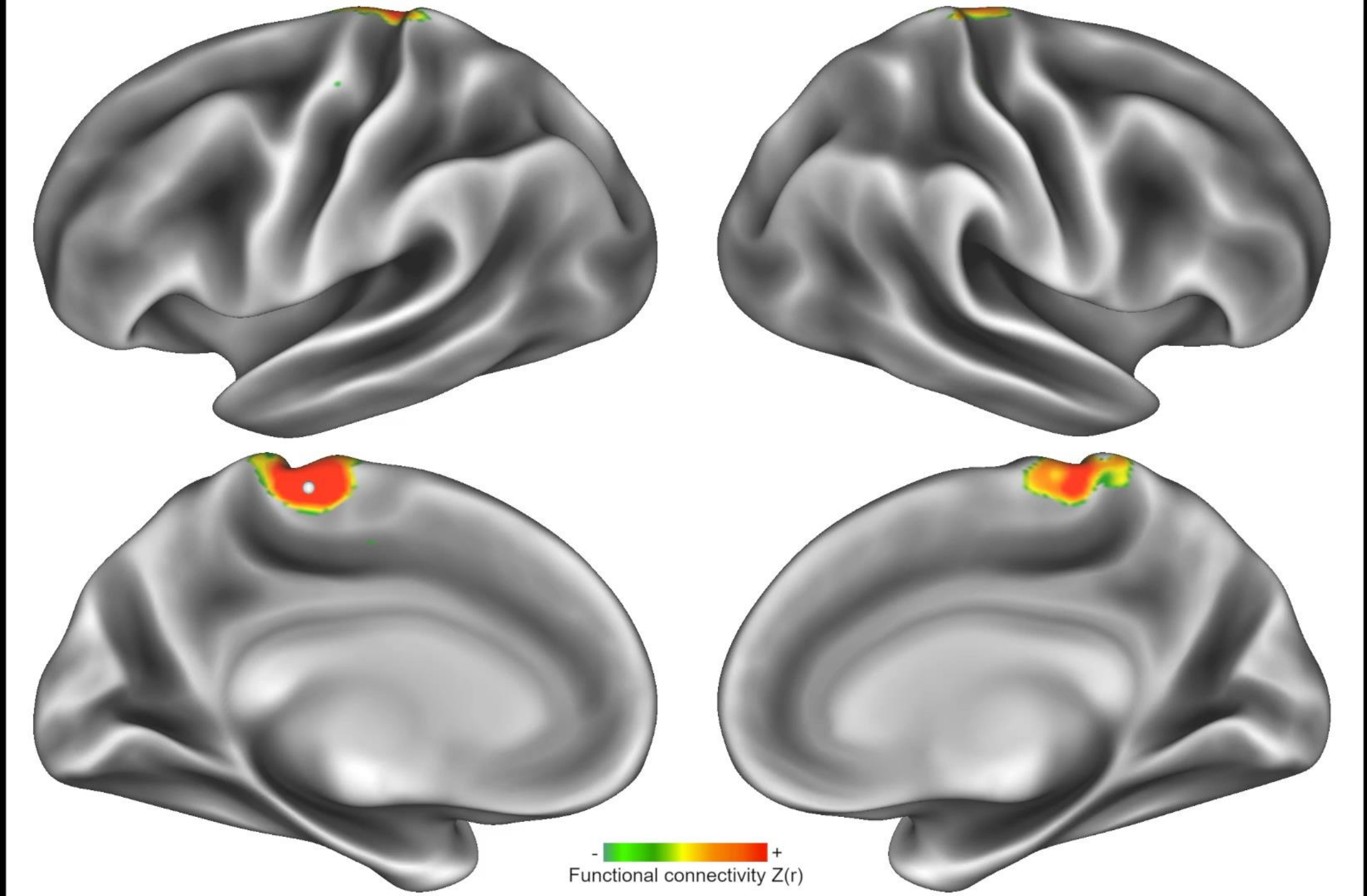
nature

Parkinson's disease as a somato-cognitive action network disorder

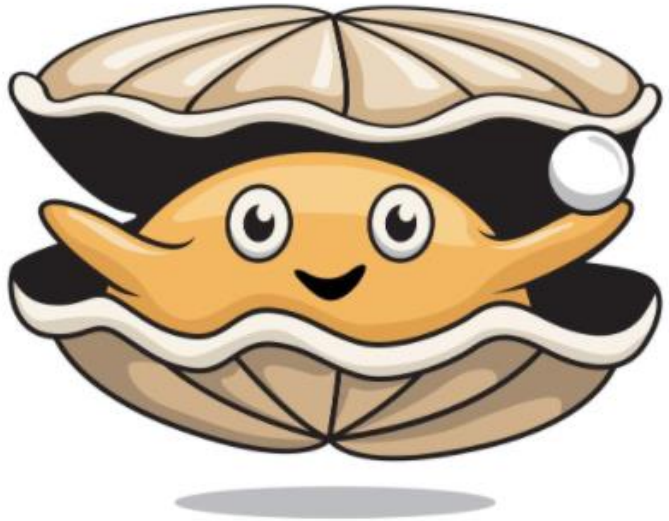


Parkinson's disease as a somato-cognitive action network disorder

Jianxun Ren[1,33✉], Wei Zhang[1,2,33], Louisa Dahmani[3,4], Evan M. Gordon[5,6], Shenshen Li[1,7], Ying Zhou[1,8], Yang Long[1,8], Jianting Huang[1], Yafei Zhu[1,2], Ning Guo[1], Changqing Jiang[9], Feng Zhang[9], Yan Bai[10], Wei Wei[10], Yaping Wu[10], Alan Bush[4,11], Matteo Vissani[4,11], Luhua Wei[12], Carina R. Oehrn[13], Melanie A. Morrison[14,15], Ying Zhu[1], Chencheng Zhang[16,17], Qingyu Hu[1], Yilin Yin[1], Weigang Cui[1], Xiaoxuan Fu[1], Ping Zhang[1], Weiwei Wang[1], Gong-Jun Ji[16,19,20], Ji He[1,21], Kai Wang[19,20], Dongsheng Fan[21], Zhaoxia Wang[12], Teresa Kimberley[3,22,23], Simon Little[15,24,25], Philip A. Starr[13,15,25], Robert Mark Richardson[4,11], Luming Li[9,26], Meiyun Wang[10,27✉], Danhong Wang[1✉], Nico U. F. Dosenbach[5,6,28,29,30,31] & Hesheng Liu[1,32✉]

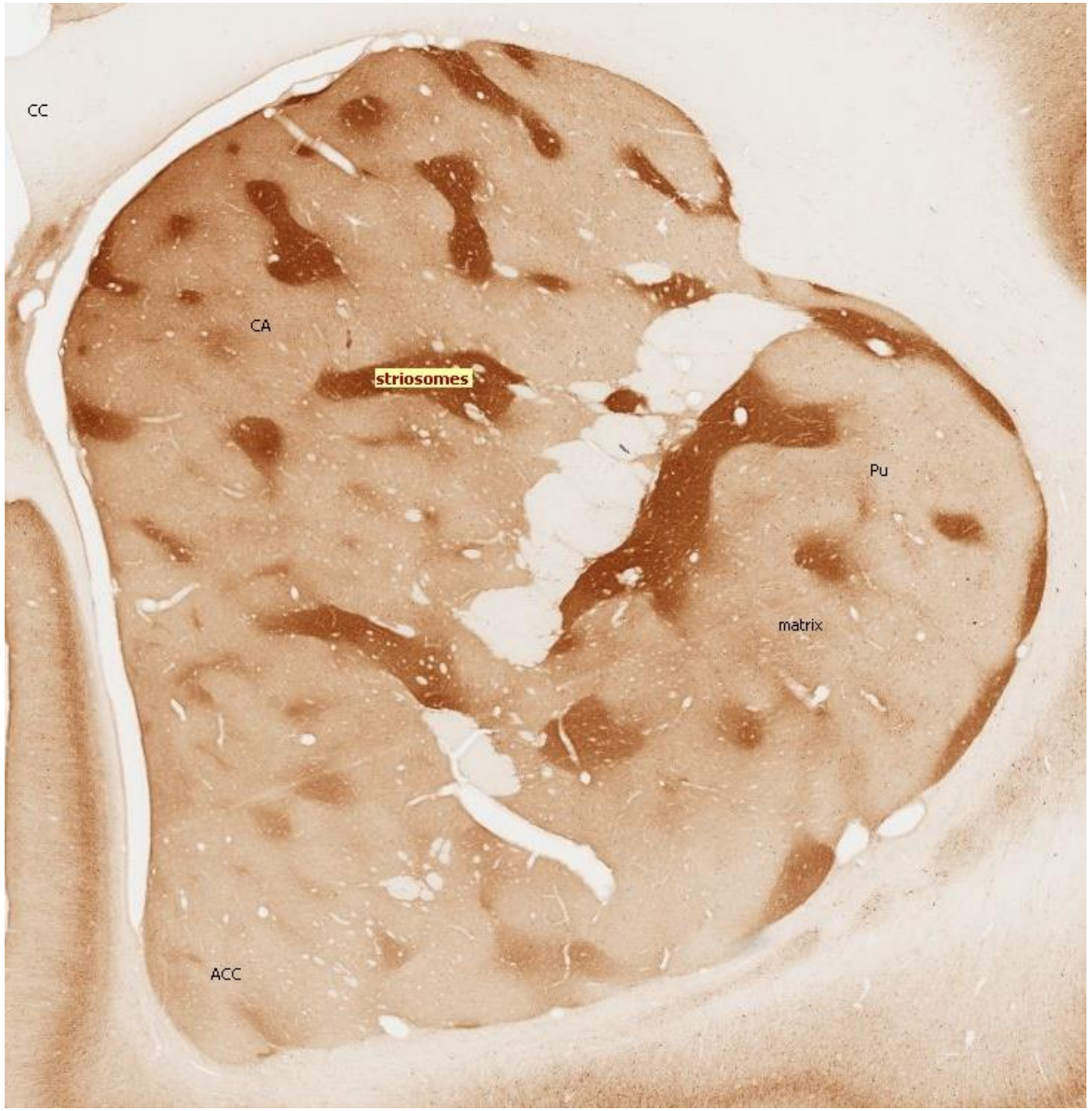

-
+
Functional connectivity Z(r)

What are the key basal ganglia structures?



Striatum

- Caudate, putamen, ventral striatum
- Cells
  - 80-95% medium spiny neurons (projection)
    - GABAeric
    - Those with D1 receptors also have the protein neurotransmitters substance P and dynorphin
    - Those with D2 receptors also have the protein neurotransmitter enkephalin
  - 5-20% aspiny interneurons, 4 classes
    - Giant aspiny cholinergic cell = TANs
    - 3 classes of GABAergic interneurons
  - Patches (striosomes), AChE-poor, are embedded in a matrix that is AChE-rich



Striosomes (patches)

- Acetylcholinesterase ‘poor’
- μ-opioid receptor high
- Important for value-based decision making

Matrix

- Acetylcholinesterase rich
- Calbindin level high

From BrainMaps.org, copyright UC Regents Davis campus

Globus pallidus

- GPi and GPe; dorsal and ventral
- SNr similar to the GPi
- Most neurons are large, parvalbumin positive, GABAergic neurons with large dendritic arbors
- Only few interneurons

Subthalamic nucleus

- Most neurons are glutamatergic with long dendrites
- 7.5% neurons are GABAergic interneurons

Substantia nigra (compacta)

- Dopaminergic neurons
- Somatotopically organized
- Variety of inputs from nuclear groups in the region including feedback loops from the other basal ganglia structures

Pedunculopontine Nucleus

(PPN)

- Compacta (PPNc)
  - Cholinergic
- Dissipatus (PPNd)
  - Glutamatergic with some cholinergic
- Other nuclei in the vicinity
  - Midbrain extrapyramidal area (MEA)
  - Peripeduncular nucleus
  - Cuneiform nucleus
  - Sub-cuneiform nucleus
  - Laterodorsal tegmental nucleus

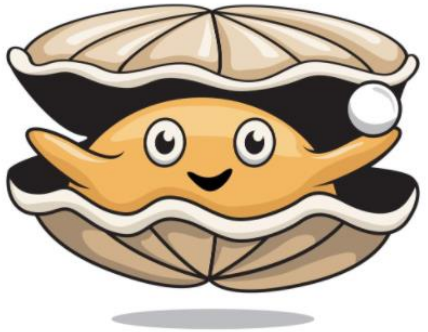
Cellular activity

- MSNs have a low firing rate, 0.5 to 2 Hz
- GPi neurons have high rate, 60-90 Hz
- General idea is that movement is produced by input to MSNs
- Results in an increase in firing via the direct pathway, leading to inhibition in the GPi which will release the thalamus from tonic inhibition
- Balanced by excitation to the GPi from GPe and STN

The Language of the Basal Ganglia

- Information is passed in oscillatory activity, at many different frequencies
- One resting rhythm between BG and cortex is in the (low) beta frequency and this goes away with movement
- During movement, there is an increase in gamma (and high beta) frequency activity
- In PD, there is excessive beta that correlates with bradykinesia
  - This beta appears to be mostly in the indirect pathway neurons (Sharott et al. 2017 J Neurosci)
- The exact information transmitted, including its patterns, is the alternative to the rate theory

What do the BG do?

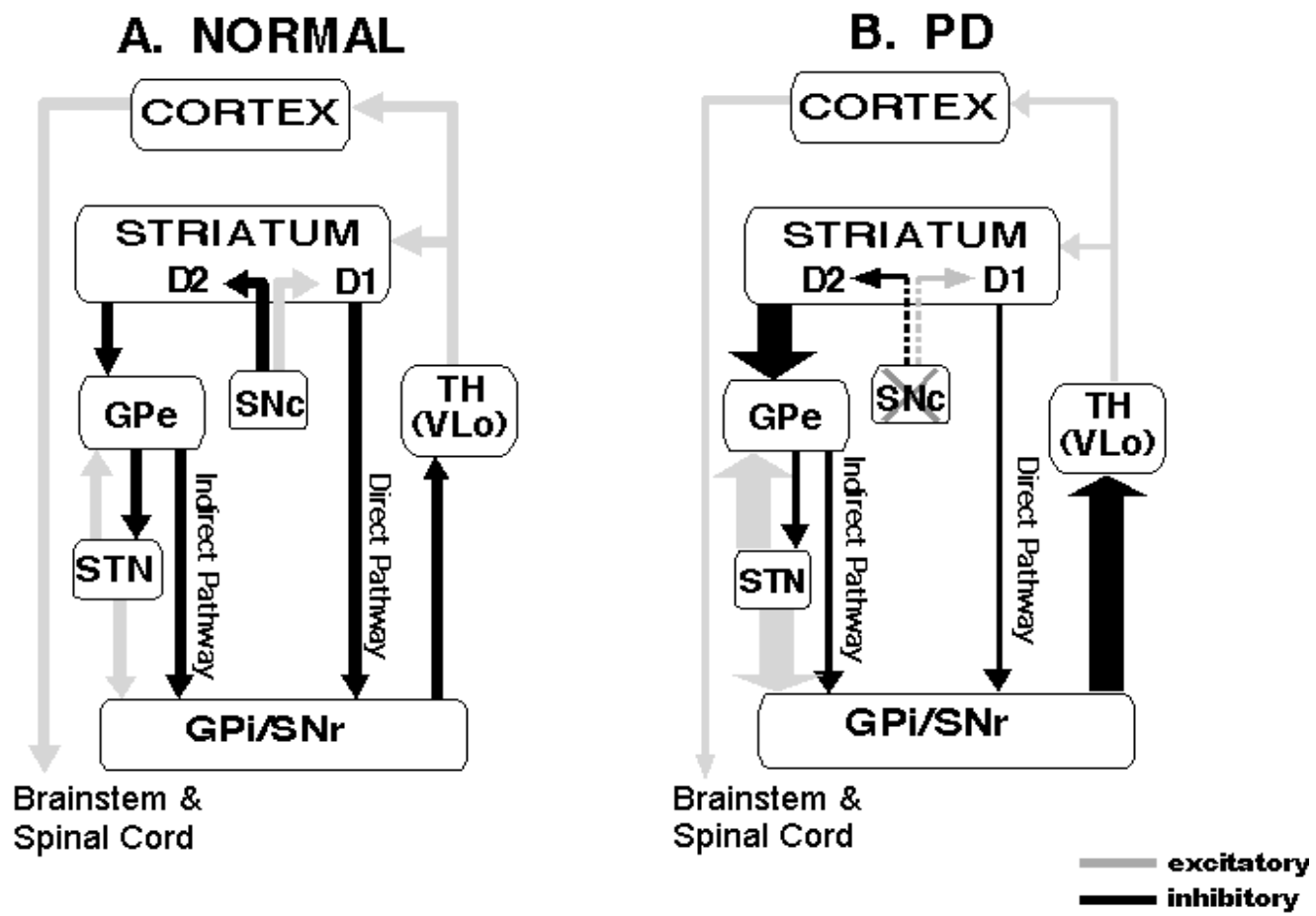


- Motor “energy”/scaling of movement
- Agility – facilitate the speed of brain processing
  - Including non-motor functions
- Movement selection (self selection, internal triggering)
  - Switching movements/sequential movement/terminating an ongoing motor program
- Surround Inhibition to sharpen motor command
- Automatic running of motor programs
- Reward, which facilitates decision making and (motor) learning, operant conditioning (habits might result)
  - Reward is a critical factor in movement selection

Do we need the basal ganglia?

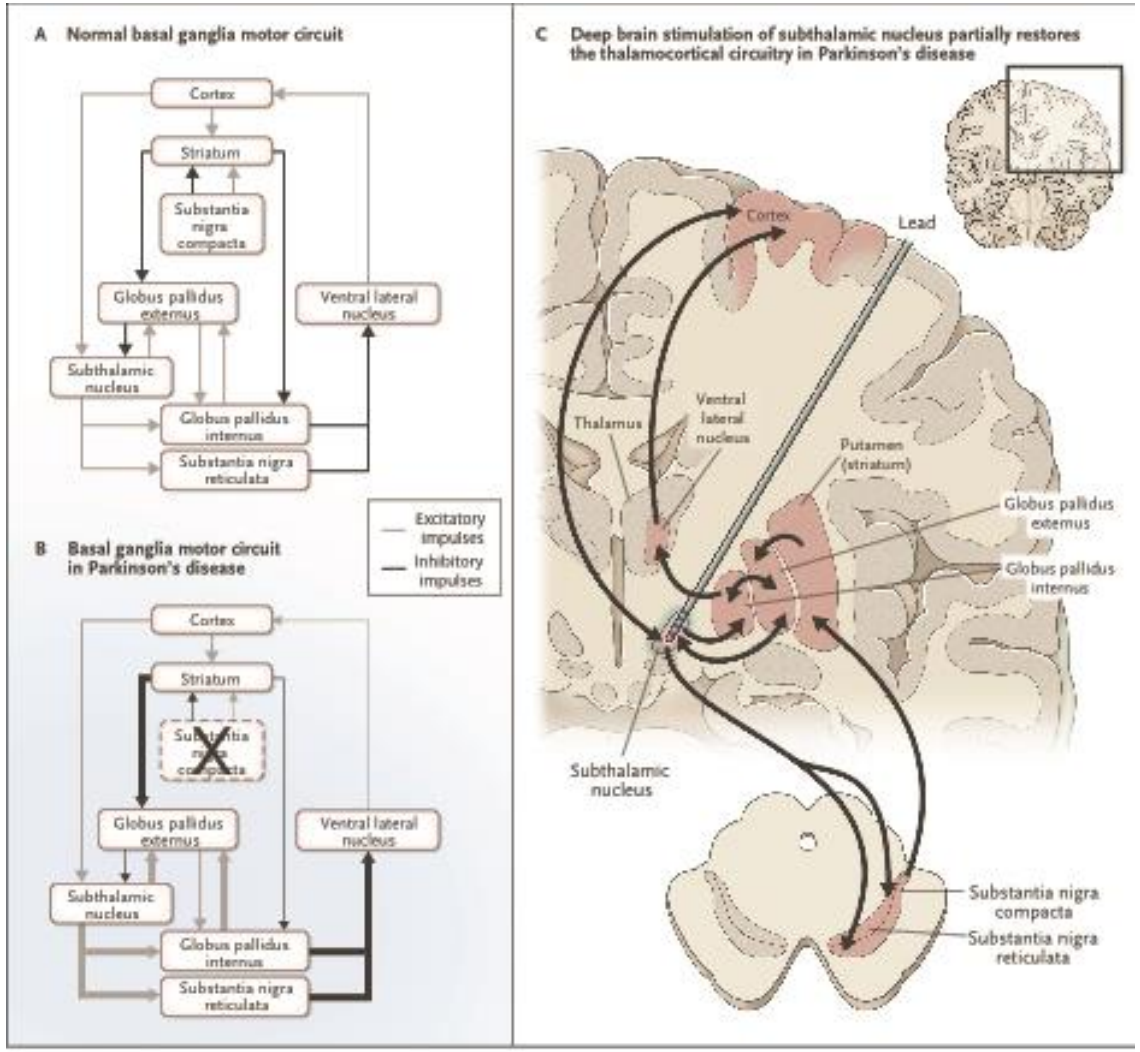
- Patients with PD who have a pallidotomy have improved function
  - They have lost most output from the BG
- This implies that no function is better than bad function
- Implies that much of the function of the BG is a parallel brain function
- BG are useful when working well, but not necessary.

The Model for Understanding Basal Ganglia Function in PD

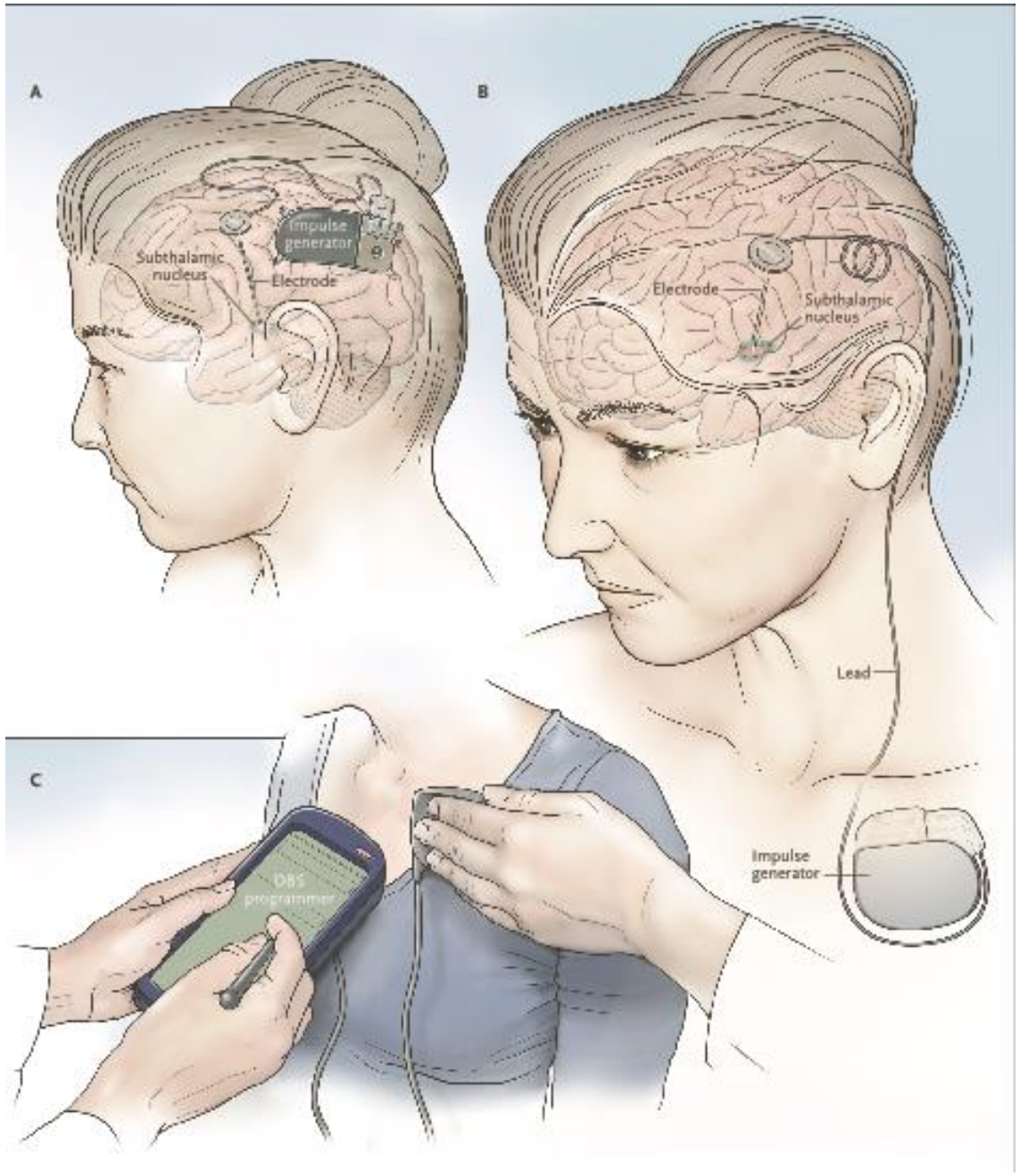








Okun, NEJM 2014



The NEW ENGLAND JOURNAL of MEDICINE

Okun, NEJM 2014

The NEW ENGLAND JOURNAL of MEDICINE

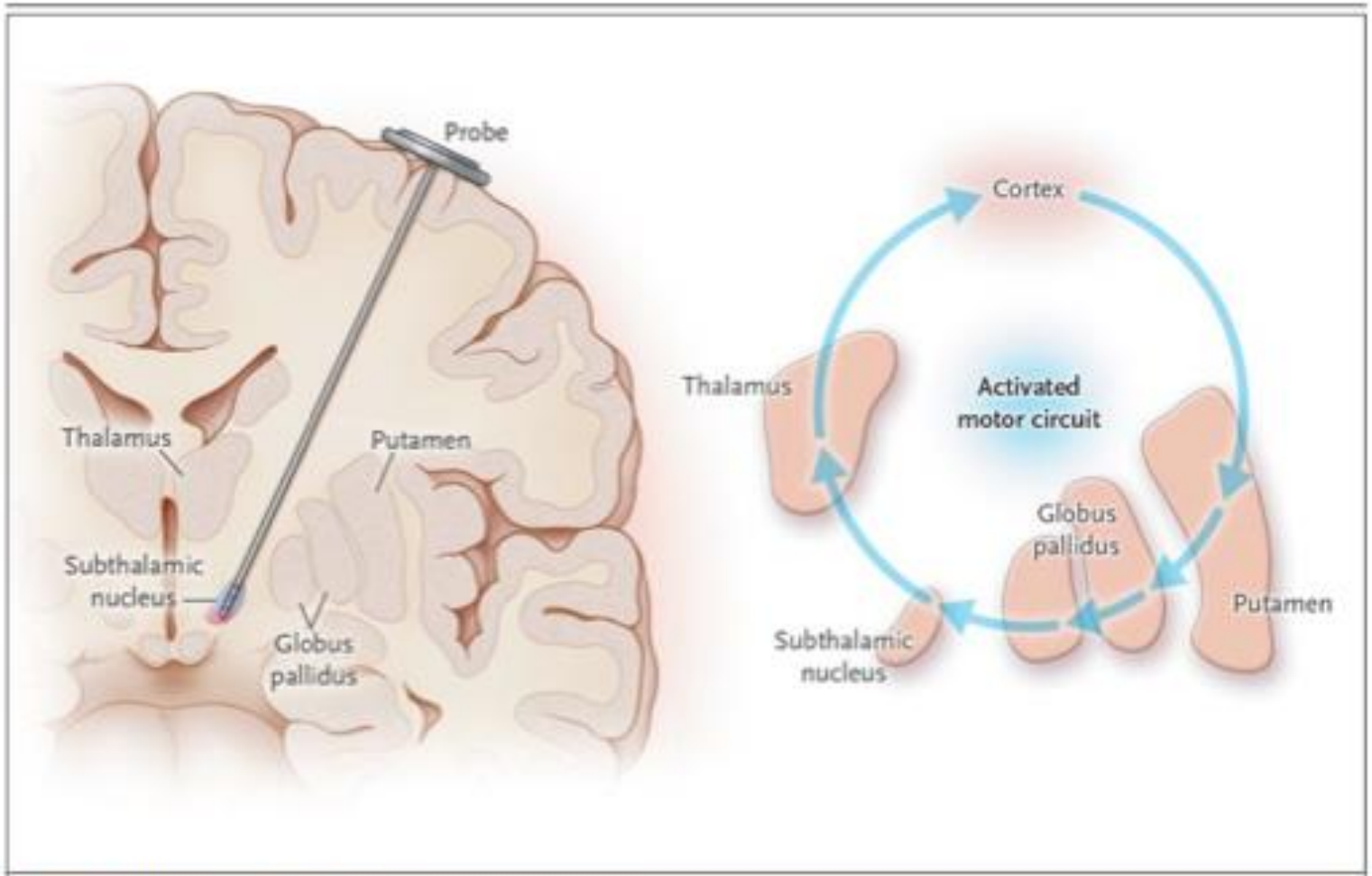
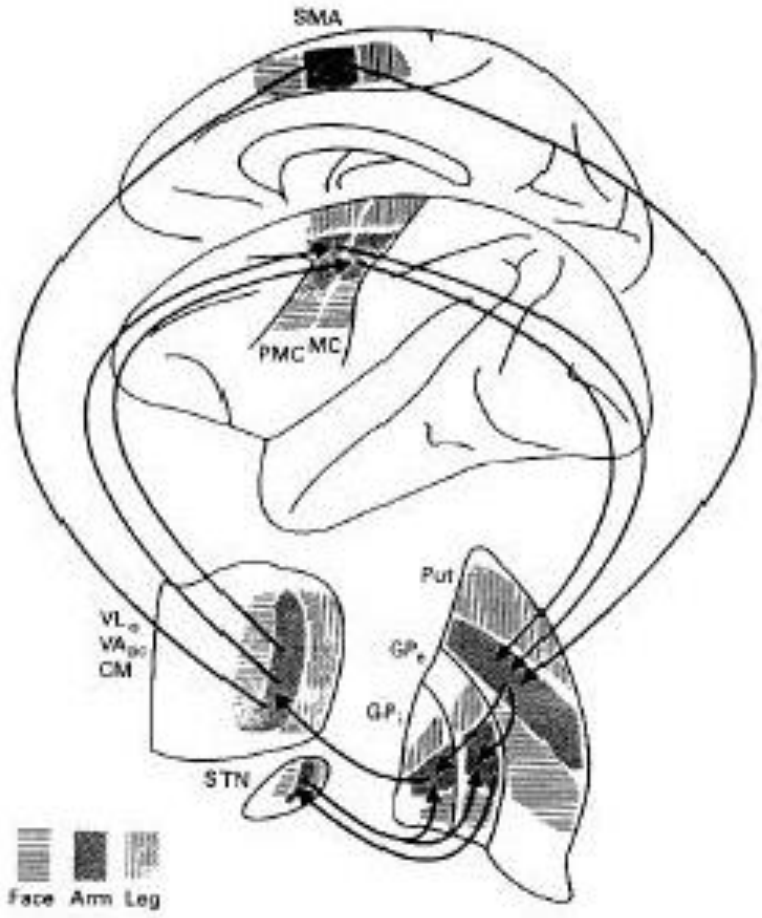


Figure 3. Network Effects of Deep-Brain Stimulation.

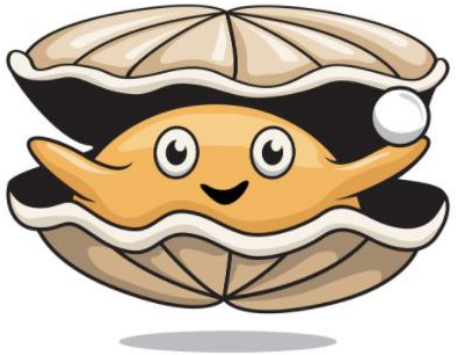
Deep-brain stimulation has broad effects on neural networks in addition to, or as a consequence of, its local influences. Motor pathways are complex, and their disturbance in Parkinson's disease is likewise far-ranging. Deep-brain stimulation modulates the feedback loops that ultimately determine motor control.

Okun, M.S. N Engl J Med. 2012 Oct 18;367(16):1529-38.

Think Loops!



Ann. Rev. Neurosci. 1986. 9 : 357-81



PARALLEL ORGANIZATION OF FUNCTIONALLY SEGREGATED CIRCUITS LINKING BASAL GANGLIA AND CORTEX*

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Mahlon R. DeLong

Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Peter L. Strick

Research Service, Veterans Administration Medical Center, Departments of Neurosurgery and Physiology, State University of New York–Upstate Medical Center, Syracuse, New York 13210

11,255 citations &
39 years later

Why was this publication so impactful?

Why does it continue to be cited?

What's new?

2013: 2537 citations (peak)
2023: 2322 citations

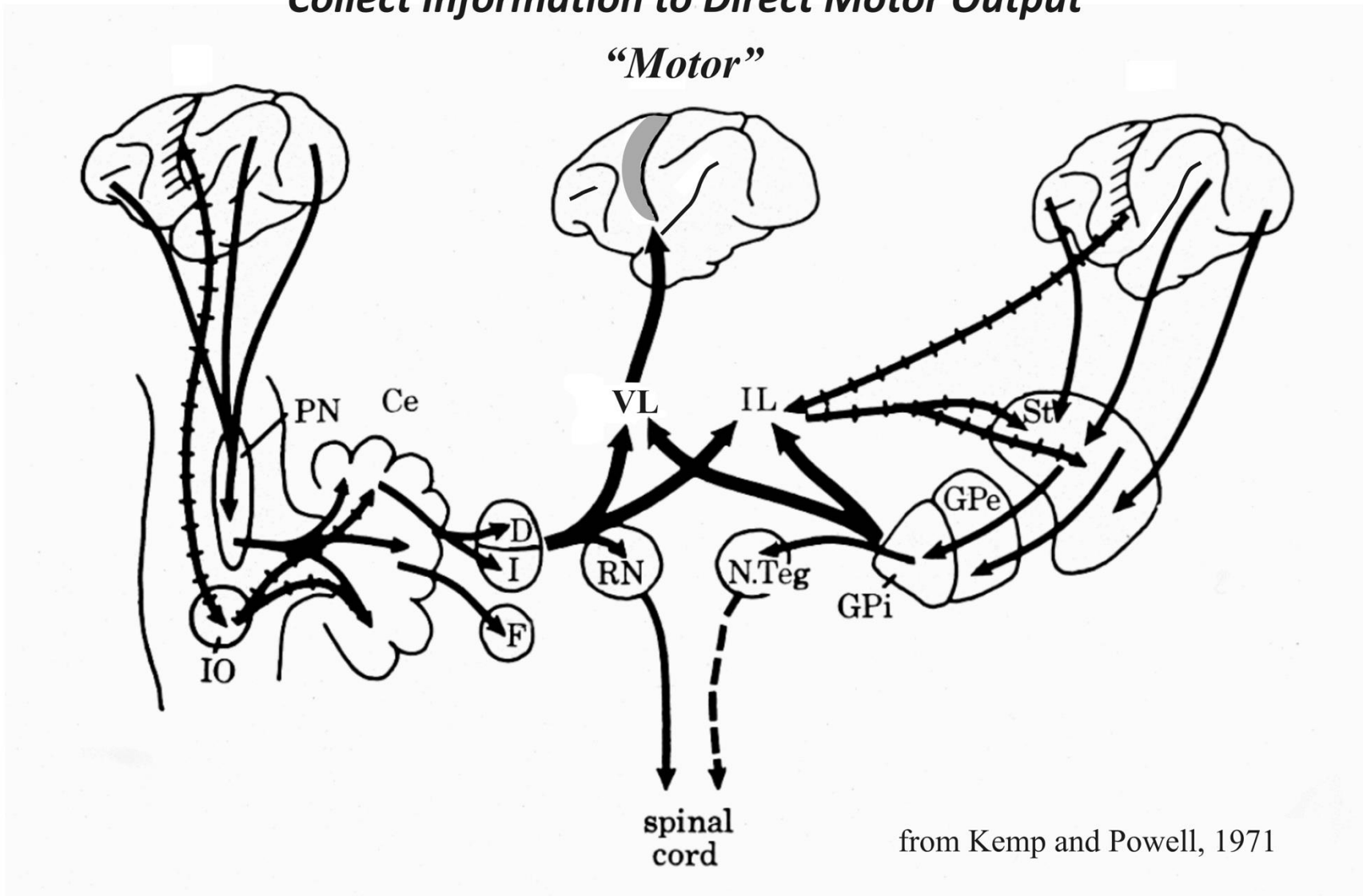
6/1/2025 4:00 PM

Kemp and Powell (1971) – Diffuse Integration Model

- **Viewpoint:** They emphasized the convergent and integrative anatomy of the basal ganglia.
- **Concept:** The basal ganglia, a funnel-like structure that collected widespread cortical inputs into common output stream.
- **Anatomy:** Based on Golgi and degeneration techniques, they described overlapping projections into the striatum, suggesting a non-parallel, integrative system.
- **Function:** The basal ganglia were thought to be involved in general motor regulation, without clear segregation of different functional domains.

Classic View of Basal Ganglia & Cerebellar Circuits

Collect Information to Direct Motor Output



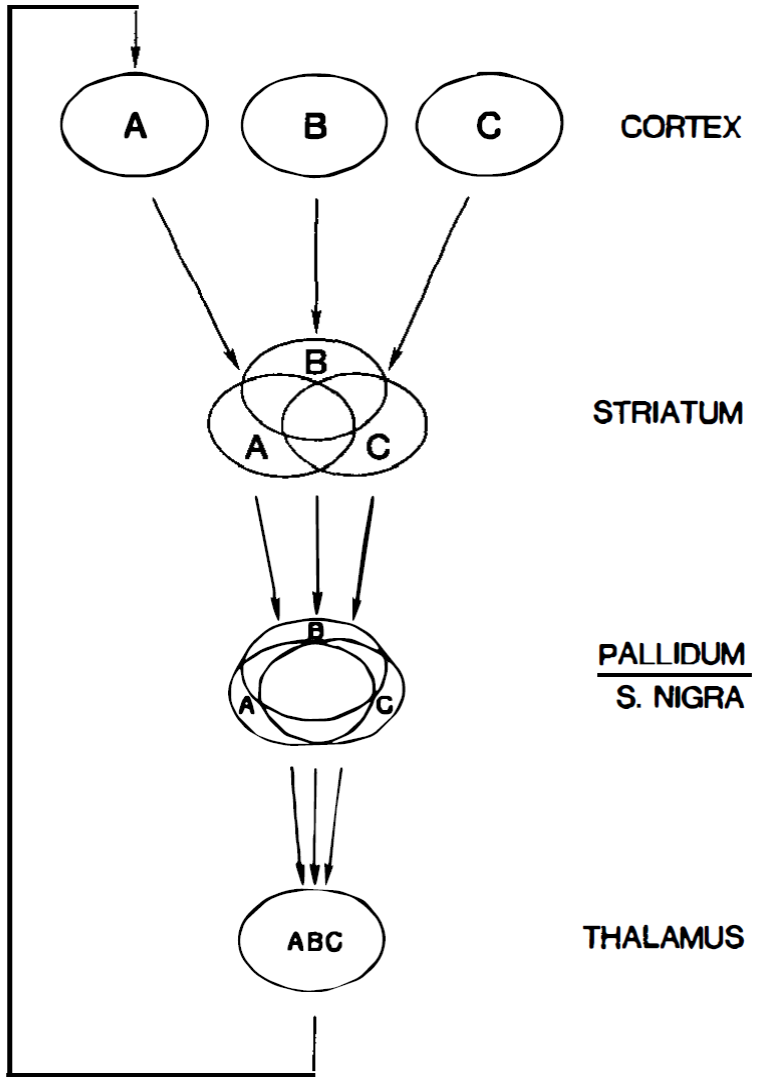
from Kemp and Powell, 1971



DeLong (1980s–1990s) and Alexander, Crutcher, and Strick (1986) – *Parallel Circuit Model*

- **DeLong (1980s–1990s) and Alexander, Crutcher, and Strick (1986) – *Parallel Circuit Model***
- **Viewpoint:** They proposed that the basal ganglia were organized into **parallel, functionally segregated circuits**.
- **Concept:** Rather than a single integrative loop, they proposed **multiple closed-loop systems**, each involved in specific functions.

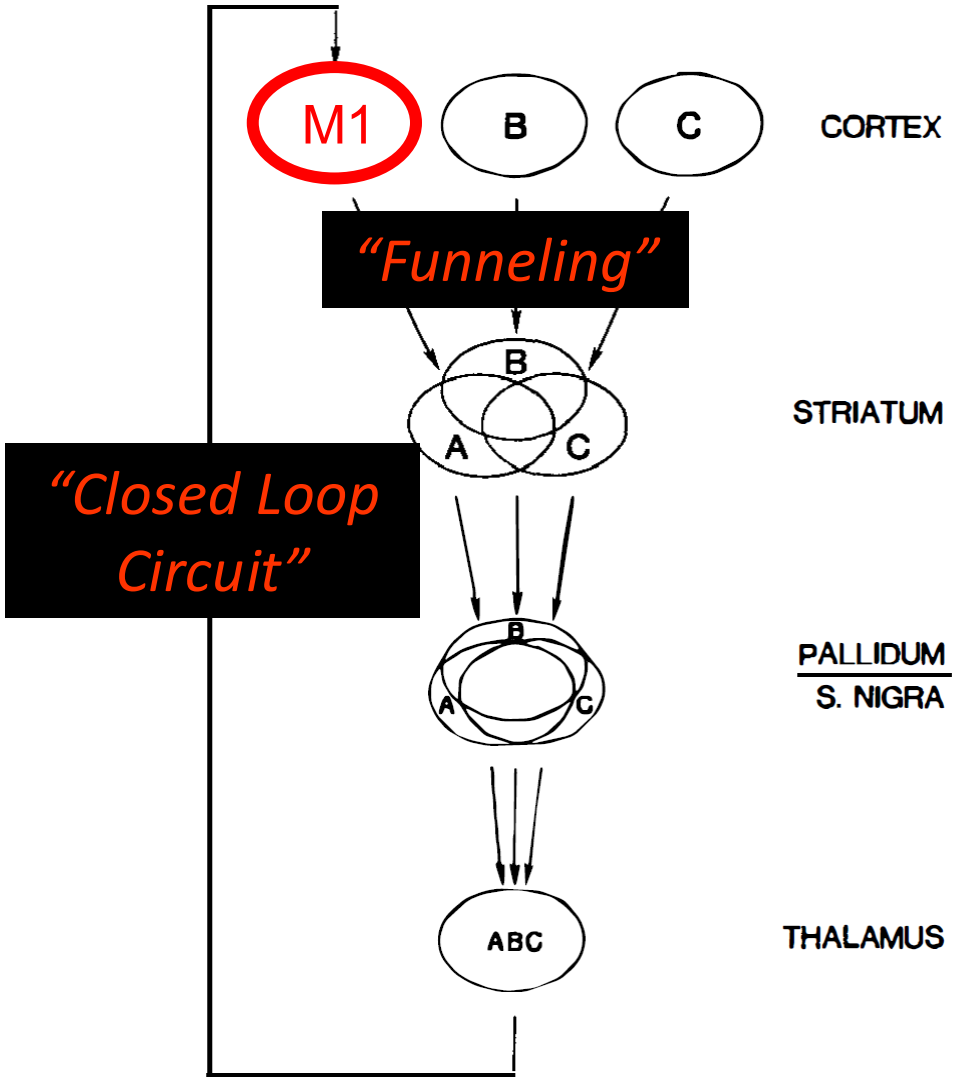
‘Skeleton Diagram’



Alexander et al., ’86, Fig. 2 (pg. 360)

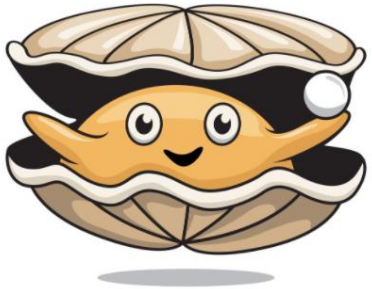


‘Skeleton Diagram’

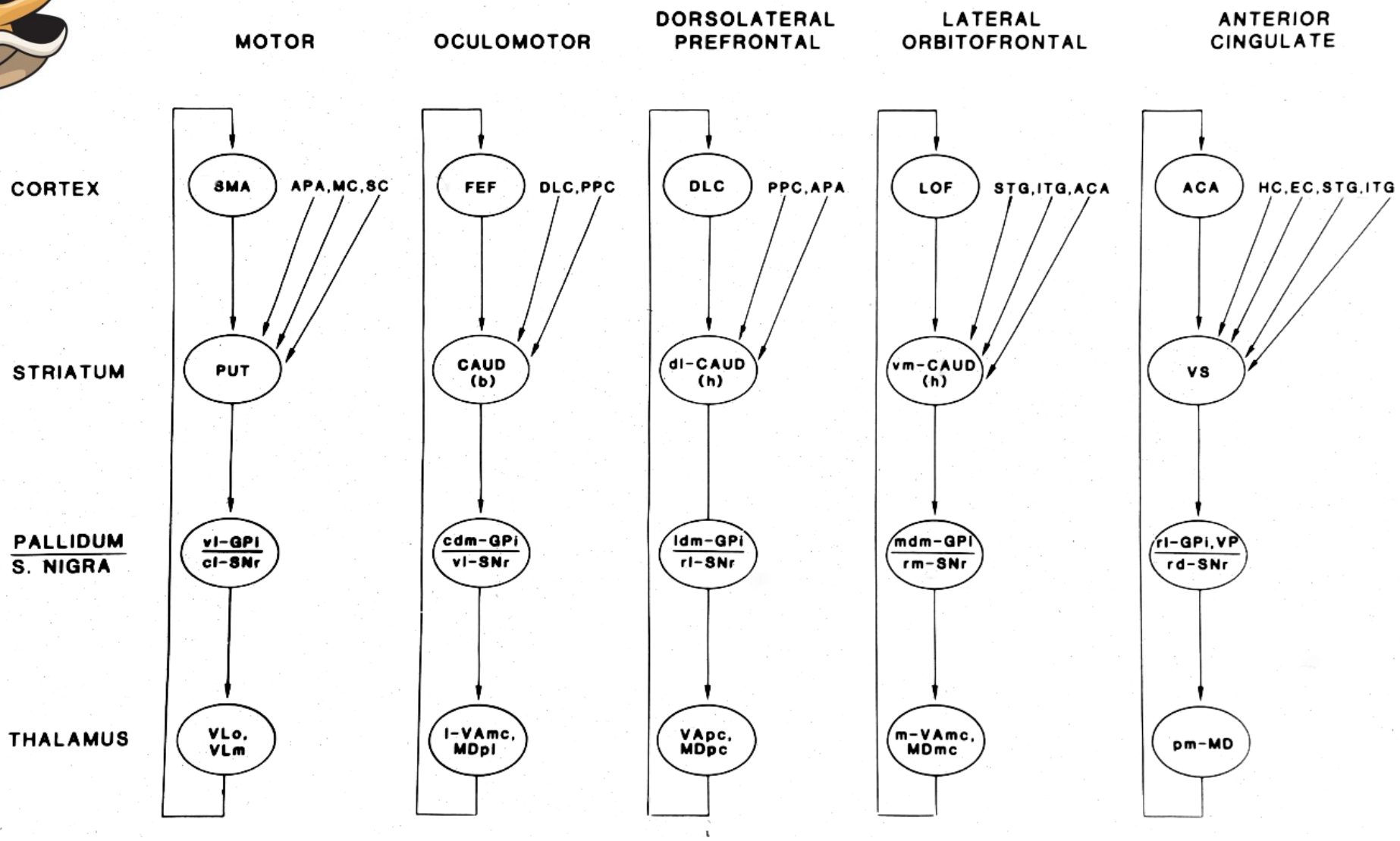


Alexander et al., ’86, Fig. 2 (pg. 360)

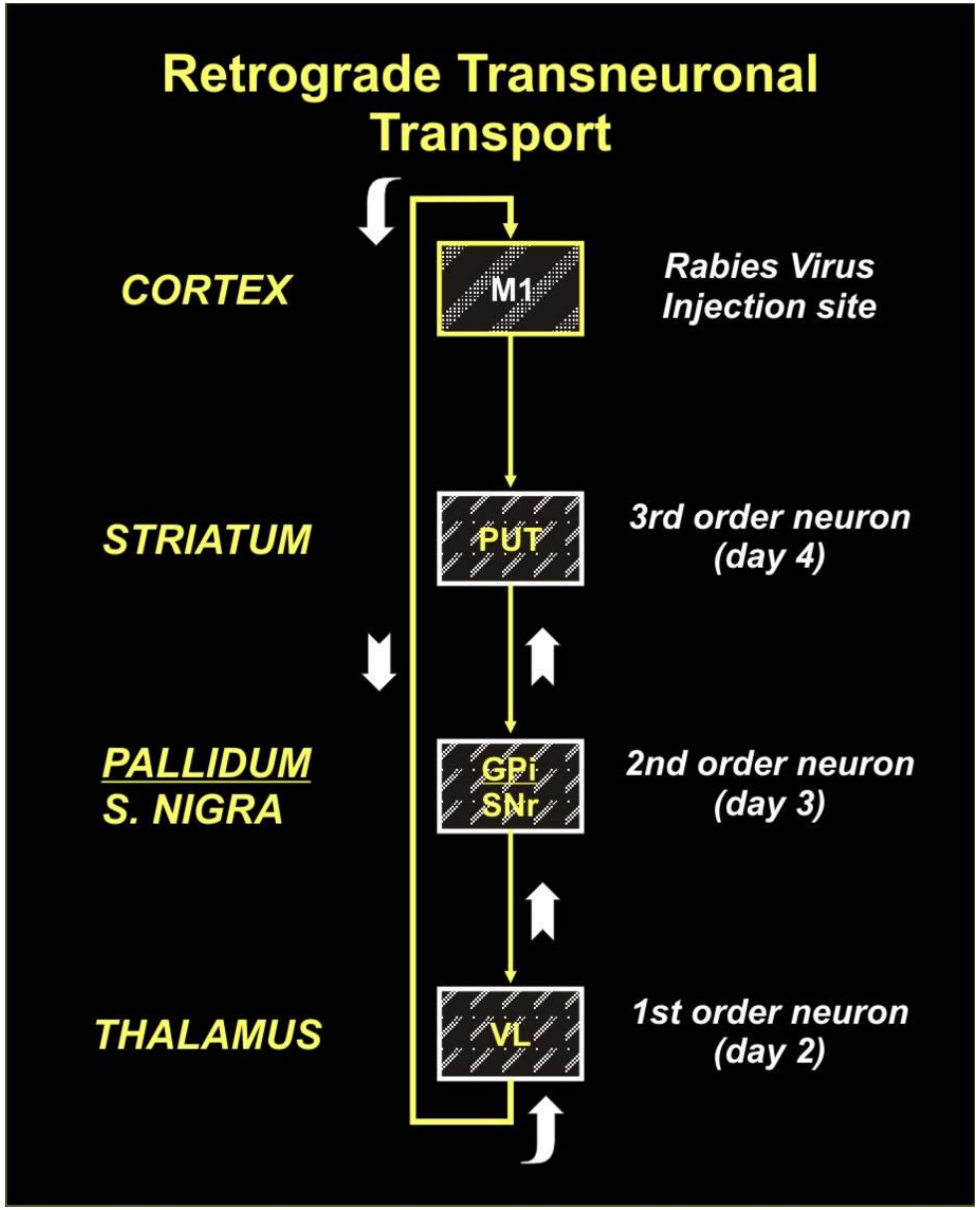




Five Parallel Circuits



Alexander et al., ’86, Fig. 3 (pg. 364)


Retrograde Transneuronal Transport
CORTEX
M1
Rabies Virus Injection site
STRIATUM
PUT
3rd order neuron (day 4)
PALLIDUM
S. NIGRA
GPi SNr
2nd order neuron (day 3)
THALAMUS
VL
1st order neuron (day 2)


Strick

Specific Areas of Each Structure Project to a Very Specific Region in Basal Ganglia

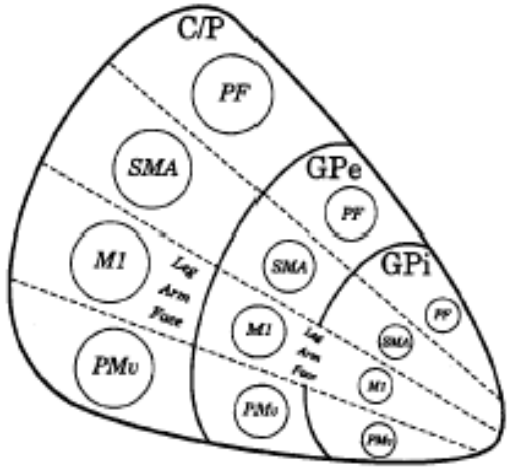


Figure 5: An illustration of the topographical structure (coronal) of the cortico-basal ganglia loop. C/P, caudate nucleus; GPe, globus pallidus external segment; GPi, the internal segment; PF, prefrontal; SMA, supplementary motor area; M1, primary motor cortex; PMv, ventral pre-motor area. (Adapted from Strick et al., 1995.)

Virus injections into different areas of cortex trace to different areas of the GPi

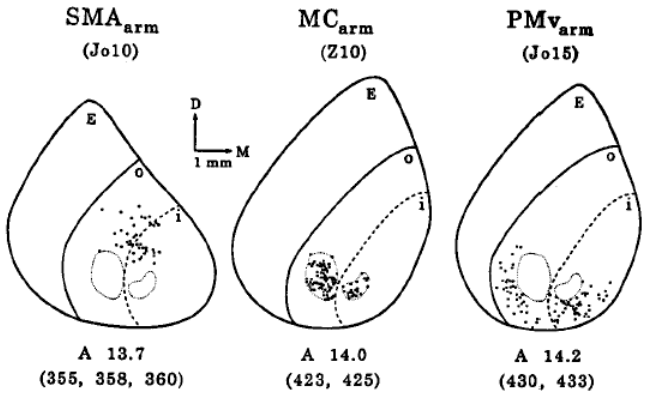


Figure 7: Coronal sections through the globus pallidus that received injections of the McIntyre-B strain of HSV-1 virus into three motor areas of the cortex. Solid dots indicate positions of neurons labeled by retrograde transneuronal transport of the virus. Data of this sort was compiled to form Figure 5. SMA, supplementary motor area; MC, primary motor cortex; PM, pre-motor cortex; E, external segment of the GP; o, outer portion of the GPi; i, inner portion of the GPi; D, dorsal; M, medial.

World's Finest Data Processor…

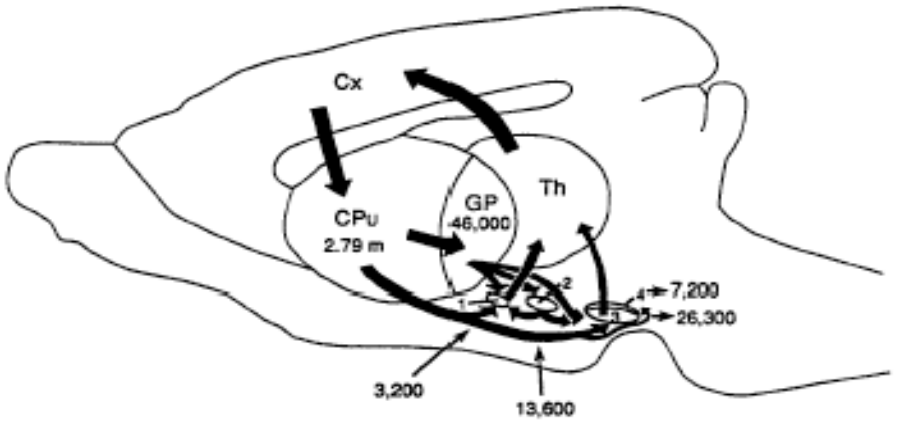
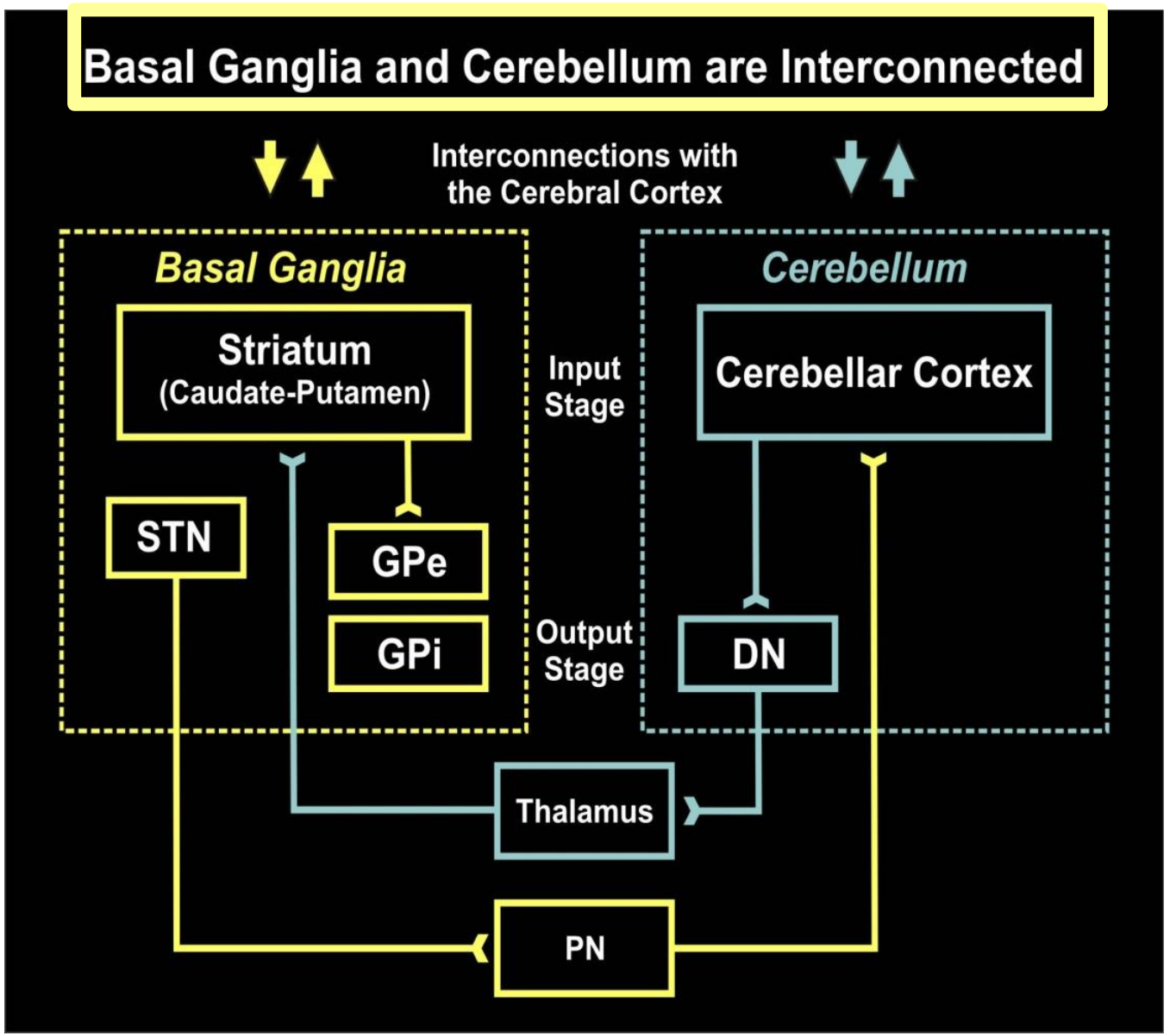


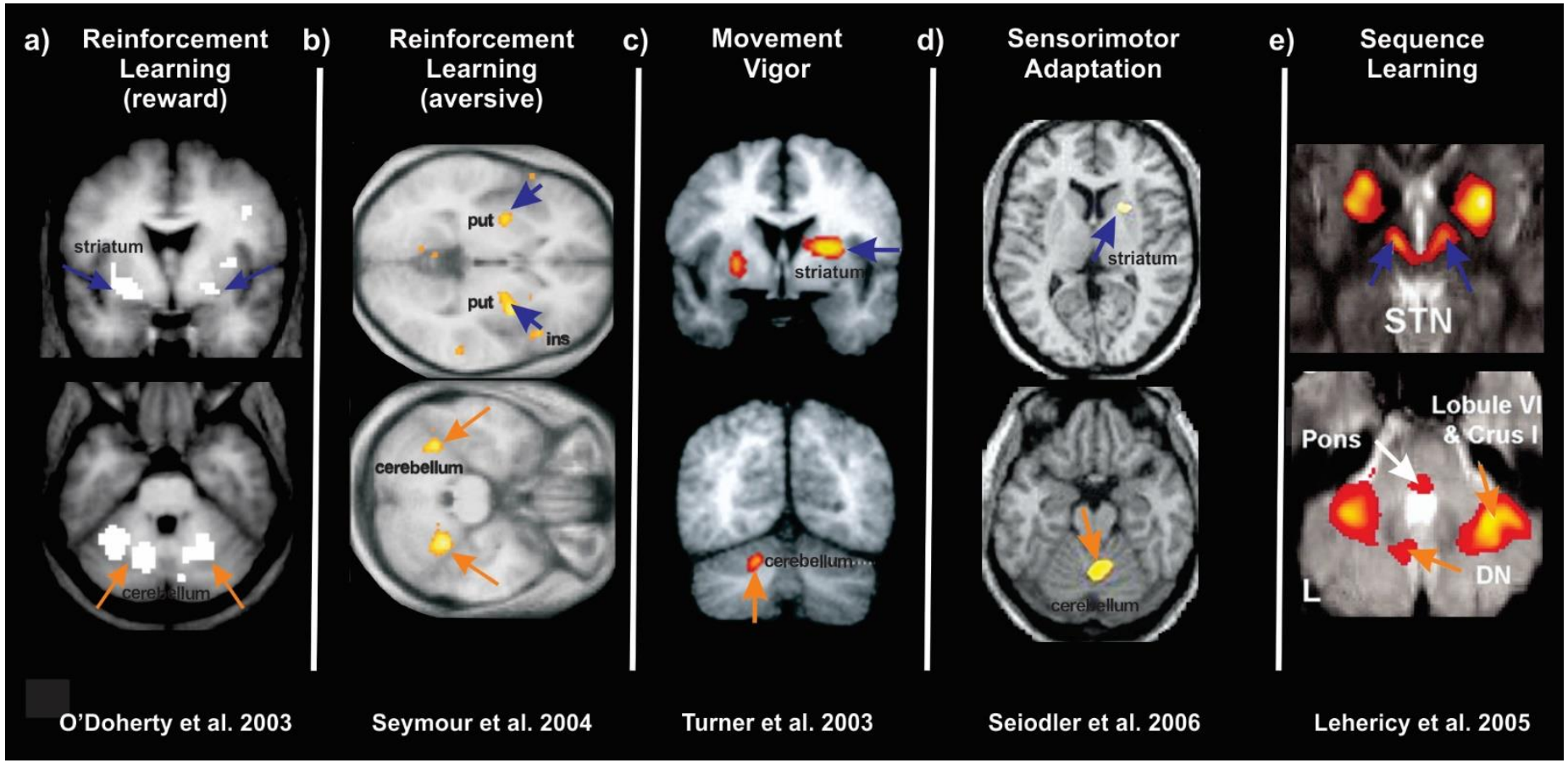
Figure 4: Number of neurons within each subdivision of the rat basal ganglia. Hundreds of millions of cortical inputs (Cx) converge on 2.79 million of striatal cells (CPu), which project to only 46,000 globus pallidus (external) cells. Note how a small number of cells in the subthalamic nucleus (STh) and substantia nigra pars compacts (SNC) and reticulata (SNR) can greatly influence basal ganglia function. (Adapted from Oorschot, 1996.)


Basal Ganglia and Cerebellum are Interconnected
Interconnections with the Cerebral Cortex
Basal Ganglia
Striatum (Caudate-Putamen)
STN
GPe
GPi
Input Stage
Output Stage
Cerebellum
Cerebellar Cortex
DN
Thalamus
PN




Strick

Cerebellar and Basal Ganglia Activation are Linked!

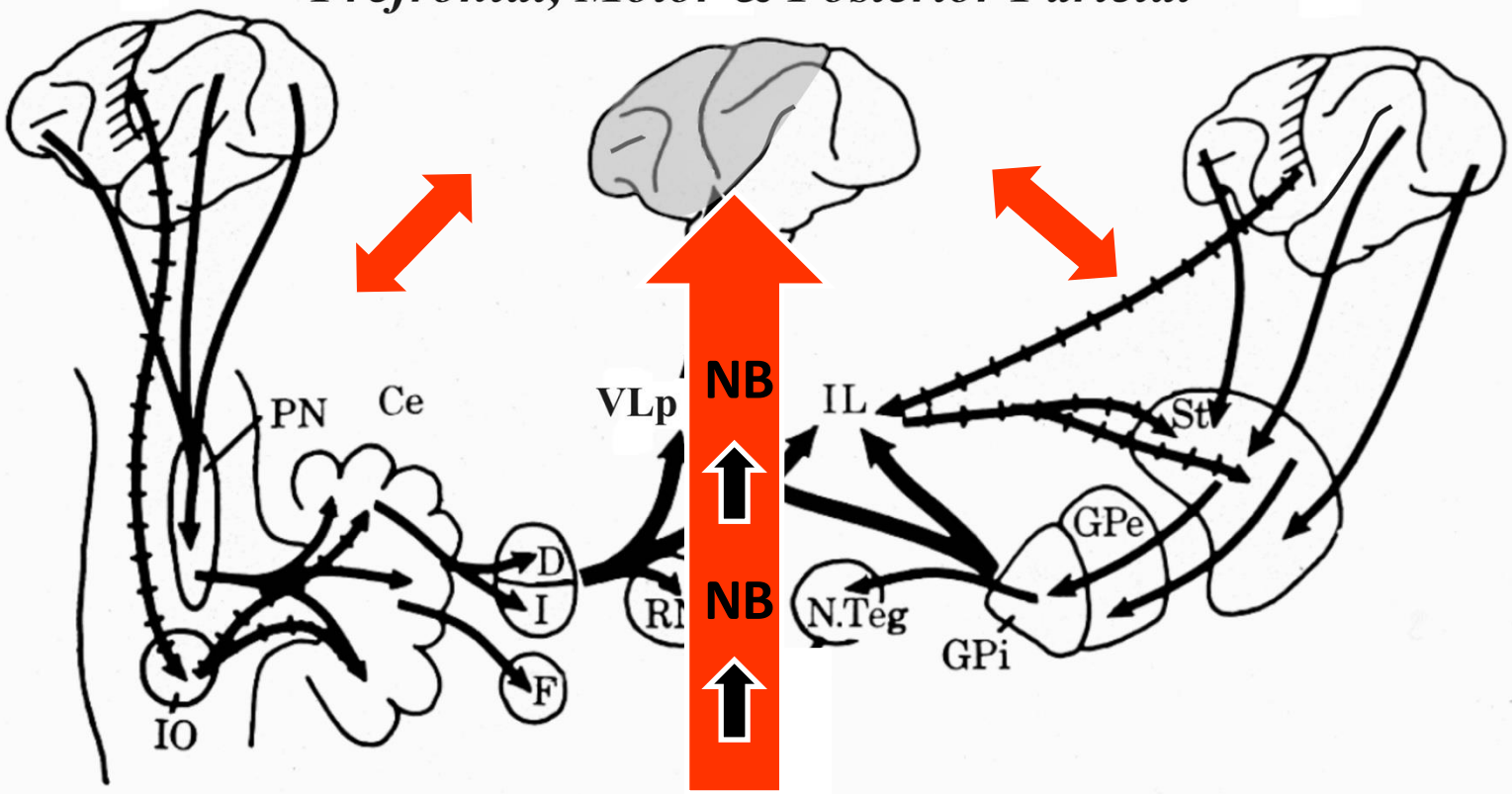




New View of Basal Ganglia & Cerebellar Circuits

Influence Movement, Cognition & Affect

"Prefrontal, Motor & Posterior Parietal"



Ventral Putamen is the Source of an 'Open Loop' Input

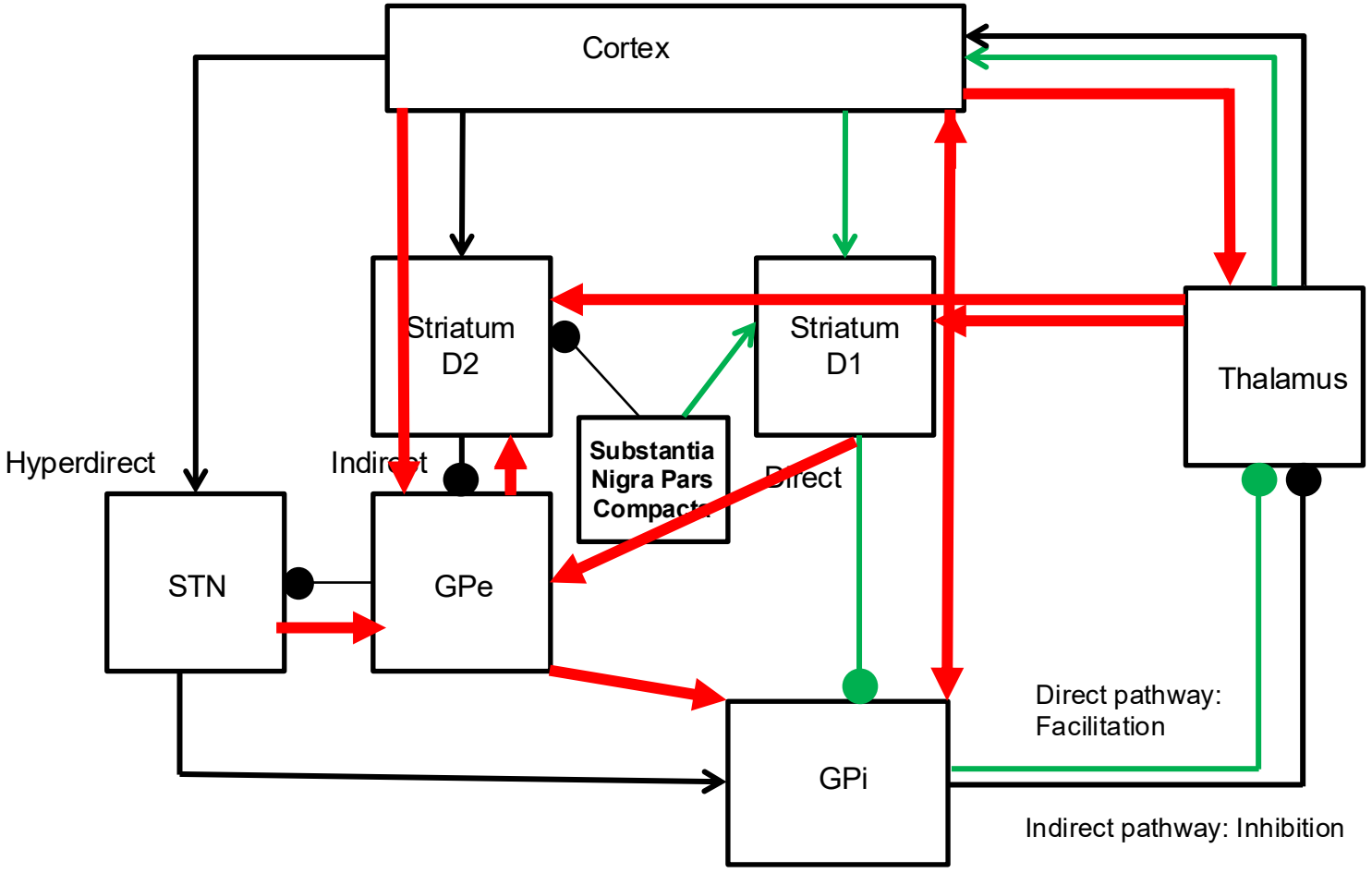


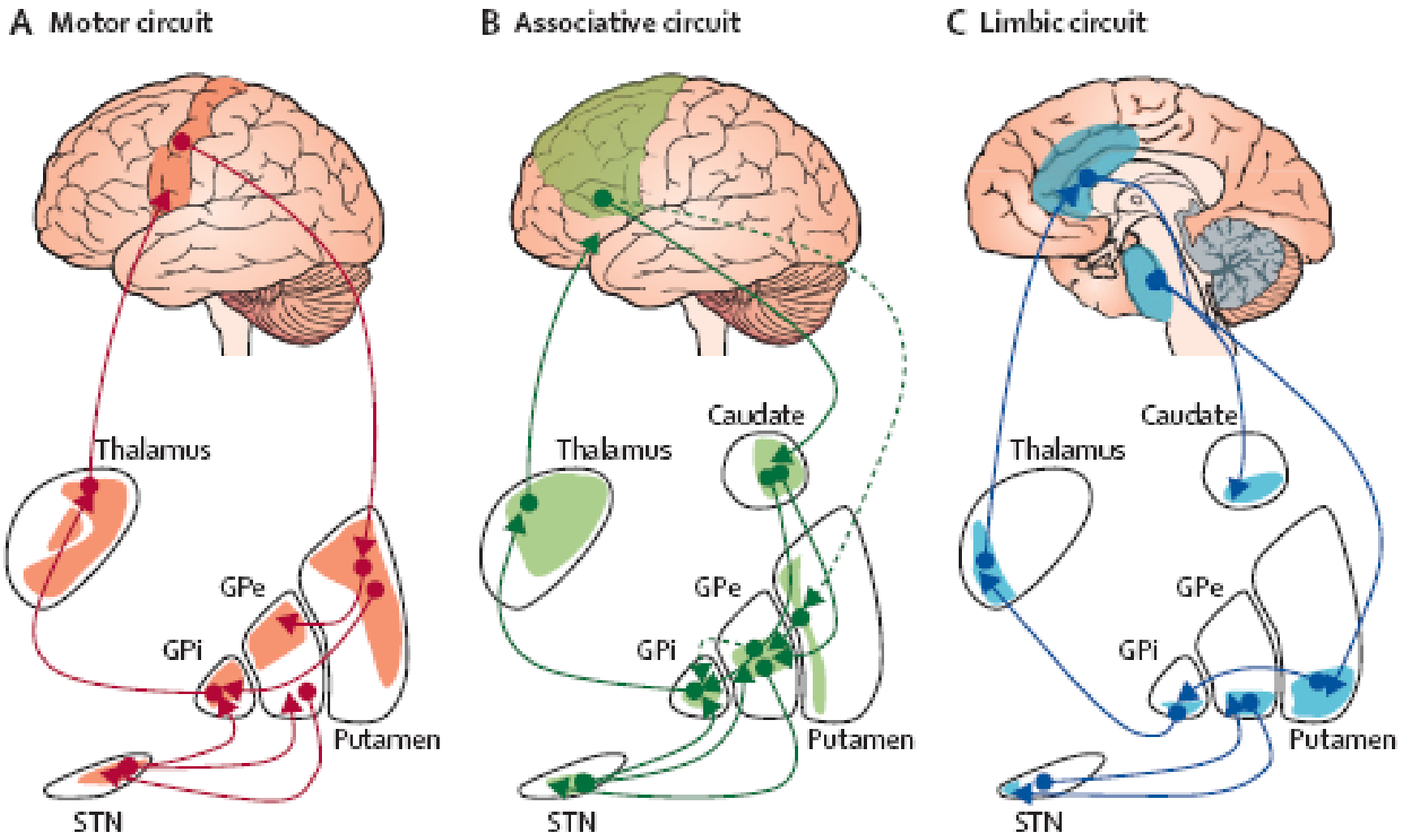
Feature	Kemp & Powell (1971)	DeLong / Alexander et al. (1980s–1990s)
Model Type	Convergent / Integrative	Parallel / Segregated Loops
Functional Organization	Diffuse	Functionally segregated (motor, limbic, etc.)
Cortex–Basal Ganglia Input	Overlapping cortical input into striatum	Topographically organized, specific loops
Methodology	Golgi, degeneration studies	Tracing studies, single-unit recordings
Main Contribution	Anatomical mapping of projections	Functional circuit model of BG–thalamocortical loops
Implication for Disorders	General motor dysfunction	Specific circuit dysfunction (e.g., motor vs. limbic in PD vs. OCD)

Basal ganglia pathways

Newer connections





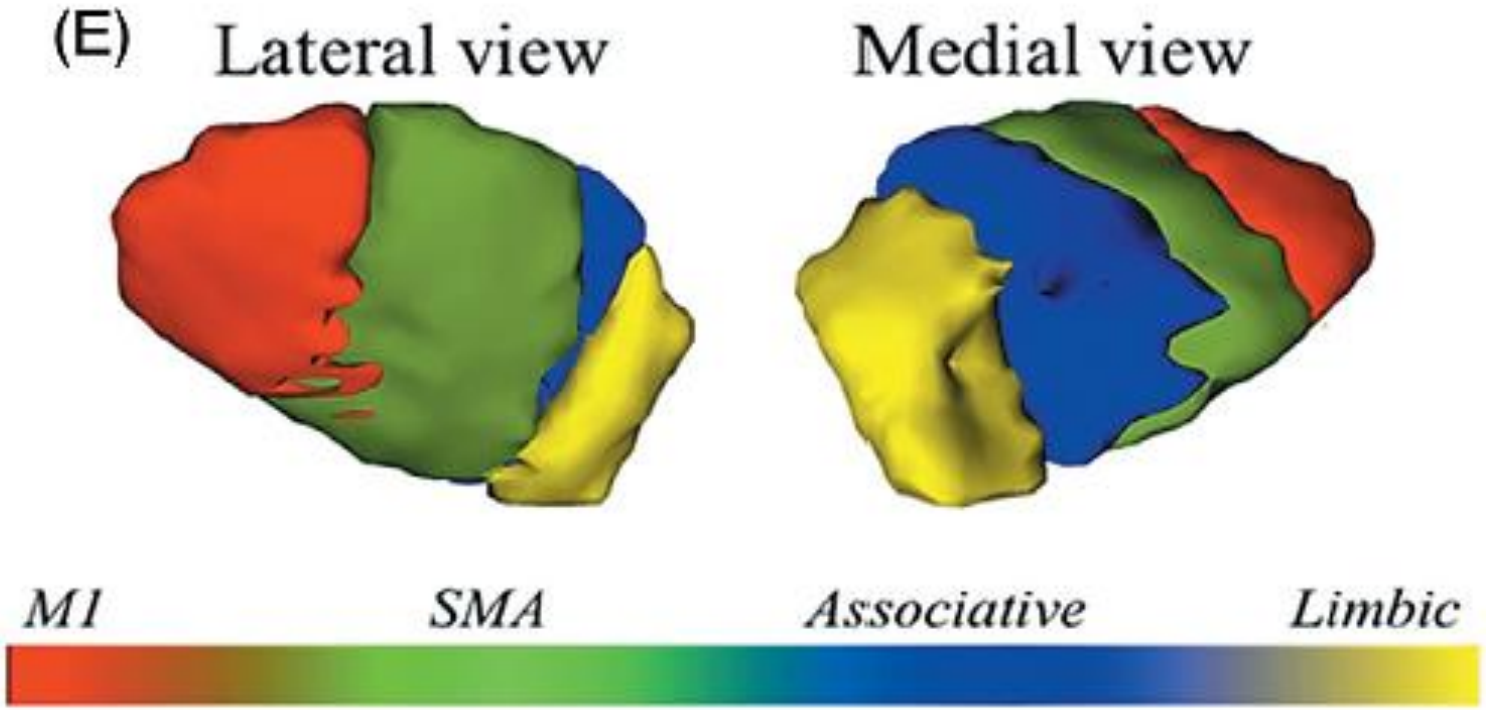


Rodriguez-Oroz et al., Lancet Neurology 2009;8:1128

Functional Topography of the Human Subthalamic Nucleus: Relevance for Subthalamotomy in Parkinson's Disease

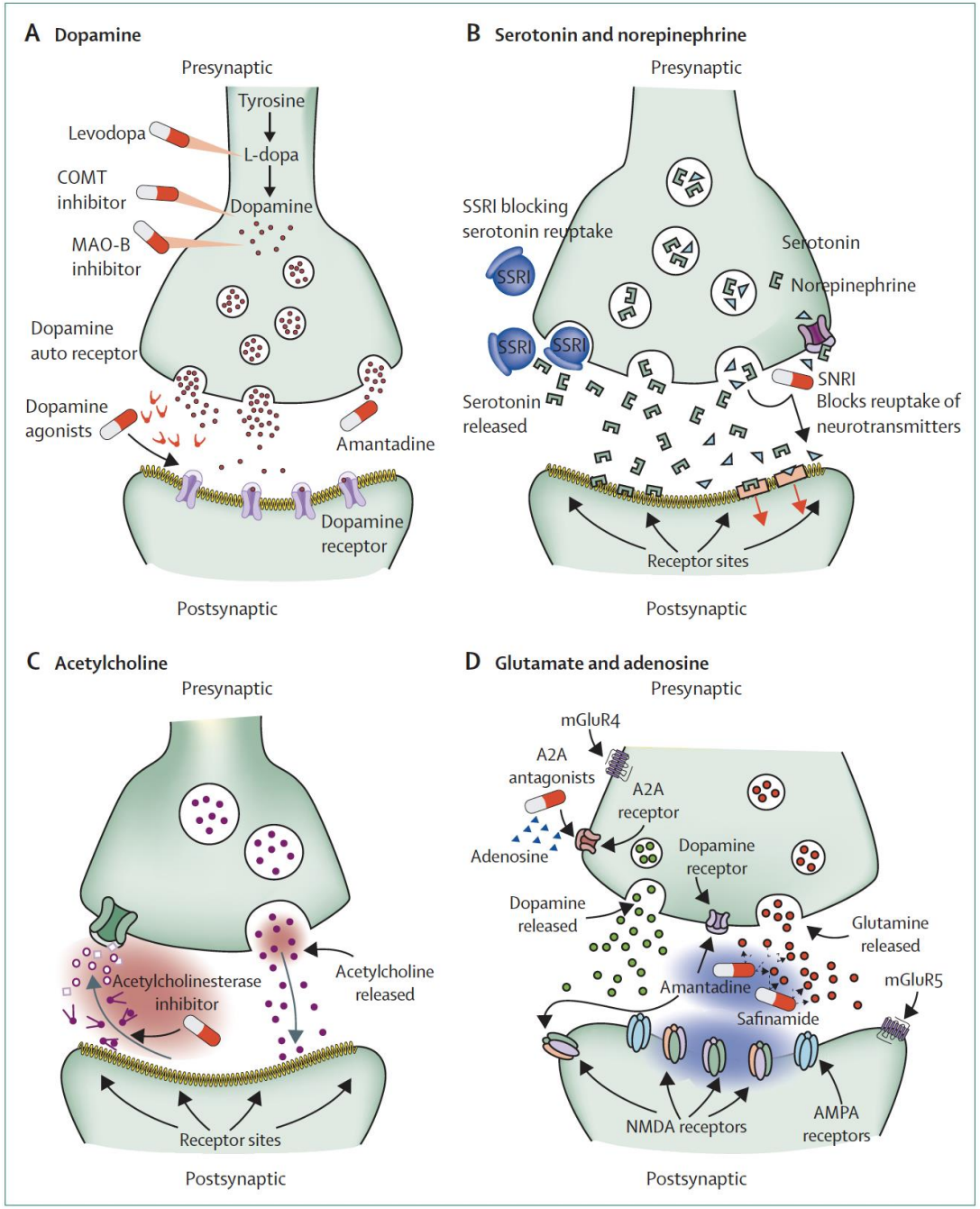
Rafael Rodriguez-Rojas, PhD,[1,2,3] Jose A. Pineda-Pardo, PhD,[1,2,3] Jorge Mañez-Miro, MD,[1] Alicia Sanchez-Turel, BSc,[1] Raul Martinez-Fernandez, MD, PhD,[1,2,3] Marta del Alamo, MD,[1] Mahlon DeLong, MD, PhD,[4] and Jose A. Obeso, MD, PhD[1,2,3*]

Movement Disorders, Vol. 37, No. 2, 2022 page 279

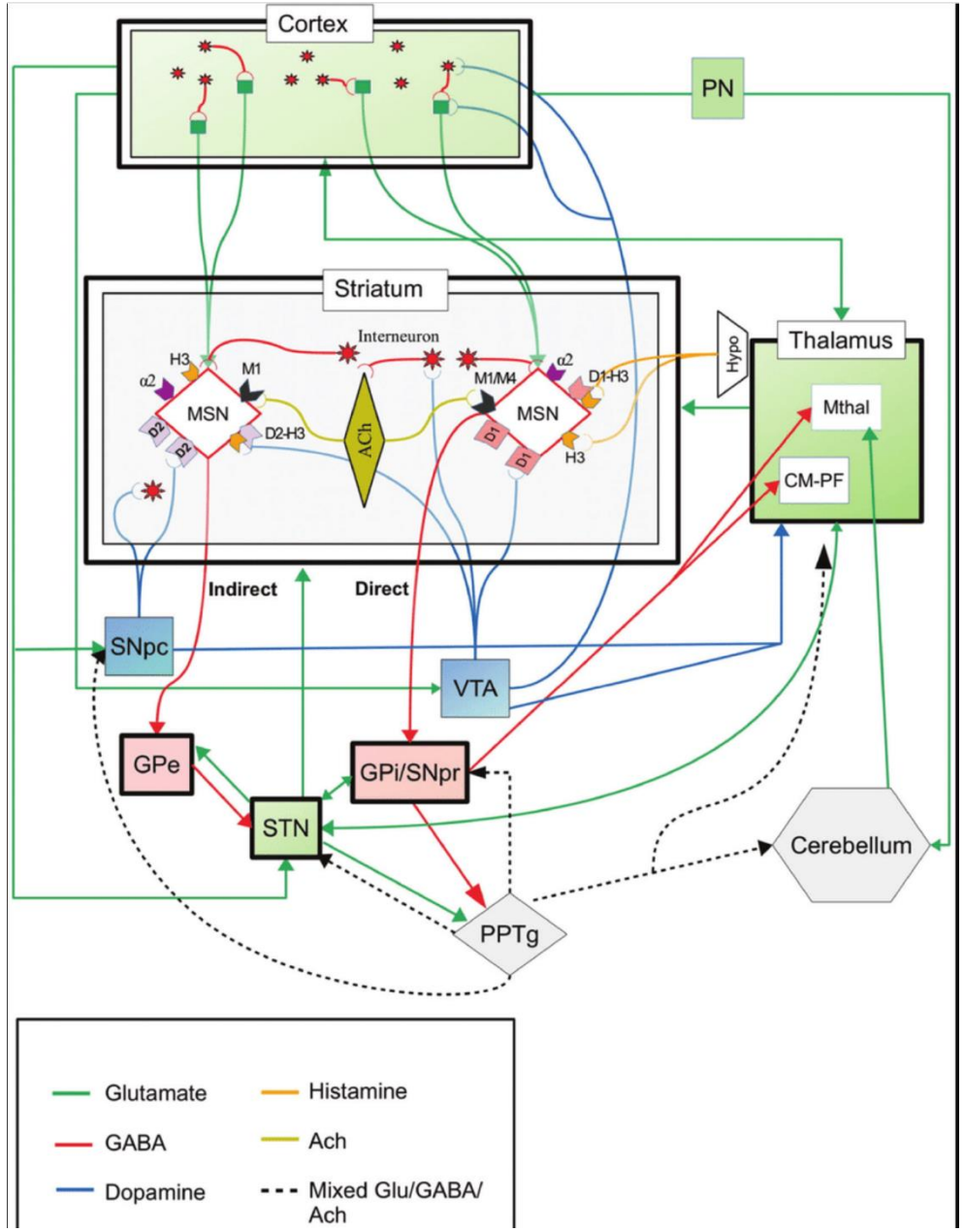


THE LANCET

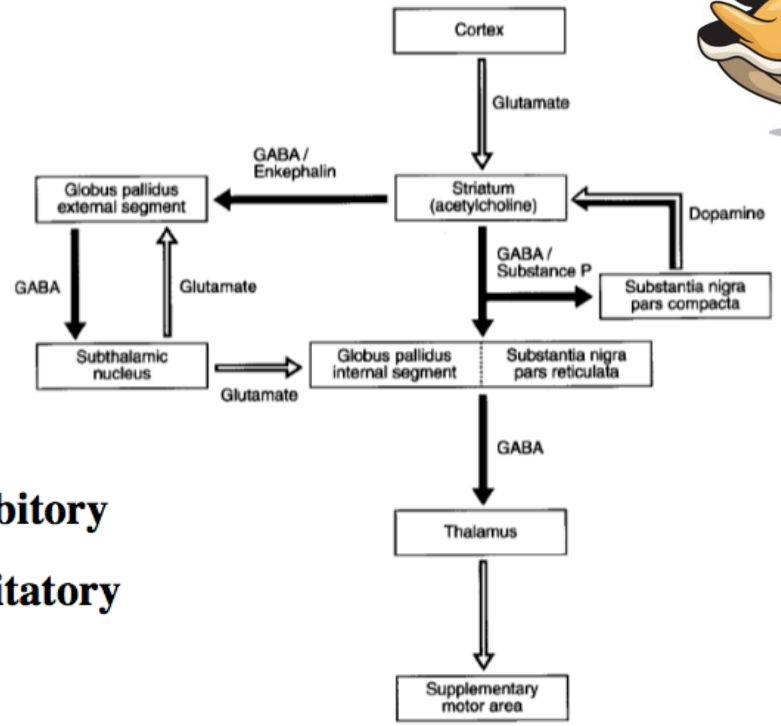
Neurotransmitters



Klein, Okun, Bloem, 2021







Black- Inhibitory

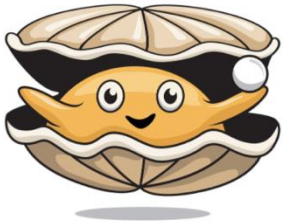
White- Excitatory

Figure 8: A schematic diagram of the different neurotransmitters used in the connections of the basal ganglia. Black arrows represent inhibitory connections; white arrow are excitatory. (Adapted from Côté and Crutcher, 1991.)

Singer, 2019, Tremor and Other Hyperkinetic Disorders

frontiers in Neural Circuits

Breaking Down a Rhythm: Dissecting the Mechanisms Underlying Task-Related Neural Oscillations



Inés Ibarra-Lecue[1,2], Saskia Haegens[1,2,3] and Alexander Z. Harris[1,2]**

Figure 1

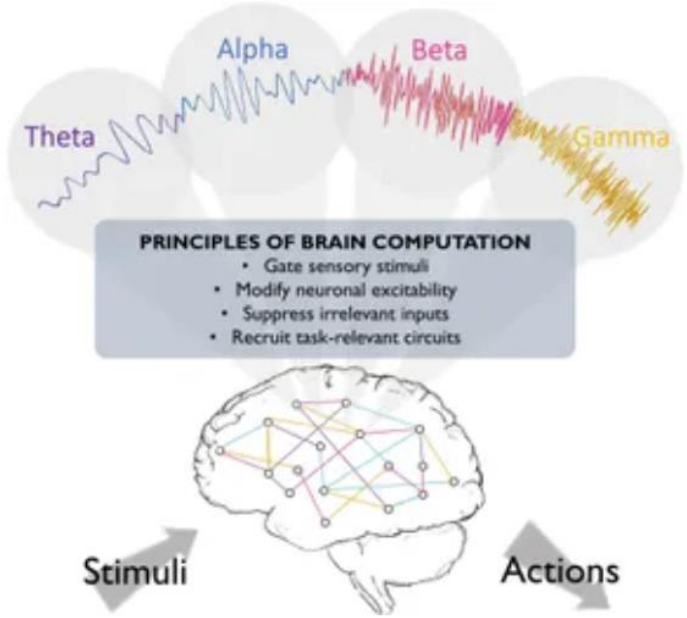
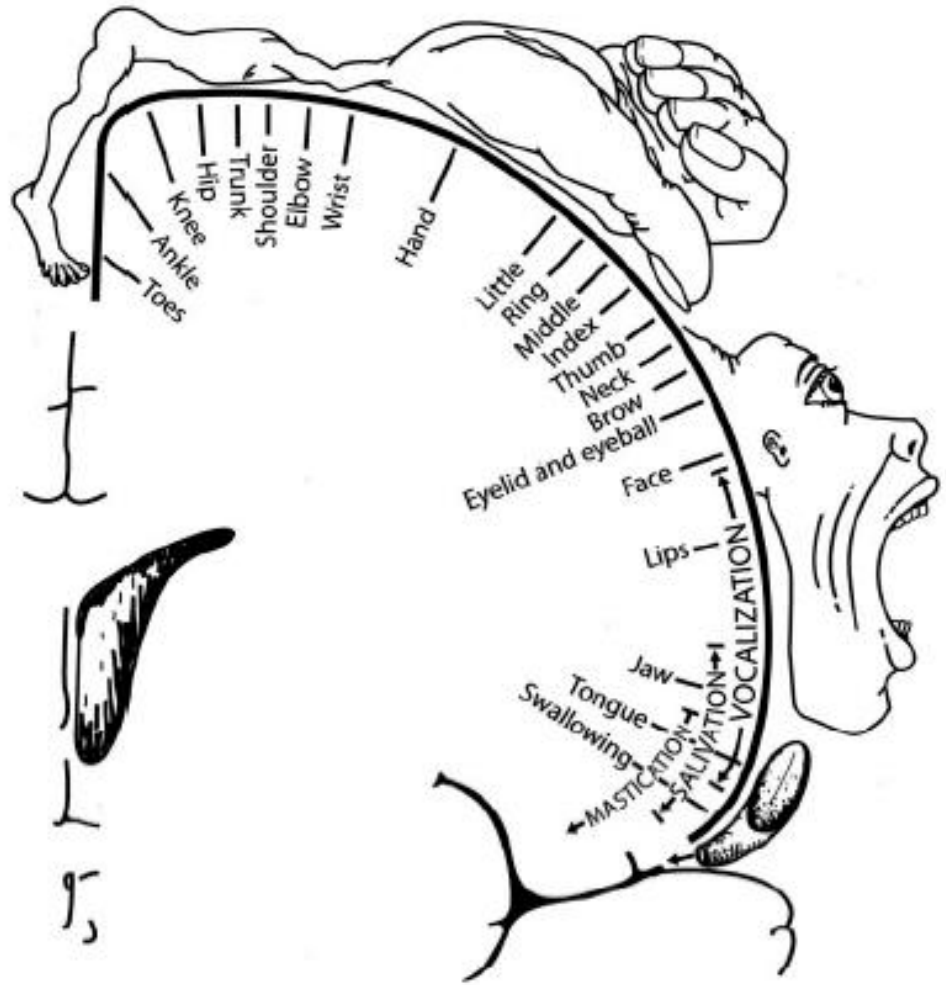


Figure 1. Fundamental roles that oscillations may play in brain function. Brain oscillations have been implicated in crucial aspects of neural circuit activity, such as stimulus perception. They have also been suggested to play a role in top-down processing, such that different oscillations might emerge to engage task-relevant circuits and silence irrelevant information, thereby optimizing brain processing and behavioral performance.

2022

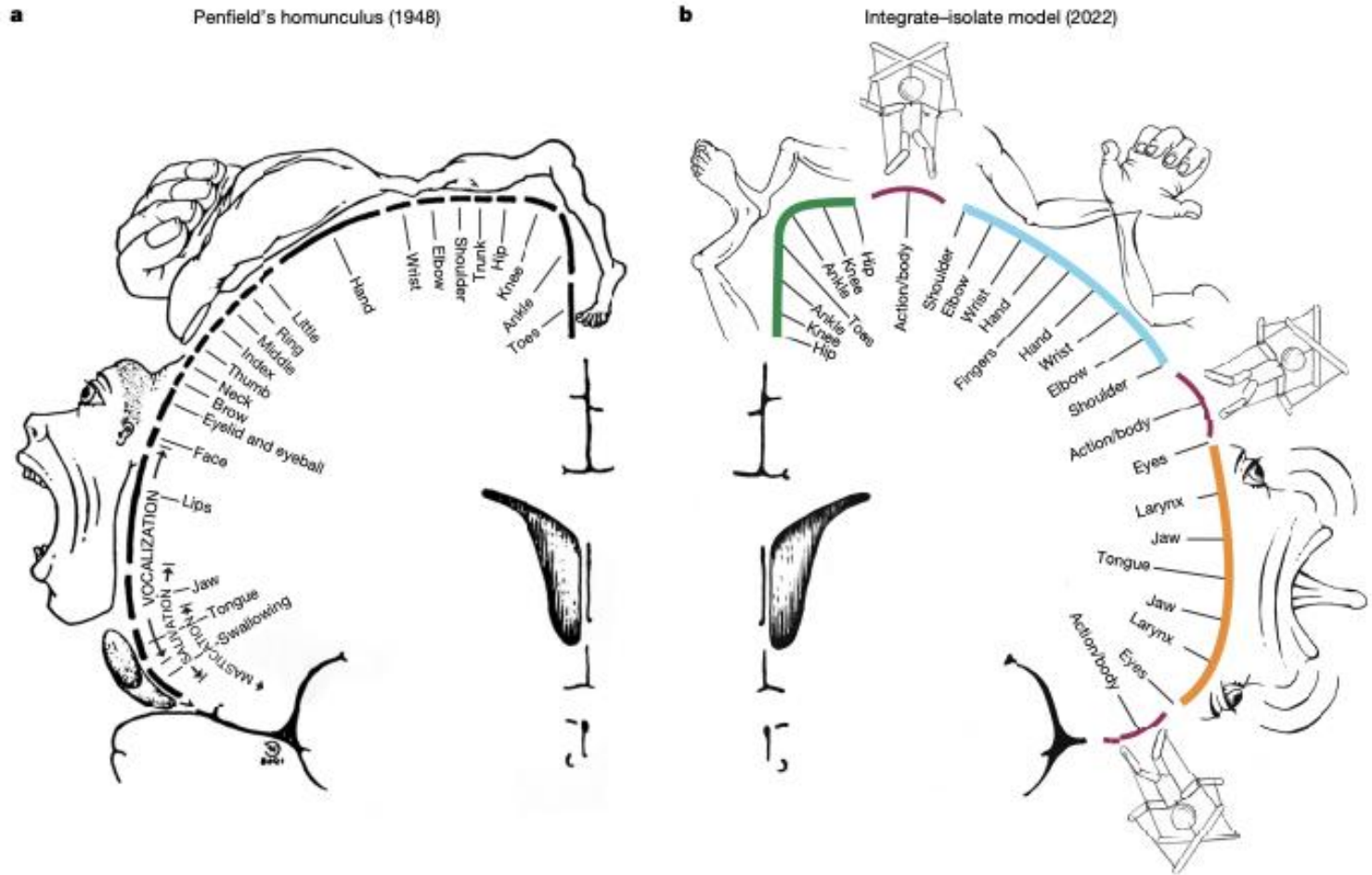
PENFIELD and RASMUSSEN, 1950



nature

Article

A somato-cognitive action network alternates with effector regions in motor cortex



A somato-cognitive action network alternates with effector regions in motor cortex

Nature

https://doi.org/10.1038/s41586-023-05964-2

Received: 2 November 2022

Accepted: 16 March 2023

Published online: 19 April 2023

Open access

Check for updates

Evan M. Gordon[1]✉, Roselyne J. Chauvin[2], Andrew N. Van[2,3], Aishwarya Rajesh[1], Ashley Nielsen[2], Dillan J. Newbold[2,4], Charles J. Lynch[5], Nicole A. Seider[2,6], Samuel R. Krimmel[2], Kristen M. Scheidter[2], Julia Monk[2], Ryland L. Miller[2,6], Athanasia Metoki[2], David F. Montez[2], Annie Zheng[2], Immanuel Elbau[5], Thomas Madison[7], Tomoyuki Nishino[6], Michael J. Myers[6], Sydney Kaplan[2], Carolina Badke D'Andrea[1,6,8], Damion V. Demeter[8], Matthew Feigelis[8], Julian S. B. Ramirez[9], Ting Xu[9], Deanna M. Barch[1,6,10], Christopher D. Smyser[1,2,11], Cynthia E. Rogers[5,11], Jan Zimmermann[12], Kelly N. Botteron[6], John R. Pruett[6], Jon T. Willie[2,5,13], Peter Brunner[3,13], Joshua S. Shimony[1], Benjamin P. Kay[2], Scott Marek[1], Scott A. Norris[1,2], Caterina Gratton[14], Chad M. Sylvester[6], Jonathan D. Power[5], Conor Liston[5], Deanna J. Greene[8], Jarod L. Roland[13], Steven E. Petersen[1,2,3,10,15], Marcus E. Raichle[1,2,3,10,15], Timothy O. Laumann[6], Damien A. Fair[7,16,17] & Nico U. F. Dosenbach[1,2,3,10,11,18]✉

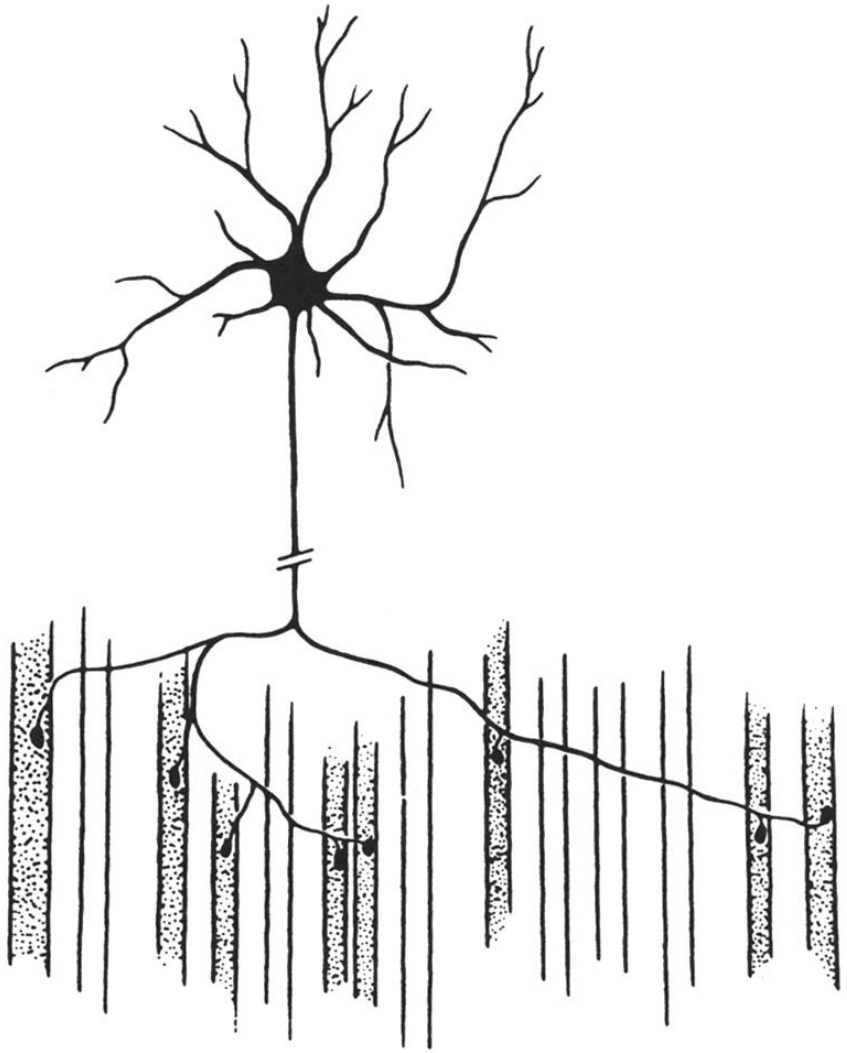
The SCAN has widespread bilateral connections for integrative function, particularly the cingulo-opercular network (CON) even including internal organs

Feature	Somatocognitive Action Network (SAN) – *Gordon et al.*	Classic Basal Ganglia Model – *DeLong et al.*
Conceptual Basis	Data-driven brain network derived from high-resolution resting-state fMRI	Anatomical and electrophysiological recordings in non-human primates
Scope	Broad **network-level** integration across cortex and subcortex linking body and thought	**Circuit-level** focus within cortico-basal ganglia-thalamic loops
Functional Role	Integrates **movement, interoception, and cognition** — a proposed hybrid of motor and default mode networks	Separates **motor**, **associative**, and **limbic loops** into parallel functional circuits
Neuroanatomy	Includes **posterior cingulate**, **precuneus**, **supplementary motor area**, **basal ganglia**, **anterior insula**, and **midline thalamus**	Includes **cortex**, **striatum**, **GPi/GPe**, **STN**, **SNr**, and **thalamus**
Neurotransmitters	Implicit in network activity; less emphasis on specific transmitters	Emphasizes **GABA**, **glutamate**, **dopamine** in direct/indirect pathways
Innovative Contribution	Proposes a **novel, integrated system** underlying embodied cognition and movement	Defined **direct and indirect pathways** and helped map PD pathophysiology

First principles

- Movement arises from contraction of muscle
- Muscles are under the control of the alpha-motoneurons

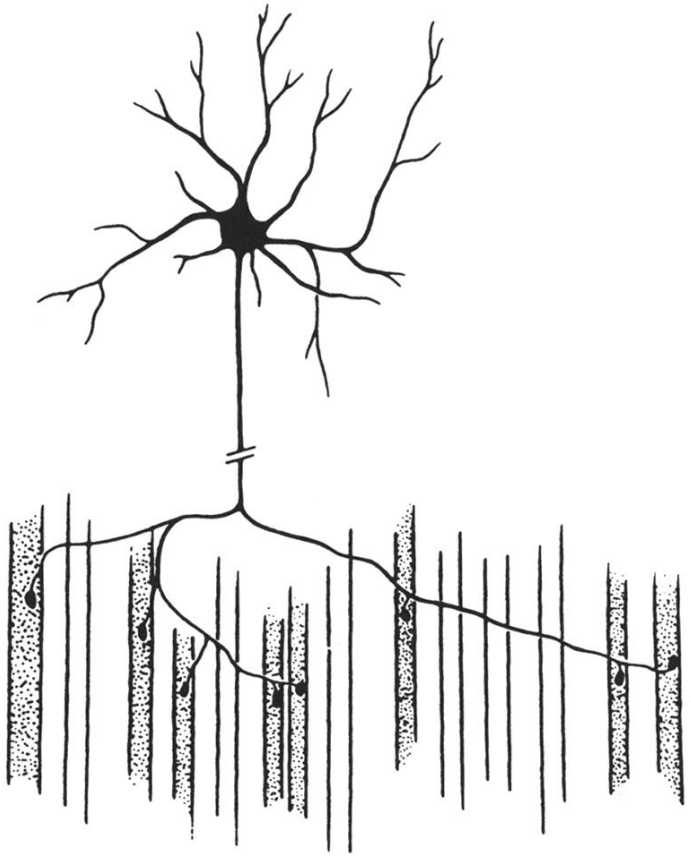
The Motor Unit



Brown 1984

Involuntary movements arising from neuromuscular conditions

- Muscle
  - Rippling Muscle Disease
- Alpha motor neuron axon
  - Hemifacial spasm
  - Peripheral myoclonus
  - Fasciculation
  - Myokymia
  - Neuromyotonia
  - Schwartz-Jampel syndrome
- Anterior horn cell
  - Fasciculation
  - Spinal Alpha Rigidity

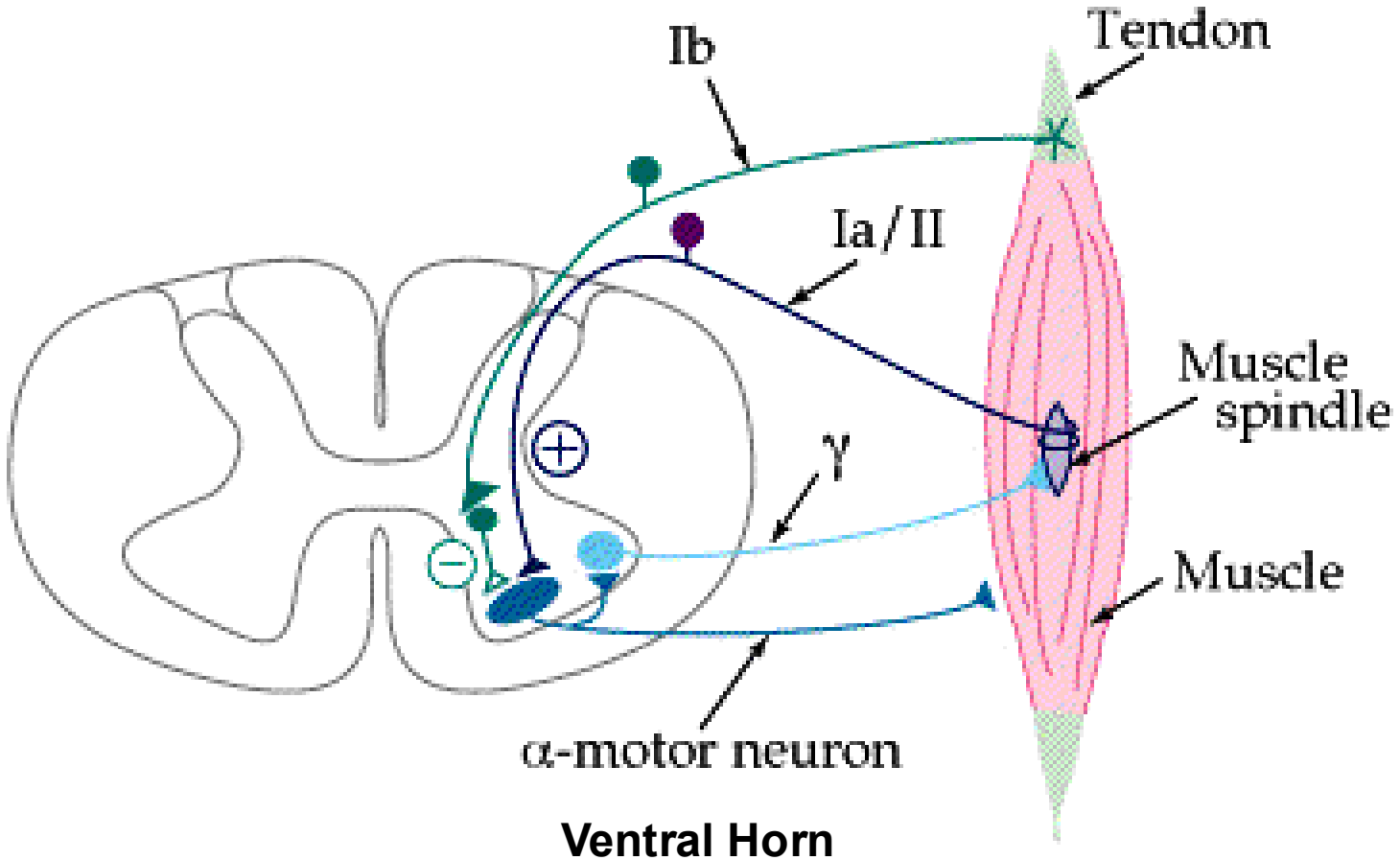


What are the segmental influences on the alpha motoneuron?



Structure	Function	Role in Movement
Spinal Segment	A segment of the spinal cord that includes a pair of spinal nerves	Receives sensory input and generates motor output; integrates local reflexes
Alpha Motor Neuron (α-MN)	Large lower motor neuron in the ventral horn of spinal cord	Innervates **extrafusal muscle fibers**, causing muscle contraction
Ia Afferent Fiber	Sensory fiber from **muscle spindle primary endings** (sensitive to stretch)	**Monosynaptically excites alpha motor neurons** during stretch reflex (e.g., patellar reflex)
Ib Afferent Fiber	Sensory fiber from **Golgi tendon organs** (sensitive to muscle tension)	**Inhibits alpha motor neurons** via interneurons to prevent excessive force (autogenic inhibition)

Spinal Segment



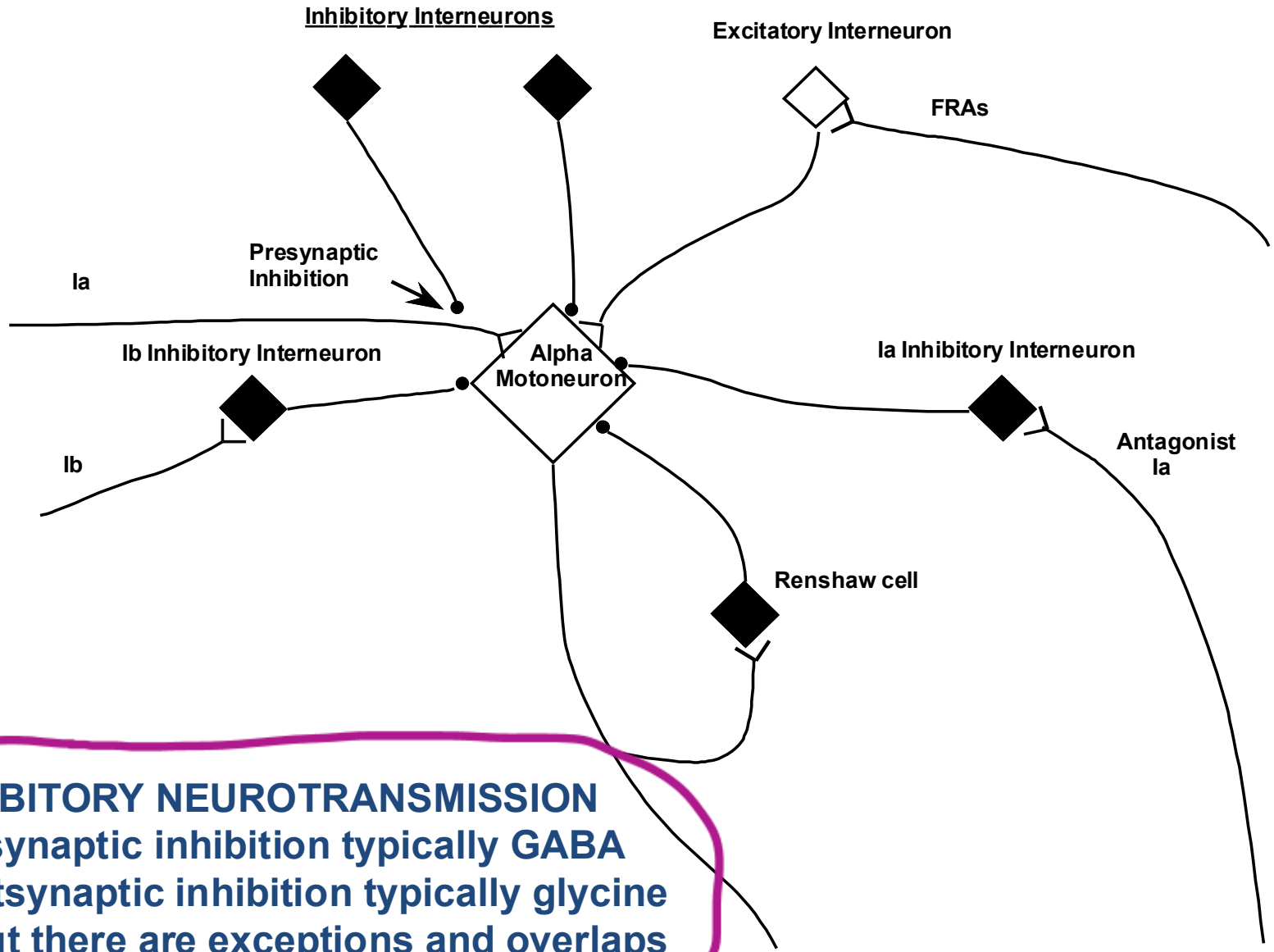
Ventral Horn

Ib Golgi Tendon

Ia Muscle Spindle

Molavi, Neuroscience Tutorial, Washington University

Segmental inputs to the alpha-motoneuron





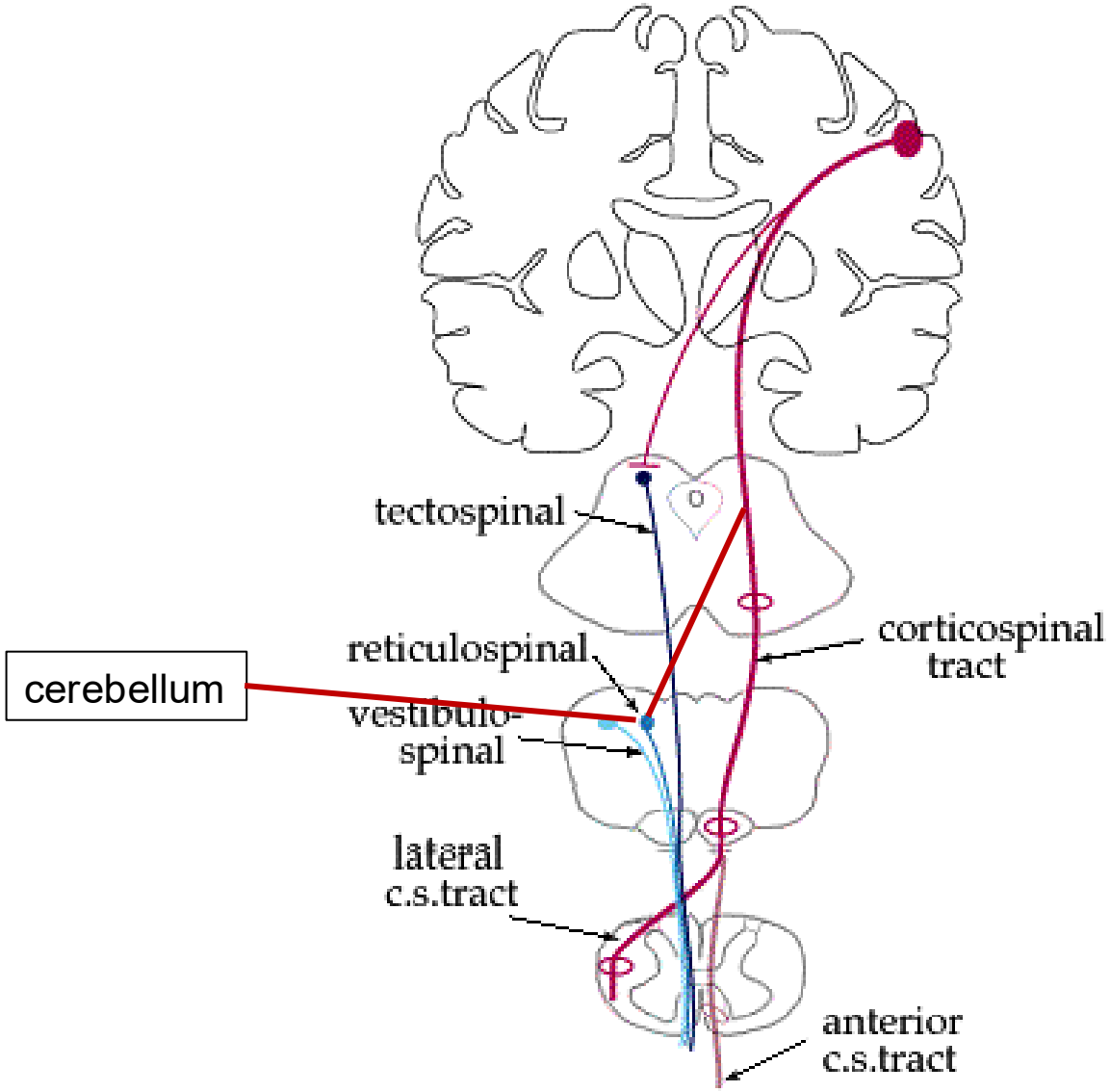
INHIBITORY NEUROTRANSMISSION
Presynaptic inhibition typically GABA
Postsynaptic inhibition typically glycine
…but there are exceptions and overlaps

Movement disorders arising from segmental dysfunction

Disorder	Mechanism
Tetanus	Tetanus toxin blocks the release of GABA and glycine at spinal synapses
Stiff person syndrome	Mainly a disorder of GABA and pre-synaptic inhibition in the spinal cord
Hereditary hyperekplexia	A disorder of glycine receptors with deficient inhibition at multiple synapses including that from the Ia inhibitory interneuron

What are the suprasegmental influences on the alpha motoneuron?

Descending Tracts



Molavi, Neuroscience Tutorial,
Washington University

Injury to the corticospinal tract

- “Upper motor neuron syndrome”
- Negative features
  - Weakness (in a “pyramidal” distribution)
  - Fatigue
  - Loss of coordination
  - Decrease of some cutaneous reflexes

Spasticity

- Clinical features
  - Increased resistance to stretch is velocity sensitive
  - Spastic catch
  - Clasped-knife phenomenon
  - Increased tendon jerks, clonus, increased flexor reflexes, spontaneous flexor spasms, and abnormal postures as well as spastic dystonia.

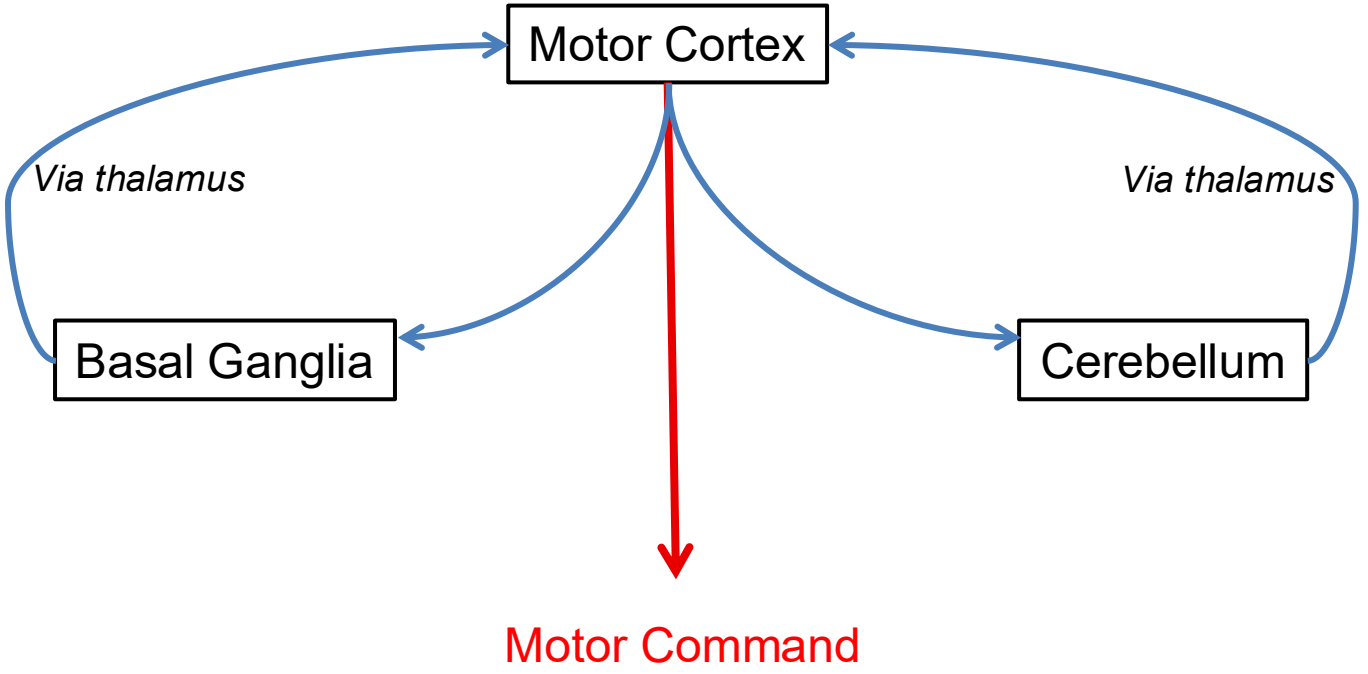
Spasticity: What is the pathophysiology



- Not the “Pyramidal tract”
- Lesions of the pyramidal tract (CST) or M1 do not cause spasticity
- Etiology still unclear, but likely involves a cortico-reticulo-spinal tract
  - Damage to premotor cortex could be etiologic
  - Dysfunction of dorsal reticulospinal tract thought likely to be relevant

What are the subcortical influences on the primary motor cortex?

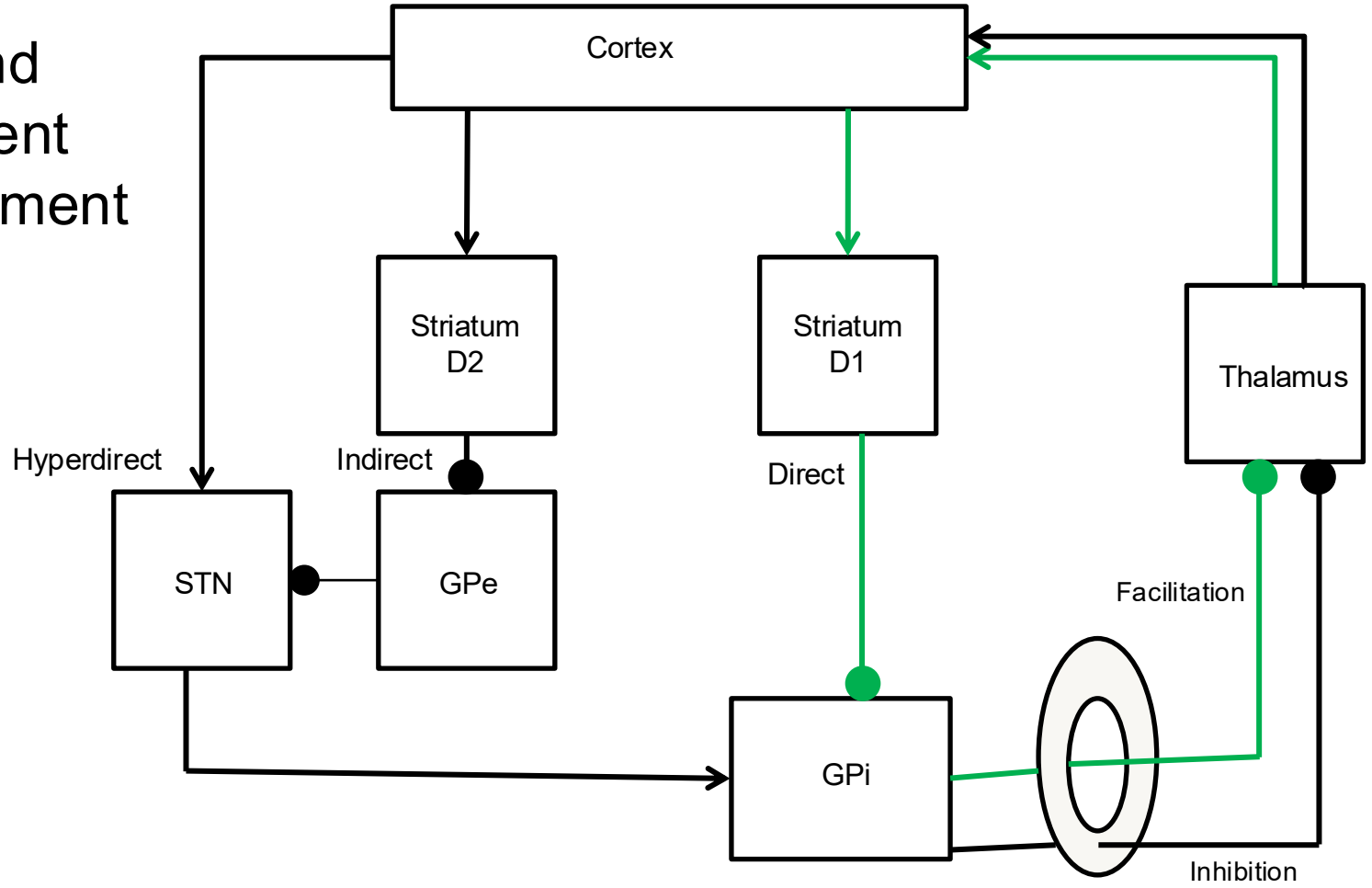
Subcortical Influences



Basal ganglia pathways

GPi Output

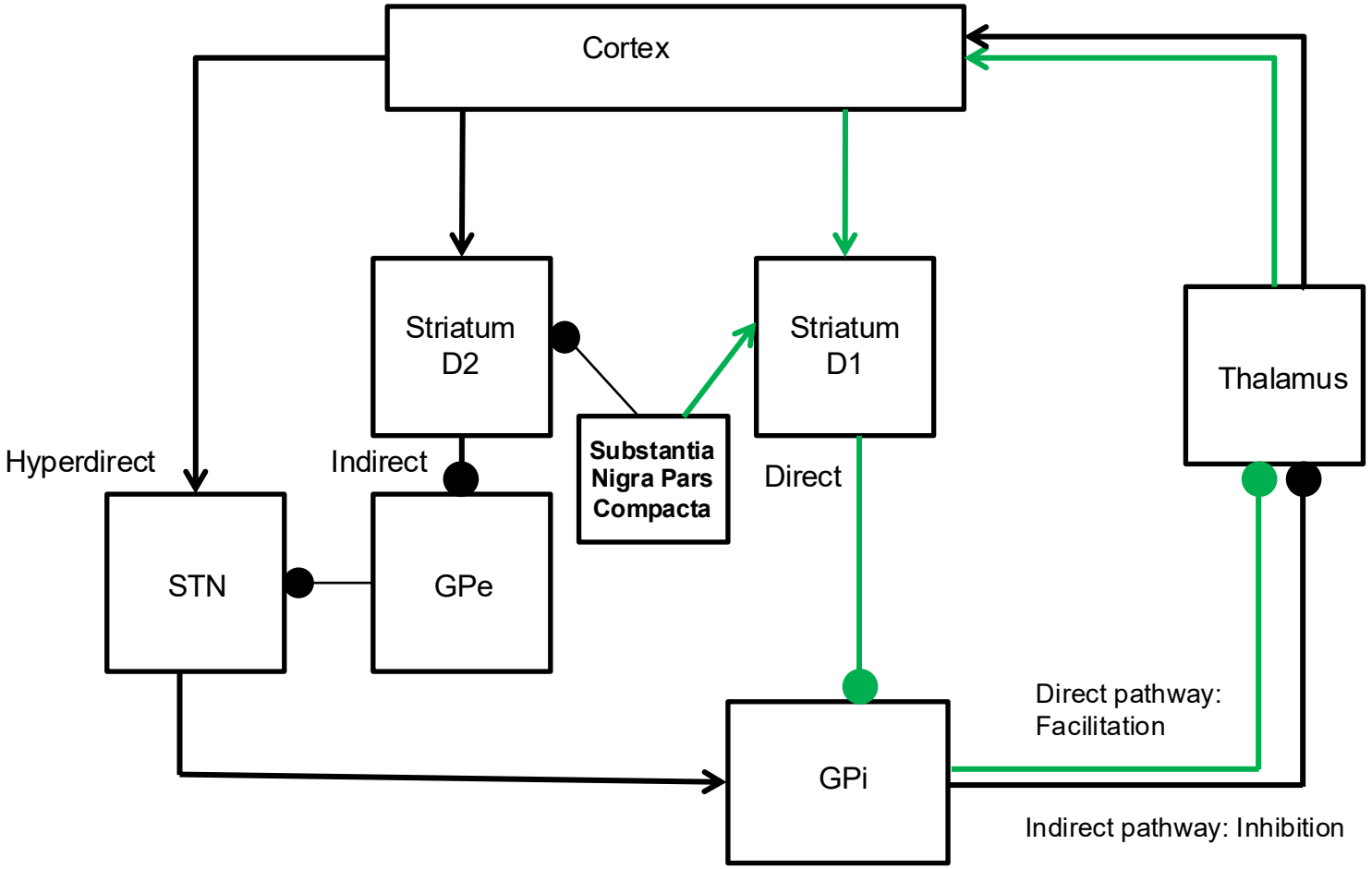
Center surround
Select movement
Sharpen movement



Facilitation occurs with reduction of GPi output
Inhibition occurs with increase in GPi output

A center-surround organization of GPi output can aid the process of selecting what movement to make and to sharpen the motor command for selected movements

Basal ganglia pathways



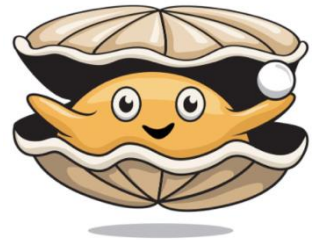
SNc facilitates the Direct Pathway

SNc inhibits the Indirect Pathway

Basal ganglia disorders

- Hypokinetic, too little movement
  - Parkinson disease
- Hyperkinetic, too much movement
  - Dystonia
  - Choreas, dyskinesias

Bradykinesia in Parkinson Disease



- Insufficient energy for movement
  - Both for movement initiation and execution
  - Greater difficulty with more complex movement
  - Sequence effect
  - Fatigue
- Insufficient scaling
- Difficulty with internal versus external triggering
- Loss of automaticity

Evolving concepts on bradykinesia FREE

Matteo Bologna, Giulia Paparella, Alfonso Fasano, Mark Hallett, Alfredo Berardelli

Brain, Volume 143, Issue 3, March 2020, Pages 727–750, https://doi.org/10.1093/brain/awz344

Redefining Bradykinesia

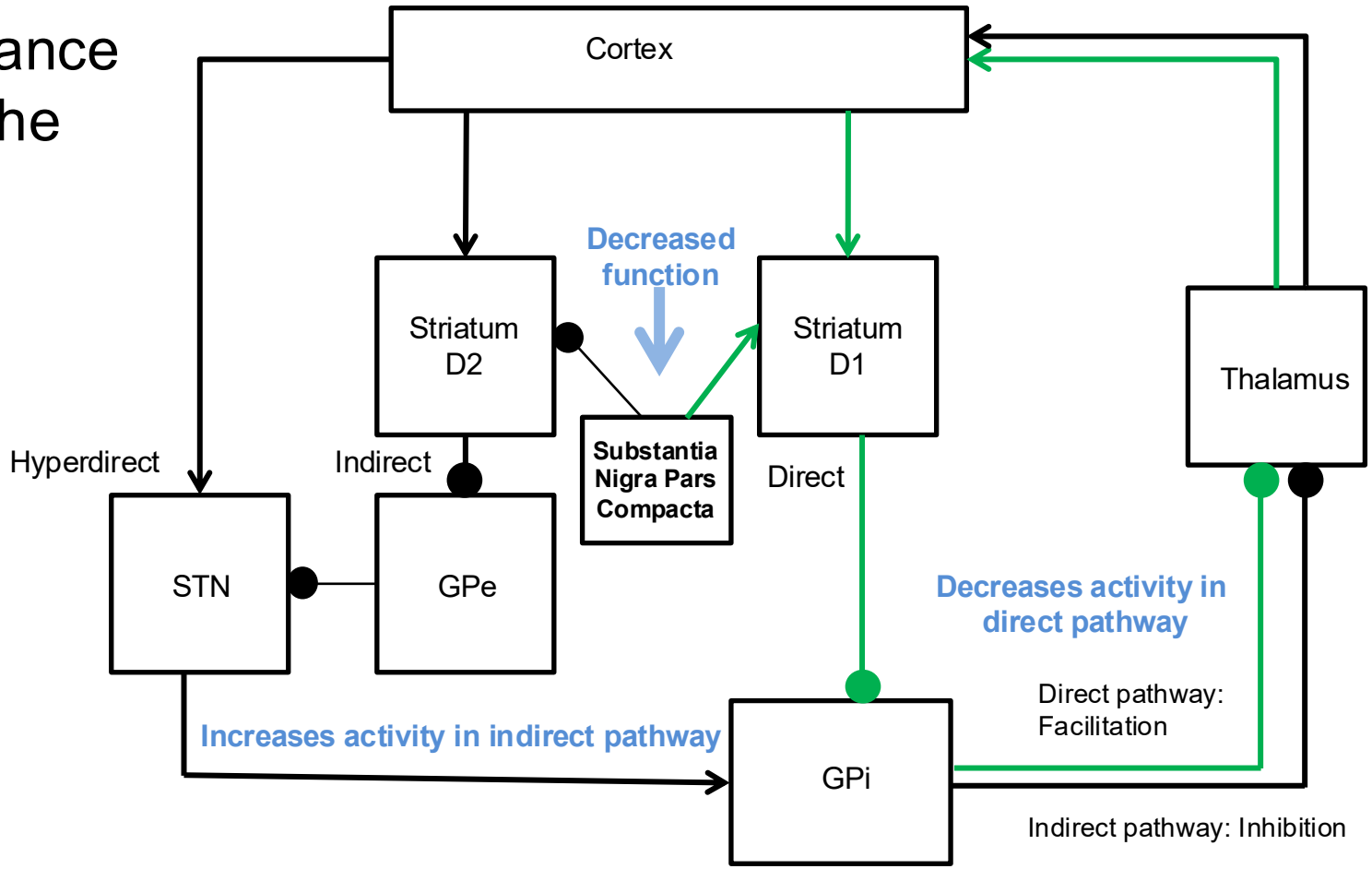
Movement Disorders, Vol. 38, No. 4, 2023

Matteo Bologna, MD, PhD,[1,2*] Alberto J. Espay, MD, MSc,[3] Alfonso Fasano, MD, PhD,[4,5,6] Giulia Paparella, MD, PhD,[2] Mark Hallett, MD,[7] and Alfredo Berardelli, MD[1,2]

Changes of function in PD

Rate Model

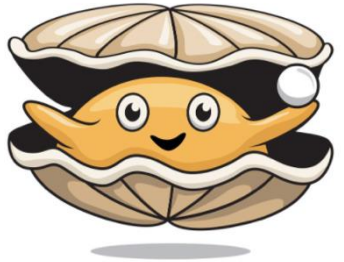
Missed ‘importance of patterns’ in the physiology



Basal ganglia pathways

(This is the “rate model” for pathophysiology)

Fundamental problem in Parkinson's

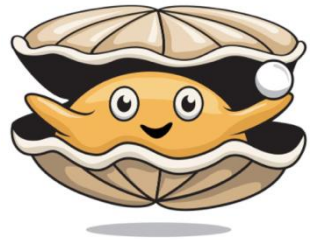


- Reduction in facilitation of movement in both the direct and indirect pathways.
- Bradykinesia is the main result of the reduction.
- Bradykinesia correlates well with the dopamine deficiency and is responsive to dopamine replacement

What about dyskinesia?

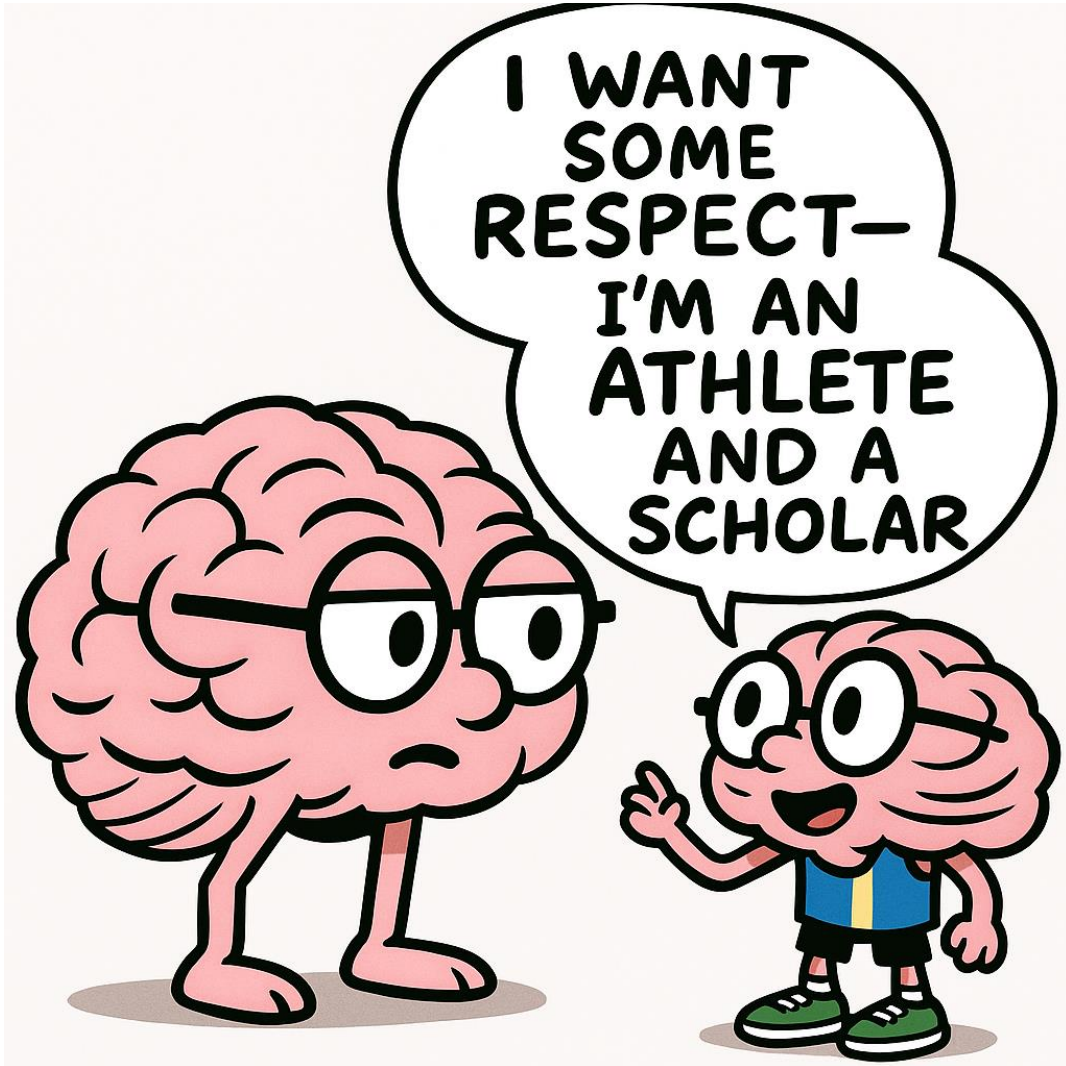
Albin et al. (1989)	Loss of dopamine → indirect pathway overactivity → motor imbalance
DeLong (1990)	Dopamine meds overstimulate direct pathway → involuntary movements
Jenner & Marsden (1993)	Pulses of L-DOPA cause abnormal brain plasticity
Bezard et al. (2001)	L-DOPA rewires striatal firing → dyskinetic circuits
Cenci & Lundblad (2006)	D1 neurons go haywire from plasticity and gene changes
Moran et al. (2011)	Brain rhythms (beta/gamma) go out of sync
Bastide et al. (2015)	Dyskinesia = plasticity + inflammation + glutamate overload

The Basal Ganglia

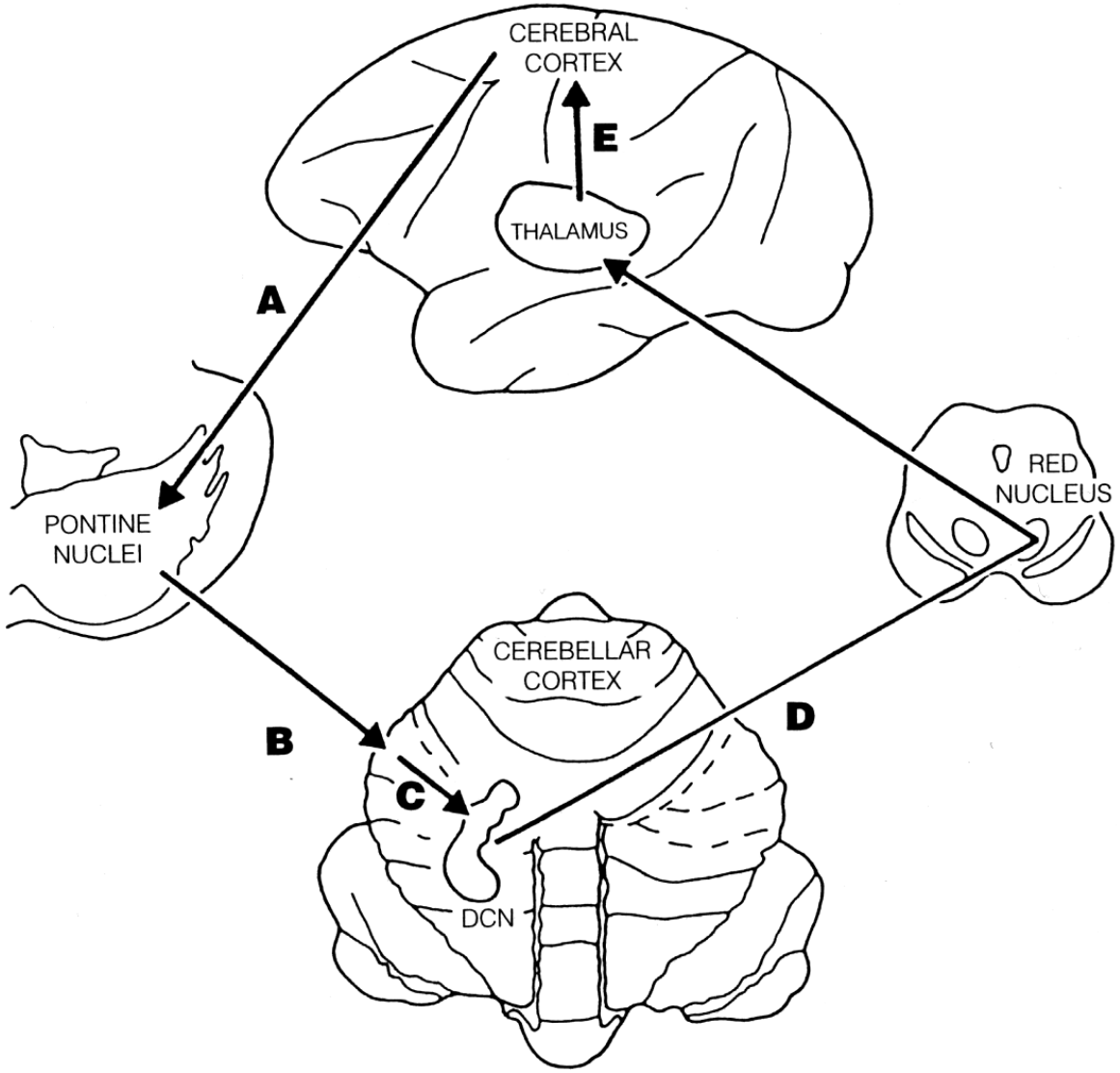


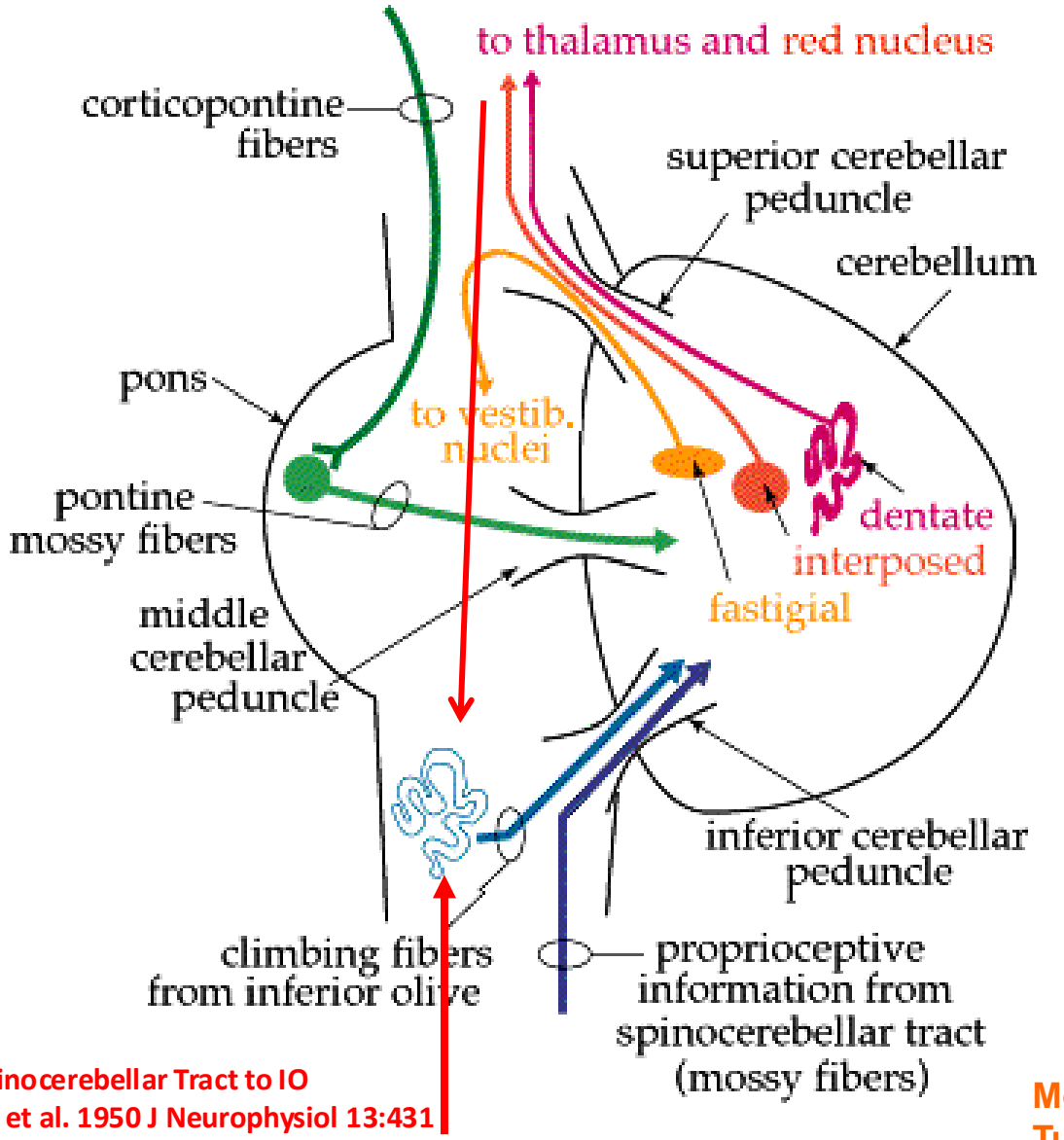
- A fundamental action is to aid in the process of movement and muscle selection and inhibition
- Disorders will lead to reduced movement or overflow and involuntary movement

THE CEREBELLUM



Cerebellar Loop

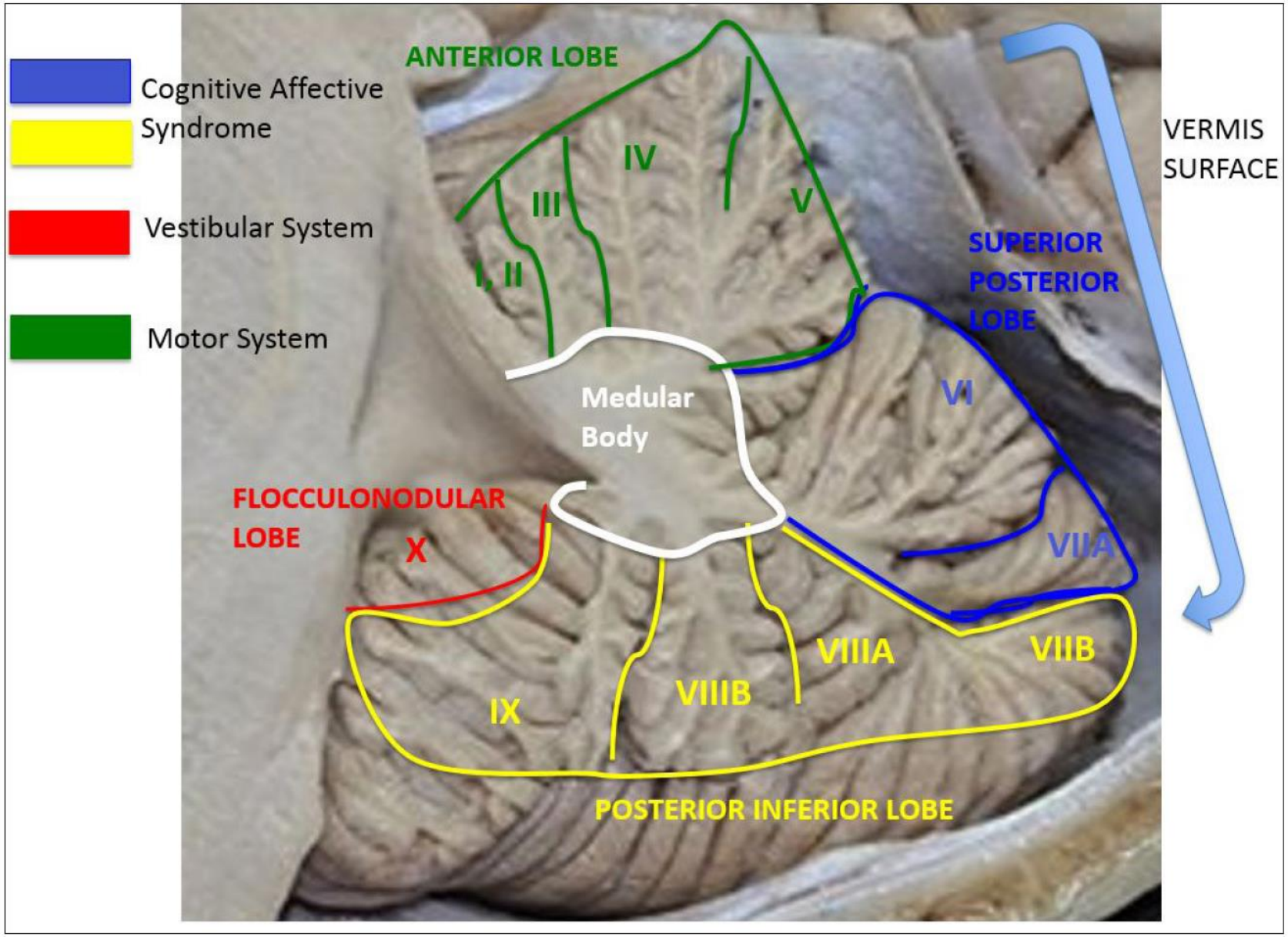




(Dorsal) Spinocerebellar Tract to IO
Ref: Brodal et al. 1950 J Neurophysiol 13:431

Modified from Molavi, Neuroscience Tutorial, Washington University

AND http://humanphysiology.academy/Neurosciences

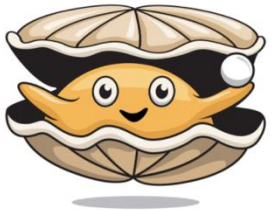


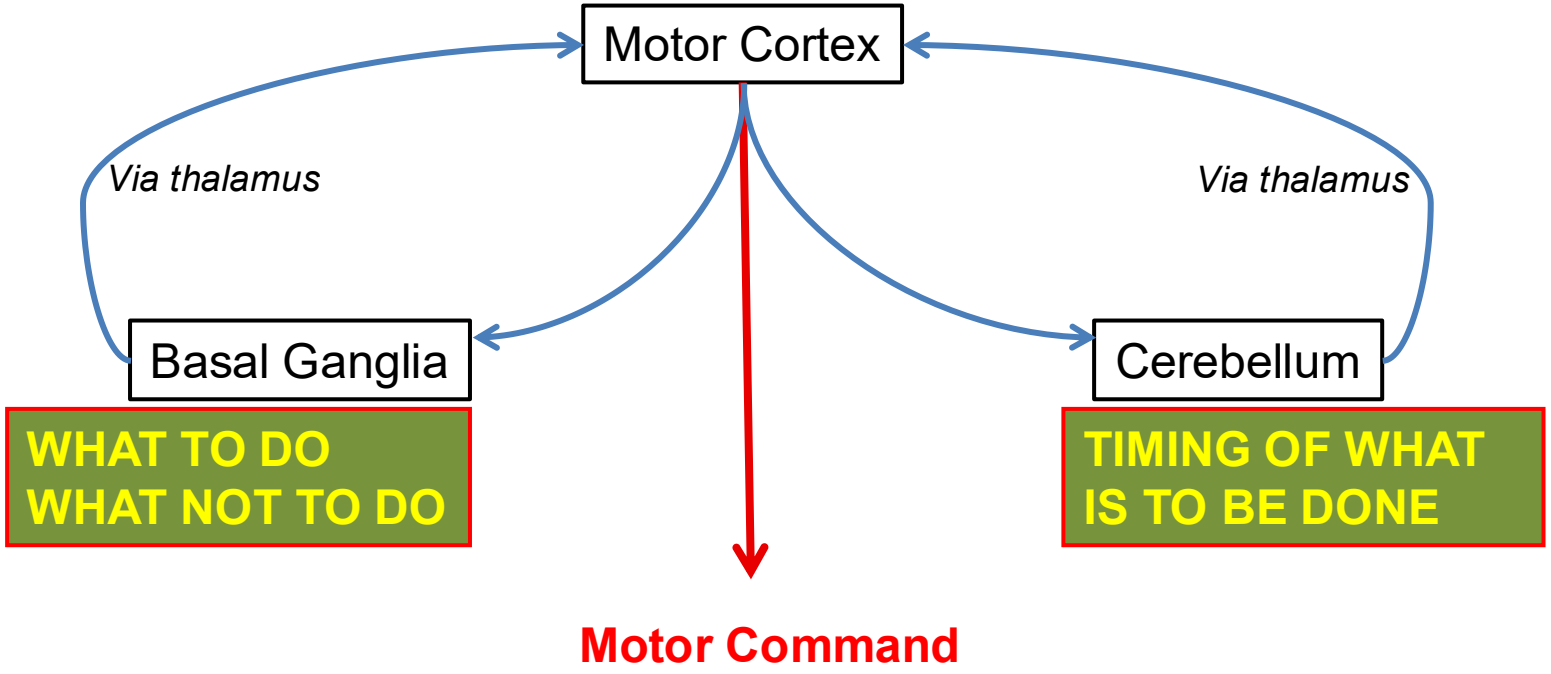
Damiani et al 2017 *J Morphol Sci* 34:123

Physiology of ataxia

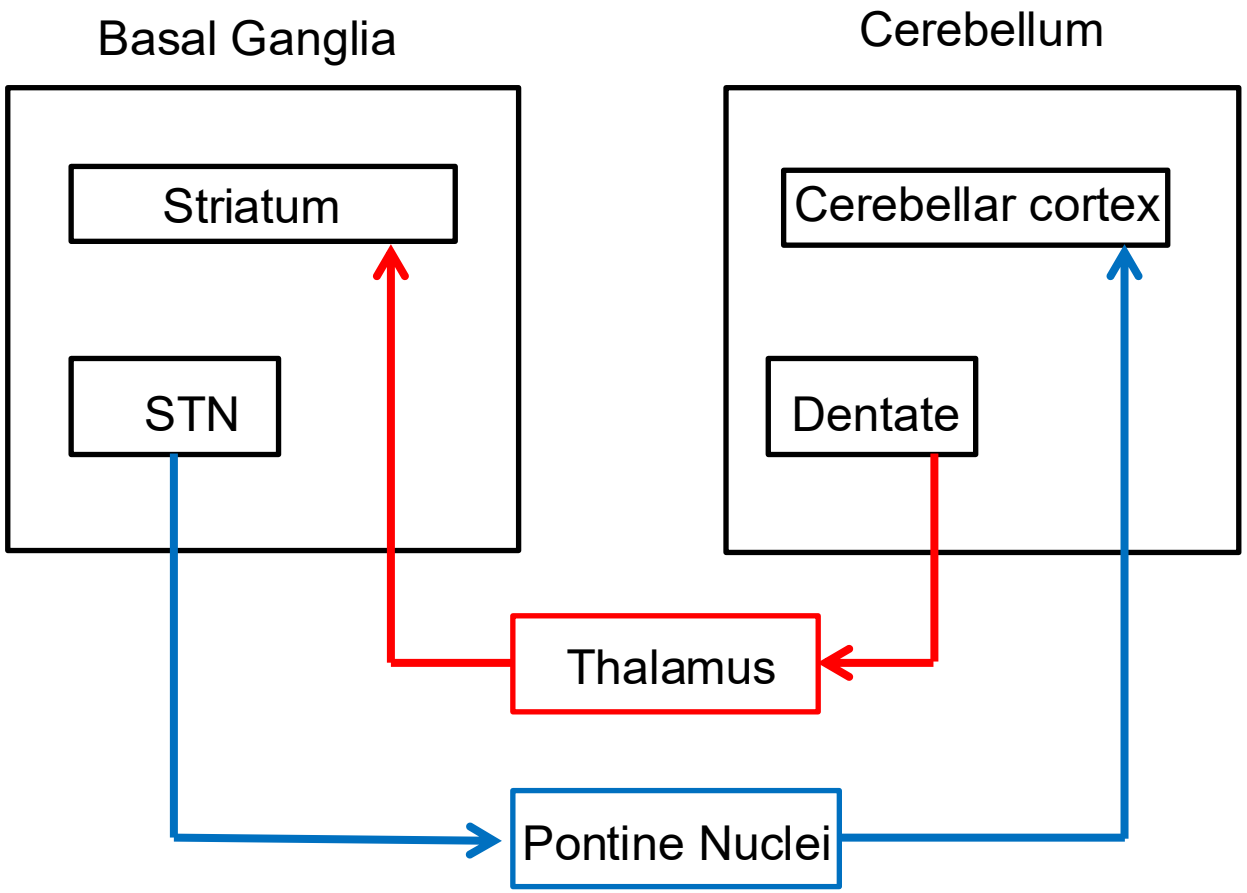
- Dysmetria
- Dyssynergia (decomposition of movement)
- Dysrhythmia
- Dysdiadochokinesia
- Tremor
- Impaired motor learning
  - particularly adaptation learning

Subcortical Influences of Basal Ganglia vs. Cerebellum





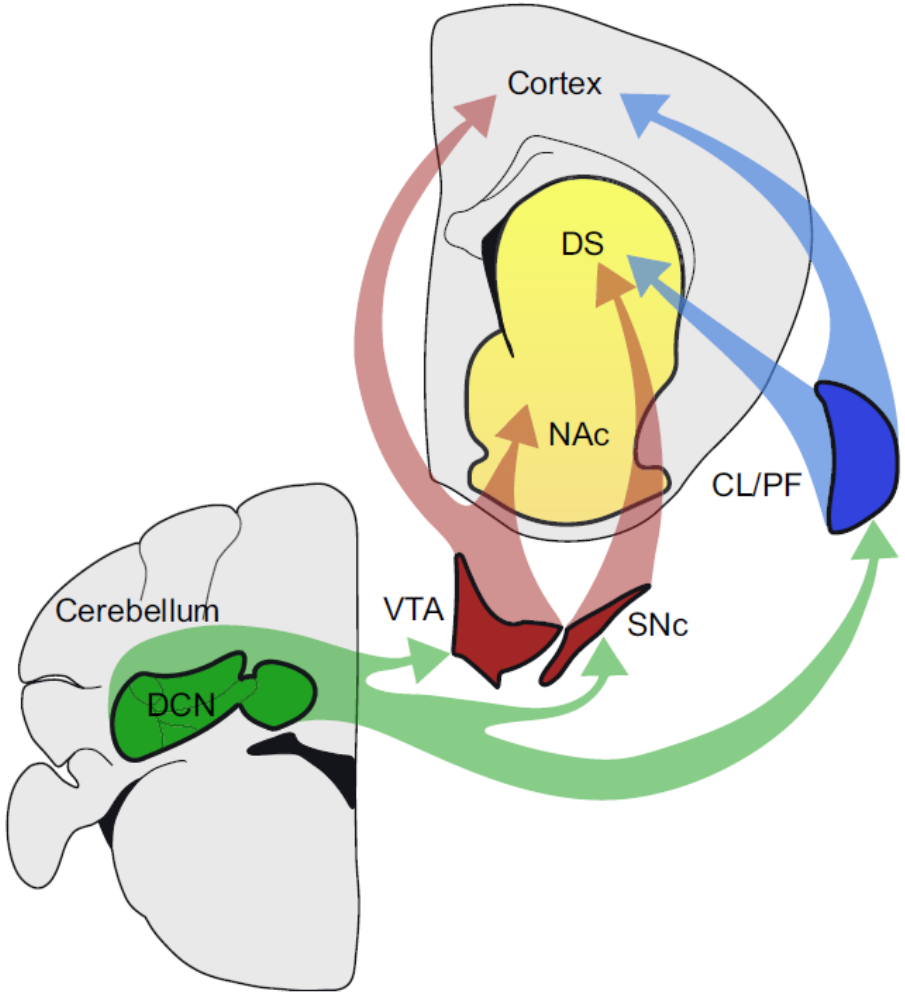
Basal ganglia and cerebellum interconnect



Cerebellar Contributions to the Basal Ganglia Influence Motor Coordination, Reward Processing, and Movement Vigor

The Journal of Neuroscience, November 9, 2022 • 42(45):8406–8415

Junichi Yoshida,[1] Maritza Oñate,[1] Leila Khatami,[1] Jorge Vera,[1] Farzan Nadim,[1,2] and Kamran Khodakhah[1]





Intralaminar Thalamus and Parkinson's

What Is the Role of the Intralaminar Thalamic Input to the Striatum and Its Potential Implications in Parkinson Disease?

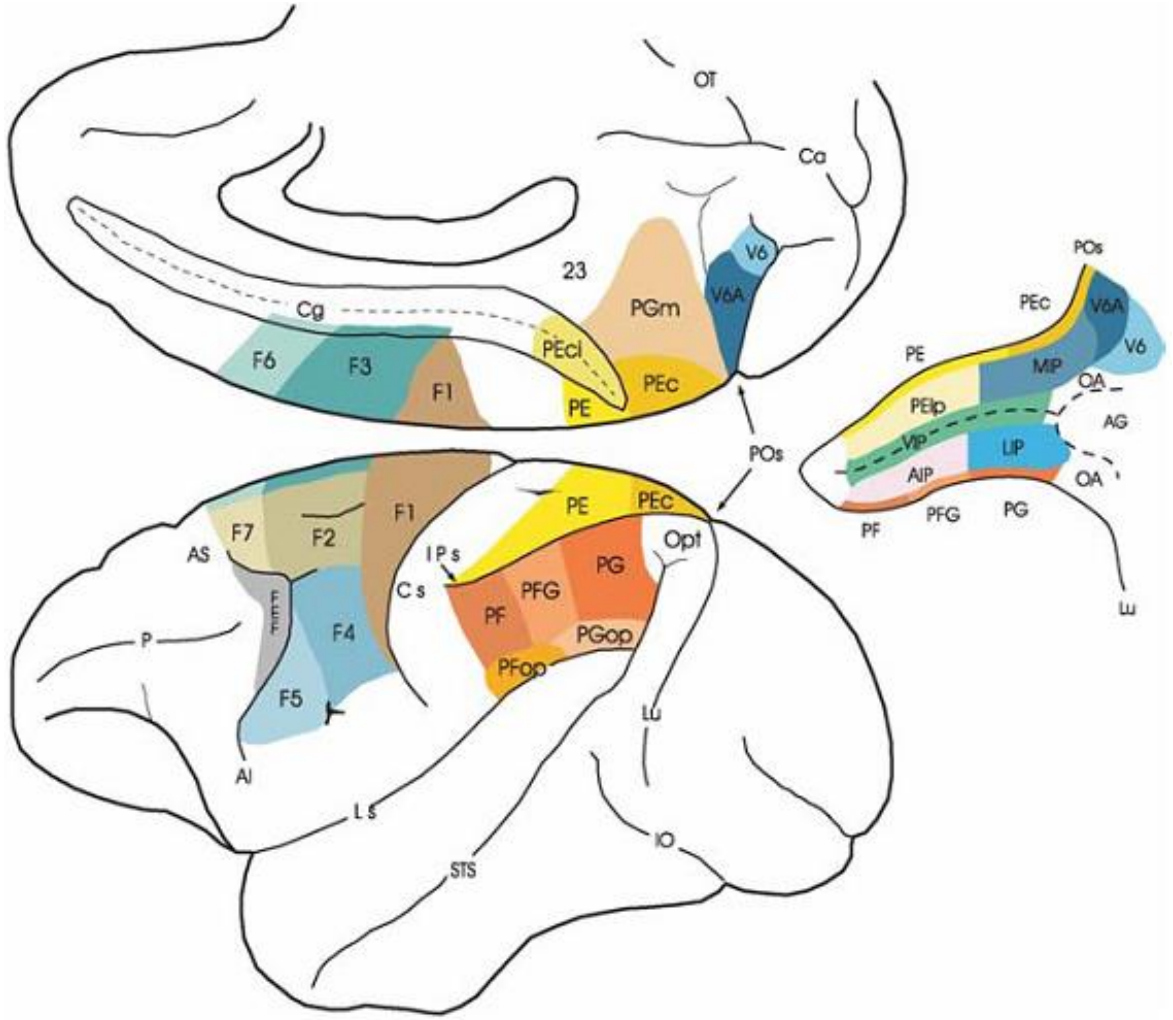
Eduardo Benarroch, MD

Neurology® 2023;101:118-123. doi:10.1212/WNL.0000000000207610

Correspondence
Dr. Benarroch
benarroch.eduardo@mayo.edu

What are the cortical influences on the primary motor cortex?

Parieto-frontal areas and their connections



Rizzolatti et al. 1998

Praxis

- Ability to perform skilled and/or learned movements

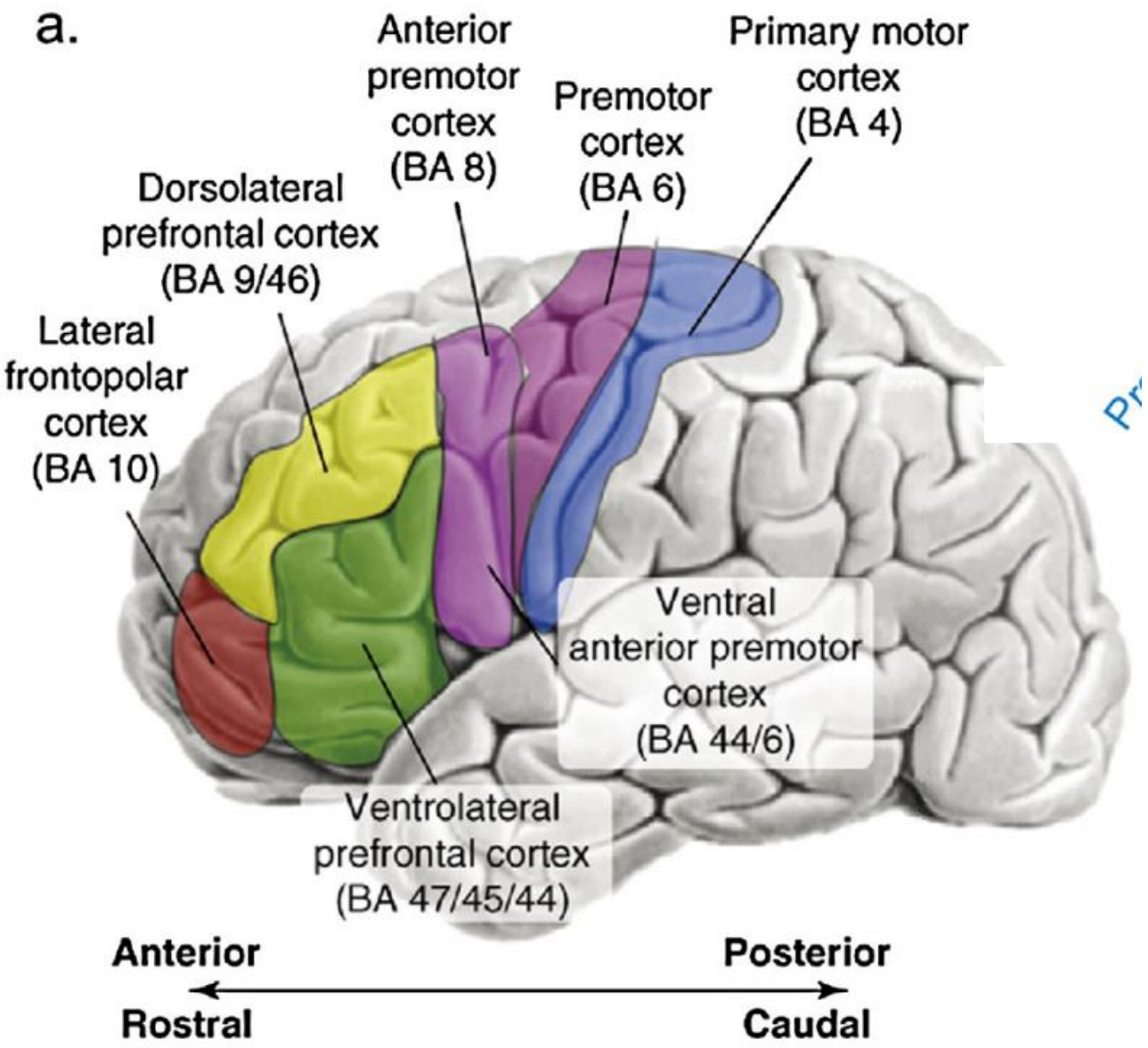


Apraxia

- Inability to perform skilled movements
- The problem cannot be ascribed to a language comprehension disorder or elemental sensorimotor deficit, including ataxia and bradykinesia

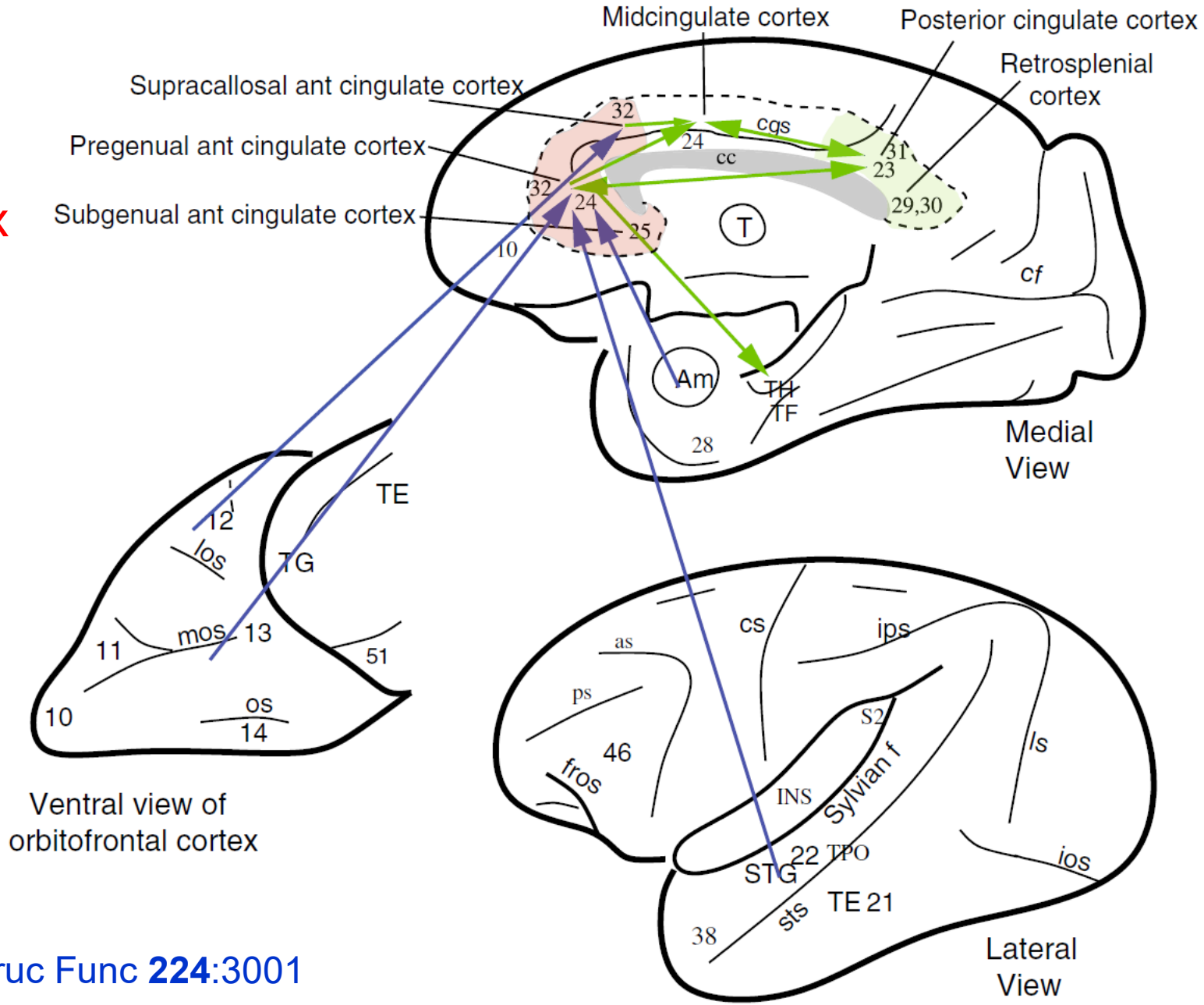
Frontal Lobe

Cognitive Influences
Emotion
Homeostasis



I. Dumontheil / Developmental Cognitive Neuroscience 10 (2014) 57–76

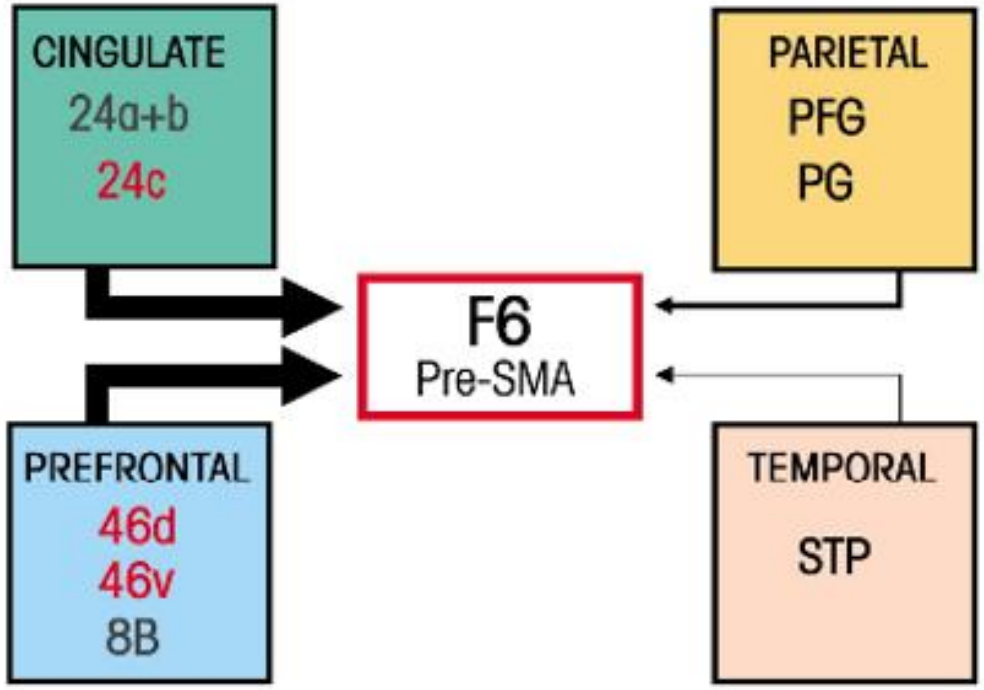
Limbic connections to anterior cingulate cortex

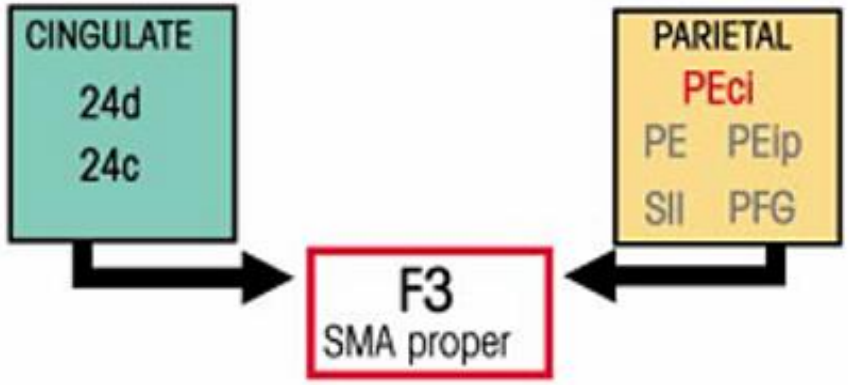


Rolls 2019 Brain Struc Func **224**:3001

Parietal and cingulate inputs to motor areas

External and Internal Drivers of Movement

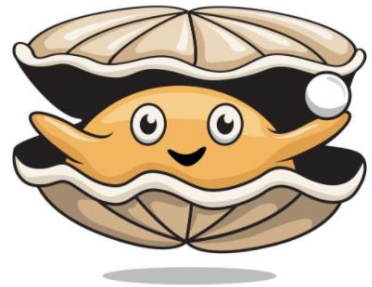




Rizzolatti & Luppino *Neuron* 2001

Voluntary Movement

Movement disorders with confusion about voluntariness



- **Tics:** often said to be voluntary, but patients cannot mimic them
- **Chorea:** early in the illness patients do not recognize their involuntary movements as being involuntary
- **Alien hand phenomenon:** unwanted movements arise without a sense of their being willed, with associated difficulty in self-initiated movement
- **Functional movements:** look voluntary but said to be involuntary
- **Schizophrenia:** look normal and are goal directed, but the patient may think that they are being externally controlled.

Physiology of Free Will

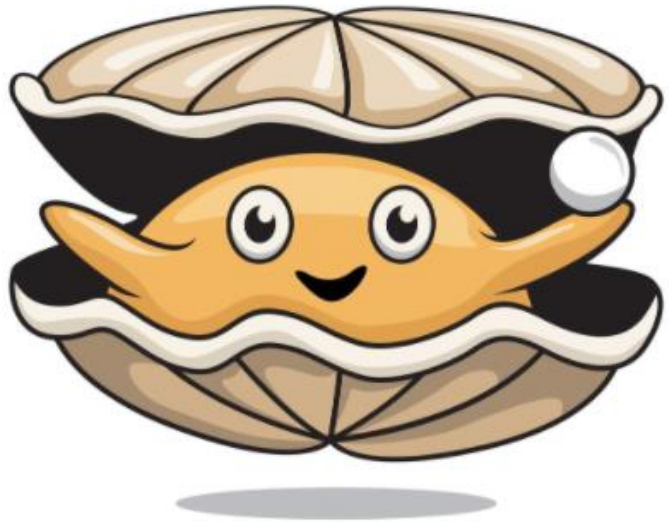
Mark Hallett, MD

Free will is a perception that people have that they choose to make their movements. This perception includes a sense of willing the movement and self-agency that they are responsible for the movement. If there is a "free will force" that plays a role in movement selection, it should precede movement. There is no evidence for a driving force, and the perception of willing is not fully processed until after the movement. The perceptions of free will likely arise from an interaction between frontal and parietal areas. Free will might be considered to exist if a person's brain is functioning normally without coercion.

ANN NEUROL 2016;80:5–12

Summary Basal Ganglia

- Kemp-Powell: funnel
- DeLong-Alexander-Strick: parallel
- Rate model now pattern model
- Importance of the cerebellum
- Emergence of neurotransmitters
- Realization of the importance of oscillations



- Muscle
- Alpha motor neuron
  - Segmental influences
  - Suprasegmental influences
- Primary motor cortex
  - Subcortical influences
    - Basal ganglia and cerebellum
  - Cortical influences
- Voluntary Movement

Neurotransmitters

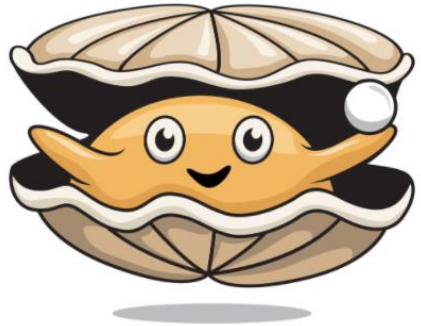
- Dopamine
- Acetylcholine
- Glutamate
- GABA
- Norepinephrine
- Serotonin
- Adenosine
- Endogenous opioids
- Neuropeptides
- Endocannabinoids

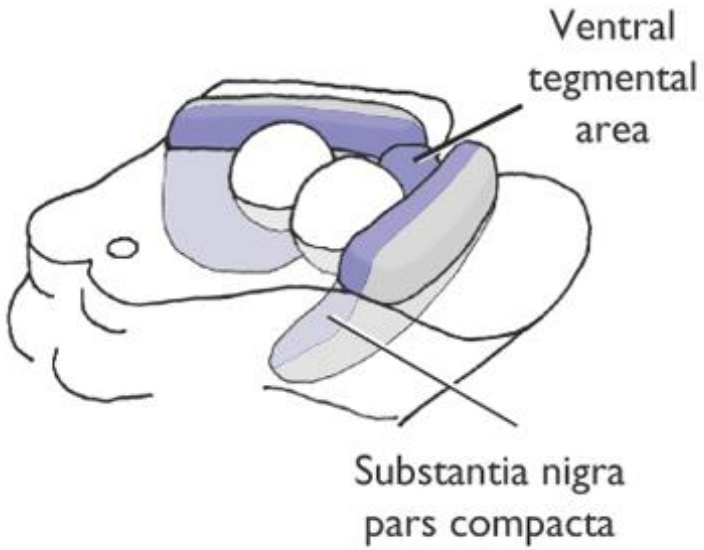
DOPAMINE PATHWAYS

Pathway	Origin
Mesolimbic	Ventral tegmental area (VTA)
Mesocortical	VTA
Nigrostriatal	Substantia nigra pars compacta (SNc)
Tuberoinfundibular	Arcuate nucleus of hypothalamus

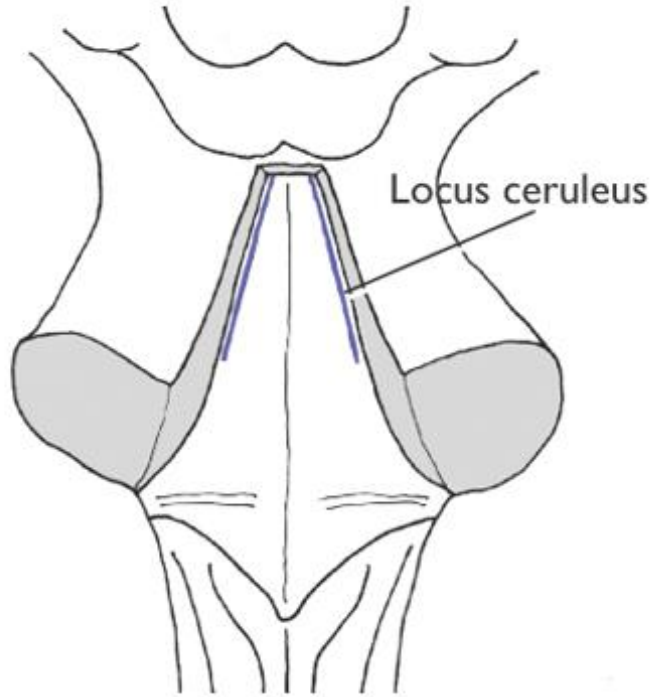
What is dopamine doing in the basal ganglia?

- Facilitates movement (tonic activity)
- Signals reward (phasic activity)
  - Relevant for motor learning
  - Relevant for motivating behavior
    - Including habits
  - Pathological relevance for drug addiction and dopamine dysregulation syndrome and maybe tics

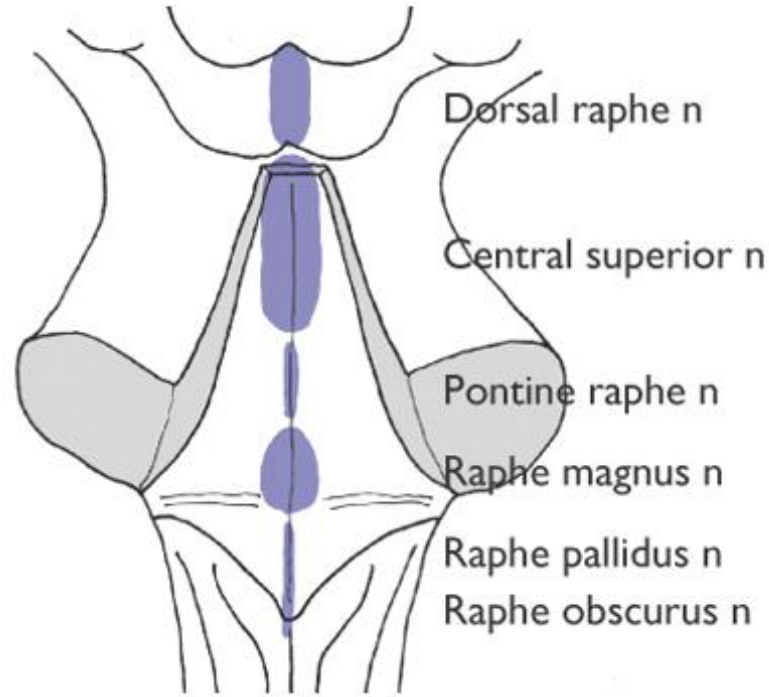




Dopaminergic nuclei



Noradrenalinergic nuclei



Serotoninergic nuclei

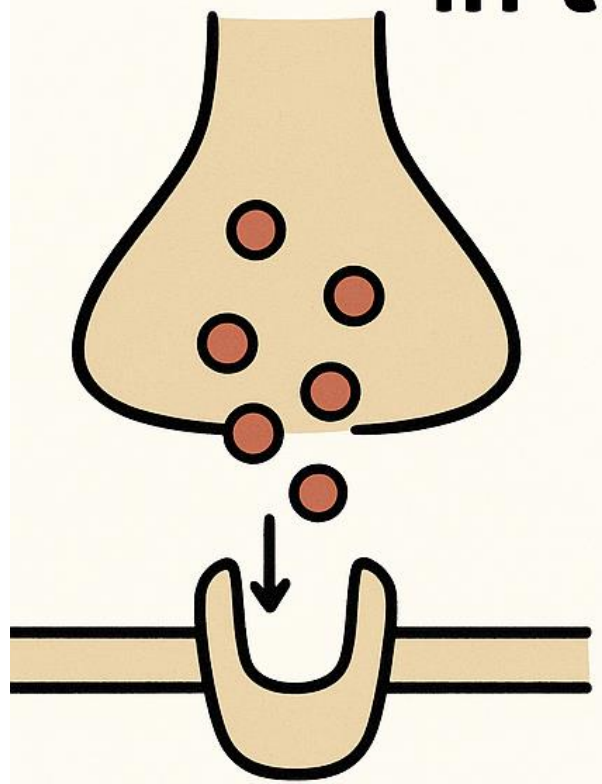
Sasaki M et al. NeuroReport 19: 1649, 2008

Acetylcholine (ACh)

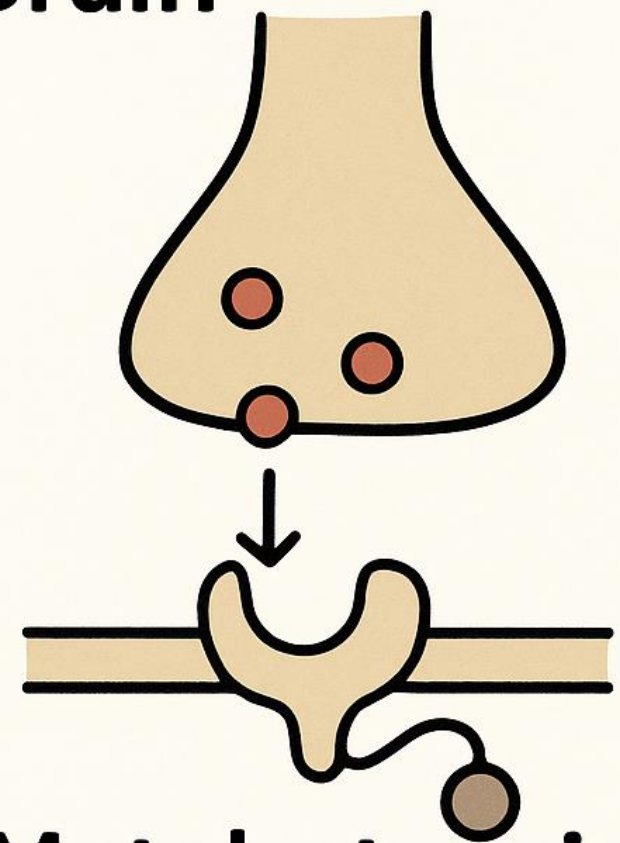
- Two neuron types
  - The “giant aspiny interneuron” of the striatum
  - A projection neuron arising in the PPN
- ACh receptors:
  - Nicotinic: ionotropic
  - Muscarinic: metabotropic, G-protein coupled

Feature	Ionotropic Receptors	Metabotropic Receptors
Mechanism	**Ligand-gated ion channels**	**G-protein-coupled receptors (GPCRs)**
Speed	**Fast** (milliseconds)	**Slow** (seconds to minutes)
Action	Directly open an ion channel upon ligand binding	Activate intracellular signaling cascades via G-proteins

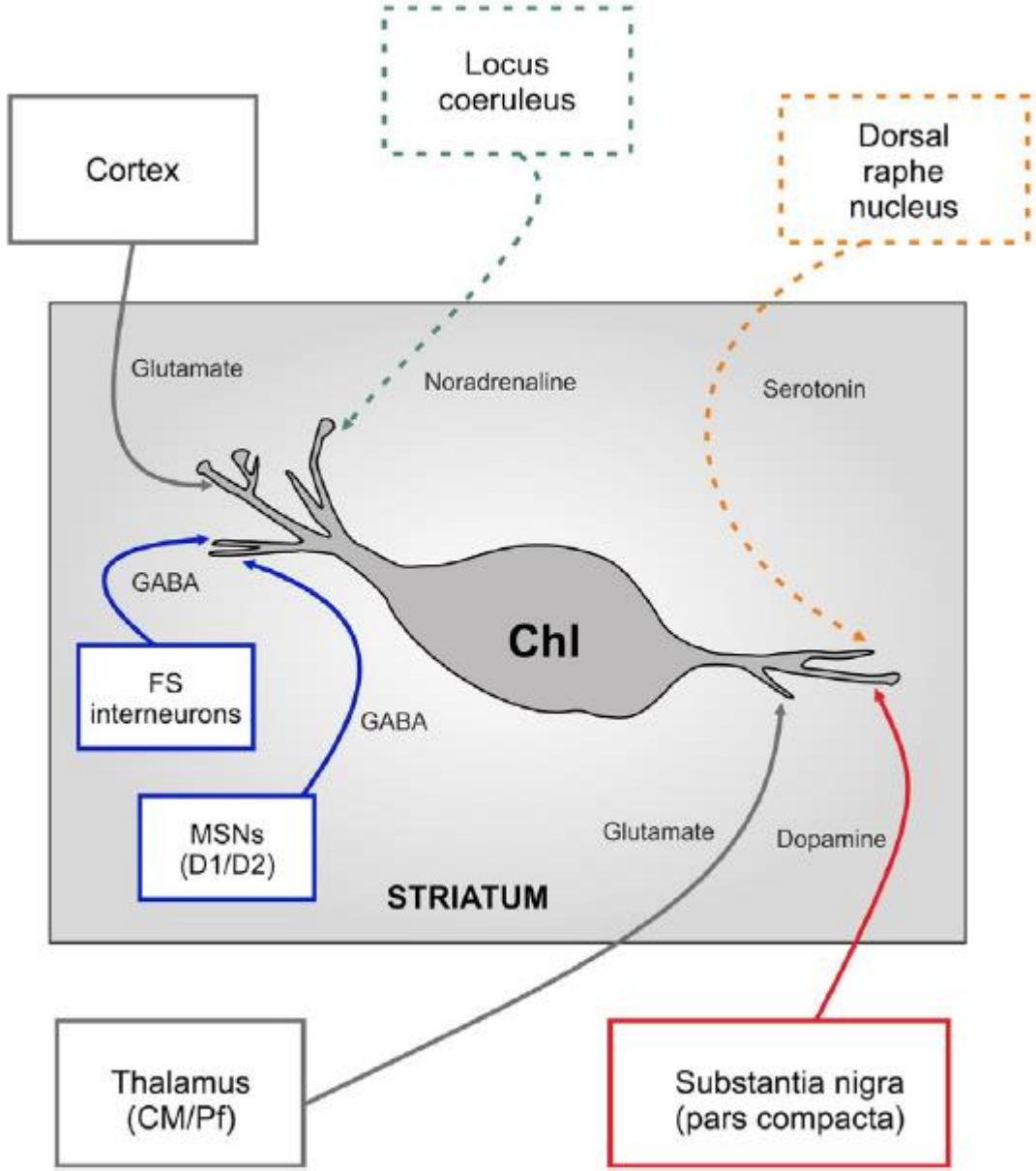
Fast and Slow Receptors in the Brain



Ionotropic
Fast

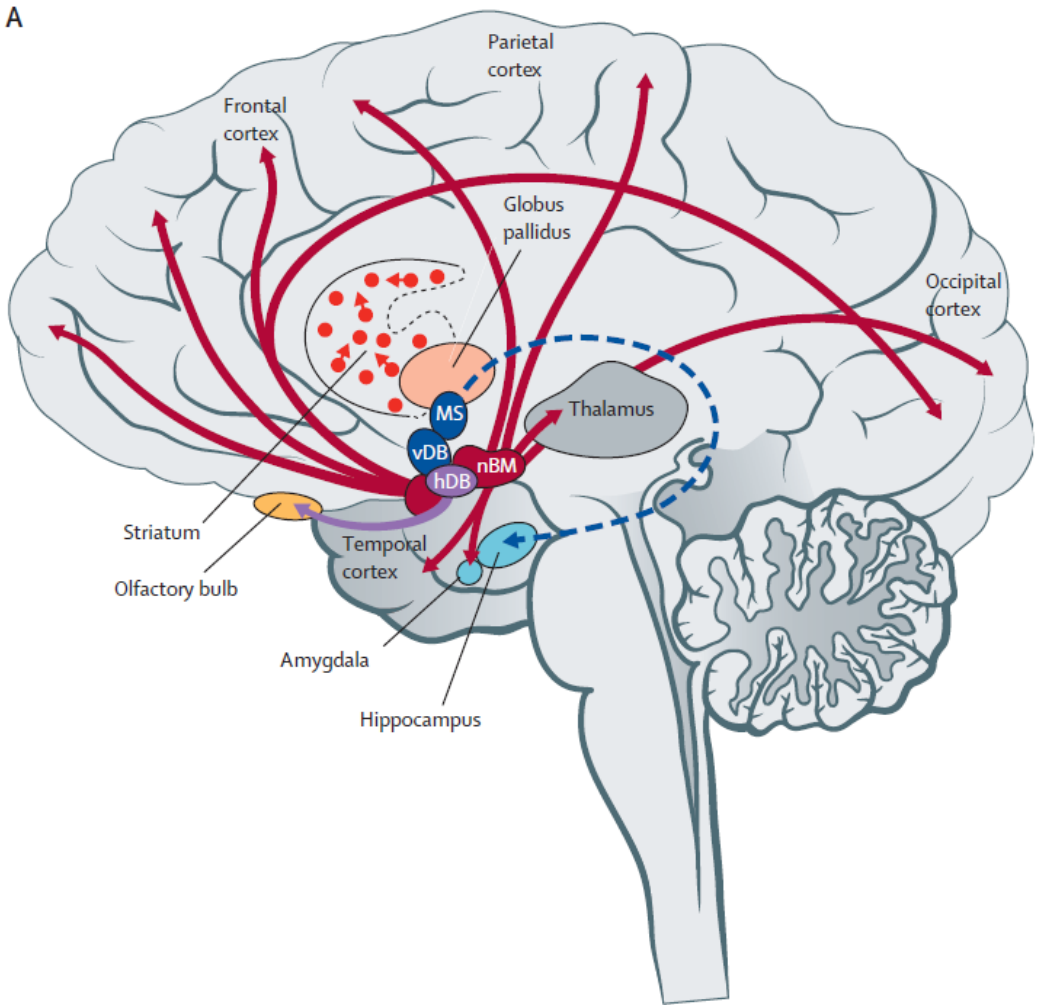


Metabotropic
Slow



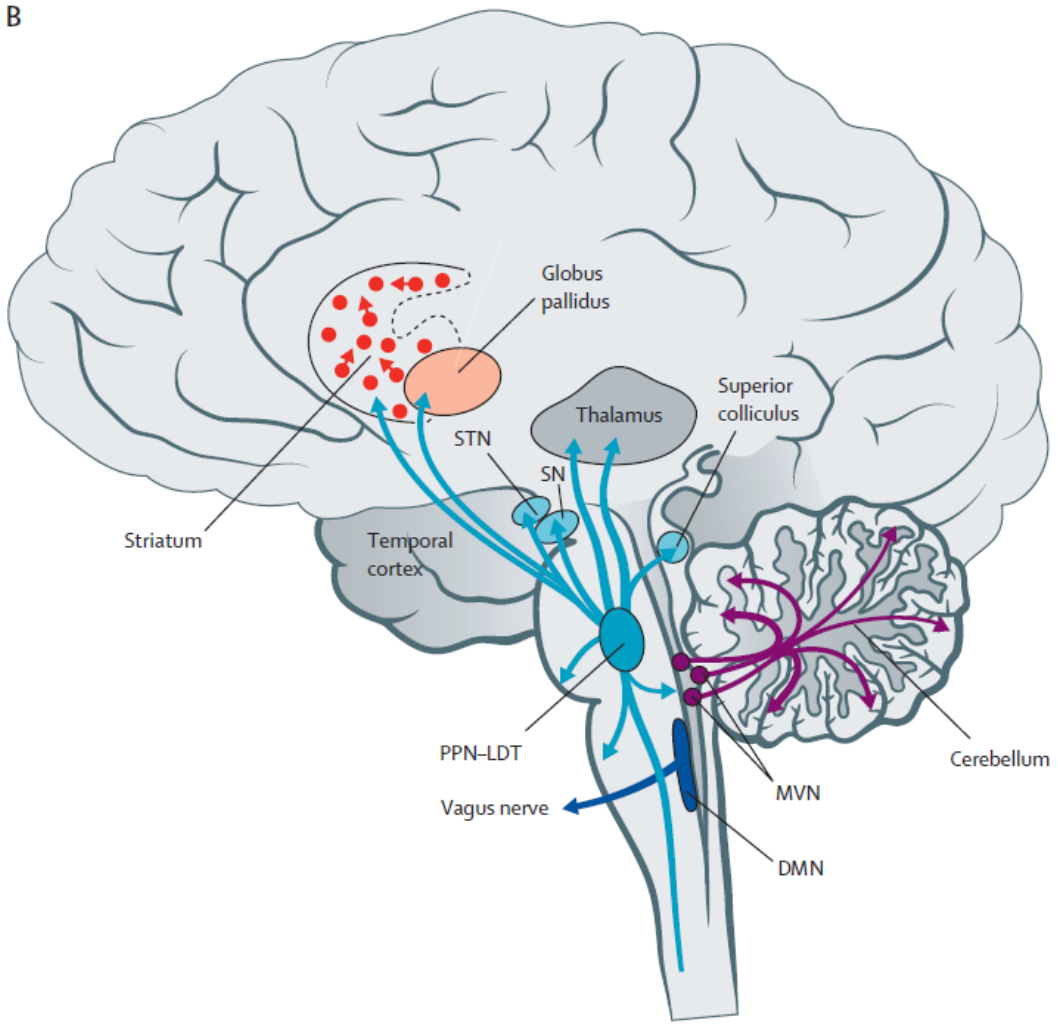
K.L. Eskow Jaunarajs et al. / Progress in Neurobiology 127–128 (2015) 91–107

Acetylcholine Projection System from Nucleus Basalis of Meynert



Bohnen et al. 2022 *Lancet Neurology*

Acetylcholine Projection System from Pedunculopontine Nucleus



Bohnen et al. 2022 *Lancet Neurology*

Glutamate

- Primary excitatory neurotransmitter
- Receptors
  - Metabotropic (3 classes)
    - Group I, II, III, depending on mGluR composition
  - Ionotropic (3 classes)
    - NMDA
    - Kainate
    - AMPA

GABA

- Primary inhibitory transmitter
- Receptors
  - GABA-A (& GABA-C): ionotropic
    - Open chloride (and potassium) channels
    - Benzodiazepine sensitive or not
  - GABA-B: metabotropic
    - Open potassium and inhibit calcium channels
    - G protein coupled

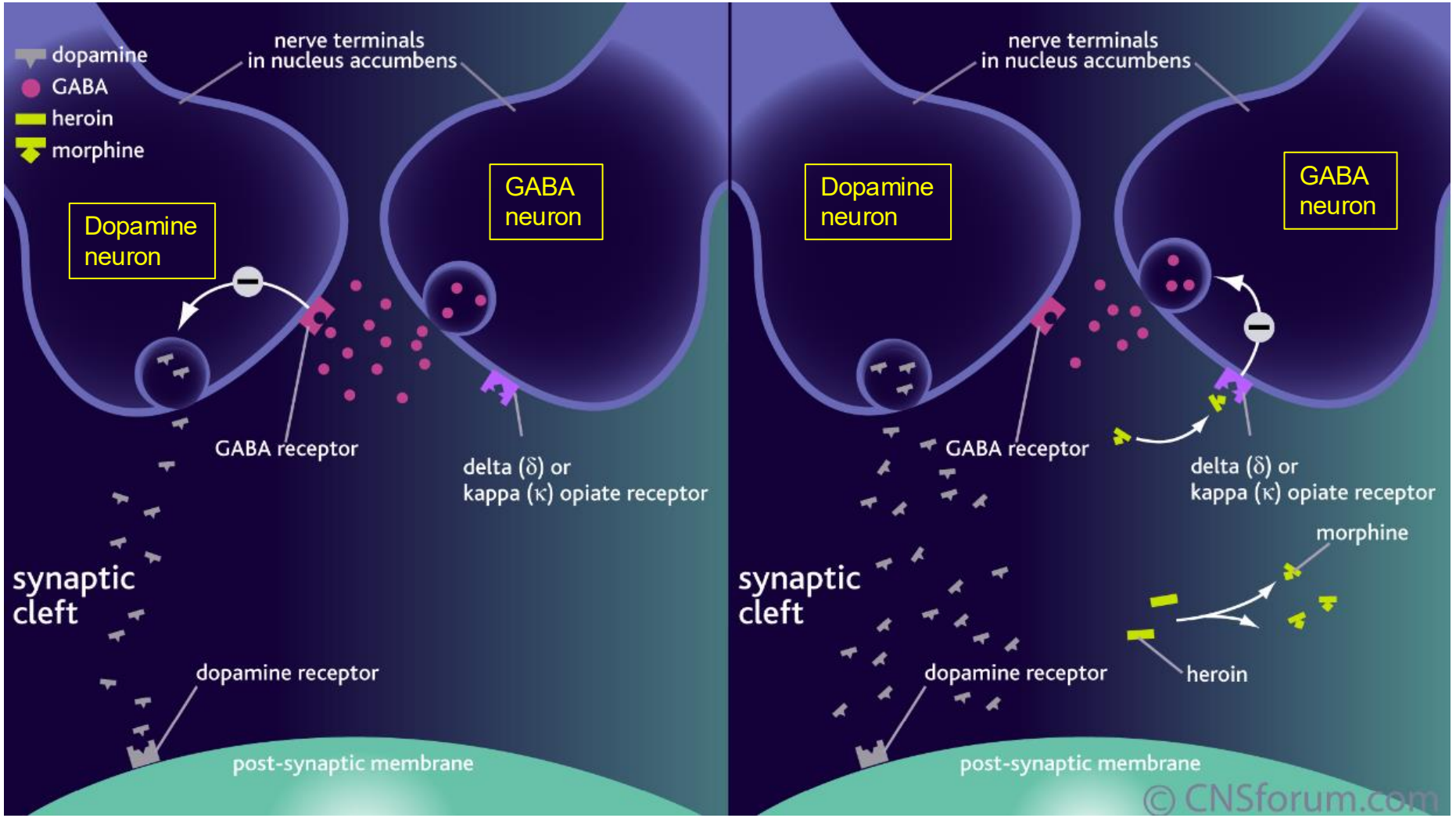
Adenosine

- Critical molecule in energy metabolism
- Plays a role as a neurotransmitter
- A2A receptors in basal ganglia, often coupled with the D2 receptor postsynaptically
  - Adenosine will reduce dopamine binding
  - Adenosine antagonists (like caffeine) will increase dopamine binding

Endogenous Opioids

- Dynorphins, enkephalins, endorphins, endomorphins and nociceptin
- Opioid receptors (G-protein coupled)
  - delta (δ)
  - kappa (κ)
  - mu (μ)
  - nociceptin receptor

Opioids Facilitate Dopamine Release



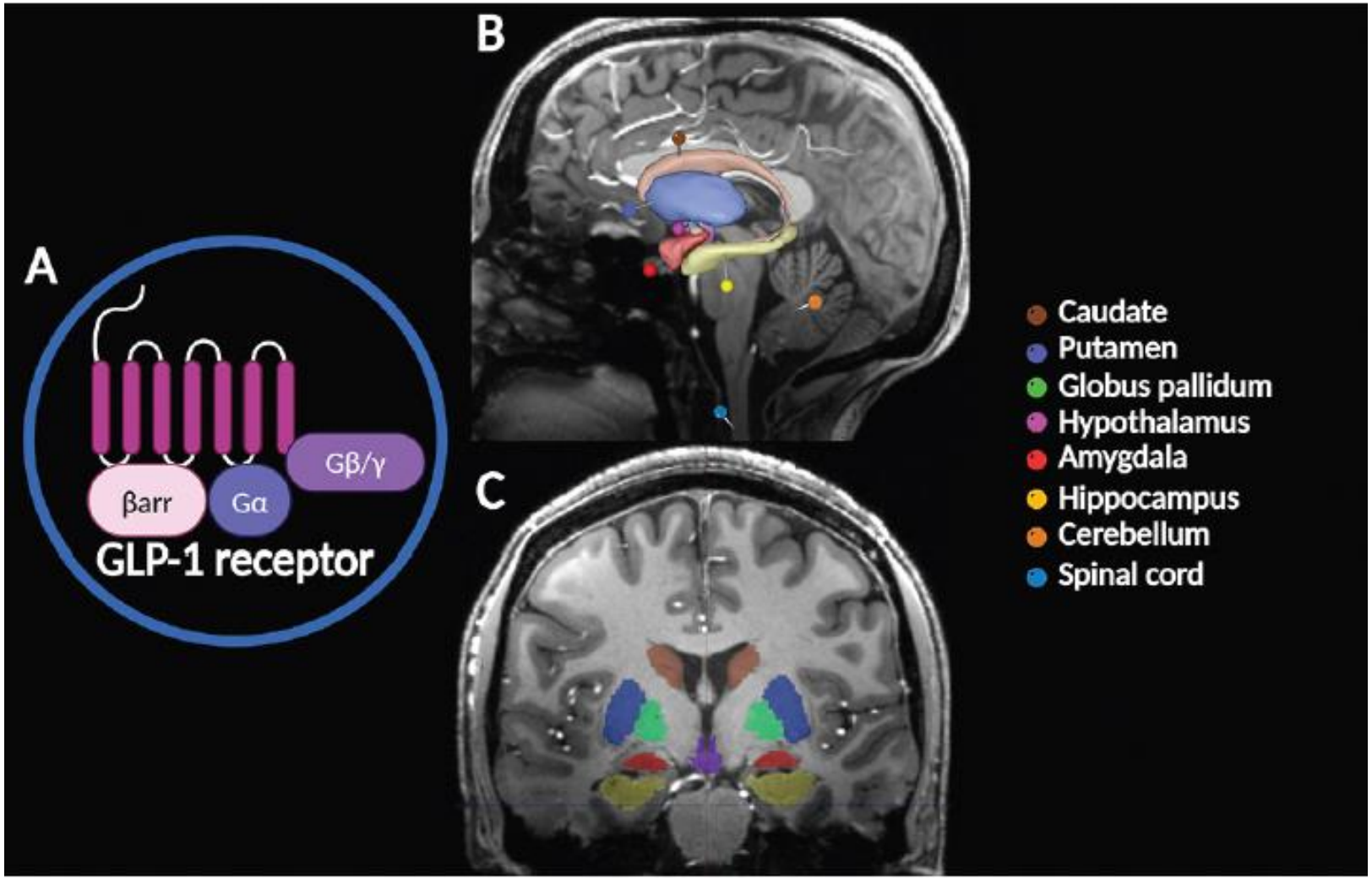
Neuropeptides (other)

- Small proteins typically co-released with other neurotransmitters
- Examples
  - Opioids
  - Substance
  - About 100 of them all together

Neuropeptide

GLP-1

Glucagon-like peptide 1

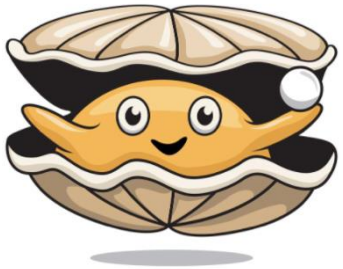


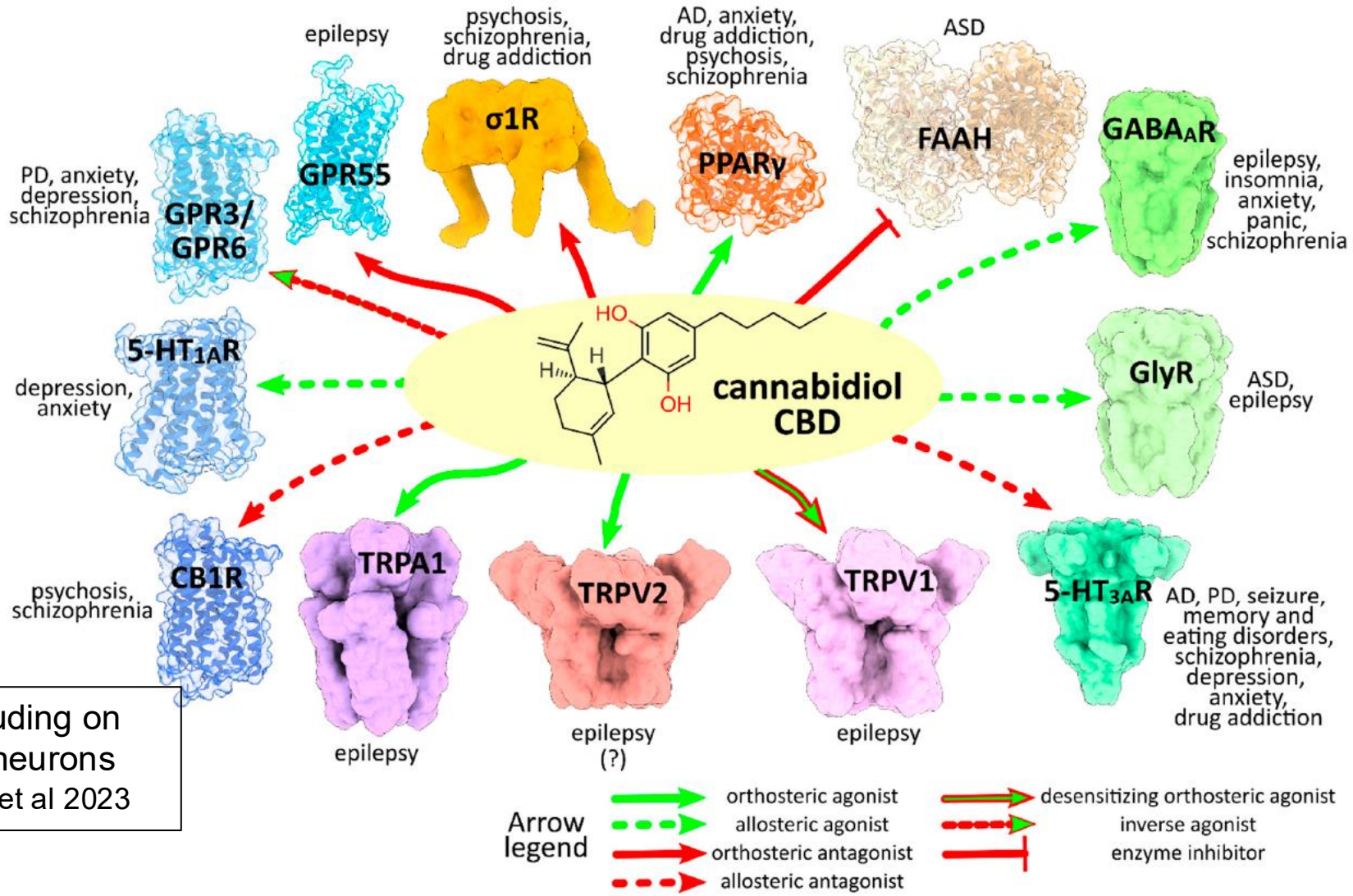
López-Ojeda & Hurley (2024) J Neuropsychiatry Clin Neurosci 36:2

Endocannabinoids

- Principal receptor in the basal ganglia is the CB1 receptor, but also the $TRVP_1$ receptor
- Natural ligands are anandamide and 2-arachidonoylglycerol
- Cannabinoids modulate dopaminergic effects, and generally seem to diminish dopamine release and slow down behavior

CBD has many influences in brain



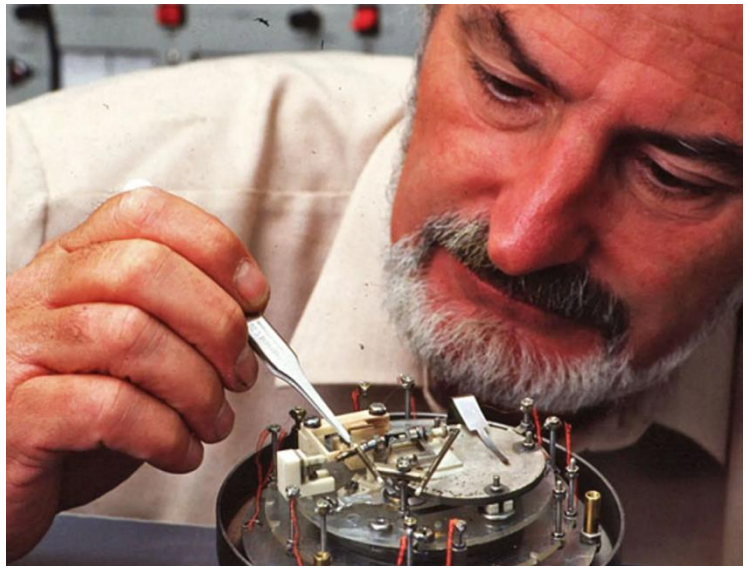


Including on DA neurons
Han et al 2023

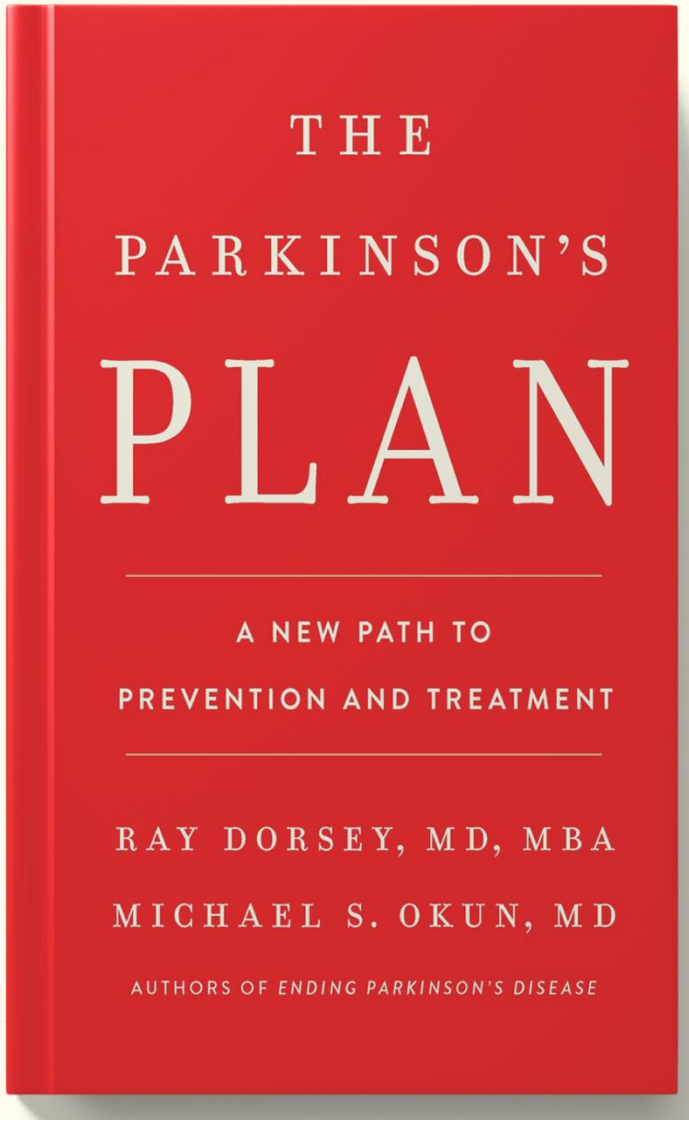
Vitale et al. 2021 Int J Molec Sci 22:4876

“Science means constantly walking a tightrope between blind faith and curiosity; between expertise and creativity; between bias and openness; between experience and epiphany; between ambition and passion; and between arrogance and conviction – in short, between and old today and a new tomorrow.”

— Henrich Rohrer



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The Parkinson's Plan, Dorsey and Okun, unpublished, 2025